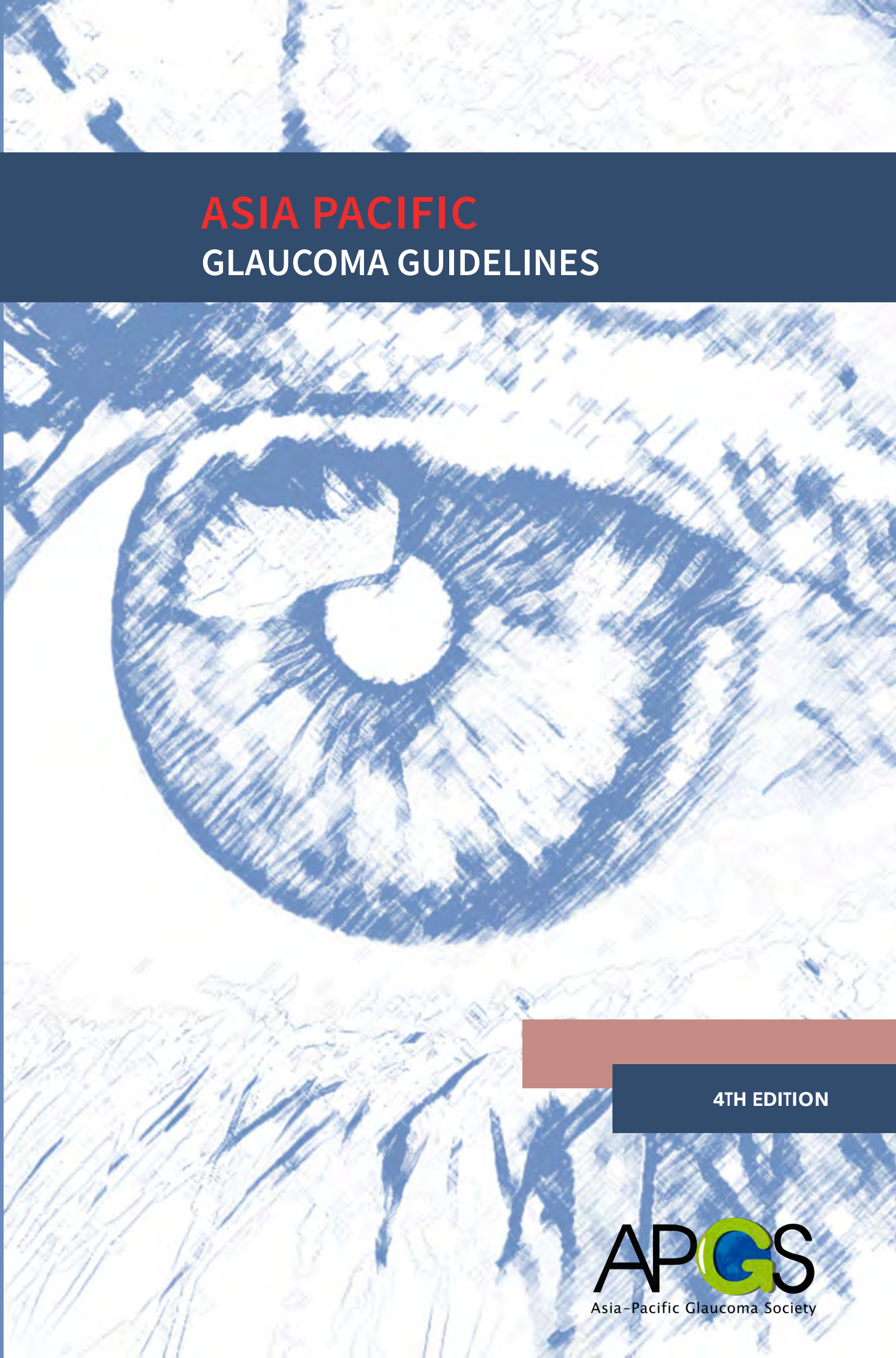
ASIA PACIFIC
GLAUCOMA GUIDELINES



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Asia-Pacific Glaucoma Society

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ASIA PACIFIC GLAUCOMA GUIDELINES

Asia-Pacific Glaucoma Society

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ABOUT THE ASIA-PACIFIC GLAUCOMA SOCIETY

The Asia-Pacific Glaucoma Society (APGS) was established to facilitate contact between glaucoma specialists in the region, encourage collaborative research and service projects, increase the opportunities for exchange of skills and knowledge in this rapidly advancing field, and assist our comprehensive ophthalmological colleagues and other eye care workers (whether medically trained or not) to be up to date with advances in all aspects of glaucoma diagnosis and management. Glaucoma is the cause of considerable blindness in Asia and is associated with specific problems in this region: the epidemiology and natural history of this disease differ from that in developed countries elsewhere. In addition, people suffering from glaucoma in Asia may have different therapeutic outcomes from their Western counterparts.

MISSION STATEMENT

To promote excellence in the diagnosis and care of patients with glaucoma of all types at both individual and community levels.

OBJECTIVES

- To improve the care of patients with all types of glaucoma and related diseases.
- To increase the understanding of such diseases in the medical profession and the general community through educational activities.
- To facilitate, conduct, and fund research programmes to expand knowledge about the causes, prevention, and treatment of glaucoma.
- To work closely with universities, medical schools, hospitals, and other institutions to advance these aims by all means considered effective and affordable.
- To maintain and promote relationships with any organization with similar goals.
- To raise, disburse, and administer funds in furtherance of these objectives.

Governance

Glaucoma members of APGS vote at an Annual General Meeting for a Board of twenty-one members, no more than two of whom can come from any one country. The Board then votes from among its members to elect a President, Vice-President, Treasurer, and Secretary.

No individual can remain a Board Member for more than eight consecutive years. After such a period of service, the individual may stand for the Board again after an absence of at least four years.

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INTRODUCTION

The Asia-Pacific Glaucoma Guidelines (APGG) are now an established source of up-to-date information on glaucoma and its management for glaucoma specialists, general ophthalmologists, healthcare providers, and policymakers in the Asia-Pacific region. Now into its fourth edition, these guidelines have been updated with the latest information and recommendations through the continued close collaboration of glaucoma specialists from the APGG Working Party and the Review Group. Therefore, the information presented is both accurate at the time of publication and based upon expert consensus where definitive evidence is not available.

In this edition, we have a new Key messages section that offers a quick go-to summary of each section, as well as some Frequently asked questions that provide additional useful information to the reader. We are very grateful to our industry sponsors (see Acknowledgments) for their generous grants, which have supported the publication and distribution of the APGG in its fourth edition.

The guidelines have been created specifically with the Asia-Pacific community in mind and hence with the understanding that patient populations, access to care, and clinical resources differ widely across the region. Through the course of developing the guidelines, our objective has been to outline the highest standard of care deserved by all our patients. We hope that you will be able to use the guidelines as they relate to your own unique clinical situation.

Tina Wong and Christopher Kai-Shun Leung
Co-Editors
Asia-Pacific Glaucoma Guidelines 4th edition

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SECTION 1

EPIDEMIOLOGY OF GLAUCOMA IN THE ASIA-PACIFIC REGION

Key messages

- Glaucoma is the leading cause of irreversible visual impairment and blindness worldwide.
- Glaucoma currently affects 76 million individuals globally and an estimated 111.8 million people will be affected by 2040.
- Asia accounts for 60% of all glaucoma cases globally.
- Within Asia, East Asia has the highest prevalence of PACG, whereas South Central Asia has the highest burden of POAG.
- NTG accounts for 70–92% of POAG cases in in the Asia-Pacific region.
- Nearly 50–90% of individuals with glaucoma worldwide are undiagnosed.
- Targeting high-risk populations and implementing cost-reducing strategies can make glaucoma screening cost-effective.

1.1 PREVALENCE OF PRIMARY GLAUCOMA

Glaucoma is a group of optic neuropathies characterised by selective and progressive loss of RGCs and their axons. It presents clinically as thinning and loss of the neuroretinal rim and RNFL with corresponding VF loss. Glaucoma is the leading cause of irreversible visual impairment and blindness worldwide.[1,2]

In 2013, the global prevalence of primary glaucoma among adults aged 40–80 years was 3.54% (95% credible interval [CrI] 2.09, 5.82), affecting 64.3 million individuals.[1] Africa has the highest prevalence of primary glaucoma (4.79%, 95% CrI 2.63, 8.03) and POAG (4.20%, 95% CrI 2.08, 7.35), whereas Asia is affected disproportionately by PACG (1.09%, 95% 0.43, 2.32). Nonetheless, Asia accounts for 60% of all glaucoma cases globally, or 1 in 2 POAG cases and 3 in 4 PACG cases, due to its sheer population size.[1] Within Asia, East Asia has the highest prevalence of PACG (1.07%, 95% CrI 0.28, 2.74), whereas South Central Asia has the highest burden of POAG.[3] Glaucoma is the leading cause of registered, permanent blindness in many countries in the region (including Hong Kong, Japan, and India).[4-6] In 2020, 4.13 million people aged 50 years and older suffered moderate and severe vision impairment, and 3.6 million were blind due to glaucoma.[2,7] **Table 1-1** shows the prevalence of primary glaucoma and reported blindness rates from different population-based studies in the region.

PROJECTED BURDEN OF GLAUCOMA

With the world's population aging, glaucoma prevalence and morbidity can be expected to increase. It was projected to affect 76 million individuals globally in 2020, with an estimated 111.8 million people affected by 2040.[1] The surge in global prevalence of glaucoma will be driven largely by Africa and Asia.[2] It is estimated that Asia will still contain the highest absolute numbers of primary glaucoma in 2040, with 18.8 million POAG and 9 million PACG cases.[1] Within Asia, South Central Asia is projected to record the steepest increase in prevalence of primary glaucoma and POAG cases, although East Asia will remain as the subregion with the highest number of PACG cases.[3] Early detection of glaucoma and its progression for timely intervention is crucial in mitigating the growing burden of glaucoma.

POAG

Prevalence of POAG

POAG is the predominant subtype of glaucoma and a significant public health problem worldwide. In 2013, the global prevalence of POAG among adults aged 40 years and older was 3.05%, with Asians accounting for over half of these cases.[1] As the population ages, prevalence studies suggest that POAG will increase by 50% worldwide, from 52.7 million in 2020 to 79.8 million in 2040. The prevalence of glaucoma varies widely among different ethno-racial groups and geographic regions. Africa is found to have the highest prevalence of POAG (4.2%), while Australia (in Oceania) has the lowest (1.8%).[8] Recent evidence on Hispanics/Latinos suggests that they have high prevalence rates of POAG, comparable to that of African Americans.[9] The prevalence rates in Asians are intermediate and similar to European populations.[8] However, the absolute number of cases is higher in Asia due to its sheer population size. The prevalence of POAG in urban populations is almost twice that in rural populations, especially in developing countries such as India and China.[10,11] Due to lack of accessible healthcare, blindness rates are higher in rural than in urban areas. NTG comprises a high proportion of POAG cases in Asia, especially in countries such as Japan and Korea.[12,13]

Incidence rates of POAG

The Chennai Eye Disease Incidence Study (CEDIS) in India reported the 6-year age- and gender-adjusted incidence of POAG to be 2.4% among subjects aged 40 years and above, which is close to that reported in black individuals in Barbados, but lower than that of Latin Americans and higher than that of white subjects in Europe and Australia.[14] The Singapore Epidemiology of Eye Diseases (SEED) study reported a slightly lower 6-year age-adjusted incidence of POAG of 1.31% in a multi-ethnic Asian population.[15] POAG incidence was similar (1.37%) in Chinese and Indians, and lower (0.80%) in Malays. Older age, higher IOP, and longer axial length were associated with higher risk of POAG in both studies.[14,15] In addition, thinner corneas with higher IOP at baseline had the highest incidence of POAG.[14]

Risk factors for POAG

Higher IOP, older age, African race or Latino/Hispanic ethnicity, family history of glaucoma, and myopia are risk factors found consistently across all studies.[8] Male sex is associated with a higher risk of POAG, which may be due to a protective effect of female hormones on RGC loss.[8] However, NTG is reportedly more common in females.[16] A thinner central cornea has been reported as a risk factor for POAG. Even though controversy exists about CCT as an "independent" risk factor because CCT alters the measurement of IOP and hysteresis, clinicians should measure CCT when evaluating patients with POAG.[17] Low ocular perfusion pressure, especially low diastolic perfusion pressure (< 50 mmHg) is associated with a high-

er prevalence of POAG.[18-21] There is increasing evidence from population-based studies suggesting that type 2 diabetes mellitus is an important risk factor for POAG, but the data is yet conflicting.[17] Other factors that have been associated with POAG include migraine headache, peripheral vasospasm (Raynaud's syndrome), sleep apnoea, cardiovascular disease, hypothyroidism, low body mass index, lower intracranial pressure affecting the translaminar pressure gradient, low corneal hysteresis, and systemic hypertension.[17-21]

OHT

The prevalence of OHT worldwide varies between 0.32% and 12.2%.[22] Most population-based studies have shown that 5.3% to 17.4% of OHT eyes develop POAG without treatment over 5 years.[23-25] The SEED study reported that Malays had a higher incidence (0.79%) of OHT than Indians (0.38%) and Chinese (0.37%).[15] Bilateral OHT, higher peak IOP, and large diurnal variation of IOP were identified as the risk factors for progression in a study from South India.[25] More recently, the Ocular Hypertension Treatment Study (OHTS) reported that the cumulative 20-year incidence of POAG was 45.6%, with one-fourth of participants developing VF loss in 1 or both eyes.[26]

NTG IN THE ASIA-PACIFIC REGION

Epidemiological studies in Asia have reported the prevalence of NTG to be between 1.7% and 3.6%.[12,13,27,28] NTG is the most common subtype of OAG in Japan, accounting for 9 out of 10 POAG cases.[13] **Table 1-1** presents the prevalence of NTG and proportion of NTG cases to high-tension glaucoma (HTG) in the Asia-Pacific region. NTG accounts for 70%–92% of POAG cases in Asia, (92.3% in Japan,[13] 84.6% in Singapore,[29] 83.58% in Northern China,[27] 82% in South India,[30] 79.3% in Southern China,[18] and 77% in South Korea,[12]), which is much higher than in patients of African descent (57.1%)[16] and Caucasians (38.9% in the Netherlands,[31] 31.7% in the United States,[32] and 30.0% in Italy[33]). This high prevalence of NTG in the Asia-Pacific region is a distinctive finding reported by several landmark epidemiological studies in many countries using the same International Society of Geographical and Epidemiological Ophthalmology (ISGEO) diagnostic criteria and therefore requires special surveillance.

Studies have reported that NTG may coexist with PACD in a clinical setting in the Asia-Pacific region.[34] This hybrid-stage disease entity, the narrow-angle NTG, showed faster rates of disease progression than wide-angle NTG during the mean 7.6-year follow-up period.[34] Advances in OCT technology have helped to identify cases of normotensive pre-perimetric glaucoma.[35] Studies evaluating the long-term clinical course of normotensive pre-perimetric glaucoma have shown that the presence of optic disc haemorrhage, higher mean IOP, and greater initial PSD on VFs were associated with development of VF defect subsequently.[35] With the advances in OCTA and artificial intelligence, new epidemiological studies will hopefully shed more light in understanding the pathogenesis of NTG.

PACG

Prevalence of PACG

PACG is a visually devastating disease and any rise in the prevalence of PACG is problematic due to the high rates of blindness associated with the disease. It is estimated that by 2050, the global population with PACG will be 26.26 million, with 18.47 million in Asia.[36] In a meta-analysis, Zhang *et al.*[37] reported that the global pooled prevalence of PACG was 0.6% [95% CI 0.5%, 0.8%] for the last 20 years (2000–2020). Despite its lower global prevalence, PACG on average carries a 3-fold increased risk of severe bilateral visual impairment than POAG.[1] Nearly 70% of those with PACG were blind at the time of examination in population-based studies (**Table 1-1**). In China, PACG accounts for 91% of vision impairment attributed to glaucoma.[38-40] The prevalence rates of PACG from different countries in the Asia-Pacific region are shown in **Table 1-1**. The risk factors associated were increasing age, female gender, higher IOP, shorter axial length, and shallower ACD.

Table 1.1. Prevalence of primary glaucoma and reported blindness rates from different population-based studies in the region

Study	Age range (years)	Number (*n*)	Setting	POAG (%)	NTG (%)	Ratio of NTG to HTG	PACG (%)	% of POAG blind	% of PACG blind
Hovsgol, Mongolia[41]	40–87	942	Rural	0.53	0.3	1.5	1.49	20.0	21.4
Andhra Pradesh, India[82]	30–70+	1399	Urban	1.62	0.96	1.4	-	18.5	-
Tanjong Pagar, Singapore[38]	40–79	1232	Urban	1.79	-	-	1.14	27.3	50
Rom Klao, Thailand[83]	50–80+	701	Urban	2.28	-	-	0.86	25.0	33.3
Aravind, India[84]	40–70	5150	Rural	1.24	-	-	0.50	9.4	-
West Bengal, India[85]	50–80	1269	Rural	2.99	-	-	0.24	5.3	0.0
Tajimi, Japan[13,86]	40–80	3021	Urban	3.94	3.6	12	0.63	1.7	5.3
Chennai-Rural, India[87,88]	40–89	3924	Rural	1.63	-	-	0.87	3.1	2.9
Liwan, China[89]	50–93	1372	Urban	2.11	1.7	5.8	1.53	17.2	42.9
Meiktila, Myanmar[42]	40–70	2076	Rural	1.88	-	-	2.50	7.7	61.5
Chennai-Urban, India[30,90]	40–80+	3850	Urban	3.51	-	-	0.88	1.5	14.7
Singapore Malay Eye Study[29]	40–80+	3280	Urban	3.17	-	-	0.24	9.6	12.5

Study	Age range (years)	Number (*n*)	Setting	POAG (%)	NTG (%)	Ratio of NTG to HTG	PACG (%)	% of POAG blind	% of PACG blind
Kandy, Sri Lanka[91,92]	40–70	1244	Rural	2.41	-	-	0.56	3.3	28.6
Andhra Pradesh, India[93]	40–70+	3724	Mixed	-	-	-	0.94	-	42.9
Beijing, China[94]	40–70+	4315	Mixed	2.57	-	-	1.02		6.8
Bin, China[46,47]	40–70+	4956	Rural	0.71	-	-	1.57	2.9	14.1
Handan, China[49,95]	40–80+	6716	Rural	1.86	-	-	0.76	2.4	41.2
Kailu, China[48]	40–70+	5158	Rural	1.42	-	-	1.74	8.2	6.7
Yunnan, China[40]	50–80+	2133	Rural	1.03	-	-	0.94	36.4	70.0
Namil, South Korea[12,96]	40–80+	1532	Rural	3.59	2.7	3.4	0.65	5.5	0.0
Bhaktapur, Nepal[97]	40–80+	3991	Rural	1.28	-	-	0.43	2.0	5.9
Blue Mountains, Australia[98]	40–80+	3654	Rural	2.38	-	-	0.27	0.0	0.0
Melbourne-Urban, Australia[99]	40–90+	3264	Urban	1.72	-	-	0.06	0.0	0.0
Melbourne-Rural, Australia[99]	40–90+	1469	Rural	1.97	-	-	0.07	0.0	0.0
Kumejima, Japan[34,43]	40–90+	3762	Rural	4.0	3.3	4.7	3.7	0.7	3.7
Shihpai Eye Study, Taiwan[44]	> 72	460	Urban	3.7	2.6	2.4	4.8	-	-

HTG: High-tension glaucoma; NTG: Normal-tension glaucoma; PACG: Primary angle-closure glaucoma; POAG: Primary open-angle glaucoma

While it is well established that Asia has the highest prevalence of PACG, there is a marked racial and geographic diversity in the prevalence rates among Asian populations. PACG is the predominant form of glaucoma in Mongolia (1.49%),[41] Myanmar (2.5%),[42] Kumejima island in Japan (3.7%),[43] Shihpai in Taiwan (4.8%),[44] and among Inuits (2.1% to 5%),[45] who are considered descendants of a migrating population from Northeast Asia. It is well known that Chinese populations have a greater risk of PACG. However, variations exist within different geographic areas of China, with higher rates of PACG reported in Northeast China[46-48] and Southwest China,[49] and the lowest rates in Northwest China.[11] A possible explanation for this geographic variation is an evolutionary modification of shallower anterior chambers that resist corneal freezing.[42,45,46]

Incidence and risk factors for PACG

The incidence rates and risk factors for development of angle closure are listed in **Table 1-2**. Risk factors reported were greater baseline lens thickness, shallower ACD, and narrower angle width. Incidence rates of symptomatic acute angle closure (given as cases/100,000 persons/year for the population aged 30 years and older) range from 4.7 in Europe (Finland)[50] to 15.5 in Chinese Singaporeans.[51] Malay and Indian individuals in Singapore have lower rates than do Chinese Singaporeans (6.0 and 6.3, respectively).[52] Over the past few decades, reduced rates of acute angle closure in Taiwan have been attributed to increasing cataract surgical rates.[53] Wide variation in incidence rates probably related to inherent differences in ethnicity.

Table 1.2. Incidence of primary angle closure disease from different population-based studies and risk factors for its development

Study	Number	Setting	Duration (years)	PACS	PAC	PACG	PACD	Risk factors
Andhra Pradesh, India[100]	1197	Rural	15	8.8	6.2	1.6	16.4	Female gender, Presence of myopia is protective
SEED study, Singapore[54]	5060	Urban	6	2.54	0.46	0.29	3.5	Increasing age, shallow ACD
Chennai Eye Incidence Study, India[102]	3350	Mixed	6	2.6	1.1	0.3	4.0	Higher IOP, increased LT, shorter AL shallow ACD, hyperopia, anteriorly positioned lens
Liwan Eye Study, China[101]	620	Urban	10	16.9	2.4	1.1	20.5	Greater baseline LT, shallower ACD, narrower angle width
Handan Eye Study, China[55]	457	Rural	5	31	5.3	0.0	32.8	Shallower ACD, narrower angle width
Community study, Japan	331	Urban	5	-	5.4	1.3	-	Shallow ACD
Hovsgol, Mongolia[104]	1717	Rural	6	20.4	-	-	-	Narrower angles by modified van Herick grading and gonioscopy

ACD: Anterior chamber depth; AL: Axial length; LT: Lens thickness; PAC: Primary angle closure; PACD: Primary angle-closure disease; PACG: Primary angle-closure glaucoma; PACS: Primary angle-closure suspect; SEED: Singapore Epidemiology of Eye Diseases

Natural history of PACD

In the SEED study, 9.38% of patients with PACS progressed to PAC or PACG over 6 years of follow-up.[54] The Handan Eye Study (HES) found that 6.08% of PACS at baseline progressed to PAC/PACG during the 5-year follow-up.[55] Baseline mean angle width was determined to be an independent predictive risk factor for the progression of angle closure. However, an Indian cohort study reported much higher rates of progression over 5 years (22% of PACS progressed to PAC and 28.5% of PAC progressed to PACG).[56,57] The different rates could be due to different definitions of angle closure.

The Zhongshan Angle Closure Prevention (ZAP) trial reported a low incidence of angle-closure disease after 3 years of follow-up (4.2 per 1000 eye-years in LPI-treated eyes compared with 8.0 per 1000 eye-years in control PACS eyes).[58] These findings were echoed in the Singapore Asymptomatic Narrow Angles Laser Iridotomy Study (ANA-LIS), where 9.4% of patients with PACS (21.84 per 1000 eye-years) progressed over 5 years of follow-up.[59] LPI was associated significantly with a 45% reduced risk of PAC progression in patients with PACS. Higher baseline IOP was a risk factor for progression. Recently, the 14-year follow-up of the ZAP study reported that while LPI significantly reduced the risk of PAC occurrence in PACS eyes by two-thirds over the long term, the cumulative risk of progression was relatively low in LPI-treated eyes compared with control eyes (hazard ratio 0.31 [95% CI, 0.21, 0.46]).[60]

1.2 PREVALENCE OF SECONDARY GLAUCOMA

In Asia, the overall prevalence of secondary glaucoma was 0.47% (95% CrI 0.09, 1.48) in 2013, affecting 6.13 million individuals and comprising 11.9% of all glaucoma cases.[2] The major causes of secondary glaucoma in Asia included PXF, pigment dispersion, neovascularization, trauma, and steroid use. The population-based data on the prevalence of PXG vary widely from 0.1% (95% CI 0.0, 0.2) in Japan to 2.2% (95% CI 1.7, 2.7) in Australia.[7] The prevalence of glaucoma among subjects with PXF reported by population-based surveys from India were higher, ranging from 7.5% to 29%.[61-64] Although secondary glaucoma represents a smaller percentage than the primary forms of the disease, it nevertheless causes significant ocular morbidity and visual impairment.

1.3 MAGNITUDE OF UNDIAGNOSED GLAUCOMA

Despite the progress made in glaucoma research, imaging technologies, and interventions, an unacceptable number of glaucoma patients continue to remain undiagnosed.[65] Early diagnosis is a crucial factor that has significant impact upon prognosis. Current estimates suggest that nearly 50% of people with glaucoma worldwide are undiagnosed, with the rates of undiagnosed glaucoma increasing up to 90% in the developing countries of Asia and Africa.[65] These rates further vary by ethnicity, human development index strata, and geographical area. Asia alone accounts for 58.4% of all undetected POAG cases worldwide due to its sheer population size. In Asia, South Asia (odds ratio 2.19; 95% CI, 1.01, 4.77) showed significant higher odds of undetected manifest glaucoma cases as compared with East Asia. Some of the reasons for undetected glaucoma include a low level of glaucoma awareness, poor disease knowledge across communities, lack of service utilization, lack of adequate resources, lack of access to services, and finally, lack of effective screening tools. Access to essential eye care services is uneven in many countries, with many rural areas having limited or no access to eye care services.[65] This may explain the higher odds of undetected POAG in rural areas worldwide. In Australia, 71% of rural inhabitants had undetected glaucoma as compared to 58% in urban settings.[66] There are differences based on ethnicity, which speaks of the inequitable uptake of resources, even in developed countries. Glaucoma was 3.65-fold more likely to be undetected among Malay than Chinese adults in Singapore,[67] whereas 72.0%–80.8% of indigenous Australians had undetected glaucoma compared to 46.6%–63.0% of non-indigenous Australians.[66] The high proportion of undetected glaucoma observed in countries with high socioeconomic status and populations with access to free or subsided eye examinations further suggest less than ideal use of eye care services.

1.4 SCREENING AND COMMUNITY MONITORING OF GLAUCOMA

Late presentation is a major risk factor for glaucoma-related blindness. The asymptomatic nature of glaucoma underscores the importance of screening for disease detection. Community-based screening programs identify patients at earlier stages compared to patients detected in clinical settings, thereby reducing the risk of glaucoma-associated low vision and blindness.[68-69] However, despite its potential benefits, implementing glaucoma screening as a policy has faced challenges due to the complexity and cost of diagnosis, as well as the low prevalence of glaucoma.[70]

Glaucoma screening can be conducted either in community-based or clinic-based settings, both of which necessitate a definite diagnosis by experienced ophthalmologists and clinical examinations using multiple modalities. Given the low prevalence of glaucoma, no single clinical assessment achieves the required sensitivity and specificity for accurately diagnosing glaucoma in asymptomatic adults. The cost-effectiveness of community-based glaucoma screening varies across countries, influenced by factors such as screening costs, healthcare infrastructure, glaucoma prevalence, and the risk for glaucoma blindness.[70-74] Glaucoma screening in the general population is not recommended because the low prevalence of glaucoma will lead to a high false-discovery rate, and therefore to an undue burden on the healthcare system and the patients. However, in certain populations with a high risk of glaucoma blindness and low screening costs, community-based screening can be cost-effective, particularly in countries like China[72] and India.[73,74] The effectiveness of screening can be further increased by targeting the elderly, myopes, and those with a family history of glaucoma.

Opportunistic clinic-based glaucoma screening can be performed on individuals aged 40 and above who visit an ophthalmic clinic for eye care by comprehensive ophthalmic examinations and should be repeated periodically. However, despite undergoing ophthalmic examinations within a year, half of glaucoma patients remain undiagnosed, denoting inadequate or improper examinations.[75,76] Therefore, establishing a consensus to optimize screening programs in primary eye care sites is crucial to enhance the effectiveness of opportunistic case findings.

Alternatively, integrating glaucoma screening into general health examinations, utilizing telemedicine,[77,78] and employing imaging-based glaucoma screening[79] can potentially enhance the cost-effectiveness of the screening process. Additionally, the use of artificial intelligence-assisted image analysis holds promise for revolutionizing glaucoma screening.[80] However, additional validation of the artificial intelligence-assisted diagnostic algorithms is essential to confirm their generalizability and effectiveness for clinical implementation.[81]

FAQ

Is PACG more common than POAG in Asian countries?
No, POAG is still more common than PACG in Asian countries.

Does PACG cause more blindness than POAG?
Population-based studies show that PACG causes 3 to 10 times proportionately more blindness than POAG.

Does the clinical presentation of angle closure vary in different parts of Asia?
Acute angle closure may be more common in China than in India. However, chronic angle closure is still much more common than acute angle closure overall.

What is the natural history of PACD?
PACS may progress to PAC/PACG over time, and the progress rate varied among cohorts and by angle closure definitions. In studies from Singapore and China, the rate of progression from PACS to PAC/PACG ranges from about 6% over 5 years of follow up to <10% over 6 years; while in Indians, it was reported that 22% of PACS progressed to PAC and 28.5% of PAC progressed to PACG over 5 years.

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2.1. INTRAOCULAR PRESSURE MEASUREMENT

Key messages

- GAT remains the gold standard for IOP measurement.
- One should be aware of the measurement errors associated with GAT and other types of tonometry.
- Further investigation is needed to determine whether home self-monitoring of IOP is cost-effective and leads to better clinical outcomes.

IOP MEASUREMENT

IOP is determined by aqueous humour production and aqueous outflow. The modified Goldmann equation describes steady-state IOP using the following key determinants:

$$IOP = [(Q-U)/C] + EVP$$

C: conventional (trabecular) outflow facility (the inverse of resistance); EVP: episcleral venous pressure; IOP: intraocular pressure; Q: aqueous humour inflow rate; U: pressure-insensitive uveoscleral outflow rate.

IOP measurement is a key aspect of ophthalmologic evaluations, playing a critical role in the management of glaucoma. Identifying and managing elevated IOP is essential because it is currently the only modifiable risk factor for glaucoma. By controlling IOP, the progression of glaucoma can be arrested or slowed, thereby preserving the quality of vision. **Table 2.1.1**. presents the factors affecting measured IOP.

Table 2.1.1. Factors affecting measured IOP

Factor	Mechanism
Circadian cycle	IOP follows a circadian cycle, varies with posture, and is often highest when the patient is horizontal at night. Diurnal (daytime) IOP fluctuation is variable between individuals.
Corneal parameters	In the initial design of the GAT, an estimated average corneal thickness of 520 microns was used to cancel the opposing forces of surface tension and corneal rigidity to allow indentation.[1] It is now known that there is a wide variation of corneal thickness among different individuals and ethnic groups. Generally thicker corneas are associated with artificially elevated IOP measurements, and thinner corneas with artificially depressed IOP measurements.

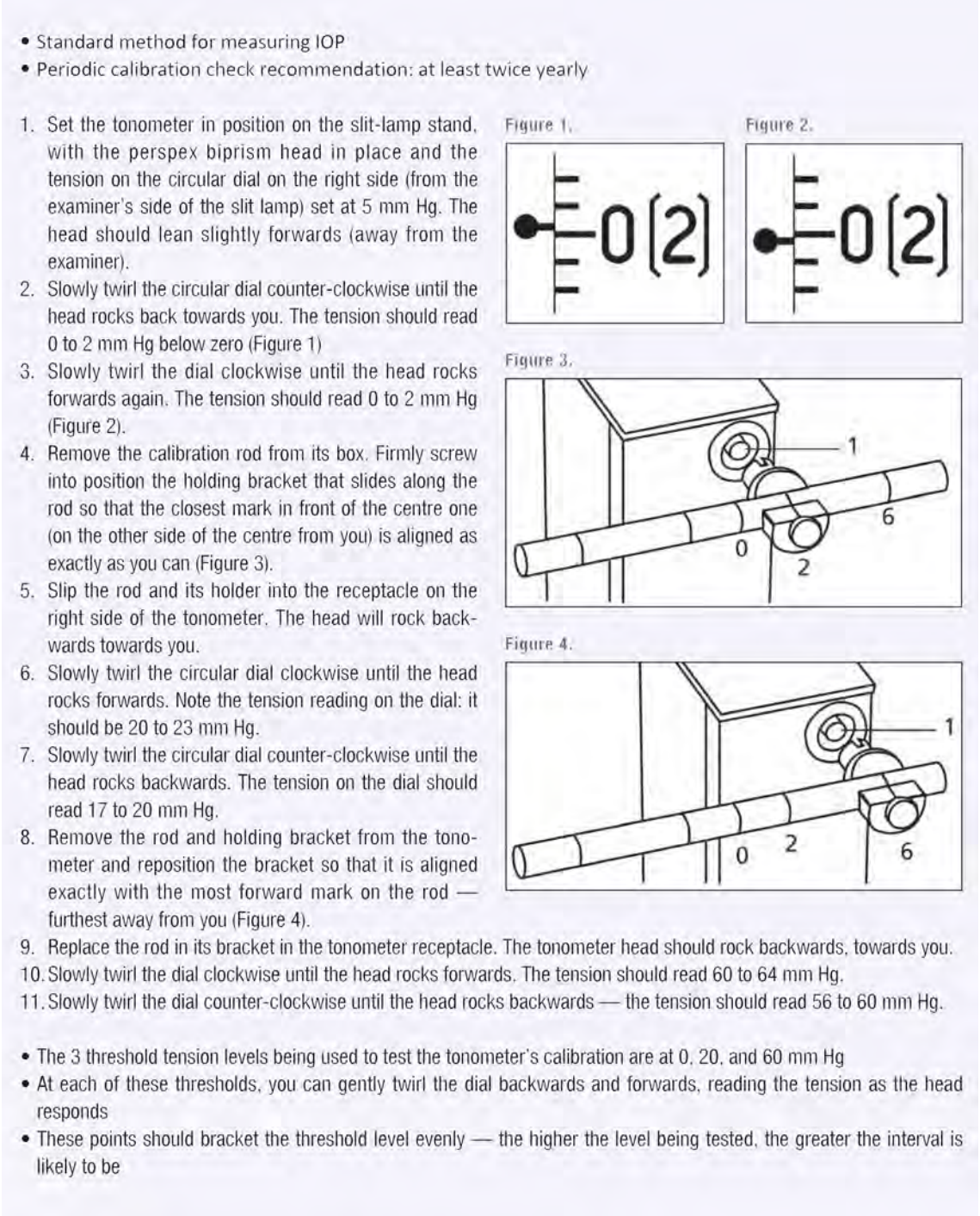
Factor	Mechanism
Corneal parameters (continued)	Correction nomograms based solely on corneal thickness are neither valid nor useful in individual patients.[2] The clinician should consider the clinical context when measuring IOP. Corneal hysteresis: Lower corneal hysteresis values are associated with greater risk of VF progression.[3,4] Thinning of the cornea after corneal refractive surgery may underestimate IOP.
Blood pressure	IOP is positively associated with systemic blood pressure,[5] however, reducing blood pressure has little impact on IOP in an individual patient.
Intra-abdominal pressure	Increased intra-abdominal pressure by playing wind instruments or Valsalva manoeuvre increases episcleral venous pressure and IOP.
Age	IOP is slightly correlated with age.
Exercise	Exercise can decrease IOP by 3 or more mmHg for 1-2 hours (by dehydration and/or acidosis), while certain postures may increase IOP acutely (e.g., head-down yoga positions).[6]
Lifestyle	Large-volume rapid fluid intake increases IOP, while alcohol and marijuana transiently decrease IOP. There is currently little evidence to demonstrate whether alcohol or marijuana influences the natural history of glaucoma.
Posture	Head-down position can double IOP levels.[6] Supine or prone position increases IOP. IOP-elevation asymmetry in lateral decubitus position is associated with asymmetric VF loss in glaucoma patients.[7]

GAT: Goldmann applanation tonometry; IOP: intraocular pressure; VF: visual field

HOW CAN IOP BE MEASURED WITH GAT?

