TERMINOLOGY AND GUIDELINES FOR GLAUCOMA

3rd Edition

EUROPEAN GLAUCOMA SOCIETY

www.eugs.org

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ACKNOWLEDGEMENT

Contents

Foreword

It gives me great pleasure to introduce thus, the third edition of the European Glaucoma Society 'Guidelines'. In the 5 years since the last edition the Guidelines have been accepted as one of the standard texts in glaucoma, widely distributed and adopted across Europe. Since the last edition significant changes have taken place in the diagnosis and management of glaucoma: we have a much clearer understanding of the pathogenesis of open angle glaucoma, and have seen a revision of the terminology and mechanisms for angle closure. There have been advances in both diagnosis and method of followup of chronic glaucoma. Treatment both medical and surgical has improved with new drug combinations and new surgical techniques entering the mainstream of practice. More importantly, there have been improvements in measuring the effect that glaucoma has on the patient, how it affects Quality of life. All these changes and more appear in the third edition.

The Guidelines owe much to the enthusiasm and effort put in by the writing team, headed by Carlo Traverso with Anders Heijl, and the many co-opted helpers. Without them this edition would not have been possible. The new 'Guidelines' build on the reputation established by the earlier versions, and should take forward the understanding of glaucoma in Europe.

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INTRODUCTION
CHAPTER

Introduction

The aim of the Guidelines is to present the view of the European Glaucoma Society (EGS) on the diagnosis and management of glaucoma. Our guidelines are intended to support the general ophthalmologist in managing patients affected by or suspected of having glaucoma.
The guidelines are to be considered as recommendations rather than offering strict treatment protocols.

These guidelines use a simplified grading system for rating the strength of recommendation and the quality of evidence.
A strong recommendation (I) can be read as "we recommend" and/or "very relevant in clinical practice" and a weak recommendation (II) as "we suggest" and/or "less relevant in clinical practice".
The quality of evidence is classified as high (A), moderate (B), low (C) or very low (D). For example, high quality evidence would be supported by high quality randomised clinical trials (RCT). Observational studies would be typically graded as low-quality evidence. Consensus from our panel would be graded as D.

> **Clinical care must be individualized to the patient, the treating ophthalmologist and the socioeconomic milieu. The availability of Randomized Controlled Trials (RCTs) makes it possible to apply scientific evidence to clinical recommendations.**

The EGS, all contributors and all sponsors disclaim responsibility and liability for any adverse medical or legal effects resulting directly or indirectly from the use of the guidelines.

TERMINOLOGY, CLASSIFICATION AND DEFINITIONS

Classification and disease definitions are arbitrary, and a consensus can be reached only if they are acceptable to most ophthalmologists on both theoretical and practical grounds.
The following factors are to be considered in order to identify and separate the different glaucoma categories.

1. Anatomy / Structure (see Ch. 1)
Open-angle, closed-angle, optic nerve head, etc.
e.g. clinical sign, exfoliation, pigment dispersion

2. Function (see Ch. 1)
e.g. visual field

3. IOP level (see Ch. 1)
3.1   At which diagnosis is made (See Ch. 2)
3.2   At which damage occurred (See Ch. 1)
3.3   Target IOP (See Ch. 3.2)

TREATMENT PRINCIPLES

A. <u>Treatment Goals (See Ch. 3.1, 3.2 and INTRO III)</u>
A.1.   Quality of life
A.2.   Quality of vision
A.3.   Cost containment

> **In general terms, the goal of glaucoma treatment is to maintain the patient's visual function and related quality of life, at a sustainable cost. The cost of treatment in terms of inconvenience and side effects as well as financial implications for the individual and society requires careful evaluation. (See Ch. INTRO III). Quality of life is closely linked with visual function and overall patients with early to moderate glaucoma damage have good visual function and modest reduction in quality of life.**

B. <u>Suggested ways of reaching the goal (see Ch. 3 and 4)</u>

B.1.   Selection of patients to be treated
B.1.1.   Identification of patients with disease
B.1.2.   Identification of patients at risk of developing the disease [I, D]
B.1.3.   Treatment of the above when actual or expected rate of decay risks to interfere with quality of life [I,C]

B.2.   Decreasing the risk of ganglion cell loss (it reduced visual function)
       - Determine the target IOP for the individual [I, D]. In general, when there is more advanced damage, lower IOPs are needed to prevent further progression [I, D]
       - IOP lowering [I, A]
       - Drugs
       - Surgery
       - Laser
       - Verify the target IOP (See Ch.3.2)
       - Monitor the Rate of Progression (Field and Disc) [I, D]
       - Adjust management according to ROP
       - Blood flow (see Ch 3.1 and Ch 1) or neuroprotection (See Ch 3.1). Both under debate [II, D]

B.3.   Incorporation of a quality of life measure in the outcome of treatment

C.   Audit outcomes e.g. efficacy, safety, cost [I, D] (See Ch. INTRO III)

C.1.   Failures include patients suffering from the consequences of insufficient IOP lowering, unnecessary treatment, surgical complications, and avoidable progression of disease.

Since resources are limited worldwide, the following points are relevant to glaucoma treatment guidelines:

- **prevention of visual disability in those at risk of decreased quality of life;**
- **avoid widespread treatment of elevated IOP per se;**
- **enforce effective treatment + follow-up in patients with severe functional loss and/or rapid progression;**
- **implement strategies to detect all patients with manifest disease.**

These points are supported by the results of Randomized Clinical Trials for glaucoma (See Chapter Introduction).

EVALUATION OF FUNCTIONAL LOSS/TIME
FOR INDIVIDUALIZED TREATMENT
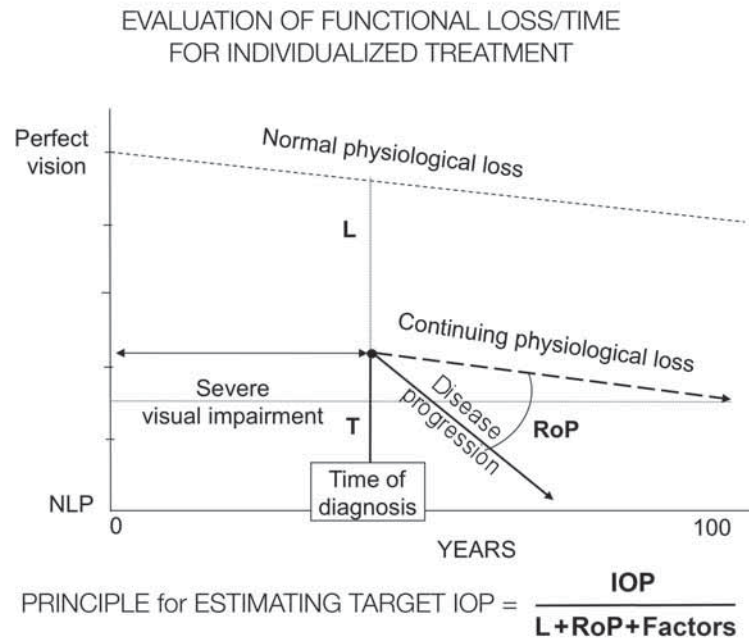
Fig. 1
Evaluation of functional loss/time for individualized treatment
L = the difference of visual function between the normal for age and the function at the time of diagnosis
RoP = angle between physiological loss and disease progression, representing progression rate
T = total functional loss at the time of diagnosis
FACTORS = individual features influencing clinical management (in alphabetic order): 1. Corneal thickness; 2. Family history; 3. Gonioscopy; 4. IOP, mean and fluctuation; 5. Life expectancy; 6. Pigment dispersion/exfoliation; 7. Rate of Progression (RoP); 8. Stage of ON damage; 9. Stage of VF damage; 10. Systemic diseases

It is important to stress that treatment guidelines are to be adapted to individual patients, socioeconomic environment, medical facilities, skills of the average ophthalmologist and health professional, and to available resources

II - RANDOMIZED CONTROLLED TRIALS FOR GLAUCOMA

While a proportion of the recommendations and definitions in the second edition were derived from common practice and consensus, it is now relevant to see how daily management of our patients can be helped by the findings of the modern, randomized, controlled trials. In the following pages we list the results from these trials, each with a summary of their layout and results, outline strengths and weaknesses, and derive comments relevant to clinical decision-making. In the future, prospective trials on management should preferably include data on cost and quality of life.

Remember that clinical trial outcomes refer to a GROUP of patients with specific inclusion/exclusion criteria and not necessarily to an individual patient. Also results from clinical trials may not translate directly to all patients with modifications coming from comorbidity whether ocular or systemic.

II.1 - TREATMENT VS NO TREATMENT TRIALS

II.1.1 - COLLABORATIVE NORMAL TENSION GLAUCOMA STUDY (CNTG STUDY)

Compared treatment versus no treatment in normal tension glaucoma. The primary outcome measure was disease progression. Eligible patients had glaucomatous optic disc abnormalities and visual field defects according to standardized criteria[1] and wither verified progression or threat to fixation. At least three reliable baseline visual fields and at least 20/30 BCVA were required. Cases with advanced damage were excluded. Ages ranged from 20 to 90 years. VF progression had to be verified. Optic disc progression was confirmed by reading masked sets of stereo disk photographs. 140 patients were randomized. The treatment goal was a 30% reduction from baseline IOP, obtained with medications (excluding beta blockers and adrenergic agents because of their potential crossover effects), laser trabeculoplasty or trabeculectomy. In patients undergoing surgery a 20% reduction was allowed without requiring repeated surgery.

Summary of results[2-5]
Treatment group:
Twenty eight eyes were treated medically or with Argon Laser Trabeculoplasty (ALT),33 surgically.
Control group: 79 eyes. Follow was over 5-7 years (CHECK THIS)
A 30% reduction from baseline was maintained in nearly 50% of the cases with medication, laser trabeculoplasty or both. Progression occurred in 12% (7/61) of treated eyes and 35 % (28/79) of controls. No correlation with absolute IOP level maintained during follow up was found in either group. Cataract among treated eyes was 38% (23/61), with 48% (16/33) of those surgically treated and 25% (7/28) of those medically treated, and in controls 14% (11/79). In the intent-to-treat analysis no benefit of treatment was found. A beneficial effect of IOP lowering was found only after the data were censored for the effect on VF of cataract formation[3].
In the treatment subgroup treated patients that progressed may be explained by their progression not pressure-dependent or that their IOP was not at target.

- Strengths
• 	Long follow-up
• 	Masked observers for VF and disc criteria

- Weaknesses
• 	Visual field criteria were changed during the course of the study[1]
• 	CCT values were not taken
• 	IOP values up to 24mmHg higher than usually defined for NPG
• 	Optic disc haemorrhage was used as a sign of progression for randomization into the study, but not as an outcome measure of progression
• 	Intent to treat analysis affected by coincident cataract formation

II.1.2 - EARLY MANIFEST GLAUCOMA TREATMENT STUDY (EMGT)

Compared treatment vs no treatment to evaluate the effectiveness of IOP reduction in early, previously untreated open-angle glaucoma. Secondary aims were to assess factors related to glaucoma progression, and to determine the natural history of the disease. During a population-based screening among 44,243 residents in Sweden, 316 eyes of 255 patients were recruited. Treated patients received a standardized treatment protocol of laser trabeculoplasty and topical Betaxolol in eligible eyes. Follow-up visits included computerized perimetry and tonometry every 3 months, fundus photography every 6 months. Treatment or no-treatment remained unchanged as long as definite progression had not occurred.
Primary outcome measure was progression of disease, defined by sustained increases of visual field loss in three consecutive C30-2 Humphrey tests, or by optic disc changes, as determined from flicker chronoscopy and side-by-side comparisons of fundus photographs performed by masked, independent grading centre[6].

Summary of results[7-12]
A 25% decrease of IOP from baseline (mean untreated IOP 20.6 mmHg) reduced the risk of progression by 50%. Treatment had positive effects in all groups of patients; with higher and lower IOP, older and younger patients, patients with early and later stage of disease.
Risk of progression decreased 10% with each mmHg IOP reduction from baseline to the first follow-up visit. Most progression was found first by perimetry, and only one first by disc photography.
Disease progression rates varied substantially between individual patients.
Risk of progression was smaller with lower baseline IOP values and with a larger initial IOP drop induced by treatment.
Some patients did not show any disease progression even after several years without treatment.
Treated patients had a considerably larger incidence of nuclear cataract than control patients
Pseudoexfoliation syndrome was a strong independent risk factor.
Later analyses showed that thin central corneal thickness was a risk factor in POAG (baseline IOP > 21 mmHg), and low blood pressure a risk factor in NTG[10] (baseline IOP < 21 mmHg).
IOP fluctuation was not a risk factor for progression[11]
Increase in lens opacity occurred after Betaxolol + laser and more than in the no-treatment group.
Quality of life did not differ between the treated and the untreated control group[9].

This study proves and quantifies the value of IOP reduction in patients with POAG, NTG and pseudoexfoliative glaucoma. The results suggest that close follow-up without treatment may be an option in eyes with mild disease and having a low risk for progression.

- Strengths
- Standardized protocol; the controlled study including glaucoma patients with elevated IOP.
- Recruitment mainly through a population-based screening
- Strict criteria for examinations, machine-based VF interpretation, independent disc photography centre.
- Examinations carried out without expensive technology
- Well designed assessment of VF progression – definite progression was associated with a mean worsening of MD of less than 2dB .
- Initial power calculations were based on the suspected difference in progression between the two groups.

- Weaknesses
- Quality of life measure was not part of the initial protocol

II.1.3 - THE OCULAR HYPERTENSION TREATMENT STUDY (OHTS)

The OHTS was a multicentre, randomized, prospective clinical trial, designed to determine the efficacy of topical ocular hypotensive medication in delaying or preventing the onset of glaucoma in patients with ocular hypertension (OH). Patients had a elevated IOP between

24 and 32 mmHg in one eye and between 21 and 32 mmHg in the other eye, with the remainder of the examination normal. 1636 patients between 40 to 80 years were recruited. Randomization was between treatment with IOP lowering medications and no treatment. The treatment goal was to lower the IOP to < 24mmHg and at least 20% from baseline. The primary outcome was the development of primary open-angle glaucoma defined as continued visual field abnormality or reproducible optic disc deterioration. All comparisons were made on an intent-to-treat basis.

Summary of results[13-18]
In the treated group the mean IOP reduction was 22.5% (SD 9.9), in the control group the decrease of IOP was 4.0% (SD 11.9). The cumulative proportion developing POAG at 60 months was 4.4% in treated eyes and 9% in controls (p < 0.0001): a 50% reduction of risk. The difference between treated and controls appears to increase with time.
Thus a large percentage of untreated patients (>90%) did not convert to POAG. Endpoints for POAG conversion were reached by both disc and VF findings in up to 10% of the cases, by disc only in around 50% and by VF only in approximately 40% of the total. Cataract formation was more common in the medication group (6.4 vs 4.3 %; p<0.06).

Baseline factors that predict the onset of POAG[15]:
Older age, larger vertical and horizontal cup-to-disc ratio, greater PSD and higher IOP were associated with conversion to POAG. The strongest association was with central corneal thickness (CCT).

CCT needs to be taken into account when measuring IOP, e.g. falsely high readings may be caused by thick corneas[16]. OHTS demonstrated that thin corneas are a definite risk factor for conversion to glaucoma.

Optic disc haemorrhage was associated with an increased risk of developing POAG.
For earliest detection of glaucomatous damage, both VF and optic disc status must be monitored, because either may show the first evidence of glaucomatous damage[18].

- Strengths
- Large sample (1636 patients).
- Strictly applied enrollment protocols.
- Careful follow-up.
- Masked assessment of endpoints.
- Attribution of endpoints by a masked committee.
- Careful quality control and feedback to technicians and photographers.
- True-incidence cases.

- Weaknesses
- Limited IOP range, i.e. no information on higher or lower IOPs than the selection criteria
- Sample is from healthy volunteers and not population based
- Relatively small number of POAG endpoints
- Limited to patients with reliable visual fields
- High thresholds for endpoints
- Some risk factors under-represented
- Criteria for conversion to POAG adjusted during study
- If a correction factor was applied at baseline for CCT, up to 57% of white subjects and up to 37% of black subjects would have corrected IOPs. If such an adjustment had been made at baseline some would not have had OH.
- Some of the patients with normal white-on-white perimetry were later reported (ARVO 2002) to have had SWAP defects at baseline, thereby casting doubt on the "normal" state of some of the participants.

II.1.4 – EUROPEAN GLAUCOMA PREVENTION STUDY (EGPS)

The EGPS was a multicentre, randomized, double-masked, placebo-controlled clinical trial[19]. The aim of this study was to evaluate the efficacy of IOP reduction by dorzolamide in preventing or delaying POAG in patients with OH.

Patients were aged between 30 and 80 years, had an IOP between 22 and 29 mmHg in at least 1 eye (without therapy or after a washout of at least 3 weeks from previously used drugs), open angles, 2 normal and reliable visual field tests and normal optic discs Exclusion criteria included a visual acuity of worse than 20/40 in either eye, previous intraocular surgery, or any sign of diabetic retinopathy or other diseases capable of causing visual field loss or optic disc deterioration. The patients were randomized into 2 groups: active therapy (dorzolamide) and placebo (which was the vehicle of the active therapy). CCT measurements were taken during the trial in a large sample of the patients: 429 in the dorzolamide group (80.0%) and 425 in the placebo group (78.5%).

Main outcome measures were visual field and/or optic disc changes[20].

Summary of results[21]

1081 patients were enrolled. The median duration of follow-up for all the patients enrolled was 55.3 months. IOP difference between the two groups was small.

The mean IOP reduction was 15% after 6 months and 22% after 5 years in the dorzolamide group. However, there was also a 9% after 6 months and 19% after 5 years in the placebo group, there was no significant difference in consensus between the two groups.

120 patients developed a POAG (120/1077, 11.1%)[22].

The same predictors for the development of POAG were identified independently in both the OHTS observation group and the EGPS placebo group—baseline older age, higher intraocular pressure, thinner CCT, larger vertical cup-to-disc ratio, and higher Humphrey VF pattern standard deviation[23]. The study failed to detect a statistically significant difference between the chosen medical therapy and placebo, either in IOP lowering effect, or in the rate of progression to POAG[24].

- Strengths
•   Large sample (1077 patients).
•   Careful follow-up examinations.
•   Randomized, double-masked protocol, placebo-controlled
•   Fixed treatment protocol
- Weaknesses
•   High drop-out rate
•   Only one type of IOP-lowering medication was evaluated.
•   IOP difference reached between the two groups was small.

II.2 – STUDIES COMPARING TREATMENTS

II.2.1 – COLLABORATIVE INITIAL GLAUCOMA TREATMENT STUDY (CIGTS)

607 patients with newly diagnosed open-angle glaucoma.
Initial treatment was either medication or trabeculectomy (with or without 5-fluorouracil).
A target IOP algorithm was used specific for each individual eye.
Primary outcome variables were VF loss and Quality of Life (QoL).
Secondary outcome variables were Visual Acuity (VA), IOP, cataract formation.

Summary of results[25-30]

VF progression Both treatment groups obtained a goal reduction in IOP only 4 years minimum did not differ significantly between surgical medical treatment groups.

IOP was lower with surgery (average 14-15 mmHg) than with medications (average 17-18 mmHg), decreasing 35% with medications and 48% with surgery. Perimetry results were equal with essentially no progression in either group. QoL was initially better with drugs.

Both medications and surgery increased the incidence of cataract extraction (6% vs 17%).

- Strengths
- Individualized target IOP approach
- Newly diagnosed patients
- QoL prospectively addressed

- Weaknesses
- Inclusion criteria may have allowed recruitment of OH resulting in a case mix with little risk of showing progression
- Follow-up might not be long enough to show differences
- Only preliminary results reported

II.2.2 – ADVANCED GLAUCOMA INTERVENTION STUDY (AGIS)

Multicentre, prospective randomized study on advanced open-angle glaucoma patients who suffered from glaucoma that could not be controlled by maximum tolerated medical therapy alone. The 591 patients of 35 to 80 years of age (789 eyes) were randomised between two treatments (what does AE stand for-followed by?) sequences for further interventions: argon laser trabeculoplasty then trabeculectomy then trabeculectomy (ATT) or trabeculectomy then argon laser trabeculoplasty then trabeculectomy (TAT). The second and third interventions were offered only after failure of the first and second interventions, respectively. The eyes enrolled had to be phakic, show a consistent elevation of intraocular pressure (IOP) of 18 mmHg or greater, a reproducible, glaucoma-type visual field defect quantified using a custom made score system, as well as a minimum visual acuity equivalent with a Snellen value of >20/80. Patients with a MD worse than 16 dB were excluded. Most of the patients were either Caucasian (325 eyes of 249 patients) or Afro-American (451 eyes of 332 patients). The follow-up time in these articles varies between 4 and 10 years[31].

Summary of results
Relationship between IOP and progression of the visual field damage over at least 6-years follow-up[31]. If you give references in the text it should be the same for each of these studies. In the last edition these were consigned to the end of the chapter, and I would keep to this.
Predictive Analysis: eyes with average IOP greater than 17.5 mmHg over the first three 6-months visits showed a significantly greater visual field deterioration compared to the eyes with IOP less than 14 mmHg in the same time period. The amount of deterioration was greater at 7 years than at 2 years, i.e. increased with longer follow-up time.
Associative Analysis: eyes with IOP less than 18 mmHg at 100% of the visits over 6 years did not show an increase of their initial visual field defect, whereas eyes that reached this value only at 75 to 100 %, 50 to 75 % or 0 to 50 % of the visits all showed a significant increase of the visual field defect. The amount of visual field decrease was greater at 7 years than at 2 years. These results indicate that low IOP and low IOP fluctuation are associated with reduced progression of a visual field defect in advanced glaucoma. Patients with the lowest range of IOP (max 18mmHg) were the only ones showing overall stability of average VF scores; this effect was well separated from the other groups only after the fifth year of follow-up. In this same group, 14.4 % of the patients showed worsening, and 18% an improvement of four of more units compared to baseline.
Relationship between treatment type and visual acuity /visual field preservation[32]. For a 7-year follow-up mean decrease of IOP was greater for eyes assigned to TAT, and the cumulative probability of failure of the first intervention was greater for eyes assigned to ATT. In Afro-American patients average percent of eyes with decreased visual acuity and visual field were less for the ATT sequence than for TAT. In Caucasians those were more favourable for ATT in the first 4 years, but then switched in favour of TAT[33,34].
Risk of cataract formation after trabeculectomy[35]. The expected 5-year cumulative probability of cataract formation was significantly increased – to 78 %.
Initial trabeculectomy retarded the progression of glaucoma more effectively in Caucasians than in Afro-Americans[36]. Some patients continued to progress despite low IOPs; some patients retained high IOPs despite multiple interventions[37]. Younger age and higher pre-intervention IOP were

associated with increased failure rates of both ALT and trabeculectomy. Trabeculectomy failure was also associated with diabetes and postoperative complications (particularly elevated IOP and marked inflammation)[38]. In both sequences less baseline visual field defects were a risk factors for sustained decrease of visual field (SDVF). In ATT sequence SDVF is associated with male gender and worse baseline acuity whereas in TAT sequence SDVF is associated with diabetes at baseline. In patients with advanced glaucoma a single confirmatory test performed 6 months after the VF worsening indicates with 72% probability a persistent defect when the worsening is defined by at least 2 units of AGIS score or by at least 2 decibels of MD[39].

TAT vs ATT differences relate manly to Afrocaribbeans.

- Strengths
- Long follow-up
- Large sample
- Standardized protocols
- Eligibility measurements were separated from baseline measurements

- Weaknesses
- The Predictive and Associative analyses were post-hoc
- Only one visual field was used as baseline
- Limited range of IOP during follow up
- Most analyses were post hoc.
- No stratification for stage of disease was attempted in the associative analysis
- Patients with far advanced damage were excluded
- Despite the title "Advanced Glaucoma" early cases of glaucoma were also included
- Some disagreement among the glaucoma specialists in characterizing the degree of disc rim notching due to the lack of a photographic classification of notching

II.3 - CLINICALLY USEFUL POINTS FROM THESE STUDIES

II.3.1 – from CNTGS

1. When IOP was lowered by 30% in NTG the disease subsequently showed a lower incidence of visual field progression.
2. The protective effect of IOP lowering was found only when the effect of cataract was removed.
3. Some of the treated eyes which progressed might have had IOP-independent disease, or the IOP reduction was not enough.
4. The study suggests that IOP plays a role in the progression of some of the NTG patients.

II.3.2 - from EMGT

1. This is the only treatment versus no-treatment study of patients with early to moderate POAG, NTG and pseudoexfoliation and IOP < 30 mmHg. Large positive treatment effects were seen in all groups of patients.
2. A standardized treatment protocol (laser + betaxolol) gave 25% IOP reduction and moderately reduced progression from 62% to 45% (IOP from 20.6 mmHg to 15.5 mmHg). at 6 years follow-up.
3. Some patients do not show any disease progression even after several years without treatment. After a median follow-up of 8 years 24% of untreated and 44% of treated patients had not progressed.
5. Visual fields almost always demonstrated progression before disc photographs.
6. High IOP and pseudoexfoliation syndrome were the most important risk factors for progression; IOP fluctuations were not a risk factor.
9. Results may not be directly applicable to patients with glaucoma with very high IOP and with advanced disease.
10. Treated patients had larger incidence of nuclear cataracts than controls.

II.3.3 - from OHTS

1. Treatment is effective: of the 10% that converted without treatment, half could be prevented by the hypotensive therapy.
2. Monitor both disc and field changes.
3. CCT may affect therefore tonometry machines and need to be taken into account.
4. Thin central cornea is an independent risk factor for conversion
5. Not every patient with OH should be treated. Offer treatment to OH patients at moderate to high risk taking into consideration age, life expectancy and likely treatment benefit. With a low risk profile no treatment is necessary (90% did not convert in 5 years). Waiting for evidence of progression is reasonable as long as careful documentation and follow-up is maintained. With a high risk profile early treatment seems acceptable.

II.3.4 - from EGPS

1. EGPS independently confirmed the OHTS findings for predictors to conversion: older age, higher intraocular pressure, thinner CCT, larger vertical cup-to-disc ratio, and higher pattern standard deviation.
2. Risk profiling in the individual pattern is essential in the management of the ocular hypertensive pattern.

II. 3.5 - from CIGTS

1. The results show that modern medical therapy is able to reduce IOP to a reasonable level.
2. Surgical treatment reduced IOP more than medications (40% vs 31%).
3. Despite these differences in IOP, the visual field progression between the medical treatment versus the surgical treatment group was similar. This result may be explained by the Target IOP approach used in CIGTS with treatment modification over time based on this .
4. The surgical group develop more cataracts (17% versus 6% in the medical treatment group). Medications may also produce cataract (confirming the incidental findings of CNTG).
5. After 4 years there was no difference in visual acuity change between the two groups.
6. The impact of cataract extraction on visual field indexes is mixed - MD improved but the pattern standard deviation worsened.
7. Quality of Vision questionnaires did not show note worthy differences between the medical and surgical group. The medically treated patients reported slightly more ocular symptoms than the patients in the trabeculectomy group.
8. Symptoms of depression and altered mood were related to self-reported visual function as assessed by the VAQ, but not to monocular clinical measures of visual function. Fear of blindness over time is related more to how much an individual is bothered by their inability to perform visual tasks than to their monocular visual acuity or visual field assessments.

II.3.6 - from AGIS

1. IOP reduction reduces VF progression.
2. Different effects on progression at different IOP levels may not appear until 5 years or later.
3. A dose-response relationship between IOP and VF progression is likely.
4. Fluctuation may be an important aspect of the damaging effect of IOP.
5. Cataract formation is a side effect of glaucoma surgery, and it increases substantially with surgical complications.
6. In patients with advanced glaucoma a single confirmatory test performed 6 months after the VF

worsening indicates with 72% probability a persistent defect when the worsening is defined by at least 2 units of AGIS score or by at least 2 decibels of MD.
7. This was a post hoc analysis with residual doubt on results.
8. VF spread very small; statistical significance achieved because of large numbers. A study that randomized for different IOP reductions is needed.
9. Whilst a dose relationship of IOP and VF progression is possible, is only one variable and thus may be difficult to unravel from other confounders.

The overall picture
These trials show that:
1. IOP reduction is of benefit in OHT/POAG of various stages. Unfortunately far advanced cases were not assessed
2. Lower IOP means better protection against visual loss
3. IOP lowering treatment will not inevitably be of benefit to all
4. Greater IOP reduction is not inevitably better for all
5. The vast majority of Ocular Hypertensives did not convert to glaucoma.
6. A 20% IOP reduction in OHT may not be sufficient to prevent conversion to glaucoma.
7 CCT measurements are unavoidable for the correct management of OHT.
8. CCT measurements have limited value for POAG assessment which is based on disk/RNFL and VF.
9. There is a large inter-individual variation in the IOP reduction / progression relationship.
10. Because of large interpretation variability of progression it may be reasonable to leave some (low risk) patients untreated and establish rate of progression first.
11. Large IOP reductions (40-50%) are needed in established glaucoma and even more so in advanced glaucoma if rate of progression threatens Quality of Vision.
12. Patients of the OHTS and CIGTS where on average 10 years younger than those of AGIS and EGMT
13. All forms of treatment may increase the incidence of cataract, especially glaucoma surgery.
14. Side-effects of surgery expressed as Quality of Vision in the long run may not be widely dissimilar to those of medical treatment if cataract extraction is allowed as part of the treatment.
15. Disease progression increases with time.
16. A larger initial IOP lowering effect has a favorable influence on progression in later years.
17. Progression of glaucomatous defects does not necessarily mean a threat to Quality of Vision.
18. The aim of treatment need not to be no progression at all, but a reduction of rate of progression to such a level that Quality of Vision is not endangered during the patients lifetime.
19. It is important to differentiate between risk of progression, which may or may not require treatment vs evidence, that is confirmed worsening of VF/Disc, which may or may not require treatment, depending on the likelihood of a decrease of Quality of Vision/Quality of life.

III - ECONOMIC EVALUATION OF GLAUCOMA CARE

Glaucoma has received very little attention from health economists for the time being[40].
By summer 2008, Pub Med revealed less than 500 hits with keywords glaucoma and cost*, less than 60 hits with glaucoma and resource*, less than 100 hits with glaucoma and cost-effectiveness and less than 20 hits with glaucoma and cost-utility. The number of patients seen with glaucoma related pathologies is predicted to increase significantly over the next few years as a result of an ageing population[41]. The overburden of glaucoma services demands a reappraisal of current management strategies.[42,43]

The goal of glaucoma treatment is to maintain the patient's visual function and related quality of life, at a sustainable cost. The cost of treatment in terms of inconvenience and side effects as well as financial implications for the individual and society requires careful evaluation. Quality of life is closely linked with visual function and overall patients with early to moderate glaucoma damage have good visual function and modest reduction in quality of life.

In addition to the need for critical evaluation of clinical research and application of evidence based medicine in every-day practice, it will be even greater challenge for ophthalmologists to be able to critically evaluate economic articles. In 2007, in a sample of 1000 Finnish physicians 80% did not know the basic concept of health economics (cost-utility) and 70% reported that their education for health economics was insufficient at medical school and during the residency program.[44] Also the peer reviewers as well editors need to learn a 'new' discipline (health economics was born in 1950's). The fact that holds true for all scientific publications is true also with health economic papers, i.e. a published article even in a high impact journal is not a synonym for good quality evidence. This was clearly shown in a recent health economic paper which was published in spite of a major flaw of using visual acuity for utility values in glaucoma patients.[45]

In 2000's it is not enough to read just the abstract of a paper but pay most attention to material and methods before reading the results. To assist critical evaluation and improve the quality and comparability of economic studies, various parties have published Users´ guides for economic analysis for clinical practice[46,47] and compiled methodological guidelines and recommendations for carrying out economic evaluations of pharmaceuticals.[48,49] Source of research funding should be paid special attention in economic papers as well since industry supported reviews of drugs have been reported to show more favourable conclusions than Cochrane reviews.[50]

III.1 - PRINCIPLES OF ECONOMIC EVALUATION

The fundamental problem facing all health care systems is how to make the system more cost-effective. To reach this objective, two approaches are available.[51] The broader one is concerned with chancing the system (e.g. initiate a systematic population screening programme), and the narrower one, making the existing system work better (e.g. improving current care).

The gap between therapeutic possibilities and resources available is broadening all the time. Much more could be done to the patients than we can afford.[52] Therefore, choices have to be made by *prioritising (rationing)* all interventions, including diagnostics tests, treatments, care processes and practices, i.e. we need to apply evidence-based health care.[53]
If resources are used for one purpose, they cannot be simultaneously used for something else, thus creating *opportunity costs* in terms of health benefits foregone elsewhere.[52] As it is especially the cumulative effect of small changes in clinical practices (e.g. adding new diagnostic tests or therapy) that has a massive impact on the healthcare budgets, clinicians need to weigh not only their benefits and risks but should also consider the costs.[46,53] *Nowadays an intervention besides being effective, should also be cost-effective.*

Every professional who makes decisions about individual and groups of patients is a decision-maker in health care. Proper decision making requires high-quality, evidence-based data where we should

consider *1) who gets the services, 2) who pays for them, and 3) who gets paid* for doing what.[54] E.g. fee-for-service has reported to create incentives to over-production of services and rewards unnecessary as well necessary care, the glaucoma medication may be considered "free" since a third party pays for them in many countries etc.[55]

Main concepts
Efficacy is an outcome of intervention in ideal settings (e.g. randomized controlled trial or selected patient material at a specialist centre), while *effectiveness* describes outcome in every-day practice. Although the best evidence of efficacy can be reached by randomized controlled trials, for economic evaluation they are often 'small and tight' due to relatively small sample sizes, tight inclusion and exclusion criteria (i.e. selected patients compared to 'usual' patients), protocol driven costs such as frequent tests and visits, as well as short follow-up considering all costs and outcomes in the course of chronic diseases.[52]

Economic evaluation of health care procedures and technologies is about assessing their efficiency, that is the produced health effects are weighed against the sacrifices or costs required attaining them. Efficiency is thus defined as a relationship between health effects and costs. Economic evaluation deals with establishing the *efficiency of the whole treatment process compared to another treatment process.*[52, 53]

The economic evaluation should be made from the *societal perspective*. This means that when studying the efficiency *all costs*, i.e. the value of *all resources* required by the process *are taken into account* regardless of who incurs them and pays for them. The principle in economic evaluation is to report the resources used separately from their unit costs. This helps to interpret the results of a study from one setting to another, as unit prices are known to vary by location and by country. Charges should be separated from costs since they may bear little resemblance to economic costs. [56] The charges may also change with time, e.g. the average charge per ALT in 2000 was 40 % of the highest average charge per procedure in 1989 although he the technology and techniques were unchanged during the decline of reimbursement for procedure.[57]

Cost-effectiveness analysis
When health effects are measured by simple indicators in 'natural' or physical units (such as lives saved, life-years or seeing-years gained, years of blindness avoided, painless/healthy days gained), or numerous disease-specific clinical measures (for example changes in visual acuity, intraocular pressure or visual field indices) and they are related to costs, we are speaking of cost-effectiveness analysis. *The cost-effectiveness can only be shown in relation to a defined alternative. A treatment is never cost-effective in itself.*[40] The efficiency criterion is the additional cost per additional unit of effectiveness *(incremental cost-effectiveness ratio)*.

The problem with this method often is that the indicators describe health effects inadequately and narrowly. Difficulties arise, if for example the main therapeutic effect of the alternatives to be compared is different (e.g. one may have an effect mainly on length of life, another on its quality) or if the side effects of the alternatives are different in amount or severity. Then the comparability across alternatives is difficult, even impossible.

Cost-utility analysis
Cost-utility analysis is presently regarded as *the best method of economic evaluation* in health care. It is a special form of cost-effectiveness analysis in which health effects are measured in terms of change *both in length and quality of life*. These changes are aggregated into a single index number by weighting length of life with people's 'exchange rate' between quality and length of life. This 'exchange rate' is elicited from population, or patients with valuation studies. This allows measuring effectiveness in terms of a change in *Quality-Adjusted Life Years (QALYs)*. QALYs are composed in the same principle as the total points in ski jumping points from the length of the jump (length of life) and points from its style (quality of life).[52] The total points (QALYs) can be increased by improving style (quality of life) and/or lengthening the jump (life). The changes in QALYs are related to changes in costs; the efficiency criterion of cost-utility analysis is thus an incremental cost-utility ratio (or as a matter of fact the ratio between change in costs and change in QALYs).

To be able to compare the efficiency of different interventions in terms of cost-utility for the same disease (or even different interventions for different diseases) against each other, it requires the measurement of changes in quality of life with *a generic (non-disease-specific) instrument*, e.g. the EQ-5D (formerly the EuroQoL), the SF6, Canadian Health Utilities Index (HUI), and 15D.[58-60] This means that one uses the same instrument for measuring quality of life regardless of what disease has brought about the changes in quality of life. In addition, the instrument must produce a single index number for quality of life that reflects a plausible exchange rate between quality and length of life on a 0-1 scale.[52]

Cost minimisation analysis

If treatments lead to the same clinical outcomes, cost minimisation analysis can be used. In this approach one is looking for the treatment alternative that produces *identical clinical outcomes at the least cost*. Unfortunately, the cases are relatively rare where clinical outcomes across alternatives are virtually the same.

Cost-benefit analysis

If health effects are measured and valued in monetary terms and they are weighed against costs, we are dealing with cost-benefit analysis. The advantage of this form of analysis is that *both the costs and benefits are measured in the same units.* It is then possible to examine the efficiency of even a single pharmaceutical, that is, whether its monetary benefits are greater than the monetary costs. The biggest problem of this type of analysis is the valuation of health effects in monetary terms: all valuation methods are more or less disputable. The efficiency criterion is cost-benefit ratio or net benefit.

Decision analytical modelling

The use of decision-analytical modelling to estimate the cost effectiveness of healthcare interventions is becoming widespread.[61,62] Ideal study design also for economic evaluation consists of a randomized design with measures of outcome, quality of life and costs, "usual" patients, "usual" treatment protocol, non-expert (in addition to expert) clinical experience, long follow-up, follow-up of drop-outs and large sample size. Sometimes the length of follow-up in the clinical trial may be too short for the purposes of economic evaluation. Modelling studies have been undertaken making projections of long-term outcomes from short-term trial data. Modelling can be used to extrapolate cost and effectiveness estimates over a longer time horizon using available epidemiological and natural history data.

Economic modelling is a relatively cheap and effective way of synthesizing existing data and evidence available on the costs and outcomes of alternative interventions. For example, *Markov models* have a long history of use in healthcare service decision-making and are particularly *suited to the modelling of progression of chronic disease over time*.[61,62] In Markov modelling disease in question is divided into distinct states and transition probabilities are assigned for movements between these states over a discrete time period (cycle). By attaching estimates of resource use and health outcome consequence to the states and transitions in the model, and then running the model over a large number of cycles, it is possible to estimate the long-term costs and outcomes associated with a disease. Markov models are particularly suited for the calculation of QALYs. Cost-utility analysis based on Markov models may be sensitive to parametric uncertainty. Probabilistic sensitivity analysis is recommended especially in cases where model parameters are based on limited number of observations.