The Goldmann applanation tonometer is considered the gold standard for measuring IOP. The measurement process involves the following steps:

1. Calibration check: The tonometer must be regularly calibrated according to the manufacturer's instructions to ensure accurate measurements (**Figure 2.1.1**).
2. Disinfection: The prism tip of the tonometer is disinfected to prevent the transmission of infections. If disposable tonometer tips are available, they can be used as an alternative.[8]
3. Anaesthetization of the cornea: A topical anaesthetic is applied to the cornea to eliminate discomfort during the measurement process.
4. Instillation of fluorescein: A small amount of fluorescein dye is instilled into the eye. This dye helps to visualize the contact area between the tonometer tip and the cornea.
5. Positioning: The patient's eyelashes are carefully kept out of the way to avoid pressure on the eye that could affect the accuracy of the measurement. The patient is also advised to relax, not to hold their breath, and if necessary, to loosen any tight clothing to prevent any increase in thoracic pressure that could artificially elevate the IOP reading.
6. Measurement: The examiner gently touches the prism tip to the central cornea while looking through the slit-lamp eyepiece. The tonometer applies a flat force to applanate (flatten) a small area of the cornea. By observing the fluorescein, the examiner adjusts the force until a specific endpoint is reached—typically, when the split tear meniscus just touches on the inside, forming a green, fluorescent semicircle.



- Standard method for measuring IOP
- Periodic calibration check recommendation: at least twice yearly

1. Set the tonometer in position on the slit-lamp stand, with the perspex biprism head in place and the tension on the circular dial on the right side (from the examiner's side of the slit lamp) set at 5 mm Hg. The head should lean slightly forwards (away from the examiner).
2. Slowly twirl the circular dial counter-clockwise until the head rocks back towards you. The tension should read 0 to 2 mm Hg below zero (Figure 1)
3. Slowly twirl the dial clockwise until the head rocks forwards again. The tension should read 0 to 2 mm Hg (Figure 2).
4. Remove the calibration rod from its box. Firmly screw into position the holding bracket that slides along the rod so that the closest mark in front of the centre one (on the other side of the centre from you) is aligned as exactly as you can (Figure 3).
5. Slip the rod and its holder into the receptacle on the right side of the tonometer. The head will rock backwards towards you.
6. Slowly twirl the circular dial clockwise until the head rocks forwards. Note the tension reading on the dial: it should be 20 to 23 mm Hg.
7. Slowly twirl the circular dial counter-clockwise until the head rocks backwards. The tension on the dial should read 17 to 20 mm Hg.
8. Remove the rod and holding bracket from the tonometer and reposition the bracket so that it is aligned exactly with the most forward mark on the rod — furthest away from you (Figure 4).
9. Replace the rod in its bracket in the tonometer receptacle. The tonometer head should rock backwards, towards you.
10. Slowly twirl the dial clockwise until the head rocks forwards. The tension should read 60 to 64 mm Hg.
11. Slowly twirl the dial counter-clockwise until the head rocks backwards — the tension should read 56 to 60 mm Hg.

Figure 1.

Figure 2.

Figure 3.

Figure 4.

- The 3 threshold tension levels being used to test the tonometer's calibration are at 0, 20, and 60 mm Hg
- At each of these thresholds, you can gently twirl the dial backwards and forwards, reading the tension as the head responds
- These points should bracket the threshold level evenly — the higher the level being tested, the greater the interval is likely to be

Figure 2.1.1. How to test calibration of a Goldmann tonometer. Images courtesy of Haag-Streit AG and Mandarin Opto-Medic Co Pte Ltd.

7. Reading and interpretation: The tonometer gauge provides a reading of the force required to applanate the cornea. This force is then converted into an IOP measurement in millimetres of mercury (mmHg). The appearance of a distinct fluorescent ring indicates successful contact and allows for an accurate measurement.

Understanding IOP levels through measurements with GAT (**Table 2.1.2**) enables clinicians to make informed decisions about the need for treatment or adjustments in the management of patients at risk of glaucoma, ultimately aiding in the preservation of sight.

Table 2.1.2. Measurement errors associated with Goldmann-style applanation tonometry[9]

Error	Possible cause
IOP reading artificially low	Insufficient fluorescein in tear film Microcystic epithelial corneal oedema
IOP reading artificially high	Excessive fluorescein in tear film Eyelid pressure on globe from blepharospasm Digital pressure on globe to hold lids apart (the lid should be held against the orbit and not on the globe) Obese patient Patient straining to reach chin/forehead rest Patient holding their breath Patient wearing constricting clothing around neck (tight shirt collar and tie for men) Hair lying across cornea distorting mires Lens-corneal (and IOL-cornea) apposition
Technical difficulties (interpret results with caution)	Corneal abnormalities (scars, graft, oedema, keratoconus) Marked corneal astigmatism Small palpebral aperture Nystagmus Tremor
PAPS	PAPS commonly occurs as an adverse effect in patients undergoing treatment with PGAs. It involves alterations in the morphology of orbital pre-adipocytes. In cases of severe PAPS, characterized by symptoms such as ptosis, DUES, and tightness of the upper eyelid tissue, referred to as tonometric PAPS, there is a substantial impact on the precision of obtaining reliable IOP measurements using GAT.[10-12]

DUES: deepening of the upper eyelid sulcus; IOL: Intraocular lens; IOP: Intraocular pressure; PAPS: Prostaglandin-associated periorbitopathy syndrome; PGAs: Prostaglandin analogs

OTHER DEVICES FOR IOP MEASUREMENT

Apart from GAT, various tonometers are available and are listed below non-exhaustively.

Clinic monitoring

Portable devices

These devices have the advantage of being portable and may be used for patients with impaired mobility and cannot be seated for a slit-lamp mounted device. They usually come with disposable cap or tips, making it a convenient option without the need for sterilisation of the tip in between use.

Tono-Pen

The Tono-Pen (Reichert Technologies, Depew, NY, USA) is a portable, battery-powered handheld version of the MacKay-Marg tonometer that combines the properties of applanation and indentation tonometry. Due to its small tip, it is especially useful for determining IOP in scarred, oedematous, irregular, or transplanted corneas.

iCare

The iCare tonometer (Icare Finland Oy, Vantaa, Finland) is a handheld rebound tonometer that measures return-bounce motion of an object impacting the cornea. Various versions of iCare devices are available for IOP measurement. In addition to being portable, it does not require topical anaesthesia, making it suitable for home monitoring by patients. iCare tonometers can be used with the patient in a lying position.

Pneumatonometer

The Pneumatonometer (Reichert Technologies, Depew, NY, USA) utilises a silicon membrane and a gas system to measure the IOP when the membrane is pressed against the cornea. The cornea must be flattened for 5–10 seconds for measurement. The Pneumatonometer can provide a continuous pulsatile record of IOP and transform this pulsatile record into an eye volume waveform.

Pulsair Mark 1

The Pulsair Mark 1 (Keeler, Windsor, UK) is a portable version of an air puff non-contact tonometer (NCT).

Non-contact tonometry

Non-contact tonometers (NCT) measure IOP without contact with the cornea, and therefore require no anaesthesia. Among the available NCT devices, air puff tonometers are commonly used, while the Ocular Response Analyzer (ORA, Reichert Technologies, Depew, NY, USA) and Corvis ST (OCULUS Optikgeräte GmbH, Wetzlar, Germany) are more novel devices that take into account corneal parameters in their measurements. However, there is yet no consensus on the interpretation of the corneal parameters recorded by ORA and Corvis ST.

Non-contact air puff tonometers measure IOP with a puff of air that hits the cornea with known and reproducible area with increasing force, and an optical sensor to determine the moment of applanation. While air puff tonometers are widely used, they require regular calibrations, and are large and table-top mounted. The Pulsair Mark 1 is a portable version that can be used for patients with impaired mobility.

ORA

The ORA utilises a rapid air impulse and electro-optical system to monitor corneal deformation caused by the air impact, providing data on viscoelastic properties of the cornea, namely, corneal hysteresis and corneal resistance factor.

Corvis ST

The Corvis ST records the reaction of the cornea to a defined air pulse using a high-speed Scheimpflug camera, which allows for a more complete characterisation of the deformation effect. Metrics derived include corneal biomechanics index and tomographic biomechanics index.

Dynamic contour tonometry

Dynamic contour tonometry (DCT) involves a slit-lamp mounted tonometer with a tip with concave surface that minimises distortion of the cornea when the pressure on both sides of the cornea is equal. IOP is measured by a concave sensor embedded at the tip of the tonometer. It measures IOP, independent of CCT or corneal curvature, as well as ocular pulse amplitude. However, certain ocular surface factors may prevent DCT measurements.

Twenty-four-hour monitoring

The SENSIMED Triggerfish (Etagnières, Switzerland) is a disposable silicone contact lens with embedded sensor that measures the changes in corneal curvature induced by IOP variations, thereby allowing for semi-continuous recording as a 24-hour IOP surrogate. Most frequently reported adverse events include blurred vision, conjunctival hyperaemia, and superficial punctate keratitis. A 24-hour measurement may be helpful before subjecting a patient with normotensive glaucoma to invasive or expensive investigations, and for patients who progress despite acceptable IOP readings during office hours.

Home monitoring

The iCare Home tonometer (Icare Finland Oy, Vantaa, Finland) is an option for self-tonometry as it does not require anaesthesia and has an built-in system to indicate alignment. Training must be provided to the individual before use. While self-tonometry is not yet a common practice among glaucoma patients, it provides the benefit of obtaining 24-hour profiles including non-office hours without hospital admissions. However, it still does not provide information on IOP profile during undisturbed sleep.

Despite there being a good number of publications on the useful aspects of various home monitoring devices, we are still awaiting more definitive evidence, i.e., good quality randomised clinical trials, to determine whether the use of home self-monitoring of IOP leads to better long-term glaucoma outcomes. Furthermore, cost-effectiveness analyses, in particular for the less wealthy countries within the Asia-Pacific region, should be conducted before we can widely recommend the practice of home self-monitoring of IOP. On the other hand, with the rapid expansion of telemedicine in the post-COVID era, it is anticipated that home IOP monitoring may assume an important role in the future for providing telemedical glaucoma care.

FAQ

Can steroid ointment used for skin lesions increase IOP?

Steroids in any form can increase IOP. A detailed drug history is necessary, especially if the response to treatment changes, for example, loss of IOP control in a previously stable patient.

Do we need to check CCT for all glaucoma patients and suspects?

Ideally, yes. IOP measurement is not precise, and there is no “correction” factor to make it accurate. CCT should be checked in suspected OHT and NTG.

What is the effect of corneal oedema on IOP measurement?

Corneal oedema can cause the tonometer to provide a falsely low reading.

Is the type of musical instrument a patient plays important for the management of glaucoma?

Playing wind instruments increases IOP considerably by the Valsalva manoeuvre, which increases episcleral venous pressure.

As the air puff non-contact tonometer works on the applanation principle, can it be used instead of the GAT?

The air puff tonometer has reasonable agreement with GAT in the physiological range of IOP. However, its variability is higher.

What is the role of the diurnal variation test? Do all patients require it?

IOP fluctuates over 24 hours and the magnitude of the fluctuations is different for each patient. Knowing the baseline before starting medication is important, as is knowing the effect of the medication during the day. As a full 24-hour diurnal variation test is logistically difficult for patients and practitioners, it is best to obtain several IOP readings during the day, or at different times for clinic visits. A 24-hour or full diurnal variation test may be helpful before subjecting a patient with NTG to invasive or expensive investigations, and for patients who progress despite acceptable IOP readings during office hours.

How is applanation IOP performed in a patient with high astigmatism (> 4 D)?

In this scenario, the usual method provides an inaccurate IOP reading. The Goldmann or Holladay methods can provide a more reliable IOP measurement, but alterations to the standard method are required. Clinically, the Holladay method is easier: measure the IOP with the tonometer prism at 90° and 180°, then take the mean of these 2 readings to derive the IOP. For the Goldmann method, the red line on the applanation prism (set at 43°) is adjusted to the flat axis of the corneal curvature and the measurement is taken as usual.

What is the relationship of blood pressure to glaucoma?

Raised blood pressure has been associated with increased IOP, but it is not a simple 1:1 relationship. Systemic hypertension has been associated with glaucoma in hospital-based studies, and some population-based studies show a link. Low perfusion pressure is a risk factor for glaucoma (and overtreatment of hypertension may contribute to this).

How should the applanation tonometer tip be sterilised?

Among 70% isopropyl alcohol, 3% hydrogen peroxide, and 1:10 dilute bleach (sodium hypochlorite), only the last is effective against adenovirus and herpes simplex virus.[8]

What is the effect of laser refractive surgery on IOP measurement?

Refractive surgery, including LASIK, LASEK, PRK, and small incision lenticule extraction (SMILE), causes a falsely low IOP measurement. A similar depth of ablation will result in a greater decline in IOP measurement following LASIK than following surface ablation. Pascal DCT and ORA are less sensitive to changes in corneal biomechanics.

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2.2. ANTERIOR CHAMBER ANGLE ASSESSMENT: GONIOSCOPY VERSUS ANTERIOR SEGMENT OCT

Key messages

- Examination of the anterior chamber angle with gonioscopy is mandatory in the diagnostic workup of glaucoma.
- Gonioscopy is indispensable for assessing the pigmentation of the TM (*e.g.*, in pigment dispersion syndrome) and neovascularization of the angle (*e.g.*, in NVG).
- While angle assessment with gonioscopy can be confounded by inadvertent indentation and slit-lamp illumination, AS-OCT offers non-contact assessment of the anterior chamber angle width and iris trabecular contact in the dark.

ANTERIOR CHAMBER ANGLE EVALUATION: GONIOSCOPY VERSUS AS-OCT

Gonioscopy is a 360° assessment of the anterior chamber angle that requires direct contact with the eye and can detect secondary causes of elevated IOP, including pigment dispersion syndrome (pigmentation of the TM) and neovascularization of the angle.[1] It enables the detection of PAS and plateau iris configuration. Its limitations include subjectivity and potential overestimation of the angle width by inadvertent corneal indentation and slit-lamp illumination.[2-4] On the other hand, anterior segment OCT (AS-OCT) is a non-contact imaging technique that provides a cross-sectional view of the anterior chamber angle configuration, enabling objective measurement of the angle dimensions in the dark.[5-8] While it cannot detect pigmentation or neovascularization of the angle, it can more precisely evaluate iris trabecular contact (ITC) in 360° compared with gonioscopy.[8]

GONIOSCOPY

Gonioscopy involves biomicroscopic examination of the anterior chamber angle, and is essential for glaucoma diagnosis, treatment, and prognosis (**Figure 2.2.1**).

To perform gonioscopy and assess ITC, it should be conducted in a dark room with minimal illumination and good anaesthesia. The procedure requires the use of a small slit-lamp beam to minimize light on the pupil, along with high magnification and dim slit illumination (**Figure 2.2.2**). The slit lamp should be set on the upper cornea, with the beam off-centre 30° to 45° nasally, and if necessary, the upper lid should be elevated. The lens should be gently placed on the eye, and the examiner should look through the upper mirror while placing the lens on the eye.

Figure 2.2.1. (Left) Gonioscopy narrow angle without indentation. **(Right)** Gonioscopy narrow angle without indentation showing PAS. Photographs courtesy of Atsuo Tomidokoro, Japan.

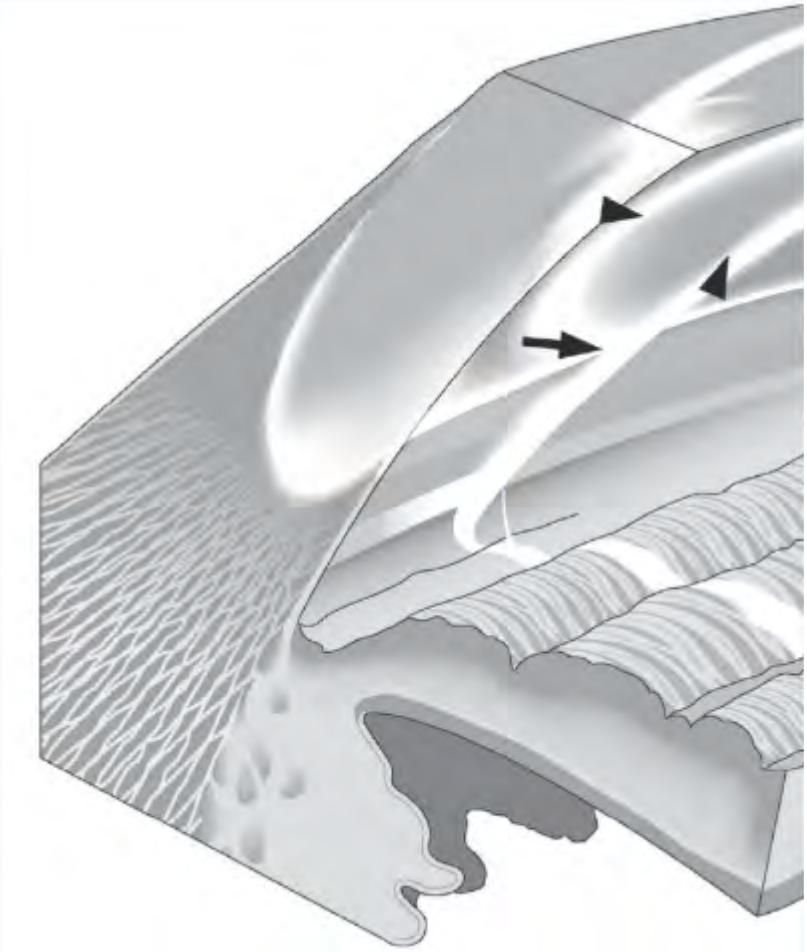

Figure 2.2.2. Corneal wedge diagram. A gonioscopic view of the drainage angle at high magnification (x 16 or x 25). The thin slit beam illuminates the angle region and splits to form the 'corneal wedge' (arrow heads). The boundaries of the wedge meet at Schwalbe's line (arrow). Schematic reproduced with permission from BMJ Books; Copyright ©2000.

VAN HERICK METHOD USES CORNEAL THICKNESS AS A UNIT OF MEASURE

Grade 0	Iridocorneal contact
Grade I	Peripheral anterior chamber depth between iris and corneal endothelium is <1/4 corneal thickness (occludable)
Grade II	>1/4 but <1/2 of corneal thickness
Grade III	≥1/2 of corneal thickness (non-occludable)

SCHAFFER METHOD

Grade	0	I	II	III	IV
Method **Shaffer**	Closed	10°	20°	30°	40°
Method **Modified Shaffer**	Schwalbe's line is not visible	Schwalbe's line is visible	Anterior TM is visible	Scleral spure is visible	Ciliary band is visible

SPAETH METHOD

1. Iris insertion
Anterior to Schwalbe's line or TM
Behind Schwalbe's lines
Centred at scleral spur
Deep to scleral spur
Extremely deep/on ciliary band

2. Angular width
Slit
10°
20°
30°
40°

3. Peripheral iris configuration
Queerly concave
Regular
Steep

4. TM pigment
0 (none) to 4 (maximal)

Figure 2.2.3. Grading system for gonioscopy.

The examination should then move to the inferior angle, followed by the superior angle after moving the slit-lamp beam inferiorly to avoid the pupil. Subsequently, the beam should be turned 90° and moved on axis before examining the nasal and temporal angles. Findings should be recorded on a goniogram (**Figure 2.2.3**), and in the presence of appositional closure, indentation should be performed to check for PAS. Additionally, altering the position of the mirror or gaze may be necessary to visualize the angle over a convex iris.[9-11]

Methods

The gonioscopic contact lens permits the angle to be seen.

Direct gonioscopy

Place the Koeppe goniolens on the anaesthetised cornea with the patient supine. Fill the space between the lens and the cornea with a contact fluid (saline or methylcellulose). View the angle with a handheld biomicroscope and an illuminator.

Indirect gonioscopy

At the slit lamp, place a mirrored lens (Goldmann-type or 4-mirror indentation) on the anaesthetised cornea:

- For the Goldmann-style 1- (or 2-) mirror lens, use viscous material (methylcellulose 2%) to fill the space between the cornea and goniolens.
- For the 4-mirror Zeiss-type lens (larger radius of curvature and small corneal contact area), no space filler is needed.
- The 4-mirror goniolens allows the entire angle to be viewed without lens rotation and permits dynamic gonioscopy through corneal indentation.
- To avoid light-induced miosis falsely deepening the angle, gonioscopy is performed as a "dark art" in a dim or dark room and with minimal slit-lamp light intensity.

Indentation (pressure/dynamic) gonioscopy

- With the 4-mirror indirect goniolens, press on the cornea to displace fluid into the angle to visualise the anatomic landmarks and to differentiate appositional from PAS closure.
- Facilitate visualisation into narrow angles by:
  - static primary position gonioscopy.
  - dynamic gonioscopy:
    - tilting lens > look over central iris.
    - patient gaze to mirror > depress peripheral iris indentation.

AS-OCT

The use of AS-OCT for the evaluation of the anterior chamber angle (**Figure 2.2.4**) has significantly advanced with the introduction of high-speed swept-source AS-OCT technology. This innovation allows for non-contact, 360° imaging of the angle even in dark conditions, providing valuable insights into the angle structures. Some AS-OCT devices are equipped with the capability to automatically detect the scleral spur and generate anterior chamber angle measurements in a polar plot, enhancing the efficiency and accuracy of angle assessment (**Figure 2.2.5**). However, a limitation of AS-OCT imaging is the potential obscuring of the superior and inferior angles by the eyelids. Pulling down the lower lid against the lower orbital rim to expose the lower limbus, and elevating the upper lid against the upper orbital rim to expose the upper limbus may be needed to minimize the impact of eyelid obscuration. Furthermore, anatomical angle closure, as determined by the 360° assessment of ITC in AS-OCT, has a greater precision than traditional gonioscopy grading in the diagnostic evaluation of angle closure. This evaluation of ITC can serve as a valuable framework for assessing the risk of PACD, with the extent of ITC being associated with the likelihood of PAC or PACG.[8]

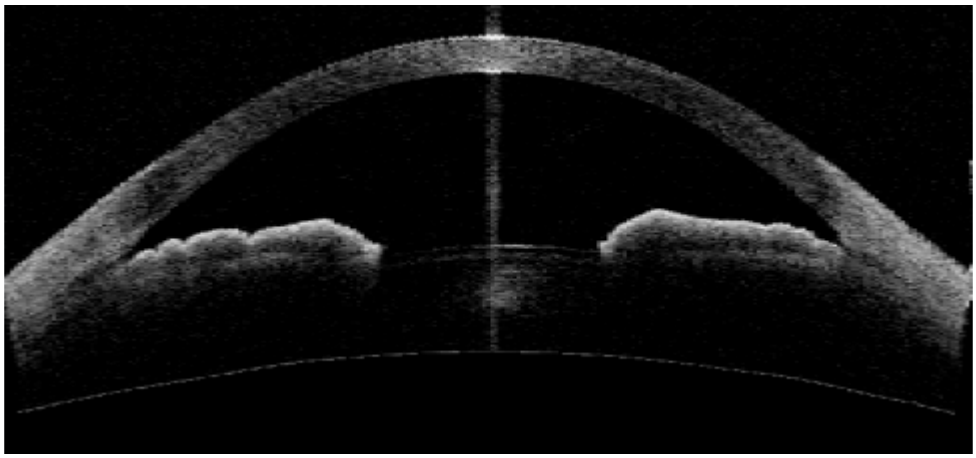

Figure 2.2.4. Anterior segment optical coherence tomography image. Photograph courtesy of Renyi Wu, China.

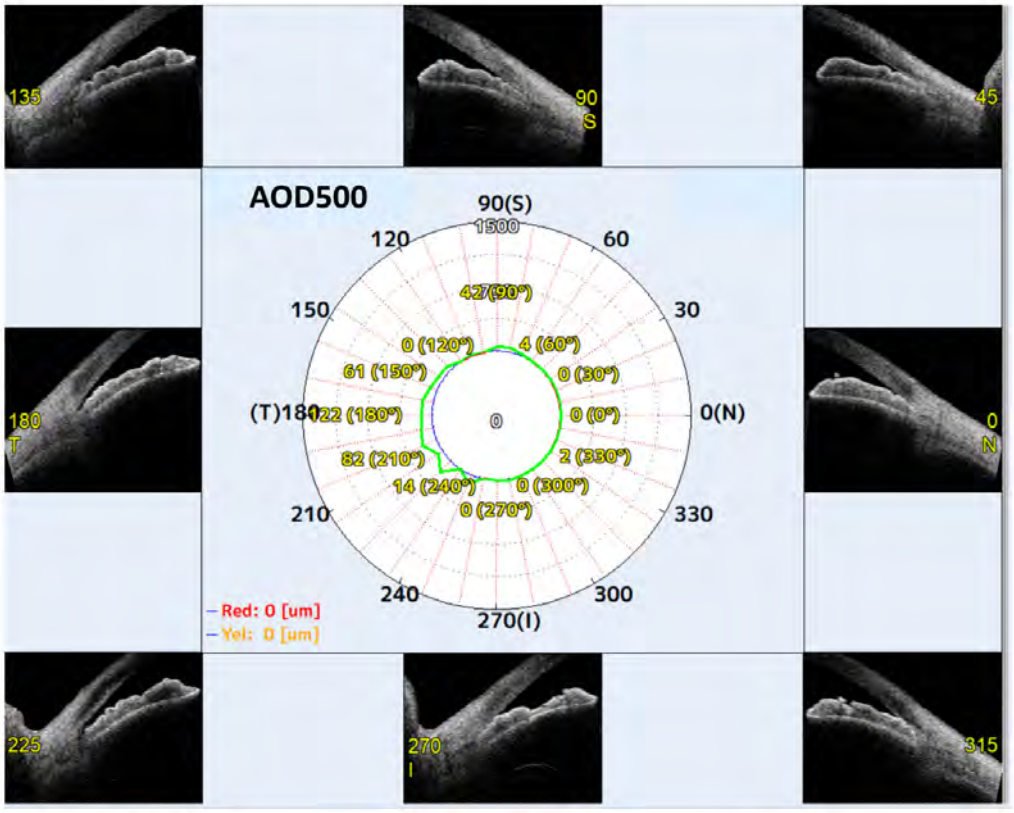

Figure 2.2.5. Polar plot of AOD500 (angle opening distance) of an eye with primary angle closure. Photograph courtesy of Christopher Leung, Hong Kong, China.

DIAGNOSTIC EVALUATION OF PACD

PAC is a condition that encompasses 3 stages: PACS, PAC, and PACG. The defining feature across these stages is the presence of gonioscopic angle closure, typically defined when the posterior trabecular meshwork is not visible for at least 180°.[5,9,11,12] The diagnostic evaluation of angle closure is presented in **Figure 2.2.6**. For plateau iris configuration, ultrasound biomicroscopy is often required to confirm the diagnosis (**Figure 2.2.7**).

PACS

PACS represents the earliest stage of the disease. It is characterized by appositional angle closure, normal IOP, and no evidence of optic nerve damage.

PAC

PAC involves gonioscopic angle closure with PAS and/or elevated IOP without evidence of optic nerve damage.

PACG

PACG shows angle closure features as seen in PAC, along with signs indicative of glaucomatous optic nerve damage.

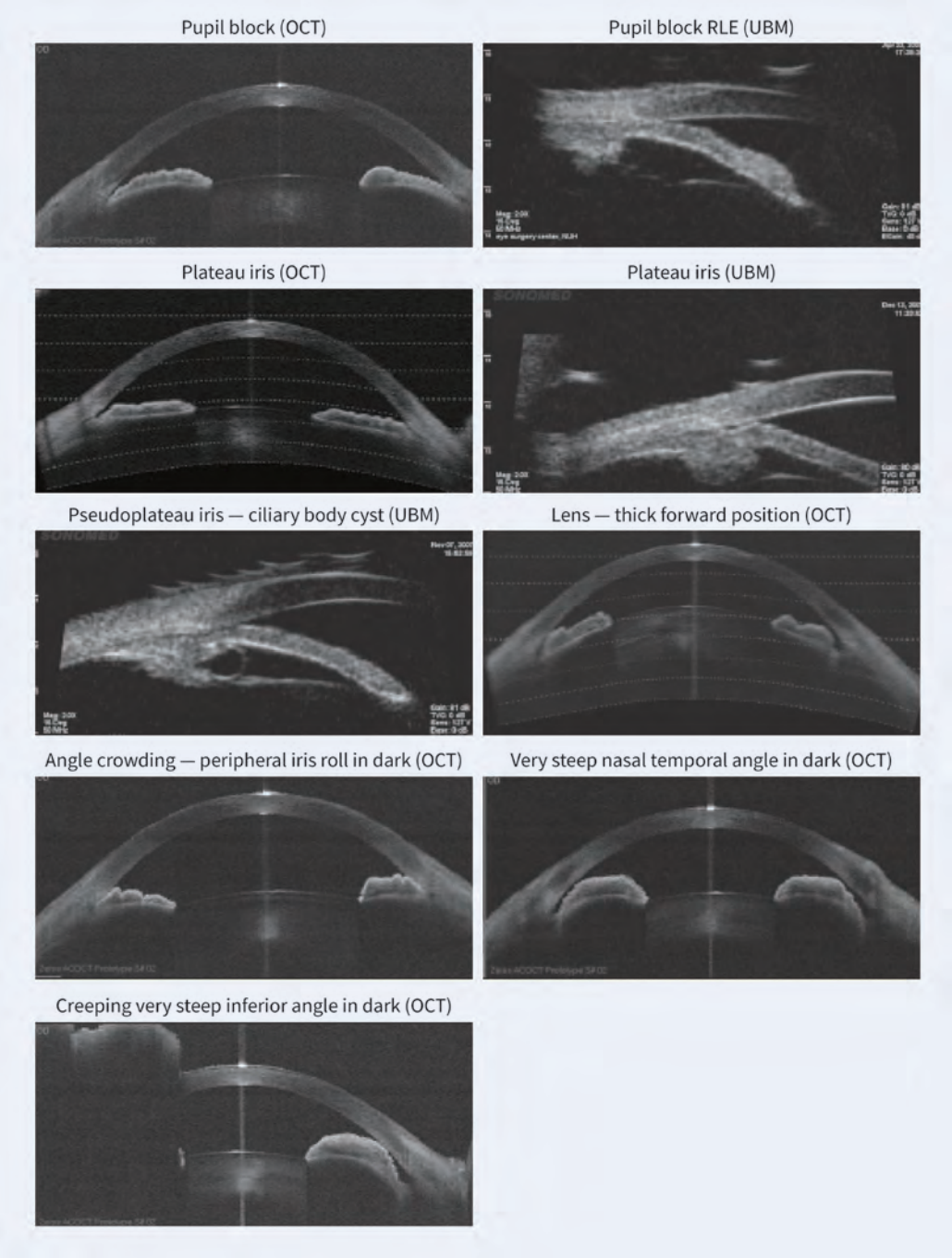

Figure 2.2.6 Mechanisms of angle closure. Photographs reproduced courtesy of Paul Chew.

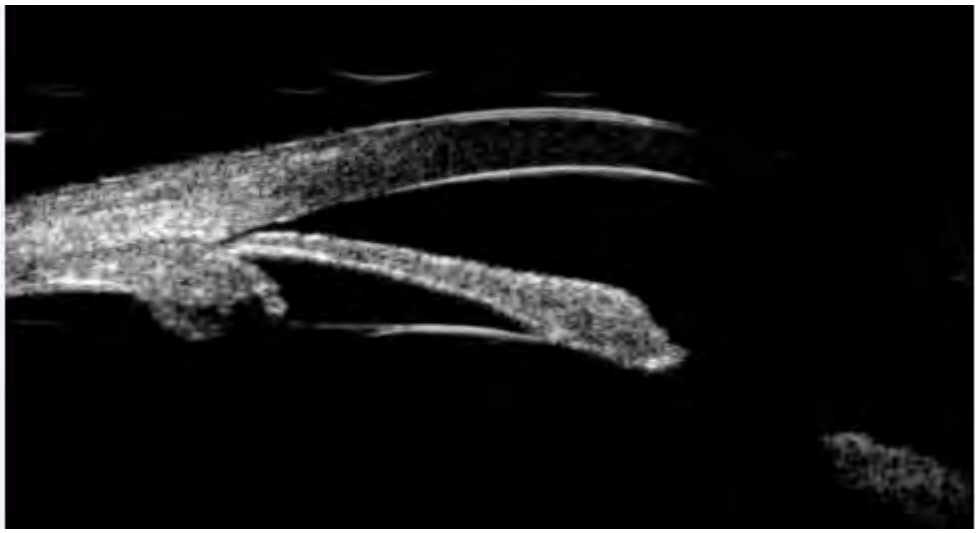

Figure 2.2.7. Ultrasound biomicroscopy. Photograph courtesy of Renyi Wu, China.

FAQ

Can the Van Herick method be used instead of gonioscopy for angle assessment in the clinic?

No, all clinic patients need gonioscopy. If it is impossible to do gonioscopy due to patient factors, as long as the Van Herick test (**Figure 2.2.9**)[13] result is at least one-quarter corneal thickness and the torchlight test is negative, it is almost 98% certain that the angle is not closed.

What is the ideal gonioprism? Can the Goldmann 3-mirror lens be used for gonioscopy?

It would be ideal to have an indentation gonioprism (Sussman, Zeiss, or Posner 4-mirror) as well as a Goldmann single or 2-mirror lens. The indentation gonioscope uses the patient's tear film as coupling fluid and allows easier indentation to look for anatomical landmarks and to distinguish appositional from synechial closure, and to perform routine gonioscopy. However, it is easier to put pressure on the eye and artificially open the angle with this type of lens. The disadvantages of the 3-mirror gonioprism are that it does not have the right optics (mirror height and distance from the centre of the lens) for gonioscopy, it is harder to use for indentation gonioscopy, it is bulky, and it needs coupling fluid. The latter disadvantage also applies to the single and 2-mirror lenses, making routine gonioscopy difficult.

How often should patients with glaucoma undergo gonioscopy? What if the patient is known to have POAG?

Gonioscopy is mandatory at the initial evaluation to assess whether the angle is closed or open and, in the presence of angle closure, to distinguish the amount of synechial versus appositional closure. How much the angle opens at indentation predicts how much it will open after LPI. In an open angle, gonioscopy identifies other findings in the angle, for example, PXF material or irregular pigmentation. After LPI, repeat gonioscopy identifies the response to the procedure (when the effect of pilocarpine has worn off). Subsequently, gonioscopy can be performed if there is a suspicion that something has changed. Patients with POAG can develop angle narrowing and require regular gonioscopy, especially if anything changes. Changes in angle configuration and other findings (pigment, new vessels) provide information about secondary risk factors within the eye.

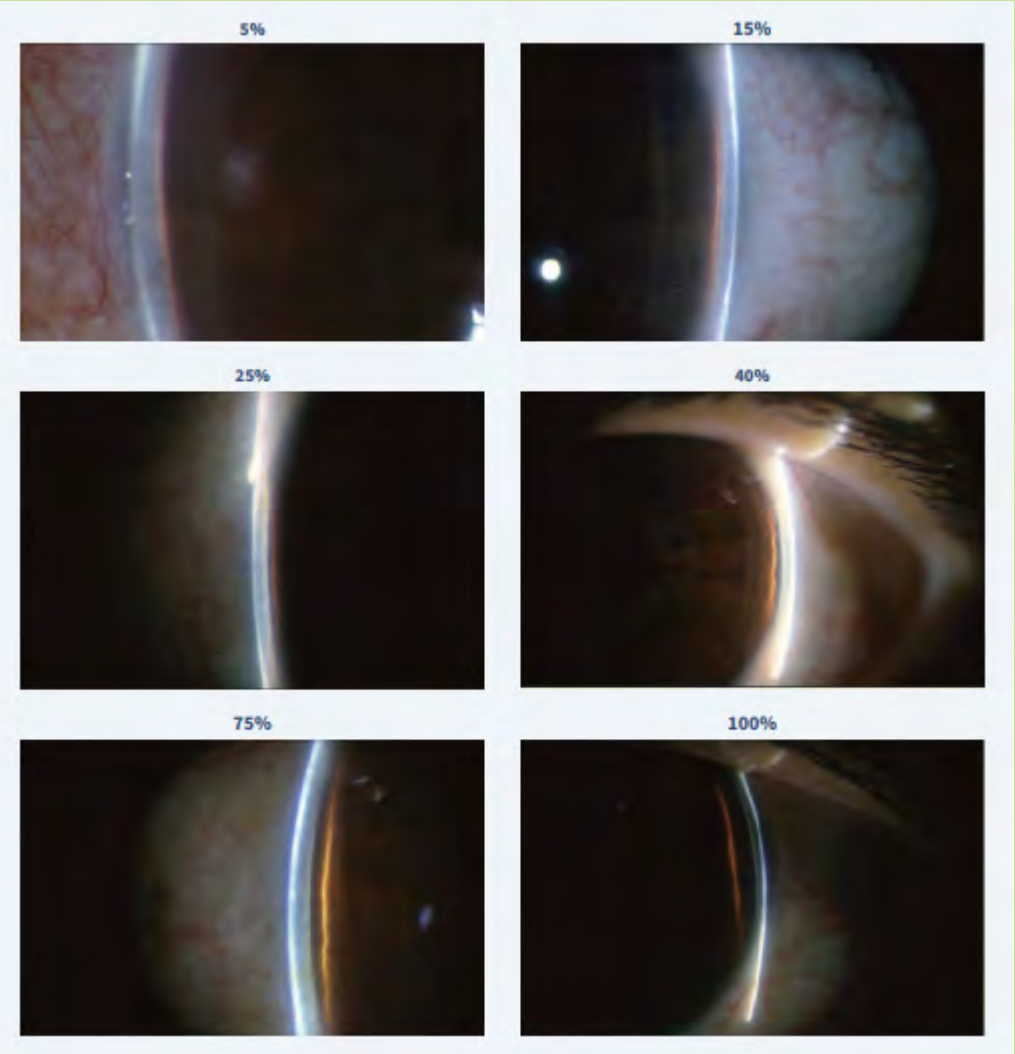

Figure 2.2.8. Modified Van Herick grading. Photographs courtesy of Paul Foster, UK. ©2008.

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2.3. ASSESSMENT OF THE OPTIC DISC, RETINAL NERVE FIBRE LAYER, AND GANGLION CELL-INNER PLEXIFORM LAYER

Key messages

- Clinical examination of the optic disc is essential to discriminate GON from non-GON.
- Widefield imaging with OCT covering the parapapillary region and the macula for RNFL and ganglion cell-inner plexiform layer (GCIPL) thickness measurement is more informative compared to circumpapillary RNFL thickness assessment in the diagnostic assessment and monitoring of glaucoma.
- Caution should be taken in interpreting the RNFL/GCIPL thickness deviation/probability maps in highly myopic eyes due to the increased false-positive errors. This is because the normative datasets in most OCT models contain RNFL/GCIPL thickness measurements obtained from eyes that are not highly myopic.
- Macular parameters may not be reliable for glaucoma assessment in eyes with macular disease.
- Change analysis of RNFL/GCIPL thicknesses for assessment of glaucoma progression requires event-based and trend-based analyses.
- The role of OCTA remains unclear in routine diagnostic evaluation of glaucoma.

CLINICAL EXAMINATION OF THE OPTIC DISC

Neuroretinal rim assessment

In assessing the optic disc's anatomy in the context of GON, the neuroretinal rim of the ONH holds importance over the cup. Clinically, the rim width spans from the inner border of the scleral ring to a point just below the level of the scleral ring. A hallmark of GON is the depletion of tissue from the rim's inner edge. Certain features indicative of glaucomatous damage include diffuse loss, narrowing, or notching of the rim, particularly towards the disc margin; rim haemorrhage; and a noticeable asymmetry in rim width between the 2 eyes when disc size asymmetry is absent (**Figure 2.3.1**). Additionally, significant asymmetry in rim width between the superior and inferior sectors of the optic disc raises suspicion. It is useful to apply the Inferior > Superior > Nasal > Temporal (ISNT) rule as a diagnostic check for evidence of glaucomatous damage.

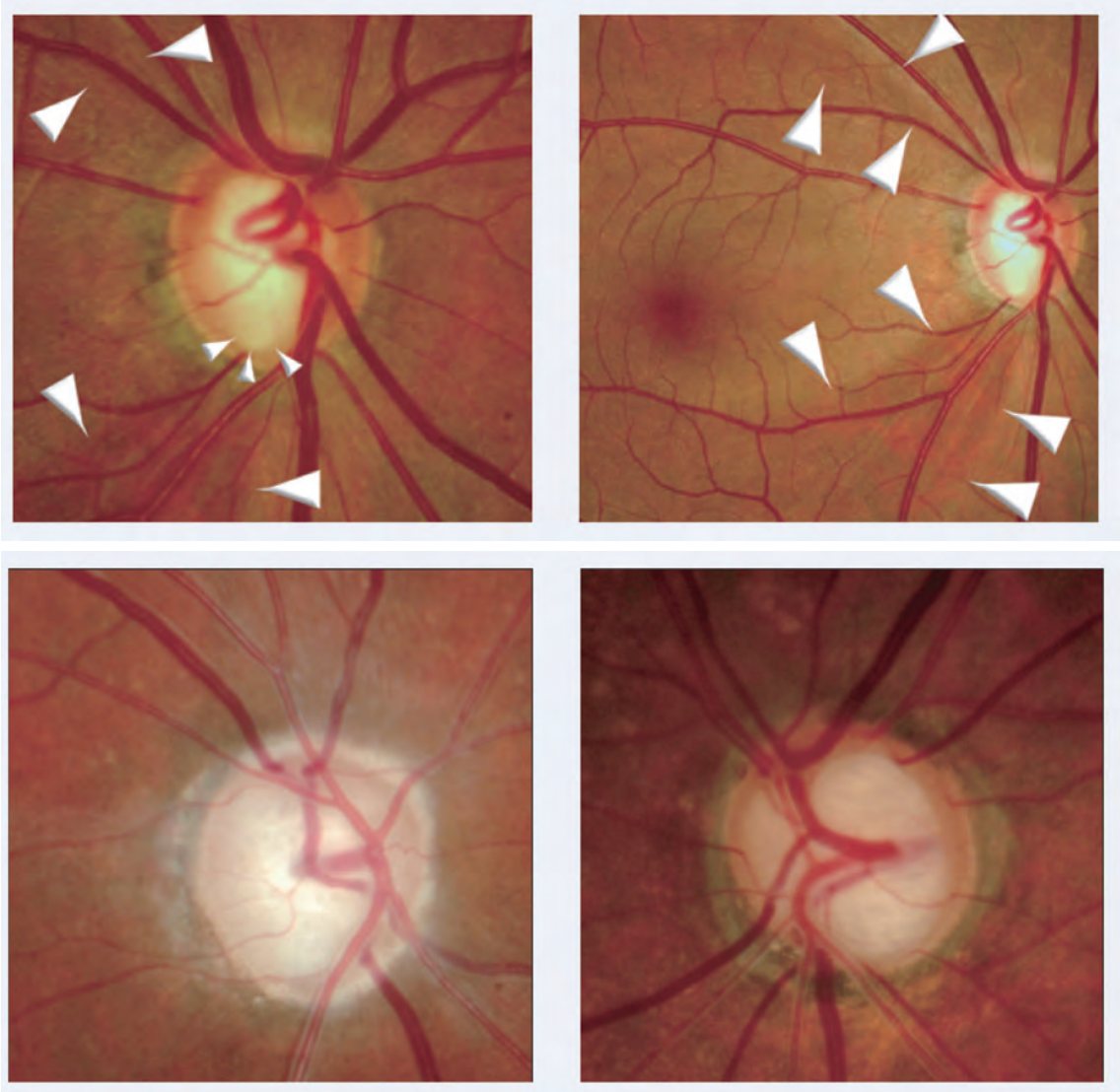

Figure 2.3.1. (Top) Moderate glaucomatous optic neuropathy (GON). Note the localised loss of both inferior and superior neuroretinal rim; classic inferior notch (small arrow heads); and retinal nerve fibre layer (RNFL) defect in both the superior and inferior arcuate area (large arrow heads). **(Bottom)** Advanced GON. Note the neuroretinal rim thinning; cup extending to the disc rim; circumlinear blood vessel baring; bayoneting of the blood vessels, and peripapillary atrophy.

ISNT rule

Normally, the thickest to thinnest parts of the neuroretinal rim of the optic disc are Inferior > Superior > Nasal > Temporal (ISNT). Any variation from this may help to detect glaucomatous damage. Of note, the ISNT rule may not be followed in up to 50% of normal discs in certain populations.[1] The essence of the ISNT rule is the T: in almost all normal eyes, independent of ethnicity, the narrowest part of the rim is in the temporal 60°.

Disc haemorrhage

The presence of disc haemorrhage increases the likelihood of glaucoma progression, with a 6-fold increase in risk according to univariate analysis and a 4-fold increase as per multivariate analysis.[2,3] Furthermore, the occurrence of recurrent disc haemorrhages amplifies the risk of optic nerve damage by 3 to 4 times compared to a single haemorrhage, underscoring the critical nature of these symptoms in the context of glaucoma progression.

OPTIC DISC CHANGES IN GLAUCOMA PROGRESSION

The progression of GON is a gradual process, posing a challenge in the timely detection of subtle changes. Regular examination of the optic disc is crucial for patients diagnosed with glaucoma. Signs indicative of potential glaucoma progression include notching and thinning of the neuroretinal rim, development or expansion of RNFL defects, and development or enlargement of disc haemorrhages. The use of baseline and serial optic disc imaging for detection of these changes cannot be understated. In this context, high-quality fundus photography is a valuable tool for monitoring glaucoma progression. It provides a consistent and detailed visual record of the optic disc, aiding in the identification of the aforementioned signs with greater accuracy. Unlike other diagnostic tools, such as visual field analysers and OCT devices, fundus photography is less influenced by variations in the instrument brands and models, offering a more stable reference over time. However, it is imperative to note that the interpretation of fundus photographs is largely subjective, requiring a considerable level of expertise that may not always be available.

OCT imaging

OCT has revolutionized the diagnostic evaluation of glaucoma by providing detailed imaging of the RNFL and GCIPL. By measuring the RNFL/GCIPL thicknesses and neuroretinal rim width, OCT offers objective and quantitative data that aids in early detection and monitoring of glaucoma.[4-12] This non-invasive imaging technique has become an invaluable tool for clinicians, enabling them to make informed decisions and provide tailored treatment plans to effectively manage glaucoma.

Widefield imaging of the RNFL/GCIPL for glaucoma assessment

Narrowing of the neuroretinal rim and thinning of the RNFL and GCIPL are 2 key diagnostic features of glaucoma.[13,14] OCT can provide objective and reproducible measurements of the neuroretinal rim width and RNFL/GCIPL thicknesses. While circumpapillary RNFL thickness measurement has long been used for detecting glaucoma, topographic analysis of RNFL thickness utilizing the RNFL thickness map and the RNFL thickness deviation/probability maps can provide more diagnostic information and surpass circumpapillary RNFL thickness in detecting RNFL defects in glaucoma (**Figure 2.3.2**).[15-17] With the advent of high-speed Fourier-domain OCT, widefield imaging that covers both the parapapillary region and the macula has emerged as the preferred method for assessing RNFL/GCIPL thickness (**Figure 2.3.3**). By capturing a larger field of view, it becomes possible to reveal the extent of RNFL defects in volume scans (3-dimensional data), thereby offering supplementary diagnostic information beyond the traditional circumpapillary RNFL thickness measurement (2-dimensional data). This ensures a more accurate and detailed assessment of glaucoma and its progression.[16,18-21] As the macula has a higher density of RGCs, GCIPL thickness is typically measured at the macula.[22,23] Widefield RNFL/GCIPL thickness measurement can augment the diagnostic performance for glaucoma detection and monitoring.[11,24,25] Clinical assessment of the colour and the width of the neuroretinal rim remains essential to differentiate GON from non-GON; rim pallor is indicative of non-GON.[26-28]

Interpretation of RNFL/GCIPL thickness abnormalities

Normative reference data are typically employed in OCT to report whether the RNFL/GCIPL thickness is within or outside the normal limits (*i.e.*, below the 1st or the 5th percentiles) in the RNFL/GCIPL thickness deviation or probability maps.[7,29] A major limitation of most normative reference databases is the inclusion of normal subjects with a limited range of refractive errors. For example, in eyes with high myopia, false-positive errors in the RNFL/GCIPL thickness deviation/probability maps are common because the normative datasets used in most OCT

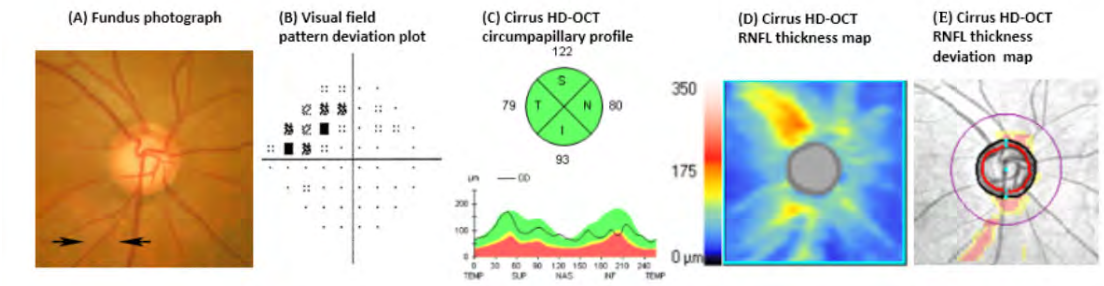

Figure 2.3.2. A glaucomatous eye with an inferotemporal retinal nerve fibre layer (RNFL) defect barely visible in the fundus photograph **(A)** had superonasal defects in the visual field pattern deviation plot **(B)**. Whereas Stratus optical coherence tomography (OCT) **(C)** and Cirrus high-definition OCT **(D)** clock-hour and average RNFL thicknesses failed to show any abnormality (all were all within normal limits), the inferotemporal RNFL defect was evident in the RNFL thickness deviation map **(E)**. Abnormal pixels of RNFL measurement are indicated in yellow or red. Adapted from Leung *et al.*[15]

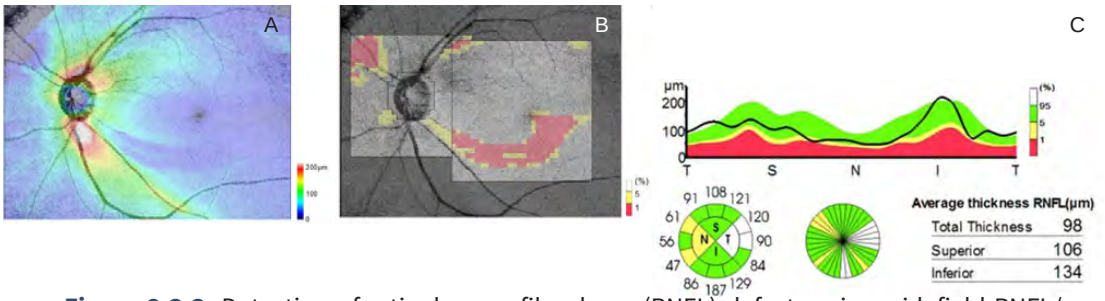

Figure 2.3.3. Detection of retinal nerve fibre layer (RNFL) defects using widefield RNFL/ganglion cell-inner plexiform layer (GCIPL) thickness probability map. It is worth noting that the inferotemporal RNFL defect is only detectable in the RNFL/GCIPL thickness probability map, but not in the circumpapillary RNFL thickness profile. **(A)** RNFL thickness map. **(B)** RNFL/GCIPL thickness probability map. **(C)** Circumpapillary RNFL thickness profile. Photographs courtesy of Christopher Leung, Hong Kong, China.

systems are based on measurements obtained from eyes that are not highly myopic.[30-33] The structural characteristics of highly myopic eyes differ significantly from those of non-myopic eyes, leading to variations in the topographic distribution of the RNFL/GCIPL thickness. Additional research and refinement of normative datasets with inclusion of highly myopic eyes are needed to improve the accuracy of OCT assessments in this patient population.

Another challenge in interpreting the RNFL/GCIPL thickness deviation/probability maps comes from the difficulty in discriminating false-positive from true-positive RNFL thickness abnormalities. This is because the borders of RNFL defects in the RNFL/GCIPL thickness/probability maps frequently do not align with the trajectories of the retinal axonal fibre bundles. RNFL Optical Texture Analysis (ROTA) is a recently developed algorithm that integrates RNFL thickness and RNFL reflectance data to uncover the optical texture and trajectories of axonal fibre bundles using conventional OCT scans,[34] unveiling the patterns and location of RNFL defects in different stages of glaucoma without relying on the normative reference databases (**Figure 2.3.4**).[34-36]

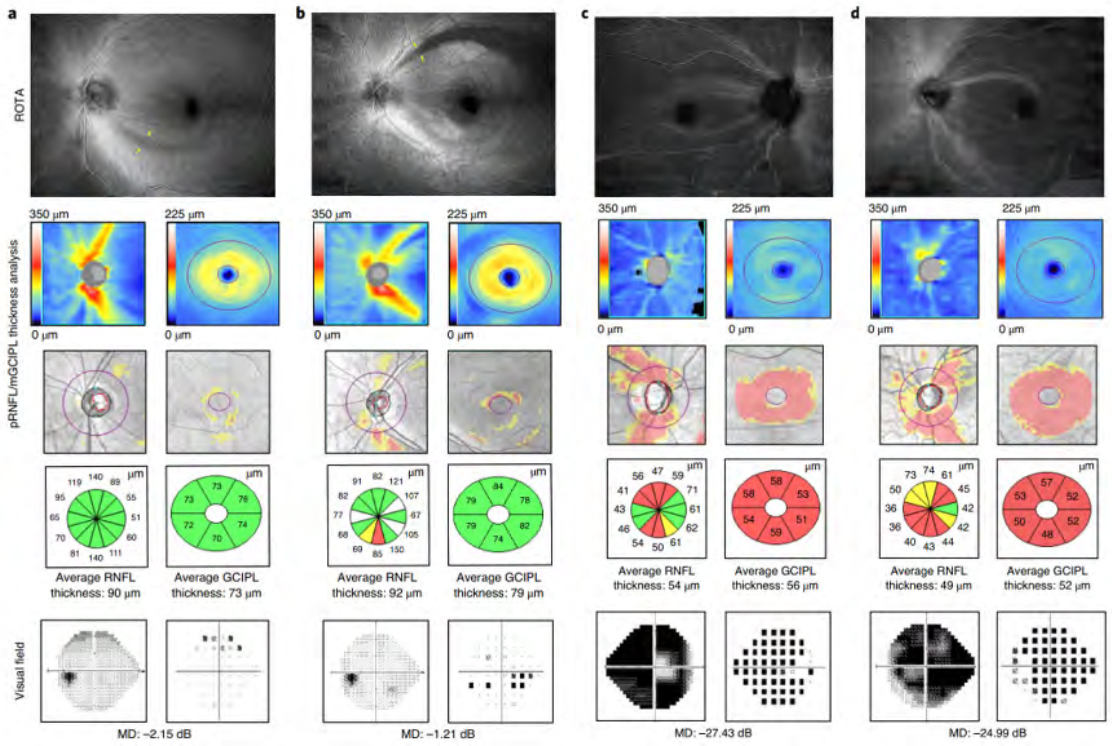

Figure 2.3.4. Retinal nerve fiber layer (RNFL) optical texture analysis (ROTA) reveals the patterns and extent of RNFL defects across different stages of glaucoma. Modified from Leung *et al.*[34]

Assessment of progressive RNFL/GCIPL thinning

Like VF progression analysis, change analysis of RNFL/GCIPL thickness measurements employs trend-based[25,37] and event-based[9,38] analyses. A trend-based analysis estimates the rate of change of the parameter of interest over time and provides the statistical significance of the slope. An event-based analysis determines progression to have occurred if the amount of change crosses a particular pre-set value (this value is generally based on the test-retest variability of the parameter). **Figure 2.3.5** shows an example of the Guided Progression Analysis (GPA) report, which employs both trend-based and event-based analyses to identify progressive RNFL/GCIPL thinning. It has been shown that progressive RNFL thinning and progressive GCIPL thinning are both predictive of visual field progression (**Figure 2.3.6**); including both is relevant to facilitate early detection of glaucoma progression.[39] Nevertheless, progression analyses from OCT only provide statistically significant change, but not clinically significant change. Therefore, OCT progression analysis reports should be interpreted in the context of the entire clinical picture, considering the stage of glaucoma, IOP levels, severity of visual function loss, and other risk factors of disease progression, such as optic disc haemorrhage and increase in beta peripapillary atrophic region.

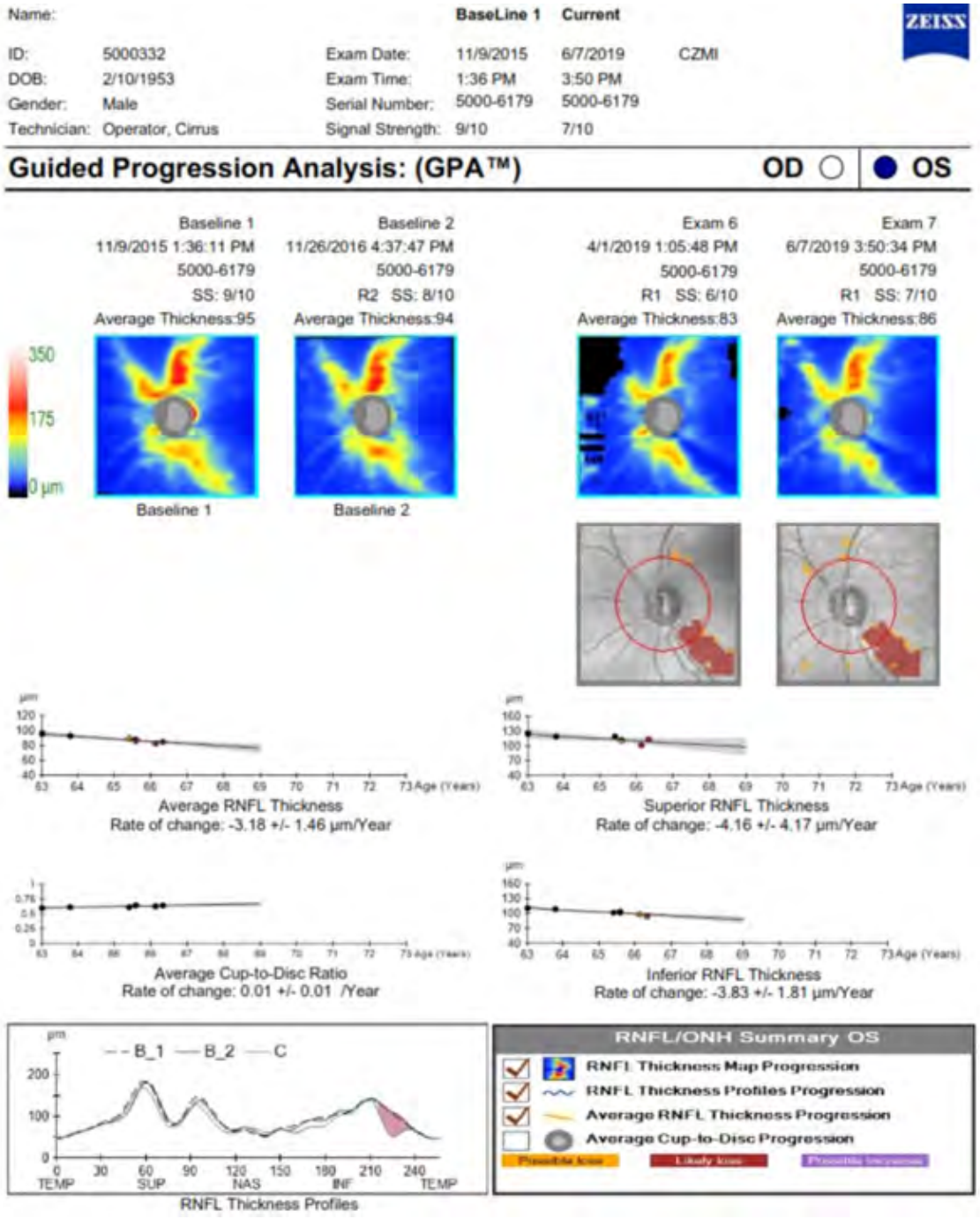

Figure 2.3.5. Guided progression analysis (GPA) of Cirrus high-definition optical coherence tomography showing structural progression on both event- and trend-based methods. The GPA printout includes 3 analyses: (1) a chronological display of retinal nerve fibre layer (RNFL) thickness maps and RNFL thickness change maps, which is an event-based analysis; (2) average cup-to-disc ratio and superior, inferior, and average RNFL thickness graphs representing the rate of change, which are trend-based analyses; and RNFL thickness profiles comparing the current exam to the baseline exams, which is an event-based analysis. Photograph courtesy of Harsha Rao, India.

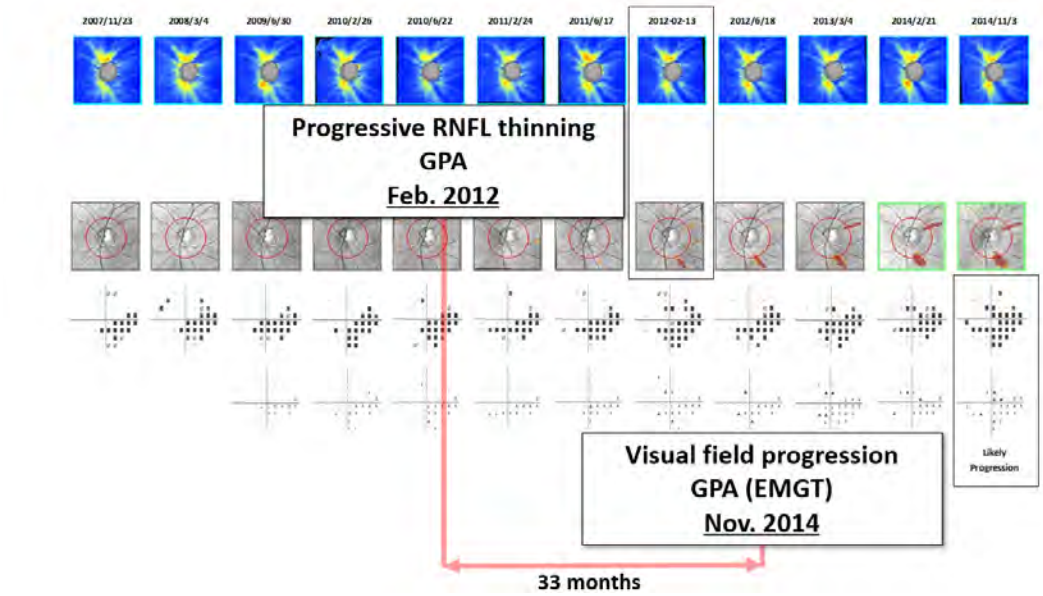

Figure 2.3.6. An example illustrating progressive retinal nerve fiber layer (RNFL) thinning detected prior to visual field progression. GPA: Guided Progression Analysis. EMGT: Early Manifest Glaucoma Trial. Photograph courtesy of Christopher Leung, Hong Kong, China.

Limitations of OCT

OCT imaging requires clear media for good quality scans. OCT scans in eyes with media opacities, such cataract, often lead to poor quality images[40,41] that may cause misinterpretation. Likewise, caution must be exercised when interpreting the reference database classifications provided by OCT in subjects with coexisting diabetic maculopathy, age-related macular degeneration, and other macular pathologies. Optic disc and RNFL/GCIPL parameters generated by different OCT devices should not be used interchangeably.[42,43] In advanced glaucoma when the RNFL is already thin, further progressive RNFL thinning causes little change in the OCT RNFL thickness measurement, resulting in a floor effect. This limits the use of OCT in detecting progression in eyes with advanced glaucoma. Of note, OCT cannot detect neuroretinal rim pallor and disc haemorrhages. OCT is a complementary tool rather than a replacement for a comprehensive clinical evaluation. The combination of clinical assessment and OCT findings allows for a more comprehensive understanding of the patient's condition and ensures a more accurate and personalized approach to patient care.

THE ROLE OF OCT ANGIOGRAPHY IN THE DIAGNOSTIC EVALUATION OF GLAUCOMA

OCTA is a non-invasive, dye-less technology that is capable of imaging large vessels as well as the microvasculature of the ONH and retina by performing multiple OCT scans of the same region. OCTA scans of the optic disc or macula are performed using volumetric scans covering a fixed area (*e.g.*, 4.5 × 4.5 mm). The volume scan can be divided into several slabs for further analysis. The superficial slab is used to assess the vasculature in the superficial peripapillary retina (especially the radial peripapillary capillaries in the RNFL), whereas the deeper slab is used to assess the deep retinal and choroidal vasculature. OCTA quantifies the ocular circulation in many parameters, the most widely used of which is vessel density. Vessel density is defined as the percentage area occupied by vessels in the measured area.[44] OCTA shows reduced vessel density inside the ONH, in the peripapillary region, and in the macula of eyes with glaucoma (**Figure 2.3.7**).[44-47] Vessel densities show a more pronounced decrease as the severity of glaucoma increases.[46,48-54] OCTA has also been used to investigate the presence of

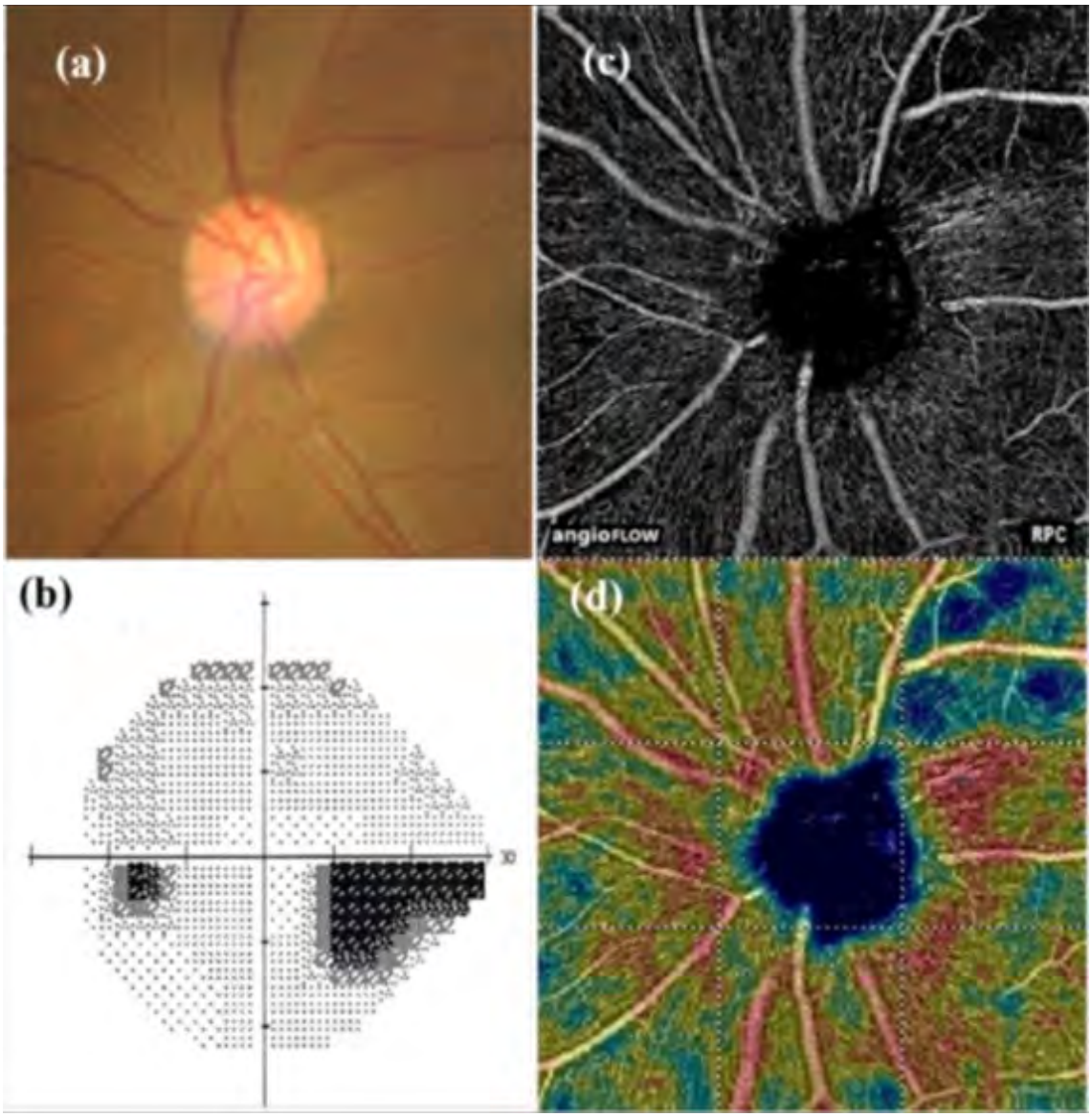

Figure 2.3.7. A glaucomatous left eye showing superior neuroretinal rim thinning with superotemporal retinal nerve fibre layer defect **(a)** with correlating inferior nasal defect on visual fields **(b)**. Optical coherence tomography angiography shows vessel density reduction in the corresponding topographic location **(c)**, better appreciated on the heat map **(d)**. Photographs courtesy of Harsha Rao, India.

choroidal microvasculature dropout (CMvD, **Figure 2.3.8**), defined as the complete loss of choriocapillaris in localized regions of parapapillary atrophy, on the deep retinal/choroidal slab in glaucoma eyes.[55,56]

The role of OCTA in the diagnostic evaluation of glaucoma is under active investigation. It has been shown that lower baseline peripapillary vessel densities are associated with a faster rate of RNFL thinning/progression in mild to moderate POAG.[57,58] Presence and enlargement of CMvD is also associated with a faster rate of RNFL thinning[59-61] and VF progression.[62,63] The floor of OCTA vessel density is lower than that of OCT RNFL measurements, and therefore peripapillary vessel density may be a better parameter than RNFL thickness to monitor progression in advanced glaucoma.[64,65]

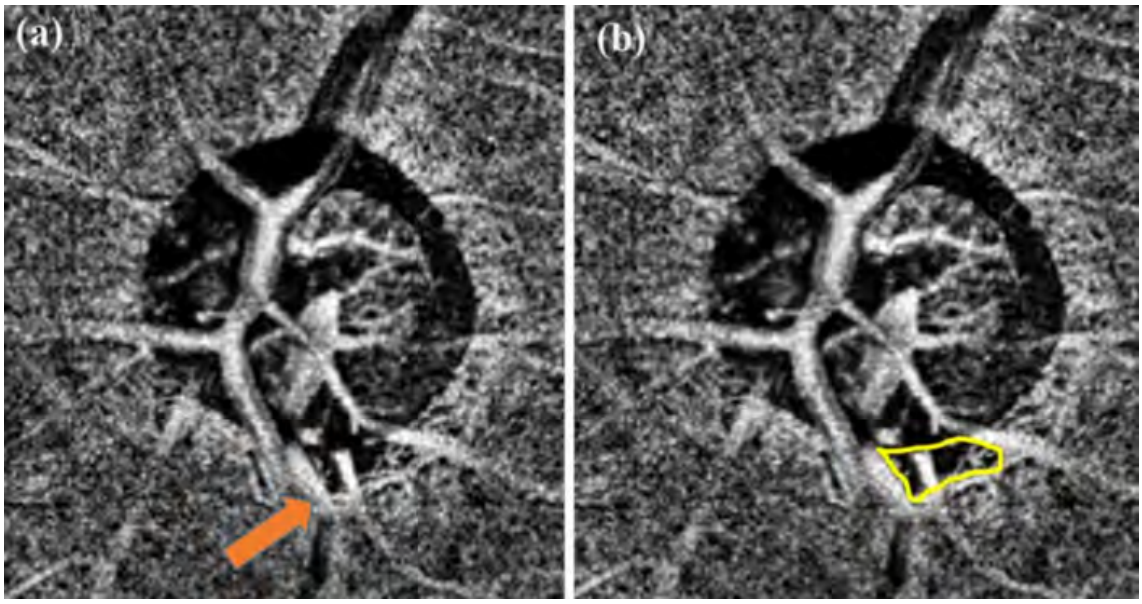

Figure 2.3.8. Optical coherence tomography angiography scan of a glaucomatous eye showing microvascular dropout, arrow in **(a)** and yellow area in **(b)**, on the choroidal slab. Photograph courtesy of Harsha Rao, India.