Modelling studies are often criticized because of *assumptions often have to be used due to inadequate evidence*.[40] Clinical and epidemiologic studies never give all relevant information but that is no reason for not investigating what such studies can offer to assist decision making process. It appears more useful for decision makers to have some information on potential cost-effectiveness than to have no information at all. A decision is necessary regardless of whether the economic evaluation is performed. A model, even if partly based on assumptions, can provide important information on potential scenarios. It has also been stated that all models are wrong - including our current mental models - since they always remain imperfect and incomplete in their attempt to represent and analyze the real world.[63] We should, thus, not worry about whether or not to use a model, but rather which model to use.

III.2 - COST-EFFECTIVENESS OF SCREENING

The problems of current evidence in relation to economic modelling are highlighted in the two recent Finnish and Scottish cost-effective studies.[64,65] The results of the two studies fully agreed in the major aspect: at this stage we do not have enough proper evidence to decide whether population screening could be cost-effective or not. Both studies, however, encourage further research to study whether – although untargeted population screening may currently not be cost-effective - screening of some subgroups could be. Their results seemingly disagreed whether screening could be cost-effective for 40 year olds compared with 60-75 year olds. The most probable reason for disagreeing result regarding the age was the fact that in the Finnish model also patients with diagnosis of glaucoma were screened in order to better target the treatment to the "right" subjects (=manifest glaucoma). The meaning of this finding emphasizes the great economical burden of false positives and over treatment in our health care systems.[66]

Current evidence of the cost-effectiveness of screening for glaucoma[66]

A. There are major shortcomings of the health care systems.
1. Unequal access to care (both between and within countries).[64]
2. Large variations in the distribution of health care services (both between and within countries).[67]

B. The performance of current glaucoma every-day practice is not optimal.
1. Several epidemiologic studies have shown that at least half of glaucoma patients are undiagnosed.[65]
2. Simultaneously, more than half of the patients currently treated for glaucoma do not have the disease.[64]
3. Considerable proportion of glaucoma patients do not use their drops (range from 5 to 80 %).[68]
4. More than half of patients with newly diagnosed glaucoma at screening have seen an ophthalmologist (or optometrist), but their disease was not diagnosed.[69,70]

C. There is a lack of adequate evidence on the values of most of the important parameters needed for the evaluation of cost-effectiveness of screening.
1. The utility data in glaucoma is so far extremely limited and based on cross-sectional pilot studies.[71,72]
2. There is no agreement how cost data should be collected and reported in glaucoma care.[67]
3. In general, the data from randomized controlled trials are too 'small and tight' due to small sample sizes for economic evaluation, tight inclusion and exclusion criteria (selected patients), protocol driven costs (frequent tests and visits), short follow-up considering all costs and outcomes and losses of follow-up. The ideal study design for economic evaluation would require randomized design (e.g. screening vs. opportunistic case finding), large sample sizes on both arms (with "usual" patients and "usual" care protocol in the opportunistic arm), long follow-up, follow-up of drop-outs and measures of outcome, QoL and costs.

C.1. High quality (= randomized) diagnostic studies are missing[73,74]
1. No single (screening) test is sufficient to discriminate persons with and without glaucoma.[65]
2. Diagnostic studies of glaucoma lack a generally approved definition of the disease.
3. The majority of diagnostic studies have so far been performed on pre-selected patient populations which may lead to over-optimistic results.[74]
4. The estimates of the sensitivity and specificity of diagnostic tests show large variability[65] and are far lower than the thresholds required for screening dominance (= screening being less costly and more effective), i.e. specificity of 98-99% in the age group < 70 years and 94-96% in the age group > 70 years.[64]

C.2. Prevalence of glaucoma, suspected glaucoma and visual disability are variable
1. Due to different definitions of the disease, studies show different estimates for prevalences and incidences of glaucoma in different age groups and races.[64,65]
2. High quality studies using severe visual impairment as an endpoint are lacking.[75]

C.3. Data of staging and progression of glaucoma from one stage to another is minimal.
1. The evidence of early, moderate and advanced stages of glaucoma in the population-based studies is extremely limited and variable regarding how these stages are defined, how long glaucoma patients stay in each state, and what is the proportion of patients in each state.
2. In randomised controlled trials (that is, in ideal settings) the progression rates have been reported for one eye only, that is, not per patients' two eyes, which determines both the HRQoL and visual disability compared to costs which are driven by the worst eye.

D. Need for future research
1. A randomised screening trial run in several countries would give the most reliable evidence of the cost-effectiveness of screening in preventing glaucoma-induced visual disability.[64,65]
2. Simultaneously, the sensitivity and specificity of diagnostic tests and their combinations could be evaluated in large non-selected populations.[64,65]
3. Establishing a gold standard definition of glaucoma would be essential.[64]
4. The HRQoL scores associated with different glaucoma stages should be measured in a longitudinal study with a generic instrument applicable to cost-utility analysis among an adequate number of individuals.[64,65]

III.3 - COST-EFFECTIVENESS OF DIAGNOSTIC AND THERAPEUTIC INTERVENTIONS AND CARE PROTOCOLS

Diagnostic tests
The evidence about the efficiency of diagnostic tests in glaucoma is practically missing. One study analyzed three case-finding strategies (all patients undergo ophthalmoscopy, but tonometry is routinely performed to all initial patients, high-risk patients only, or no one), concluded that routine in all initial ophthalmic patients tonometry is cost-effective.[76] To study effectiveness and cost-effectiveness of glaucoma diagnostics, we would gain best evidence from a randomized trial in which one arm receives the standard test (e.g. white-on-white perimetry) and the other arms additional tests (e.g. imaging of the fundus) and then evaluate whether the additional tests improve patient outcome and quality of life with affordable costs.
In glaucoma care, we do not know what the impact of high resource utilization (e.g. early diagnosis and treatment, frequent visits and testing, several examination methods) have on important outcome, i.e. prevention of glaucoma induced visual disability. As the current legal and cultural environments exert tremendous pressure to do more, it is important to remember that greater expenditure as such does not guarantee better outcomes but might sometimes even be worse.[77-79] Missing a rare – or in case of glaucoma, very early diagnosis - may currently be regarded worse than over-testing. With the shift of spectrum of detected disease, as newly detected cases will in general be milder cases (or in case of glaucoma, have no manifest disease at all), outcomes seem to improve. This in turn creates stimulus to do even more. With more to do, there is also more worry, more unnecessary treatment, more mistakes – and more costs.[77]

In diagnostics and follow-up, it is currently not known the 'optimum' number of diagnostic tests, i.e. how many tests are enough and what number represents over-testing with no additional gain incurring unnecessary expenditure. In addition, we do not know how often we should take the tests during the follow-up. With different examination methods we do not know what should be the 'correct' and most cost-effective threshold for initiating and intensifying treatment in order to prevent glaucoma induced visual disability.[52]

Several papers have shown that increased costs are associated with increased disease severity.[80] From a priority setting perspective the most important question is whether the lower threshold for treatment – in spite of increase in costs - would be cost-effective in the long run in preventing visual disability. Such studies are not available at present.[67]

Medical, laser and surgical therapy
There are no studies on cost-effectiveness or cost-utility comparing surgical, laser and medication therapies with each other. Further research is needed to establish the efficiency of the alternative treatment modes for glaucoma.

Based on very limited data comparing different treatment modes, it is possible that (initial) laser therapy is less expensive than (initial) medication therapy and that from strictly economic point of view, surgery may not be cost-effective within a 3-4 year perspective. However, with increasing follow-up (up to 8 years) the difference in costs between surgery and medication may even out.[67]

The current economic literature regarding glaucoma treatment is predominantly focused on identifying the short-term direct, particularly the precise quantification of glaucoma drug costs and provide only one component of real-world costs for glaucoma.[81,80] Using the European and US treatment guidelines as a benchmark, it is evident that the current body of literature does not satisfy the needs of decision-makers, although certain studies provide some valuable information, which is a step towards reaching this goal. 80The main methodological issue in the economic models is an absence of a clinically relevant long-term effectiveness measure, or where this measure is produced, there is a lack of transparency and validation of the methods used. Future evaluations of the burden of glaucoma need to consider the issues of comparability between, and generalisability of, study results.[80]

Using cost-utility analysis (Markov modelling), Kymes et al (2006)[82] modeled a hypothetic cohort of people with ocular hypertension and different treatment thresholds from 'treat no one' to 'treat everyone'. 'Treat everyone' cost more and was less effective than other options. The treatment of patients with >2% annual risk of the development of glaucoma was likely to be cost-effective. Another study using OHTS data for economic modelling suffers from major methodologic flaw when using visual acuity for utility values.[45]

Care protocols

In spite of large variations in care protocols, studies from different countries show similar overall trends: 1) an increase in the number of prescriptions and costs of glaucoma medications (e.g. in Scotland and Ireland the costs of medical therapy increased 10-16 % per year in 1994-2003), 2) a decrease in the rate of laser trabeculoplasty, except for Canada where the number of selective laser procedures started to increase in the 2000's, 3) a decrease in the rates of glaucoma surgery, and 4) Increase in the rate of the cataract surgery (despite a decline in trabeculectomy surgery).[67]

Despite the fact that there is now good evidence that many interventions are both clinically effective and cost effective, ignorance about how to translate evidence into practice is considerable.[83] Even if data are available about the costs and benefits on interventions, practitioners and regulators often adopt interventions, which are demonstrably not cost-effective - and while doing this - enhance the perception of under-funding.[83] Typically, physicians practice in the fragmented, isolated tradition and do not have good enough administrative information available by which they could monitor 1) what they produce in terms of activity, case mix and outcome, 2) how they produce, i.e. what criteria they use to abandon and adopt new treatments and technologies, 3) how much they produce relative to their peers, and 4) to whom they deliver care.

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GLOSSARY

AION	=	Acute Ischemic Optic Neuropathy
ALT	=	Argon Laser Trabeculoplasty
BCVA	=	Best Corrected Visual Acuity
BID	=	Twice daily
CAI	=	Carbonic Anhydrase Inhibitors
CCT	=	Central Corneal Thickness
CME	=	Cystoid Macular Edema
C/D o CDR	=	Cup-Disc ratio
Ch	=	Chapter
CPMP	=	Committee for Proprietary Medicinal Products (EMEA)
Dx	=	Diagnosis
EMEA	=	the European Agency for the Evaluation of Medicinal Products
FC	=	Flow Chart
FDA	=	Food and Drug Administration (USA)
FDT/FDP	=	Frequency Doubling Technology / Perimetry
5FU	=	5 Fluoracil
IOP	=	Intra Ocular Pressure
ITC	=	Irido Trabecular Contact
LTP	=	Laser Trabeculoplasty
MD	=	Mean Defect or Mean Deviation in visual field testing
MMC	=	mitomycin-C
MS	=	Mean Sensitivity in visual field testing
NLP	=	No light perception
NPFS	=	Non Perforating Filtration Surgery
OD	=	Right Eye
OH	=	Ocular hypertension
ONH	=	Optic Nerve Head
OS	=	Left Eye
OU	=	Both Eyes
PAS	=	Peripheral Anterior Synechia
PSD	=	Pattern Standard Deviation in visual field testing
QD	=	Once daily
QHS	=	Daily, at bedtime
QID	=	Four times a day
QoL	=	Quality of Life
RCT	=	Randomized Controlled Trial
R/D o RDR	=	Rim-Disc ratio
RNFL	=	Retinal Nerve Fiber Layer
RoP	=	Rate of Progression
Rx	=	Treatment
SAP	=	Standardized Automated Perimetry
SWAP	=	Short Wavelength Automated Perimetry
TID	=	Three times a day
TM	=	Trabecular Meshwork
VA	=	Visual Acuity
VF	=	Visual Field
XFG	=	Exfoliative Glaucoma
XFS	=	Exfoliation Syndrome

FLOWCHARTS

I. SUGGESTED QUESTIONS FOR YOUR GLAUCOMA PATIENT

AT BASELINE

HISTORY/RISK FACTORS

SPECIFICALLY ENQUIRE ABOUT

- OTHER MEDICATIONS
- FAMILY HISTORY (GENERAL/OPHTHALMOLOGICAL)
- CORTICOSTEROID THERAPY (TOPICAL/SYSTEMIC)
- OCULAR TRAUMA (CONTUSION)
- REFRACTIVE SURGERY
- CARDIOVASCULAR OR RESPIRATORY DISEASES/OTHER CHRONIC OR SEVERE DISEASES
- VASCULAR DISORDERS
- DRUGS ALLERGY

DIRECT QUESTIONS AT FOLLOW-UP

- HOW ARE YOU?
- HOW DO YOU THINK YOUR EYES ARE DOING?
- DO YOU THINK YOUR CONDITION IS BETTER, STABLE OR WORSE?
- DO YOU HAVE DIFFICULTY WITH YOUR DAILY TASKS?
- DO YOU UNDERSTAND YOUR DIAGNOSIS?
- ARE THE GLAUCOMA MEDICATIONS INTERFERING WITH YOUR DAILY ACTIVITIES?
- ARE YOU WORRIED ABOUT YOUR EYES?
- HAVE YOU BEEN USING YOUR EYE DROPS AS PRESCRIBED?
- DO YOU ADMINISTER THE DROPS BY YOURSELF OR BY A RELATIVE?
- IF BY YOURSELF, PLEASE SHOW ME HOW YOU DO IT

PLEASE SHAKE HANDS WITH PATIENTS. BESIDES BEING KIND AND ENCOURAGING, YOU WILL FEEL THE TEMPERATURE OF THEIR PERIPHERAL SKIN.

II. DIAGNOSTIC COMPONENTS

PRIMARY OPEN-ANGLE GLAUCOMA AND RELATED CONDITIONS

ON VF IOP — N N >21 → OHT

ON VF — N S / N N → POAG SUSPECT / ARTEFACT

ON VF — N A → OTHER CAUSES / CONSIDER EARLY POAG WITH SMALL DISC

ON VF — S N → POAG-SUSPECT / LARGE DISCS / CONGENITAL ONH ABNORMALITY / PRE-PERIMETRIC GLAUCOMA

ON VF — S S → CONGENITAL DISC ABNORMALITY / EARLY POAG / POAG-SUSPECT / CONSIDER ARTEFACT

ON VF — S A → CONSIDER ARTEFACT / POAG / POAG-SUSPECT

ON VF — A N → EARLY POAG

ON VF — A S → POAG

ON VF — A A → POAG

Legend

IOP = INTRAOCULAR PRESSURE
ON = OPTIC NERVE
VF = VISUAL FIELD
N = NORMAL
S = SUSPICIOUS
A = ABNORMAL

ABNORMAL FINDINGS SHOULD BE CONFIRMED BY REPEATED EXAMS

III. ABNORMAL THRESHOLD VISUAL FIELD

THE 1ST EXAM IS NOT NORMAL → **REPEAT** AS SOON AS POSSIBLE TO ESTABLISH BASELINE

REPEAT → NORMAL / ABNORMAL

NORMAL → LEARNING EFFECT

ABNORMAL → BETTER / SAME OR WORSE

BETTER → LEARNING EFFECT

BETTER → CHECK RELIABILITY INDICES

SAME OR WORSE → CHECK RELIABILITY INDICES

CHECK RELIABILITY INDICES → LOW RELIABILITY

CHECK RELIABILITY INDICES → NORMAL RELIABILITY

LOW RELIABILITY → CAREFUL REINSTRUCTION RUN A DEMO CONSTANT SUPERVISION
―――――――
CONSIDER GOLDMANN KINETIC PERIMETRY

NORMAL RELIABILITY → STAGING

STAGING → EARLY → F/U 12 MONTHS OR EARLIER

STAGING → MODERATE → F/U 6 MONTHS OR EARLIER

STAGING → ADVANCED → F/U 6 MONTHS OR EARLIER

DURING FOLLOW-UP → IDEALLY, OBTAIN 6 VFS IN 2 YEARS TO IDENTIFY THE RATE OF PROGRESSION

IDEALLY, OBTAIN 6 VFS IN 2 YEARS → BETTER / STABLE / WORSE

BETTER → FLUCTUATION OF DAMAGE

STABLE → FLUCTUATION OF DAMAGE

FLUCTUATION OF DAMAGE → 3 TO 12 MONTHS

WORSE → PROGRESSION OF CATARACT

WORSE → RELIABILITY

PROGRESSION OF CATARACT → VERIFY AND CONSIDER QoL

RELIABILITY → LOW / NORMAL

LOW → REPEAT VF

NORMAL → PROGRESSION OF DAMAGE - ASSESS RATE OF PROGRESSION

REPEAT VF → PUPIL SIZE

PUPIL SIZE → SMALLER / NO CHANGE

SMALLER → REPEAT VF

NO CHANGE → PROGRESSION OF DAMAGE - ASSESS RATE OF PROGRESSION

PROGRESSION OF DAMAGE - ASSESS RATE OF PROGRESSION → CHANGE TREATMENT → F/U AS NEEDED
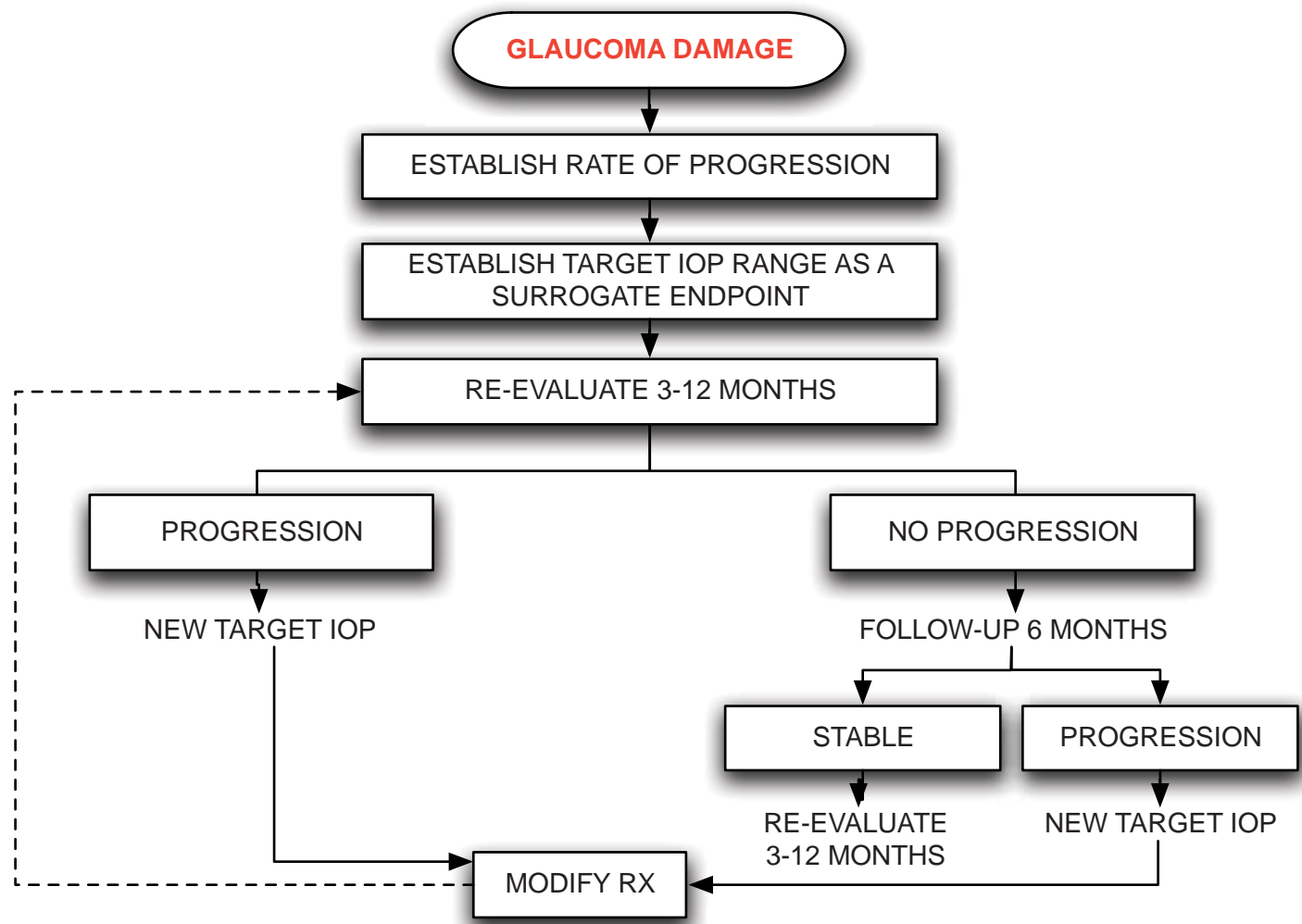
BEFORE ACCEPTING VF DEFECTS AS REAL, THEY MUST BE CONFIRMED AT LEAST ON TWO CONSECUTIVE EXAMS (EXCLUDING THE INITIAL ONE). FOLLOW-UP INTERVALS ARE JUST SUGGESTIONS. THE FREQUENCY OF TESTING IS TO BE ADAPTED TO THE SEVERITY OF DAMAGE AND ROP.

IV. ASSESSMENT AND FOLLOW-UP

OPTIC NERVE HEAD	IF ELEVATED IOP CONSIDER CCT	VISUAL FIELD

IF CONFIRMED IOP IN THE HIGH TWENTIES
OR
IF IOP VERY HIGH REPEAT ACCORDING TO IOP LEVEL
AFTER 1-12 MONTHS

OPTIC NERVE HEAD		VISUAL FIELD
NORMAL		NORMAL
NORMAL	ARTEFACT OR OTHER CAUSES	ABNORMAL
NORMAL	REPEAT TEST — COUNSEL	SUSPICIOUS
ABNORMAL	REPEAT TEST — COUNSEL	NORMAL
SUSPICIOUS	REPEAT TEST — COUNSEL	NORMAL
SUSPICIOUS	REPEAT TEST — COUNSEL	SUSPICIOUS
SUSPICIOUS	EARLY GLAUCOMA/GLAUCOMA SUSPECT REPEAT TEST 3-12 MONTHS	ABNORMAL
ABNORMAL	EARLY GLAUCOMA/GLAUCOMA SUSPECT REPEAT TEST 3-12 MONTHS	SUSPICIOUS
ABNORMAL	GLAUCOMA DAMAGE	ABNORMAL

GLAUCOMA DAMAGE

↓

ESTABLISH RATE OF PROGRESSION

↓

ESTABLISH TARGET IOP RANGE AS A
SURROGATE ENDPOINT

↓

RE-EVALUATE 3-12 MONTHS

- PROGRESSION → NEW TARGET IOP → MODIFY RX
- NO PROGRESSION → FOLLOW-UP 6 MONTHS
  - STABLE → RE-EVALUATE 3-12 MONTHS
  - PROGRESSION → NEW TARGET IOP → MODIFY RX

FOLLOW-UP INTERVALS ARE JUST RECOMMENDATIONS

V. GONIOSCOPICALLY OPEN ANGLE

SOME DIAGNOSTIC CLUES

Condition	Diagnostic clue
POAG	NORMAL ANGLE
CONGENITAL GLAUCOMA CHILDHOOD GLAUCOMA	ANGLE POORLY DIFFERENTIATED TRABECULODYSGENESIS BARKAN'S "MEMBRANE" ANTERIOR INSERTION OF THE IRIS
EXFOLIATIVE GLAUCOMA	BLACK PIGMENTED UNDULATING LINE ON ANTERIOR TO SCHWALBE'S LINE (SAMPAOLESI'S LINE) HEAVILY PIGMENTED TRABECULUM
PIGMENTARY GLAUCOMA	MID TRABECULAR BAND OF BROWN PIGMENT PIGMENT ON SCWALBE'S LINE
OPEN ANGLE GLAUCOMA SECONDARY TO UVEITIS	SCATTERED PIGMENT, NEW VESSELS, PERIPHERAL ANTERIOR SYNECHIA
POST-TRAUMATIC GLAUCOMA	ANGLE RECESSION, IRREGULAR IRIS INSERTION POSSIBLE INCREASE OF PIGMENT
OPEN ANGLE GLAUCOMA SECONDARY TO NEOVASCULARIZATION	NEOVASCULAR MEMBRANE

VI. TARGET IOP

SLOW	HIGH	SHORT	EARLY
RATE OF PROGRESSION	**UNTREATED IOP**	**LIFE EXPECTANCY**	**GLAUCOMA DAMAGE**
FAST	LOW	LONG	ADVANCED

HIGHER TARGET IOP

LOWER TARGET IOP

THE ABOVE FACTORS NEED TO BE CONSIDERED AS A WHOLE IN DECIDING THE INDIVIDUAL TARGET PRESSURE REQUIRED

VII. TREATMENT STEPLADDER FOR OAG and OH

JUVENILE

MEDICAL RX [2]

↓

FILTRATION SURGERY [3]
TRABECULOTOMY

POAG/EXFOL/PIGM

SEE CHAPTERS INTRO, 2 AND 3

MEDICAL RX [2]

→

LASER TRABECULOPLASTY [1]

→

FILTRATION SURGERY [3]

OCULAR HYPERTENSION

SEE CHAPTERS INTRO, 2 AND 3

CONSIDER TREATMENT
IN PATIENT WITH REPEATED IOPs
IN THE HIGH 20s EVEN WITHOUT
ADDITIONAL RISK FACTORS.
ALWAYS CONSIDER CORNEAL
THICKNESS MEASUREMENT

→

MEDICAL RX [2]

IF THE ABOVE NOT SUCCESSFUL, CONSIDER REPEAT FILTRATION SURGERY+ANTIMETABOLITES OR
LONG-TUBE DRAINAGE IMPLANT/CYCLO DESTRUCTIVE PROCEDURE

[1] LASER TRABECULOPLASTY CAN ALSO BE CONSIDERED AS PRIMARY TREATMENT

[2] UP TO 2-3 DIFFERENT DRUGS. DO NOT ADD A DRUG TO A NON-EFFECTIVE ONE; CONSIDER SWITCHING

[3] IN CERTAINS CASES, IT MAY BE NECESSARY TO CONSIDER FILTRATION SURGERY WITHOUT RESORTING TO MEDICAL TREATMENT OR LASER TRABECULOPLASTY

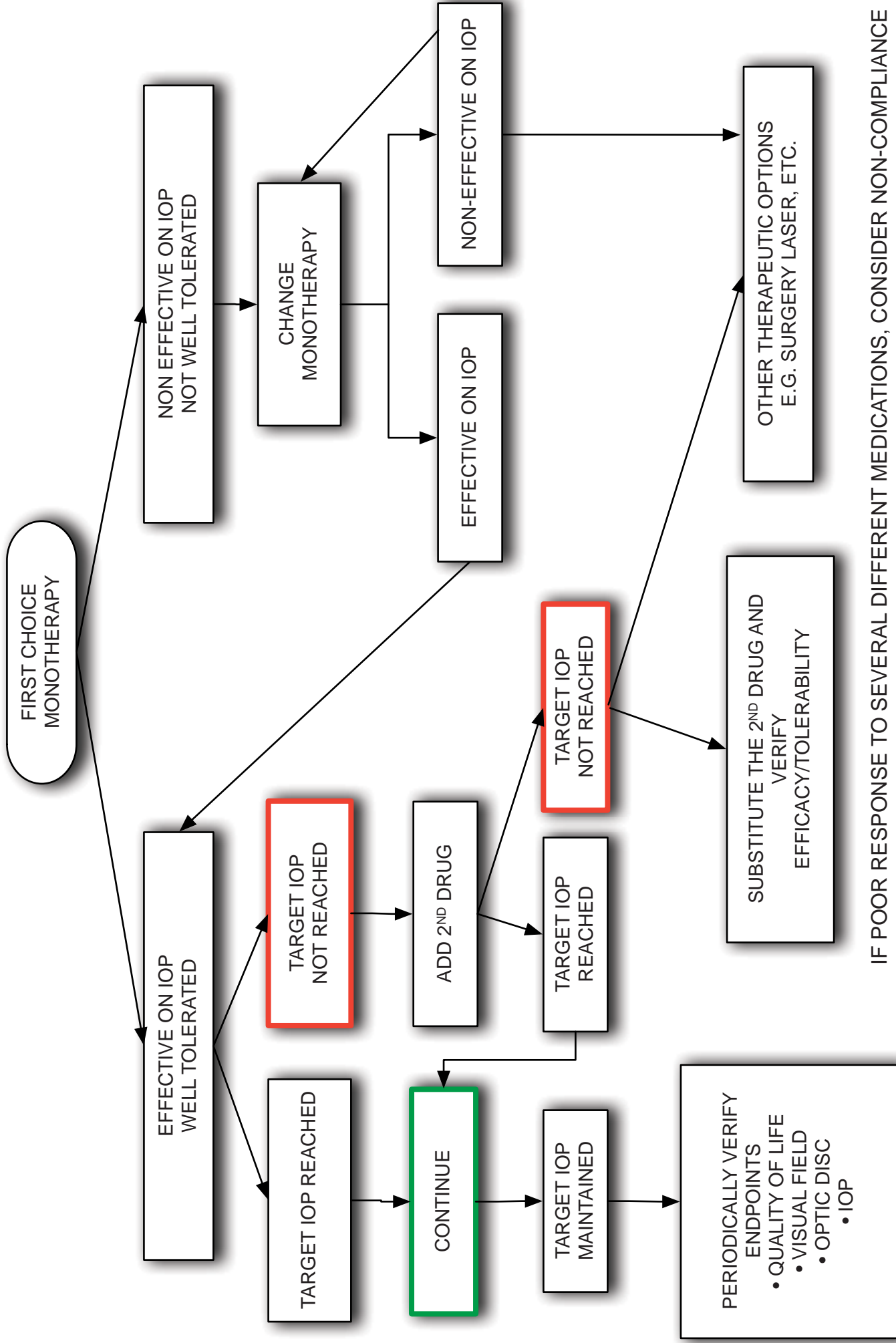**OAG** = Open Angle Glaucoma, **OH** = Ocular Hypertension
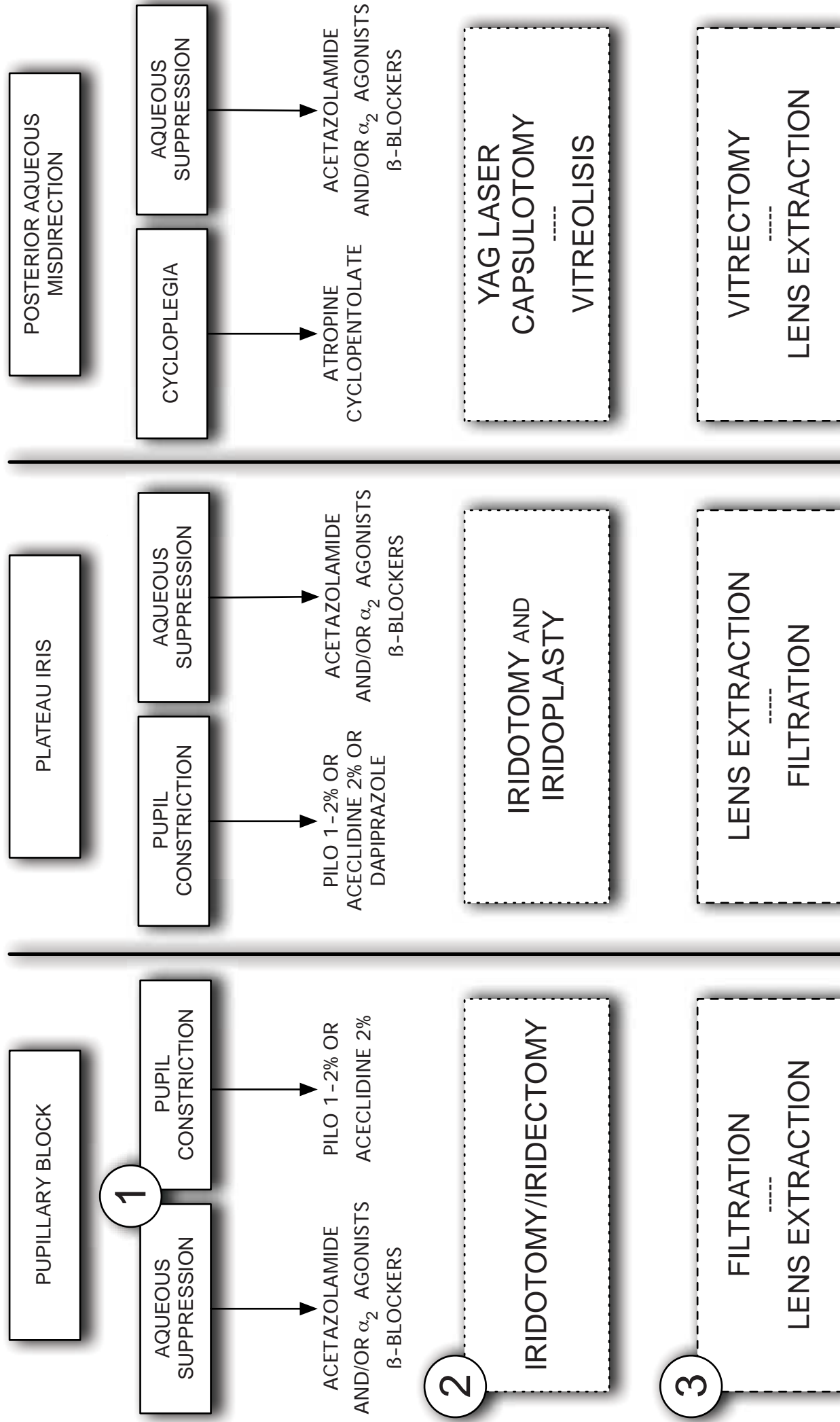
FLOWCHARTS

VIII. MONOTHERAPY
(IN ALPHABETICAL ORDER)

1ST CHOICE

α_2 AGONIST
ß-BLOCKERS
CAIs
PROSTAGLANDINS
PROSTAMIDES

EFFECTIVE AND
NOT CONTRAINDICATED
AND NO SIDE EFFECTS

CONTINUE

NON-EFFECTIVE OR
CONTRAINDICATED
OR SIDE EFFECTS

SWITCH AMONG 1ST CHOICE
ALTERNATIVES

2ND CHOICE

ADRENERGIC
CHOLINERGIC
GUANETHIDINE
OTHERS
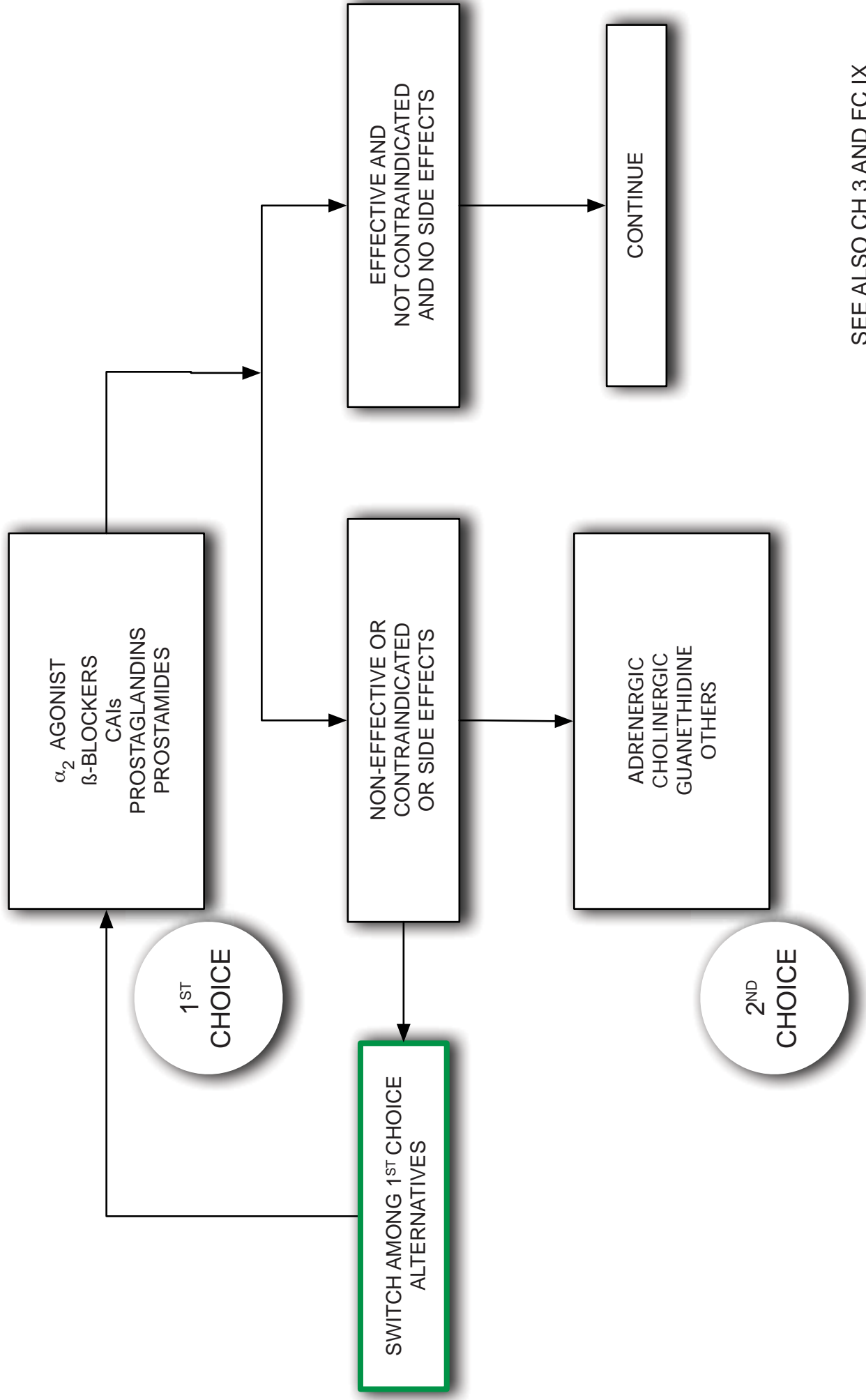
IX. THERAPEUTIC TRIAL OF GLAUCOMA MEDICATIONS

FIRST CHOICE MONOTHERAPY

NON EFFECTIVE ON IOP NOT WELL TOLERATED

CHANGE MONOTHERAPY

NON-EFFECTIVE ON IOP

EFFECTIVE ON IOP

OTHER THERAPEUTIC OPTIONS E.G. SURGERY LASER, ETC.

EFFECTIVE ON IOP WELL TOLERATED

TARGET IOP NOT REACHED

ADD 2ND DRUG

TARGET IOP REACHED

TARGET IOP NOT REACHED

SUBSTITUTE THE 2ND DRUG AND VERIFY EFFICACY/TOLERABILITY

TARGET IOP REACHED

CONTINUE

TARGET IOP MAINTAINED

PERIODICALLY VERIFY ENDPOINTS
• QUALITY OF LIFE
• VISUAL FIELD
• OPTIC DISC
• IOP

IF POOR RESPONSE TO SEVERAL DIFFERENT MEDICATIONS, CONSIDER NON-COMPLIANCE

X. PATHOGENETIC APPROACH TO ANGLE CLOSURE

PUPILLARY BLOCK

(1)

PUPIL CONSTRICTION
→ PILO 1 - 2% OR ACECLIDINE 2%

AQUEOUS SUPPRESSION
→ ACETAZOLAMIDE AND/OR α_2 AGONISTS ß-BLOCKERS

(2) IRIDOTOMY/IRIDECTOMY

(3) FILTRATION

LENS EXTRACTION

PLATEAU IRIS

PUPIL CONSTRICTION
→ PILO 1 - 2% OR ACECLIDINE 2% OR DAPIPRAZOLE

AQUEOUS SUPPRESSION
→ ACETAZOLAMIDE AND/OR α_2 AGONISTS ß-BLOCKERS

IRIDOTOMY AND IRIDOPLASTY

LENS EXTRACTION

FILTRATION

POSTERIOR AQUEOUS MISDIRECTION

CYCLOPLEGIA
→ ATROPINE CYCLOPENTOLATE

AQUEOUS SUPPRESSION
→ ACETAZOLAMIDE AND/OR α_2 AGONISTS ß-BLOCKERS

YAG LASER CAPSULOTOMY

VITREOLISIS

VITRECTOMY

LENS EXTRACTION

IN ACUTE ELEVATION OF IOP: EXTRAVASCULAR FLUID REDUCTION WITH MANNITOL/GLYCEROL

FLOWCHARTS

XI. ACUTE ANGLE CLOSURE WITH PUPILLARY BLOCK – MANAGEMENT

IMMEDIATE

i.v./oral ACETAZOLAMIDE OR i.v./oral OSMOTIC

TOPICAL: PILOCARPINE 2%

ß-BLOCKERS

α_2 AGONIST (APRACLONIDINE/BRIMONIDINE)

STEROIDS

CORNEAL INDENTATION USING 4 MIRROR LENS

OPTIONAL

KEEP PATIENT SUPINE
ANALGESIA
ANTI-EMETICS

1-2 HOURS

→ ATTACK BROKEN → IRIDOTOMY (OR IRIDECTOMY) → REMEMBER: IRIDOTOMY FOR FELLOW EYE

→ ATTACK NOT BROKEN → REPEAT i.v. CAI OR OSMOTICS

REPEAT i.v. CAI OR OSMOTICS → CLEAR CORNEA → IRIDOTOMY (OR IRIDECTOMY) → REMEMBER: IRIDOTOMY FOR FELLOW EYE

REPEAT i.v. CAI OR OSMOTICS → CLOUDY CORNEA → TRY TOPICAL 10% GLICERINE → IRIDOTOMY OR IRIDOPLASTY OR IRIDECTOMY → REMEMBER: IRIDOTOMY FOR FELLOW EYE

PATIENT EXAMINATION

1.1 - INTRAOCULAR PRESSURE (IOP)

Normal value of intraocular pressure
The 'normal' IOP is a statistical description of the range of IOP in the population, and is not applicable to the individual subject. There is some evidence that IOP increases by about 1 mm Hg with each decade after 40 years of age in most Western populations, although this does not appear to occur in all populations. The IOP follows a circadian cycle often with a maximum between 8 a.m. and 11 a.m. and a minimum between midnight and 2 a.m. This cycle is more dependent on the sleep cycle than the daylight cycle. The diurnal variation can be between 3 and 5 mm Hg and is wider in untreated glaucoma[1-3].

Anesthetic effects on the IOP measurement.
The IOP measurement by applanation necessitates topical anaesthesia of the cornea, which does not affect the pressure. However, in young children, topical anaesthesia is not sufficient and a general anaesthetic has to be given. The most used substances are halothane (inhaled), ketamine (intra-muscular) and chloral hydrate (oral). In general, halothane lowers the IOP, whereas ketamine can cause a transient rise in IOP. Under ketamine the IOP is usually about 4 mm Hg higher than under halothane. Oxygen given during the anaesthesia has a hypotensive effect and carbon-dioxide a hypertensive effect. Succinylcholine can produce a transitory IOP increase of about 15 mm Hg. Nitrous oxide causes a slight increase in IOP [4-7].

Normal IOP in children.
The IOP increases by about 1 mm Hg per 2 years between birth and the age of 12 years, rising from 6 to 8 mm Hg at birth to 12 ± 3 mm Hg at age 12. In healthy adults IOP ranges from about 10 to 21 mmHg (16 mmHg ± 2.5) and tends to increase with age[8-9].

Cornea
Corneal characteristics that can affect the IOP measurements are corneal thickness, curvature and hydration[2,10-15]. Other biomechanical properties of the cornea (e.g. those quantified by hysteresis) may also influence IOP measurements[16]. The condition of the cornea should be considered both cross sectionally when comparing individuals or groups, and longitudinally when evaluating any patient. [II,D] See next page.

Other artefacts
A tight collar or tie, Valsalva's manoeuvre, holding breath, a lid speculum or squeezing the lids can all falsely increase the IOP reading[17,18].

Tonometry
The principle of the method of tonometry is based on the relationship between the intraocular pressure and the force necessary to deform the natural shape of the cornea by a given amount (except Dynamic Contour Tonometry). The deformation can be achieved by indentation, as with the Schiøtz tonometer, or by applanation, as with the Maklakoff and the Goldmann tonometers[2]. Although the pressure measured is external to the eye, the term used is "intraocular pressure".

Method of measurement

Applanation tonometry

The most frequently used instrument, and the current gold standard, [I,D] is the Goldmann applanation tonometer (GAT), mounted at the slit lamp. The method involves illumination of the biprism tonometer head with a blue light obtained using a cobalt filter and applanation of the cornea after applying topical anaesthesia and fluorescein in the tear film. The scaled knob on the side of the instrument is then turned until the inner border of the hemicircle of fluorescent tear meniscus visualized through each prism just touch (Fig. 1a, 1b).
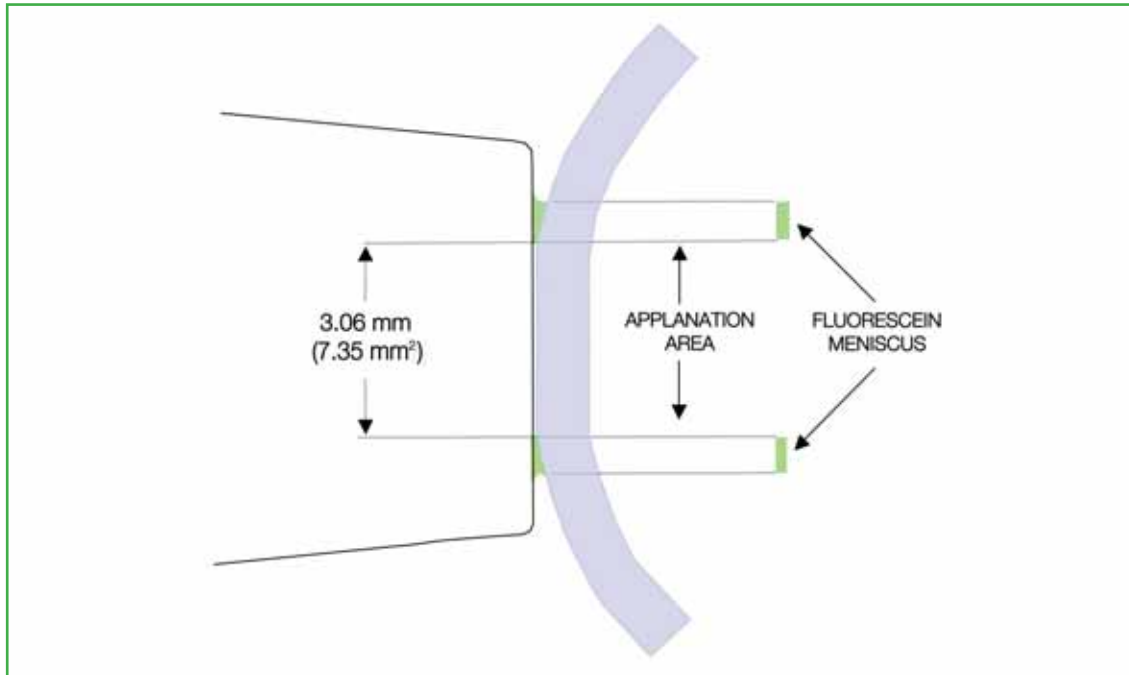
Fig. 1a. The Fluorescent Ring of Applanation Tonometry
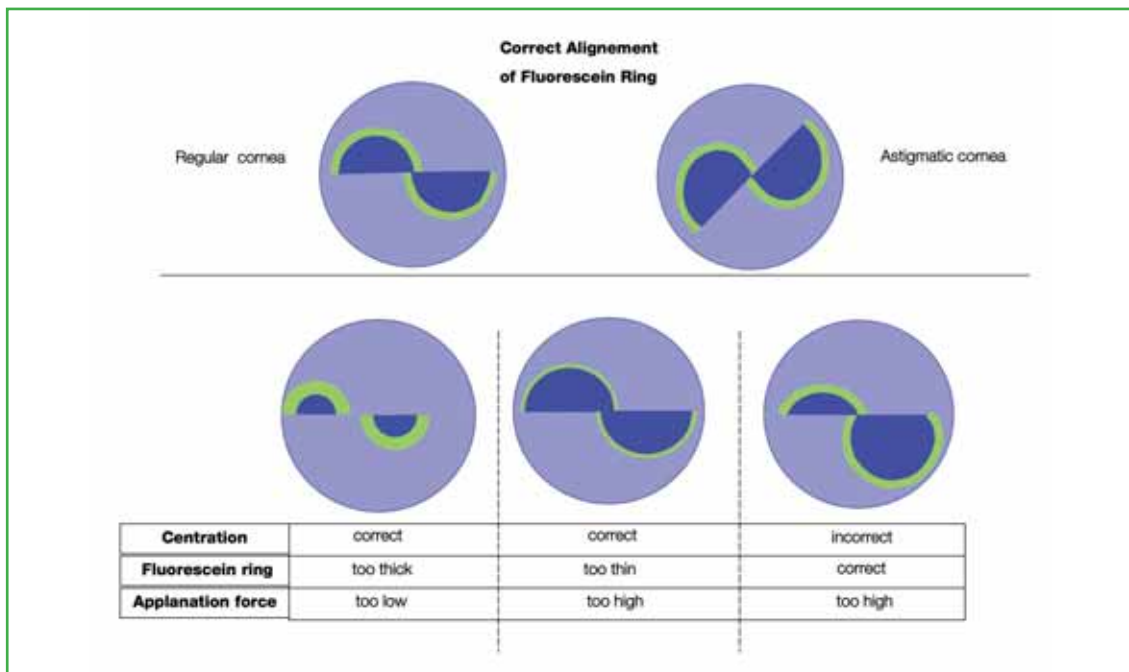
Fig. 1b. Correct Alignment of Fluorescein Ring

Goldmann's original equation is based on the Imbert- Fick law and assumed the following: the cornea had a constant radius of curvature, the rigidity was the same in all eyes, the globe was spherical, aqueous would not move away from the AC during measurement. These factors add to the expected inter and intra observer variability15. The relevance of CCT was already outlined when this tonometer was introduced.

Other methods[16,19-30]:

Air-puff tonometry
The noncontact tonometer deforms the corneal apex by means of a pulsed jet of air. The exposure time is between 1 and 3 msec. Since this is 0.002 of a cardiac cycle, the ocular pulse can be a significant source of variability. Topical anethesia is not necessary. Air-puff tonometry is not recommended for evaluating patients with glaucoma because of the high variability [I, B]

Pneumatonometry
In this device, a sensor measures air pressure. The measurements are well correlated with those made with the Goldmann applanation tonometer, with a tendency to higher IOP estimates. It is useful in eyes with scarred, edematous and irregular cornea. [II, C]

Tono-Pen XL
This portable electronic aplanation tomoter uses a strain gauge to convert the IOP into an electrical signal transmitted to a microprocessor. The software automatically selects the acceptable measurements and rejects the inappropriate ones. An average of at least three good IOP measurements are determined and displayed. It is useful in patients (particularly in children) who cannot sit at the slit-lamp or those with corneal lesions with only one portion of intact cornea, corneal edema or irregularities. [II, C]

Ocuton self-tonometry
This is an applanation self-tonometry method which requires topical anesthesia. Patients may learn the technique of this self-tonometry, and that can provide data on their diurnal IOP curve.

The Proview (based on the perception of phosphenes) and the Diaton (based on indentation) are trans-palpebral self-tonometers. Studies have not been supportive of their accuracy.

Pascal dynamic contour tonometry (DCT)
This slit-lamp mounted instrument contains a sensor tip with concave surface contour and a miniaturized pressure sensor. The result and a quality score measure are provided digitally. This technique is considered less influenced by corneal thickness than Goldmann applanation tonometry.
DCT overestimates the IOP compared to GAT. The DCT additionally measures the ocular pulse amplitude (OPA) which is the difference between the mean systolic and the mean diastolic IOP. The usefulness of OPA is under investigation.

Ocular Response Analyser (ORA)
This non-contact air pulse tonometer provides information both on IOP and other corneal biomechanical properties (hysteresis) and seems less influenced by CCT in nonglaucoma patients
ORA overestimates the IOP compared to GAT.

Rebound (Icare) tonometry
Using this hand-held, portable tonometer, IOP is calculated on the basis of deceleration of the moving part of the probe on the cornea. No topical anaesthesia is needed. The measurements are not independent of corneal properties and appear to correlate well with Goldmann applanation tonometry. The rebound tonometer can be useful in children. [II, C]

A correlation between thicker corneas and OHT as well as between thinner corneas and NPG were found[10,31-33].

INFLUENCE OF CORNEAL STATUS ON THE INTRAOCULAR PRESSURE VALUE
MEASURED WITH THE GOLDMANN APPLANATION TONOMETER[15,23,34]

CORNEA STATUS	IOP READING	
	Erroneously high	Erroneously low
Thinner		+
Thicker	+	
Edema		+
Increased power	1mmHg/3 dioptres	
Decreased power		1mmHg/3 dioptres
Astigmatism with the rule*		1mmHg/4 dioptres
Astigmatism against the rule*	1mmHg/4 dioptres	
Astigmatism irregular	+/-	+/-
Tear film too abundant		+
Tear film insufficient	+	
Corneal Refractive surgery**		
Lamellar cut		+
Radial keratotomy		+
Surface excimer laser (PRK) MYOPIC		++
Intrastromal excimer laser (LASIK) MYOPIC		++

Note: to minimize the reading errors of IOP, the biprism should be aligned to the center of the cornea. In case of high or irregular astigmatism, two measurements should be made, the first with the biprism in horizontal position and the second in vertical position and the readings should be averaged.

* To correct for regular astigmatism > 3 D, the axis of the minus cylinder should be aligned with the red mark of the prism holder

** Corneal refractive surgery alters tonometry reading since it modifies thickness, curvature and structure of the cornea

Central Corneal Thickness (CCT) measurement
- CCT varies among normal individuals: 540 ±30 mμ[35-39]
- CCT could be associated with the risk of development and progression of glaucoma[40-43]
- There is no agreement as to whether there is a validated correction algorithm for GAT and CCT44
- Taking CCT into consideration may prevent overtreatment of patients with apparent OHT [I,B]
- CCT variations after corneal refractive surgery make difficult to interpret tonometry. Ideally a record of pre-operative CCT should be available. [I,D]

IOP diurnal variations can be substantial. IOP diurnal variations are larger in glaucoma patients. Higher long-term IOP variability in treated glaucoma with low mean IOP may be associated with glaucoma progression[45].
Single IOP measurements are made during only a few seconds of a patient's day.
Diurnal curves and 24h phasing can be useful in selected patients [I,D]

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1.2 – GONIOSCOPY

Gonioscopy is a relevant part of the co mprehensive adult eye examination and essential for evaluating patients suspected of having, or that do have glaucoma1-3 [I,D] (see FC V).
Purpose of gonioscopy is to determine the topography of the anterior chamber angle. It is based on the recognition of angle landmarks, and must always consider at least the following:

      a) level of iris insertion, both true and apparent
      b) shape of the peripheral iris profile
      c) estimated width of the angle approach
      d) degree of trabecular pigmentation
      e) areas of iridotrabecular apposition or synechia4.

1.2.1 - ANATOMY

Reference landmarks

Schwalbe's line: this is a collagen condensation of the Descemet's membrane between the trabecular meshwork and the corneal endothelium and appears as a thin translucent line. Schwalbe's line may be prominent and anteriorly displaced (posterior embryotoxon) or there may be heavy pigmentation over it. Confusion between a pigmented Schwalbe's line and the trabecular meshwork may occur, particularly when the iris is convex. Indentation gonioscopy is helpful in these cases.

Trabecular Meshwork (TM): this extends posteriorly from Schwalbe's line to the scleral spur. Most difficulties concerning the examination of this region relate to the determination of features as normal or pathological, particularly pigmentation, blood vessels and iris processes.

Pigmentation: pigment is found predominantly in the posterior meshwork. It is seen in adults (rare before puberty) and is highly variable. The most common conditions associated with dense pigmentation are: exfoliation syndrome, pigment dispersion syndrome, previous trauma, previous laser treatment of the iris, uveitis and acute angle-closure attack.

Blood vessels: these are often found in normal iridocorneal angles. They characteristically have a radial or circumferential orientation, have few anastomoses and do not run across the scleral spur. They can be seen most easily in subjects with blue irides. Pathological vessels are thinner, have a disordered orientation and may run across the scleral spur (neovascular membrane). Abnormal vessels are also seen in Fuch's heterochromic iridocyclitis and chronic anterior uveitis.

Schlemm's canal: this is not normally visible, though it may be seen if it contains blood. Blood reflux from episcleral veins may occur in cases of carotid-cavernous fistulae, Sturge Weber syndrome, venous compression, ocular hypotony, sickle cell disease or due to suction from the goniolens.

Iris processes: these are present in 1/3 of normal eyes and are frequently found in brown eyes and in youths. They follow the iris concavity and do not block the iris movements during indentation gonioscopy. When numerous and prominent they may represent a form of Axenfeld-Rieger syndrome.

Ciliary band and iris root: the iris insertion is usually at the anterior face of the ciliary body, though the site is variable. The ciliary band may be wide, as in myopia, aphakia or following trauma, or narrow or absent as in hyperopia and anterior insertion of the iris.
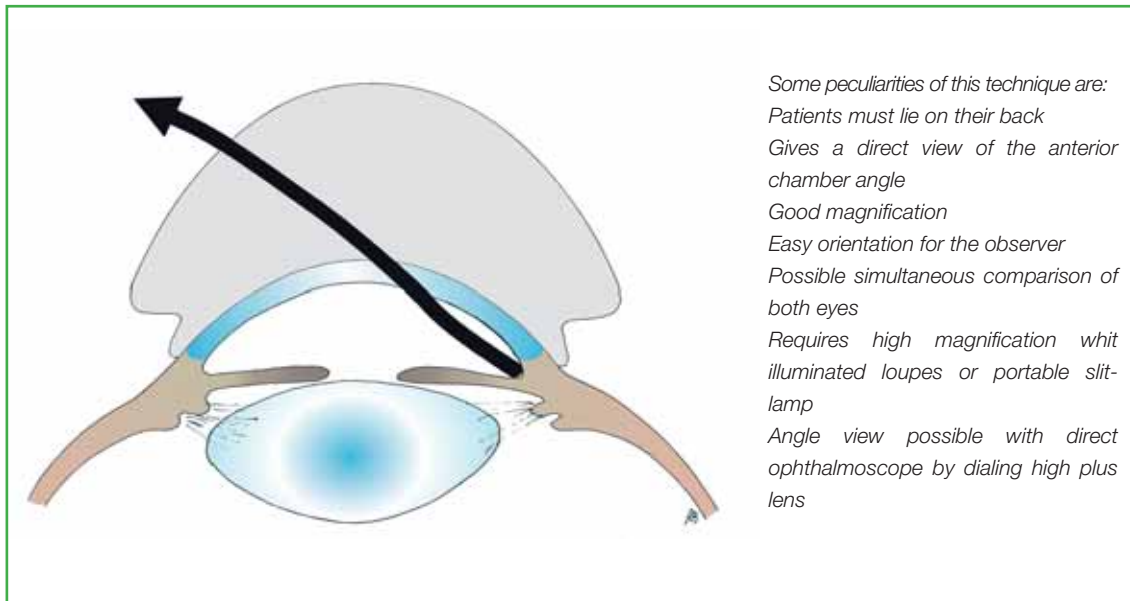
1.2.2 - TECHNIQUES

Gonioscopy is an essential part of the evaluation of all glaucoma patients [I,D]
Gonioscopy should always be performed in a dark room, using the thinnest slit beam, taking care to avoid shining the light through the pupil5,6 [I,D]

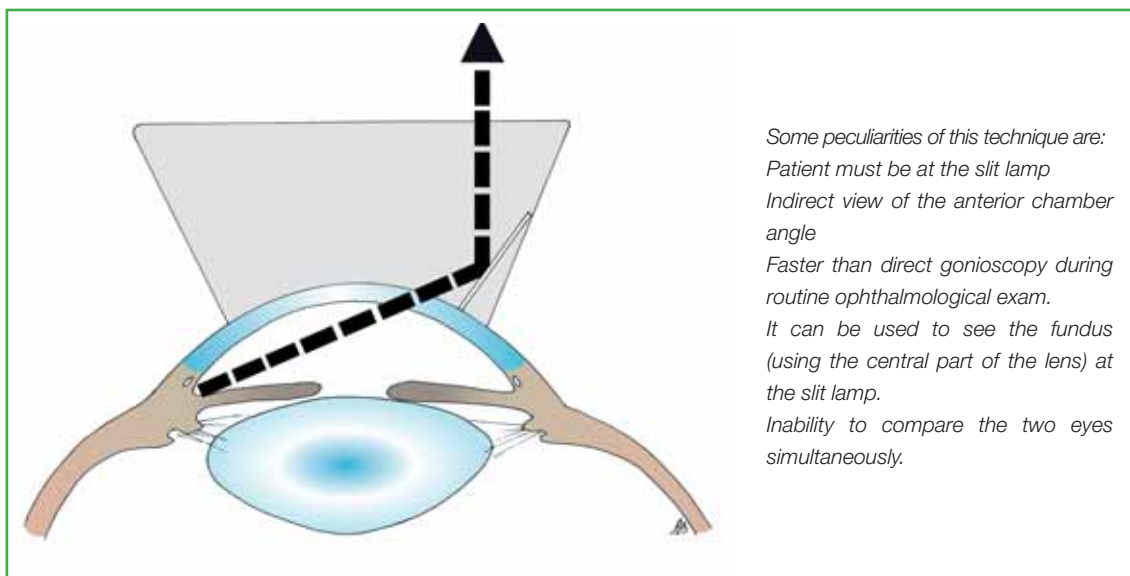There are two principal techniques for viewing the anterior chamber angle:

Direct Gonioscopy

The use of a contact goniolens like the Koeppe lens permits the light from the anterior chamber to pass through the cornea so that the angle may be viewed.

Some peculiarities of this technique are:
Patients must lie on their back
Gives a direct view of the anterior chamber angle
Good magnification
Easy orientation for the observer
Possible simultaneous comparison of both eyes
Requires high magnification whit illuminated loupes or portable slit-lamp
Angle view possible with direct ophthalmoscope by dialing high plus lens

Indirect Gonioscopy

The light from the anterior chamber is made to exit via a mirror built into a contact glass.

Some peculiarities of this technique are:
Patient must be at the slit lamp
Indirect view of the anterior chamber angle
Faster than direct gonioscopy during routine ophthalmological exam.
It can be used to see the fundus (using the central part of the lens) at the slit lamp.
Inability to compare the two eyes simultaneously.

The most common Gonioscopy lenses:

Direct   Koeppe (contact fluid required)
                Layden (sized for infants; contact fluid required)
                Worst
Indirect   Posner or Zeiss or Sussman 4 mirror (contact fluid not required)
                Goldmann lens, 1 to 4 mirrors (contact fluid required)
                CGA 1.4© Lasag (contact fluid required)
                Magnaview (contact fluid required)

Dynamic Indentation by 4-mirror Gonioscopy

For this technique the ideal 4 mirror lens has a flat anterior surface and a posterior surface with a radius of curvature of 7.7 mm. Since this is greater than the average corneal radius of curvature it allows corneal contact via the tear film without the need for a contact medium. The diameter of the contact surface of the lens is less than the corneal diameter, therefore when gentle pressure is applied by the lens on the centre of the cornea, the aqueous humour is pushed back. When the iris lies in contact with the trabecular meshwork in appositional angle-closure, the angle can be re-opened. If there is adhesion between the iris and the meshwork, as in goniosynechia, that portion of angle remains closed (Fig.2). This technique is specifically useful where the angle is narrow and the curvature of the iris surface is convex, making it difficult to recognise the different angle structures listed in 1.2.1. [I,D]

Dynamic indentation gonioscopy should be performed in a) all cases being evaluated for narrow angles, (b) whenever a Van Herick is suggestive of possible angle closure [I,D]

When pupillary block is the prevalent mechanism the iris becomes peripherally concave during indentation. In iris plateau configuration this iris concavity will not be extended by indentation to the extreme periphery, which is a sign of anteriorly placed ciliary body or iris root. When the lens has a role, indentation causes the iris to move only slightly backwards, retaining a convex profile (Fig. 2).
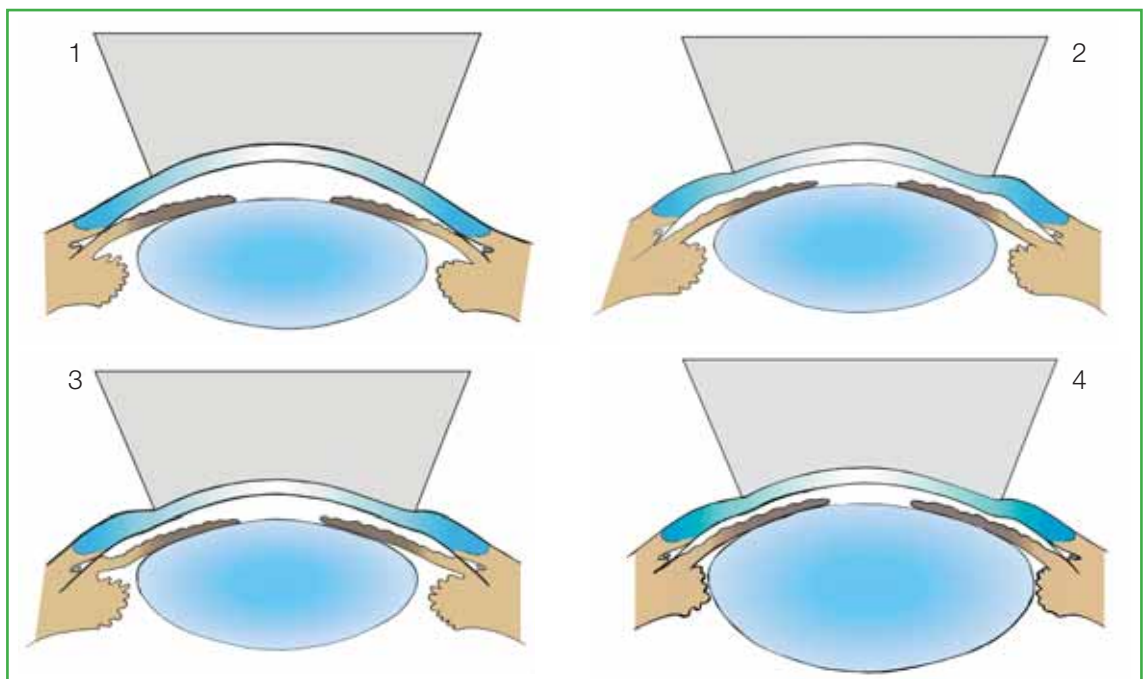
Fig. 2. Dynamic indentation gonioscopy. When no angle structure is directly visible before indentation, angle-closure can be synechial or appositional or optical, the latter being apparent closure due to the curvature of the peripheral iris (1). If during indentation the iris moves peripherally backwards and the angle recess widens (2), the picture in (1) is to be interpreted as appositional closure and a suspicion of relative pupillary block is raised (2). When during indentation the angle widens but iris strands remain attached to the angle outer wall (3), the picture in (1) is to be interpreted as synechial closure. A large and\or anteriorly displaced lens causes the iris to move only slightly and evenly backwards during indentation (4) making the lens a likely component of angle-closure.

Dynamic indentation gonioscopy is extremely useful to differentiate optical from either appositional or synechial closure, as well as for measuring the extent of angle-closure [I,D]

Gonioscopy technique without indentation

With indirect Goldmann-type lenses it is preferable to start by viewing the superior angle, which often appears narrower, and then to continue rotating the mirror, maintaining the same direction in each examination [II,D] The anterior surface of the lens should be kept perpendicular to the observation axis so that the appearance of the angle structure is not changed as the examination proceeds. The four quadrants are examined by a combination of slit-lamp movements and prism rotation.
In case of a narrow approach, it is possible to improve the visualization of the angle recess by having the patient rotate the globe towards the mirror being used.

Problems
        Related to the technique
The most widely used technique is indirect gonioscopy where the angle is viewed in a mirror of the lens. The position of the globe is influential. If the patient looks in the direction opposite of the mirror the angle appears narrower and viceversa.
A second pitfall is related to the degree of pressure of the lens against the cornea and especially occurs when the diameter of the lens is smaller than the corneal diameter (as with the small Goldmann lens, the Posner or the Zeiss lenses). This effect is useful for indentation or dynamic gonioscopy with the Posner or Zeiss lenses; inadvertent pressure over the cornea however, will push back the iris, and gives an erroneously wide appearance to the angle. With the Goldman lens indentation is transmitted to the periphery of the cornea and narrows the angle.

        Related to the anatomy
Recognition of angle structures may be impaired by variations in the anterior segment structures like poor pigmentation, iris convexity or existence of pathological structures. The examiner should be familiar with all the anatomical structures of the angle: Schwalbe's line, trabeculur meshwork, scleral spur, ciliary band and iris.

Pharmacological mydriasis
Dilation of the pupil with topical or systemic drugs can trigger iridotrabecular contact or pupillary block, eventually leading to angle-closure. Angle-closure attacks can occur, even bilaterally, in patients treated with systemic parasympatholytics before, during or after abdominal surgery and has been reported with a serotonergic appetite suppressant.
Although pharmacological mydriasis with topical tropicamide and neosynephrine is safe in the general population even in eyes with very narrow approach, in occasional patients raised IOP and an angle occlusion can be observed.
Theoretically, although any psychoactive drugs have the potential to cause angle-closure, it is unlikely that pre-treatment gonioscopy findings alone are of help to rule out such risk. In eyes with narrow angles, it makes sense to repeat gonioscopy and tonometry after initiation of treatment [II,D] Prophylactic laser iridotomy needs to be evaluated against the risks of angle-closure or of withdrawal of the systemic treatment. [II,D] (See Chapter 2 - 4). None of these drugs is contraindicated per se in open-angle glaucoma.
Ciliochoroidal detachment with bilateral angle-closure has been reported after oral sulfa drugs and topiramate[7].

1.2.3 - GRADING

The use of a grading system for gonioscopy is highly desirable2,8,9 [I,D] It stimulates the observer to use a systematic approach in evaluating angle anatomy, it allows comparison of findings at different times in the same patients, or to classify different patients.
A grading method is also very helpful to record the gonioscopy findings and should always be used on patients' charts.
The Spaeth gonioscopy grading system is the most detailed and recommended (chapter 1.2.1) 2 [I,D]

Other grading systems are useful though less specific; we list the most widespread (Fig. 3).
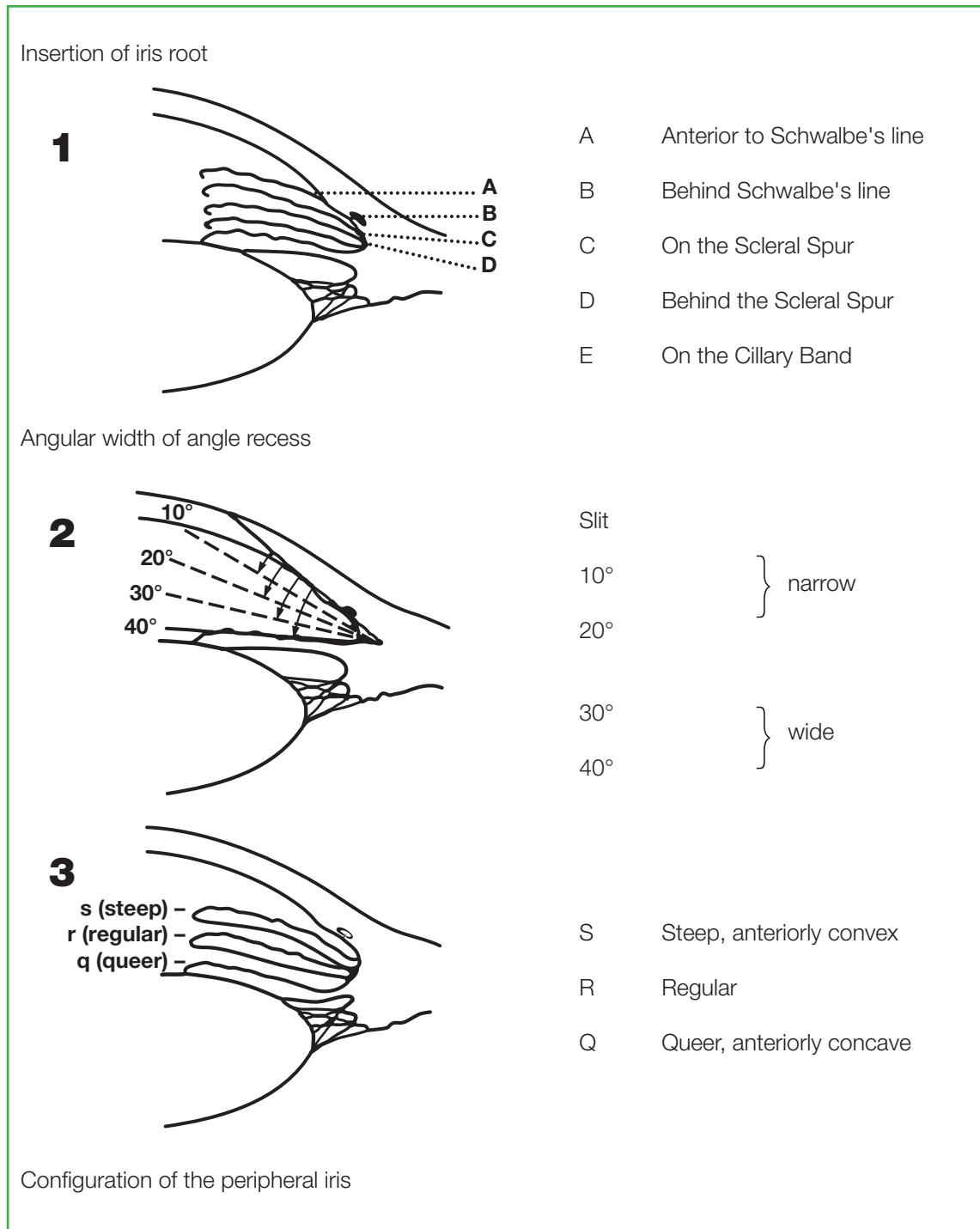
Insertion of iris root

1

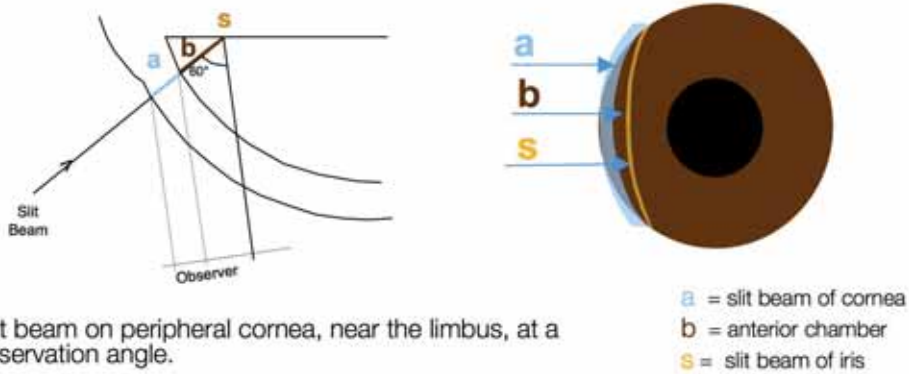A   Anterior to Schwalbe's line

B   Behind Schwalbe's line

C   On the Scleral Spur

D   Behind the Scleral Spur

E   On the Cillary Band

Angular width of angle recess

2

Slit

10°   } narrow

20°

30°   } wide

40°

3

s (steep) –
r (regular) –
q (queer) –

S   Steep, anteriorly convex

R   Regular

Q   Queer, anteriorly concave

Configuration of the peripheral iris

Fig. 3. The Spaeth classification

1.2.3.1 - Slit lamp-grading of peripheral ac depth - The Van Herick Method

The Van Herick grading is a fundamental part of any comprehensive eye examination (Fig. 4) [I,D]
Grade 0 represents iridocorneal contact.
A space between iris and corneal endothelium of < 1/4 corneal thickness, is a grade I.

When the space is ≥ 1/4 < 1/2 corneal thickness the grade is II.
A grade III is considered not occludable, with an irido/endothelia l distance ≥ 1/2 corneal thickness.
This technique is based on the use of corneal thickness as a unit measure of the depth of the anterior chamber at the furthest periphery. This method is very useful if a goniolens is not available[10,11]. [I,D]

Fig. 4

Thin slit beam on peripheral cornea, near the limbus, at a 60° observation angle.

a = slit beam of cornea
b = anterior chamber
s = slit beam of iris

b/a: ratio of slit thickness of the cornea (a) to the depth of the anterior chamber (b)

b/a: **Grade:**
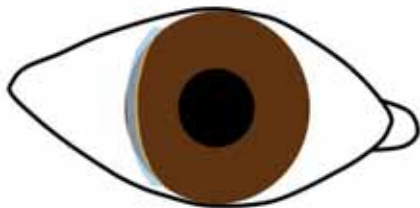
0   0 Angle closed
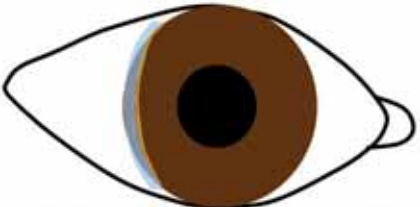
<1/4   1 Angle closure likely (10°)
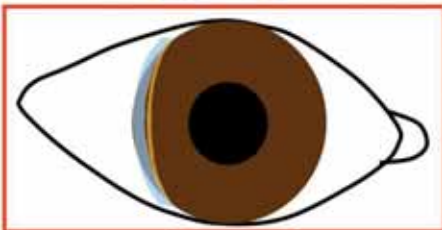
1/4   2 Angle closure possible (angle 20°)
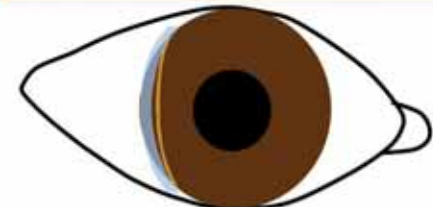
1/2   3 Angle closure unlikely
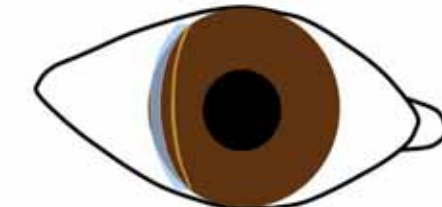
1   4 Angle closure very unlikely

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1.2.4 - ANTERIOR SEGMENT IMAGING TECHNIQUES

UBM, anterior segment OCT and Scheimpflug cameras can be useful in some circumstances. Added to gonioscopy, these techniques help elucidate the mechanism of angle-closure in many cases [II, D]. Due to their limited availability and costs however, they are applied to cases which are most difficult to interpret[12-19].