Motion artifacts are more common with OCTA than OCT RNFL/GCIPL imaging due to the longer scanning time despite available methods to account for such artifacts.[66-69] Media opacities, especially vitreous opacities, can significantly affect the quality of OCTA scans and the quantification of vessel densities. OCTA may not be able to provide a comprehensive evaluation of the deeper retinal and choroidal vasculature due to projection artifacts, *i.e.*, obscuration cast by the superficial retinal vessels projected onto the deeper retinal vasculature.[70]

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2.4. PERIMETRY

Key messages

- ❖ Standard automated perimetry (SAP) is usually performed using a Goldmann size III stimulus in the central 24° or 30°, although testing the central 10° is also important for patients with retinal nerve fibre layer (RNFL)/ganglion cell-inner plexiform layer (GCIPL) defects over the macula.
- ❖ Reliability indices should be checked before interpreting perimetry results.
- ❖ Test frequency should be tailored according to the stage of glaucoma and the rate of progression. Advanced glaucoma or rapid progression requires more frequent testing.
- ❖ Progression analysis of VF sensitivity requires event-based and trend-based analyses.

VF TESTING

VF testing holds a pivotal position in the evaluation and management of glaucoma. Assessing VF progression and identifying rapid progression holds significant clinical value for optimizing care and adjusting treatment strategies. Static computerized perimetry has become the gold standard over kinetic perimetry, such as Goldmann perimetry, due to its ability to detect VF damage earlier and the provision of numerical results alongside computer-assisted interpretations. Standard automated perimetry (SAP) refers to static computerized threshold perimetry that uses standard Goldmann white stimuli on a white background. It is usually performed using a Goldman size III stimulus in the central 24° or 30° field. Various models of standard automated perimeters are available, including the Octopus Perimetry (Haag-Streit, Köniz, Switzerland) and the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA). The Humphrey Field Analyzer is the most widely used perimeter in Asia. There are various testing strategies to estimate the threshold sensitivity at each test location. When the strategies are different between tests, caution is needed in the interpretation. Commonly used threshold algorithms in the Humphrey perimeter are SITA Standard, SITA Fast, and SITA Faster.

INTERPRETING VF TEST RESULTS

Test data elements

- Numerical Threshold Map: Displays raw threshold values at each test point.
- Grey Scale Map: Offers a graphical representation of the numerical threshold map.
- Total Deviation Map: Highlights the differences between the patient's values and those of age-matched normal threshold sensitivity at each test point.
- Pattern Deviation Map: Adjusts for diffuse sensitivity loss, emphasizing localized loss.

- Probability Map: Assesses the statistical significance of numerical deviations against age-matched normative data.

Reliability indices

Comprehensive judgment should incorporate an analysis of false-negative responses, false-positive responses, fixation losses, and the eye gaze tracker of the perimeter. Proper patient instruction prior to testing is crucial, with the necessity for repeat tests if the reliability indices indicate unreliable results.

Summary indices

The Mean Deviation (MD) in the Humphrey perimeter or Mean Defect in the Octopus perimeter reflects the overall difference between the patient's sensitivity values and those of age-matched normals across all test points. The Visual Field Index (VFI) in Humphrey, analogous to the MD but with a weighting towards central values, alongside the Humphrey PSD and the Octopus Loss Variance (LV) index, are tailored to identify localized losses.

TYPICAL GLAUCOMATOUS VF DEFECTS

Glaucomatous VF defects are identified using several criteria, including the Hodapp-Anderson-Parrish criteria adapted for the SITA 24-2 examination from its initial application in the Full Threshold 30-2 examination. The criteria encompass:

1. A Glaucoma Hemifield Test "outside normal limits," or
2. A cluster of 3 points with a probability less than 5%, including at least one point with a probability less than 1%, or
3. A PSD with a probability less than 5%.

Typical defects observed in glaucomatous VFs include nasal step defects, arcuate scotoma along the Bjerrum area, hemifield VF defects, double arcuate defects, and temporal islands (**Figures 2.4.1 to 2.4.5**).

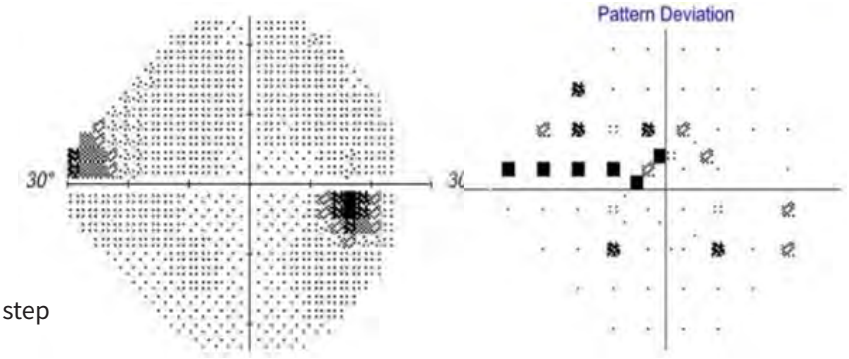

Figure 2.4.1. Nasal step visual field defect.

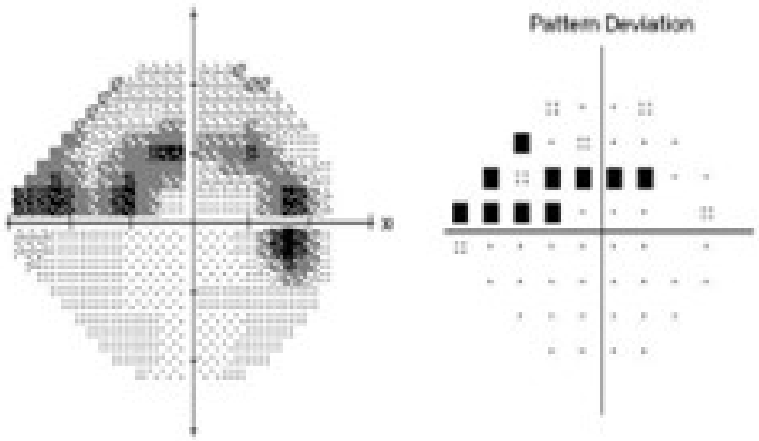

Figure 2.4.2. Arcuate scotoma.

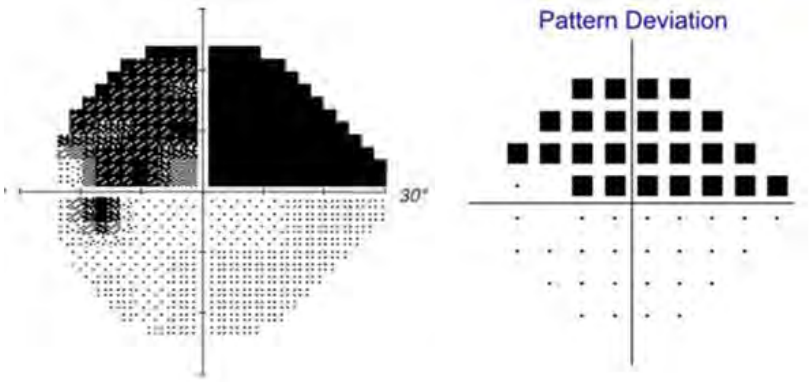

Figure 2.4.3. Hemifield visual field defect.

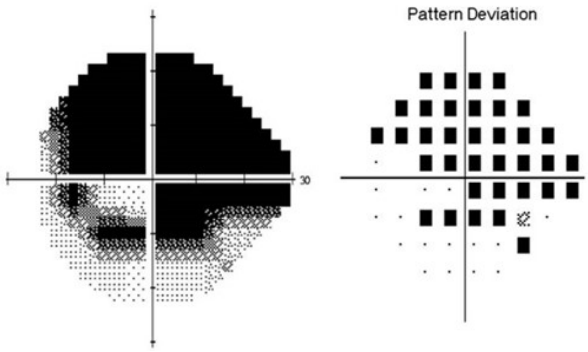

Figure 2.4.4. Double arcuate scotoma.

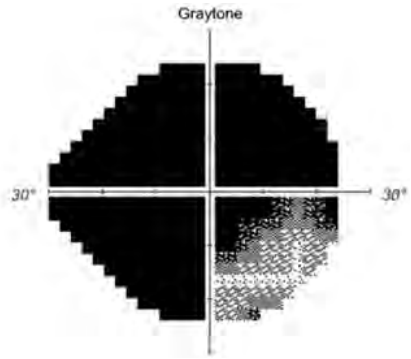

Figure 2.4.5. Temporal and nasal defects.

STAGING THE VF DEFECTS

Glaucoma staging is determined by assessing the extent of damage to the VF. Various staging systems have been crafted for this purpose. A straightforward system, derived from Hodapp's classification, categorizes the severity of damage based solely on the MD values. This classification is structured as follows:

- Early stage: MD value greater than or equal to -6 dB.
- Moderate stage: MD value between -12 and -6 dB.
- Severe stage: MD value less than -12 dB.

VF TESTING FREQUENCY

Given the diversity in glaucoma progression among patients, a personalized testing strategy is advisable. Factors such as disease stage, patient's age, and current progression status should guide the frequency of VF testing. By customizing the testing schedule, clinicians can ensure more effective monitoring and management of glaucoma, enhancing patient care. While initial frequent testing is crucial for establishing a disease progression baseline, subsequent testing frequencies should be adjusted based on the patient's individual needs and disease status.This tailored approach ensures that each patient receives optimal care tailored to their specific condition.

THE ROLE OF VF 10-2 AND 24-2C

There is growing evidence that involvement of the central VF region carries a high risk of future progression and visual acuity loss (**Figure 2.4.6**).[1-4] Additionally, reports indicate that glaucoma patients with vascular risk factors tend to present and progress in the central VF region.[3-5] In early glaucoma, the involvement of the papillomacular and papillofoveal bundles has been shown to exceed 70%.[6] Consequently, additional tests focusing on the central 10° have been emphasized.

While it may not be recommended to reduce the frequency of standard 24° or 30° testing by replacing these tests with 10° tests, conducting additional tests targeting the central 10° region using 10° tests could be beneficial for certain patients.[7-9] The 24-2C test could be another option.[7,10,11]

PROGRESSION ANALYSIS

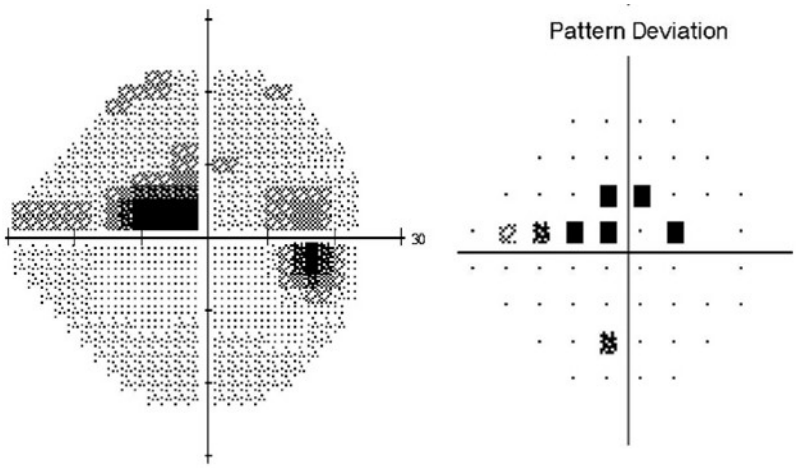

Figure 2.4.6. Central scotoma.

The assessment of functional changes in glaucoma patients is primarily conducted through VF analysis using 2 statistical approaches: event analysis and trend analysis. Event analysis reports progression when the change between baseline and follow-up tests is greater than the test-retest variability. Trend analysis not only identifies glaucoma progression but also quantifies the rate at which the disease progresses. VF progression in glaucoma includes widening or deepening of pre-existing VF defects, or emergence of new defects. A generalized depression across the VF suggests cataracts, miosis, or issues with test reliability. To ensure reliability, any detected changes in the VF should be verified through repeated testing. Software designed to pinpoint locations of change, such as the Guided Progression Analysis (GPA), plays a critical role in identifying visual field deterioration effectively. GPA is important to facilitate a more reliable approach to monitor disease progression compared with visual inspection of serial VFs, enabling timely intervention and management strategies. In the evaluation of VF progression, one should also look for structural changes of the optic disc and the RNFL in the corresponding location.[12,13]

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2.5. RISK FACTORS FOR GLAUCOMA

Key messages

- ❖ Major risk factors for development of POAG include elevated IOP, small CCT, and increased age, CDR, and VF PSD.
- ❖ Risk factors for progression of glaucoma include older age, exfoliation/pseudoexfoliation, bilateral disease, higher IOP, worse VF mean deviation, small CCT, and disc haemorrhage.
- ❖ Major risk factors for progression of PACD include older age, small axial length, small ACD, and small anterior chamber angle width.

RISK FACTORS FOR POAG DEVELOPMENT

The Ocular Hypertension Treatment Study (OHTS)[1] and the European Glaucoma Prevention Study (EGPS)[2] have identified 5 risk factors associated with the development of glaucoma from OHT:

1. Higher baseline IOP.
2. Low CCT.
3. Older age.
4. Increased vertical CDR.
5. Increased PSD in the VF.

There are other risk factors that have been reported to play a significant role in glaucoma development:

- Ethnic background: The prevalence of glaucoma is higher among individuals of African ancestry than Asians and Caucasians.[3]
- A positive family history of glaucoma: First-degree relatives of patients with POAG face an approximately 9-fold increased risk of developing glaucoma.[4] The risk of inheriting glaucoma may further escalate with the number of affected relatives diagnosed with the disease.
- Rate of RNFL loss: Glaucoma suspects with a faster rate of RNFL loss are at risk of developing VF loss.[5]
- Myopia:[6] Myopia is associated with a higher prevalence of glaucoma. The risk escalates as myopia severity increases.
- Low socioeconomic status:[7,8] Glaucoma is more prevalent among individuals with low socioeconomic status. This association may be linked to factors such as delayed detection, treatment delays, and poor adherence.
- Low cerebrospinal fluid (CSF) pressure:[9] An elevated trans-lamina cribrosa pressure difference and a steeper trans-lamina cribrosa pressure gradient are important for glaucomatous optic nerve damage in normal-pressure glaucoma.
- Low ocular perfusion pressure (OPP):[10,11] Epidemiological studies have consistently shown an association between reduced OPP and an increased prevalence of glaucoma. The premise is that inadequate perfusion and vascular dysregulation, leading to optic nerve head ischaemia, contribute to glaucomatous damage.

- Low systemic blood pressure (SBP):[12-13] Several large studies have demonstrated that low systemic blood pressure has an increased risk of developing open-angle glaucoma (OAG).
- Vasospasm.[14]

However, the association of the following risk factors with glaucoma is less clear:

- Nutritional status and diet.
- Diabetes mellitus.[15,16]
- Arterial hypertension.[17,18]
- Body mass index.[19]
- Obstructive sleep apnoea (OSA): OSA patients were found to have 1.67 times greater likelihood of developing glaucoma over a 5-year follow-up period.[20]
- Oral contraceptive pills.[21]
- Gender.[22-24]
- Smoking.

Assessment for secondary OAG development:

- Exfoliation/Pseudoexfoliation syndrome.
- Pigment dispersion syndrome.
- History of ocular trauma/surgery.
- History of uveitis.
- Corticosteroid responder and/or user.

RISK FACTORS FOR PROGRESSION OF OAG

The Advanced Glaucoma Intervention Study (AGIS, 1998),[25] Collaborative Initial Glaucoma Treatment Study (CIGTS, 2001), Early Manifest Glaucoma Trial (EMGT, 2002),[26] and United Kingdom Glaucoma Treatment Study (UKGTS, 2015)[27] identified several risk factors associated with glaucomatous progression:

- Older age (EMGT, AGIS).
- Exfoliation/Pseudoexfoliation syndrome (EMGT).
- Bilateral disease (EMGT, UKGTS).
- Higher baseline IOP (UKGTS, CIGTS).
- Worse mean deviation on the baseline VFs (EMGT, CIGTS).
- Smaller CCT (EMGT).
- Disc haemorrhage (EMGT, UKGTS).
- Decreased OPP (EMGT).

Additional factors were also reported:

- Rate of RNFL loss: Helps identify patients who are at risk for developing VF loss.
- Myopia: The risk of glaucoma progression increases with the degree of myopia.
- IOP fluctuations (only in patients with low mean IOP) (AGIS)
- Longer follow-up (AGIS).
- Increased number of glaucoma interventions (AGIS).

RISK FACTORS FOR PACD

Demographic risk factors

- Older age.
- East Asian ethic origin.[23,28]
- Female.
- Axial hyperopia.

Anatomical risk factors

- Small cornea.
- Shallow central ACD.[29]
- Smaller anterior chamber volume.
- Smaller anterior chamber area.
- Thick lens.
- Anterior lens position.
- Thicker irides.
- Greater iris curvature.
- Greater lens vault.
- Shorter axial length.
- Narrower baseline mean angle width.[29]

RISK FACTORS FOR PROGRESSION FROM PACS TO PAC/PACG

- Older age.[30]
- Bilateral PACS.[31,32]
- Small anterior chamber angle width.[30]
- Flatter horizontal iris curvature.[30]
- Shallow limbal and central ACD.[33]

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SECTION 3
MANAGEMENT APPROACH

3.1. OCULAR HYPERTENSION

Key messages

- The decision to treat OHT should be carefully discussed between ophthalmologist and patient after weighing the risks and benefits of treatment.
- The decision to treat OHT is suggested in patients who have higher risk of conversion to POAG, such as those with higher pre-treatment IOP, older age, thinner CCT, larger vertical CDR, and higher PSD in the VF.
- The Ocular Hypertension Treatment Study (OHTS)-European Glaucoma Prevention Study (EGPS) risk calculator serves as a good reference to categorize patients based on their risk of progressing from OHT to glaucoma.

DEFINITION OF OHT

Although the definition of OHT varies between studies, OHT generally describes the following features:

- Untreated IOP > 21 mmHg.
- Normal VF, optic disc, and RNFL.
- Open angle under gonioscopy.
- No secondary causes of elevated IOP (including trauma, steroid use, uveitis).

DIAGNOSTIC WORKUP

The workup to diagnose OHT involves the following:

- Good history taking and slit-lamp examination to rule out secondary causes.
- IOP measurement with GAT.
- CCT measurement.
- Examination of the ONH and RNFL.
- Dark room gonioscopy.
- Reliable VF and OCT examinations.

The decision to initiate treatment versus continuing to monitor without treatment should be made after a thorough discussion between the ophthalmologist and patient that weighs the risks and benefits of both options. To date, there has yet to be a common consensus as to who should be treated, although some suggestions have been proposed. One may decide the treatment/monitoring scheme according to the risk factors for the conversion of OHT to POAG, as outlined in the section below.

RISK FACTORS

The 5 main risk factors associated with progression of OHT to POAG are mainly based on the results of the Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Study (EGPS):[1,2]

1. Older age.
2. Higher IOP.
3. Higher PSD in the VF.
4. Smaller CCT.
5. Larger vertical CDR.

The 5-year risk of POAG development can be estimated by the OHTS-EGPS risk calculator (http://ohts.wustl.edu/risk/). The resulting calculated risk could aid the decision whether to treat OHT:[3]

- Low risk (< 5%): OHT could be observed.
- Moderate risk (5%–15%): Consider treatment decisions between doctor and well-informed patients.
- High risk (> 15%): OHT should be treated.

Other potentially useful risk factors to consider

- Presence of PXF.[4]
- IOP asymmetry:[5] Every 1 mmHg increase of IOP asymmetry was associated with a 21% increase in risk for developing POAG.[5]
- Lower corneal hysteresis.[6-11]
- Presence of disc haemorrhage.[2,12,13]
- Vertical CDR asymmetry.[2,12,13]
- Other features of optic disc morphology (small rim-disc area ratio, larger CDR asymmetry, and presence of disc crescent).[14]
- Parameters based on OCT,[15-19] as OCT can detect the glaucomatous change of RNFL and other optic disc structural changes several years before VF defects become detectable.[20-23] The risk factors based on these OCT parameters are mainly based on studies that involved glaucoma suspects (including OHT patients) with no evidence of optic disc damage as well as patients with optic disc damage assessed by stereophotograph review without VF defects:
  - thinner baseline RNFL.
  - abnormal classification of RNFL.
- Other visual field parameters:
  - VF asymmetry: Eyes with reduced sensitivity on at least 1 VF test point than the fellow eye had a higher risk of POAG development in OHT participants.[5]
- Genetics: Patients having the TMCO1 risk alleles. The OHTS found a 12% higher cumulative frequency of POAG conversion at 13 years than OHT subjects without the risk alleles.[24]

TREATMENT

- Pre-perimetric glaucoma can be overlooked if OCT is not performed (structural changes of RNFL and ONH detected by OCT could effectively differentiate normal eyes from early glaucoma and glaucoma suspects).[15,23,25]
- Topical IOP-lowering eye drops or SLT can be offered as first-line treatments. The latter is supported by the Laser in Glaucoma and Ocular Hypertension (LiGHT) trial.[26]
- For OHT subjects with low to moderate risk, medication treatment could still be safely taken off even if treatment has been initiated, provided that the OHT subject is carefully monitored.[27]
- Ideally, the assessment should be repeated because the parameters (especially IOP, VF, and CDR measurement) are prone to variability.[28-30] The risk calculation is also prone to within-subject variability and may affect treatment decision.[31,32]
- Initiation of treatment should also be considered in circumstances when the risk of POAG conversion is likely to be high (*e.g.*, IOP > 30 mmHg, presence of optic disc haemorrhage, and non-compliance with regular follow-up).

FAQs

How often should we monitor OHT patients?

As of the time of writing, there is no consensus. OHT with a 5-year estimated risk under 6% may be monitored every 12 months; more than 6% risk may be monitored every 6 months.[33]

Is it cost-effective to treat OHT?

Cost-effectiveness analyses suggested that treating higher-risk group patients may be more cost-effective than treating all OHT.[34,35] However, this may vary between regions because of the different healthcare systems and willingness-to-pay values.

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3.2. PRIMARY OPEN-ANGLE GLAUCOMA

Key messages

- ❖ Target IOP should be individualized and reviewed at every follow-up visit based on disease severity, rate of progression, and life expectancy.
- ❖ SLT is a first-line alternative to medical topical treatment in achieving optimal IOP control.

DEFINITION

POAG is a chronic, progressive optic neuropathy in adults in which there is an acquired loss of RGCs and RNFL, associated with characteristic morphological changes at the ONH.[1] This condition is associated with an elevated IOP and open anterior chamber angle found on gonioscopy.

PATHOPHYSIOLOGY

Genetics

- The following genes have been linked to POAG through family-based genetic linkage analysis:
  - Myocilin (*MYOC*).[2,3]
  - Optineurin (*OPTN*).[4]
  - WD repeat domain 36 (*WDR36*).
  - Cytochrome P450, family 1, subfamily B, polypeptide 1 (*CYP1B1*).
  - Neurotrophin 4 (*NTF4*).[5]
- The following highly heritable and polymorphic endophenotype traits are related to POAG pathogenesis:[5]
  - IOP.
  - CCT.
  - Vertical CDR.
  - Disc area.
  - RNFL thickness.

Mechanical theory

- IOP-induced stress and strain may result in compression, deformation, and remodelling of the lamina cribrosa, with consequent mechanical axonal damage and disruption of axonal transport.[6,7]
- Abnormally low cerebrospinal fluid pressure in the optic nerve subarachnoid space, resulting in a large pressure gradient across the lamina cribrosa.[8,9]

Vascular theory

- Impaired microcirculation, altered immunity, excitotoxicity, and oxidative stress cause RGC neurodegeneration.[6]

RISK FACTORS

- IOP: Population-based studies have shown that elevated IOP is strongly linked to the incidence of POAG.[10-12]
- Age: Older age is an important risk factor for the presence and progression of POAG.[10,12-14]
- Family history of glaucoma: The Rotterdam Eye Study showed a 9-fold increase in risk of developing POAG in subjects who have a first-degree relative with POAG.[15,16]
- Race or ethnicity: The prevalence of POAG is higher in Hispanics/Latinos, Africans, and South Central Asians.[15,17,18]
- CCT: A thinner central cornea has been reported as a risk factor for POAG. CCT may be a biomarker for structural or physical factors involved in the pathogenesis of POAG.
- Ocular perfusion pressure: Population-based studies have provided evidence that low diastolic perfusion pressure (< 50 mmHg) is associated with a higher prevalence of POAG.[10-12]
- Myopia: Numerous studies suggest that individuals with myopia have a higher prevalence of OAG than those without myopia.[19,20]

The following have been suggested as potential risk factors, as there is still insufficient evidence for their role in POAG:

- Hypothyroidism.
- Low corneal hysteresis.
- Low systolic blood pressure.
- Nocturnal systemic hypotension.
- Obstructive sleep apnoea.

CLINICAL EXAMINATION

History

History-taking for POAG should include the following information:

- Race/ethnicity.
- Family history of glaucoma.
- Ocular history: refractive error, trauma.
- Prior ocular surgery (including refractive procedures, *e.g.*, LASIK, small incision lenticule extraction [SMILE], Implantable Collamer Lens [ICL]).
- Systemic history including sleep apnoea, cardiovascular disease, diabetes, and hypertension.
- Medications: All medications, especially corticosteroids.

Physical examination

Physical examination for POAG should include the following:

- Visual acuity
- Pupillary examination for relative afferent pupillary defect (RAPD).
- Slit-lamp assessment to exclude secondary aetiologies such as uveitis, PXF, rubeosis, and pigmentary deposition.
- IOP assessment.
- Macular and peripheral fundus assessment.
- ONH and RNFL assessment:
  - Vertical elongation of the optic nerve cup with an associated decrease in neuroretinal rim width.
  - Enlargement of the optic nerve cup.
  - Diffuse or focal narrowing of the neuroretinal rim, especially superotemporal and/

or inferotemporal.
  - Optic disc haemorrhages involving the disc rim, parapapillary RNFL, or lamina cribrosa.
  - Nasalisation of central ONH vessels.
  - Baring of the circumlinear vessel.
  - Absence of pallor in the neuroretinal rim.
  - Diffuse or focal thinning of the RNFL.
  - Beta-zone parapapillary atrophy.

Diagnostic evaluation

Diagnostic evaluation for POAG should include the following:

- IOP (see Section 2.1).
- VF testing (see Section 2.4).
  - Standard white-on-white automated perimetry (SAP), with a fixed testing matrix covering at least the central 24° is preferred for the diagnosis of glaucomatous VF loss.
  - Testing with a 10-2 program may also be useful to detect early VF damage in the central 10°.
- OCT imaging of the RNFL, GCIPL, and ONH (see Section 2.3).

MANAGEMENT

The aim of POAG management is to maintain functional vision throughout the patient's lifetime with minimal detrimental effects on their quality of life. The treatment algorithm for POAG management is outlined below and detailed in **Figure 3.2.1**.

1. Setting the target IOP: Target IOP is an estimate and must be individualised and/or adjusted throughout the course of the disease. The initial target pressure is commonly set at least 20%–35% lower than baseline IOP. A lower target IOP may be needed if there is advanced optic nerve damage, rapid disease progression, or if other risk factors such as strong family history and/or vascular risk factors are present.
2. Pharmacotherapy.
3. SLT.
4. Incisional surgery.

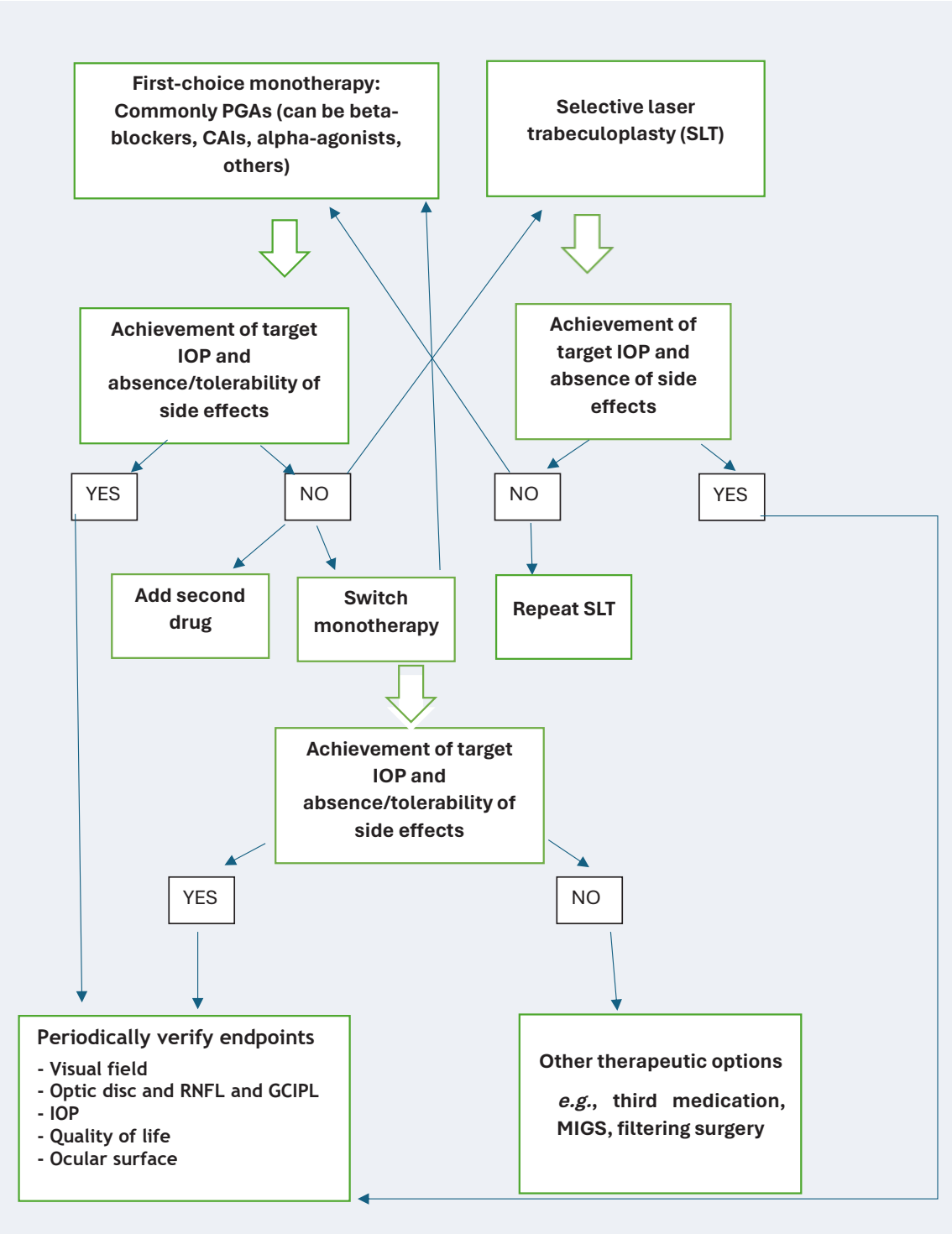

Figure 3.2.1. Treatment algorithm for management of primary open-angle glaucoma. CAIs: Carbonic anhydrase inhibitors; GCIPL: Ganglion cell-inner plexiform layer; IOP: Intraocular pressure; MIGS: Minimally invasive glaucoma surgery; RNFL: Retinal never fibre layer; SLT: Selective laser tarbeculoplasty

Follow-up

Follow-up evaluations for POAG should include tonometry, VF testing, and OCT imaging. The recommended follow-up schedule for POAG is presented in **Table 3.2.1**.

Table 3.2.1. Recommended follow-up schedule for primary open-angle glaucoma*

Target IOP achieved	Progression of damage	Duration of control (months)	Approximate follow-up interval (months)*
Yes	No	< 6	6
Yes	No	> 6	12
Yes	Yes	NA	1–2
No	Yes	NA	1–2
No	No	NA	3–6

**Source: American Academy of Ophthalmology's Preferred Practice Pattern® (PPP) Guidelines 2020.*

Risk factors for progression

- IOP: Higher baseline,[21] higher peak IOP, IOP fluctuation,[21,22] inadequate IOP control.[23,24] Older age.[21,23]
- Disc haemorrhage.[25,26]
- Larger cup-to-disc ratio.[23,27]
- Beta-zone parapapillary atrophy.[27-29]
- Thinner central cornea.[30,31]
- Decreased corneal hysteresis.[30,32]
- Lower ocular perfusion pressure.[31,33]
- Poor adherence to medications.[22,34]

Change in treatment

POAG treatment may require adjustment due to ocular surface disorders, poor adherence to medication, and disease progression despite achieving target/low IOP.

FAQ

How to determine target IOP in POAG patients?

There is strong evidence that failing to achieve clinician-defined target IOP is a significant predictor of disease progression across all levels of glaucoma.[35] Target IOP range is determined from the baseline IOP, stage of disease, estimated progression rate, and life expectancy. Target IOP is dynamic and should be individualised. It changes with life expectancy and risks of intervention weighed against the risk of visual disability from the disease process. For example, target pressure reduction of ≥ 40%–77% or 1–2 SD below the population mean (9–12 mmHg) is recommended for POAG patients with a high risk of progression.[24,33]

What is the role of SLT as a primary treatment in POAG?

Treatment of early POAG with first-line SLT, with re-treatments as required, provides effective IOP control with good quality of life.[36] The Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial has identified that patients treated with SLT primarily were more likely to achieve target IOP and have reduced need for glaucoma surgeries.[37]

What is the role cataract surgery in POAG management?

Cataract and POAG commonly coexist, and the ageing lens contributes to increased levels of IOP.[38] Cataract surgery alone can reduce IOP in POAG patients by 1.4 to 4 mmHg.[39,40] However, there is insufficient evidence to support that IOP reduction from cataract surgery can protect against VF deterioration.

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3.3. NORMAL TENSION-GLAUCOMA

Key messages

- ❖ IOP reduction is the primary objective in the treatment of NTG.
- ❖ The choices of topical IOP-lowering treatment are similar to those used to treat POAG.

DEFINITION

NTG is a progressive optic neuropathy with open anterior chamber angles and IOP within normal range[1] whose main features involve:

- Untreated IOP < 21 mmHg.
- Typical glaucomatous optic disc changes and RNFL thinning with corresponding VF defects.
- Open angles on gonioscopy.
- No secondary causes of GON (*e.g.*, angle closure, uveitis, trauma, or steroid use).

DIAGNOSTIC WORKUP

- NTG is only diagnosed after other forms of optic neuropathy (*e.g.*, ischemic, traumatic, toxic-inflammatory, infectious, congenital, and compressive) have been ruled out.
- A comprehensive systemic history must be obtained regarding migraine, Raynaud's phenomenon, episodes of shock, head trauma, headache, and other neurological symptoms.
- GAT, gonioscopy, optic disc photography, OCT, and the Humphrey VF Analyzer are the most important diagnostic assessment for NTG.
- Flame-shaped haemorrhages of the optic disc (Drance haemorrhage), deep and focal notching of the optic disc neuroretinal rim, and peripapillary atrophy may be observed more frequently in NTG than in high-tension POAG.[2,3]
- VF defects in NTG are comparable to those in high-tension POAG. Patients with NTG appear to have scotomas that are deeper, more localized, and closer to fixation at an earlier stage of the disease.[4]

RISK FACTORS

Despite featuring an IOP within the statistically normal range, an IOP-dependent mechanism still remains an important pathophysiologic risk factor in NTG.[5,6] However, IOP-independent risk factors have been suggested, including vascular dysregulation, haematologic abnormalities, and other systemic diseases that cause ONH susceptibility.[7] It has also been suggested that NTG and POAG exist on a continuum, with IOP playing a larger role in POAG.