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1.3 - OPTIC NERVE HEAD AND RETINAL NERVE FIBRE LAYER

Glaucoma changes the surface contour of the optic nerve head (ONH). Contour changes can best be appreciated with a stereoscopic view. Therefore the initial examination, and follow-up examinations for contour change, should be made through a dilated pupil. [I,D] Interim examination, for disc hemorrhages, can be performed through an undilated pupil. [II,D] Stereoscopic examination of the posterior pole is best performed with a:
• indirect fundus lens with enough magnification at the slit-lamp,[I,D] or
• direct fundus lens (central part of Goldmann and Zeiss 4-mirror) at the slit-lamp [II,D]

The direct ophthalmoscope is very useful for ONH and retinal nerve fibre layer (RNFL) examination and can give additional information such as RNFL defects and disc haemorrhages [I,D]. Three-dimensional information using parallax movements is possible. [II,D]
The ophthalmoscopic clinical evaluation of the ONH and retinal nerve fibre layer RNFL should assess the following features:[I,D]

1.3.1 - QUALITATIVE

a)   shape and width of the neuroretinal rim
b)   evaluation of the retinal nerve fibre layer
c)   optic disc haemorrhages

1.3.2 - QUANTITATIVE

a)   optic disc size (vertical disc diameter)
b)   rim width
c)   retinal nerve fiber layer thickness

1.3.1.a - Shape and Width of the Neuroretinal Rim

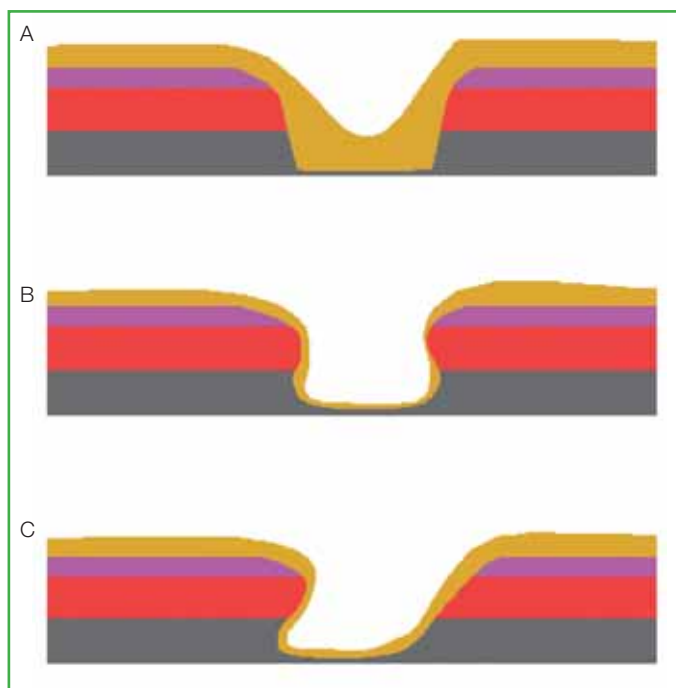In a healthy eye, the shape of the rim is influenced by optic disc canal (Fig. 5).

Fig. 5. Different shapes and widths of the neuroretinal rim: A) normal, B) glaucomatous, C) tilted.

The disc is usually slightly vertically oval. In normal sized discs, the neuroretinal rim is at least as wide at the 12 and 6 o'clock positions as elsewhere and usually widest (83% of eyes) in the infero-temporal sector, followed by the supero-temporal, nasal and then temporal sectors (the 'ISNT' rule)1. This pattern is less marked in larger discs, in which the rim is distributed more evenly around the edge of the disc (Fig. 6) and in a smaller discs where cup is not evident. Larger and a smaller discs are harden to interpret[2]. Black subjects often have larger discs as a result of a greater vertical disc diameter[3].
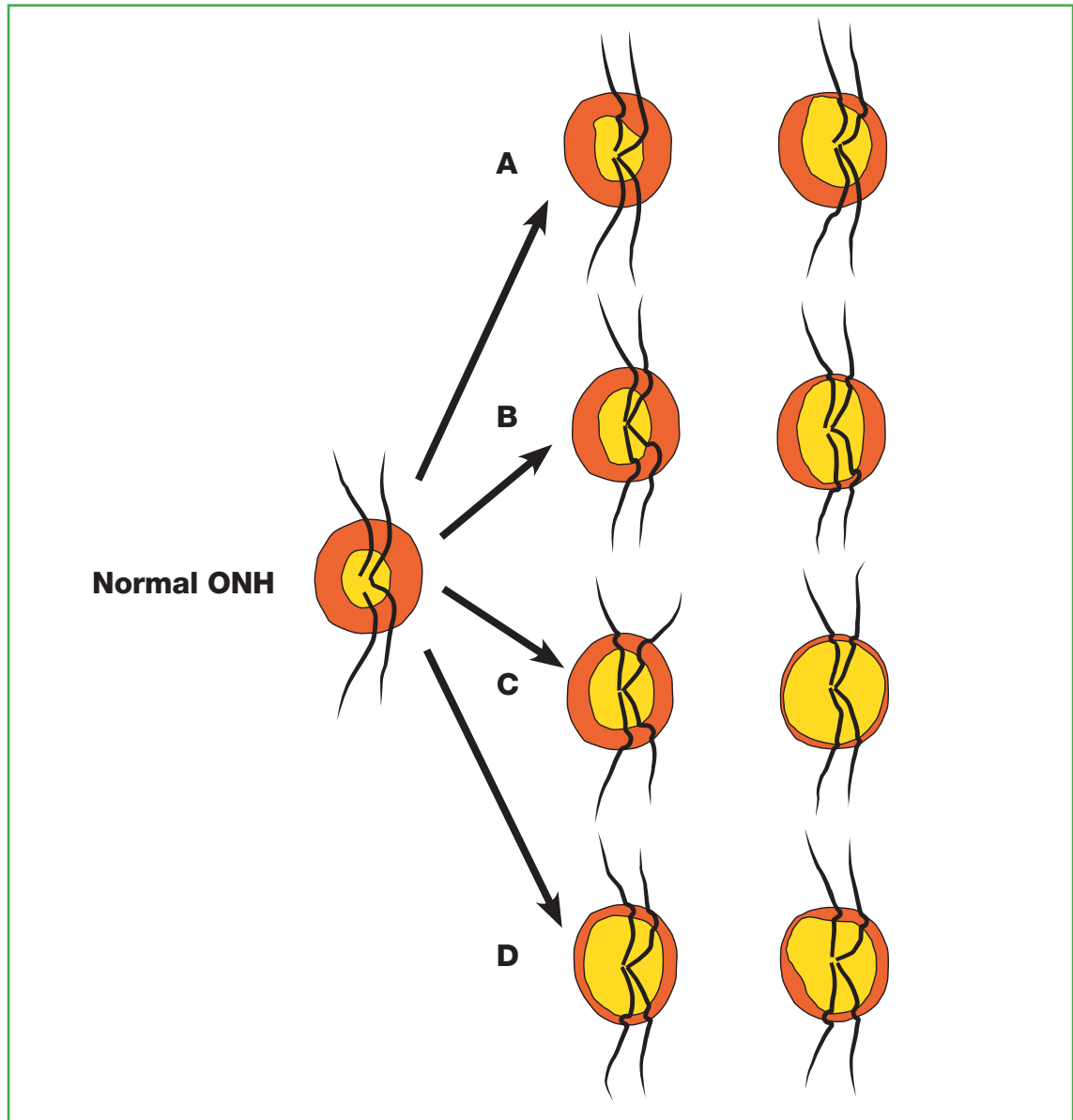
Fig. 6. Progression of glaucomatous damage at the optic disc:
A) Localized nerve fiber loss (notch).
B) Localized nerve fiber loss (polar notches).
C) Diffuse or concentric nerve fiber loss.
D) Localized and diffuse nerve fiber loss.

The exit of the optic nerve from the eye may be oblique, giving rise to a tilted disc. Tilted discs are more common in myopic eyes, and give rise to a wider, gently-sloping rim in one disc sector and a narrower, more sharply-defined rim in the opposite sector. Discs in highly myopic eyes are harder to interpret.

Glaucoma is characterized by progressive narrowing of the neuroretinal rim. The pattern of rim loss varies and may take the form of diffuse narrowing, localized notching, or both in combination (fig. 2). Narrowing of the rim, while occurring in all disc sectors, is generally greatest at the inferior and superior poles[4-8].

POAG has been divided into various subtypes on the basis of ONH features. However, there is no clear separation between these subtypes (e.g.: focal ischemic, senile sclerotic, etc..). ONH findings are not pathognonomic for a specific type of glaucoma[9,10].

1.3.1.b - Evaluation of the retinal nerve fibre layer

The RNFL is best assessed with a red-free (green) light in the parapapillary region and around the vascular arcades. [I,D] In healthy eyes, retinal vessels are embedded in the RNFL. The RNFL surface is best seen if the focus is finely adjusted just anterior to the retinal vessels. [I,D]

The fibre bundles are seen as silver striations. From about two discs diameters from the disc the RNFL thins and feathers-out. Slit-like, groove-like, or spindle-shaped apparent defects, narrower than the retinal vessels, are seen in the normal fundus. The RNFL becomes less visible with age, and is more difficult to see in lightly pigmented fundi.

Defects are best seen within two disc diameters of the disc. [I,D] Focal (wedge and slit) defects are seen as dark bands, wider than retinal vessels and extending from reach the disc margin (unless obscured by vessels). These are more easily seen than generalized thinning of the RNFL, which manifests as a loss of brightness and density of striations, and is a difficult sign to objectively confirm. When the RNFL is thinned, the blood vessel walls are sharp and the vessels appear to stand out in relief against a matt background. The initial abnormality in glaucoma may be either diffuse thinning or localized defects. Since the prevalence of true RNFL defects is < 3% in the normal population, their presence is very likely to be pathological [11-16]

1.3.1.c - Optic disc haemorrhages

The prevalence of small haemorrhages on or bordering the optic disc has been estimated to 0.2% or smaller in the normal population[17-19]. On the other hand, a large proportion of all glaucoma patients have optic disc haemorrhages (ODH) at one time or another. ODHs are intermittent and, therefore, absent in any one patient at most examinations. They are often overlooked at clinical examinations, and easier to find on photographs. Many studies have shown that ODHs are associated with disease progression (Fig. 7).
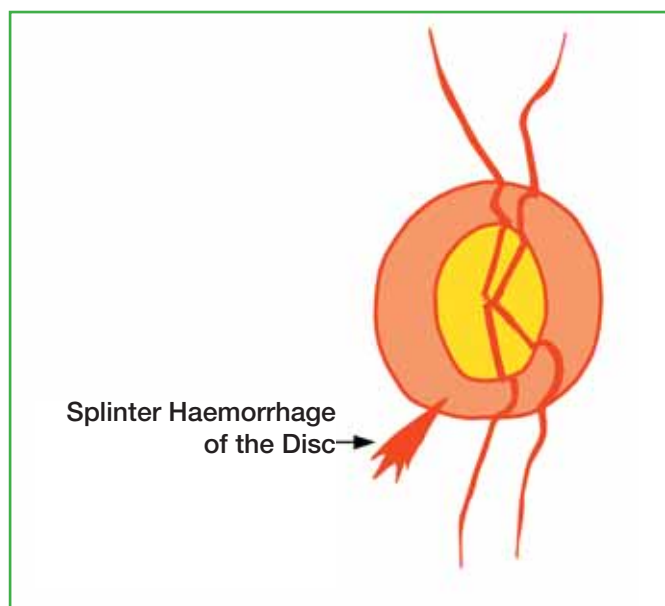

Fig. 7. Optic disc haemorrhage

1.3.1.d - Peripapillary atrophy [20,22]

A temporal crescent of peripapillary atrophy is common (80% in the normal population). However, the frequency and area covered increases in glaucoma. Peripapillary atrophy is least frequent in normal eyes in the nasal disc sector. The site of the largest area of atrophy tends to correspond with the part of the disc with most neuroretinal rim loss. The extent of atrophy may be greater in NPG. Because some degree of atrophy is present in many normal eyes, a large area of atrophy should be regarded as an extra clue, and not as a definite sign of glaucoma (Fig. 8-Ch.1). [I,D]
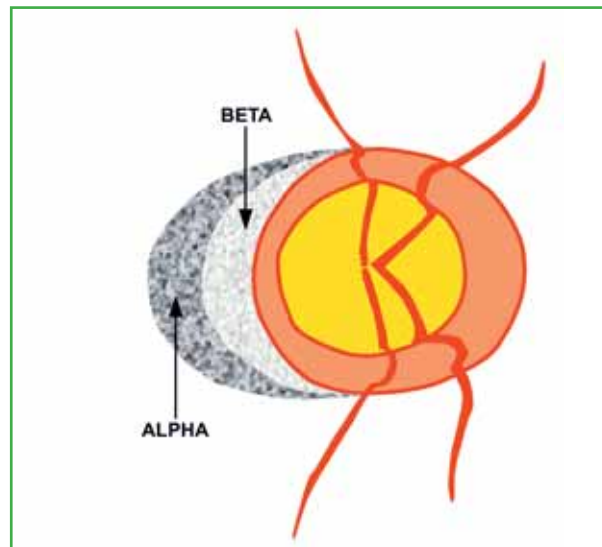
Fig. 8. ONH with parapapillary atrophy: Alpha dystrophy is located peripheral to beta dystrophy, characterized by irregular hypopigmentation and hyperpigmentation; Beta dystroph is adjacent to the optic disc edge, outer to the Elshnig rim, with visible sclera and visible large choroidal vessels.

Measured vertical diameter of optic disc			
	Small	Medium	Large
Disc area	*<1.6 mm^2*	*1.6 to 2.8 mm^2*	*>2.8 mm^2*
Volk 60 D	<1.65 mm	1.65 to 2.2 mm	>2.2 mm
78 D	<1.3 mm	1.3 to 1.75 mm	>1.75 mm
90 D	<1.1 mm	1.1 to 1.45 mm	>1.45 mm
Superfield	<1.15 mm	1.15 to 1.50 mm	>1.5 mm
Digital 1.0x	<1.5 mm	1.5 to 1.95 mm	>1.95 mm
Super 66	<1.45 mm	1.45 to 1.9 mm	>1.9 mm
Nikon 60 D	<1.45 mm	1.45 to 1.9 mm	>1.9 mm
90 D	<0.95 mm	0.95 to 1.25 mm	>1.25 mm
Haag-Streit Goldmann	<1.3 mm	1.3 to 1.7 mm	>1.7 mm

1.3.2.a - Optic disc size (vertical disc diameter)

The width of the rim and, conversely, the size of the cup, varies physiologically with the overall size of the disc [23].
The size of optic discs varies greatly in the population.
The vertical diameter of the optic disc can be measured at the slit lamp using a contact or a not contact lens. The slit beam should be coaxial with the observation axis; a narrow beam is used to measure the vertical disc diameter using the inner margin of the white Elschnig's ring as the reference

landmark. The magnification corrections needed vary with the lens used for measurement. The ONH size should be written in the chart. [II,D]

1.3.2.b - Rim width

Large Cup/ Disc Ratio (CDR) have been used as a sign of glaucoma damage over decades. However depending on the absolute disc size, large CDR in large discs may be erroneously considered glaucomatous and a small CDR in small discs may be erroneously considered as normal[24] (Fig. 9).
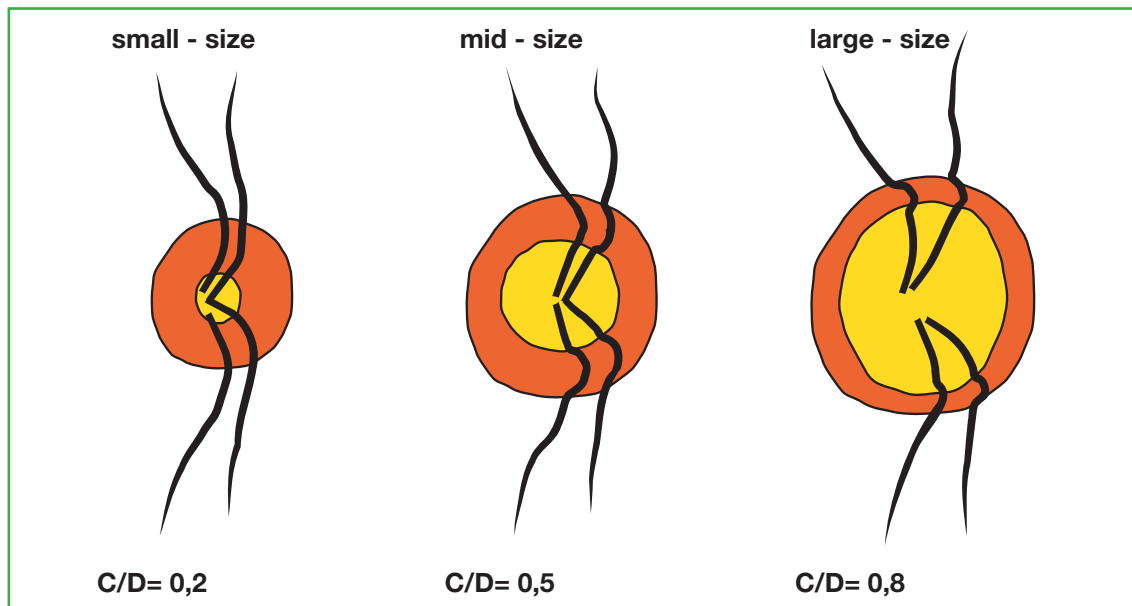

small - size	mid - size	large - size
C/D= 0,2	C/D= 0,5	C/D= 0,8

Fig. 9. Optic nerve heads with different disc area but with the same rim area and same retinal nerve fiber number: small size disc (disc area less than 2 mm² and C/D=0.2), mid size disc (disc area between 2 and 3 mm², C/D=0.5) and large disc (disc area greater than 3 mm² and C/D=0.8).

A difference in CDR between eyes (with equal optic disc size) is suggestive of acquired damage. Cupping tends to be symmetrical between the two eyes, the vertical CDR difference being less than 0.2 in over 96% of normal subjects.

1.3.3 - RECORDING OF THE OPTIC NERVE HEAD (ONH) FEATURES

At baseline some form of imaging may be useful to provide a record of ONH appearance. [I,D]
If colour photos are not available, detailed manual drawing is recommended, even if it is difficult to draw a good picture of an ONH; the act of making a drawing however encourages a thorough clinical evaluation of ONH. [II, D]
Colour photography provides an image almost identical to that seen during clinical examination. Those obtained with scanning devices are monochromatic and interpretation of images is dependent on instrument software. Colour photography with a 15° field gives optimal magnification.
Stereoscopic photographs are the preferred method, but if it is not possible monoscopic images are also acceptable. [II,D]

1.3.4 - QUANTITATIVE IMAGING

Quantitative imaging devices are in widespread use for glaucoma management. Quantitative imaging supports diagnosis and progression monitoring. [I,C] More details are described in "Optic Nerve Head and Retinal Nerve Fibre Analyses" [25]. The main features of available systems are mentioned below in alphabetical order.

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1.3.4.1 - GDx Nerve Fibre Analyzer (GDx)

The GDx (Carl Zeiss Meditec Inc.,Dublin, CA) is a scanning laser polarimeter (780nm light source) and quantifies the NFL thickness by providing a map of the retardation of polarized light in the parapapillary retina. The GDxVCC contains a variable corneal compensator, to provide patient-specific neutralization of corneal light retardation. A recent software upgrade, the GDxECC, gives more accurate measurements in myopic eyes and eyes with a pale fundus. [26,27]

1.3.4.2 - Heidelberg retina tomograph (HRT)

The HRT (Heidelberg Engineering, Heidelberg, Germany) is a confocal scanning laser ophthalmoscope (670nm light source) and provides quantitative measurements of ONH (such as disc, rim and cup size) together with a 3-dimensional surface topography (height map) of the ONH and parapapillary retina[28,29]. A recent software, the Glaucoma Probability Score gives an ONH assessment without drawing contour line.

1.3.4.3 - Optical coherence tomography (OCT)

OCT is available as (a) time-domain and (b) spectral-domain. Both techniques do provide a quantitative estimate of the RNFL thickness. Spectral-domain OCT is able to acquire 3-dimensional image volumes and offers a higher resolution than time-domain OCT[30].

Diagnosis
A glaucoma diagnosis should not be based entirely on imaging data, but the diagnostic modalities mentioned above provide useful diagnostic information. [I,C] The GDx VCC, HRT and Stratus OCT have similar, moderately high diagnostic accuracy, of the same magnitude as that of expert observers reading stereo photographs of the optic disc. When interpreting reports from imaging devices, clinicians need to consider image quality, and remember to use imaging results for clinical management only in the context of all other relevant clinical data[31-34]. [I,D]

Progression
Fundus photography is a mature technology. This provides advantages when very long follow-up periods are considered. Further colour photographs show the optic disc and the RNFL in the same way as clinicians see them during the clinical examinations, and photographs can, therefore, be interpreted by all ophthalmologists. Disc haemorrhages can be easily identified on photographs. Photography, however, also has disadvantages for follow-up. Interpreting series of disc photographs is time-consuming and difficult; the variability is large even between experts, and changes are difficult to quantify.
Optic disc and RNFL imaging are developing technologies. Some early techniques have already become obsolete. The current instrument with the longest retro-compatibility is the HRT. A great advantage of the imagers is that they – as opposed to photographs -provide quantitative data. [I,D] It is likely that they image-based methods to assess progression and rate-of-progression will prove important in the future. It is, however, not yet clear how best to use the imaging devices, e.g., frequency of testing, or how the data should best be interpreted[35-41].

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1.4 - PERIMETRY

1.4.1 - PERIMETRY TECHNIQUES

Visual field testing is a mandatory part of glaucoma management, for diagnosis and even more so in follow-up. [I,D] The goal of glaucoma treatment as formulated in these Guidelines is to prevent a loss of quality of life at an affordable cost. Loss of visual function is associated with loss of quality of life, and it is therefore always necessary to know each patient's amount of visual field loss. The large controlled, randomised glaucoma treatment trials (EMGT, AGIS and CNTGS) have shown that disease progression is common also at normal levels of intraocular pressure. Therefore tonometry alone is never sufficient in follow-up of glaucoma patients regardless of IOP; perimetry must also be performed. [I,A]

Computerised perimetry and Goldmann perimetry
Static computerised perimetry should be preferred in glaucoma management. Kinetic Goldmann perimetry is not suitable for detection of early glaucomatous field loss and small defects will often be lost between isopters.[1] Computerised perimetry is also less subjective; the results are quantitative and tools for computer-assisted interpretation are available.

An exception, when Goldmann perimetry could be used, is a severely damaged field, where ordinary static computerised perimetry results in an almost black printout. [II,D]

Standard Automated Perimetry – SAP
Glaucoma perimetry has become more standardised over time and today the term Standard Automated perimetry (SAP) is often used. SAP refers to static computerized threshold perimetry of the central visual field performed with ordinary white stimuli on a white background.

Test algorithms
In glaucoma care threshold perimetry is the recommended standard. [I,D] Commonly used threshold algorithms are: SITA Standard and SITA Fast in the Humphrey perimeter. These two algorithms have replaced the older Full Threshold and Fastpac algorithms. In the Octopus perimeter the standard threshold algorithms are called the normal Threshold and Dynamic strategies. The TOP algorithm (tendency-oriented perimetry) is not similar to the common threshold algorithms. With the rapid TOP algorithm only one stimulus is shown at each test point location. The calculated local thresholds are influenced by the responses to neighbor locations. Therefore this test may represent small local scotoma as slightly wider but less deep than traditional threshold algorithms.

Test point patterns
Glaucoma perimetry is performed in the central 25 – 30° field where the great majority of retinal ganglion cells are located. It is thus acceptable to ignore the peripheral field. [I,D]

Common test point patterns are the identical 30-2 and 32 test point patterns of the Humphrey and Octopus perimeters respectively and G1 and G2 patterns of the Octopus, which covers the central 30°. A very commonly used pattern is the 24-2 pattern of the Humphrey perimeter, that cover a somewhat smaller area. Only a small amount of information is lost if the smaller patterns are used as compared to the larger ones, and common test artefacts from, e.g., trial lens rims or droopy lids are less common with the more central patterns. [II,D]

Selecting a test
It is recommended that ophthalmologists select and familiarise themselves with one test, that they use in the majority of cases. [I,D] This should be a SAP test with white stimuli. Most common choices in the Humphrey system are SITA Standard 24-2 or 30-2 or SITA Fast. In the Octopus system good SAP tests would be the G2 or 32 programmes with normal threshold strategy or the Dynamic programme which uses the same patterns. In both perimeters one may use test point patterns covering only the central 10° of the field in eyes who have only tunnel fields left. [I,D]

The Humphrey Field Analyzer and the Octopus perimeter, are the two most commonly used SAP perimeters in Europe. Several other less frequently used SAP perimeters having threshold programmes are available. Patients with manifest glaucoma followed with one these instruments should preferably continue to be followed with the same test to facilitate estimation of progression. [I,D] An overview display including full series of fields will help to estimate velocity of progression in perimeters lacking automated progression analyses. [II,D]

Non-conventional perimetry

There are other modalities of computerised perimetry where the stimulus is no longer a white dot on an evenly illuminated white background. Examples are SWAP (Short Wavelength Automated Perimetry) or blue-yellow perimetry, FDT (Frequency Doubling Technology) and HRP (High-pass resolution perimetry or ring perimetry) and flicker perimetry.

These techniques were developed with the hope that by stimulating sub-populations of ganglion cells they would be able to recognise glaucomatous field loss earlier than conventional SAP. These hopes have not been confirmed. Systematic literature reviews show that no other perimetric techniques can consistently show field defects before SAP. [I,A] Recent publications revealed SWAP to be similar, or inferior, to SAP in early detection of visual field defect/loss[2,3,4]. The first FDT instrument, including only 17 or 19 large test locations, was not particularly sensitive to early defects[5], while the second type, Matrix, including the same number of test locations as the 24-2 SAP, is more likely to perform similar to SAP. The same is true for detection of progression. SWAP has never been properly evaluated for progression. Test-retest variability with SWAP is about twice as large as that for SAP, and SWAP is also considerably more sensitive to increasing cataract making SWAP less suitable for follow-up of patients with manifest glaucoma. [I,D] The early FDT instrument has too few test locations to being able to measure small steps of progression, and therefore makes it less suitable to use than SAP. The newer Matrix has not being available long enough to allow any comparisons with SAP. [I,D] There is a lack of well-designed longitudinal studies that can provide good evidence on early detection or early detection of progression. Non-conventional perimetric tests should never be performed at the expense of SAP [I,D][6].

Patient instructions

Even in computerised perimetry the role of the operator is of great importance. [I,D] To patients who are naive to the test, the operator must explain what to expect and how to react to stimuli. A short demonstration, done by setting the instrument in "demo" mode, before the actual test starts will also help patients understand the test. The operator should have taken the tests to better understand the "feel" of it. If threshold tests are used it is necessary to explain to the patient that the perimeter will seek the limit of what the patients can see in a large number of points. Therefore many stimuli will be shown that cannot be seen even by persons with normal vision, and visible stimuli will usually be very dim. Such instructions will remove unnecessary patient tension.

Patients who understand the nature of the test usually have nothing against frequent visual field testing. The operator needs to be in the vicinity of the perimeter to react to patient any queries. [II,D] It is also important that physicians motivate their patients for perimetric testing. [II,D] Patients who understand that test results are necessary to optimise their glaucoma management are usually eager to include perimetry at least once or twice a year in their glaucoma care.

1.4.2 - PERIMETRY RESULTS

Printouts

Humphrey and Octopus both provide similar single field printouts, each containing six different maps of the visual field plus global visual field indices and other means of interpreting a field as normal or pathological[II,D].

The numerical threshold map provides the unprocessed results of the tests – estimated threshold values at each test point location. This map does not lend it self to intuitive interpretation.

The grey scale map, on the other hand, is intuitively easy to read. Yet some other printouts – particularly the probability maps (see cf below) – provide even better information and user should avoid the temptation to look primarily at the grey scale map. The grey scale map is particularly difficult to interpret in patients who have concurrent media opacities.

The numerical total deviation map shows differences between the age corrected normal threshold value at each test point location and measured value.

The numerical pattern deviation map shows the same values but after correction for components of diffuse loss of sensitivity, typically caused by cataract or less frequently by miotics.

Probability maps have the advantage of translating the test results in to a comprehensive format after statistical analysis. Threshold values that are depressed enough to be unusual in normal individuals of the same age are marked by dark symbols.

The total deviation probability map shows the significance of the worsening as compared to the age-corrected normal reference values in all test point locations.

The pattern deviation probability map is probably the single most important part of the visual field printout. The pattern deviation concept again corrects for cataract and cataract surgery. Pattern deviation does not work in severely depressed fields, and recently Humphrey has removed pattern deviation maps from printouts of severely depressed fields with MD values (cf below) worse than -20dB.

Reliability indices
High frequencies of false positive answers (FP), are clearly detrimental, but frequencies of false negatives (FN) are of little value being related with degree glaucomatous field loss. Pay attention to frequencies of false positive answers only in eyes with field loss. [II,D]

High rates of fixation losses (FL), as measured by the blind spot method (Heijl-Krakau method)[7], often correctly depict the patient's ability to keep a steady fixation throughout the test, but in some tests the rate of fixation loss is high despite perfect or almost perfect fixation was observed. Rate of fixation loss is of no value if the blind spot has been erroneously located at start of test. One can assume that fixation has been good if the blind spot is visible in the grey scale map.

Visual field indices
Visual field indices are numbers summarising perimetric test results. The most useful index is MD (mean defect in the Octopus system or mean deviation in the Humphrey system). [I,D] MD represents the average difference between normal age-corrected sensitivity values and the measured threshold values at all test point locations. Thus, a normal field has an MD value around 0 dB. In the Humphrey perimeter worsening is associated with negative MD values – a perimetrically blind field has MD values between -27 and -34 dB; in the Octopus the values become more positive with increasing defects.

A new index developed for the Humphrey perimeter is VFI, which is similar to the MD value, expressed in percent rather than in decibels, more resistant to cataract and cataract surgery and centrally weighted.[8]

The other traditional indices are less valuable. [I,D] They are PSD (Humphrey) and CLV (Octopus), which represent the irregularity of the measured field as compared to the age corrected normal field. PSD and CLV can be used for diagnosis, but they are much less efficient than looking at the field maps themselves, particularly probability maps. Following the development of a glaucomatous field with PSD and CLV is not recommended. PSD and CLV increase in the beginning of the disease development, but peak in early advanced stages of field loss and then decrease again. PSD, CLV and SF (Short-term Fluctuation) were developed in the early 1980, when it was believed that indices such as these could be effectively used for early diagnosis. This is not the case and it is questionable whether PSD, CLV and SF have a clinical role today.

Two new indices are available in the Octopus perimeter, DD (diffuse defect) and ARA (abnormal response area). DD is designed to display the general diffuse component of the total field loss, while ARA is meant to show the local component. Octopus also provide a graph, "defect vs fiber angle" showing the localization of the field defects in the retinal nerve fibre layer.

Summarising diagnostic features

The Glaucoma Hemifield Test (GHT)

The Glaucoma Hemifield Test is incorporated in the Humphrey perimeter. This analysis has been developed for glaucoma diagnosis and classifies results as within normal limits, outside normal limits or borderline. The classification "outside normal limits", "within normal limits", "borderline", "general depression of sensitivity", "abnormally high sensitivity" is rather specific for glaucoma. If "borderline" and "outside" are both considered abnormal the test is very sensitive[9]. Two more GHT classifications are "general depression of sensitivity", which is displayed in fields with generally depressed sensitivity without localised glaucomatous field loss – typically in eyes with cataract but no manifest glaucoma – and "abnormally high sensitivities" which is a sign that the patient is pressing the response button even when not seeing a stimulus.

The Bebié curve

The Bebié curve or the cumulative defect curve in the Octopus system is a summary graph of localised and diffuse sensitivity loss. In entirely diffuse loss the curve of the measured sensitivities is lower than but parallel to the displayed normal curve. In focal loss (typical for glaucoma) the right part of the measured curve is depressed as compared to the normal reference curve.

Diagnosis based on clustered points

Clustered test point locations with significantly reduced sensitivities are more reliable indicators of early glaucomatous field loss than scattered points.
Visual field loss can therefore be based on the occurrence of a cluster of significantly depressed points. The rule, which is often used stipulates a minimum of three clustered points with significantly depressed sensitivity, of which one should have a significance of p<1%. Usually the test point locations immediately surrounding the blind spot are ignored in this analyses The Glaucoma Hemifield Test (GHT) of the Humphrey perimeter, also exploits clustering. A "cluster defect" graph, displaying average defect depth at clustered significantly depressed points, is available in the Octopus perimeter

Assessing a single field
The easiest way of classifying a visual field is to look at the Glaucoma Hemifield Test, which has good sensitivity and specificity[9]. [I,D] Another good approach is to look at the pattern deviation probability maps. [I,D] Small glaucomatous defects typically consist of clustered significantly depressed points often following the course of the retinal nerve fibre layer. Early defects are of course somewhat more common in the nasal areas of the field. They are also slightly more common in the superior hemifield than in the inferior hemifield.

Confirmation of findings
Most patients are first diagnosed with clear-cut glaucoma. In such instances field defects are often very clear and do not need confirmation to be convincing. [I,D] Glaucoma suspects (e.g. patients with ocular hypertension) who are followed with initially normal fields show much more discrete field defects when field loss first appears. It is typical that in such patients defects are first visible in the probability maps – even before they can be seen in grey scale maps (particularly if defects appear more paracentrally). In early stages it is typical for defects to appear as clustered depressed points with variable significance. Such defects often need confirmation in a second or even a third test before one can be sure that glaucomatous loss has really developed. One should not expect the depressed pattern of points to look identical at each test, but depressed points will usually appear in the same area of the field.

Assessing progression

Perimetry is even more important in glaucoma follow-up than in diagnosis. [I,D] In follow-up it is important to know whether a visual field of an eye is deteriorating and also the rate of progression. [I,D] As a rule apparent progression needs to be present in two or more tests before clinical action should be taken, depending on the magnitude of apparent progression. [I,D]

Both Humphrey and Octopus (EyeSuite software) provide overview graphs displaying full series of chronologically ordered fields. These printouts help clinicians to quickly get a subjectively based hint about the disease progression. [II,D]

Computer-assisted progression
can be divided into two groups:
1.   Event based analyses are designed to answer the question of *whether* the field has progressed, and
2.   trend based analyses are primarily designed to *determine the rate of progression*.

Event based analyses

Glaucoma Change Probability Maps

Event based analyses have been used in all the large randomised controlled glaucoma trials, e.g. EMGT, AGIS and CIGTS[10,11,12] The EMGT analysis is based on commercially available Glaucoma Change Probability Maps (GCPMs) that have been incorporated in the Humphrey perimeters since the early 1990ies. With GCPMs all visual field tests are compared to baseline consisting of an average of two baseline tests. The default baseline consists of two initial tests of an eye, but the baseline can be selected by the operator. Random test-retest variability in glaucomatous field depend on field status, test point sensitivity and eccentricity.[13] This has been modelled in to GCPMs and test point locations that have deteriorated more than random variation are flagged.

The rules used in EMGT are part of Humphrey's glaucoma progression analyses program (GPA). Briefly eyes that show deterioration of at least three test point locations are flagged as *possibly progressing* if the finding is repeated in two consecutive tests and *likely progressing* if existing in three consecutive tests.

The Progressor program

The Progressor program is available from an independent manufacturer and can also be used to determine if an eye is progressing. Progressor provides a linear regression analysis of threshold values from each test point location. Significance of changes is shown through colour coding. It is important that a decision on progression is not made on the basis on only one progressing point. Instead three significantly progressing points are recommended, otherwise specificity becomes unacceptably low.[14]

Number of tests

Both Glaucoma Change Probability Maps and Progressor analyses require access to at least five and preferably more tests to detect progression. The theoretical minimum to display likely progression with glaucoma change probability maps is five tests, and in general linear regression analyses require even more tests than GCPMs.[15] This demonstrates the need for relatively frequent perimetry in those eyes where it is considered necessary to find early progression.

Rule-based analyses

There are also a multitude of rules to identify progression based on changes of threshold values expressed in dB. Such rules may differ between identification of new defects, deepening of or expansion of pre-existing defects.[16] The rules are quite arbitrary and work-intensive, why computer assisted analysis should nowadays be preferred.

Global trend analyses

Most glaucomatous eyes will progress if followed long enough with reasonably sensitive diagnostic tools, like conventional SAP. Loss of measurable quality of life occurs when approximately half the binocular field has disappeared.

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Plotting the MD value of an eye and the observed progression rate in an age/visual function diagram can show if the observed rate of progression is likely to lead to loss of quality of life during the patient's life-time (Fig. 1- Intro). Both the Octopus and the Humphrey systems provide graphs of patient MD over time. This type of analysis quickly summarises the disease trend for patients who have been followed for a couple of years provided that a reasonable number of fields have been obtained.

The new GPAII analyses for the Humphrey perimeter provides a similar graph with a new index called VFI, which is rather resistant to media opacities and to cataract and cataract surgery.

The Octopus perimeter also provides graphs of trend analysis and slopes for DD and ARA.

Calculation of AGIS and CIGTS scores used for progression analyses in the AGIS and CIGTS studies is very work-intensive requiring determination of clustering of points, depressions from age corrected normal values or significance levels and are therefore not useful in full clinical practice. [I,D].

Recommended number of field tests
Determining the rate of progression of an individual eye requires a long enough time span (at least two years) and enough field tests. [II,D] A recent publication contains analyses the required number of fields per year to detect different progression rates.[6]

It is recommended that all newly diagnosed glaucoma patients should be tested with SAP three times per year during the first two years after diagnosis. [II,D] In this way rate of progression can be determined early, and rapidly progressing eyes be revealed with great certainty.

1.4.3 - GLAUCOMA STAGING

When discussing disease stages in glaucoma, the status of the visual field is often used as the most important reference. A recent staging system is that suggested by Mills et al.[17] It is a modification of the earlier Bascom Palmer staging system.[16] The Brusini staging system uses a combination of MD and PSD.[18] Staging system may be of great interest in scientific studies, cost studies et cetera, but they are of limited value in clinical management. Clearly glaucoma management must be able to detect and quantify disease progression in small steps than from one stage to the next. [I,A]

THE HODAPP CLASSIFICATION[16]

EARLY GLAUCOMATOUS LOSS
a) MD < - 6 dB
b) Fewer than 18 points depressed below the 5% probability level and fewer than 10 points below the p < 1% level
c) No point in the central 5 degrees with a sensitivity of less than 15 dB

MODERATE GLAUCOMATOUS LOSS
a) MD < -12 dB
b) Fewer than 37 points depressed below the 5% probability level and fewer than 20 points below the p < 1% level
c) No absolute deficit (0 dB) in the 5 central degrees
d) Only one hemifield with sensitivity of < 15 dB in the 5 central degrees

ADVANCED GLAUCOMATOUS LOSS
a) MD > -12 dB
b) More than 37 points depressed below the 5% probability level or more than 20 points below the p < 1% level
c) Absolute deficit (0 dB) in the 5 central degrees
d) Sensitivity < 15 dB in the 5 central degrees in both hemifields

Tools for diagnosis:

Humphrey users:
- Glaucoma Hemifield Test
- Pattern Deviation Probability Map

Octopus users:
- The Bebié curve
- Corrected Probability Map

Tools for progression:
In clinical practice trend analyses of global indices are more important than event analysis,but some type of event analysis are able to indicate location of progression

Humphrey users:
- VFI over time
- Mean Deviation over time
- Glaucoma Change Probability Maps

Octopus users:
- ARA over time
- Mean Defect over time
- Trend - Clusters

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1.5 - BLOOD FLOW

Vascular factors are probably involved in the pathogenesis of glaucoma. Recent epidemiological studies have shown an association between low systemic diastolic blood pressure and low ocular perfusion pressure and the incidence, prevalence and progression of glaucoma[1-4].