IOP-dependent risk factors

- High IOP (high-normal range of IOP):[8] IOPs tend to be higher than those in the general healthy population.[8]
- IOP asymmetry:[9,10] Some studies suggested that IOP asymmetry was not related to VF asymmetry.[11,12]
- Wider diurnal IOP fluctuation.[8,13,14]
- Elevated nocturnal IOP (nocturnal IOP spikes):[8,15] Nocturnal IOP spikes may affect nocturnal orbital blood perfusion pressure, causing optic nerve susceptibility even with normal diurnal IOP.[16]
- Low CCT:[17] CCT was lower in NTG than in POAG subjects, which may be associated with IOP underestimation.[18]

IOP-independent risk factors

Ocular vascular abnormalities

Optic disc haemorrhage.[19,20]

Findings that imply chronic vascular insufficiency of the ONH include:[21-26]

- Reduced diastolic ophthalmodynamometry levels.
- Reduced ocular pulse amplitude.
- Focal arteriolar narrowing around the optic nerve.
- Increased vascular resistance in the ophthalmic artery (colour Doppler analysis).
- Increased mean ocular perfusion pressure fluctuations.

Systemic vascular abnormalities

Cardiovascular dysregulation[2,27]

Vascular dysfunction and ischaemia have been identified as significant contributors to the progression of NTG.[28,29] Factors linked to cardiovascular dysregulation include:

- Systemic hypertension.
- Systemic hypotension.
- Nocturnal hypotension (greater nocturnal blood pressure drop).[30,31]
- Cardiac arrhythmia.
- Lower heart rate variability: autonomic dysfunction with sympathetic predominance.[32]

Systemic abnormal vasoregulation[2]

Cold hands and feet, as an over-reaction to cold or stress, are suggestive of defective vasoregulation:[33,34]

- Raynaud's phenomenon.
- Headaches with or without migraine features.[35]

Haematologic abnormalities

- Increased blood and plasma viscosity.[36,37]
- Hypercholesterolemia.[38]

Other systemic risk factors

- Obstructive sleep apnoea syndrome (OSAS):[39,40] OSAS may harm the ONH by creating transient hypoxaemia and increasing vascular resistance.
- Smoking and high body mass index:[41] In the Blue Mountain Eye Study, smokers were found to have a higher IOP than non-smokers.[42]
- Metabolic syndrome:[43] Dyslipidaemia, impaired glucose tolerance.

Genetic predispositions

Genetic mutations in the following genes may predispose toward NTG:[44]

- Optineurin (*OPTN*).
- TANK binding kinase (TBK1): Duplication of the TANK-binding kinase 1 (*TBK1*) gene can be a rare cause of NTG.[45]
- Myocilin (*MYOC*).

TREATMENT

The only known modifiable risk factor that can alter the progression of POAG and NTG is IOP reduction. For the majority of patients with NTG, IOP reduction remains the primary objective of the treatment.[6]

The Collaborative Normal Tension Glaucoma Study (CNTGS) demonstrated the benefit of IOP reduction for the treatment of patients with NTG. The study concluded that a 30% reduction in IOP at baseline significantly reduced the risk of disease progression. During 5 years of follow-up, the risk of glaucoma progression was 12% in the treatment group versus 35% in the non-treatment group.[4] Initiation of treatment for NTG patients in the CNTGS was based on the following criteria: documented progression of the VF or optic nerve, VF loss threatening fixation, or presence of disc haemorrhage.

From the perspective of medical treatment, prostaglandin derivatives tend to have a greater IOP-lowering effect, which may be the most important factor to consider.[46] Dorzolamide-timolol fixed combinations constitute safe and efficacious IOP-lowering agents in NTG patients.[47,48] Brimonidine has been found to improve retinal vascular autoregulation in patients with NTG.[49,51,52]

Laser and surgical treatment options for NTG are identical to those for POAG. In the CNTGS, an IOP reduction of 30% was achieved in only 57% of patients by topical medication and/or laser trabeculoplasty, while the remaining 43% required filtering surgery.[52,53]

In addition to IOP-lowering therapy, other factors should be considered in the management of NTG patients, including cardiovascular conditions that may compromise ONH perfusion such as systemic hypotension, nocturnal hypotension, anaemia, and cardiac arrhythmias.[54] While consultation with physicians can be useful in addressing these concerns, there is yet insufficient evidence to confirm a treatment benefit for NTG.

FAQs

What is the prognosis for patients diagnosed with NTG?

The prognosis for visual preservation is favourable for patients who receive adequate IOP reduction treatment. In the CNTGS trial, 65% of patients in the control group with NTG did not progress, even without treatment.[4] Considering the relatively high incidence of non-progression in this study, some clinicians have recommended a cautious “wait and see” approach to initiating treatment. Nonetheless, this recommendation should be made with caution, as it can be difficult to predict which patients will progress and other studies have found variable progression rates for this disease.[55]

Are there any racial or gender differences in NTG epidemiology?

Female subjects have a higher prevalence of NTG than male counterparts.[56] It has been reported that the prevalence of NTG in East Asian populations, in which it occurs in approximately 30% to 40% of POAG patients, is higher than in Western populations.[6,12,46] The Japanese Tajimi study revealed that NTG comprised 92% of POAG patients in its study population, and the Korean Namil study reported a comparable rate of 77%.[57] In addition, it has been demonstrated that Asians have a slower rate of progression.[58]

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3.4. PRIMARY ANGLE-CLOSURE DISEASE

Key messages

- ❖ Not all cases of PACS require a prophylactic LPI.
- ❖ LPI is recommended for PAC.
- ❖ Early lens extraction instead of LPI can be offered to selected patients with PACG.

PACS

Routine LPI is not advised for all cases of PACS. Evidence based on the Zhongshan Angle Closure Prevention (ZAP) trial from China showed that LPI halved the risk of new angle-closure disease (hazard ratio [HR] 0.53 over 6 years), *i.e.*, raised IOP and/or new PAS, but the rate of new disease in both treated and untreated eyes was very low (4.2 versus 8.0 cases of PACD per 1000 eye years).[1] There were no cases of incident glaucoma identified in this trial in treated or untreated eyes, and no cases of severe visual impairment.

Similar results were reported in the Singapore Asymptomatic Narrow Angles Laser Iridotomy Study (ANA-LIS) study in Singapore.[2] The risk of incident sight-threatening angle-closure disease (symptomatic or asymptomatic) in people with occluded drainage angles (PACS) and no other abnormality or risk factor was less than 1/1000 per year. Hence, no benefit from large-scale prophylactic was found for LPI treatments.

LPI is can be considered for individuals with PACS with additional risk factor/s such as:

- Only one functioning eye (monocular).
- The contralateral eye in patients with acute angle closure in the fellow eye.
- A family history of significant angle-closure disease.
- High hypermetropia.
- Diabetes or another condition necessitating regular pupil dilation.
- Use of antidepressants or medication with an anticholinergic action.
- Individuals living in remote areas or without access to healthcare.

PAC

LPI

LPI is recommended in PAC when presenting IOP < 30 mm, PAS is not extensive, and there is significant pupillary block. Given that there is no consistent evidence for LPI location influencing dysphotopsia, LPI may be placed at either superior (12 o'clock) or temporal locations.[3] There is no need to stop anticoagulants for LPI when INR < 3.[4] Residual irido-trabecular contact (ITC) is common after LPI (seen in 20%–80% of cases). No further interventions are recommended for ITC alone. It may be used to risk-stratify follow-up after LPI. More than half of patients diagnosed with PAC require additional medical or surgical intervention subsequent to LPI.

Post-LPI

If the angles remain closed and IOP remains high after LPI, medical treatment should be considered. Although LPI opens the angles, it has been shown to have no IOP-lowering benefit. The overall effectiveness of LPI was lower when compared to PGA treatment.[5]

If the angles are open and the TM is visible, but IOP still remain high after LPI, medical treatment should be considered. SLT is another option for IOP reduction in PAC eyes. The mean IOP reduction following SLT was similar to PGA therapy at 6 months. However, repeat laser may be required.[6]

Phacoemulsification

Phacoemulsification lens extraction is preferred over LPI in cases of PAC with IOP > 30 mmHg in which lens mechanism predominates.[7] LPI may still be considered if the pupil block mechanism predominates. There is no significant difference in IOP-lowering effects between phacoemulsification and phacoemulsification with goniosynechialysis (GSL).[8,9] Adjunctive GSL does not have any added benefit.

PACG

Figure 3.4.1 shows a flowchart depicting the management of PACG, which depends on the assessment of the following factors:

- Presence of coexistent cataract.
- Severity of PACG.
- Whether IOP is medically controlled or not.
- Extent of ITC and PAS on gonioscopy.

PACG without cataract

Mild to moderate PACG

In patients with PACG without cataract and mild to moderate disease, the options of LPI and clear lens extraction exists. It is important to discuss with the patient the options, risks, and benefits of clear lens extraction versus LPI.

LPI

LPI may be considered in:

- Early PACG without cataract.
- Predominant pupil block mechanism (according to WGA recommendations).[1,2]
- In younger patients with the need for accommodation.
- Risk-averse patients.
- Presence of comorbidities.
- Good IOP control.

Persistent or residual ITC and suboptimal IOP control has been reported after LPI in patients with PACG.[10] In advanced PACG or in eyes with extensive PAS, LPI alone is unlikely to reduce IOP effectively in the long term. Hence, all PACG patients should be monitored after LPI,[11] and additional medical therapy and/or incisional surgery may be required to achieve IOP control.

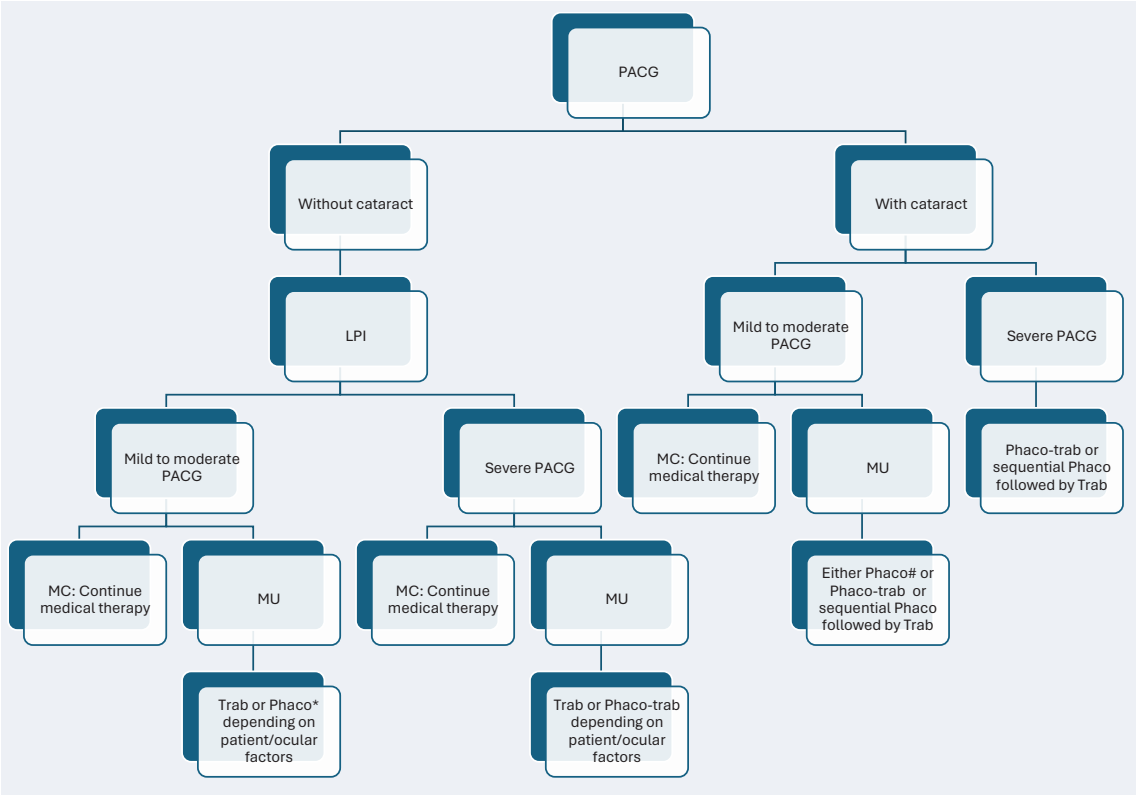

Figure 3.4.1. Flowchart depicting the management of PACG. Adapted from the WGA module flowchart for management of PACG. LPI: Laser peripheral iridotomy; MC: Medically controlled; MU: Medically uncontrolled; Phaco: Phacoemulsification with intraocular lens implantation; Phaco-trab: Phacoemulsification with intraocular lens implantation and trabeculectomy with mitomycin C; Trab: Trabeculectomy with mitomycin C; *: Risks of clear lens extraction to be explained to the patient; #: Need for subsequent trabeculectomy to be explained to the patient

Clear lens extraction

Based on the evidence from the Effectiveness in Angle-Closure Glaucoma of Lens Extraction (EAGLE) study,[7] phacoemulsification is offered as an option in cases of mild to moderate PACG without cataract. The EAGLE trial found that clear lens phacoemulsification was superior to PI in terms of patient-reported health status, IOP control, need for glaucoma medications/surgery, and cost-effectiveness.

The results of the EAGLE study might not be generalizable outside its inclusion criteria, and an individualized approach may be required for PACG patients without cataract. Cases involving older patients, high hypermetropia, presence of high lens vault, presence of plateau iris, and poor IOP control may benefit from phacoemulsification.

Severe PACG

In medically uncontrolled PACG eyes without cataract, trabeculectomy with MMC may be indicated, particularly in younger patients with accommodative ability and who are unlikely to need cataract surgery for many years. Although trabeculectomy with MMC was found to be more effective than phacoemulsification in medically uncontrolled PACG eyes with a clear lens, especially if medication reduction is of high priority, surgical complications were higher.[12]

PACG with cataract

In patients with coexisting visually significant cataract and medically controlled PACG, phacoemulsification is the treatment of choice for the management of early to moderate PACG. Lens extraction may reduce IOP by up to 30% in PACG eyes postoperatively.[13-15]

For medically uncontrolled PACG with coexisting cataract and severe disease, phacoemulsification combined with trabeculectomy with MMC (phaco-trabeculectomy) may be considered. Phaco-trabeculectomy resulted in lower postoperative IOP and lower glaucoma medication usage than phacoemulsification alone in a 2-year follow-up study, but was associated with more complications.[16] However, if only phacoemulsification is preferred in cases of advanced PACG with uncontrolled IOP and concurrent cataract, patients should be advised that subsequent trabeculectomy with MMC may be required after lens extraction.

Modifications to the surgical technique of trabeculectomy in PACG have been suggested to avoid complications and improve outcomes. These include:

- Placing the sclerostomy more anteriorly.
- Avoiding extreme IOP fluctuations during the intraoperative period by maintaining a deep anterior chamber and preplacement of sutures before the sclerostomy.
- Avoiding postoperative hypotony by applying multiple, tight scleral flap sutures, conservative suture lysis or removal.
- Use of cycloplegic therapy.

Medical management

The medical armamentarium for PACG is similar to that of OAG, encompassing beta blockers, PGAs, alpha agonists, and carbonic anhydrase inhibitors. Studies have shown a higher efficacy of PGAs compared to timolol monotherapy for IOP-lowering in eyes with PACG post-LPI.[17-19] Pilocarpine may be beneficial in PACG with plateau iris.[20]

Adjunctive treatment options

GSL for extensive PAS

Phacoemulsification-GSL does not have additional IOP-lowering ability and is not indicated in long-standing PACG. It is likely that TM function is impaired in long-standing PACG or the IOP lowering effect may not be long standing due to reformation of PAS.[8,9] However phaco-GSL may have a role in PACG eyes when the surgery is performed within 6 months of treatment for acute angle closure.[21]

Laser peripheral iridoplasty

Laser peripheral iridoplasty may decrease IOP in PAC and PACG patients by reducing appositional angle closure.[22,23]

SLT

SLT can be performed in angle-closure eyes post-LPI when at least 90° of the angles are open. SLT has been shown to be a generally safe procedure in PACG,[6] with a modest efficacy in terms of IOP lowering of 15%–20% at 6–12 months, similar to PGA therapy, but decreasing over time.[6,24,25]

Cyclophotocoagulation

Even though trans-scleral/endoscopic cyclophotocoagulation (TCP/ECP) and micropulse transscleral cyclophotocoagulation (MP-TCP) are generally effective in lowering IOP, the risk of chronic inflammation, hypotony, and phthisis cannot be ignored.[26-28]

Minimally invasive glaucoma surgery

Even though minimally invasive glaucoma surgery (MIGS) devices have a generally favourable safety profile, their effectiveness is insufficiently proven in angle-closure disease.[29-32] Several types of MIGS are currently in the market, with the majority aiming to bypass the TM through a small device, often implanted during cataract extraction. In PACG eyes, the narrow anterior chamber angles are in close proximity to the iris, which may result in obstruction of the device by the iris.[29]

Glaucoma drainage device surgery

Glaucoma drainage devices (GDD) such as the Baerveldt (Johnson & Johnson, New Brunswick, NJ, USA) and Ahmed tube (New World Medical, Rancho Cucamonga, CA, USA) implants are another surgical treatment option for eyes with high risk of failure of trabeculectomy.[33] GDD surgery can be considered in individuals with sufficiently deep anterior chambers. In pseudophakic eyes with a shallow chamber, tube placement can be performed in the ciliary sulcus.

In The Tube Versus Trabeculectomy (TVT) study, which compared tube surgery and trabeculectomy in eyes with either previous trabeculectomy and/or cataract extraction, tube surgery had a higher success rate (defined as IOP < 21mmHg or > 20% IOP reduction) and lower frequency of additional glaucoma surgeries at 5 years.[34] Interestingly, in the Primary Tube Versus Trabeculectomy (PTVT) study, which included eyes with no previous incisional surgery,[35] the trabeculectomy group had a higher success rate with lower IOP and need of fewer glaucoma medications than the tube surgery group at 1 year.

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3.5. ACUTE ANGLE CLOSURE

Key messages

- ❖ Medical therapy including topical IOP-lowering medications, acetazolamide and hyperosmotic agents constitutes the initial therapy to reduce IOP and to clear corneal oedema.
- ❖ LPI should be performed when the cornea is clear to relieve pupillary block.
- ❖ Argon laser peripheral iridoplasty (ALPI) can be attempted in cases with shallow anterior chambers or severe corneal oedema when peripheral iridotomy is detrimental to the corneal endothelium.
- ❖ Cataract/early lens extraction is the definitive management to relieve pupillary block.

DEFINITION

Acute angle closure (AAC) is an ocular emergency that is caused by rapid increase in IOP due to obstruction of aqueous humour outflow. The signs and symptoms of AAC are:

- Intermittent/episodic blurring.
- Glare and coloured rings around lights.
- Ocular pain.
- Frontal headache with nausea and malaise.
- High IOP, often above 40 mmHg.
- Mid-dilated pupil and reduced or no reactivity to the light.
- Venous congestion and ciliary injection.

WORKUP

Early stage

- Slit-lamp examination.
- Goldmann applanation tonometry.
- Anterior segment optical coherence tomography (OCT) (when available)
- Ultrasound biomicroscopy (if non-pupillary block mechanism is suspected).
- Gonioscopy.

Follow-up

- ONH and RNFL imaging.
- VF examination.

RISK FACTORS

- Older age.
- Family history.
- Female gender.
- Hypermetropia.
- South and East Asian ethnicity.
- Thick peripheral iris.
- More anterior iris insertion.
- More prominent and anterior lens vault.

Pharmacological agents

Several classes of pharmacological agents may precipitate AAC.

Topical agents

- Cholinergic or anticholinesterase agents may induce AAC in spherophakia, PXF syndrome, phacomorphic glaucoma, and malignant glaucoma.[1]
- Phenylephrine, as well its prodrugs dipivefrin and apraclonidine, is commonly used in-office for pupillary dilation and has been documented to induce AAC.[2,3]
- Anticholinergic/cycloplegic agents used for pupillary dilation may also lead to AAC.[1,2]
- Botulinum acts on the peripheral cholinergic synapses, inhibiting the release of acetylcholine. When injected periocularly (*e.g.*, for hemifacial spasm), botulinum may cause pupillary dilation, which can induce AAC.[4]

Antibacterial agents

- Sulpha drugs may induce AAC through lenticular swelling, retinal oedema, and choroidal effusion, resulting in secondary shallowing of the anterior chamber.[5-7]

Central nervous system agents

- Antidepressants such as tricyclic agents (amitriptyline and imipramine) and non-tricyclic drugs (mianserin hydrochloride, paroxetine, fluoxetine, maprotiline, fluvoxamine, venlafaxine, citalopram, and escitalopram).[8]
- Antipsychotics (*e.g.*, perphenazine, trifluperazine, fluphenazine) have a lower possibility of inducing AAC. Benzodiazepines can induce AAC because they induce relaxation of the sphincter muscle of the iris and have a mild anticholinergic effect. Diazepam, clotiazepam and alprazolam have documented associations with AAC.[8]
- Anti-Parkinsonians such as cabergoline, a dopamine D2 receptor agonist, are associated with choroidal effusion.[9]
- The anticonvulsant agent topiramate can induce AAC within the first 2 weeks of initiation, and in almost all cases in both eyes.[5]
- Ecstasy and marijuana.[10] Cocaine has indirect sympathomimetic activity and causes mydriasis.[11]

Respiratory agents

- Epinephrine.[12]
- Ipratropium bromide.[13]

Cardiac agents

- Disopyramide.[14,15]

Haematologic agents

- Anticoagulants, by precipitating spontaneous choroidal hemorrhages.[16]

Anti-Inflammatory agents

- Promethazine, an H1-blocker agent, has been shown to produce an idiopathic swelling of the lens.[17]
- Mefenamic acid, a non-steroidal anti-inflammatory agent, may induce secondary non-pupillary block AAC.[18]

Gastrointestinal agents

- Cimetidine and ranitidine, H2-blocker agents, have weak anticholinergic properties.[19]

TREATMENT

Medical therapy is prescribed to lower IOP. Iridotomy/iridectomy should be performed as soon as possible to eliminate the pupillary block and the pressure gradient between the posterior and anterior chamber. The treatment algorithm for AAC is outlined in **Figure 3.6.1**.

Medical therapy

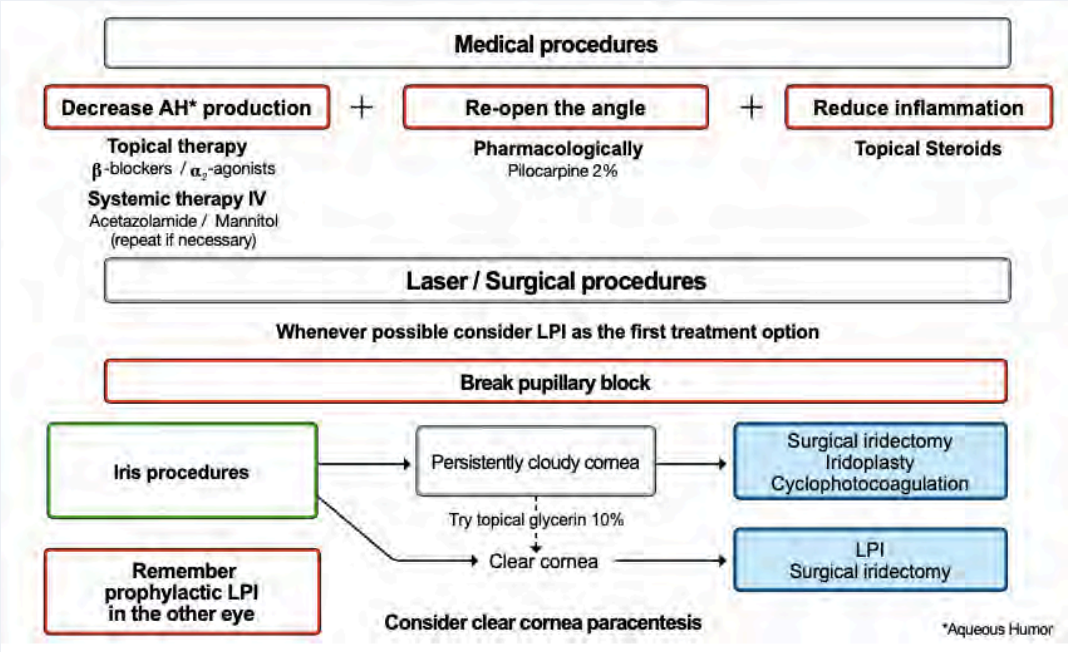

Figure 3.6.1. Management algorithm of acute primary angle closure attack.

- Reduction of aqueous humour production: (1) Acetazolamide 10 mg/kg intravenously (IV) for systemic medication with possible contraindication in people with poor renal function or sulpha allergy; (2) topical beta blockers; and (3) alpha agonists.
- Dehydration of the vitreous body: Hyperosmotic agents are effective to lower IOP, although they carry significant systemic risks in some patients. Patients must be evaluated for heart or kidney disease because hyperosmotic increase blood volume, which increases the cardiac load. Glycerol may alter glucose blood levels and may not be prescribed to diabetic patients. Glycerol: 1.0–1.5 gr/kg orally; mannitol: 1.0–2.0 gr/kg IV over 30 minutes.
- Pupillary constriction: Pilocarpine.
- Reduction of inflammation: Topical steroid, application frequency depends on the se-

verity of inflammation.

Laser and surgical treatment

Laser treatment

Nd:YAG LPI should be attempted if the cornea is sufficiently clear. Surgical iridectomy is an alternative when Nd:YAG LPI is not possible. In addition to medical therapy, ALPI can effectively halt an AAC.

Surgical treatment

Anterior chamber paracentesis

Anterior chamber paracentesis may be useful in cases that are refractory to medical management and when there is no access to laser.[20]

Lens extraction

Numerous studies have documented that lens extraction significantly widens the anterior chamber angle in eyes with PACD.[21-25] In prospective and retrospective studies, cataract surgery has been shown to lower IOP and reduce postoperative medication requirements.[26-28] Nonetheless, it also has been documented that cataract extraction alone does not result in as low an IOP as cataract surgery combined with trabeculectomy.[29] The risks and benefits should be considered before choosing the most appropriate type of surgery.

In AAC, phacoemulsification performed soon after initial medical reduction of IOP is effective in maintaining IOP control and reducing the need for glaucoma medication.[27,30] However phacoemulsification also carries a greater risk due to the small dimensions of the anterior chamber and the tendency of choroidal expansion.

The Effectiveness of Early Lens Extraction for the Treatment of Primary Angle-Closure Glaucoma (EAGLE) study found clear lens extraction with IOL implantation to be superior to LPI for the treatment of PAC (IOP > 30 mmHg at diagnosis) and PACG.[28]

Trabeculectomy

Trabeculectomy achieves long-term IOP control in many cases, although some patients do require further therapy or repeat surgery.[31] Trabeculectomy is indicated in cases where medications or lasers are not suitable or have failed to control the disease. It is also indicated in patients with advanced glaucoma and high IOP at presentation.[31]

FAQ

What is the most common mechanism for AAC?

Pupillary block is the most common mechanism for AAC. In a few cases, circumferential iris apposition to the trabecular meshwork (TM) and total obstruction of trabecular outflow may lead to an acute rise in IOP to very high levels *e.g.* 50–70 mmHg. Increased resistance to transpupillary aqueous flow due to an increased contact between the iris and the lens probably results from mid-dilated pupil with co-activation of both sphincter and dilator muscles. This may occur in response to physiological *e.g.* low light levels, or pharmacological stimuli.

What are the incidence rates of symptomatic AAC?

Incidence rates of symptomatic AAC (given as cases/100,000 persons/year for the population aged 30 years and older) range from 4.7 in Europe (Finland)[32] to 15.5 in Chinese Singaporeans.[33] Malay and Indian individuals in Singapore have lower rates than do Chinese Singaporeans (6.0 and 6.3, respectively).[33]

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3.6. NEOVASCULAR GLAUCOMA

KEY MESSAGES

- The use of anti-vascular endothelial growth factor (anti-VEGF) in conjunction with panretinal photocoagulation (PRP) is recommended for control of retinal or ocular ischaemia.
- Optimizing the management of the underlying systemic disease is crucial for controlling and preventing NVG.

DEFINITION

NVG is a refractory, sight-threatening secondary glaucoma primarily caused by retinal or ocular ischaemia, and characterised by the development of new blood vessels over the iris and the proliferation of fibrovascular tissue in the anterior chamber angle. This anomalous tissue can obstruct the TM and/or cause PAS, resulting in increased IOP.

DIAGNOSTIC WORKUP

1. Identifying the underlying aetiology: *e.g.*, diabetes mellitus (DM), retinal vascular occlusion, ocular tumours, uveitis.
2. Detailed anterior and posterior segment examination including gonioscopy, OCT for the macula and ONH, and fundus fluorescein angiography (FFA) or OCT-angiography (OCTA).
3. Formulating a management plan (**Figure 3.5.1**) after evaluating the cause, stage, systemic and ocular conditions (visual acuity, media clarity, IOP, and ONH/RNFL) at presentation.

RISK FACTORS

Systemic risk factors

- DM: DM contributes one-third of NVG cases and is associated with proliferative diabetic retinopathy but can also be seen without neovascularisation of the disc (NVD) or neovascularisation elsewhere (NVE).[1,2]
- Central retinal vein occlusion (CRVO): CRVO is the second most common cause of NVG and develops in 40%–45% of ischaemic CRVO eyes, often within the first 3 months (90-day glaucoma).[3]
- Ocular ischaemic syndrome: The third most common cause of NVG.[2] It can present with ocular angina and neovascularization of the iris (NVI)/neovascularisation of the angle (NVA), with or without the presence of NVD/NVE.[4,5] A carotid Doppler study is mandatory in suspected cases.
- Central retinal arterial occlusion: This is an uncommon cause which has been reported in 1%–20% of cases, often associated with underlying carotid disease.[2]

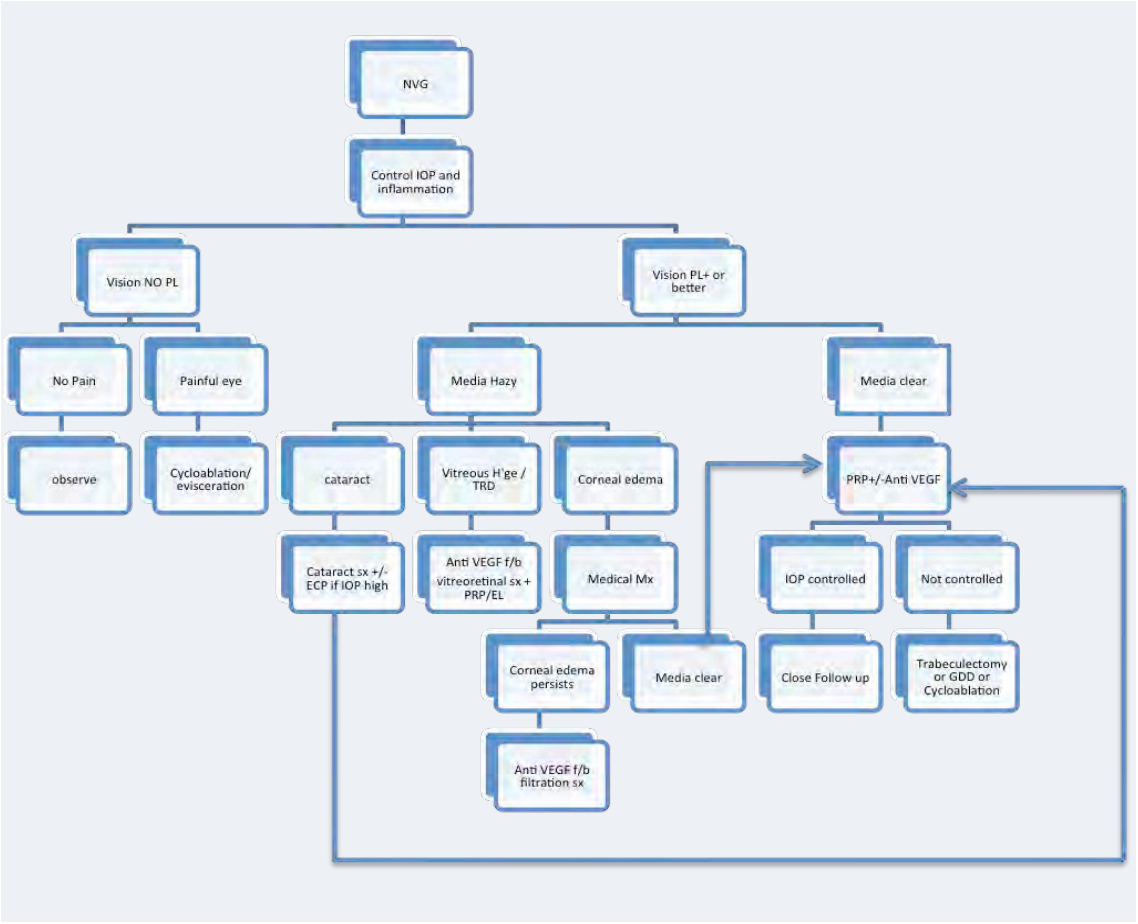

Figure 3.5.1. Treatment algorithm for neovascular glaucoma. Anti-VEGF: Anti-vascular endothelial growth factor; ECP: Endoscopic cyclophotocoagulation; EL: Endolaser; GDD: Glaucoma drainage device; GFS: Glaucoma filtration surgery; IOP: Intraocular pressure: LP: Light perception; NVG: neovascular glaucoma; PRP: Panretinal photocoagulation; Trab: Trabeculectomy; TRD: Tractional retinal detachmen

Ocular risk factors

- Tumours.[6-9]
- Retinal detachment.[2,10]
- Uveitis.[11-13]
- Trauma.[1]
- Radiation.[14-1]

STAGES OF NVG

1. Pre-rubeotic/rubeotic glaucoma: NVI/ NVA is present, while angles are open and IOP is normal. Fluorescein angiography will show leakage from vessels at pupillary margin and capillary non-perfusion (CNP) areas in the retina.
2. OAG: Presence of NVI/NVA along with the fibrovascular membrane blocking the TM, causing a rise in IOP.
3. ACG: Contracture of the fibrovascular membrane pulls the iris over the TM, forming PAS and leading to zipper angle closure. As the progression to this stage is very rapid, close monitoring is required.

MANAGEMENT

Aims

- To control IOP, inflammation, and preserve visual function.
- To treat the underlying the systemic disease (*e.g.*, DM, hypertension, carotid artery stenosis).
- To reduce the underlying retinal ischaemia by means of PRP and anti-VEGF treatment.
- To provide pain relief by means of cycloablation.

Initial medical management

- Topical antiglaucoma medications: Should be prescribed in line with the systemic comorbidities. PGAs should be avoided in eyes with active inflammation and macular oedema.
- Oral CAIs: If target IOP not achieved, CAIs are prescribed as an interim measure until definite filtration surgery can be performed.
- Topical steroids and cycloplegics: To counter associated pain and inflammation.

Subsequent management

Combination PRP/anti-VEGF therapy

If the media is clear at presentation, PRP is the mainstay of treatment.[17] If the media is hazy, intravitreal anti-VEGF injections are first given followed by PRP.[18] Depending on the cause, cataract surgery or vitrectomy may be needed to clear the media.

Surgical management

Filtration surgery is recommended in the majority eyes with NVG. Glaucoma drainage devices or trabeculectomy with antimetabolites may be considered[19] once neovascularization has been quiescent for a certain amount of time.

Cycloablation

Endoscopic cyclophotocoagulation can be combined with cataract surgery. In eyes with poor visual potential anterior, retinal cryopexy (to decrease retinal ischaemia) with trans-scleral cyclocryotherapy/diode laser cyclophotocoagulation can be performed to provide symptomatic pain relief.

FAQs

Can PGAs be used in NVG?

PGAs and cholinergic drugs, such as pilocarpine, may increase inflammation by further compromising the blood-aqueous barrier. However, if there are no significant cells or flare in the anterior chamber, and no macular oedema, PGAs may be prescribed with caution.

Do all cases of CRVO develop NVG?

NVG develops in nearly half of ischaemic CRVO cases. FFA is an important diagnostic tool (to be performed once retinal haemorrhages have cleared) to determine if reperfusion has been established.[2]

Can neovascularisation reappear or not regress after PRP?
If the underlying systemic or ocular condition is not controlled (poor glycaemic control, deranged renal function, inadequate PRP), the retinal ischaemia can persist, releasing VEGFs and causing neovascularisation to reappear. If CNP areas are visible on FFA, PRP augmentation may be needed in terms of more tightly packed spots as well as ablation of the peripheral retina.