Conventionally ocular perfusion pressure is estimated as the difference between the systemic arterial blood pressure and intraocular pressure.

Several methods have been developed to measure ocular blood flow. Their value in clinical practice has not yet been determined[5-15].

At the present time the clinical role of blood flow measurements in glaucoma management is unclear. Clinical vascular risk factors should be taken into account in glaucoma management especially when the IOP is low over 24 hours with normal CCT and visual fields show severe and progressive alteration [II,D].

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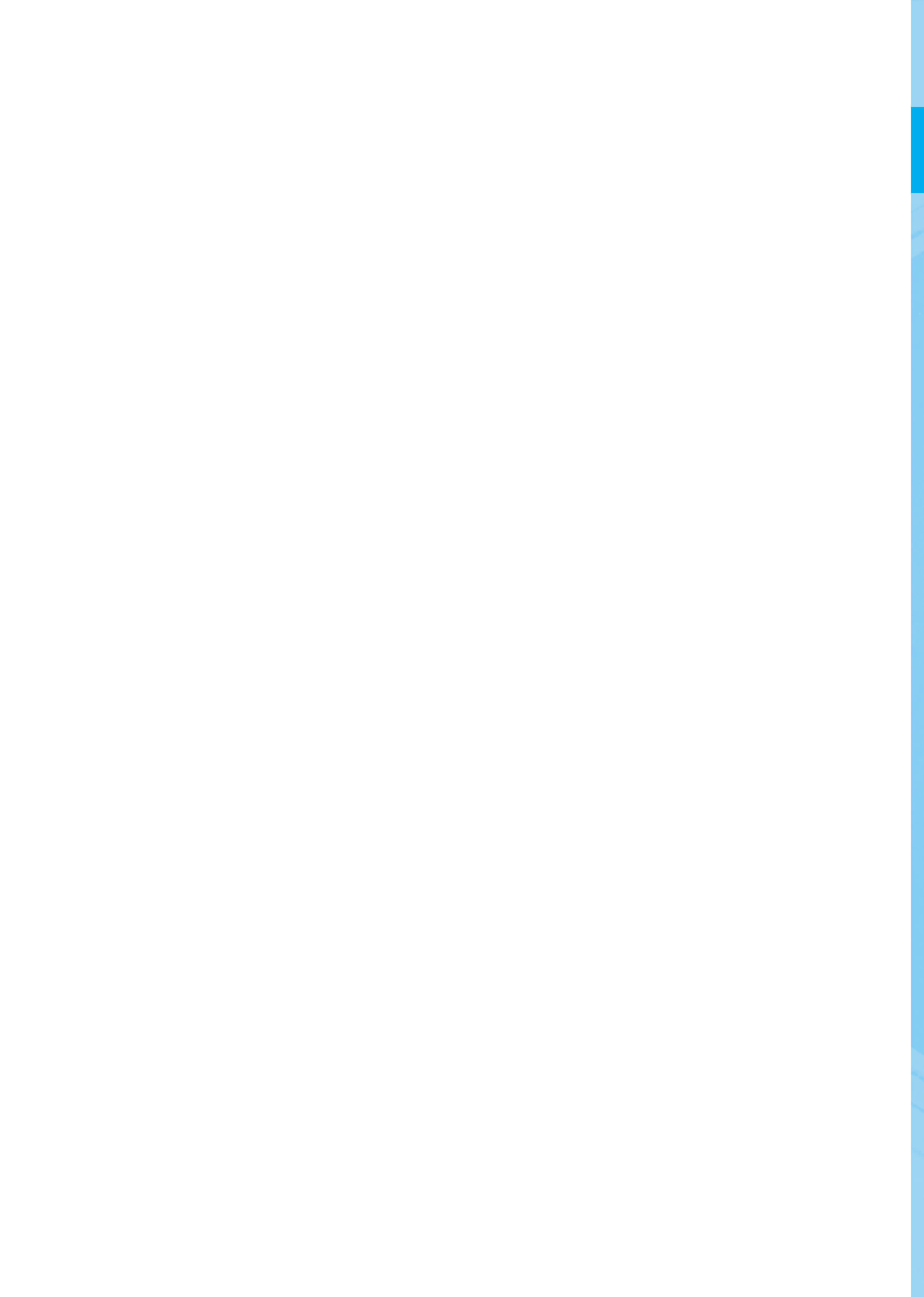
CHAPTER 2

CLASSIFICATION AND TERMINOLOGY

Classification and terminology

All forms of glaucoma should be classified into primary and secondary forms based on:
• Anterior chamber angle at gonioscopy
• Slit-lamp biomicroscopy
• Optic Nerve Head findings
• Visual field defects
Exfoliation Syndrome and Pigment dispersion are risk factors for secondary open-angle glaucomas.

2.1 - PRIMARY CONGENITAL FORMS

2.1.1 - PRIMARY CONGENITAL GLAUCOMA / CHILDHOOD GLAUCOMA

Etiology: Angle dysgenesis.
Pathomechanism: Decreased aqueous outflow
Features: Isolated trabeculodysgenesis is the most common form of primary congenital glaucoma, but overall it is a rare disease, about 1 in 10,000 births. Severe visual disability is common. Early diagnosis and appropriate therapy can make a huge difference in the visual outcome. Surgical treatment is necessary. [I,C]
Onset: from birth to 10th year of life. It is bilateral in 70% of patients.
Heredity: recessive inheritance with variable penetrance or sporadic
Gender: more common in males (65%)
Specific chromosomal abnormalities have been identified at 1p36 and 2q21
Signs and symptoms:
Photophobia, tearing, blepharospasm, eye rubbing
IOP in general anesthesia: insufficient alone to confirm the diagnosis unless extremely elevated since general anesthesia may lower the IOP
Corneal diameter > usually 12 mm in the first year of life and increased axial length (buphthalmos when the eye becomes very large)
Corneal edema (+/- ruptures of Descemet's Membrane, or Haab's striae, not to be confused with forceps delivery trauma.)
Optic nerve head: pressure distension/uniform cup enlargement (CDR >0.3)
Gonioscopy: anterior insertion of the iris, forming a scalloped line.
poorly differentiated structures
trabeculodysgenesis so called Barkan′s "membrane"
or / and anterior insertion of the iris
Cases with later manifestation usually do not have enlargement of the globe and may have a more favourable outcome with surgery.

2.1.2 - GLAUCOMA ASSOCIATED WITH CONGENITAL ANOMALIES

a.   Goniodysgenesis: a.1 - Axenfeld-Rieger syndrome
                                               a.2 - Peter's anomaly
b.   Sturge-Weber syndrome
c.   Aniridia
d.   Neurofibromatosis
e.   Marfan's syndrome
f.   Pierre's Robin syndrome
g.   Homocystinuria
h.   Lowe's syndrome
i.   Microspherophakia (weill- Mareshani)
j.   Microcornea
k.   Rubella
l.   Chromosomal abnormalities
m.   Broad thumb syndrome
n.   Persistent hyperplastic primary vitreous

2.2 - PRIMARY OPEN-ANGLE GLAUCOMAS

The open-angle glaucomas are chronic, progressive optic neuropathies, that have in common characteristic morphological changes at the optic nerve head and retinal nerve fibre layer in the absence of other ocular disease or congenital anomalies. Progressive retinal ganglion cells death and visual field loss are associated with these changes[1].

RISK FACTORS

a) - <u>For conversion to POAG</u>.
From OHT to Glaucoma. See Ch. Intro under RCTS, OHTS and EPGS.

b) - <u>For deterioration of OAG</u>.
IOP and disk haemorrhages[2, 3]
Severity of damage
Age
Perfusion pressure
History of cardiovascular disease
CCT in high pressure POAG.

c) - <u>For increased prevalence and incidence of POAG</u>[4].
1. Intra-ocular pressure (IOP); the risk of having glaucoma for those with IOP > 26 mmHg is 13 times higher than that for those with lower IOP.
2. Age; the prevalence of OAG in people over 40 years is 2.1% (95% CI 1.7 to 2.5), and ranges from 0.3% (95% CI 0.1 to 0.5) in people aged 40 years to 3.3% (95% CI 2.5 to 4.0) in people aged 70 years.
3. Race, particularly Afro-Caribbean; the relative risk of OAG for people of this ethnicity compared with white people is 3.80 (95% CI 2.56 to 5.64).
4.Positive family history of glaucoma; associated with OAG (RR 3.14, 95% CI 2.32 to 4.25). The strongest association is for siblings of an affected case.
5. Diabetes; there is almost twice the risk of OAG in people with diabetes compared with those without diabetes (relative risk 1.93, CI 1.38 to 2.69).
6. Myopia; the combined relative risk of OAG in myopes compared with those without myopia is 1.88 (95% CI 1.53 to 2.31).

2.2.1 - PRIMARY JUVENILE GLAUCOMA

<u>Etiology</u>: Unknown
<u>Pathomechanism</u>: Decreased aqueous outflow
<u>Features</u>:
    Onset: tenth to 35th year of life
    Heredity: family history may be present. Genes associated with primary juvenile glaucoma have been identified on chromosome 1 (1q21-q31) and MYOC[5, 6]

    Signs and symptoms:
        Asymptomatic until field loss is advanced
        Peak IOP ≥ 21 mm Hg without treatment (diurnal tension curve)
        Optic nerve head: Diffuse rim damage typical, but any type of ONH glaucomatous neuroretinal rim loss is possible
        Nerve fiber layer: typical diffuse defects
        Visual field: glaucomatous defects present
        Gonioscopy: wide open anterior chamber angle

2.2.2 - PRIMARY OPEN-ANGLE GLAUCOMA/HIGH PRESSURE GLAUCOMA (POAG/HPG)

The relative risk for POAG rises continuously with the level of the intra-ocular pressure (IOP), and there is no evidence of a threshold IOP for the onset of the condition. It is presumed that risk factors other than IOP have a relatively greater importance if there is glaucomatous optic neuropathy at the lower (statistically 'normal') pressure levels. POAG has been arbitrarily subdivided into High Pressure and Normal-Pressure disease to reflect this, even though they may represent a spectrum of optic neuropathies variably sensitive to the IOP.

See Ch. Introduction and 2.2
Etiology: Unknown
Pathomechanism: Unknown. TIGR and Myoc mutations may be associated[2,3]
Features:
       Onset: from the 35th year of age onwards
       Signs and symptoms:
              Asymptomatic until field loss advanced
              Elevated IOP without treatment (diurnal tension curve)
              Optic nerve head: acquired characteristic glaucomatous damage and/or retinal nerve fiber layer changes (diffuse or localized defects) (See Ch. 1)
              Visual field: usually detectable glaucomatous defects corresponding to the optic disc damage may be present
              Gonioscopy: open anterior chamber angle (not occludable, no goniodysgenesis). See Ch. 1 and Ch. 2.

2.2.3 - PRIMARY OPEN-ANGLE GLAUCOMA/NORMAL–PRESSURE GLAUCOMA (POAG/NPG)

See Ch. Introduction and Ch. 2.2.3, FC II.
Etiology: Unknown
Pathomechanism: Unknown. Optineurin mutation has been found in families with NPG
Features:
       Onset: from the 35th year onwards
       Signs and symptoms:
              Normal IOP without treatment (diurnal curve or 24-hour phasing). Asymptomatic until field loss advanced
              Optic nerve head damage typical of glaucoma
              Disc haemorrhages
              Visual field defects typical of glaucoma; e.g. paracentral defects
              Gonioscopy: open anterior chamber angle (exclude intermittent angle-closure; see Ch. 2)
              No history or signs of other eye disease or steroid use.

Consider central corneal thickness if findings do not match; CCT may be thinner than average (see Ch. 1.1).

2.2.4 - PRIMARY OPEN-ANGLE GLAUCOMA SUSPECT (POAG)

See also Ch. Introduction, Ch. 2.2, FC II.
Etiology: Unknown
Pathomechanism: Unknown
Features:
              Visual field and/or optic disc and/or nerve fiber layer normal or suspicious, with at least one being suspicious

2.2.5 - OCULAR HYPERTENSION (OH)

<u>Etiology</u>: Unknown
<u>Pathomechanism</u>: Unknown
<u>Features</u>:
      Signs and symptoms:
            IOP > 21 mm Hg without treatment
            Visual field: normal
            Optic disc and retinal nerve fibre layer: normal
            Gonioscopy: open anterior chamber angle (exclude intermittent angle-closure. See Ch. 2.4.3)
            No history or signs of other eye disease or steroid use.
            Other risk factors: none

High IOP is associated with, but not proven to be causal of vein occlusion, especially in patients with high blood pressure, hypercholesterolemia or obesity.

Evaluate corneal thickness. See Ch. 1.

> Although in the past it has been used as a diagnosis and still is usually separated for research and classification purposes, the term ocular hypertension (OH) should be used just to indicate that the IOP is consistently outside two or three standard deviations from the normal mean, <u>with all other ocular findings within normal limits.</u>

> SUPPLEMENTARY INVESTIGATIONS IN GLAUCOMA [II,D]
> I - Central corneal thickness (CCT) can be useful to evaluate the IOP applanation value (see Ch. 1.1) especially in patients with OHT to predict the risk of conversion.
> II - Imaging of the visual pathways (CT or MRI scan) may be indicated if there is an atypical appearance of the optic disc, or the visual field defects are suspicious of neurological disease, or disc and visual field findings are inconsistent.
> III - Doppler ultrasound of supra-aortic vessels, particularly when disc and visual field findings are inconsistent with the IOP and there is suspicion of ocular ischemic syndrome.

2.3 - SECONDARY OPEN-ANGLE GLAUCOMAS

Elevated IOP causing progressive typical glaucomatous optic neuropathy and visual field loss, caused by ophthalmological or extraocular disease(s), drugs and treatments. Assessment of the glaucomatous damage to visual function, including visual field staging as well as risk estimation may be difficult because of the underlying ophthalmological diseases or complex clinical picture.

The following classification is primarily based on pathophysiologic mechanisms. Distinct clinical glaucoma types are discussed at the corresponding point of the mechanistic classification.

When no etiology and pathomechanism are evident, a primary glaucoma should be considered when the diagnosis is set.

In secondary open-angle glaucomas the anterior chamber-angle is open for at least 270°.

In several forms of secondary glaucoma pathomechanisms leading to both secondary open-angle and angle-closure glaucoma are combined. Since the number of the combinations is very high, in each case individual evaluation is necessary.

2.3.1 - SECONDARY OPEN-ANGLE GLAUCOMAS CAUSED BY OCULAR DISEASE

2.3.1.1 - Exfoliative Glaucoma[7, 8]

Etiology: The background condition is exfoliation syndrome, in which an abnormal fibrillo-granular protein (exfoliation material) is produced in the eye and several other parts of the body. Certain variants of the LOXL1 gene are very strongly associated with exfoliation syndrome as well as exfoliative glaucoma, in which exfoliation material and pigment granules accumulate in the trabecular meshwork causing decreased aqueous humour outflow and significantly elevated IOP. Exfoliative glaucoma develops in approximately 1/3rd of the eyes with exfoliation syndrome in a 10-year period. Pathomechanism: Reduction of the trabecular outflow owing to the exfoliation material.
Features:

       Onset: usually older than 60 years
       Frequency: large racial variations
       Asymptomatic until visual field loss advanced
       One or both eyes affected, often bilateral and asymmetrical
       Sign and symptoms:

              IOP: > 21 mm Hg, frequently higher than in average POAG cases
              Visual field loss as in POAG; frequently severe at least in one eye
              Slit lamp examination: dandruff-like exfoliation material on the pupil border and on the surface of the anterior lens capsule except the central zone, better visualized after pupillary dilation. The pupillary collarette is irregular and typically has a moth-eaten appearance.
              Frequently associated with nuclear cataract, pigmentary loss from the central or mid-iris, pigment granules in the angle. When pigment accumulates along an ondulating line on or anterior to Schwalbe's line, it is called Sampaolesi's line. Loose zonules are frequent with occasional phacodonesis, lens subluxation and complications at cataract surgery.
Narrow or closed-angle is relatively common.

2.3.1.2 - Pigmentary Glaucoma[9]

Etiology: Melanin granules accumulate in the trabecular meshwork, where TM function decreases.
Pathomechanism: Reduction of the trabecular outflow owing to melanin granules. Melanin granules are released from the iris as a result of rubbing between the zonules and the posterior surface of the iris. According to the theory of 'reverse pupillary block' the iris works as a valve resulting in IOP higher in the anterior chamber than in the posterior chamber, causing peripheral posterior bowing of the iris. This theory was not uniformly confirmed by clinical results.
Features:

> Onset: typically third to fifth decades
> Frequency: 1-1.5 % of the total glaucoma cases, mostly Caucasians, more in myopic males
> One or both eyes
> Sign and symptoms:
>> Uncommonly mild to moderate pain during acute episodes of IOP rise. Haloes around lights.
>> IOP: > 21 mm Hg, characteristically with large variations. Significant increase may occur after exercise, pupillary dilation or blinking. Gradual decrease of IOP with age over 60 years has been reported.
>> Slit lamp examination: deep anterior chamber, midperipheral iris pigment epithelial atrophy with radial pattern especially well visible with retroillumination. Pigment dispersed on the trabecular meshwork, Schwalbe's line, the iris surface, the lens equator and on the corneal endothelium, where often shapes itself as a central, vertical spindle (Krukenberg's spindle).

Dim light in the examination room is recommended, in order to enhance the gonioscopic observation of the peripheral iris shape. UBM examination can be helpful to confirm reverse pupillary block.

2.3.1.3 - Lens-induced Secondary Open-Angle Glaucoma

Etiology: Obstruction of the trabecular meshwork by lens proteins and/or inflammatory cells induced by lens proteins.
Pathomechanism:
- Lens proteins from a mature or hypermature cataract with intact capsule (phacolytic glaucoma)
- Lens particles from a traumatically or surgically injured lens (lens particle glaucoma)
- Granulomatous inflammation of the TM after uneventful cataract surgery when the fellow eye was already operated and its lens proteins sensitized the immune system (phacoanaphylactic glaucoma)

Features:

> Age of onset and acute or chronic course depend on the pathomechanism
> Sign and symptoms:
>> Often painful with redness and inflammation
> IOP > 21 mm Hg
> Slit lamp examination: injured lens and/or cataract or after cataract surgery, with or without iritis

2.3.1.4 - Glaucoma associated with intraocular haemorrhage

Etiology: Obstruction of the trabecular meshwork by rigid red blood cells (ghost cell glaucoma, Sickle cell disease) or by a large quantity of normal red blood cells (hyphaema).
Pathomechanism: Red blood cells (ghost cells) from an old vitreous hemorrhage, via a ruptured anterior hyaloid face, or from the iris (for example trauma, intraocular surgery) obstruct the trabecular meshwork

Features:
>Sign and symptoms:
>>Pain, redness, recurrences possible
>>IOP > 21 mm Hg

2.3.1.5 - Uveitic Glaucoma

Etiology: Several forms of anterior and intermediate uveitis can cause unilateral or bilateral obstruction of the trabecular meshwork. The most frequent conditions are juvenile rheumatoid arthritis, Fuchs' heterochromic iridocyclitis, Posner-Schlossman syndrome (glaucomatocyclitic crisis), herpes simplex, herpes zoster, syphilis, sarcoidosis, Behçet disease, sympathetic ophthalmia, pars planitis.
Pathomechanism: Obstruction and edema of the trabecular meshwork caused by inflammatory cells, precipitates, debris, secondary scarring and neovascularization of the chamber angle. Secondary angle-closure glaucoma due to synechiae can also develop.
Features:
>Onset depends on underlying condition. Any age
>Sign and symptoms:
>>Pain, redness, photophobia, decreased vision are possible.
>>IOP > 21 mm Hg. Some forms are associated with wide oscillations or periodic rise of IOP.

2.3.1.6 - Glaucoma due to intraocular tumours

Etiology: Reduced aqueous humour outflow due to primary or secondary intraocular (anterior segment) tumours
Pathomechanism: Compression or tumour extension to the trabecular meshwork and/or outflow channels. Trabecular meshwork obstruction due to tumour related inflammation, tumour necrosis, haemorrhage and pigment dispersion. (Secondary angle-closure glaucoma may also develop)
Features:
>Sign and symptoms:
>>IOP > 21 mm Hg
>>Onset and clinical picture highly variable, combining evidence for both the tumour and the glaucoma

2.3.1.7 - Glaucoma associated with retinal detachment

Etiology: Although retinal detachment is usually associated with lower than normal IOP, the same disease processes can also cause both reduced trabecular outflow and retinal detachment
Pathomechanism: Neovascularization, proliferative retinopathy, scarring, pigment dispersion and inflammation (e.g. photoreceptor sensitization), obstruction of TM with cellular debris from retinal cells' outer segments (Schwartz's syndrome). Cases in which surgery for retinal detachment causes glaucoma are discussed in part 2.5. See also Ch. 2.3.1.8
Features:
>Sign and symptoms:
>>IOP > 21 mm Hg
>>Redness, pain are possible
>>Retinal detachment is present
Note
In general, retinal detachment is associated with lower than normal IOP.
Surgery for retinal detachment repair can cause glaucoma. See also Ch. 2.3.2.2.

2.3.1.8 - Open-Angle Glaucoma due to ocular trauma

Ocular trauma leads to glaucoma by several different mechanisms. The secondary traumatic glaucomas can be caused by both open-angle and angle-closure pathomechanisms. To identify the etiology one must carefully evaluate all traumatic damage to the eye.

Etiology: Reduced trabecular outflow due to traumatic changes of the trabecular meshwork

Pathomechanism: Scarring and inflammation of the trabecular meshwork, obstruction by red blood cells and debris, lens induced glaucoma, angle recession. Positive steroid responsiveness to be also considered (see Ch. 2.3.2.1).

Features:

Highly variable

Signs and symptoms:

Redness, pain, decreased vision, or no symptoms

IOP > 21 mm Hg. Elevated intraocular pressure can be present immediately, but slow elevation occurring during months, or up to decades later are also possible.

Slit lamp examination: chemical burns, hyphema, traumatic cataract, swollen lens, uveitis, angle recession, ruptured iris sphincter.

2.3.2 - IATROGENIC SECONDARY OPEN-ANGLE GLAUCOMAS

2.3.2.1 - Glaucoma due to corticosteroid treatment

Etiology: Reduced trabecular outflow due to trabecular changes caused by corticosteroids (TIGR/MYOC protein)[5, 6, 10]

Pathomechanism: Topical, intravitreal as well as high dose and long-term systemic corticosteroid therapy induces changes in the trabecular extracellular material (glycoproteins) which leads to decreased outflow facility. Usually pressure elevation is reversible if the corticosteroid is stopped. A TIGR gene modification was demonstrated.

Features:

Individual, hereditary susceptibility can occur. Myopic, diabetic subjects and POAG patients may be more susceptible

Signs and symptoms:

No pain, no redness, corneal oedema is possible

IOP > 21 mm Hg

Typical glaucomatous optic nerve head and visual field damage if the disease is long-standing

2.3.2.2 - Secondary Open-Angle Glaucoma due to ocular surgery and laser

Ocular surgery can cause secondary open-angle glaucoma by some of the mechanisms discussed above: pigmentary loss from uveal tissue, lens material, haemorrhage, uveitis and trauma. See also ch.s 2.3.1.1 to 2.3.2.1

Etiology: Reduced trabecular outflow

Pathomechanism:

- Viscoelastic material, inflammatory debris, intra-operative application of alpha-chymotrypsin, lens particles, vitreous in the anterior chamber after cataract surgery, prostaglandin release. IOP elevation is usually transient.
- Acute onset secondary IOP elevation after Nd:YAG laser iridotomy, capsulotomy and laser trabeculoplasty. Usually transient, within the first 24 hours, most frequent in the first 4 hours after treatment.
- Emulsion of silicone oil implanted intravitreally enters the anterior chamber and is partially phagocytosed by macrophages and accumulates in the trabecular meshwork (especially in the upper quadrant).

- Uveitis -glaucoma- hyphema (UGH) syndrome. Episodic onset, associated with anterior chamber pseudophakia. IOP elevation is induced by recurrent iris root bleeding and anterior uveitis.

Features:

Sign and symptoms:

Pain, redness, corneal oedema are possible

IOP > 21 mm Hg

Visual field loss when IOP elevation is sufficient/prolonged

2.3.3 - SECONDARY OPEN-ANGLE GLAUCOMA CAUSED BY EXTRABULBAR CONDITIONS

2.3.3.1 - Glaucoma caused by increased episcleral venous pressure

Etiology: Increase of the episcleral venous pressure which causes reduced trabecular outflow and elevated intraocular pressure

Pathomechanism: Episcleral, orbital or general causes for reduced episcleral venous outflow:

* Dural shunts
* Chemical burn, radiation damage of the episcleral veins
* Endocrine orbitopathy
* Orbital (retrobulbar) tumour, pseudotumour,
* Orbital phlebitis
* Orbital or intracranial arteriovenous fistula
* Sturge-Weber syndrome
* Nevus of Ota
* Cavernous sinus thrombosis
* Jugular vein obstruction (radical neck dissections)
* Superior vena cava obstruction
* Pulmonary venous obstruction
* Idiopathic forms

Features:

Onset can be acute

Signs and symptoms:

Wide variations of clinical features

IOP > 21 mm Hg

Dilated, congested episcleral veins, chemosis, facial lymphoedema, orbital bruit

Vascular bruits in case of A/V fistulae

2.4 - PRIMARY ANGLE-CLOSURE

The acute angle-closure literature has been suffering from the lack of a uniform definition and specific diagnostic criteria. Only in recent years there has been a strong push to standardize the definitions of the various forms of angle closure disease.

Angle-closure is defined by the presence of iridotrabecular contact (ITC). Appositional or synechial closure of the anterior chamber angle is due to a number of possible mechanisms. This may result in raised IOP and may cause structural changes in the eye. Primary angle-closure (PAC) is defined as an occludable drainage angle and features indicating that trabecular obstruction by the peripheral iris has occurred. The term glaucoma is added if glaucomatous optic neuropathy is present: Primary angle-closure glaucoma (PACG). The principal argument to strictly separate primary angle-closure glaucoma from primary open-angle glaucoma is the initial therapeutic approach (i.e. iridotomy or iridectomy) and the possible late complications (synechial closure of the chamber angle) or the complications resulting when this type of glaucoma undergoes filtering surgery (uveal effusion, cilio-lenticular block = malignant glaucoma)[11, 12].

PROVOCATIVE TESTS
In general provocative tests for angle-closure provide little additional information since even when negative they may not rule out the potential for angle-closure. In addition they may be hazardous, triggering an acute angle-closure attack even while the patient is monitored. [II,D]

2.4.1 - PRIMARY ANGLE-CLOSURE (PAC)

Angle-closure is defined by the presence of iridotrabecular contact (ITC). Gonioscopy remains the standard technique for identifying ITC. Primary angle-closure (PAC) results from crowding of the anterior segment, and as such, usually occurs in eyes with smaller than average anterior segment dimensions. Pathological angle-closure is defined by the presence of ITC combined with either elevated intraocular pressure (IOP) or peripheral anterior synechiae (PAS), or both. The absence of ocular pathology which may induce the formation PAS (uveitis, iris neovascularisation, trauma and surgery) defines primary angle-closure. Additionally, angle-closure resulting from the action of forces at the level of the lens or behind the lens is usually regarded as secondary (i.e. cataract, massive vitreous haemorrhage, and silicone oil or gas retinal tamponade) as the successful management is aimed at the underlying lens or posterior segment pathology. Angle-closure may impair aqueous outflow through simple obstruction of the trabecular meshwork (TM), or by causing irreversible degeneration and damage of the TM.

Natural History of PAC
PAC becomes more likely as the separation between the iris and TM decreases[13]. The risk of iridotrabecular contact in a "narrow" angle begins to increase once the iridotrabecular angle is </= 20 degrees[14]. With angles of 20 degrees or less, signs of previous angle-closure, such as PAS or iris pigment on the trabecular meshwork, should be carefully sought as signs of previous closure. Most angle-closure occurs asymptomatically. Although symptoms of pain, redness, blurring of vision or haloes may help identify people with significant angle-closure, the sensitivity and specificity of symptoms for identifying angle-closure are very poor. The most commonly identified sign which indicates that treatment is required is ITC. An international group of experts reached a consensus that 2 quadrants or more of ITC is an indication for prophylactic treatment[15]. Clearly, in established disease (high IOP, established PAS or glaucomatous optic neuropathy) any potential for angle-closure should be considered and treated on individual merits.

Staging of Primary Angle-closure[16]

1. Primary Angle-closure Suspect (PACS)
Two or more quadrants of iridotrabecular contact (ITC), normal IOP, no PAS, no evidence of glaucomatous optic neuropathy (GON).

2. Primary Angle-closure (PAC)
Iridotrabecular contact resulting in PAS and or raised IOP. No evidence of glaucomatous optic neuropathy (GON).

3. Primary Angle-closure Glaucoma (PACG)
Iridotrabecular contact causing glaucomatous optic neuropathy (GON), PAS and raised IOP may be absent at the time of initial examination

Ocular Damage in Angle-closure
Primary angle-closure (PAC) may cause ocular tissue damage in many ways. Corneal endothelial cell loss occurs after symptomatic ("acute") angle-closure. With very high IOP's the iris may suffer ischaemic damage to musculature causing iris whirling (distortion of radially orientated fibres) and/or a dilated, unresponsive pupil. The lens epithelium may suffer focal necrosis causing "glaukomflecken". The trabecular meshwork can be damaged by the formation of PAS, or as the result of long-standing appositional closure. Optic neuropathy in angle-closure may manifest in at least 2 ways. After an "acute" symptomatic episode, the disc may become pale but flat, suggesting an anterior ischaemic optic neuropathy. Typical glaucomatous optic neuropathy manifests in with an excavated surface and a pattern of visual field loss indistinguishable from open-angle glaucoma. Angle-closure accounts for 50% of all glaucoma blindness worldwide, and is probably the most visually destructive form of glaucoma.

Outcome following treatment
In asymptomatic ("chronic") angle-closure, a high presenting pressure (> 35 mmHg), more than 6 clock hours of peripheral anterior synechiae and/or established glaucomatous optic neuropathy are signs that a case of angle-closure will not respond fully to a laser iridotomy, and that a trabeculectomy may be needed to control pressure[17]. [II,D]

Mechanisms of angle-closure
It is important to identify secondary causes of narrow or closed-angles, such as phakomorphic, uveitic and neovascular cases, as the management of these cases is initially directed at controlling the underlying disease. In isometropic eyes it is helpful to compare axial anterior chamber depths of the two eyes. Asymmetry of > 0.2 mm (3 standard deviations) is suggestive of a <u>secondary</u> pathological process. A-mode or ultrasound biomicroscopy may be helpful in measuring axial dimensions (length, AC depth and lens thickness) and defining anatomical relationships. In primary angle-closure these will be the same in each eye. Mechanisms responsible for angle-closure are described in terms of anatomical location of obstruction to aqueous flow, successively, at the pupil, the iris and ciliary body, the lens and behind the lens. This is also order of decreasing frequency of each mechanism. Two mechanisms may co-exist, especially levels I and II (i.e. pupil and iris/ciliary body). Often, one mechanism predominates.

I) Pupillary block mechanism

Pupillary block is the predominant mechanism in around 75% of cases of primary angle-closure. Pupillary block is an exaggeration of a physiological phenomenon in which the flow of aqueous from the posterior chamber through the pupil to the anterior chamber is impeded causing the pressure in the posterior chamber to become higher than the pressure in the anterior chamber. As a result, the peripheral iris bows forward and comes into contact with the trabecular meshwork and/or peripheral cornea.

In a minority of cases, this becomes a self-perpetuating cycle with obstruction of trabecular outflow leading to a rise in IOP up to 50-80 mm Hg. When total trabecular obstruction occurs rapidly (within a few hours), it causes the symptoms and signs of acute angle-closure (AAC).

The increased resistance to trans-pupillary aqueous flow is believed to result from co-activation of both sphincter and dilator muscles, causing the pupil margin to grip the anterior surface of the lens. This may occur in response to physiological stimuli, such as reading in poor light, or pharmacologically, such as with miotic therapy and concomitant dilator muscle stimulation by phenylephrine (the Mapstone provocation test). In most cases, the predisposition to pupil block is created by a narrow anterior segment and the age-related increase of lens volume (see Ch. 2.5.1 and 2.5.3).

The prevalence of PAC is higher in elderly people women and in some races (especially East Asians). There is a weaker association with hypermetropia, exfoliation syndrome, diabetes and retinitis pigmentosa.

II) Obstruction at the level of the iris and/or ciliary body ("plateau iris")

This group of anterior, non-pupil-block mechanisms are sometimes erroneously referred to under the umbrella term "plateau iris". They are the result of variations is iris and ciliary body anatomy the bring the peripheral iris into contact with the trabecular meshwork. These include a thicker iris, a more anterior iris insertion and a more anterior ciliary body position. These anatomical factors predict failure of a laser iridotomy to open an appositionally closed angle[18].

Anteriorly positioned ciliary processes cause "typical" plateau iris configuration[19]. Plateau iris "syndrome" should be differentiated from plateau iris configuration." The "configuration" refers to a situation in which the iris plane is flat and the anterior chamber is not shallow axially. In most cases, the angle-closure glaucoma associated with the plateau iris configuration is cured by a peripheral iridectomy. "Plateau iris syndrome" refers to a post-laser condition in which a patent iridotomy has removed the relative pupillary block, but gonioscopically confirmed angle closure recurs without shallowing of the anterior chamber axially. Plateau iris syndrome is rare compared to the configuration, which itself is not common. It usually occurs in a younger age group than pupillary-block angle-closure. The treatment is laser iridoplasty or the longterm use of pilocarpine postoperatively as long as it is needed. [I,D] This syndrome must be considered in the differential diagnosis when the intraocular pressure rises unexpectedly following an adequate peripheral iridectomy procedure for angle-closure glaucoma[20]. [I,D]

Ideally, treatment should be instituted before synechial closure of the angle occurs (see Ch. 4.4.1). [I,D]

III) Obstruction at the Level of the Lens

The most widely recognised risk factor for primary angle-closure is a shallow anterior chamber. The anterior surface of the lens marks the depth of the anterior chamber, and as such, PAC patients typically have a thicker, more anteriorly positioned lens than people with wide open angles. Nuclear sclerotic cataract is a frequent finding in primary angle-closure. If a separate pathological or iatrogenic process causes the lens to suddenly increase in thickness (e.g. "classic" diabetic or post-traumatic cataract), become more anteriorly positioned (retinal gas or oil tamponade) or subluxate (Marfan syndrome or trauma), this may cause secondary angle-closure (see Ch. 2.5.1 and 2.5.3.).

IV) Obstruction Posterior to the Lens (Aqueous misdirection syndrome)

In rare cases, aqueous misdirection can be the complicate the management of primar angle-closure. This may occur following trabeculectomy, lens extraction, laser iridotomy and other surgical procedures. Forward movement of the lens iris diaphragm causes secondary angle-closure resulting in IOP elevation. In these cases, typically have very small eyes (axial length < 21 mm) and higher hypermetropic refraction (> +6D). It is believed that the ciliary processes come into contact with the lens equator, and/or a firm zonule/posterior capsule diaphragm, causing misdirection of aqueous

into the vitreous[20, 21]. As a consequence, the lens/iris diaphragm is pushed forward and occludes the anterior chamber angle. After iridotomy or iridectomy, the use of miotics raises the IOP, whereas the use of cycloplegics reduces the IOP. This 'inverse' or 'paradoxical' reaction to parasympathomimetics should be tested only after iridotomy has been performed. Ultrasound biomicroscopy can demonstrate abnormal posterior chamber anatomy in these rare cases (see Ch. 2.5.3).

Asymmetry of anterior chamber depth is a cardinal sign of secondary (types III and IV) angle-closure.

Systemic drugs and angle-closure:
Systemic drugs which may induce angle-closure in pre-disposed individuals are: nebulised brochodilators (ipratropium bromide and/or salbutomol), selective serotonin re-uptake inhibitors (SSRI's), tricyclic antidepressants, proprietary cold and flu medications, muscle relaxants and other agents with a parasympatholytic and sympathomimetic action (see Ch. 1.4).

Demographic Risk factors for Primary Angle-Closure[20, 22]
• Older age
• Female
• Asian Race
• Family history if primary angle-closure

Primary angle-closure. Descriptions of subtypes:

Primary angle-closure has previously been divided into 3 clinical subtypes according to mode of presentation: *There is debate around whether this approach to classification is useful in determining the prognosis or optimal management.*

• Acute Angle-Closure (AAC)
• Intermittent Angle-Closure (IAC)
• Chronic Angle-Closure (CAC)

2.4.1.1 - Acute Angle-Closure (AAC)

Etiology: circumferential iris apposition to the trabecular meshwork with rapid and excessive increase in intraocular pressure (IOP) that does not resolve spontaneously.
Pathomechanism: see Ch. 2.4.1
Features:
     Signs:
          IOP >21 mm Hg, often to 50-80 mm Hg
          Decreased visual acuity
          Corneal edema, initially mostly epithelial edema
          Shallow or flat peripheral anterior chamber
          Peripheral iris pushed forward and in contact with Schwalbe's line.
          Gonioscopy: iridotrabecular contact 360 degrees
          Pupil mid-dilated and reduced or no reactivity
          Venous congestion and ciliary injection
          Fundus: disc edema, with venous congestion and splinter hemorrhages, or the disc may be normal or show glaucomatous escavation
          Bradycardia or arrhythmia
          Gonioscopy clues from the other eye

Symptoms:
Blurred vision
"Halos" around lights
Pain
Frontal headache of variable degree on the side of the affected eye
Nausea and vomiting, occasionally
Palpitations, abdominal cramps, occasionally

2.4.1.2 - Intermittent Angle-Closure (IAC)

<u>Etiology</u>: similar but milder clinical manifestations than AACG, it resolves spontaneously.
<u>Pathomechanism</u>: see above ch. 2.4.1
<u>Features</u>:
Signs:
May vary according to amount of iridotrabecular contact of chamber angle and mimic acute angle-closure in a mild form.
When not on miotics, pupil is round and reactive
The optic disc rim may show atrophy with an afferent pupillary defect
Symptoms:
Mild, intermittent symptoms of acute angle-closure type

2.4.1.3 - Chronic Angle-Closure (CAC)

<u>Etiology</u>: permanent synechial closure of any extent of the chamber angle as confirmed by indentation gonioscopy.
<u>Pathomechanism</u>: see Ch. 2.4.1
<u>Features</u>:
Signs:
Peripheral anterior synechiae of any degree at gonioscopy
IOP elevated to a variable degree depending on the extent of iridotrabecular contact, above 21 mm Hg
Visual acuity according to functional status (may be normal)
Damage of optic nerve head compatible with glaucoma
Visual field defects "typical" of glaucoma may be present
Superimposed intermittent or acute iridotrabecular contact possible
Symptoms:
Visual disturbances according to functional states
Usually no pain; sometimes discomfort
Transient "haloes" when intermittent closure of the total circumference causes acute IOP elevations

2.4.1.4 - Status Post Acute Angle-closure Attack

<u>Etiology</u>: previous episode of acute angle-closure attack
<u>Pathomechanism</u>: see Ch. 2.4.1
<u>Features</u>:
Signs:
Patchy iris atrophy
Iris torsion/spiralling
Posterior synechiae
Pupil either poorly reactive or non reactive
"Glaukomflecken" of the anterior lens surface
Peripheral anterior synechiae on gonioscopy
Endothelial cell count can be decreased

2.4.2 - THE "OCCLUDABLE" ANGLE; ACR (ANGLE-CLOSURE RISK)

<u>Etiology</u>: pupillary block, plateau iris or lens; each component plays different roles in different eyes
<u>Pathomechanism</u>: see Ch. 2.4.1
<u>Features</u>:
      Signs:
            iridotrabecular contact and/or PAS
            IOP elevation may be present
            Fellow eye of acute angle-closure attack
            Fellow eye of documented non-secondary angle-closure

2.5 - SECONDARY ANGLE-CLOSURE

The pathogenesis in secondary angle-closure is many fold and varies according to the underlying condition. By definition, in acute angle-closure, the chamber angle is closed by iridotrabecular contact that can be reversed, whereas in chronic secondary angle-closure, the angle-closure is irreversible due to peripheral anterior synechiae.

2.5.1 - SECONDARY ANGLE-CLOSURE WITH PUPILLARY BLOCK

Etiology: The following is a limited list of other etiology for relative or absolute pupillary block:
Swollen lens (cataract, traumatic cataract)
Anterior lens dislocation (trauma, zonular laxity; Weil-Marchesani's syndrome, Marfans's syndrome etc.)
Posterior synechiae, seclusion or occlusion of the pupil
Protruding vitreous face or intravitreal silicone oil in aphakia
Microspherophakia
Miotic-induced pupillary block (also the lens moves forward)
IOL-induced pupillary block (ACL, anteriorly dislocated PCL)[23]

Pathomechanism: Pupillary block pushes the iris forward to occlude the angle. In iritis or iridocyclitis, the development of posterior synechiae may lead to absolute pupillary block with consequent forward bowing of the iris or "iris bombé". Acute secondary angle-closure glaucoma may result.

Features:
IOP > 21 mmHg
Disc features compatible with glaucoma

2.5.2 - SECONDARY ANGLE-CLOSURE WITH ANTERIOR "PULLING" MECHANISM WITHOUT PUPILLARY BLOCK

Etiology: Neovascular glaucoma where the iridotrabecular fibrovascular membrane is induced by ocular microvascular disease
Iridocorneal Endothelial (I.C.E.) Syndrome, with progressive endothelial membrane formation and progressive iridotrabecular adhesion
Peripheral anterior synechiae, due to prolonged primary angle-closure glaucoma; this is theoretically a primary glaucoma.
Epithelial and fibrous ingrowth after anterior segment surgery or penetrating trauma
Inflammatory membrane
After argon laser trabeculoplasty (ALT), early and late peripheral anterior synechiae and endothelial membrane covering the trabecular meshwork
Aniridia
Endothelial Posterior polymorphous dystrophy

Pathomechanism: The trabecular meshwork is obstructed by iris tissue or a membrane. The iris and/or a membrane is progressively pulled forward to occlude the angle.

Features:
IOP > 21 mmHg
Disc features compatible with glaucoma

2.5.3 - SECONDARY ANGLE-CLOSURE WITH POSTERIOR 'PUSHING' MECHANISM WITHOUT PUPILLARY BLOCK

2.5.3.1 - Aqueous misdirection (ciliary block or malignant) glaucoma

Etiology: Angle-closure is caused by the ciliary body and iris rotating forward

Pathomechanism:
* The lens may be proportionally abnormally large or swollen, as in phacomorphic mechanism
* Aqueous humour accumulates in the vitreous body (posterior aqueous humour misdirection) or behind and around the crystalline lens (perilenticular misdirection) or behind the iridocapsular diaphragm or posterior chamber intraocular lens (PCL) after extracapsular cataract surgery, with or without PCL implantation (retrocapsular misdirection)
* Frequently precipitated by ocular surgery and flat anterior chamber
* Predisposition may be similar in both eyes particularly in small eyes

2.5.3.2 - Iris and ciliary body cysts , intraocular tumors

2.5.3.3 - Silicon oil or gas implanted in the vitreous cavity[24]

2.5.3.4 - Uveal effusion[25, 26] due to:

a - Inflammation as in scleritis, uveitis, HIV infection
b - Increased choroidal venous pressure as in nanophthalmos, scleral buckling, panretinal photocoagulation, central retinal vein occlusion, arterio-venous communication
c - Tumor

2.5.3.5 - Retinopathy of prematurity (stage V)

Features:
Signs and Symptoms:
      Variable discomfort, pain, redness, corneal edema
      IOP ≥ 21 mm Hg
      Axially shallow anterior chamber

2.5.3.6 - Congenital anomalies that can be associated with secondary glaucoma

Etiology: Familial iris hypoplasia, anomalous superficial iris vessels, aniridia, Sturge - Weber syndrome, neurofibromatosis, Marfan's syndrome, Pierre Robin syndrome, homocystinuria, goniodysgenesis, Lowe's syndrome, microcornea, microspherophakia, rubella, broad thumb syndrome, persistent hyperplastic primary vitreous

Pathomechanism: Angle-closure is caused by pushing forward the ciliary body and iris. Increase of volume of the posterior segment of the eye

<u>Features</u>:

Signs and Symptoms:

        IOP > 21 mm Hg

        Pain, redness, corneal edema

        Axially shallow anterior chamber

        Laser iridotomy and surgical iridectomy are not effective

Some differential diagnoses:

Acute IOP elevation with corneal edema but open-angle may result from Posner Schlossman syndrome (iridocyclitic crisis), or from endothelitis/trabeculitis (as in disciform herpetic keratitis).

Neovascular glaucoma may be associated with an open or closed-angle and may mimic some signs and the symptoms of acute angle-closure.

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TREATMENT PRINCIPLES AND OPTIONS

Treatment principles and options

3

3.1 - GENERAL PRINCIPLES OF GLAUCOMA TREATMENT

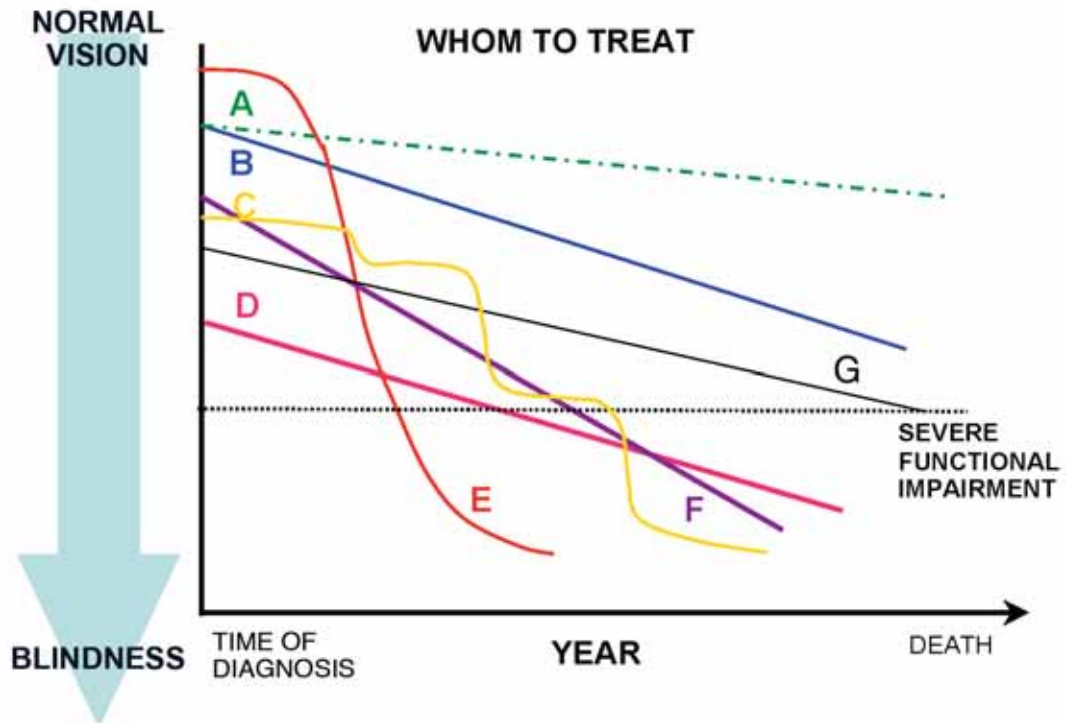• The purpose of this chapter is to give a summary overview and it is not meant to be all-inclusive

Fig. 3.1 - The "whom to treat" graph [I,D]
The rate of ganglion cell loss and consequent functional decay is different in different individuals and can vary within the same eye due to changes in time of the risk factors. To preserve the quality of life, patients must remain above the threshold of significant functional impairment. Line A represents the effect of aging alone. The patient identified by line B is worsening due to disease, but might not need treatment while those following lines C, D , F and G will be disabled within their lifetime unless successfully treated. To assess the likely Rate of Progression (RoP) is an important part of patient management.

> **The goal of glaucoma treatment is to maintain the patient's visual function and related quality of life, at a sustainable cost. The cost of treatment in terms of inconvenience and side effects as well as financial implications for the individual and society requires careful evaluation. (See Ch. INTRO III). Quality of life is closely linked with visual function. Overall patients with early to moderate glaucoma damage have good visual function and modest reduction in quality of life, but more advanced disease leads to considerable reduction of quality of life (QoL).**

Glaucoma is a leading cause of blindness in Europe[1]. Major risk factors for glaucoma blindness are the severity of the disease at presentation and life expectancy[2]. Obviously a 60 years old patient with moderate visual function damage has a greater risk of blindness than an 85-year-old patient with the same damage. Similarly a young patient with mild bilateral damage is at much larger risk of disability in his lifetime than an 80-year-old patient with unilateral disease even if there is advanced functional loss in the affected eye. Thus, treatment must be individualised to the needs and rate of progression (RoP) of each patient (Fig. 1 Ch INTRO).

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A large proportion of patients with progressive glaucoma still remain undiagnosed until too late. To discover and treat those at risk of losing functionally significant vision is a more important goal for effective glaucoma management than widespread treatment of patients with ocular hypertension.

Disease progression rates in POAG, the most common form of glaucoma in Europe, differ very much between patients, from rapid to very slow. This makes it necessary to determine the RoP in patients with manifest glaucoma.

Many patients with POAG/NTG show no or only small deterioration even after years of follow-up[3,4]. while rapid progression is common in others, e.g. in exfoliative glaucoma[4].

Worsening is common in treated glaucoma patients, even with IOP levels within the statistically normal range. Relying on tonometry alone for glaucoma follow-up is, therefore, insufficient regardless of IOP level[3,4].

> **Individualized glaucoma treatment aims at providing glaucoma management tailored to the individual needs of the patient; patients with severe functional loss or younger patients with manifest disease should have more aggressive treatment and closer follow-up than patients with little or no risk, e.g., patients with ocular hypertension (or elevated IOP) and otherwise normal findings, or elderly patients with mild field loss and low IOP levels[5-9] [I,D]. (See Fc VI)**

In most patients with advanced glaucoma and reasonable life expectancy, aggressive IOP lowering treatment might be recommended[10,11]. Very old patients with mild loss, relatively low IOP levels and other dominating health problems, might prefer being followed without treatment (see also Ch. Introduction) [II,D]. When treatment options are discussed with a patient, his/her general health status and personal preferences must also be considered and respected. It is also important to ensure that patients are able to comply and persist with therapy [I,D].

Individualized glaucoma management offers advantages for patients and it is also necessary for optimal allocation of resources.

Approximately half of patients with manifest glaucoma are undiagnosed in most Western countries[12-15]. Improved case finding, and possibly screening of high risk groups, are necessary to allow earlier diagnosis at disease stages where the patient is still non-symptomatic. Screening options for high risk groups should be evaluated.

Currently, the only approach proven to be efficient in preserving visual function is lowering the IOP[17-20]. (see Ch. Introduction II, FC VII – VIII IX) [I,A]. Other areas are under investigation, including ocular blood flow and neuroprotection.

There is theoretical evidence as well as evidence from population–based studies indicating that perfusion pressure may be relevant in glaucoma[20-26]. An increase of IOP leads to a reduction of perfusion pressure. Blood pressure itself may also be relevant to glaucoma[3,25-26]. However, there is no solid evidence supporting the treatment concept of increasing perfusion pressure by manipulating blood pressure or ocular blood flow in glaucoma patients.

> **Approximately half of patients with manifest glaucoma are undiagnosed in most Western countries[12-15].**

Neuroprotection can be defined as a "therapeutic approach" aiming to directly prevent, hinder and, in some cases, reverse neuronal cell damage. Since glaucoma patients can continue deteriorating in spite of an apparently well controlled IOP, the need for effective non-IOP related treatments is widely acknowledged. Several compounds have been positively tested as neuroprotectant in animal models of experimental glaucoma[28-32]. So far, no one reached a sufficient level of evidence in humans to be nowadays considered as a neuroprotectant.

A large long-term randomized trial using a neuroprotective agent, memantine, has been analysed in 2008 with negative results.

3.2 - TARGET IOP AND QUALITY OF LIFE

3.2.1 - TARGET INTRAOCULAR PRESSURE (TARGET IOP)

Target pressure is a useful concept in the practical management of glaucoma patients [I,D]. It can be described as the highest IOP level that is expected to prevent further glaucomatous damage or that can slow disease progression to a minimum. This level varies between patients and eyes and is strictly individual. (see Ch. Introduction, FC VI). There is no single IOP level that is safe for every patient.

Target IOP depends on[5,17,33] [I,D]:
- IOP level before treatment
  - the lower the untreated IOP levels, the lower the target IOP should be
- Stage of glaucoma
  - the greater the pre-existing glaucoma damage, the lower the target IOP should be.
- Rate of progression during follow-up
- Age and life expectancy
  - Younger age requires lower target IOP
- Presence of other risk factors, e.g., exfoliation syndrome

The least amount of medication and thus of side effects to achieve the desired therapeutic response should be a consistent goal

The target IOP should be re-assessed during follow-up and may need adjustment, e.g., if the visual field continues to worsen at a rate that may threaten Quality of Life during the patient's life-time [I,D]. Measuring rate of progression (RoP) of glaucomatous damage is, therefore, necessary to update target IOP according to the observed development of the disease. [I,D]

As an example, in a newly diagnosed patient Target Pressure will be based on risk factors for progression and current evidence. After sufficient follow up to determine the RoP, preferably 2-3 years, the importance of risk factors decreases considerably, and future target IOPs should be based on observed RoP, IOP levels under treatment, life expectancy, and current level of visual function damage[5-8] [I,D].

One of the limitations of the target IOP approach is that we only know with hindsight whether the target pressure selected initially was adequate or not. In other words a patient will get worse before we know that the target pressure was inadequate.

3.2.2 - INITIAL TREATMENT FOR OAG

Most patients with OAG are treated initially with topical medication. Laser trabeculoplasty is also an effective initial option. Surgery may be considered in some circumstances, e.g., if there is severe glaucoma, very high IOP and concerns about compliance. [I,D] (See FC VII).
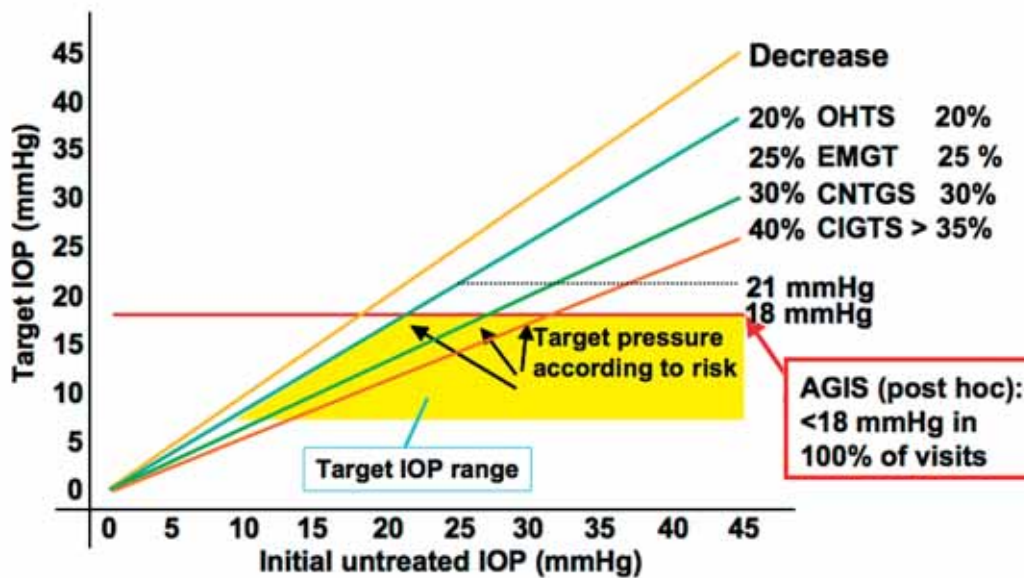
Fig. 3.2.1 - Target IOP
Diagrammatic evaluation of the desired IOP lowering. The target pressure is frequently situated within the shaded area. The percentage of IOP reduction targeted (i.e. 20%, 30%, 40% respectively) depends mainly on the degree of VF damage at diagnosis and on rate of progression (RoP).

Overall patients with early and moderate glaucoma have good visual function and modest or no reduction in quality of life, but more advanced disease leads to considerable reduction of quality of life (QoL). QoL is usually not measured in clinical care, and will change in a measurable way much too late in the course of a disease in order to be able to be used as an outcome that can direct disease management in the individual patients. It is, however, one of the most important aspects for patients. (See FC I)

Patients quality of life may be affected in several ways[34-38], alone or in combination (see FC I):
a)   Diagnosis of glaucoma.
        Being diagnosed as having a chronic and potentially blinding disease generates worries
        and anxiety in patients and their families.
b)   Functional loss due to the disease
c)   Inconvenience of the treatment
d)   Side effects of the treatment
e)   Cost of the treatment

Assessment of QoL is a subjective process based on the patients' experience. There are a number of QoL assessment tools available to help standardise this process[39].
To maintain a good QoL in glaucoma patients, we, therefore, need to focus not only on the treatment of the disease process and to prevent loss of visual function, but also on the effects of both the diagnosis and the treatment on the individuals [I,D]. The ophthalmologist should be aware of the reduction of QoL that is associated with receiving a diagnosis of glaucoma. The entity, by some called "pre-perimetric glaucoma", is difficult to diagnose without the risk of many false positives, and the loss of QoL with the diagnosis may be a reason to postpone making diagnoses of glaucoma until the disease can be established with certainty [I,D]. "Pre-perimetric glaucoma" is characterized by a normal standard white-on-white automated perimetry despite the presence of characteristic optic

disc and nerve fiber layer changes, strongly suggestive of glaucoma[41,42]. Such changes could be found when using imaging technique like OCT, HRT or GDx,

At present we do not know for certain the stage of glaucoma damage at which QoL starts to deteriorate in a clinically significant way.

There is a lack of large studies on the impact of glaucomatous visual function loss on traffic accidents and almost none on occupational performance or risks.

Falls: Visual field loss is the primary vision component that increases the risk of falls and hip fractures.
Compared with control subjects, patients with glaucoma were found over three times more likely to have fallen in the previous year[43-46].

Driving: Several follow-up studies have investigated visual field impairment. Some studies found that patients with glaucoma who have moderate or severe visual field impairment in the central 24 degrees radius field in the worse-functioning eye were at increased risk of involvement in a vehicle crash. These glaucoma patients were over three times more likely to have been involved in motor vehicle collisions and over four times more likely to have been at fault than were patients with glaucoma who had no defect[45-47].

On the contrary, another study found that some patients with glaucoma seem to have significantly higher levels of avoidance for driving at night, in fog, in rain, during rush hour and on the highway. Therefore older persons with glaucoma seems to drive at least as safely as, if not more safely than, older persons without glaucoma[48].

Patients may be asked about their own perceptions of their vision and subjective changes over time and to describe their difficulties with daily tasks (see FC).

When the disease is not likely to interfere with the QoL during the patients' lifetime, not initiating or witholding treatment is an option to be discussed with the patient. [I,D]

Laser trabeculoplasty is an effective option for initial treatment of open-angle glaucoma.

It is important when selecting the medical treatment of glaucoma to understand not only the aims of therapy, but also the mode of action, side effects and contraindications of each individual medication.

Many antiglaucoma drugs are available[49-58]. The choice of therapy must take into account not just IOP lowering, but also tolerability , cost and compliance. As a rule, medical therapy should start with one drug (cf. below). Generally, if more than two topical medications are required to control the disease, then other forms of therapy, such as laser trabeculoplasty or surgery, should be considered.

Beta-blockers have been used for many years as the first choice of therapy since they are effective, non-expensive, and usually well tolerated[50-52]. Caution must be exercised if the patient suffers from broncho-pulmonary disease or cardiac arrhythmia, since the systemic absorption of these drugs may cause relevant adverse systemic effects.

Prostaglandins/Prostamides have been approved as first line treatment for several years and are increasingly used as first choice treatment[50-52].
If the first choice medication alone is effective in lowering IOP, but not enough to reach target IOP, then adjunctive therapy can be added to the therapeutic regime.

3.3 - ANTIGLAUCOMA DRUGS

Many antiglaucoma drugs are available[49-58]. Medical therapy should as a rule start with one drug (cf. below). The choice of management strategy must take into account efficacy, safety, tolerability, quality of life, adherence and cost.

It is important when selecting the medical treatment of glaucoma to understand not only the aims of therapy, but also the mode of action, side effects and contraindications of each individual medication [I,D].
Some of the findings of the randomized controlled trials relevant to the medical treatment of glaucoma are summarized in Ch. Introduction.
Over the past few years, with the introduction of newer drugs, there has been a gradual shift in the choice of medical therapy[51, 52] (See Fc VIII).

Prostaglandins/Prostamides have been approved as first line treatment for several years. They are increasingly used as first choice treatment; the main reasons are: a) fewer installations (QD vs. BID), b) the lack of relevant systemic side effects and c) IOP lowering efficacy. However, they are costly.

If the first choice monotherapy alone is not effective on IOP or not tolerated, it is preferable to switch to any of the other topical agents that can be initiated as monotherapy, If the first choice monotherapy is well tolerated and effective, but not sufficient to reach the target IOP, or there is evidence of progression and the target IOP is being reconsidered, then adjunctive therapy in the form of any other topical agent can be initiated (see FC IX).
It is rare nowadays for patients to be maintained on oral carbonic anhydrase inhibitors, because of their adverse systemic side effects.

INITIAL TREATMENT

> **When medical treatment is changed because of uncontrolled intraocular pressure, an apparent improvement in IOP with the new or added drug may be explained at least in part by the "regression to the mean" effect**

- First choice treatment:
   A drug that a physician prefers to use as initial IOP lowering therapy.
- First line treatment:
   A drug that has been approved by an official controlling body (i.e. EMEA, CPMP or FDA) for initial IOP lowering therapy.

Therapeutical trial
Where practical, topical treatment is started in one eye first. The differential IOP will give a better idea of the effect, with less influence from diurnal variations. For some drugs, a cross-over effect to the fellow eye must be taken into account [41-50].

Treatment is considered "effective" on the IOP when the observed IOP lowering effect on the treated patient is comparable to the published average effect for the same compound on a similar population. Such an effect must be larger than tonometry errors / variations.

Many studies are available to compare the IOP lowering efficacy and the safety of topical preparations. Published studies vary considerably in population sample, methodology, criteria for definition of the outcome, statistical analysis graphics and overall quality. Exact comparisons are therefore difficult.

Most importantly, comparative studies among drugs typically use IOP as main outcome measure, rather than visual function outcomes, and have a short follow-up.

Meta-analysis comparing latanoprost and timolol showed a 5% difference in IOP lowering effect in

favour of latanoprost[59].

Three meta-analyses are available for most of the drugs used for glaucoma; however, these meta-analyses do not include combination products or adjunctive therapy [59-61].

While meta-analyses focus on IOP reduction, other aspects like patient characteristics, quality of life, side effects, convenience/compliance and cost effectiveness should be taken into consideration in making a drug therapy choice – particularly when IOP differences between the compounds are small.

Meta-analysis of randomised controlled trials on IOP-lowering effect of topical medication (modified from[59])

Generic name	% IOP difference from baseline		
		Peak	Trough
Bimatoprost	Range 31-33%	-33	-28
Travoprost		-31	-29
Latanoprost		-31	-28
Timolol		-27	-26
Brimonidine		-25	-18
Betaxolol		-23	-20
Brinzolamide		-20	-17
Dorzolamide		-20	-17

Table of IOP – lowering effect of topical iop-lowering medications as determined by meta-analysis

Drug use under everyday circumstances may differ from the situation in a clinical trial due to the selection of patients and the experimental setting.
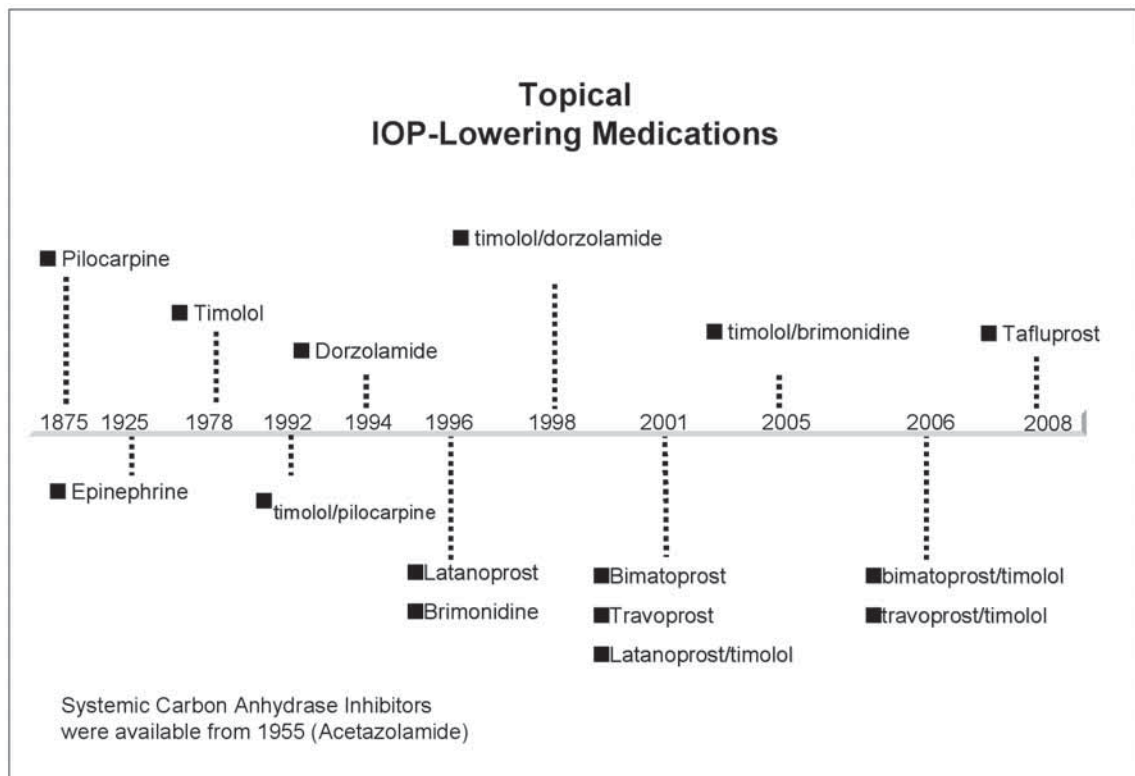

Diagram – Introduction Years of Topical IOP-Lowering Medications

Practical points for topical medical treatment [61, 62] [I,D]

- The human tear volume is approximately 7 μl with a turnover rate of approximately 1 μl per minute. The use of topical drugs in the eye doubles this rate.
- The spontaneous tear flow will cause complete washout of medication from the conjunctival sac within 5 minutes.
- The volume of an eye drop is between 30 and 50 μl. Once a drop has been instilled into the eye, only 20% manages to enter the eye, the rest will be drained through the nasolacrimal duct or will run down the chin.
- A substantial systemic absorption takes place through the highly vascularised nasal mucosa which might lead to systemic side effects. The installation of one drop of timolol 0.5% may lead to a serum concentration of timolol that equals the intake of a 10 mg tablet[63].
- To minimize drainage into the nose or throat and systemic side effects, patients should be instructed to use finger pressure exerted on the medial canthus for 1-2 minutes following installation of the eye drop, or alternatively to close their eyes for the same amount of time. The availability of the drug in the eye is increased to 35% when the lacrimal punctum is occluded following the drug installation[63-65].
- Excess solution around the eye should be removed with a tissue and any medication on the hands should be rinsed off.
- Preservatives contained within topical eye drop preparations may cause inflammatory conjunctival side effects and toxicity of the ocular surface[66,67]. The use of preservative-free preparations/delivery systems may be considered to avoid such problems; this can be relevant for certain conditions, e.g., dry eyes or eyes with other ocular surface disorders. There are preservative-free preparations of timolol, betaxolol, dorzolamide, a fixed combination of timolol-dorzolamide, and tafluprost (see below). Preservatives have been safely used for over 30 years. The most important consideration is the overall tolerability profile of the drug.

See also Ch 3.4

The pre-post IOP graph shown below is a useful tool to show the IOP changes induced by treatment and its use should be encouraged in publications.
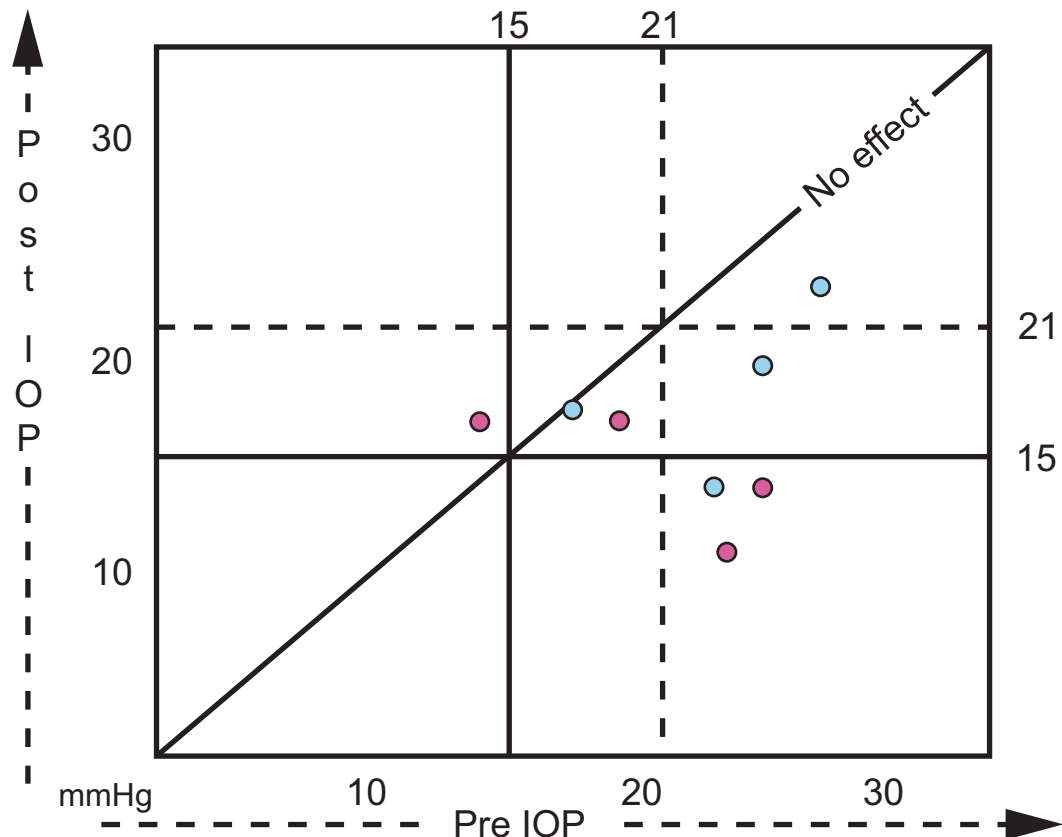

Fig. 3.3 - The Pre -Post IOP Graph
A simple graph can be used to show the IOP lowering effect. Different shapes/colours can be used to show different patient series or different observation times. Vertical and horizontal lines show respectively Pre and Post Treatment IOP levels of interest, here placed as examples at 15 and 21mmHg. Areas of desired effect under the oblique "no effect" line can thus be defined.

REMEMBER: [I,D]
*   Assess each eye individually when deciding the most appropriate therapy.
*   It is essential to involve patients as informed partners in decisions regarding the management of their condition.
*   The least amount of medication (and consequent inconvenience, costs and side effects) to achieve the therapeutic response should be a consistent goal.
*   A therapeutic medical trial on one eye first is useful to determine the IOP lowering efficacy, although not always logistically feasible or advisable (e.g., very high IOP or advanced disease).
*   Usually there is no need to start treatment until all baseline diagnostic data are collected (unless the IOP is very high and there is severe damage).
*   After diagnosis it is advisable to measure untreated IOP more than once before initiating IOP-lowering treatment

The following pages outline the most frequently used anti-glaucoma medications, and emphasize their mode of action, dosage and side effects. The text should be considered as a general guide, and cannot be all-inclusive.

It is important when selecting medical treatment of glaucoma to understand not only the aims of therapy, but also the mode of action, side effects and contraindications of each individual medication.

The choice of therapy must take into account efficacy, tolerability and safety, quality of life, adherence and cost[I,D] .

These guidelines do not contain all drugs, nor all their indications, contraindications and side effects but only the most common ones. Before starting each treatment please carefully read the product information sheet [I,D].

For each drug category: Action, Dosage and Administration, Indications, Major contraindications, Major side effects, Pregnancy and nursing mothers precautions, Drug interaction, Wash-out are summarized.

When more than one drug is referred to under any heading, the drugs are listed in alphabetical order.

MAIN FEATURES OF SIX FAMILIES OF ANTIGLAUCOMA AGENTS

	ß Blockers	Alpha-2 selective adrenergic agonists (Brimonidine)	Prostaglandin derivatives Prostamides	Topical CAIs	Pilocarpine	Dipivefrin Epinephrine
Local effects:						
IOP reduction	20–25%	20–25%	25–33%	15–20%	20-25%	15-20%
Instillation frequency	1-2 times daily	2-3 times daily	Once daily (*)	2–3 times daily	3-4 times daily	2–3 times daily
Topical tolerability	+++	++	++ to +++	+to+++	++to+++	+++
Topical allergies	+/-	++++	+/-	+/-	+/-	++
Preservative free	Yes	No	+/- (**)	Yes	Yes	No
Conjunctival hyperaemia	+/-	+ to ++	+ to ++	-	-	-
Hypertrichosis/skin pigmentation	-	-	+ to +++	+/-	+/-	++ to +++
Iris darkening	+/-	-	+ to +++ permanent	-	-	-
Uveitis	-	-	+ to +++	-	-	-
CME	-	-	+ to +++	-	-	-
Corneal oedema	-	-	+/-	+/-	-	-
Recurrence HSV keratitis	-/+	-	-/+	-	-	-/+
Miosis, browache	-	-	+/-	+/-	+++	-
Systemic effects:						
Bradyarrhythmias/ Hypotension	+	-	-	-	-	-
Tachycardia/hypertension	-	-	-	-	-	+
Bronchoconstriction	+++	-	-	-	++	-
Elevated serum lipids	+++	-	-	-	-	-
Increased falls in the elderly	++	-	-	-	-	-
Apnoea in infants	-	++	-	-	-	-
Drowsiness/anergy/fatigue	++	+++	-	-	-	-
Dry mouth	+/-	+ to +++	-	-	-	-
Cost	+	++	+++	++	+	+

CAIs = carbonic anhydrase inhibitors. CME: Cystoid macular edema

(*)   Unoprostone: 2 times daily, 20% IOP reduction
(**)   Tafluprost (preservative free prostaglandin) available from summer 2008 onwards depending on the country.
        Where figures are not used, the scale 0 (minimum) to ++++ (maximun) is used

3.3.1.1 - Category: ADRENERGIC AGONISTS[53,54]

	Generics	Tradenames
Non-selective:	Dipivefrin 0.1%	Propine, Epinal, d-Epifrin, Glaucothil
	Epinephrine 0.25-2.0%	Epinephrine
Alpha-2 selective:	Apraclonidine 0.5-1.0%	Iopidine
	Brimonidine 0.2%	Alphagan
	Clonidine 0.125 -0.5%	Isoglaucon, Catapres, Glaucopres Aruclonin, Clonidophthal

Mode of Action

Non-selective: Decreases aqueous humor production
Increases aqueous humor outflow

Alpha-2 selective: Apraclonidine
Decreases aqueous humor production
Maximum effect: 4-5 hours
Duration of effect: 12 hours
Reduces IOP 25-39% as monotherapy
Is additive to timolol
Additivity to maximum medical therapy

Brimonidine
Decreases aqueous humor production
Increases uveoscleral outflow
Duration of effect: 12h
Reduces IOP up to 27% as monotherapy
Selectivity for <2 vs <1 adrenoceptors is 1000/1. This selectivity results in no mydriasis and the absence of vasoconstriction.

Clonidine
Decreases aqueous humor production
Duration of effect: 6-12 hours
Little effect on pupillary diameter or accommodation

Dosage and administration

Non-selective:	Dipivefrin 0.1%	2 times daily
	Epinephrine 0.25-2.0%	3 times daily
Alpha-2 selective:	Apraclonidine 0.5-1.0%	2-3 times daily
	Brimonidine 0.2%	2 times daily
	Clonidine 0,125-0,5%	3 times daily

Indications [I,D]

Non-selective:	Dipivefrin 0.1%:	2 times daily Elevation of intraocular pressure in patients where the IOP can be deleterious for the preservation of visual function.
	Epinephrine 0.25-2.0%:	3 times daily The same

Alpha-2 selective:	Apraclonidine 0.5%:	For temporary chronic dosing as adjunctive treatment on maximally tolerated medical therapy where additional IOP lowering is required (increased risk of allergy with time). The addition of apraclonidine to patients already using two aqueous suppressing drugs (i.e. beta-blocker plus carbonic anhydrase inhibitor) may not provide additional IOP lowering effect.
	Apraclonidine 1.0%	To control or prevent severe elevations in IOP following anterior segment laser procedures.
	Brimonidine 0.2%	Elevation of intraocular pressure in patients where the IOP can be deleterious for the preservation of visual function. Useful as adjunctive treatment or as monotherapy.
	Clonidine 0,125-0,5%	Elevations of intraocular pressure in patients where the IOP can be deleterious for the preservation of visual function.