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3.7. UVEITIC GLAUCOMA

Key messages

- ❖ Effective management requires addressing both the underlying inflammation caused by uveitis and the resulting elevated IOP.
- ❖ A collaborative approach involving ophthalmologists, rheumatologists, and primary care providers is essential for successful management.

UVEITIC GLAUCOMA

Uveitic glaucoma is a complex condition that arises when uveitis, an inflammation of the uveal tract of the eye, leads to IOP elevation, which can lead to GON. The management of uveitic glaucoma requires a comprehensive approach that addresses both the underlying inflammation and the elevated IOP.

PATHOPHYSIOLOGY

Anterior uveitis is most frequently associated with uveitic glaucoma. Common etiologies include idiopathic uveitis, autoimmune disorders (*e.g.*, seronegative spondyloarthropathies, Behçet disease, granulomatosis with polyangiitis, sarcoidosis, and juvenile idiopathic arthritis), infectious diseases (*e.g.*, herpes simplex, herpes zoster, syphilis, and tuberculosis), lens-associated uveitis, and trauma.

Mechanisms of IOP elevation

- Open-angle mechanism: TM obstruction consequential to inflammatory cells and debris clogging the TM. Direct inflammation of the TM, trabeculitis, can further disrupt aqueous outflow.
- Closed-angle mechanism: Formation of PAS secondary to chronic inflammation that causes the iris to adhere to the TM, blocking aqueous humor outflow. Posterior synechiae can lead to acute angle closure due to iris bombé. Forward rotation of the ciliary body due to uveal effusion may also lead to angle closure.
- Steroid-induced glaucoma: Steroids, often used to treat uveitis, can increase IOP in susceptible individuals.

MANAGEMENT STRATEGIES[1,2]

Managing uveitic glaucoma requires a comprehensive and individualized approach that targets both the uveitis and the elevated IOP. Collaboration between ophthalmologists and rheumatologists or other specialists may be beneficial in providing comprehensive care. Early diagnosis, aggressive management of inflammation, careful selection of IOP-lowering treatments, and regular monitoring are key to preserving vision in patients with uveitic glaucoma.

Detailed patient history

Understanding the onset, duration, and severity of symptoms, as well as any previous treatments.

Complete eye examination

A complete eye examination should include visual acuity, IOP measurement, gonioscopy to assess the angle and possible PAS, a dilated fundus exam, OCT imaging of the optic disc and RNFL, and VF.

Addressing inflammation

Controlling the underlying uveitis is paramount in managing uveitic glaucoma, for which there are several treatment options.

Corticosteroids

Topical corticosteroids are the mainstay for reducing inflammation but must be used carefully due to the risk of steroid-induced glaucoma. Among the topical steroids, prednisolone acetate demonstrates the strongest clinical potency due to corneal penetration than action at receptor sites, while rimexolone and loteprednol cause a weaker steroid response with a corresponding weaker anti-inflammatory effect.

Insufficient response to topical administration may require periocular injections with agents such as dexamethasone phosphate, prednisolone succinate, triamcinolone acetonide, or methylprednisolone acetate. Other forms of administration include intraocular sustained-release steroids such as fluocinolone acetonide or dexamethasone, or a systemic corticosteroid such as prednisone.

Non-steroidal anti-inflammatory drugs

Topical or systemic non-steroidal anti-inflammatory drugs (NSAIDs) in the form of prostaglandin synthetase inhibitors, such as aspirin, imidazole, indomethacin, and dipyridamole, are used when corticosteroids are contraindicated or inadequate. NSAIDs may partially block the IOP-lowering effects of certain antiglaucoma medications such as latanoprost and brimonidine.[3] Newer cyclo-oxygenase inhibitors, such as flurbiprofen, ketorolac, suprofen, and diclofenac, are also an option.

Systemic immunosuppressive therapy

Systemic immunosuppressive therapy requires coordination with a uveitis specialist or rheumatologist. Drugs in this category include cyclosporine, azathioprine, and methotrexate, as well as anti-TNF-alpha antibody therapy such as infliximab, etanercept, and adalimumab. Adalimumab was approved in 2016–2018 for patients aged 2 years and above and has been shown to decrease the frequency of flareups and reduce the need for topical or systemic corticosteroids.[4]

Cycloplegic agents

Cycloplegic agents are indicated to prevent posterior synechiae and relieve the ocular pain caused by ciliary muscle spasms. Mydriatic-cycloplegic drugs include atropine 1%, homatropine 1% to 5%, and cyclopentolate 0.5% to 1%.

Managing IOP

Parallel to treating inflammation, managing elevated IOP is crucial. The options to manage IOP include medications, laser therapy, and surgery.

Medications

The options for medical therapy in uveitic glaucoma are summarised in **Table 3.7.1**. Topical beta blockers, alpha agonists, and CAIs can reduce IOP. PGAs may exacerbate inflammation, although PGAs have also been shown in some studies to be safe and effective for OHT associated with uveitis.[5-8]

Laser therapy

Laser trabeculoplasty may not be effective in uveitic glaucoma due to trabecular meshwork damage. It may cause an acute flare-up of uveitis leading to a significant rise in IOP. A few studies, however, have shown SLT can be considered for steroid-induced glaucoma with quiescent uveitis.[9,10] However, laser peripheral iridotomy may be beneficial in cases with pupillary block.

Surgery

In refractory cases, surgical intervention such as trabeculectomy with antimetabolites or glaucoma drainage devices may be necessary although uveitis is a known risk factor for surgical failure. Glaucoma drainage device (GDD) surgery is an effective intervention in cases with significant postoperative inflammation and in cases with risk for trabeculectomy failure. Minimally invasive glaucoma surgeries (MIGS) are being evaluated for their role in uveitic glaucoma.

Monitoring and follow-up

Regular follow-up is essential to monitor the efficacy of treatment, adjust therapy as needed, and detect complications early. The frequency of visits depends on the severity and stability of the disease.

Table 3.7.1. Medical therapy options for uveitic glaucoma

Medication class	Therapeutic use	Remarks/Contraindications
Non-selective beta blockers	First line	Except metipranolol due to anterior granulomatous uveitis[11]
Topical and systemic CAIs	First line Positive effect in preventing and treating CME coexistent with UG	Avoid in patients with compromised corneal endothelium and corneal endothelial injury[12]
Alpha-2 adrenergic agonists	Second line	May reactivate anterior uveitis[12]
PGAs	Used in cases of quiescent uveitis without previous complicated intraocular surgery or pre-existing CME	Avoid in herpetic keratitis or keratouveitis[13]
Rho kinase inhibitors	Can be used safely as an option if the eye is a responder[14]	
Hyperosmotics	Rapid onset of action and useful for marked IOP elevation	
Tissue plasminogen activator	In eyes with acute fibrinous anterior uveitis and impending pupillary block with or without PAS at a dose of 6.25–12.5 μg[15]	

CAIs: Carbonic anhydrase inhibitors; CME: Cystoid macular oedema; PAS: Peripheral anterior synechiae; UG: Uveitic glaucoma

FAQ

How long should a patient with uveitis be treated with steroids?
Topical corticosteroids are preferred for anterior segment disease. They may be administered every hour with gradual reduction in frequency as inflammation subsides. Consideration of the different side effects must be noted, including steroid-induced glaucoma. Special dosing requirements are required in children at risk of growth retardation.[16]

When should we perform glaucoma surgery on a patient with uveitis?
Intraocular surgery is avoided whenever possible in cases with active intraocular inflammation. Surgery may be necessary when medical therapy is insufficient to lower IOP. Control of intraocular inflammation for a minimum of 3 months may be ideal before surgery according to Carreño,[17] but may not be realistic. IOP control is critical both preoperatively and postoperatively.[16]

If a patient develops steroid-induced glaucoma, how do we balance the use of steroids and antiglaucoma medications?
The first line of defence may be to discontinue the corticosteroids, which typically resolves the glaucoma within 1 to 4 weeks. The duration of steroid therapy may influence the speed at which IOP elevation is reversed. Additional antiglaucoma medications may be prescribed for patients who need continued steroid therapy, with the option of shifting to a steroid with less potential for IOP elevation. The use of NSAIDs, cyclo-oxygenase inhibitors, and immunomodulatory agents may be considered.[16]

In uveitic patients who have pre-existing glaucoma, is it better to do a combined procedure to remove the cataract and decrease the IOP, or a staged procedure?
Combined phacoemulsification and trabeculectomy was found to have a similar success rate as that of trabeculectomy alone based on some studies; however, other studies reported worse results than with trabeculectomy alone. Less postoperative flares may be observed in trabeculectomy alone than combined surgery due to the significant inflammation in uveitis. Adequate control of inflammation should be achieved preoperatively when combined glaucoma and cataract surgery is indicated. Intensification of postoperative steroid treatment is necessary, especially in cases of recurrent uveitis.[12]

How much better is performing a GDD compared to trabeculectomy in controlling the IOP?
GDDs are the preferred first-line surgery in uveitic glaucoma, especially in patients with active inflammation. Good success rates were obtained with the use of the Ahmed Glaucoma Valve, Molteno aqueous shunt, and Baerveldt implant. Although antiproliferative agents with trabeculectomy may be used in patients with uncontrolled IOP, intense and persistent inflammation may cause trabeculectomy to fail.[17]

Should we prescribe systemic steroids to patients with uveitis prior to surgery to improve surgical outcomes?
Preoperative topical or oral steroid treatment (0.5 to 1 mg/kg/day of oral prednisolone) may be prescribed to patients prior to filtration surgery to decrease inflammatory intraocular conjunctival cells.[12]

Which antiglaucoma medications are contraindicated in uveitis patients?
Cholinergic agonists are contraindicated in uveitic eyes due to exacerbation of inflammation via breakdown of the blood-aqueous barrier and posterior synechiae formation. PGAs are not the ideal first-line agents, though they may be used in patients with controlled uveitis but are contraindicated in patients with a history of herpetic keratitis or keratouveitis.[12]

How important is the use of antimetabolites in glaucoma surgery for uveitic patients?
The intraoperative use of antifibrotics may delay postoperative wound healing in glaucoma surgery in uveitic patients. MMC has been found to be more efficient in improving the success rate of glaucoma surgery compared to 5-FU. In patients with uveitis, careful use of MMC is recommended to avoid prolonged hypotony and the risk of phthisis bulbi due to the associated injury to the ciliary body.[12,16]

Do MIGS procedures have a role in glaucoma management in uveitic patients?
MIGS procedures have not been well studied for uveitic glaucoma. PAS have been observed with the use TM devices (iStent and Hydrus) even in non-uveitic eyes that its use should be carefully considered. Use of Ex-PRESS shunt which maybe promising in some cases due to less inflammation and risk of blockage still warrants larger trials to establish long-term efficacy.[12,16]

Does SLT work for uveitic glaucoma?
There is insufficient clinical evidence for the use of SLT in uveitic glaucoma with an open-angle mechanism as it may cause an additional rise in IOP. It is contraindicated in these cases because of the risk of exacerbating inflammation.[12,16] A few studies, however, have shown SLT can be considered for steroid-induced glaucoma with quiescent uveitis.[9,10]

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SECTION 4

MEDICAL TREATMENT

4.1. OVERVIEW OF MEDICAL TREATMENT AND RECOMMENDATIONS

Key messages

- Antiglaucoma medication is a widely available and effective modality to lower IOP for most patients.
- IOP-lowering eye drops are generally considered the first-line treatment for glaucoma.
- When choosing antiglaucoma medication for a patient, ophthalmologists should consider the drug's mechanism of action, systemic risk factors, other special considerations (children, pregnant, and breastfeeding women), potential side effects, ease of eye drop application and medication adherence.

TOPICAL MEDICAL THERAPY

Eye drops are the cornerstone and first line for the management of IOP in glaucoma. There are currently several classes of drugs that mainly focus either on increasing outflow facility or reducing aqueous humour production (**Table 4.1.1**). Widely available and with a generally effective therapeutic index, eye drops achieve adequate IOP control in the majority of glaucoma patients. Optimising medication performance requires adequate medication compliance at 4 levels:

1. Obtaining the medication.
2. Using the medication each day.
3. Timing the doses appropriately.
4. Correctly instilling eye drops.

Table 4.1.1. Mechanism of action of different antiglaucoma drug classes[1-13]

Mechanism of action	Drug class and target site of action	Preparations
Increase in aqueous outflow	Prostaglandin analogues Uveoscleral outflow	Latanoprost Travoprost Bimatoprost Tafluprost
	Prostanoid E2 receptor agonist Uveoscleral and trabecular outflow	Omidenepag isopropyl
	Alpha-1 blockers Uveoscleral outflow	Bunazosin
	Alpha-2 agonists	Brimonidine Apraclonidine
	Alpha-1-beta blockers Uveoscleral outflow	Nipradirol
	Cholinergics Trabecular outflow	Pilocarpine Carbachol
	Rho kinase inhibitors Trabecular outflow and episcleral venous pressure (for netarsudil)	Ripasudil Netarsudil
Decrease in aqueous production	Beta blockers	β1-Non-selective antagonist Timolol Levobunolol Carteolol β1-Selective antagonist Betaxolol
	Alpha-2 agonists	Brimonidine Apraclonidine
	Alpha-1 beta blockers	Nipradirol
	Carbonic anhydrase inhibitors	Systemic Acetazolamide Methazolamide Dichlorphenamide Topical Dorzolamide Brinzolamide

The current role of neuroprotection in glaucoma

Currently, there is no clinical evidence for neuroprotection as an isolated strategy. Calcium channel blockers (CCB) might help in the presence of marked vasospastic disease (migraine and/or Raynaud's phenomenon). Alpha-2 agonists are prescribed primarily for their IOP-lowering effects. Phase III trials of N-methyl-D-aspartate (NMDA) receptor blocker (memantine) yielded mixed results.[13]

Eyedrop escalation

There are now a multitude of options of classes of drugs available as well as fixed combinations and preservative-free options (**Table 4.1.2**). The choice of medications in eye drop escalation can often be challenging. There are, however, several factors that aid in the decision-making process, which include the intended target IOP, synergistic effects of the eye drops prescribed, patient likelihood of adherence, cost, and exposure to possible increase in ocular and systemic side effects from polypharmacy (**Table 4.1.3**). **Figure 4.1.1** illustrates a treatment algorithm that can be used to guide ophthalmologists.

Table 4.1.2. Efficacy and dosing frequency of various drug classes[1-8,15-22]

Drug class	Daily dosage	Efficacy
Prostanoid FP receptor agonist (FP agonist) or prostaglandin analogues (PGAs)	1x	25%–35%
Prostanoid EP2 receptor agonist	1x	15%–35%
Beta blockers†	1x to 2x	20%–25%
Alpha-1 blockers	2x	15%–20%
Alpha-2 agonists‡	2x to 3x	18%–25%
Alpha-1-beta blockers	2x	20%
Carbonic anhydrase inhibitors (CAIs)		
Topical	2x to 3x	20%
Systemic	2x to 4x	30%–40%
Rho-kinase (ROCK) inhibitors	1x to 2x	20%–25%
Cholinergics	3x to 4x	20%–25%
Hyperosmotic agents	Stat dose(s)	15%–30%
Proprietary fixed combinations		
Beta blocker + CAI	2x	25%–30%
Beta blocker + PGA	1x	25%–35%
Beta blocker + Alpha-2 agonist†‡	2x	25%–35%
CAI + Alpha-2 agonist	2x to 3x	25%–35%
ROCK inhibitor + Alpha-2 agonist	2x	25%–35%
ROCK inhibitor + PGA	1x	25%–35%

† In patients taking systemic beta blockers, the IOP-lowering efficacy of topical beta blockers is likely reduced and the potential for systemic side effects increased: consider other drug classes first.

‡ Alpha-2 agonists are absolutely contraindicated for patients taking monoamine oxidase inhibitors (MAOIs) and children < 2 years.

Table 4.1.3. Special consideration when initiating glaucoma medications

System	Conditions	Special considerations
Respiratory	Asthma and COPD with hyper-responsive airways and/or reduced lung capacity	Beta blockers
Cardiovascular	Cardiac arrhythmias (heart block)	Beta blockers, alpha agonists
	Systemic hypotension	Beta blockers
	Systemic hypertension	Systemic beta blockers may mask IOP elevation
Endocrine	Diabetes mellitus Hyperthyroidism	Beta blockers may mask symptoms of hypoglycaemia and thyrotoxicosis
Central nervous system	Early dementia Depression	Affect drug adherence, exacerbate dry eye symptoms. If using anti-depressant, beta blockers could also contribute to depression, α-agonists are contraindicated if taking MAOIs
Musculoskeletal	Osteoarthritis Rheumatoid arthritis (RA)	Affect the ability to administer eye drops. RA-related dry eyes can be worsened by eye drops
	Myasthenia gravis	Beta blockers could exacerbate MG
Urogenital	Renal stones Renal failure	Systemic CAIs
Drug allergy	Sulphur allergy	Systemic and topical CAIs
Systemic medications	Steroids Traditional Chinese medicine (may have steroidal activity)	May cause ocular hypertension and POAG
	Anticholinergic, tricyclic antidepressants, anticonvulsants (*e.g.*, topiramate)	Can cause angle closure
	Systemic β-blockers and calcium channel blocker (CCB)	May interact with topical beta blockers
	Patients taking MAOIs for depression, migraine prophylaxis, or Parkinson's disease	Alpha agonists are contraindicated
Pregnancy and lactation	Present or possible, renders all interventions potentially hazardous , PGAs, β-blockers, α-agonists	

COPD: Chronic obstructive pulmonary disease; MAOIs: monoamine oxidase inhibitors; POAG: primary open-angle glaucoma

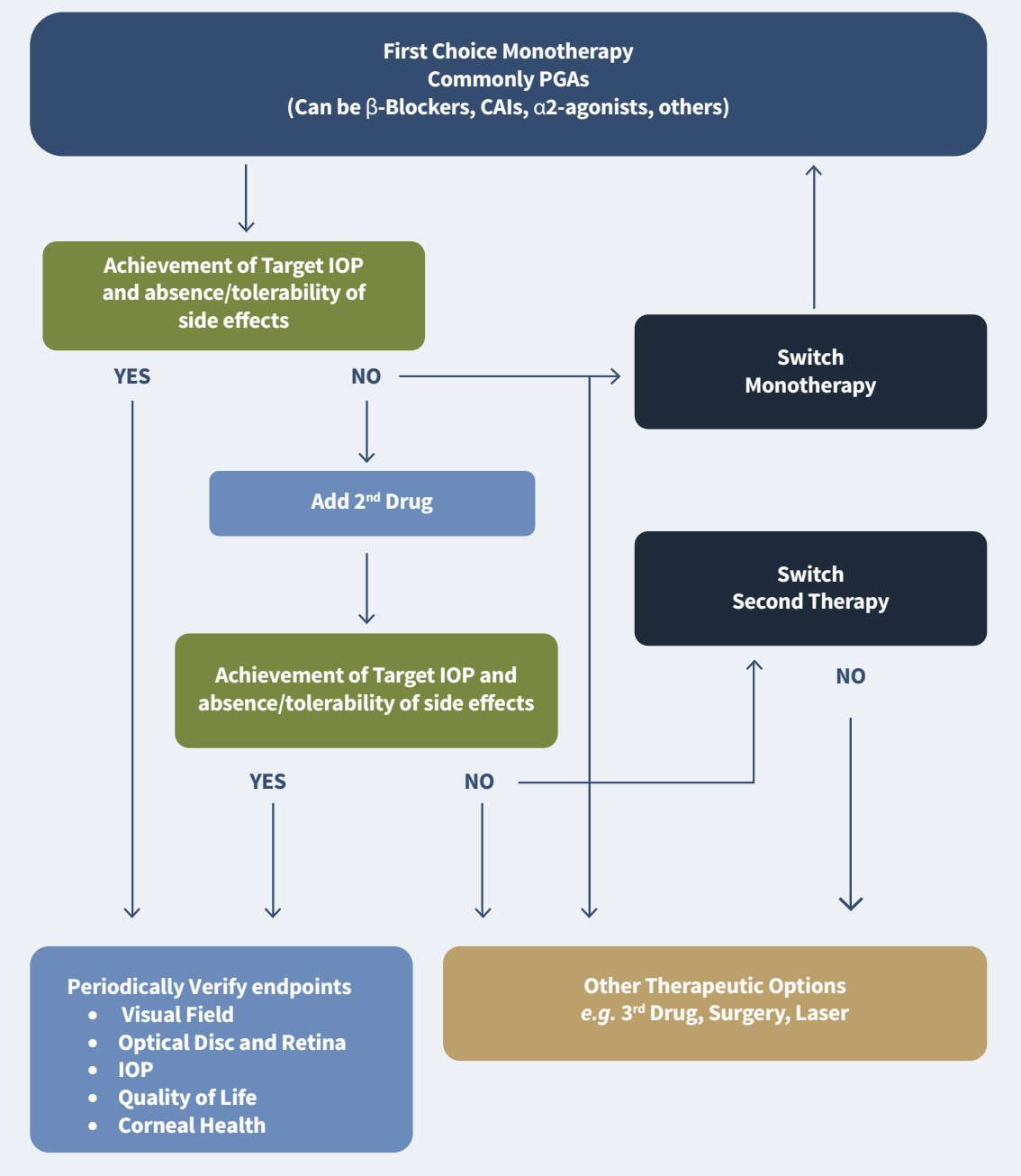

Figure 4.1.1. Medical treatment algorithm for glaucoma.

PRINCIPLES OF MEDICAL THERAPY

- Efficacy of additional medication diminishes as the number of drugs increases.
- Laser trabeculoplasty may be used in place of or as an adjunct to medical therapy.
- Surgery may be an appropriate alternative in certain situations.

Choose the most appropriate medication

- Greatest chance of reaching target IOP.
- Best safety and tolerability profiles.
- Minimal inconvenience using fixed-combination drugs.
- Affordable.
- Maximal likelihood of adherence considering ocular side effects of the number of drops.

Start low and slow

- Minimal concentration.
- Minimal frequency.

Monocular therapeutic trial

- May be helpful in some situations.
- Start treatment in the worse eye, then reassess after 2–4 weeks to evaluate IOP response, side effects, and patient's tolerability to the medication.
- If acceptable and effective, make treatment bilateral.

Inadequate initial response

If the response is inadequate to achieve the target pressure, switch before adding:

- Switch to a different class of medication (switching within the PGA class may be useful, but adherence and regression to the mean [of IOP] need to be considered).
- If a drug fails to reduce IOP from baseline or produces significant side effects, one should switch to a second drug.
- Use more than 1 agent only if each has demonstrated efficacy but is insufficient to reach the target IOP on their own:
  - Apply this principle also to fixed combinations.
  - Do not combine 2 drugs with the same pharmacological action.
  - Do not use 2 fixed combinations containing overlapping categories.
  - In cases where a substantial IOP reduction is needed, it may be necessary to start with more than 1 active agent.

Maximize the likelihood of adherence[15]

- Establish a therapeutic alliance with the patient and their family: they need to view the doctor as an ally against the disease.
- Discuss potential side effects with patient from the beginning of treatment.
- Emphasize patient and family education.
- Select the least complex regimen.
- Select the regimen that causes the least lifestyle disruption.
- Encourage the patient to set up a reminder system (*e.g.*, cell phone-based alarms), as it significantly improve adherence.

Teach the technique for eye drop instillation[23]

- Demonstrate the preferred method, including punctal occlusion and eyelid closure for at least 3 minutes (double DOT technique: "don't open the eyelid" and "digital occlusion of the tear duct").
- Ensure the patient can do it.
- If ≥ 2 drops are to be instilled, wait at least 5 minutes between drops.
- Provide educational materials.

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4.2. FIXED-DOSE COMBINATIONS

Key messages

- Fixed-dose combinations (FDC) simplify medication regimens, which may improve medication adherence, provide synergistic IOP reduction efficacy, and reduce medication side-effects.
- The development of preservative-free FDC would further improve the advantages.

FIXED-DOSE COMBINATION EYEDROPS

Effective management of glaucoma often involves the use of topical medications, primarily in the form of eyedrops. One of the treatment options available are fixed-dose combination (FDC) eyedrops, which combine 2 or more active ingredients in a single formulation. FDC eye drops offer a convenient and effective treatment option for managing glaucoma. They combine multiple active ingredients into a single formulation, providing enhanced IOP reduction compared to individual medications. While they simplify the treatment regimen and improve medication adherence, potential side effects and limited dosage titration should be taken into consideration. Combination therapy is usually not recommended as first therapy. In some cases, such as advanced glaucoma and/or very high IOP, the target pressure is unlikely to be achieved by a single agent and combination therapy may be advisable.[1]

TYPES OF FDC EYE DROPS

PGAs with beta blockers

This combination is the most commonly available. It typically includes a PGA (such as latanoprost, bimatoprost, tafluprost, or travaprost) and a beta blocker (such as timolol). PGAs enhance aqueous humour outflow via the uveoscleral pathway, while beta blockers reduce aqueous humour production. The combination offers additive IOP-lowering effects. This FDC eyedrop is usually used once a day, either in the morning or evening. Compared to morning use, Kontas *et al.* showed that using tafluprost/timolol FDC in the evening may have more superior 24-hour efficacy.[2]

Beta blockers with CAIs

These combinations involve a beta blocker and a CAI. Beta blockers reduce aqueous humour production, while carbonic anhydrase inhibitors further enhance this effect. Together, they offer additive effects for IOP lowering.[3] This FDC is prescribed for twice daily dosing and has significant IOP-lowering effects when used with a PGA.[4]

Beta blockers with alpha 2 adrenergic agonists

While beta blockers work by reducing the production of aqueous, alpha agonists enhance drainage of fluid from the eye. By combining these 2 mechanisms of action, this FDC eye drop provides a potent and complementary effect. It is applied twice daily and has a rapid onset of action.

Alpha-2 adrenergic agonists with CAIs

This FDC is an option for those patients in which beta blockers are contraindicated. It combines 2 distinct mechanisms of action to provide a synergistic IOP-lowering effect. This FDC is administered twice daily and had a significantly lower IOP-lowering effect than either standalone drug.[5]

Rho kinase inhibitors with PGAs

This novel combination is also without a beta blocker.[6] Rho kinase inhibitors lower IOP primarily by increasing trabecular outflow facility, while reducing both aqueous production and episcleral venous pressure, thus targeting trabecular and uveoscleral outflow simultaneously. This FDC is another option for those patients in which beta blockers are contraindicated.

EFFICACY OF FDC EYEDROPS

FDC eyedrops have demonstrated significant efficacy in reducing IOP levels, which is crucial for managing glaucoma progression. Clinical studies have shown that FDC eyedrops provide greater IOP reduction compared to individual medications used separately.[5,7] The combination of different mechanisms of action improves treatment outcomes, allowing for better IOP control.

SAFETY PROFILE OF FDC EYEDROPS

Overall, FDC eyedrops are generally safe and well-tolerated.[7,8] However, as with any medication, they may be associated with potential side effects. The safety profile can vary depending on the specific combination used. Some common side effects include ocular irritation, stinging, redness, and blurred vision. Systemic side effects are rare but may occur, particularly with beta blockers, such as bradycardia, bronchospasm, and fatigue. It is important for patients to be aware of these potential side effects and report them to their health care provider promptly. The availability and use of preservative-free FDC may result in better tolerability of these anti-glaucoma eyedrops.[9]

ADVANTAGES OF FDC EYE DROPS

- Simplified treatment regimen: FDC eye drops offer the advantage of combining multiple medications into a single bottle, simplifying the treatment regimen for patients. This can improve medication adherence, as patients only need to administer 1 drop rather than multiple individual eyedrops.[10,11]
- Enhanced convenience: With FDC eye drops, patients do not need to handle and administer multiple eyedrop bottles, reducing the risk of errors and confusion. This can be particularly beneficial for elderly patients or those with dexterity issues.
- Cost-effectiveness: FDC eyedrops can potentially be more cost-effective compared to purchasing individual medications separately. This benefit arises from the reduced number of co-payments and the streamlined manufacturing process.
- Side effects: There may be fewer side effects from FDC due to lower exposure to preservatives compared to the use of multiple eyedrops. This may improve tolerability, which in turn improves adherence to the eyedrop regimen.
- Elimination of the washout effect from the second drop.

DISADVANTAGES OF FDC EYE DROPS

- Limited individual dose titration: FDC eyedrops may limit the ability to adjust the dosage of each component independently. If a patient requires a specific dosage adjustment for one medication, FDC eyedrops may not provide the flexibility to achieve that.
- Increased risk of allergic reactions: Since FDC eye drops contain multiple active ingredients, there is a slightly higher risk of developing an allergic reaction compared to individual eyedrops. It is also challenging to determine which of the component is causing the allergic reaction or even both active components.
- Availability of specific combinations: The availability of FDC eyedrops can vary depending on the region or country. Not all possible combinations may be commercially available, limiting the treatment options for some patients.

EXAMPLES OF COMMERCIALLY AVAILABLE FDC EYE DROPS

- Xalacom (Pfizer, New York, NY, USA): This combination eyedrop comprises latanoprost, a PGA, and timolol, a beta blocker. Latanoprost enhances aqueous humour outflow, while timolol reduces its production.
- Ganfort/Ganfort PF (Allergan, Dublin, Ireland): Ganfort combines bimatoprost, another PGA, with timolol. Bimatoprost improves aqueous humour outflow, while timolol reduces aqueous humour production.
- Duotrav (Novartis, Basel, Switzerland): Duotrav contains travoprost, a PGA, and timolol. Travoprost increases aqueous humour outflow, while timolol decreases its production.
- Tapcom/Tapcom-S (Santen Pharmaceutical Co., Ltd, Japan): Tapcom is a FDC of tafluprost, a PGA, and timolol. Tafluprost enhances aqueous humour outflow, while timolol reduces its production.
- Simbrinza (Alcon, Geneva, Switzerland): Simbrinza combines brinzolamide, a CAI, with brimonidine, an alpha-2 adrenergic agonist. Brinzolamide decreases aqueous humour production, while brimonidine enhances its outflow.
- Cosopt/Cosopt-S (Santen Pharmaceutical Co., Ltd.): Cosopt contains dorzolamide, a CAI, and timolol. Dorzolamide reduces aqueous humour production, while timolol further enhances the effect.
- Azarga (Novartis, Basel, Switzerland): Azarga combines brinzolamide, a CAI, with timolol. Brinzolamide reduces aqueous humour production, while timolol enhances the effect.
- Combigan (Allergan, Dublin, Ireland): Combigan comprises brimonidine, an alpha-2 adrenergic agonist, and timolol. Brimonidine enhances aqueous humour outflow, while timolol reduces its production.
- Rocklatan (Santen Pharmaceutical Co., Ltd.): Rocklatan combines netarsudil, a ROCK inhibitor, with latanoprost, a PGA. Netarsudil improves TM outflow and reduces episcleral vein pressure, while latanoprost reduces uveoscleral outflow.

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4.3. NOVEL MEDICATIONS FOR GLAUCOMA TREATMENT

Key messages

- New medications and classes of drugs have been developed recently, broadening our treatment options.
- A selective EP2 receptor agonist and Rho kinase (ROCK) inhibitors have shown comparable efficacy to currently available medication, with different side-effect profiles.

RECENT DEVELOPMENTS IN GLAUCOMA MEDICAL THERAPY

Nearly a decade ago, the mechanism of action of the most commonly used topical medical therapies had been limited to decreasing production of aqueous humour and/or increasing its outflow through the uveoscleral pathway. There existed 4 major classes of topical medications: topical beta blockers, selective alpha agonists, CAIs, and PGAs. There are a handful of different medication options available in most of these classes. Still, beta blockers are used commonly as topical agents in the treatment of glaucoma and OHT, but may have systemic absorption, and so their use in patients with asthma, chronic airflow limitation, or cardiac disease is generally avoided.[1] The use of alpha-2 agonists can be often limited by localized adverse effects in adults, such as ocular allergic reaction or erythema, and irritation. In children, these agents have also been known to cause adverse events related to the central nervous system.[2] Topical CAIs remain beneficial as supplementary treatment options for IOP lowering, although their IOP-lowering effect is limited. Compared to these agents, aqueous outflow facilitator agents are reported to reduce IOP exclusively by increasing aqueous outflow, including PGAs, to increase uveoscleral outflow.

This section discusses new class of medications that have been recently developed, thus widening the options in the medical treatment of glaucoma: the EP2 receptor agonist omidenepag isopropyl (EYBELIS, Santen Pharmaceutical Co., Ltd., Japan), and the Rho kinase (ROCK) inhibitors ripasudil (Glanatec, Kowa Company, Nagoya, Japan) and netarsudil (Rhopressa, Santen Pharmaceutical Co., Ltd.).

EP2 RECEPTOR AGONIST

Prostaglandin FP receptor agonists are commonly used as first-line agents in the treatment of POAG through eye drops. They are favoured because they need to be applied only once a day and exhibit the most potent intraocular pressure (IOP)-lowering effect among glaucoma eye drops. However, localized side effects in the periocular area are a concern. These side effects include prostaglandin-related periorbital symptoms such as deepening of the upper eyelid sulcus and ptosis, as well as changes in iris and eyelid pigmentation, and eyelash elongation.

In 2018, a breakthrough came with the introduction of the selective EP2 receptor agonist omidenepag isopropyl, under the brand name EYBELIS (ophthalmic solution 0.002%) in Japan, before becoming available in other countries. Clinical trials demonstrated that EYBELIS was as effective as latanoprost ophthalmic suspension 0.005% for reducing IOP. Additionally, safety studies indicated that EYBELIS did not cause the prostaglandin-associated periorbital symptoms, hyperpigmentation, or eyelash elongation that are common with FP receptor agonists. This suggests that EYBELIS represents an eye drop medication with an optimal balance between efficacy and safety.

EYBELIS functions differently from traditional FP receptor agonists as it selectively binds to the EP2 receptor. Prostaglandin E2 (PGE2) and prostaglandin F2 alpha (PGF2α) are known to have IOP-lowering properties. Similar to FP receptor agonists, EYBELIS is believed to primarily enhance fluid outflow from the eye through the uveoscleral outflow tract. Moreover, it is believed to facilitate outflow through the trabecular meshwork, which is the eye's main fluid drainage pathway.[3]

Efficacy

Non-inferiority and safety of EYBELIS compared to latanoprost

A multicentre, randomized, evaluator-blind, parallel-group study was conducted to compare the IOP-lowering efficacy between EYBELIS and latanoprost.[4] A total of 190 Japanese subjects diagnosed with POAG or OHT participated in the study. The subjects were randomly assigned to receive either EYBELIS 0.002% or latanoprost 0.005%. Prior to the treatment, a 1-month washout period was observed. Subsequently, the eye drops were administered once daily for 4 consecutive weeks. The study results indicated that EYBELIS was non-inferior to latanoprost in terms of the mean daily change in IOP, with both groups experiencing significant reductions in IOP from their respective baselines.

Investigating the safety and IOP-lowering effects of long-term EYBELIS administration

In the study, 125 Japanese subjects with POAG, PXG, pigmentary glaucoma, or OHT were administered EYBELIS 0.002% for 52 consecutive weeks following a 1-month washout period.[5] The subjects were categorized into 3 groups:

1. Normal IOP Group (IOP ≤ 21 mmHg): Forty-eight patients received EYBELIS 0.002%. Throughout the 52-week study, IOP reductions were observed at every time point, showing a significant difference compared to the baseline IOP of 18.7 mmHg. At 52 weeks, an average IOP reduction of -3.7 mmHg was achieved in 37 patients.
2. High IOP Group (IOP > 21 mmHg): Thirty-seven patients received EYBELIS 0.002%. There was a significant reduction in IOP at all time points compared to a baseline IOP of 24.1 mmHg, with an average reduction of -5.6 mmHg at 52 weeks (31 subjects).
3. High IOP Group with Combination Therapy (IOP > 21 mmHg): Forty patients received a combination of EYBELIS 0.002% and timolol 0.5%. There was a significant reduction in IOP at all time points compared to a baseline IOP of 23.1 mmHg. After 52 weeks, the average reduction in IOP was -8.4 mmHg (27 subjects).