Major contraindications [I,D]

| Non-selective: | Occludable angles (iridotomy needed) |
| | Aphakic patients (macular edema) |

| Alpha-2 selective: | Oral monoamine oxidase (MAO) inhibitor users |
| | Pediatric age |

Most frequent side effects

| Non-selective: | Follicular conjuctivitis, tachycardia, arrhythmias and arterial hypertension |

Alpha-2 selective:	Dry mouth
	Lid elevation
	Pupil dilation for apraclonidine
	No effect on the pupil for brimonidine
	Allergy or delayed hypersensitivity after months of usage (brimonidine up to 15%, apraclonidine up to 36%)
	Periocular contact dermatitis.
	Decrease in systolic blood pressure (clonidine)
	Fatigue, sleepiness (brimonidine), especially in children.

Pregnancy and nursing mothers [I,D]

Only to be used if the potential benefit justifies the potential risk to the fetus or the infant.

Drug interactions
Possibility of additive or potentiating effect with CNS depressants. Caution is advised in the patients taking tricyclic antidepressant [I,D].

Apraclonidine and brimonidine should not be used in small children and patients receiving MAO *inhibitors.*

Wash-out time
1-3 weeks

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3.3.1.2 - Category: ADRENERGIC ANTAGONISTS[53,54]

β-Blockers

	Generics	Tradenames
Beta-1 selective:	Betaxolol 0.5% - 0,25%	Betoptic, Betoptic S, Betoptima
Non-selective:	Befunolol 0.5%	Betaclar
	Levobunolol 0.25, 0.5%	Betagan , Vistagan
	Metipranolol 0.1, 0.3%	Betaman, Beta-ophtiole, Optipranolol, Turoptin
	Timolol 0.1%, 0.25, 0.5%	Aquanil, Arutimol, Cusimolol, Nyogel, Optimol, Oftamolol, Timoptic, Timoptic-XE, Timoptol, Timoptol, Timabak, Timogel, Timolabak, Timosine XE, Timosan
With ISA*:	Carteolol 0.5-2.0%	Carteolol 0,5%,1%, 2% Carteol, Carteabak Ocupress, Teoptic, Arteoptic
	Pindolol 2%	Pindoptic

*ISA: Intrinsic Sympathomimetic Activity. The clinical relevance of ISA in glaucoma therapy has not yet been proven.

Action
Decreases intraocular pressure by reduction of the aqueous humor production. Peak effect in 2 hrs.

Dosage and administration [II,D]
Starting dose is one drop of lowest concentration of solution in the affected eye once or twice a day. If the clinical response is not adequate, the dosage may be increased to one drop of a higher concentration. Nyogel, Timolol in gelrite (Timoptic-XE, Timacar Depot, Timoptol XE, and Timosan) is given once daily.
No dose response curves for the different beta-blocker treatments have been established. The lowest concentration that would give the expected clinical effect should be used to avoid side defects. Dosing more than twice daily will not give any further pressure lowering effect.
Minimal extra effect with dipivefrine. No extra effect with adrenaline (epinephrine). Additive effect with most other IOP-lowering agents.
Preservativa-free preparations are available and may be considered.

Indications [II,D]
Elevation of intraocular pressure in patients where the IOP can be deleterious for the preservation of visual function.
Beta-1 selective adrenergic antagonist despite lowering IOP less than non selective, protect visual field as well as non selective ones.

Major Contraindications [I,D]
Non-selective: Asthma, history of obstructive pulmonary disease, sinus bradycardia (< 60 beats/min), heart block, or cardiac failure
Beta-1 selective:Relative contraindication in asthma, history of obstructive pulmonary disease, sinus bradycardia (< 60 beats/min), heart block, or cardiac failure

Most frequent side effects
Non-selective: ***Systemic***: Bradycardia, arrhythmia, heart failure, syncope, bronchospasm, and airways obstruction.
Distal edema, hypotension. Depression. Hypoglycemia may be masked in insulin dependent diabetes

mellitus. Betablocking agents have been associated with nocturnal hypotension, which may be a risk factor in progression of glaucomatous optic nerve damage[52].

Ocular (uncommon): Epithelial keratopathy, slight reduction in corneal sensitivity.
Beta-1 selective: Better tolerated in most patients sensitive to non-selective agents.

Pregnancy and nursing mothers [I,D]
Only to be used if the potential benefit justifies the potential risk to the fetus or the infant.

Drug interactions
Oral or intravenous calcium antagonists: caution should be used in the co-administration of beta-adrenergic blocking agents and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension [I,D].
Digitalis and calcium antagonists: the concomitant use of beta-adrenergic blocking agents with digitalis may have additive effects in prolonging conduction time.
Catecholamine-depleting drugs: possible additive effects and the production of hypotension and/or marked bradycardia.

Wash-out time
2-5 weeks.

3.3.1.3 - Category: CARBONIC ANHYDRASE INHIBITORS[68]

	Generics	Tradenames
Topical:	Brinzolamide 1%	Azopt
	Dorzolamide 2%	Trusopt
Systemic:	Acetazolamide	Diamox, Diamox Sequels, Diamox Retard, Ödemin.
	Dichlorphenamide	Antidrasi, Daranide, Glaumid, Oralcon
	Methazolamide	Neptazane

Mode of Action

Topical: Carbonic anhydrase inhibitor. Reduces aqueous formation resulting in lowered IOP.
Systemic: Carbonic anhydrase inhibitor. Reduces aqueous formation resulting in lowered IOP.

Dosage and administration

Topical:	Dorzolamide 2%	Monotherapy: three times daily. As adjunctive therapy with topical betablocker: two times daily
	Brinzolamide 1%	Monotherapy: two - three times daily As adjunctive therapy with topical betablocker: two times daily
Systemic:	Acetazolamide	250 mg tablets (given q.i.d.as full dose) 500 mg slow- release capsule (given b.i.d. as full dose)
	Dichlorphenamide	50 mg 1-3 times daily
	Methazolamide	50-100 mg 2-3 times daily

Indications [I,D]

Topical: Elevations of intraocular pressure in patients where the IOP can be deleterious for the preservation of visual function.

Systemic: When topical medications not effective or feasible. When long-term systemic CAI are needed, glaucoma surgery should be considered.

Major contraindications

Topical: Hypersensitivity to any component of the product

Systemic: Contraindicated in situations in which sodium and/or potassium blood levels are depressed, in cases of kidney and liver disease or dysfunction, in suprarenal gland failure, and in hyperchloremic acidosis.

Precautions

Topical: For the treatment of acute angle-closure glaucoma attack with corneal edema and inflamed conjunctiva, systemic CAI treatment is preferable.
In patients with low corneal endothelial cell count, there is increased risk of corneal edema.
Since no data on patients with severe renal impairment (CrCl < 30 mL/ml) are available, they should not be used in such patients. The concomitant use of topical and oral carbonic anhydrase inhibitors is not additive and not recommended.

These compounds are sulfonamides; the same kind of adverse reactions that are attributable to any sulphonamide may occur.

Systemic:　　Increasing the dose may increase the incidence of drowsiness and /or paresthesia. Adverse reaction common to all sulfonamide derivatives may occur ike anaphylaxis, fever rash (erythema multiforme), Stevens-Johnson syndrome, bone marrow depression, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia and agranulocytosis. Some of the above can be irreversible and lethal. If the patient is on another diuretic orally periodic monitoring of serum electrolytes is indicated.

Most frequent side effects

Topical:　　Ocular burning, stinging, bitter taste, superficial punctate keratitis, blurred vision, tearing, headache, urticaria, angioedema, pruritus, asthenia, dizziness, paresthesia and transient myopia.

Systemic:　　Paresthesias, hearing dysfunction, tinnitus, loss of appetite, taste alteration gastrointestinal disturbances such as nausea, vomiting and diarrhoea. Depression, decreased libido, gastrointestinal symptoms, kidney stones, blood dyscrasias. Metabolic acidosis and electrolyte imbalance may occur.

Adverse reaction common to all sulfonamide derivatives may occur like anaphylaxis, fever rash (erythema multiforme), Steven-Johnson syndrome, bone marrow depression, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia and agranulocytosis.

Pregnancy and nursing mothers [I,D]

Topical:　　Only to be used if the potential benefit justifies the potential risk to the fetus or the infant.

Systemic:　　Only to be used if the potential benefit justifies the potential risk to the fetus or the infant. (Teratogenic effect seen from high doses of systemic CAIs in some animal species). Women of childbearing age should be warned of possible teratogenic effect.

Drug interactions

Topical:　　Specific drug interaction studies have not yet been performed.

Systemic:　　Should be used with caution in patients on steroid and systemic hypertension diuretic therapy because of the potential for developing hypokalemia [I,D].

Wash-out time
　　　　　Topical CAI 1 week
　　　　　Systemic CAI 3 days

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3.3.1.4 - Category: PARASYMPATHOMIMETICS (CHOLINERGIC DRUGS)[69,70]

	Generics	Tradenames
Direct-acting:	Pilocarpine 0,5-4%	E-pilo, Isopto Carpine, Pilagan, Pilocar, Pilogel, Pilomann, Pilopine, Pilopine HS Gel, Pilostat, Spersacarpine, Isopto Carpine
	Aceclidine 2%	Glaucostat Glaucostate, Glaunorm
	Carbachol 0.75-3%	Isopto Carbachol, Karbakolin Isopto
	Acetylcholine 1%	Miochol
Indirect-acting:	Demecarium bromide 0.125, 0.25%	Humorsol, Tosmilen
	Ecothiophate iodide 0.03, 0.25%	Phospholine Iodide, Echodide
	Physostigmine	Eserine
Combinations:	Pilocarpine + Physostigmine	Piloeserine
	Carbachol 0.75% + Pilocarpine 2% +HCl Procaine 2%	Mios

Mode of Action
Increase in facility of outflow of aqueous humor.
Direct action on longitudinal ciliary muscle.

Dosage and administration

Direct-acting:

	Pilocarpine 1-4%	Lowers IOP after 1 hr, lasts 6-7 hrs; usually given QID or TID in solutions with hydrophilic polymers.
	Pilocarpine gel	Once daily at bedtime.
	Ocuserts 20 or 40 µg/hr	Usually once weekly
	Carbachol 0.75%, 1.5%, 2.25%, and 3%	Three times daily.
	Acetylcholine 1:100 solution	For intracameral use during surgery
	Aceclidine 2%	B.i.d. (induces less accommodative spasm, a smaller increase in lens thickness and a lower reduction of the chamber depth compared to pilocarpine).

Indirect-acting:

	Demecarium bromide 0.125 and 0.25%	Twice a day, at bedtime and in the morning.
	Ecothiophate iodide 0.03%, 0.06%, 0.125% and 0.25%	Once or twice a day, at bedtime and in the morning.

Indications [II,D]

Direct-acting: Elevation of intraocular pressure in patients where the IOP can be deleterious for the preservation of visual function.

Indirect-acting: POAG in aphakia / pseudophakia where surgery is refused or not feasible, in cases that are not controlled on other less potent agents.
These cases may respond satisfactory to ecothiophate iodide 0.03% or demecarium bromide 0.125% twice a day.

Major contraindications [I,D].

Direct-acting: Age < 40 yrs, cataract, uveitis and neovascular glaucoma. Assess possible worsening of pupillary block in each case of angle-closure glaucoma.

Indirect-acting: Active uveitis.

Precautions[I,D].

Direct-acting: Axial myopia, history of retinal detachment or rhegmatogenous retinal lesions.
Indirect-acting: Should be used with extreme caution in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy and Parkinsonism. Priory history of retinal detachment or rhegmatogenous retinal lesions.
General anesthesia with curarization.

Most frequent side effects

Direct-acting: Systemic: Intestinal cramps, branchospasm.
Ocular: Miosis, pseudomyopia (up to 8D), browache, retinal detachment, ciliary spasm, increased pupillary block.

Indirect-acting: Systemic: Cardiac irregularities, intestinal cramps.
Ocular: Stinging, burning, lacrimation, browache, pseudomyopia, retinal detachment, conjunctival thickening, increased pupillary block, iris cysts, cataract.

Pregnancy and nursing mothers [I,D].

Direct-acting: Only to be used if the potential benefit justifies the potential risk to the fetus or the infant.
Indirect-acting: Contraindicated

Drug interactions [I,D]

Direct-acting: A competitive interaction on outflow with prostaglandins is assumed, since contraction of the ciliary muscle reduces the uveoscleral space.
Indirect-acting: Patients undergoing systemic anticholinesterase treatment should be warned of the possible additive effects of the indirect-acting parasympathomimetics. General anesthesia with muscle relaxants.

Wash-out time
Direct acting: 3 days
Indirect acting: several weeks. Some are irreversible.

3.3.1.5 - Category: PROSTAGLANDIN DERIVATIVES AND PROSTAMIDES[61,72-91]

Tradename	*Lumigan®*	*Xalatan®*	*Taflotan®***	*Travatan®*	*Rescula®*
Active ingredient*	*Bimatoprost*	*Latanoprost*	*Tafluprost*	*Travoprost*	*Unoprostone*
Category	*Prostamide*	*Prostaglandin*	*Prostaglandin*	*Prostaglandin*	*Docosanoid*
Formulation	*0.03%*	*0.005%*	*0.0015%*	*0.004%*	*0.12%, 0.15%*
Preservative	*BACl*	*BAC*	*Preservative free*	*BAC*	*BAC*
Preservative%	*0.005%*	*0.02%*	*0%*	*0.015%*	*0.01%*
Dosage	*Once daily*	*Once daily*	*Once daily*	*Once daily*	*Twice daily*

*   in alphabetic order
**   approved in Denmark April 2008 and in Germany May 2008.

Mode of Action

For bimatoprost, latanoprost tafluprost and travoprost the most evident action is the increase of the uveo-scleral outflow, reducing IOP 20% - 35%.
The IOP lowering effect of unoprostone is up to 18% from baseline. Unoprostone 0.12% has been available in Japan since 1994.

Pressure lowering effect:[72-91]
Bimatoprost   7-8 mmHg (baseline 26 mmHg)
Latanoprost   6-8 mmHg (baseline 24-25 mmHg)
Tafluprost   5-8 mmHg (baseline 24-25 mmHg)
Travoprost   7-8 mmHg (baseline 25-27 mmHg)
Unoprostone   3-4 mmHg (baseline 24-25 mmHg)

Reduction of the intraocular pressure starts approximately 2-4 hours after the first administration with peak effect reached within approximately 8 to 12 hours. Maximum IOP lowering is often achieved 3 to 5 weeks from commencement of treatment

Dosage and administration

Bimatoprost 0.03%, latanoprost 0.005%, tafluprost 0.0015% or travoprost 0.004% solution: once daily, preferably in the evening.
Unoprostone 0.12% and 0.15: b.i.d. (twice daily)

Indications [II,D]

Bimatoprost 0.03%, latanoprost 0.005%, and travoprost 0.004% solutions have received European (EMEA) and FDA approval as first line drug for reducing intraocular pressure(IOP) in patients with open-angle glaucoma or ocular hypertension.

The prostaglandin analogues and prostamides appear to be effective, well-tolerated agents for the reduction of intraocular pressure (IOP) in patients with primary open-angle glaucoma and ocular hypertension. Most of the long-term data are published on latanoprost.
There are a few published clinical trials with bimatoprost, latanoprost, travoprost and unoprostone in treating angle-closure glaucoma, inflammatory and neovascular glaucoma. Most of the large clinical trials of unoprostone are on the Japanese population. There are no comparative trials comparing these agents with laser trabeculoplasty.
This drug class offers potential as first choice drugs or an alternative for patients who do not achieve control the target IOP with another topical antiglaucoma agent or for those with a contraindication to initial therapy with beta-adrenergic antagonists [II,D]. Based on meta-analysis of clinical data, bimatoprost, latanoprost, and travoprost appear to be at least as effective and even more effective on IOP as timolol, 59 while the effectiveness of unoprostone is slightly less.
Prostaglandin analogues/prostamide may be used in conjunction with other antiglaucoma medications.

Fixed combinations of prostaglandin analogues/prostamide and timolol are now available in many European countries. Administered in the evening these fixed combinations are at least as effective (non-inferior) as the components of the fixed combinations given concurrently[92-103].

Whether clinical experience will yield outcomes in favour of one of these products remains to be determined.

Patients should be educated on associated adverse events especially pigmentation of the iris and eyelashes [I,D].

Major contraindications [I,D]

Known hypersensitivity to bimatoprost / latanoprost / tafluprost / travoprost / unoprostone, benzalkonium chloride, or any other product ingredient.

Patients should not administer these drugs while wearing contact lenses, but contact lenses can be reinserted 15 minutes following administration of the drugs.

Precautions	Cystoid macular edema in aphakes/pseudophakes has been reported in few cases, most occurring in aphakic patients, in pseudophakic patients with a posterior lens capsule rupture, or in patients with known risk factors for macular edema[104,105].
	Bimatoprost, latanoprost, tafluprost, travoprost and unoprostone should be used with caution in these patients although concurrent administration of nonsteroidal anti-inflammatory agents, such as diclofenac, might decrease this side effect
	Unilateral treatment may cause a difference in iris colour and in length, thickness, pigmentation, and number of lashes between the eyes.
	Patients with uveitis[106].
Side effects	
Local:	Conjunctival hyperemia burning and stinging, foreign body sensation and itching. Hyperemia is often transient and usually mild, without associated symptoms.
	Increased pigmentation of periocular skin and eyelash changes (increased length thickness, pigmentation, and number of lashes), both reversible after cessation of medication.
	Increased iris pigmentation, especially seen in patients with green-brown, blue/gray-brown or yellowbrown irides. The long-term effects on the iris or other parts of the eye are currently unknown. This effect is to be considered permanent [107-111.] Unoprostone is less likely to change iris color.
	Cystoid macular edema in aphakes/pseudophakes has been reported in few cases, most occurring in aphakic patients, in pseudophakic patients with a posterior lens capsule rupture, or in patients with known risk factors for macular edema[104,105].
	Reactivation of herpes keratitis[107]
	Anterior uveitis[106].
Systemic:	The following events have been identified during postmarketing use of prostaglandin analogues in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.
	The events include: dyspnea, asthma and exacerbation of asthma. Prostaglandin derivatives and prostamides appears to have very few systemic side effects in comparison with β-blockers and selective α2-agonists[112].

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Pregnancy and nursing mothers [I,D]

There are no adequate and well controlled studies in pregnant women. Only to be used during pregnancy if potential benefit justifies the potential risk to the fetus.
It is not known whether the drugs or their metabolites are excreted in human milk.

Drug interactions

Precipitation occurs when thiomerosal-containing eye drops are mixed with bimatoprost, latanoprost, or travoprost. Administer such drugs at least 5 minutes apart [I,D].

Wash-out time
4-6 weeks.

There is some ongoing discussion regarding differences between prostaglandin derivatives and prostamides, which has not been settled yet in the scientific community, but recently the prostamide receptor was described[113,114]. Some patients have been shown to respond differently to these agents. The EMEA has approved the use of the term prostamide.

3.3.1.6 - Osmotics

Hyperosmotics are the most effective agents to control acutely elevated IOP [I,D]. The patients must be evaluated for heart or kidney disease because hyperosmotics increase blood volume which increases the load on the heart [I,D]. They may alter glucose blood levels and should be given to diabetics only with great caution and monitoring [I,D].
- Glycerol 1.0 - 1.5 g/Kg orally
- Mannitol 1.0 - 1.5 g/Kg intravenously

3.3.2 - COMBINED DRUGS PREPARATIONS

Monotherapy fails to achieve a satisfactory IOP reduction in 40-75% of glaucoma patients after more than two years of therapy[115,116]. If monotherapy does not appear to lower the IOP satisfactory, replacement or switching monotherapy should be attempted before adding a second drug [II,D].(See FC IX) Multiple topical treatment should be avoided if possible as compliance is likely to suffer [I,D]. laser trabeculoplasty, if not done, should also be considered in open-angle glaucoma [II,D].

However, there are cases in which one drug is inadequate to lower a patient´s IOP to a desirable target pressure and add-on therapy is then required [I,D]. Use of β-blocker preparations with either a prostaglandin/prostamide, a carbonic anhydrase inhibitor, pilocarpine or with brimonidine have been shown to be more effective at IOP lowering than the use of one of these drugs separately[118-129].

Rationale for adjunctive drug therapy
Antiglaucoma eye drops can be combined with each other, as well as added to laser and surgical treatments [I,D].
Drugs which belong to the same pharmacological group should not be used in combination (e.g. do not combine two different beta-blockers or two prostaglandin derivatives) [I,D].

-       When available, fixed-combined drugs preparations may be preferable than two separate instillations of the same agents; albeit not demonstrated so far, this might improve compliance by decreasing dosing schedule. [II,D] With fixed combinations the eyes may be exposed to a reduced daily amount of preservative.

-       In most patients is not recommended to use more than two drugs in two separate bottles or to add more than one single drug to a fixed-combination. [II,D] (see Ch. 3.4).

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-        The additional drug(s) should be used only if needed to obtain the aimed-for target IOP.

-        The effect of drug combinations is only measured in terms of IOP reduction.

-        Assuming equal IOP effects, no drug combination is yet known to be preferable in terms of ONH or VF preservation.

-        If the first choice treatment has no effect, or tachyphylaxis occurs, change the initial therapy rather than adding a further drug.

-        Increasing the recommended dosage will not result in increased IOP lowering and will only cause more side effects.

DRUG COMBINATIONS – ADDITIVE EFFECT					
CURRENT DRUG	ADDITIONAL DRUG				
	α2 agonists	β-blockers	Topical CAIs	Cholinergic	Prostaglandin/ Prostamides
α2 agonists		+	+	+	+
β-blockers	+		+	+	+
Topical CAIs	+	+		+	+
Cholinergic	+	+	+		+/-
Prostaglandin/ Prostamides	+	+	+	+/-	

ADJUNCTIVE TOPICAL THERAPY

Starting*	Add-onl*	Remarks
α2-agonists	β-blockers topical CAI prostaglandins prostamides	Good additive IOP - lowering effect
	sympathomimetics	Additional IOP lowering effect is relatively poor
β-blockers	α2-agonist	Good additive IOP - lowering effect
	topical CAIs	Good additive IOP - lowering effect Available in combined preparation
	Prostaglandins/prostamides	Good additive IOP - lowering effect Available in combined preparation
	sympathomimetics	
Topical CAIs	α2-agonists β-blockers	Good additive IOP - lowering effect Available in combined preparation
	prostaglandins prostamides sympathomimetics	Additional IOP lowering effect is relatively poor
Cholinergic	α2-agonists β-blockers	Good additive IOP - lowering effect Available in combined preparation
	topical CAIs	
Prostaglandin	α2-agonists β-blockers	Good additive IOP - lowering effect Available in combined preparation
	Topical CAI sympathomimetics	
Prostamides	α2-agonists β-blockers	Good additive IOP - lowering effect Good additive IOP - lowering effect Available in combined preparation
	Topical CAI sympathomimetics	

* these columns are listed in alphabetic order

FIXED-COMBINATION DRUG PREPARATIONS

The findings mentioned above have led to the development of fixed-combination eye drops containing two therapeutic agents in a single bottle. The fixed-combination eye drops have many advantages, particularly the potential for improved patient compliance and less side effects due to a reduced level of preservatives. [I,D]The combined preparations have also been shown to result in less ocular side effects[117-128] [II,D] .As all these fixed-combination eye drops contain a β-blocker, it is mandatory to exclude contraindications to β-blockers when prescribing these new fixed-combination drugs. To combine two bottles with fixed combinations is not advised as the amount of the active drug will be doubled with the potential of more side effects [I,D].

Drug	Combined with β-blocker	Brand name	Company
Bimatoprost 0.03%	timolol 0.5%	Ganfort	Allergan
Latanoprost 0.005%	timolol 0.5%	Xalcom, Xalacom	Pfizer
Travoprost 0.0004%	timolol 0.5%	Duotrav	Alcon
Brimonidine 0.2%	timolol 0.5%	Combigan	Allergan
Dorzolamide 2%	timolol 0.5%	Cosopt	Merck, MSD
Pilocarpine 2%	timolol 0.5%	Fotil	Santen
Pilocarpine 4%	timolol 0.5%	Fotil forte	Santen
Pilocarpine 2%	Metipranolol 0.1%	Ripix, Normoglaucon	Novartis Angelini
Pilocarpine 2%	Carteolol 2%	Carpilo	Bausch & Lomb

Application for approval of the fixed combination brinzolamide + timolol (brand name Azarga) 0.5% has been submitted by Alcon in 2008.

3.3.2.1 - Category: Adrenergic Antagonists And Parasympathomimetics

ß-Blockers & Pilocarpine

Generics	Tradenames
Metipranolol 0.1% and pilocarpine 2%	Ripix, Normoglaucon
Timolol 0.5% and pilocarpine 1% to 4%	Fotil (Timpilo not available since 2004)
Carteolol 2% and Pilocarpine	Carpilo

For mode of action, dosage and administration, indications and major controindications see single components from Ch. 3.3.1 onwards.

3.3.2.2 - Category: Adrenergic Antagonists And Topical C.A.I.[92,93]

ß-Blockers & topical CAI

Generics	Tradenames
Timolol 0.5% and dorzolamide 2%	Cosopt

For mode of action, dosage and administration, indications and major controindications see single components from Ch. 3.3.1 onwards.

3.3.2.3 - Category: Prostaglandins And Adrenergic Antagonists[97-103]

Prostaglandin & ß-Blocker

Generics	Tradenames
Bimatoprost 0.03% and Timolol 0.5%	Ganfort
Latanoprost 0.005% and Timolol 0.5%	Xalcom, Xalacom
Travoprost 0.004% and Timolol 0.5%	Duotrav

For mode of action, dosage and administration, indications and major controindications see single components from Ch. 3.3.1 onwards.

3.3.2.4 - Category: Alpha-2 Selective Adrenergic Agonists And Adrenergic Antagonists[94-96]

Brimonidine & ß-Blocker

Generics	Tradename
Brimonidine 0.2% and Timolol 0.5%	Combigan

For mode of action, dosage and administration, indications and major controindications see single components from Ch. 3.3.1 onwards.

**THE WASH-OUT TIME NEEDED FOR A TOPICALLY ADMINISTERED DRUG
TO COMPLETELY LOSE ITS EFFECT VARIES GREATLY[130-132]**

Betablockers	2-5 weeks
Sympathomimetics	2 weeks
Direct acting miotics	1-3 days
Indirect-acting miotics	1 month-permanent
Topical CAI	1 week
Oral CAI	1 week
Prostaglandins/ Prostamides	4-6 weeks

3.4 – ADHERENCE, COMPLIANCE AND PERSISTENCE IN GLAUCOMA

Since glaucoma is a chronic, progressive disease, which frequently requires topical medication and regular follow-up appointments, patients' continuous co-operation is essential for successful management.

Adherence to the prescribed regimen has two components
- Compliance: taking a medication as directed
    - correct dose, time, route
- Persistency: continuing to take a drug that has been prescribed
    - re-filling prescriptions over a period of time

To be effective, medical treatment requires adherence to the instructions: **patients fill their prescriptions (persistency) and take their medications as directed (compliance).**

In principle, medication compliance is not possible without persistency because patients must fill prescriptions before using them. Over time, patients who do not fill their prescriptions do not receive adequate treatment, making lack of persistency equivalent to withdrawal of therapy.

Compliance with glaucoma medications is considerably less than presumed by doctors and many patients fail to attend follow-up appointments. Non-compliance is likely to have an important role in the progression to blindness from glaucoma. In this context, argon laser trabeculoplasty is an attractive option for initial treatment of open-angle glaucoma as compliance is not relevant. Glaucoma patients are frequently old and may have diminished cognitive abilities, poor hearing and other ailments which, like arthritis, may reduce their ability to actually administer medication [II,D].

Drug interactions and diminished drug tolerance must be taken into consideration. [I,D] Consultation with other medical practitioners involved in the patient's care may be necessary [II,D].

Persistence and compliance issues must be taken into account when the type of treatment is selected.

Poor compliance can be summarized as follows:
1. Failure to instil eye drops (including ineffective technique of self-administration)
2. Excessive use of eye drops (extra drops may cause systemic side effects)
3. Self-administration of non-prescribed eye drops
4. Improper timing of eye drops and eye drop administration for wrong reasons (a more frequent problem if numerous drops are to be instilled and after changes in the patient's topical medication regimen)

A systematic literature review, until February 2004, found that the proportions of patients who deviate from their prescribed medication regimen ranged from 5% to 80%[133]. However, there was large incomparability of the studies and no meta-analysis was performed from 34 articles describing 29 studies in the review.

Risks for non-compliance[133]
- Men are more likely to be non-compliant than women.
- Patients with better visual acuity are at greater risk of non-compliance.
- A dose frequency of more than twice daily is associated with greater non-compliance (once-daily regimen was not compared to twice-daily regimen).

Factors not reported being associated with greater non-compliance[132]
- No relation between age and non-compliance (nine studies).
- Use of complex regimens was not associated with greater non-compliance.
- No relation was found between non-compliance and frequency of side-effects.

The impact of non-compliance on clinical outcome has not yet been established, i.e. it is not clear how much compliance would be enough to achieve clinical effectiveness and what degree of non-

compliance would be a risk factor for progression. Interventions aiming at improving compliance showed a significant but small improvement in compliance[132].

Some studies have not found a relationship between number of glaucoma medications and quality of life[134], while other studies suggest a relationship between number of glaucoma medications and an poorer compliance and quality of life[135]. Glaucoma specialists and patients may place differing values on various eye drop characteristics. When compared with glaucoma and glaucoma suspect patients, more ophthalmologists were willing to pay extra for desirable eye drop attributes[136].
Data-based measure of adherence show that a large proportion of patients stop and restart medications over time. The data confirm that adherence to treatment with glaucoma medications is poor[137]. Resupply rates have been reported to be highest for prostaglandins or the dorzolamide-timolol combination eyedrops, compared with beta-blockers, alpha-agonists or carbonic anhydrase inhibitors. Among the prostaglandins, there was no significant difference in the risk of ceasing supply between latanoprost and bimatoprost, but the risk was significantly higher for travoprost[138].
More than 2 eye drops per day was found to be a significant predictor of noncompliance[139].

How to improve Compliance and Quality of Life?
(See FC I)
1. Eye drop installation should be linked to landmarks of daily routine
2. Teach the patient how to install eyedrops correctly: intervals, lid closure, punctual occlusion
3. Written and audiovisual information can be added to verbal education
4. Communicate with the family of the patient
5. Communicate with the family physician

3.5 - LASER SURGERY

3.5.1. - LASER IRIDOTOMY[140-144]

Indications: [I,D]

Clinically relevant or suspected pupillary block.

Prevention of acute and chronic angle closure (prevention of peripheral anterior synechiae formation)

Preoperative preparation [II,D]
- Pilocarpine 2% or 4% single instillation (unfolds the iris, reduces iris thickness, facilitates perforation)
- Prevention of IOP spikes
  - Oral or intravenous acetazolamide in patients with severe glaucoma or acute angle-closure.
  - Topical alpha 2 agonist (apraclonidine 1% or brimonidine)
    One hour prior to the procedure and/or immediately afterwards, diminishes the frequency and magnitude of the acute postoperative IOP spikes and decreases bleeding due to the vasoconstrictor effect.
    > Remember to check for known drug intolerance or other systemic contraindications.
- Topical anaesthesia
- Topical glycerine, systemic acetazolamide, intravenous mannitol or oral hyperosmotic agents to be considered if the cornea is oedematous in cases of acute angle-closure closure attacks

Procedure

A laser iridotomy contact lens is needed to keep the lids open, stabilize the eye, focus the laser beam and act as a heat sink, while providing additional magnification [I,D].

Lens
- Abraham (+66 dioptres)
- Wise (+103 dioptres)
- CGI © LASAG CH

Iridotomy site [II,D]
- superior quadrants of the iris covered by the upper lid (to prevent monocular diplopia and visual symptoms)
- avoid the 3 o'clock and 9 o'clock positions to lessen discomfort and reduce the risk of hitting the iris vessels
- avoid visible vessels
- as far peripherally as possible within the arcus senilis
- choose a thin looking area or an iris crypt
- electively superonasal to reduce the likelihood of a macular injury when using the Argon laser

Laser parameters [II,D]

Nd:YAG Laser Iridotomy

Power: 1-6 mJ
Spot size: 50-70µm (constant for each laser model)
Pulses per burst: 1-3

Check that defocus is set to zero
Focus the beam within the iris stroma rather than on the surface of the iris

Lens capsule damage is possible above 2 mJ energy. Use the least amount of energy that is effective. With most Lasers it is unlikely that more than 5 mJ per pulse will be needed.
When a hole has been made it should be enlarged horizontally to obtain an adequate size (200-500 μ).

Argon Laser Iridotomy

When no Nd:YAG laser is available, the Argon laser may be used. [II,D]
There is no single group of laser parameters for all types of iris and for all surgeons
The laser parameters need to be adjusted intraoperatively

Preparatory stretch burns: [II,D]
Spot size: 200-500 μm
Exposure time: 0.2-0.6 seconds
Power: 200-600 mW

Penetration burns: [II,D]
Diameter: 50 μm
Exposure time: 0.2 seconds
Power: 800-1000 mW

For pale blue or hazel irides, the following parameters are suggested: [II,D]

First step: to obtain a gas bubble -	Diameter	50μm
	Exposure time	0.5
	Power	1500 mW
Second step: penetration through the gas bubble	Diameter	50μm
	Exposure time	0.05 seconds
	Power	1000 mW

For thick, dark brown irides: [II,D]

Chipping technique	Diameter	50 μm
	Exposure time	0.02 seconds
	Power	1500-2500 mW

The purpose of the procedure is to obtain a full thickness hole of sufficient diameter to resolve the pupillary block [I,D].
Once a hole has been made in the iris , it should be enlarged horizontally to achieve an adequate size iridotomy [I,D].
The optimal size of the iridotomy is 150 to 500 μm [II,D][143].
Perforation is assumed when pigment, mixed with aqueous, flows into the anterior chamber. The iris falls back and the peripheral anterior chamber deepens. Patency must be confirmed by direct visualization of the lens through the iridotomy. Transillumination through the pupil or the iridotomy is not a reliable indicator of success [II,D].

Complications:

Visual disturbances
        Halo, lines, crescent, ghost image, glare, spots, shadows, blurring: (these symptoms are more likely to occur in patients who have partially or fully exposed laser iridotomies than in those in whom the iridotomy is completely covered by the lid)
Temporary blurring of vision
Corneal epithelial and/or endothelial burns with Argon
Intraoperative bleeding, usually controlled by a gentle pressure applied to the eye with the contact lens
Transient elevation of the IOP
        In case of PAS the small amount of TM which is not closed is likely to have compromised outflow function (and is secondarily closed by the iris pigment and tissue generated by the PI). The result is acute (or chronic) rise in IOP . The amount of PAS should be checked before the procedure to decide the best choice of glaucoma surgery (laser or conventional surgery)

Postoperative inflammation
Posterior synechiae
Late closer of the iridotomy
Localized lens opacities - progression of existing lens opacities[144]

Rare complications include retinal damage, cystoid macular edema, sterile hypopion, malignant glaucoma

Post-operative management:

Check the IOP after 1-3 hours, and again after 24-48 hours. [II,D] With prophylactic treatment to avoid IOP spikes and in absence of glaucomatous damage, immediate post-operative IOP check may not be necessary [II,D].
Topical corticosteroids for 4-7 days [I,D]
Repeat gonioscopy (to check peripheral anterior synechiae and /or plateau iris configuration) [I,D]
Pupillary dilatation to break posterior synechiae [II,D]
Verify the patency of the peripheral iridotomy [I,D]

3.5.2 - LASER TRABECULOPLASTY[145-164]

Indications: [I,D]
a - Consider it as initial treatment for POAG, exfoliative and pigmentary glaucoma
b - POAG, exfoliative and pigmentary glaucoma when IOP is not satisfactorily controlled with a single medication
c - Overall, in POAG, exfoliative and pigmentary glaucoma when IOP is not satisfactorily controlled with medications, when the latter are contraindicated, or where compliance is a problem, such as in the elderly.

Preoperative preparation: [I,D]
- prevention of IOP spikes: topical apraclonidine 1% (or brimonidine) and/or oral acetazolamide one hour prior to the procedure and immediately afterwards
- topical anaesthesia

Procedure: [II,D]

Argon laser (Green or Blue/Green)
Diode laser
Selective laser (SLT): large spot size, high power, low energy Q-switched, frequency doubled neodymium:YAG (532 nm) system

Lens:
- Goldmann type gonioscopy lens
- Ritch trabeculoplasty lens©
- CGA © Meridian
- Latina (SLT)
- Magnaview goniolens

• Identify angle landmarks
• Laser burns placed between the anterior pigmented trabecular meshwork and the non-pigmented trabecular meshwork ie mid to anterior third of the trabecular meshwork over 180 or 360 degrees. [I,D]
If necessary, repeat 2 weeks later over the other 180 degrees if only half circumference was initially treated. [II,D]
When electing to perform two sessions of 180 degrees, make sure not to repeat the treatment in the same quadrant. [I,D]

Laser parameters: [I,D]
Argon

Diameter: 50 µm
Exposure time 0.1 seconds
Power 500-1200 mW according to the reaction on the
trabecular
meshwork
Optimal reaction transient blanching or small gas bubble formation

SLT
Diameter 400 µm (fixed)
Exposure time 3 ns (fixed)
Power 0,4 to 1, 2 mJ
Optimal reaction blanching or cavitation bubble are not desirable= start at
0,8 mJ and decrease the energy by increments of 0,1
mJ until there are no visible bubbles

Complications:
Transient decrease in visual acuity due to gonioscopy contact fluid, inflammation, significant IOP elevation
Transient iritis
Early and transient IOP elevations
hemorrhage
Visual field loss as a consequence of IOP spikes
Peripheral anterior synechiae, especially after posteriorly placed burns, or a narrow drainage angle
Late IOP rise due to loss of effect (not infrequent after longer follow-up)[34]

Post-operative management: [II,D]

- Check the IOP during the first 1-6 hours. If this is not possible, treat with oral CAIs to prevent IOP spikes in susceptible patients.
- Topical corticosteroids or non-steroidal anti-inflammatory agent TID or QID for 4-7 days.

Close monitoring is suggested in the following cases: advanced glaucomatous optic nerve damage with severe field loss, one-eyed patients, high pre-laser IOP, exfoliation syndrome, previous laser trabeculoplasty[II,D]

Effectiveness of laser trabeculoplasty

A recent systematic review on the effectiveness of laser trabeculoplasty for OAG showed that, in people with newly diagnosed OAG, the risk of uncontrolled IOP was higher in people treated with medication used before the 1990s when compared to laser trabeculoplasty at two years follow up. Trabeculoplasty was less effective than trabeculectomy in controlling IOP at six months and two years follow up[163].
In the Glaucoma Laser Trial Follow-up Study, after 7 years of follow-up, patients with ALT had lower IOP (1.2 mmHg) than patients on medical treatment, and no difference in progression of glaucoma[147-149].
There is no evidence to determine the effectiveness of laser trabeculoplasty compared to contemporary medication (prostaglandin analogues, topical anhydrase inhibitors and alpha2-agonists) and also with contemporary surgical techniques. Also there should be further investigation in to the effectiveness of laser trabeculoplasty in specific racial groups, specific diagnostic groups, such as exfoliative and pigmentary glaucoma and different stages of OAG. More research is also required determining cost-effectiveness of laser trabeculoplasty in the management of glaucoma. Laser trabeculoplasty appears to be less costly than current medical treatment[161].

Laser trabeculoplasty is intially effective in about 85% of treated eyes with a mean reduction in IOP of 6 to 9 mm Hg.

Laser trabeculoplasty seems to be more effective than trabeculectomy for African American patients with advanced glaucoma who where uncontrolled on maximum medical therapy but in white patients laser trabeculoplasty is less effective than surgery.

Argon efficacy is related to the pigmentation of the trabecular meshwork (TM): ALT is less successful in eyes with no pigmentation of the TM; SLT seems to be less dependant than ALT on TM pigmentation.

Young subjects (< 40 y.o.) did not respond well to ALT except patients with pigmentary glaucoma

Patients with exfoliation respond well to LT with a greater mean drop in IOP compared to POAG

SLT seems to be as effective as ALT in patients with open angle glaucoma.

SLT is effective in pseudophakic and phakic patients unlike ALT seems to be less effective in pseudophakic eyes

Alternative laser systems for laser trabeculoplasty:

Those found effective in reducing IOP in glaucoma include trabeculoplasty with continuous wave lasers of red and infrared wavelengths[164].

3.5.3 - LASER IRIDOPLASTY[165,166]

Indications: [II,D]

Elimination of appositional closure in the presence of a patent iridotomy without extend peripheral anterior synechiae (on indentation gonioscopy) [II,D]

Prevention of peripheral anterior synechiae formation [II,D]

To widen the angle approach by shrinking the peripheral iris using a thermal effect [II,D].

- Plateau iris syndrome after laser peripheral iridotomy [II,D]
- In preparation for ALT when the angle approach is narrow, in order to better visualize the TM [II,D]
- Angle closure in nanophthalmos [II,D]

For some authors management of acute angle closure [II,D]

Preoperative preparation [II,D]
As for ALT

Lens
Same as PI or the central non-mirrored part of Goldman lens.

Contraindications [II,D]
severe corneal edema or opacification
flat anterior chamber
synechial angle closure (ie extend peripheral anterior synechiae)

Laser parameters [II,D]

Contraction burns (long duration – low power- large spot size)
Diameter	300-500 µm
Duration	0.3-0.6 seconds
Power	200-400 mW
Location	the aiming beam should be directed at the most peripheral portion of the iris

Goal of treatment is contraction of the peripheral iris with flattening of the peripheral iris curvature.
Ideal number of impacts: 20-40 applications over 360° leaving 2 beam diameters between each spot and avoiding visible radial vessels

Complications:
mild iritis
corneal endothelial burns
transient post-operative IOP elevation
posterior synechiae of the pupil
permanent pupil dilatation

Postoperative treatment:
topical steroids for 4-7 days
prevention of IOP spikes

3.5.4 – CYCLOPHOTOCOAGULATION[167-170]

Indications: [II,D]

When filtration surgery is likely to fail, has failed, or is not feasible.
As an alternative to drainage devices.

Laser Diode cyclophotocoagulatioon with the G Probe is the cyclodestructive procedure of choice because of the reduced incidence of complications compared with other cyclodestructive procedures [I,D]

Trans scleral
• Nd:YAG (1064 nm)
Divided into contact and non-contact, as well as continuous wave and pulsed laser systems

Non-contact	the laser energy is transmitted through air from a slit lamp delivery system
Contact	transmission directly from the delivery system to the ocular surface via a fiberoptic hand-held probe placed on the conjunctiva
Pulsed	transmits energy at relatively short, predetermined time intervals
Continuous	allows longer sustained energy delivery with time intervals selected by the surgeon

Technique: [II,D] Peribulbar or retrobulbar injection of a 50:50 mixture of 2% lidocaine and 0.75% bupivicaine with hyaluronidase
Shields trans-scleral lens
Distance from limbus 1-3 mm (ciliary body should be localized with transillumination)
Applications: 8-25 over 180°, energy 1.5-10J per pulse

• Diode (810 nm)

Technique: [II,D] Peribulbar or retrobulbar injection of a 50:50 mixture of 2% lidocaine and 0.75% bupivicaine with hyaluronidase
Distance from limbus : 1, 2 mm behind the limbus perpendicular to the sclera 0.5-2.0 mm (ciliary body should be localized with transillumination)
Standard laser settings: 2 sec-2000 mW. The energy is adjusted to just avoid audible "pops"
Applications: 10-20 over 180°, energy 5-6 J per pulse, total treatment per session up to 270° of circumference (avoid 3 and 9 o`clock positions to avoid the long posterior ciliary nerves). Some surgeons prefer to use lower energy and more applications. Re-treatments are commonly needed but the incidence of severe complications is low. [II,D]

- Endoprobe

Endoscopic techniques combined with laser technology allow the photocoagulation of ciliary processes not readily visible via the transpupillary route. The approach can be limbal or via the pars plana.
- Argon laser
- Diode laser

- Transpupillary

This procedure is possible only in cases of aniridia, through a large surgical iridectomy or when broad peripheral anterior synechiae cause anterior displacement of the iris.
- Argon laser
- Diode laser

Complications

Persistent inflammation
Hyphema
Corneal decompensation
Loss of best corrected visual acuity
Chronic hypotony
Phthisis

Post operative management [II,D]

Consider analgesia. Topical steroids and topical atropine are advised for a few weeks.
The effectiveness of treatment is assessed after 4 weeks. In the immediate post-operative period the intraocular pressure should be monitored and the anti-glaucoma medication tapered accordingly.

3.6 - INCISIONAL SURGERY

GENERAL PRINCIPLES

The different techniques of incisional surgery have different indications depending on the type of glaucoma. Their adoption depends on: [I,D]
1.	the target IOP chosen for the individual situation
2.	the previous history (surgery, medications, degree of visual field loss)
3.	the risk profile (i.e. single eye, occupation)
4.	the preferences and experience of the surgeon
5.	the patient opinion, expectation and post operative complicance

The decision to recommend glaucoma surgery should be made in the light of published clinical trials[150,171]. In the individual patient, a multitude of factors must be taken into account when deciding treatment including compliance, stage of glaucoma etc. What is suitable for one patient may not be ideal for the next. Nevertheless, surgery is being used more frequently at an earlier stage, rather than as a last resort, if inadequate control is achieved by other forms of therapy or if the patient has a high IOP at presentation.

Angle closure glaucoma is usually initially approached by laser iridotomy or peripheral iridectomy. Primary congenital glaucoma is usually treated with surgery, likely trabeculotomy or goniotomy, or combinations of filtration surgery with antifibrotic agents.

For repeated surgery, cyclodestructive procedures and tube implants are more commonly used.

See FC VII

TECHNIQUES

Since glaucoma surgery is practiced in different ways by different ophthalmologists, a detailed description of surgical techniques is not within the scope of this text.

The primary goal of surgery is to achieve a sufficiently low IOP without additional medication.

For practical treatment of glaucoma, additional medications can be used if the target IOP is not reached by surgery alone. For the scientific evaluation of a surgical method however, success rates in terms of IOP lowering can be best evaluated in the absence of adjunctive medical treatment. The number of preoperative versus postoperative medications may also depend on the variable compliance of the individual patient before and after surgery. Also, it is useful to count the percentage of "successes" below a defined cut-off line for IOP as in Fig. 3.3. It is also important to consider not just the IOP but complications rates and ultimately functional outcomes which matter to the patient.

3.6.1 - PENETRATING GLAUCOMA SURGERY

3.6.1.1 - Trabeculectomy

The current operation of choice in OAG is the trabeculectomy, which produces a 'guarded' fistula between the anterior chamber and the subconjunctival space[172]. The introduction of improved operating microscopes, instruments and suture materials, has led to numerous modifications and refinements of the original operation. Modifications include the size, shape and thickness of the scleral flap, limbal or fornix based conjunctival flaps, fixed, releasable or adjustable sutures and the use of antimetabolites and other antiscarring agents delivered in different ways to reduce wound healing. In the hands of experts the success rate of filtering surgery (alone, or with adjunctive medical therapy) in a previously unoperated eye is reported up to 90% at 2 years; there are large differences however in the criteria used for the definition of success[173-188]. Long-term IOP control is achieved in many cases, although some patients do require further therapy or repeat surgery. The alternatives of trabeculectomy in OAG as primary surgery include non-penetrating surgeries and drainage devices[189-196].

INDICATIONS [II,D]

1. In cases where other forms of therapy (namely medicine or laser) have failed.
2. In cases where other forms of therapy are not suitable (eg. where compliance or side-effects are a problem) or appropriate medical treatment is not available.
3. In cases where a target pressure is required to prevent clinically significant disease progression that cannot be reached with topical medications and/or laser.
4. In cases which have such advanced glaucoma and high IOP at presentation that other forms of treatment are unlikely to be successful.

Modern glaucoma surgery is generally considered a safe and effective method of achieving good IOP control when ALT is not applicable or successful.

Some studies have indicated that in terms of field survival, primary trabeculectomy was superior to medical treatment, but these studies may not be relevant to current medical practice as the evaluation of visual field was not done with today's standards, and the medical treatment options were very limited[146]. A more recent one has had less conclusive results, with similar visual field survival between medical and surgical groups[188]. The ophthalmologist must assess the risks and benefits of early surgery in each individual case.

LONG-TERM RISKS OF TRABECULECTOMY

Accelerated progression of senile cataracts is frequently seen after filtration surgery. Patients undergoing trabeculectomy should be warned about the possible risks of infection of the drainage bleb which may lead to endophthalmitis and blindness if management is delayed. This event is much more common (up to 10 times) if blebs are interpalpebral or in the lower fornix. Lid position should be taken into account in each patient. [I,D] A long-tube drainage device should be used if the bleb cannot be positioned under the upper lid. Endophthalmitis is also more common if the bleb is thin and cystic – a situation more commonly found with the use of a small treatment area of antimetabolites or full thickness filtration procedures. Patients should be advised of the symptoms of a developing blebitis/endophthalmitis including red eye, tearing, discharge or decreased vision and should be warned to immediately seek the help of an ophthalmologist if any of these symptoms develop in the operated eye.

3.6.1.2 - Trabeculotomy

Trabeculotomy[197,198] is generally used for congenital glaucoma and is less effective in adults. [I,B] It should be performed by individuals familiar with this technique. [I,D]

Arguments in favor of non-penetrating glaucoma surgery: [II,D]
- reduced incidence of hypotony-related complications and cataract
- reduced incidence of intraoperative complications (iris prolapse, expulsive hemorrhage)

Arguments against non-penetrating glaucoma surgery: [II,D]
- Less efficient in IOP reduction (mean IOP 2-4 mmHg higher) than after trabeculectomy
- Difficult technique (learning curve)
- Nd:YAG laser gonio puncture often needed for IOP control

Arguments in favor of trabeculectomy: [II,D]
- lower long-term postoperative IOP
- fewer IOP-lowering medications needed postoperatively

Arguments against trabeculectomy: [II,D]
- possible higher rate of cataract formation
- postoperative bleb complications
- higher risk of postoperative hypotony and related complications (Choroidal detachment)

3.6.2 - NON PENETRATING GLAUCOMA SURGERY

These techniques have recently been advocated as operations for open-angle glaucoma. Two different modifications are presently used as "non-penetrating" surgery[199-217].

3.6.2.1 - Deep Sclerectomy[199-214]

In this technique, a deep lamella of corneosclera underneath the scleral flap is excised thus removing the outer wall of Schlemm's canal. The outer layer of the inner wall of Schlemm's canal is frequently also removed. Percolation of aqueous occurs through the porosity of the remaining trabecular meshwork, possibly through microperforations. When the scleral flap is repositioned, a "scleral lake" is created. A collagen implant or a hyaluronic acid device is often used to keep this scleral lake open. In a number of cases, a filtration bleb forms; long-term IOP control was reported to be less effective than with trabeculectomy[212].

3.6.2.2 - Viscocanalostomy

In this technique hyaluronic acid is injected into Schlemm's canal in addition to the dissection and excision of a deep lamella. The mechanism claimed to increase the outflow is the widening of Schlemm's canal and of the collector channels as well as diffusion of aqueous from the "scleral lake"[186, 187, 215-217]. The majority of randomised controlled trials suggests that the pressure lowering of NPS is not as marked as with trabeculectomy.

3.6.3 – METHODS OF PREVENTING FILTERING BLEB SCARRING

3.6.3.1 - Antimetabolites

Healing and scarring are the main determinant of the long term intraocular pressure control after trabeculectomy[244-255].
Antimetabolites such as 5-Fluorouracil (5-FU) and Mitomycin-C (MMC) are now used frequently in patients undergoing glaucoma filtration surgery in order to reduce scarring and improve drainage. [II,D] The use of these substances is being refined, following the outcome of several studies. Indications and technique needs to be carefully considered particularly the use of larger antimetabolite treatment areas to minimise thin cystic blebs [I,D] [218,219]. The risk of corneal epithelial erosions, epitheliopathy, late hypotony, bleb leaks and bleb infections must be considered. [I,D] New compounds are being investigated to more specifically target the biological processes causing excessive scarring, with the aim of reducing complications[220,221].

The use of these substances, especially MMC is potentially hazardous, and requires careful surgical technique to prevent overdrainage and hypotony, or a a thin focal drainage bleb with a higher risk of infection. [I,D]

Aim: - to prevent postoperative conjunctival scarring with resultant failure of filtration
         - to reach a low target pressure

Increased risk for scarring:[35,219]
         Neovascular glaucoma
         Previous failed glaucoma filtration surgery
         Previous cataract surgery (conjunctival incision)
         Aphakia (intracapsular surgery)
         Recent intraocular surgery (<3 months)
         Inflammatory eye disease e.g. uveitis, ocular pemphigoid, Stevens-Johnson Syndrome,
         Afro-Caribbean / Hispanic race
         Young age
         Chronic topical medications

Drugs used:

5-Fluorouracile
Dose: 5 mg for subconjunctival injection. 50 mg/ml the most commonly used. Administered intra- or post-operatively.

Intraoperative use[II,D]
Administrated intra operatively on a filter paper or a sponge 25 or 50 mg/ml undiluted solution Time of exposure usually 5 minutes (shorter time has minimal effect)
Rinse with at least 20ml of balanced salt solution

Post-operative use[II,D]
Relative contraindication if epithelial problems present
5 mg injections. 0.1ml of 50mg/ml undiluted solution
Small calibre needle (e.g. 30 G needle on insulin syringe)
Adjacent to but not into bleb (pH 9)
Repeated injections often necessary.

Mitomycin C:
Dose: 0,1-0,5 mg/ml. Available in different preparations; care must be taken in diluting it to the desired concentration. Administered intra - operatively, or postoperatively[165-170].

Intraoperative use[II,D]
Concentration: 0.1 – 0.5 mg/ml
Administered intraoperatively on a filter paper or a sponge for 1-5 minutes
Avoid contact with cut edge of conjunctive flap
After application rinse with approximately 20ml of balanced salt solution

Post-operative use[II,D]
Concentration: 0.02 mg/ml 0.002 mg injections.
Small calibre needle (e.g. 30 G needle on insulin syringe)
Adjacent to but not into bleb - a very small amount of MMC entering the eye will irreversibly damage the endothelium. It is useful for some needling situations but recommended only in experienced hands.

Complications:
Corneal epitheliopathy (5FU)
Wound Leak
Bleb leak
Hypotony
Blebitis
Endophthalmitis

GENERAL PRECAUTIONS

The use of cytotoxics increases the requirement for accurate surgery. If aqueous flow is not well controlled persistent hypotony will occur. Strategies to increase control of flow include smaller sclerostomies, larger and/or thicker scleral flaps, tighter suturing of the scleral flap, and releaseable or adjustable sutures. [II,D]

Recent research has suggested that a large surface area of cytotoxic treatment together with large scleral flaps and fornix based conjunctival flaps leads to more diffuse, posteriorly extended non-cystic blebs with a considerable reduction in bleb related complications such as blebitis and endophthalmitis[251,252]. [I,B]
It is advisable for a surgeon not familiar with these drugs to start with weaker agents (e.g. 5-FU rather than MMC) or lower concentrations of MMC [II,D].
Cytotoxic agents should not enter the eye. [I,D] 5-FU has a pH of 9.0. One drop (0.05ml) of MMC causes irreversible endothelial damage.

Observe precautions for use and disposal of cytotoxic substances. [I,D]

IMPORTANT: assess each individual case for risk factors, and/or for the need of low target IOP and titrate the substance and dosage used accordingly based on local experience

5-FU and MMC are not officially approved for ocular applications. Their use in selected cases as adjunctives in filtration surgery, however, has become standard clinical practice.

3.6.3.2 - Alternative methods of preventing filtering bleb scarring

Irradiation, PDT and inhibition of growth factors have been proposed. No long-term clinical study to support their use is available yet.

3.6.4 - COMPLEX CASES

Complicated glaucoma cases such as those that have failed previous surgery, secondary glaucomas, congenital glaucomas, etc. require specialist treatment.

In addition to trabeculectomy, other forms of therapy may be necessary such as drainage devices, and ciliary body ablation (see Ch. 3.5.4, 3.6.5 and FC VII)

3.6.5 - LONG-TUBE DRAINAGE DEVICES

The use of long-tube drainage devices such as those described by Molteno[222-227], Krupin[228,229], Baerveldt [230-235], Ahmed[229,236-240] or Schocket[241,242] are generally reserved for patients with risk factors for a poor result with trabeculectomy [II,D] with antimetabolite although current trials are underway to establish their efficacy and safety as a primary surgical procedure.
Factors include previous failed filtering surgery with antimetabolites, excessive conjunctival scarring due to previous ocular surgery, with severe conjunctival or surface disease, active neovascular disease, paediatric aphakia, or where filtration surgery is going to be technically difficult[222-243]. [II,D]

3.7 - CATARACT AND GLAUCOMA SURGERY

When glaucoma surgery is indicated and there is a visually significant cataract the two procedures can be performed combined or sequentially. The decision is to be made according to the clinical findings, after discussing with the patients advantages and disadvantages of each approach [I,D].
In case of angle closure or narrow angle approach, it is important to evaluate the lens as a component of the raised IOP [I,D] (see also Ch 4.4.1)
Small-incision phacoemulsification cataract extraction is one of the most relevant surgical advances for our glaucoma patients. It allows faster and better visual recovery, and with appropriate techniques it is safely applicable in cases with small pupil, shallow AC or pre-existing filtering blebs, and can be combined effectively and safely with filtration surgery[256,257]. The success rate of combined phacoemulsification and filtration surgery is not as favourable as filtration surgery alone and the use of antimetabolites is recommended in all cases[257,258]. Despite the improved results of small incision phacoemulsification and of filtration surgery with anti-metabolites there is no evidence to support a generalized switch from sequential to combined surgery [I,D].

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TREATMENT GUIDELINES

Treatment
guidelines

4.1 - PRIMARY CONGENITAL FORMS

See FC VII

4.1.1 - PRIMARY CONGENITAL GLAUCOMA /CHILDHOOD GLAUCOMA

4.1.2 - GLAUCOMA ASSOCIATED WITH CONGENITAL ANOMALIES

The management of these cases is particularly challenging.
Medical treatment is usually not effective nor practicable in long term. [I,D] Medications, including oral CAIs can be used while decision is made on a surgical approach and in case of failed surgery while awaiting for further options. [I,D]

Primary surgery: early goniotomy or trabeculotomy or filtration surgery may be indicated if these are unsuccessful. [I,B] Repeat surgery is relatively frequent.

Treatment to be adapted to the primary anomaly, the mechanism of IOP elevation and the quality of life of the patient. [I,D] These cases require highly specialized care. [I,D]

4.2 - PRIMARY OPEN-ANGLE GLAUCOMAS

See FC VII

4.2.1 - PRIMARY JUVENILE GLAUCOMA

a)   Medical therapy: any effective and well tolerated topical regimen. [I,D]
        Pilocarpine causes fluctuating myopic shift, visual symptoms and headache particularly in the young and should be avoided. [II,D]
b)   Surgery: early surgery often required
                        filtering procedure or trabeculotomy; consider antimetabolites[II,D]
c)   Laser trabeculoplasty: not recommended due to poor and short-lived IOP lowering effect[I,D]

4.2.2 - PRIMARY OPEN-ANGLE GLAUCOMA – HIGH PRESSURE GLAUCOMA (POAG-HPG)

Refer also to Introduction II and Ch. 3.1

A target pressure is to be identified for each case (See also Ch. 3.1.1, 3.2 and FC) [I,D]. It is essential to involve the patient as an informed partner in decisions regarding management of their case. [I,D]
a)   Medical treatment (see Flow Charts)
        1. Mono therapy
        2. Combination therapy as needed in selected patients
b)   Laser trabeculoplasty (LTP)
c)   Filtration Surgery with / without antimetabolites
        Adjunctive medical therapy when needed
d)   Insertion of aqueous long- tube drainage implants
e)   Cyclodestructive procedures
Choice of primary therapeutic modality needs to be made on an individual patient basis. [I,D]

Laser trabeculoplasty can be considered as primary treatment and as an alternative to additional medications. [I,A]

4.2.3 – POAG NORMAL-PRESSURE GLAUCOMA (POAG-NPG)

Refer also to Introduction II and Ch. 3.1.

There are few prospective clinical trials indicating clearly the advantages of treatment. [II,D]
Target pressure: in most cases a peak IOP = 8 mm - 15 mm Hg on diurnal curve
                                          or
                        a 30% IOP reduction from baseline (see Ch. 3.2) [II,D]
a)   Medical therapy: Any drug singly or in combination which is effective and tolerated, whose IOP lowering effect is sufficient to reach a maintain the target IOP. [I,D]
                        Avoid medications with potential vasoconstrictive effects or with systemic hypotensive effects [II,D]
                        Oral calcium channel blockers are being investigated in selected patients by some investigators. [II,D]
b)   Laser trabeculoplasty often of little use as outflow facility is normal [I,D]
c)   Glaucoma Surgery: in cases of progressive glaucomatous damage, in spite of maximal medical therapy or laser trabeculoplasty, or failure to reach target pressure. [I,D] Intensive postoperative care with bleb manipulation may be needed to maintain low IOPs. [I,D]

Follow-up at intervals of 3 -12 months, with examination of:[II,D]
- Optic disc
- Visual field
- IOP
- ONH and RNFL documentation initially and every 2-3 years

4.2.4 - PRIMARY OPEN-ANGLE GLAUCOMA SUSPECT (POAG-HPG SUSPECT)

Risks and benefits of treatment need to be weighed against the risk of the development of glaucomatous disc damage. [II,D]
The risk of developing glaucoma increases with the number and strength of risk factors.
It is essential to involve the patient as an informed partner in decisions regarding management of their case. [I,D]

Management: The indication for any form of therapy is relative[II,D]

a) Medical therapy: any topical agent alone or in combination as long as well tolerated and effective
Avoid adjunctive medical treatment unless strictly needed[II,D]
b) Laser trabeculoplasty: not usually indicated[II,D]
c) Filtering operation: not indicated[I,D]
d) Follow-up[II,D] at intervals of 6 months initially, to be increased if all parameters remain normal with examination of:
- Optic disc
- Visual field
- IOP
- ONH RNFL documentation initially and every 2-3 years

4.2.5 - OCULAR HYPERTENSION (OH)

Although in the past it has been used as a diagnosis, Ocular Hypertension should be used to indicate that the IOP is consistently outside 2 or 3 standard deviations above the mean. Consider corneal thickness (see Introduction II and Ch. 1.1; FC II and IV).
A modest increase in IOP is not sufficient reason for treatment, but consider it in patients with repeated IOPs in the high twenties, even without risk factors. [II,D] For treatment modality see Ch. 4.2.3-a. (See also Ch. 2.2.3. and flow-charts)

- If left untreated (see Ch. Introduction II)
* up to 9.5% develop glaucoma over 5 year of follow-up
* the risk of developing glaucoma increases with increasing IOP
* prophylactic IOP-lowering therapy to be discussed with individual patientsconsidering the presence of risk factors [I,D]

Follow-up [II,D] at intervals of 12 months initially, to be increased if all parameters remain negative, with examination of:
- Optic disc
- Visual field
- IOP
- ONH and RNFL photographs initially and every 2-3 years
Patients for the ocular hypertension treatment study (Ch. Introduction II) were selected excluding myopes, labile diabetics, poor compliance. In most of Europe black Africans are a minority.

NOTE:
Assess each patient individually when deciding whether or not to treat. [I,D]

4.3 - SECONDARY OPEN-ANGLE GLAUCOMA

4.3.1 - SECONDARY OPEN-ANGLE GLAUCOMAS CAUSED BY OCULAR DISEASE

4.3.1.1 - Exfolation glaucoma

a)   Topical medication [I,C]
b)   ALT [I, B] often achieves a large IOP decrease
c)   Glaucoma Surgery [I,C]

4.3.1.2 - Pigmentary glaucoma

a)   Topical medication [I,C]
        Beware drugs which dilate the pupil may cause additional pigment liberation and therefore a spike in IOP [I,D]
        Check peripheral retina for tears before using pilocarpine [II,D]
b)   ALT [I,C]
        The heavily pigmented trabecular meshwork warrants power lower than usual [I,D]
        The IOP response is highly variable
c)   Filtering procedure [I,D]
d)   Peripheral Nd:YAG laser iridotomy for eliminating reverse pupillary block if present [II,B]
        The potential long-term benefit could be decreased iris rubbing and less pigmentary release with a prophylactic role by preventing irreversible trabecular damage [II, B]

4.3.1.3 - Lens-induced open-angle glaucoma

Topical anti-inflammatory medication followed by extraction of lens or lens fragments, and vitrectomy if needed [I,D]

4.3.1.4 - Glaucoma associated with intraocular haemorrhage

a)   Topical and systemic IOP lowering medication as needed [I,D]
b)   Paracentesis and wash-out of the anterior chamber [II,D]
c)   Vitrectomy for removing RBCs from vitreous [II,D].

4.3.1.5 - Uveitic glaucoma

a)   Topical and systemic anti-inflammatory therapy [I,D]
b)   Topical and systemic IOP lowering medication as needed [I,D]
c)   Treatment of the underlying disease [I,D]
d)   Glaucoma Surgery [I,D].

4.3.1.6 - Glaucoma due to intraocular tumour

a)   Irradiation, surgical tumour excision, enucleation [I,D]
b)   Topical and systemic IOP lowering medication as needed [I,D]
c)   Cyclodestruction [I,D]
d)   Trabeculectomy not indicated [I,D]

4.3.1.7 - Glaucoma associated with retinal detachment

a)   Topical and systemic IOP lowering medication as needed [I,D]
b)   Surgery for retinal detachment, vitrectomy, cryosurgery, filtration surgery as needed [I,D]

4.3.1.8 - Open-angle glaucoma due to ocular trauma

a)   Anti-inflammatory treatment [I,D]
b)   Topical and systemic IOP lowering medication as needed [I,D]
c)   Long-term follow up with measurement of intraocular pressure since rise in intraocular pressure after trauma may be delayed for years [I,D]
d)   Glaucoma Surgery [I,D]

4.3.2 - IATROGENIC SECONDARY OPEN-ANGLE GLAUCOMAS

4.3.2.1 - Glaucoma due to corticosteroid treatment

a)   Discontinue corticosteroid medication [I,D]
b)   Topical and systemic IOP lowering medication as needed [I,D]
c)   Laser Trabeculoplasty has very limited effect [I,D]
d)   Glaucoma Surgery according to the specific condition [I,D]

4.3.2.2 - Secondary open-angle glaucoma due to ocular surgery and laser

a)   Topical and systemic IOP lowering medication as needed [I,D]
b)   Anti-inflammatory treatment [II,D]
c)   Removal of silicone oil or of the intraocular lens [II,D]
d)   Glaucoma Surgery according to the specific condition [I,D]

4.3.3 - SECONDARY OPEN-ANGLE GLAUCOMA CAUSED BY EXTRABULBAR DISEASE

4.3.3.1 - Glaucoma caused by increased episcleral venous pressure

a)   Treatment of the underlying disease [I,D]
b)   Topical and systemic IOP lowering medication [I,D]
c)   Glaucoma surgery according to the specific condition [I,D]

4.4 - PRIMARY ANGLE-CLOSURE

4.4.1 - PRIMARY ANGLE-CLOSURE (PAC)

Angle-closure with plateau iris mechanism

See FC X
Medical treatment:

Pupillary constriction to pull centripetally the peripheral iris [I,C]
In plateau iris configuration, a modest pupillary constriction may prevent further angle-closure[I,D]

- pilocarpine 1%, aceclidine 2%, carbachol 0.75%
- dapiprazole 0.5%

Surgical treatment:

Iridotomy is helpful in confirming the diagnosis and will eliminate the pupillary block component if present [I,D]

- Peripheral laser iridoplasty stretches the iris and deepens the chamber angle [I,C]

Angle-closure with posterior aqueous misdirection

See FC X
Medical treatment

- Parasympatholytics (atropine, cyclopentolate) may be useful as a prophylactic or curative regimen [I,C]
- Aqueous production suppressants given orally and/or topically[I,D]
- Hyperosmotics (Ch. 3.3.1.3) [I,D]

Surgical treatment
- A patent iridotomy must be present or, if not present, iridotomy should be performed [I,D]
- YAG laser vitreolysis/capsulotomy, especially in aphakia, pseudophakia [II,C]
- Anterior vitrectomy, especially in aphakia, pseudophakia [II,C]
- In selected cases lens extraction [II,D]

4.4.1.1 - Acute angle-closure with pupillary block mechanism

See FC XI

Iridotomy or iridectomy is the preferred definitive treatment of acute angle-closure glaucoma with a pupillary block component [I,D]

Medical Treatment

Medical treatment serves to lower IOP, to relieve the symptoms and signs so that laser iridotomy or iridectomy is possible [I,C]

Medical therapy aims at
(1) withdrawal of aqueous from vitreous body and posterior chamber by hyperosmotics,
(2) pupillary constriction to free the chamber angle, and
(3) reduction of aqueous production
(4) reduction inflammation.

All the following steps should be implemented concurrently

Consider contraindications to each of the medications to be used
- Reduction of aqueous production[I,D]
  - acetazolamide 10 mg/Kg intravenously or orally.
  - topical alpha-2 agonists
  - topical betablockers

Topical CAIs are not potent enough to break pupillary block.
- Dehydration of vitreous body[I,D]

Hyperosmotics are the most effective agents. The patients must be evaluated for heart or kidney disease because hyperosmotics increase blood volume which increases the load on the heart [I,D] Glycerol may alter glucose blood levels and should not be given to diabetics (FC X) [I,D]
  - glycerol   1.0 - 1.5 g/Kg orally
  - mannitol   1.0 - 1.5 g/Kg intravenously

- Pupillary constriction[I,D]
  - pilocarpine 1% or 2% or aceclidine 2% twice or three times within 1 hour

Note:
while the sphincter is ischaemic and the pupil non-reactive to light[sphincter paresis], multiple application of parasympathomimetics is not helpful, will not cause pupillary constriction and may cause forward rotation of the ciliary muscle, thereby increasing the pupillary block [I,D] Miotics in large doses can cause systemic side effects since they are absorbed transnasally and can cause abdominal cramps. It is now recognised that intensive parasympathomimetics are no longer indicated to treat this condition [I,D] Miotics will constrict the pupil only after IOP has been lowered.
  - dapiprazole 0.5%
Alpha-1 blockers relax the dilator muscle. They do not reduce pupil size when the sphincter-muscle is paretic.

- Reduction of inflammation.
Topical steroid every 5 minutes for three times, then 4-6 times daily.

Surgical treatment

- Neodymium YAG laser iridotomy [I,C]
Laser iridotomy should be attempted if the cornea is sufficiently clear [I,C] Some glaucoma specialists prefer surgical iridectomy in all cases of manifest angle-closure glaucoma and use laser iridotomy only as prophylactic treatment of the contralateral eye and in cases of 'occludable angle' [II,D] Argon laser iridotomy is rarely performed nowadays.

- Surgical iridectomy [II,D]
1) Transcorneal approach.
Advantages: no conjunctival scarring
                       a water-tight self-sealing incision is possible.
Disadvantages: technically more difficult in dilated fixed pupil and flat anterior chamber.
                       More traction on iris with increased risk of haemorrhage.

2) Corneoscleral approach.
Advantages: iridectomy can be 'basal'.
Disadvantages: conjunctival wound may lead to scarring compromising the outcome of a
                       filtering procedure which may become necessary at a later stage
                       insufficient wound closure and aqueous misdirection may occur in rare
                       cases.

General advantages of surgical iridectomy:

                it can be performed even when the cornea is cloudy

                it allows deepening of the anterior chamber, breaking freshly formed PAS.

General disadvantages of surgical iridectomy:

                all the potential risks of any intraocular procedure.

Anterior chamber paracenthesis is being evaluated to break the attack in cases refractory to medical management [II, C].

4.4.1.2 - Intermittent Angle-Closure Glaucoma (IACG)

Pupillary constriction, iridotomy, iridoplasty or lens extraction are to be considered according to the main mechanism determining angle occlusion [II,D]

4.4.1.3 - Chronic angle-closure glaucoma

Medical treatment rarely effective
If the synechial closure is less than half the circumference, iridectomy/iridotomy may be sufficient [I,C] Since complications of iridotomy are uncommon, its use as the initial procedure is justified in practically every case [I,D]
Argon laser trabeculoplasty is not indicated as it may increase synechial angle-closure [I,D]

If IOP cannot be controlled, a filtering procedure is indicated [II,D] These eyes are more frequently prone to develop posterior aqueous misdirection and the necessary precautions must be taken when considering surgery.
Lens removal may be considered and could relieve the problem [II,D]

4.4.1.4 – Status Post Acute angle- closure attack-

Management according to angle, lens, IOP and disc/ VF.

4.4.2 - THE "OCCLUDABLE" ANGLE; ACR (ANGLE-CLOSURE RISK)

If fellow eye of primary angle-closure, treatment is clearly indicated, starting with laser iridotomy [I,B]. All other cases must be assessed individually [II,D]. In general, the risks of treatment are to be balanced against the perceived risk of angle-closure.

4.5 - SECONDARY ANGLE-CLOSURE GLAUCOMAS

4.5.1 - SECONDARY ANGLE-CLOSURE GLAUCOMAS WITH PUPILLARY BLOCK

Several steps may be considered, according to the clinical picture of causative mechanisms [II,D]
    a)   Topical and systemic IOP lowering medication
    b)   Nd:YAG laser iridotomy
    c)   Peripheral surgical iridectomy
    d)   Lens extraction, vitrectomy
    e)   Discontinuing miotics in miotic-induced pupillary block
    f)   Pupillary dilation
    g)   Nd:YAG laser synechiolysis of posterior synechiae

4.5.2 - SECONDARY ANGLE-CLOSURE GLAUCOMAS WITH ANTERIOR "PULLING" MECHANISM WITHOUT PUPILLARY BLOCK

4.5.2.1 - Neovascular glaucoma [II,D]

    a)   Topical atropine or equivalent
    b)   Topical steroid initially
    c)   Topical and systemic IOP lowering medication as needed
    d)   Retinal ablation with laser or cryotherapy
    e)   Cyclodestruction
    f)   Filtering procedure with antimetabolites
    g)   Aqueous drainage devices
            Miotics are contraindicated
Intravitreal injection of anti-VEGF compounds has shown some benefit but is not approved yet for this indication [II,C]

4.5.2.2 - Iridocorneal endothelial syndrome [II,D]

    a)   Topical and systemic IOP lowering medications as needed
    b)   Filtering procedure, with antimetabolite according to risk factors
    c)   Aqueous drainage device

4.5.2.3 - Posterior polymorphous dystrophy [II,D]

    a)   Topical and systemic IOP lowering medication as needed
    b)   Filtering procedure, with antimetabolite according to risk factors

4.5.2.4 - Peripheral anterior synechiae due to prolonged primary angle-closure glaucoma [II,D]

    a)   Topical and systemic IOP lowering medication as needed
    b)   Filtering procedure

4.5.2.5 - Epithelial and fibrous ingrowth after anterior segment surgery or penetrating trauma [II,D]

a) Topical and systemic IOP lowering medication as needed
b) Excision, destruction of the immigrated tissue
c) Filtering procedure, with antimetabolite according to risk factors
d) Aqueous drainage device
e) Cyclodestruction

4.5.2.6 - Inflammatory membrane [II,D]

a) Anti-inflammatory medications and cycloplegics
b) Topical and systemic IOP lowering medication as needed
c) Filtering procedure with antimetabolite
d) Aqueous drainage device
e) Cyclodestruction

4.5.2.7 - Peripheral anterior synechiae after ALT and endothelial membrane covering the trabecular meshwork late after ALT [II,D]

a) Topical and systemic IOP lowering medication as needed
b) Filtering procedure

4.5.2.8 – Aniridia [II,D]

a) Topical and systemic IOP lowering medication as needed
b) Trabeculotomy
c) Filtering procedure with antimetabolites
d) Aqueous drainage device
e) Cyclodestruction

4.5.3 - SECONDARY ANGLE-CLOSURE GLAUCOMAS WITH POSTERIOR "PUSHING" MECHANISM WITHOUT PUPILLARY BLOCK

4.5.3.1 - Aqueous misdirection glaucoma [II,D]

a) Long-term pupillary dilation and cycloplegia
b) Topical and systemic IOP lowering medication as needed
c) Laser or surgical dissection of the anterior hyaloid face or lens capsule and/or iridotomy
d) Vitrectomy with dissection of the anterior hyaloid face
Miotics are contraindicated

4.5.3.2 - Iris and ciliary body cysts, intraocular tumours [II,D]

a) Topical and systemic IOP lowering medication as needed
b) Cyst destruction with laser or surgical excision
c) Tumour irradiation
d) Filtering surgery
e) Cyclodestruction

4.5.3.3 - Silicon oil or gas implanted in the vitreous cavity [II,D]

a)   Topical/systemic IOP lowering medications as needed
b)   Silicon oil or gas aspiration
c)   Filtering surgery
d)   Drainage device
e)   Cyclodestruction

4.5.3.4 - Uveal effusion due to [II,D]

1.   inflammation (scleritis, uveitis, HIV infection)
2.   increased choroidal venous pressure (nanophthalmos, scleral buckling, panretinal photocoagulation, central retinal vein occlusion, artero-venous communication)
3.   tumour

a)   Anti-inflammatory medication (for 1)
b)   Topical and systemic IOP lowering medication as needed (for 1,2 and 3)
c)   Relaxation of scleral buckling; vitrectomy, sclerectomy in nanophthalmus (for 2)
d)   Tumour excision or irradiation (for 3)
e)   Cyclodestruction

4.5.3.5 - Retinopathy of prematurity (stage V) [II,D]

a)   Topical and systemic IOP lowering medications
b)   Cyclodestruction
c)   Filtering procedure with or without antimetabolite
d)   Drainage devices

4.5.3.6 - Congenital anomalies that can be associated with secondary glaucoma

Treatment to be adapted to the primary anomaly, the mechanism of IOP elevation and the quality of life of the patient [II,D]

References

For references, see corresponding topics in Ch. 2 and Ch. 3.