Efficacy of switching to EYBELIS 0.002% ophthalmic drops in patients non-responsive to latanoprost

After a washout period of 1 to 4 weeks, 26 Japanese subjects with POAG or OHT were treated with latanoprost 0.005% for 8 consecutive weeks. Subjects whose IOP changed by 15% or less were switched to EYBELIS 0.002% without a drug holiday.[6] After the switch, the mean diurnal IOP, which was 23.0 mmHg at the time of switching, decreased by -3.0 mmHg after 4 weeks.

Side effects

It is important to note that the administration of EYBELIS is contraindicated in cases with IOL insertion or aphakia. The main side effects were:

- Conjunctival hyperaemia.
- Corneal thickening.
- Iritis.
- Macular oedema (in pseudophakic/aphakic patients).[7,8]

Selecting EP2 receptor agonists

The study confirmed that EYBELIS does not cause fat atrophy (manifested as upper eyelid sulcus deepening),[9] hyperpigmentation,[10] or eyelash elongation.[11] When prescribing new medication, EYBELIS is likely to be chosen for a wide range of patients, from young to old, who desire to avoid the local ocular side effects associated with FP receptor agonists. This is particularly true for naïve patients who use single eye drops or are concerned about cosmetic appearance, as well as existing PGA patients who have experienced local ocular side effects from FP receptor agonists.[12]

ROCK INHIBITORS

Recent developments have been seen with ROCK inhibitors such as ripasudil (Glanatec; approved in Japan in 2014) and netarsudil (Rhopressa; approved in the United States in 2017), which are approved for the treatment of glaucoma.[13] The IOP-lowering effect of ROCK inhibitors appears to increase outflow facility through the conventional pathway, which results from modification of the TM and Schlemm's canal cytoskeleton and cellular function.[14,15] This class has several benefits, lowering IOP through the conventional pathway and reducing episcleral vein pressure, as well as possible neuroprotection.[16] ROCK inhibitors are effective alone and when combined with other known ocular hypotensive medications, but are mostly used as adjunctive treatment because their IOP-lowering effect is modest compared with PGAs currently in use.[11] Side effects of topical ROCK inhibitors are predominantly local, including transient conjunctival hyperaemia and blepharitis.[17,18]

Efficacy

Efficacy of ripasudil

A large-scale post-marketing surveillance study to evaluate the long-term safety and effectiveness of ripasudil in 3,178 Japanese patients with glaucoma or OHT was conducted in a real-word clinical setting. The study included ripasudil-naïve patients with glaucoma or OHT who were initiating treatment with ripasudil according to the Japanese approved indication. IOP decreased significantly from baseline with ripasudil; the least-squares mean ± standard error change in IOP from baseline to 24 months was −2.6 ± 0.1 mmHg ($p < 0.001$); after 24 months, patients had a mean ± SD IOP of 14.5 ± 4.2 mmHg. Significant IOP changes were seen in 4 types of glaucoma: POAG, NTG, PACG, and secondary glaucoma, as well as in OHT.[17]

In a meta-analysis of the IOP-lowering effect for a treatment duration of 1–3 months, IOP reduction by ROCK inhibitor was non-inferior to timolol 0.5% twice-daily after 4–8 weeks (mean difference = 0.39 mmHg [0.01, 0.76], $P = 0.043$) and 12 weeks (mean difference = 0.48 mmHg [0.11, 0.85]; $P = 0.011$).[18]

In a multicentre historical cohort study in 332 eyes from 332 patients with secondary glaucoma, the mean overall IOP reductions from baseline at 1, 3, and 6 months were -5.86 ± 9.04 mmHg (-19.4 ± 25.1%), -6.18 ± 9.03 mmHg (-20.0 ± 27.1%), and -7.00 ± 8.60 mmHg (-23.4 ± 25.6%), respectively.[19]

Efficacy of netarsudil

A multicenter, prospective, interventional, open-label, phase 4 study to access the real-world efficacy of netarsudil, either as monotherapy or concomitant therapy, was conducted in patients with OAG or OHT requiring modification of IOP-lowering treatment. Mean IOP in patients who were treatment-naïve at baseline and using netarsudil as monotherapy (n = 24) decreased by 16.9%. Netarsudil monotherapy was comparable in efficacy to prior therapy across subgroups, and those who replaced PGA (n = 57) monotherapy demonstrated reduction of 2.5% from PGA-treated baseline values. Among patients who used netarsudil as concomitant therapy (n = 151), reductions in mean IOP (± standard deviation) to week 12 were seen across subgroups who added netarsudil to a single agent (4.3 ± 2.88 mmHg; 20.5%) or more than or equal to 2 classes of concomitant therapy (4.5 ± 4.08 mmHg; 20.9%) and who used netarsudil to replace more than or equal to 1 other drug classes (0.4 ± 2.47 mmHg; 1.7%).[20-25]

Side effects

The most common ocular adverse events of ROCK inhibitor were conjunctival hyperaemia (19%–65%), followed by conjunctival haemorrhage (6%–20%), and cornea verticillata (13%–26%).[17]

Among 3,374 Japanese patients with glaucoma or OHT who were enrolled in the 24-month, prospective, open-label, observational study, 853 (25.3%) patients experienced adverse drug reactions: (ADR) the most common were blepharitis (8.6%), conjunctival hyperaemia (8.5%), and conjunctivitis (6.3%). Multivariate analyses demonstrated that patients were more likely to experience the ADR blepharitis with ripasudil treatment if they were female (hazard ratio [HR] 1.307; $p = 0.040$), had comorbid or a previous history of blepharitis (HR 2.178; $p = 0.001$), or had a history of allergy to pollen (HR 1.645; $p = 0.003$) or medication (HR 2.276; $p < 0.001$).[18]

Selecting ROCK inhibitors

In patients with glaucoma or OHT, treatment with ROCK inhibitor showed effective IOP reduction non-inferior to timolol as monotherapy and as adjunctive therapy, and was not associated with any significant safety concerns after 24 months of follow-up. ROCK inhibitor can be a reliable IOP control medication. However, its higher incidence of some ocular complications should be considered.

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4.4. SIDE EFFECTS OF MEDICAL THERAPY

Key messages

- ❖ IOP-lowering eyedrops may have a wide range of side effects.
- ❖ During medical treatment for glaucoma, ophthalmologists should be attentive to ocular surface disease (OSD) and prostaglandin-associated periorbitopathy (PAP) as they can affect quality of life, IOP measurement accuracy, and success rates of future surgery.
- ❖ Closing the eyes for three minutes directly after application of the eye drops may increase their ocular efficacy and decrease their systemic side effects.

OCULAR SURFACE DISEASE

Ocular surface disease (OSD) is a multifactorial disorder of the conjunctival epithelium, corneal epithelium, lacrimal glands, and meibomian glands that results in either deficient or inappropriate tear production and leads to decreased visual clarity and ocular discomfort through various inflammatory pathways.[1] In glaucoma patients, OSD can be a pre-existing condition that is exacerbated by topical therapy or a novel disease that manifests after initiation of topical glaucoma therapy, affecting 49%–59% of glaucoma patients.[2] Additionally, there is a notable positive and significant correlation between the prevalence of OSD and the severity of glaucoma. As demonstrated by Sarimiye *et al.*, OSD prevalence stands at 43% in the mild stage, rises to 65% in the moderate stage, and peaks at 85% in severe cases.[3,4]

OSD negatively impacts patients' medication adherence, quality of life, and glaucoma filtration surgery outcomes. Studies have shown that ocular surface inflammation secondary to glaucoma medication use intensifies the wound healing response to incisional surgery, increasing the risk of filtration bleb fibrosis and failure.[5] Manifestations of OSD in glaucoma patients include:

- Superficial punctate keratitis.
- Tear-film instability.
- Dry eye disease.
- Allergic conjunctivitis and dermatitis.
- Pseudopemphigoid.
- Vortex keratopathy.

Evaluation of OSD

- Functional questionnaires such as the Ocular Surface Disease Index (OSDI) questionnaire, which consists of 12 items that evaluate symptoms, functional limitations, and environmental factors.[6]
- Fluorescein staining of the ocular surface: punctate epithelial erosions.
- Evaluating tear health:

- Tear film stability measured by tear breakup time: Subjective assessment of tear film stability was measured in seconds after asking the patients to blink naturally 3 times. Values of 8–15 seconds were categorised as being normal; 5–7 seconds indicated mild instability; 1–4 seconds indicated moderate instability; and immediate breakup was categorised as severe instability.
- Tear production measured by Schirmer's test.
- Tear evaporation measured by osmometry: Chronic ocular surface inflammation in glaucoma patients may manifest as dysfunction of the meibomian glands, leading to an evaporative dry eye state with resultant hyperosmolarity. Osmolarity represents a balance between evaporation, drainage, and production of tears. Osmolarity testing can be easily performed in a busy clinic using a handheld osmometer to collect a tear sample which is analysed in several seconds. Hyperosmolarity indicates more rapid tear evaporation and has been demonstrated in eyes treated with topical glaucoma medications.[7] Infrared meibography, such as LipiView (Johnson and Johnson, New Brunswick, NJ, USA), may demonstrate significant gland truncation or loss.
- Tear film lipid layer analysis: Lipid layer thickness (LLT) was found to be significantly thinner in patients on glaucoma medications than in normal eyes, and longer duration of medication use and greater number of drops were associated with a thinner LLT.[8]

Impact of different classes of topical glaucoma eye drops on the ocular surface

Alpha agonists

- Conjunctival follicular reaction, allergic conjunctivitis, and hyperaemia.
  - Brimonidine although an alpha-2 agonist, is known to cause vasoconstrictive effects by its limited action on the alpha-1 receptor. Vasoconstriction and reactive hyperaemia of the conjunctiva occurs in 11.0%–13.9% of subjects using this agent, often resulting in patients discontinuing the drug. These adverse effects occur several months to years after initiation of the drug and stopping the offending drug helps to resolve the condition.
- Contact dermatitis of the periocular area and eyelids.
  - Apraclonidine causes contact dermatitis occurs due to a portion of the drug binds to the dermal protein to form a complex hapten, which sensitizes the individual. When the drug is re-instilled, it induces a delayed hypersensitivity reaction, which is the cause for allergy.
- Ectropion of the eyelid which progresses to cicatricial ectropion in some patients.
  - In individuals with pre-existing lid laxity, tissue oedema due to allergy can worsen the pre-existing problem resulting in ectropion. Chronic allergy with skin excoriation can also cause fibrotic changes and tissue shortening that can lead to ectropion.[9]

Beta blockers

- Inhibit proliferation of corneal epithelial cells and lead to a decrease in goblet cell density and tear production.[10]

CAIs

- The low pH of CAIs associated with damage to the ocular surface.
- Scaling in the periorbital area, periorbital dermatitis.
- Stinging and burning sensation on instillation, causing conjunctival hyperaemia in up to 20.7% of patients.

- Allergic conjunctivitis, follicular conjunctivitis, and limbal conjunctival follicles can be reported several months after initiation of therapy.
- An increase in CCT can be seen in patients using dorzolamide and brinzolamide, especially in the presence of pre-existing corneal endothelium dysfunction, with resultant corneal oedema or decompensation.

PGAs

- Hyperpigmentation of eyelid skin.
  - The pigmentation gradually diminishes 1 month after cessation of the drug and almost completely resolves in approximately 4 months.
  - These changes occur due to the upregulation of tyrosinase activity in the melanocytes.
- Hypertrichosis and hyperpigmentation of the eyelashes. Increased lengthening of the eyelashes is often noted, which may need trimming.
  - This may occur due to the stimulation of resting hair follicles and may be reversed by stopping the medication.
- Known to cause recurrence of herpetic keratitis, reactivation of dormant disease, and may also cause pseudodendrites or punctate keratitis.

Miotics

- Severe burning sensation on instillation of the drug.
- Due to its pro-inflammatory nature and enlargement of the permeability of the blood-aqueous barrier, pilocarpine can precipitate graft rejection.[11]

Rho-kinase inhibitors

Conjunctival hyperaemia due to vasodilation, blepharitis, allergic conjunctivitis, punctate keratitis, cornea verticillata, and increased lacrimation.[12]

Preservatives

Benzalkonium chloride (BAK), a quaternary ammonium compound with bacteriostatic, bactericidal, and surfactant properties, is the most widely used preservative in antiglaucoma ophthalmic eyedrops.[13] BAK causes decreased corneal, conjunctival, TM, and ciliary epithelial cell survival, corneal epithelial cell injury, conjunctival goblet cell loss, delayed corneal wound healing, lymphocyte infiltration of conjunctival epithelium and stroma, and elevated inflammatory marker concentrations in ocular tissues.[14] Alternatives to BAK include Purite (Allergan, Irvine, CA, USA), SofZia (Alcon, Geneva, Switzerland), and Polyquad (Alcon).

Management

Selecting preservative-free glaucoma medication

While it's logical to consider prescribing preservative-free (PF) glaucoma medication for patients based on their risk of OSD, these patients represent a significant portion of the glaucoma population. Without a cost premium, prescribing PF glaucoma medication for all patients seems appropriate. However, in the real world, where PF medication is still considerably more expensive than preserved medication, it's suitable to consider subsets of the glaucoma population that would benefit most from PF therapy.[15] The following are some subset patient groups that we may consider:

- Newly diagnosed patients with OSD.
- Patients on multiple eye drops.
- Younger adult patients.
- Contact lens users.

- Patients who work in air-conditioned environments or who use electronic screens frequently.

Medical treatment

- Preservative-free glaucoma medications.
- Artificial tears and lubricants, preferably preservative-free.
- Topical cyclosporine.
- Placement of novel drug delivery system: Sustained-release formulations allowing for a depot release of glaucoma medications that could last for several months are currently entering the clinics.
- Improving meibomian gland dysfunction with rigorous lid hygiene, thermal pulsation, and intense pulsed light.
- Topical mucin secretagogue.[16]

Surgical treatment

- Punctal occlusion by plugs or cautery.
- Early SLT to reduce medication burden.
- Minimally invasive glaucoma surgery (MIGS).
- Filtration surgery, *e.g.*, trabeculectomy or glaucoma drainage device, to reduce topical medication use.

PROSTAGLANDIN-ASSOCIATED PERIORBITOPATHY

Prostaglandin-associated periorbitopathy syndrome (PAPS) is the constellation of eyelid and orbital changes that result from topical administration of PGAs. The exact clinical findings associated with PAPS are: [17]

- Upper lid ptosis.
- Deepening of the upper eyelid sulcus (DUES).
- Involution of dermatochalasis.
- Periorbital fat atrophy.
- Mild enophthalmos.
- Inferior scleral show.
- Increased prominence of lid vessels.
- Tight eyelids.

Frequency and grading

The percentage of patients who experience PAPS is yet unknown, but it is commonly observed among PGA users. In Asian populations, it has been reported that 53.4% of PGA users had at least one PAPS sign, which were DUES (24.1%), eyelid pigmentation (19.0%), eyelid erythema (19.0%), dermatochalasis involution (10.3%), eyelid retraction (5.2%), and ptosis (3.4%).[18] These side effects may affect the quality of life of glaucoma patients, which may affect medication adherence and ultimately lead to patients discontinuing their glaucoma therapy.

Considering that topical PGA therapy is the current first-line treatment for OAG, it is important to continuously assess whether there is onset of PAPS on patients under treatment with topical PGAs. While there is no consensus definition regarding the severity of PAPS, **Table 4.4.1** can serve as a general guideline.

Table 4.4.1. Shimane University prostaglandin-associated periorbitopathy (SU-PAP) grading

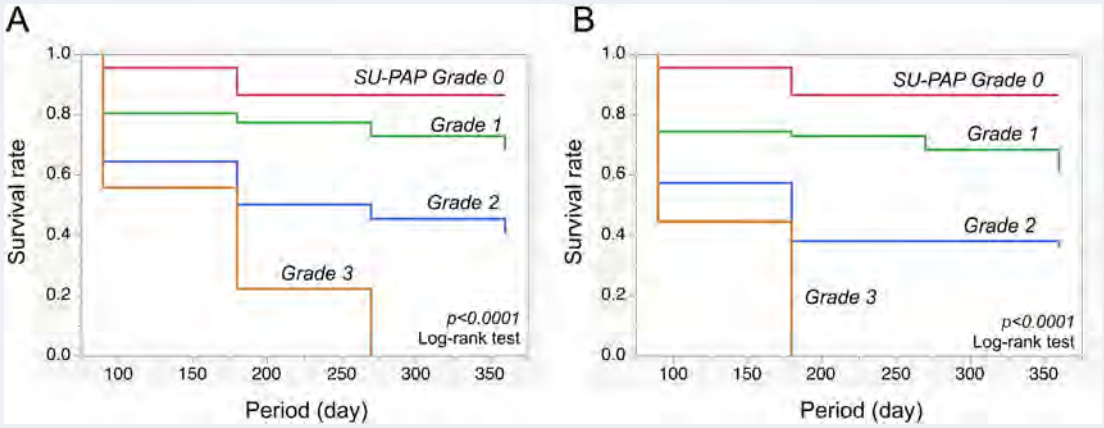
Grade	0	1	2	3
Grade Name	No PAP	Superficial cosmetic PAP	Deep cosmetic PAP	Tonometric PAP
Definition	No cosmetic change	Cosmetic change(s) including eyelid pigmentation and/or eyelash growth	Cosmetic change(s) with at least 1 sign of PAP including DUES, blepharochalasis involution, periorbital fat loss, or enophthalmos	Difficulty in performing GAT and/or reduced reliability of GAT-measured IOP due to PAP-related DUES, hardening of eyelids, ptosis, or enophthalmos

DUES: deepening of the upper eyelid sulcus, GAT: Goldman applanation tonometry, IOP: intraocular pressure

Table reproduced from Tanito et al.[19]

Effect on IOP measurement and surgical outcomes

In the presence of DUES and no pre-septal fat, lifting a tight lid without applying pressure to the globe is difficult,[20] resulting in difficulty performing GAT. The role of PAPS in the overestimation of IOP measured by GAT as well as differences in the frequency and severity of PAP among different PGAs have been reported.[19] Furthermore, the success rates of trabeculectomy in POAG patients were worse in eyes with higher SU-PAP grades than in eyes with lower grades (**Figure 4.4.1**).[21] Therefore, PAP is not merely a cosmetic side-effect, but one that also affects glaucoma management. In particular, glaucoma patients who exhibit PAP signs, such as DUES, and undergo trabeculectomy, the postoperative IOP lowering can be more challenging to maintain and therefore should be followed up closely.[22]



(A) postoperative IOP > 15 mmHg **(B) postoperative IOP > 12 mmHg**

Definitions of failure	
• Postoperative IOP > 15 mmHg (A) or 12 mmHg (B) • IOP reduction < 20%	• Hypotony: Postoperative IOP < 6 mmHg • Surgical intervention other than laser suture lysis

Figure 4.4.1. Comparison of success rates of trabeculectomy among POAG groups stratified by SU-PAP grades 0 to 3. Figure reproduced from Ishida *et al.*[21] SU-PAP: Shimane University prostaglandin-associated periorbitopathy; IOP: intraocular pressure

PAP management

PAPs should be considered when initiating glaucoma treatment for naïve patients. For existing PGA patients, PAPs is usually reversible by discontinuation of PGAs. Switching to another class of antiglaucoma medication or considering laser/surgery, which are equally effective at lowering IOP, may be a feasible alternative. If a patient cannot stop a PGA altogether, switching to another PGA associated with a lower likelihood of PAPS (*e.g.*, latanoprost or tafluprost) may be effective in reversing signs of DUES, the most common symptom of PAPS.[23-25] Patient education regarding correct eye drop instillation is an effective measure to reduce the risk of PAPs. Patients should be instructed to always wipe off any excess eye drops leaked from their eyelids after instillation, and if possible, to apply PGAs before bathing or washing their face, ensuring they wipe off any excess eye drops on the skin surface around their eyes.

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4.5. PATIENT ADHERENCE AND DRUG DELIVERY SYSTEMS

Key messages

- ❖ Medication adherence is critical to prevent disease progression and visual impairment.
- ❖ Ophthalmologists and patients can overestimate medication adherence, which tends to be poor.
- ❖ Adherence can be improved by identifying the barriers and addressing them strategically.
- ❖ Novel drug delivery systems may help to improve overall adherence.

GLAUCOMA MEDICATION ADHERENCE

High adherence to medication is essential to prevent visual impairment, but is a universal challenge worldwide.[1,2] Adherence tends to be poor (range: 10–83%), with adherence patterns in the first year being crucial as they predict subsequent 3-year adherence.[3-7] "White coat compliance", defined as an increased adherence to treatment regimens directly before a visit with a health care provider,[8] should also be taken into consideration during the assessment of any disease progression in relation to eye drop efficacy. Hence, poor compliance between follow-up visits often goes undetected by clinicians, leading to inadequate IOP control. It is essential to attempt to accurately quantify patient adherence to prescribed medications, whilst taking into consideration that patients overestimate their own adherence.[9]

Barriers to adherence

Barriers to adherence barriers are multifactorial and each patient has a unique set of barriers.[10] The greater the number of obstacles identified, the greater the likelihood of non-adherence.[10] Barriers to adherence include the following:[11,12]

- Medication-related factors:
  - Complex regimen.
  - Side effects.
  - Cost.
- Patient-related factors:
  - Disease/medication knowledge.
  - Forgetfulness or life stress.
  - Challenges with eye drop instillation technique.
- Health services-related factors:
  - Unclear instructions.
  - Mistrust of physician.

- Sociocultural factors:
  - Lack of support.
  - Discrimination.

Improving adherence

While improving adherence can focus on several areas outlined below, a multifaceted approach might yield additional improvements in adherence.[13]

- Education and patient communication:[14]
  - Educate about the progressive nature of glaucoma and the need for ongoing treatment.
  - Inform of potential side effects.
- Simplified medication schedule:[15]
  - Design a simple and easy-to-follow medication schedule tailored to the patient's lifestyle.
  - Consider once-daily dosing regimens or fixed-dose combination medication.
- Reminder system:[16,17]
  - Encourage the patient to set up smartphone alarms or pill organizers.
  - Link medication administration to daily routines or existing habits.
- Tailored care:[18]
  - Provide individualized counselling delivered in-person to address the patient's issues.
  - Formulate a personalized care plan.
  - Tailored care was the most effective method according to a network meta-analysis.[13]

NOVEL DRUG DELIVERY SYSTEMS

To address the problems of patient adherence and to minimize the side effects of daily eye drop administration, technological advances have seen significant efforts to develop sustained drug delivery systems (DDS) to replace to use of daily eye drops.[19] Such systems aim to increase drug bioavailability and maintain a consistent IOP-lowering effect without the need to rely on patients administering the medications at set times every day. The anatomical sites for DDS have considered almost every possible route and include:

- Drug-eluting punctal plugs.[20]
- An ocular ring placed in the inferior fornix.[21]
- Drug-impregnated contact lenses.[22]
- Subconjunctival injections/devices.[23]
- Intracameral delivery systems.[24]
- Drug-eluting intraocular devices (*e.g.* supraciliary implants, microneedles, and intravitreal implants).[25]

New drug delivery systems

Durysta

Durysta (Allergan, Irvine, CA, USA)[26] is an implant that consists of a rod-shaped, biodegradable polymer matrix containing 10 µm of bimatoprost, approved by the Food and Drug Administration (FDA) in 2020 for a single, one time application in open-angle eyes. The implant is injected intracamerally with a 28-gauge delivery system and the patient is instructed to sit upright for at least an hour while the implant sinks down into the iridocorneal angle.

The phase I/II trial with a single implant showed similar efficacy to topical bimatoprost 0.03% through 24 months of follow-up.[27] At 6 months after a single implant insertion, 71% of the patients had a persistent effect.[24] Phase III studies (ARTEMIS 1 and 2) with 3 implant applications spaced by 4 months showed non-inferior IOP-lowering effects to twice-daily timolol.[28,29] Corneal endothelial cell density after a single application was equivalent to topical treatment.[24,27] Patients in phase III trials were reported to have significant endothelial cell loss, due to the cumulated, stacked implants.[28,29]

iDOSE

The iDose (Glaukos, Aliso Viejo, CA, USA) is a long-acting intracameral implant that delivers continuous therapeutic levels of travoprost inside the eye for extended periods. The iDose is made from medical-grade titanium, and is implanted through the TM and the back wall of Schlemm's canal, directly into scleral tissue. Once implanted, 75 µg of preservative-free travoprost continuously elutes into the anterior chamber via membrane-controlled diffusion and provides continuous release of medication. A minor surgical procedure is required to implant the device in the TM, which is identical to the technique used to implant the iStent (Glaukos) MIGS device.

The pivotal phase III clinical trials conducted in the United States comprised 2 randomized, double-masked, prospective studies and included a total of 1,150 participants. Nearly 81% of slow-release implant participants were free of topical anti-glaucoma medications at 12 months.[30,31] The implants also demonstrated good safety profiles, with no corneal surface events or endothelial cell loss at 12 months. The FDA approved the iDose as a one time, single-use device in open-angle eyes in December 2023.

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SECTION 5
SURGICAL AND LASER TREATMENT

5.1. LASER TREATMENT

Key messages

- In SLT, pre-laser treatment with topical alpha-2 agonists helps reduce post-treatment IOP spikes.
- Higher baseline IOP is associated with greater IOP reduction after SLT and ALT.
- A useful tip to reduce laser power for laser iridotomy is to choose a small iris crypt or thin iris area that is located peripherally as possible.
- Peripheral iridoplasty can help to break an attack of acute angle closure as initial treatment.

TYPES OF LASER TREATMENT

- OAG:
  - Outflow enhancement: Laser trabeculoplasty.
  - Inflow reduction: Cyclophotocoagulation (usually for end-stage disease).
- Angle closure (± glaucoma):
  - Pupillary block relief: Laser peripheral iridotomy.
  - Modification of iris contour: Laser peripheral iridoplasty.
  - Inflow reduction: Cyclophotocoagulation (usually for end-stage disease).
- Post-filtering surgery:
  - Outflow enhancement: Argon laser suture lysis (ALSL).

LASER TRABECULOPLASTY

Laser trabeculoplasty is a relatively effective and non-invasive laser procedure that increases TM outflow. Laser trabeculoplasty is easy to perform and allows bypassing non-adherence to medical therapy.

Indications

- Medical therapy failure
- Adjunct to medical therapy.
- Primary treatment if appropriate.

Steps in management

Pre-laser

- To reduce post-treatment IOP spikes or inflammation, consider 1%[1] apraclonidine[2,3] or 0.15%–0.2% brimonidine[4] and/or 2%–4% pilocarpine[3] (pilocarpine may decrease the blood-aqueous barrier, which may increase inflammation), and/or beta blocker and/or steroid drops before the procedure.
- Topical anaesthesia.

Laser

Types of lasers

- Argon green or blue-green.[5]
- Frequency-doubled Nd:YAG (532 green) or diode laser (SLT).[6-9]
- Diode laser trabeculoplasty (DLT).
- Micropulse laser trabeculoplasty (MLT).

Types of lenses

Lenses should be coated to minimize reflection and hazard to observers.

- Latina SLT gonio laser lens.
- Goldmann gonioscopy lens.
- Ritch trabeculoplasty lens.
- CGA LASAG/Meridien CH.
- Magna View Gonio argon/diode laser lens.

Placement of laser spots

- Laser spots should be placed on the pigmented TM (**Table 5.1.1**).
- Power: 300–1200 mW depending on the tissue reaction.
- Number of spots: 80–100 effective laser burns over 360°.

Table 5.1.1. Selective laser trabeculoplasty versus argon laser trabeculoplasty

Variables	Selective laser trabeculoplasty	Argon laser trabeculoplasty
Number of spots	30–50	50
Exposure time (nanoseconds)	3	100,000,000
Fluence (mJ/mm^2)	6	40,000
Power	0.4–1.4 mJ	300–600 mW
Laser requirements	Ultrashort pulse duration Low laser energy	

Effectiveness

- ALT and SLT have similar efficacy.
- Laser trabeculoplasty is initially effective in 80%–85% of treated eyes with a mean IOP reduction of 20% to 25% (6–9 mmHg). The effect wears off over time for both ALT and SLT.[10]
- In the Glaucoma Laser Trial, at 7 years of follow-up, patients who had undergone ALT had lower IOP (1–2 mmHg) than patients on medical treatment and no difference in progression of glaucoma.[11] SLT has been shown to decrease IOP to a degree similar to that of PGAs after 9–12 months follow-up[12] and is repeatable.[13]

- The Laser in Glaucoma and Ocular Hypertension Trial (LiGHT) found SLT to be a safe treatment for OAG and OHT, providing better long-term disease control than initial eye drop therapy, with reduced need for incisional glaucoma and cataract surgery over 6 years of follow-up.
- Studies evaluating SLT as a primary treatment are currently being undertaken.

Predictors of efficacy

- Higher baseline IOP is associated with a greater IOP reduction after SLT and ALT.[14,15]
- The effectiveness of ALT is influenced by the treating surgeon and success rates are higher with more experienced surgeons.[15,16]
- Pigmentation of the TM is important for ALT. ALT is less successful in eyes with no pigmentation of the TM. Younger subjects (less than 40 years old) usually show a decreased response to ALT.[17]

SLT

Laser settings and treatment steps

- The optimal level of energy for each patient is determined by the degree of pigmentation in TM. In general, the TM is more heavily pigmented in the inferior 180° versus the superior 180°.
- The treatment spot size with SLT is fixed at 400 µm, which covers the entire width of the TM.
- Common energy settings for SLT vary between 0.4mJ and 1.0 mJ. The higher energy level corresponds to lighter TM pigmentation and the lower energy level for darker TM pigmentation.
- Energy should be titrated at 0.1 mJ increments until the appearance of micro-cavitation bubbles are observed next to the TM. This is evidence that the correct treatment threshold is obtained.
- Patients with pigmentary glaucoma or PXG are at an increased risk of post-SLT IOP spikes.

Complications

- Temporary blurred vision.
- IOP spikes with possible VF loss.
- Transient iritis.
- Chronic increase in IOP
- Corneo-refractive changes.
- Suprachoroidal effusion.[18]

Post-laser management

- Immediately following treatment, administer another dose of an alpha agonist anti-glaucoma agent should be administered and IOP rechecked after approximately 1 hour.
- If the postoperative IOP is elevated, the patient will require additional treatment and more careful follow-up with a repeat IOP check the next day.
- If IOP is normal or reduced, follow-up visits are typically scheduled at 1 week, 4 weeks, and 3 months.
- Patients may resume their glaucoma eye drops immediately afterwards.
- Topical steroid 4 times a day for 4–14 days is recommended for ALT.[19,20]

- Closer monitoring is suggested for certain patients:
  - Advanced glaucoma with severe VF loss.
  - Monocular.
  - High pre-laser IOP.
  - Previous laser trabeculoplasty.
  - Pigmentary glaucoma.

Repeat treatment

- Initial treatment may not be long-lasting. Laser trabeculoplasty can be repeated, especially in eyes that have shown a prolonged response to previous treatment.[21]
- SLT is relatively safe to repeat twice.[22]

LASER IRIDOTOMY

Laser iridotomy, also described as "laser peripheral iridotomy" (LPI), is an effective medical procedure in relieving pupillary block that uses argon/YAG laser to create a hole in the iris, thereby allowing aqueous humour to traverse directly from the posterior to the anterior chamber and, consequently, relieve a pupillary block**.** It is relatively non-invasive and preferable to surgical iridectomy in most situations.

LPI is performed with the Q-switched Nd-YAG laser (1,064 nm wavelength), using the principle of photo-disruption. The Q-switch enables production of an extremely short, high-powered laser pulse, ideal for photo-disruption, with no thermal effect and lower failure and complication rates than photothermal lasers.

Indications

- Laser treatment to connect the anterior and posterior chambers to relieve pupillary block.
- PAC: Significant pupillary block.
- PACG: Significant pupillary block.
- PACS (absolute):
  - PAC in the fellow eye.
- PACS (relative):
  - Need for repeated dilated examinations.
  - Poor access to regular ophthalmic care.
  - Confirmed family history of PACG.
- Secondary angle closure with pupillary block.
- LPI may not be helpful in angle closure where pupillary block is not the dominant mechanism, *e.g.*, uveitis, iris cysts, or uveal effusions.

Contraindications

- Extensive corneal oedema or opacity when the anterior chamber and iris are not visible.
- Very shallow or flat anterior chamber.
- Conditions causing extensive synechial angle closure, including acute uveitis, NVG, and ICE syndrome.

Patient examination prior to LPI

- Best-corrected visual acuity, IOP, corneal assessment.
- ACD, gonioscopy to assess the grade and pigmentation of angle or PAS.
- Iris configuration and vasculature.
- Any causes of secondary pupillary block.
- Coexisting ocular problems that may affect procedure or prognosis: *e.g.*, cataract, uveitis, zonular weakness, iridodonesis, vitreoretinal pathology.
- Systemic problems: *e.g.*, bleeding disorders, patients on anticoagulants, head tremors.

Laser parameters

- Defocus: Set at zero, thus delivering laser energy at the point of focus.
- Power: Set at 1.5–3 mJ depending on thickness of the iris.
- Pulse: Select triple shots (total power: 1.5–3 mJ × 3 = 4.5–9 mJ).
- If single shot selected, start with higher power (more shots will be needed).
- Focus on the anterior iris stroma (just behind the iris surface).

Site selection to ensure a successful LPI

- A site between 11 and 1 o'clock is preferred as LPI holes are covered by the upper lid and patients do not experience diplopia or glare from polycoria.
- Choose a small iris crypt or thin iris area, as peripheral as possible.
- A miosed pupil (with pilocarpine) causes iris stretch, which is maximum in the periphery. The iris is thinnest and easiest to perforate in the periphery.
- A mid-peripheral site is best avoided, as this involves going through the belly of the muscle, which is thicker, and may require higher energy and more shots, with a higher risk of iris bleed and hitting the lens capsule behind. In addition, an LPI in the mid-periphery is liable to become occluded during pupillary dilatation. Large crypts are usually associated with blood vessels at their edges and are best avoided.

Steps in management

Pre-laser

- Instil 2%–4% pilocarpine.
- To reduce post-treatment IOP spike/inflammation, consider 1% apraclonidine or 0.15%–0.2% brimonidine, and/or a beta blocker, and/or oral CAI, and/or steroid drops before the procedure.
- Topical anaesthesia: Three applications of proparacaine in 5-minute intervals.
- Topical glycerine if the cornea is oedematous.
- Lenses: Abraham (+66 diopters), Wise (+103 diopters), or CGI©LASAG CH lens (procedure).
- As mentioned above, the LPI site is usually chosen in the superior quadrants of the iris, well covered by the upper eyelid, in a thin looking area or a small iris crypt.
- A temporally placed iridotomy may lead to reduced visual symptoms.[23]
- Care should be taken to perform iridotomies peripherally and the laser should not be placed at the junction of eyelid margin to avoid diplopia.
- Patients should be warned of the low risk of visual symptoms, which can occur regardless of the site of the iridotomy.

Laser

- Nd:YAG[24]
- Argon[24]
- "Sequential" laser: argon followed by Nd:YAG.
- Sequential LPI is useful in eyes with thick irides as well as in patients receiving systemic

anticoagulation or antiplatelet medication to reduce the risk of hyphaema.

LASER PARAMETERS FOR CONTINUOUS-WAVE ARGON LASER

Preparatory stretch burns

- Spot size: 200–500 µm.
- Exposure time: 0.2–0.5 seconds.
- Power: 200–600 mW.

Penetration laser burns

- Spot size: 50 µm.
- Exposure time: 0.05–0.1 seconds.
- Power: 700–1000 mW.

Parameters according to iris colour

Pale blue or hazel irides

1. Obtain a gas bubble:
   - Spot size: 50 µm.
   - Exposure time: 0.5 seconds.
   - Power: 1500 mW.
2. Penetration through the gas bubble:
   - Spot size: 50 µm.
   - Exposure time: 0.05 seconds.
   - Power: 1000 mW.

Thick dark brown irides (chipping technique)

Choose and modify parameters depending on individual response.[25]

- Spot size: 50 µm.
- Exposure time: 0.05–0.1 seconds.
- Power: 600–1000 mW.

LASER PARAMETERS FOR ND:YAG LASER

- Energy: 1.5 -3 mJ; use minimum energy, 1–3 pulses per burst.
- Once penetration has occurred, and gush of pigment and aqueous is seen. It is then best to reduce the power to continue enlarging the iridotomy horizontally[26] and penetrating as lens damage and zonule weakness is possible above 2 mJ per pulse once the iris has been penetrated.
- Choose an iris crypt or an area of thin iris.
- Can be effectively combined with argon laser.
- To facilitate penetration of a uniformly thick iris, argon laser pre-treatment can:
  - Coagulate.
  - Stretch.
  - thin the target area.

LASER PARAMETERS FOR SEQUENTIAL LASER–ARGON LASER FOLLOWED BY ND:YAG LASER

Preparatory burns with argon laser (chipping technique)

Apply preparatory burns through the iris stroma, until iris pigment epithelium reached (pigment puff).

- Spot size: 50 µm
- Exposure time: 0.02–0.05 seconds.
- Power: 500–1000 mW, depending on iris pigmentation, *i.e.*, darker irides require lower power.[26]

Complications

Complications are rare and often can be avoided with careful and proper technique.

- Temporary blurring of vision.
- Corneal epithelial and/or endothelial burns with argon (especially with bubble formation and proximity to the endothelium).[27]
- Transient IOP spikes.
- Post-laser inflammation.
- Intraoperative bleeding: Bleeding usually stops by pressing the lens on the eye for a few minutes.
- Iridotomy closure. This may occur if the iridotomy is small and enlargement will be required.[28]
- Localised lens opacities or cataract progression.[29]
- Rarely: retinal damage, retinal and subhyaloid haemorrhage,[30] cystoid macular oedema, ciliary block glaucoma,[31] endothelial decompensation,[32-34] decompression retinopathy,[35] Descemet's membrane detachment.[36]
- Visual disturbances occur in 6%–12% and are less likely to occur when the iridotomy is completely covered by the eyelid.[37,38]
- Elevation of IOP 1 hour after iridotomy occurs in approximately 10% of PACS eyes.[39]

Post-laser management

- Particularly if IOP spike prevention treatment is not available:
  - Re-check IOP 1 hour after laser procedure.
  - Systemic acetazolamide or mannitol may be indicated if IOP rises rapidly.
  - Discharge the patient only when IOP is stable at a safe level.
- Topical steroid (or NSAIDs) at least 4–6 times/day for 7–14 days depending on inflammation reduces post-laser inflammation.
- Stop topical pilocarpine and taper any other topical IOP-lowering drugs as indicated.
- Verify the patency of the LPI by transillumination. However, it is best to observe the LPI under magnification in the slit-lamp. It is possible that following LPI, synechiae may occur in the iris or anterior lens capsule at a later stage.
- Repeat gonioscopy when the effect of pilocarpine has worn off. If the appositional closure remains and IOP is high, consider laser peripheral iridoplasty or cataract extraction[40] if lens mechanism is identified.
- Pupillary dilation to break posterior synechiae when suspected.
- Surgical iridectomy may have a role in certain conditions such as inflamed eye with acute PAC, iris bombé in anterior uveitis, and with poor corneal visibility.

PERIPHERAL IRIDOPLASTY

Peripheral iridoplasty[41] is a non-invasive laser treatment to contract the peripheral iris in order to:

- To flatten the peripheral iris.
- To widen the anterior chamber angle inlet.
- To re-open appositionally closed segments of the drainage angle.

Indications

- To break an attack of acute angle closure as initial treatment[42-48] or as adjunctive measure when systemic medications fail to control IOP.
- In cases where the angle remains occludable following LPI, *e.g.*, plateau iris.[49,50]
- To break an attack of secondary forms of acute angle closure (*e.g.*, phacomorphic glaucoma)[51-53]
- Facilitate access to the TM for laser trabeculoplasty.[42]
- As an adjunct to goniosynechialysis.[54,55]
- To treat plateau iris syndrome.

Steps in management

Pre-laser

- Instil 2% or 4% pilocarpine.
- To reduce post-treatment IOP spikes/inflammation, use 1% apraclonidine or 0.15%–0.2% brimonidine, and/or a beta blocker, and/or oral CAI, and/or steroid drops before the procedure.
- Topical anaesthesia: 3 instillations of proparacaine in 5-minute intervals.

Laser

Lenses

Any laser iridotomy contact lens, generally Abraham (+66 diopters), Wise (+103 diopters), CGI©LASAG CH lens, or the central non-mirrored part of the Goldmann lens.

Procedure

- The endpoint is iris contraction with peripheral anterior chamber deepening.
- Different types of continuous wave lasers can be used: argon laser, diode laser (810 nm) and the frequency doubled Nd:YAG laser (532 nm).
- Aim laser spot at the most peripheral location.
- If the peripheral anterior chamber is too shallow, a mid-peripheral laser spot is placed first to deepen the anterior chamber, before a more peripheral laser spot is subsequently applied.
- Presence of iris charring or a “pop” sound indicates that the power is to high; thus reduce the power before continuing.

Laser parameters

- Power: 150–240 mW depending on the reaction.
- Spot size: 500 µm; both small-spot and large-spot patterns can be used with appropriate adjustment of power settings. Generally, the smaller the spot size, the lower the power setting.
- Exposure time: 0.5 seconds.

- Number of spots: 10–40 applications over 360°, leaving at least 1- to 2-spot diameters between spots; 180° treatment may also be effective.[23]
- Do not overtreat.

Complications[41,46,48]

- Mild iritis.
- Transient IOP spike.
- Iris atrophy and non-dilatable pupil are established complications.
- Corneal endothelial burns.
- PAS and/or posterior synechia.
- Rarely: Decompression retinopathy[56] and Urrets-Zavalia syndrome[57] (iris ischaemia causing a dilated and irregular fixed pupil).

Postoperative treatment

- If preventive treatment for IOP spikes is not available, check IOP within 1 hour and again at 24–48 hours depending on the status of the patient.
- Topical corticosteroids 4–6 times/day for 7 days or more depending on post-laser inflammation.
- Repeat gonioscopy to evaluate the anterior chamber angle and identify any other mechanism(s) of angle closure that might necessitate further intervention.
- According to the World Glaucoma Association Consensus Series 3,[58] 2 additional situations should be noted:
    1. When iridoplasty needs to be repeated because of recurrence of appositional closure at some point after the angle has been initially opened, it is possible to place the contraction burns further peripherally than had been initially possible. The reason for this is evident when conceptualizing the geometry of the peripheral iris. When the angle is closed, burns placed just inside the point of apposition pull open the angle and expose the iris stroma further peripherally. This area can be treated on a subsequent occasion, if necessary.
    2. A few angles have a very sharply defined plateau, which on indentation forms almost a right angle and takes firm pressure to indent open. This type of plateau iris often does not respond well to contraction burns placed with the Abraham lens but require burns placed through one of the angled mirrors with magnification buttons directly into the peripheral angle. A 200 µm spot size should be used in this circumstance.

CYCLOPHOTOCOAGULATION

Cyclophotocoagulation (CPC) or cyclodiode is an effective modality for reducing aqueous inflow by coagulative destruction of the ciliary epithelium. It is preferable to cyclocryoablation due to less collateral damage and inflammation. CPC can be titrated if further IOP-lowering is required and can also be repeated if there is loss of IOP-lowering efficacy over time. Though it is most commonly performed trans-sclerally, it can also be delivered transpupillary or via endolaser.

Indications

- Painful blind eyes or eyes with poor vision.
- Sighted eyes where the benefits and risks of cyclodiode are believed to outweigh those for incisional surgery.
- Failed multiple filtering surgeries.

- As a primary procedure to alleviate pain in secondary glaucomas with poor visual potential.
- When incisional surgery is not appropriate, *e.g.*, extensive conjunctival scarring or thinning.

Steps in management

Pre-laser

- Prior to commencing the trans-scleral technique, careful slit-lamp examination to identify suitable/unsuitable sites for laser application should be performed.
- Topical and sub-Tenon's anaesthesia, or retro-/peribulbar anaesthesia.
- General anaesthesia when indicated.

Techniques

- Transpupillary.
- Trans-scleral.
- Endolaser.
- Conservative, incremental applications avoiding the 3 and 9 o'clock positions.

Contact trans-scleral diode laser

- Diode laser with transscleral contact probe.
- With the G-probe, the fibreoptic laser tip is 1.5 mm behind the anterior edge of the footplate and protrudes 0.7 mm.
- A cold light source can be used to transilluminate sclera, allowing identification of the ciliary body position.
- The laser tip should be placed over the ciliary body, *i.e.*, the dark band posterior to the perilimbal halo seen with transillumination.
- Indentation improves energy delivery and blanches the conjunctival blood vessels.

Laser parameters

- Wavelength: 810 nm.
- Exposure time: 0.5–2.0 seconds.
- Power: 1000–2500 mW.
- Number of burns: 20-40 over 180°–360° (depending on IOP lowering required).
- Location: Anterior edge of footplate, alternating 0.0–1.0 mm from the limbus to cover the full width of the ciliary body. Avoid the 3 and 9 o'clock positions due to the long ciliary nerves and vessels.

Endolaser

Endolaser can be performed with diode endoscopic laser or argon laser. The laser parameters depend on the laser system employed, for which the instruction manual and clinical updates should be consulted.

Ultrasonic cyclodestruction

Ultrasonic circular cyclocoagulation using high-intensity focused ultrasound delivered by a circular miniaturized device, although not commonly used, has also been reported to reduce IOP in refractory glaucoma.[59,60]

Complications

- Pain.
- Persistent inflammation.
- Loss of visual acuity.[61,62]

- Hypotony.[63]
- Phthisis.[64]
- Scleral thinning[65,66] or rupture.[67]
- Pupillary distortion.[68]
- Macular oedema.
- Retinal detachment.[69]
- Aqueous misdirection syndrome.[64]
- Sympathetic ophthalmia.[70]
- Complication rates are higher in NVG and with treatment protocols using more than 80 J per session.[71]

Postoperative management

- Analgesia.
- Continue any current treatment as the effect of cyclophotocoagulation is not immediate.
- Check IOP after 24–48 hours if concerned over the potential effect of an IOP spike.
- Topical corticosteroids 4–6 times/day for 14 days or more depending on post-laser inflammation.
- Cycloplegia 2–4 times/day for 7–14 days.
- Continue any current IOP-lowering treatment; taper as indicated.

MICROPULSE LASER

Micropulse laser (MPL) is another modality for cyclophotocoagulation. Compared to conventional cyclophotocoagulation, it has the potential advantage of a more homogeneous distribution of energy resulting in less energy use and lower rate of complications. It can be titrated if further IOP-lowering required and repeated if there is loss of IOP-lowering efficacy over time.

Steps in management

Pre-laser

- Careful slit-lamp examination to identify suitable/unsuitable sites for laser application.
- Cease anticoagulants if possible to minimise subconjunctival haemorrhage.
- Can be performed under topical anaesthesia, but anaesthetic block with or without sedation is preferable.

Laser

A coupling gel is used, *e.g.*, lubricating gel or lignocaine gel, and the heel of the probe is placed on the limbus. A sweeping motion is used to deliver the laser. The typical treatment pattern is to move the probe in a continuous back-and-forth manner across a hemisphere over 20 seconds, then reverse direction like a pendulum. Treating by quadrant using a 10-second sweep is also possible, according to the preference of the surgeon.[72] Stopping and restarting during the treatment cycle is acceptable to optimize probe positioning. The 3 o'clock and 9 o'clock positions should be avoided.

Laser parameters

The following parameters correspond to the Cyclo G6 laser with MicropPulse P3 (Iridex Corporation, Mountain View, CA, USA).

- Wavelength: 810 nm.
- Duty cycle: 31.3%.
- Power: 2500 mW.

- Treatment time: 160-240 seconds (80-120 seconds per hemisphere. 20-30 seconds sweep speed per hemisphere).
- Titrate according to individual patient characteristics.

Post-laser management

- Postoperative pain is less than with conventional cyclodiode.
- Continue any current glaucoma treatment. Meaningful IOP lowering is seen at 1 week with optimal effect seen at 1 month. Titrate glaucoma eye drops based on IOP response.
- Follow-up is typically after 1 week and then 1 month.
- Topical steroids and/or topical NSAIDS are used in various dosage regimens ranging from 1 to 4 weeks.

LASER SUTURE LYSIS

Laser suture lysis is an effective, non-invasive postoperative laser treatment for IOP titration by selectively lysing the subconjunctival scleral flap suture(s) without disturbing the overlying tissues. Laser suture lysis allows for postoperative titration of IOP by increasing outflow,[73] and avoids early bleb failure and staged postoperative IOP control.

Indication

Commonly within 7–28 days of glaucoma filtering surgery.

Steps in management

Pre-laser

- Topical anaesthesia.

Laser

Types of laser

- Argon green or blue-green.
- Diode.
- Frequency-doubled Nd:YAG.

Types of lenses

- Ritch.
- Hoskins.
- Mandelkorn.
- Zeiss 4-mirror.
- Glass rod.

Uses of lenses

- Blanch the conjunctival vessels.
- Focus on the suture.
- Open the lids and stabilise the globe.

Placement of laser spots

Laser spots should be placed in subconjunctival scleral flap sutures (nylon).

Laser parameters

- Spot size: 50 µm
- Exposure time: ≤ 0.1 sec
- Power: 300–800 mW
- Number of spots: 1 or more, as needed.
- Cut suture close to one end or the other.
- Technique: Cut one suture per session to fully evaluate the response. If blood is present under the conjunctiva, choose a different suture to cut, or use a longer wavelength laser, or use a short exposure time.

Complications

- Conjunctival burn, leak.
- Hypotony.
- Shallow anterior chamber.
- Bleeding from ostium.
- In the presence of subconjunctival haemorrhage, one must be cautious, since lasering this area may cause charring and sometimes a button hole in the conjunctiva, leading to a leak.

Post-laser management

- Continue current postoperative regimen.
- If the bleb does not form spontaneously, apply pressure, *e.g.*, around the scleral flap.
- Recheck IOP and outflow 1 hour after laser and within 1 week.
- Examine the bleb and if not formed do some controlled massage. If a bleb is formed one may check the IOP and then wait for an hour and recheck the IOP to see if the IOP remains lower than before the laser suture lysis. This often gives an indication of the efficacy of the procedure.

FAQ

Is MicroPulse transscleral cyclophotocoagulation as effective standard cyclodiode?
Both forms of diode lasers are effective forms of trans-scleral cyclophotocoagulation of the ciliary body ablation. MicroPulse is thought to be safer, but less efficacious in terms of IOP lowering compared with standard cyclodiode. The technique chosen is based on surgeon preference and equipment availability.

Do I perform laser peripheral iridotomy (LPI) on all my angle-closure patients?
Prophylactic laser in PACS, who by definition have no symptoms to suggest an IOP rise, has been shown to have only a small benefit. Once patients become symptomatic, *e.g.*, headaches, haloes, or starburst, especially at night, LPI is indicated.

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5.2. TRABECULECTOMY

Key messages

- ❖ Trabeculectomy is the most performed glaucoma filtering surgery.
- ❖ Antifibrotic agents are applied to a large surface area of subconjunctival-tenon pocket to reduce the risks of bleb fibrosis and failure.
- ❖ Postoperative care during the first 12 weeks after surgery is critical to long-term outcome in IOP control.
- ❖ MMC and 5-FU are the 2 antifibrotic agents that are used intraoperatively and postoperatively, for their effectiveness in reducing filtering bleb scar formation.
- ❖ Care must be taken after 5-FU subconjunctival and MMC injections to avoid corneal toxicity resulting in epitheliopathy and thin blebs leading to blebitis. Copious irrigation after injection is recommended.

THE GOLD STANDARD OF PENETRATING SURGERY

Trabeculectomy is the most performed filtering surgery in glaucoma to lower IOP by creating a fistula under a scleral flap. The aqueous is then drained to the subconjunctival-Tenon's space. The technique allows for several modifications, including adjunctive use of antifibrotic agents and implants to reduce scar formation of the filtering bleb as well as suturing technique and scleral flap designs to reduce complications. It is effective in lowering IOP in eyes where topical medication and/or laser have failed to do so or are deemed unlikely to provide satisfactory IOP control. The procedure is conventionally considered the gold standard of penetrating surgery to create a subconjunctival bleb without the need of an implant, resulting in a cost-effective approach to the surgical treatment of glaucoma.

INDICATIONS

- Glaucoma status, *e.g.*, moderate to severe, that requires a low target IOP that is unlikely to be achieved with medication or laser.
- Failed medical and/or laser treatment.
- In cases where other forms of therapy are inappropriate: *e.g.*, poor adherence, side effects, socioeconomic problems. In patients who cannot tolerate medical therapy or unwilling to take medication or comply poorly to treatment regimen. Sometimes, it could be performed in the setting that accessibility to medical care is limit.

STEPS IN MANAGEMENT

Preoperative assessment

- Evaluate visual acuity and estimate predicted visual outcome.
- Evaluate the conjunctival health of the selected location for the filtering bleb, as well as its mobility and adhesion. The scleral flap and filtering bleb should be located in the superior quadrant under cover of the eyelid.
- Identify risk factors for treatment failure, such as:[1]
  - Asian, African, and Hispanic ethnicity.
  - Previous ocular surgery.
  - Young age.
  - Aphakia.
  - Pseudophakia.
  - Active ocular inflammation: When possible, active ocular surface or intraocular inflammation should be mitigated in prior to surgery.
  - Prolonged use of topical antiglaucoma medication, in particular preserved.[2]
  - Tendency to form keloid scars.
  - NVG and secondary glaucoma.

Surgical technique

- Topical, sub-Tenon's or peribulbar anaesthesia.
- Use a corneal traction suture, usually 8-0 suture material, to rotate the globe inferiorly and expose the upper conjunctiva.
- Use either fornix-based or limbus-based conjunctival flaps:
  - Both have similar success rates.[3]
  - Limbus-based conjunctival flaps may cause posterior wound limitation resulting in a "ring of steel" that leads to greater subconjunctival scarring and anterior cystic ischaemic blebs compared to fornix-based flaps.[3]
- Blunt-tip Wescott scissors are recommended while undermining the conjunctiva to prevent conjunctival tear or button hole.
- Intraoperative antimetabolites are applied to a large surface area of the conjunctival-Tenon's pocket by either soaked sponges or injection to reduce the risk of bleb failure.
- Copious irrigation with balanced salt solution on the treated area is performed to prevent over-exposure to the antimetobolite and reduce the risk of the development extensive tissue avascularity.[4]
- Different scleral flap shapes — triangular, semicircular, or trapezoidal — provide similar long term success rates.[5,6] The size and architecture should encourage posterior flow and a diffuse bleb.
- The fistulizing technique can be performed by:
  - Creating a partial-thickness fistula (conventional trabeculectomy) with a blade and scleral (Kelly) punch.
  - Using micro drainage devices (see Section 4.4 on minimally invasive glaucoma surgery [MIGS]):
    - EX-Press shunt (Optonol Ltd., Zug, Switzerland) inserted under a trabeculectomy flap:
      * Modified guarded technique with partial-thickness scleral flap insertion.[7]
      * Technically less challenging and more standardized.
      * Similar efficacy, but potentially less postoperative hypotony compared to trabeculectomy.[8]

- ◆ PRESERFLO MicroShunt (Santen Pharmaceutical Co., Ltd, Japan) inserted through a needle tract:
  - * An alternative to avoid making the scleral flap.
  - * Standardized flow resistance through a 70-µm lumen and 8.5-mm tube length.[9]

- Different techniques of suturing the scleral flap and titrating the filtration. A 10-0 nylon suture is preferred. Pre-placing scleral flap sutures (fixed or releasable), viscoelastic, and/or inserting an infusion cannula can reduce periods of hypotony during surgery.
- Meticulous Tenon's and conjunctival closure to prevent leaks using 10-0 nylon.
- Use of anti-inflammatory agents such as topical or systemic NSAIDS and corticosteroids.
- Use of laser suture lysis or releasable sutures: Adjustable or releasable sutures add an extra dimension of flexibility towards a gradual and titratable postoperative modulation of aqueous flow and attaining the desirable targeted IOP.
- The additional use of a biodegradable collagen matrix implant, *i.e.*, Ologen (Aeon Astron Europe, Leiden, The Netherlands), placed on top of the scleral flap before closing the conjunctiva is a safe and effective procedure, but has shown no significant benefit over trabeculectomy with MMC.[10]

Postoperative management

- The first 12 postoperative weeks are critical for outcomes.
- Examine the patient on the first or second postoperative day and thereafter as clinically indicated.
- Prescribe intensive topical steroids for 8–12 weeks, starting at 2–3 hourly and gradually tapering off depending on the clinical findings and level of bleb inflammation observed. Steroids may need to be continued for up to 4–5 months postoperatively for patients at persistent risk of scar formation.
- Prescribe topical antibiotics until the topical steroids frequency is reduced to 2-3 times daily.
- Consider cycloplegics for 2–6 weeks, especially for those at risk of ciliary block (short axial length and preoperative shallow anterior chamber).
- Provide intensive individualized postoperative care (globe indentation/massage, suture lysis or release, subconjunctival 5-FU/MMC, or bleb needling).

COMPLICATIONS OF TRABECULECTOMY SURGERY[11]

- Failure to control IOP.
- Hypotony with or without maculopathy or choroidal detachment.
- PAS.
- Pupillary distortion.
- Faster progression of cataract.
- Sclerostomy blocked by iris, blood, vitreous, or fibrin.
- Bleb-related complications, *e.g.*, blebitis, leakage.
- Bleb-related endophthalmitis.
- Aqueous misdirection.
- Suprachoroidal haemorrhage.

USE OF ADJUNCTIVE AGENTS IN GLAUCOMA SURGERY

Scarring is the major cause of failure following filtration surgery. Antimetabolite agents (MMC and 5-FU) have been shown to inhibit scarring and increase the success rate.[12] The use of antimetabolites, though beneficial in lowering IOP, can result in serious complications. Therefore, use with caution and monitoring are mandatory.[13]

- MMC: Used widely in filtering surgery.
- 5-FU: Used less with filtering surgery due to reduced efficacy compared to MMC.[14] 5-FU is more commonly used postoperatively combined with needling.
- Adjunctive anti-VEGF therapy facilitates initial management in NVG, but its role in increasing success rates in trabeculectomy or glaucoma tube shunt surgery is not as promising as that of antimetabolites.[15,16]

Indications

Adjunctive agents are the current gold-standard intraoperative treatment for bleb-forming surgeries, especially in eyes with a high risk of failure following standard filtering surgery, *e.g.*, in cases of repeat surgery, NVG, uveitic glaucoma, aphakic glaucoma, younger age, and populations of African descent. Note that antimetabolites are contraindicated in pregnancy and lactation.

Steps in management

Intraoperative application

Dose

- Sponge soaked in MMC (varying doses of 0.2–0.5 mg/ml) applied for 1–4 minutes.
- Sponge soaked in 5-FU (50 mg/ml) for 1–5 minutes.
- Another technique is to inject the antifibrotic agent under Tenon's and protect the conjunctival edge.
- Subconjunctival or Sub-Tenon's MMC injection is utilized with the subconjunctival Xen Gel Stent (Allergan, Dublin, Ireland). The suggested dosage is approximately 0.1 ml of 0.1 or 0.2 mg/mL MMC.[17,18]

Mode of application

- Minimise exposure of the conjunctival edge and cornea to antimetabolites
- Place the sponge under Tenon's: A wide sub-Tenon's dissection allows multiple sponges or a large single sponge to be placed.[12] Count the sponges to avoid leaving in the pocket.
- Apply to a large surface area under the conjunctiva to reduce the risks bleb thinning and cystic blebs with increased risk of blebitis.[19]
- Copious irrigation of the treated area with balanced salt solution.
- For the Xen Gel Stent, MMC should be injected with 30-gauge needle to avoid leakage, 6–7 mm posterior to the limbus, superior to the target placement area.[17,18]

Postoperative application

Postoperative bleb needling with antimetabolites forms an important part of trabeculectomy management. Both MMC and 5-FU can be injected subconjunctivally when indicated.

Mode of application

Using a 28-gauge needle attached to a 1 ml syringe, 1% lidocaine is injected into the subconjunctival space where the antimetabolite will be given. A second syringe containing 5–10 mg-of 5-FU should be injected a little away from the bleb. The needle should be advanced into the bleb along a long track to reduce the risk of backflush of the injected 5-FU post-injection. Copious irrigation with normal saline is performed after the injection. MMC can also be used instead of 5-FU. Currently, there is no consensus on which antimetabolite is superior in exerting antifibrotic effect.

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5.3. GLAUCOMA DRAINAGE DEVICES

Key messages

- ❖ Non-valved glaucoma drainage devices (GDDs) result in greater postoperative hypotony than valved devices.
- ❖ Postoperative hypertensive phase is common with any shunt and may require medical therapy for management.
- ❖ Similar rates of surgical success were observed with both the valved Ahmed and non-valved Baerveldt implants at 5 years.
- ❖ Before implanting a GDD, its tube should be primed with irrigation for valve function in valve type and patency in the non-valve.

GLAUCOMA DRAINAGE DEVICES

Glaucoma drainage devices, or GDDs, are devices that drain aqueous consisting of a long silicone tube which extends from the anterior chamber to a reservoir plate placed posteriorly at the inter-rectus muscles. GDDs allow aqueous to flow from the anterior chamber into a bleb that forms around the plate of these devices. Aqueous diffuses through the capsule and is collected by blood vessels in the surrounding capsule. The postoperative hypertensive phase is common with any shunt and may require medical therapy to reduce IOP. It indicates the start of device encapsulation. GDD surgery and its postoperative management can be complex.

Up to a particular surface area of the plate, the size of the implant plays a role in IOP control. Beyond a certain size, a larger plate does not result in better IOP control in the long term.[1] The plate material of the implants is another important factor for IOP control, with silicone plates providing greater IOP control.[2]

TYPES OF GDDS

The 2 different types of GDDs are valved and non-valved devices.[1,3]

Valved GDDs

Valved tubes may have a lower rate of immediate hypotony, but postoperative hypotony can occur via peritubular leak.

- Ahmed Glaucoma Valve (New World Medical, Rancho Cucamonga, CA, USA).
- The possibility of developing an encysted bleb is much higher with the Ahmed implant and the hypertensive phase is more significant.

Non-valved GDDs

Non-valved GDDs have shown greater IOP reduction and lower rates of re-operation, but can be associated with a greater risk of postoperative hypotony compared to valved devices.

- Molteno: single and double, with and without pressure ridge (Nova Eye Medical, Fremont, CA, USA).

- Baerveldt Glaucoma Implant (Johnson and Johnson Vision, Irvine, CA, USA).
- Aravind Aqueous Drainage Implant (Aurolab, Madurai, India).
- Ahmed ClearPath (New World Medical, Rancho Cucamonga, CA, USA).
- Paul Glaucoma Implant (Advanced Ophthalmic Innovations, Singapore).

COMPARATIVE STUDIES

The Tube Versus Trabeculectomy study: Five-year results comparing Baerveldt drainage devices with trabeculectomy + MMC in patients who had previous trabeculectomy and/or cataract extraction with IOL.[4] Both procedures were associated with similar IOP reduction and use of supplemental topical medical therapy at 5 years. Additional glaucoma surgery was needed more frequently after trabeculectomy with MMC than tube shunt placement

Similar rates of surgical success were observed with both the Ahmed and Baerveldt implants at 5 years. The Baerveldt implant provided greater IOP reduction and a lower rate of re-operation than the Ahmed valve, but was associated with twice as many failures due to persistent hypotony or device explantation.[5]

INDICATIONS

- Previous failed trabeculectomy with antimetabolites.
- Insufficient conjunctiva due to scarring:
  - Prior surgical procedure.
  - Traumatic, inflammatory, or chemically induced surface scarring.
- Complicated and refractory glaucomas:
  - Uveitic glaucoma.
  - Intraocular membrane formation likely to occlude a non-implant drainage procedure (*e.g.*, in ICE syndrome, NVG).
  - Paediatric and developmental glaucoma that fails angle and filtering surgery.

STEPS IN MANAGEMENT

Surgical technique

1. Deep sub-Tenon's, peribulbar, or retrobulbar block. Can be performed under general anaesthesia when indicated.
2. Corneal traction suture to expose upper conjunctiva and inter-rectus sclera.
3. Creation of subconjunctival space with or without radial relaxing incision depending on surgeon's preference.
4. Insertion of plate in subconjunctival inter-rectus space:
   - Valved GDD: Requires irrigation through the tube prior to insertion (to confirm the valve opens properly) .
   - Non-valved GDD: Requires aqueous flow restriction to prevent postoperative hypotony.
     - One-stage technique:[6] Ligate tube with absorbable material to prevent immediate over- drainage for 4-6 week then the material would be dissolved, allowing aqueous drainage. Can perform venting slits at pre-ligated locations to blunt off high IOP.
     - Two-stage technique:[7,8] Plate is inserted into the subconjunctival space 6–8 weeks prior to tube insertion into the anterior chamber.

5. Creation of scleral tunnel for entering the anterior chamber or ciliary sulcus space.
6. Placement of the tube through scleral tunnel with good clearance from the cornea and iris. Truncate the tube to a good length and place either in the anterior chamber resting on the iris surface or in the sulcus. For anterior chamber tube siting, the tube should be cut bevel up and for sulcus placed tubes, bevel down. This is to avoid the possibility of suction of the iris up the tube lumen.
7. Suturing of donor corneal/scleral graft or other patching material to prevent conjunctival erosion.
8. Close the wound with either 10-0 nylon or 8-0 vicryl depending on surgeon preference.

COMPLICATIONS SPECIFIC TO GDD SURGERY[1]

- Hypotony (more frequently associated with non-valved GDDs).
- Plate encapsulation with high IOP.
- Tube blocked by iris, blood, vitreous, or fibrin.
- Corneal endothelial decompensation.
- Aqueous misdirection.
- Suprachoroidal haemorrhage.

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5.4. MINIMALLY INVASIVE GLAUCOMA SURGERY

Key messages

- Minimally invasive glaucoma surgery (MIGS) initially referred to ab interno devices and procedures usually targeting Schlemm's canal. However, the term has currently broadened to include ab externo bleb-forming procedures with little or no scleral dissection.
- Blood reflux from the stent or transient blanching of the episcleral vessels are indicators of correct stent placement.
- Gonioscopy should be performed postoperatively to assess stent placement and ensure no blockage.
- MIGS procedures in all forms have limited use in angle closure, given that open angles and a visible TM are necessary for performing the procedure.
- Subconjunctival MIGS devices are sometimes referred to as minimally invasive bleb-forming surgery (MIBS).

MINIMALLY INVASIVE GLAUCOMA SURGERY

In the last decade, MIGS have been increasingly adopted by many as part of the glaucoma treatment paradigm. While the term initially referred to ab interno devices and procedures usually targeting Schlemm's canal, this soon grew to include ab externo bleb forming procedures with little or no scleral dissection.1 MIGS can be broadly classified into 3 categories:

1. TM MIGS:
   - Stents.
   - Procedures.
2. Subconjunctival MIGS devices (this group is sometimes referred to as minimally invasive bleb-forming surgery or MIBS).
3. Suprachoroidal MIGS devices.

Traditional glaucoma filtration surgery and glaucoma drainage devices (GDDs) have a variable success rate and can result in a significant complication rate of up to 35%.2 MIGS procedures aim to reduce IOP, medication burden, and the aggressiveness of treatment while avoiding these complications. The efficacy is less than that of traditional surgery with a much higher safety profile, though the incidence and types of adverse events and complications does differ between the different types of MIGS procedures.

MIGS can be performed as a standalone procedure or in conjunction with cataract surgery. Several studies have described the efficacy of these procedures over the long term. In general, these procedures are expensive but have shown cost-effectiveness in certain scenarios. The availability of these procedures vary by country.

TRABECULAR MESHWORK MIGS

TM MIGS are generally indicated for use in:

- Stable and well-controlled mild to moderate OAG.
- OHT.
- Patients on 1–3 ocular hypotensive medications.
- Usually in conjunction with cataract surgery but can also be done as a standalone.

Stents

The following recommendations enhance the success of MIGS stent implantation:

- Proficiency with intraoperative gonioscopy is imperative.
- Injection of a miotic helps to pull the iris away from the angle but is not always necessary.
- Choose patients with moderate TM pigmentation and easily identifiable angle structures.
- Blood reflux from the stent or transient blanching of the episcleral vessels are indicators of correct stent placement.

Contraindications

- Angle-closure disease.
- NVG.
- Uveitic glaucoma.
- Secondary glaucoma with raised episcleral venous pressure.
- Lens-induced glaucoma.
- Traumatic/angle-recession glaucoma.

iStent trabecular micro-bypass stents

The first-generation iStent trabecular micro-bypass (Glaukos, Laguna Hills, CA, USA) was first approved by the FDA in 2012. Since then, the device has been refined in subsequent generations.

- iStent: The first-generation iStent consists of a heparin-coated titanium stent 1 mm long, L-shaped, with a 120 µm lumen diameter.
- iStent Inject: The second-generation iStent consists of 2 conically shaped heparin-coated titanium stents, 360 µm in length and 230 µm at its widest diameter.
- iStent Inject W (G2W): The third-generation iStent is very similar to the iStent Inject, comprising 2 stents with a 360 µm diameter and a central lumen diameter of 80 µm, allowing 4 attempted deployments.
- iStent Inject Infinite: The 3 G2W stents allows unlimited number of deployments.

<u>Surgical steps</u>

1. Surgeon usually positioned temporally.
2. Rotate the patient's head and operating table 30°–40° away from the surgeon to facilitate a gonioscopic view of the angle.
3. Place the surgical gonioprism on the cornea with or without a coupling solution (ophthalmic viscosurgical device [OVD]) and view angle under high magnification.
4. Avoid pressure on the eye with the goniolens, which causes corneal striae that impedes the view.
5. Avoid pressure on the wound when inserting the trochar to avoid expressing OVD from the eye.
6. Ensure a clear en-face or straight-on view is achieved before inserting the applicator into and across the anterior chamber towards the nasal angle.

7. With the sleeve in place, the injector approaches the TM perpendicularly.
8. Pull back the sleeve and visualize the trochar before engaging the TM and pushing against the posterior wall of Schlemm's canal until it dimples slightly. Avoid pushing hard enough to distort the angle.
9. Deploy the stents by squeezing the release button on the injector.
10. Hold the injector in place for a moment (2–3 seconds) before pulling back, providing time for the stents to fully release.
11. Remove all OVD.

Hydrus Microstent

The Hydrus Microstent (Alcon, Geneva, Switzerland) is a crescent-shaped trabecular scaffold comprised of nitinol, 8 mm in length with a variable lumen diameter between 185 µm and 292 µm that allows for trabecular bypass as well as dilation and scaffolding of Schlemm's canal.

Surgical steps

1. The surgeon is usually positioned temporally.
2. Rotate the patient's head and operating table 30°–40° away from the surgeon to facilitate a gonioscopic view of the angle.
3. Place the surgical gonioprism on the cornea with or without a coupling solution (OVD) and view angle under high magnification.
4. Avoid pressure on the eye with the goniolens, which causes corneal striae that impedes the view.
5. Avoid pressure on the wound when inserting the trochar to avoid expressing OVD from the eye.
6. Ensure a clear en-face or straight-on view is achieved before inserting the applicator into and across the anterior chamber towards the nasal angle.
7. The delivery cannula can be rotated on the injector, allowing optimization of each surgeon's hand orientation.
8. The cannula penetrates the TM at a small angle tangential to its surface. Subsequently, flatten out the cannula, keeping the tip firmly in place and slowly advance and implant the Hydrus Microstent using the tracking wheel on the delivery system.
9. When approximately 1 mm of the proximal Microstent protrudes as an inlet from the TM into the anterior chamber, release the injector by pressing gently backwards and slowly removing it.
10. Remove all OVD.

Tips for stents

- Proficiency with intraoperative gonioscopy imperative
- Injection of a miotic helps to pull the iris away from the angle but is not always necessary.
- Choose patients with moderate TM pigmentation and easily identifiable angle structures.
- Blood reflux from stent or transient blanching of the episcleral vessels are indicators of correct stent placement.

Postoperative management for TM MIGS

- Perform postoperative reviews at Day 1, Week 1, and Month 1.
- Prescribe antibiotic and steroid use as per post phacoemulsification regimen.
- Consider supplemental non-steroidal anti-inflammatory agents to allow earlier discontinuation of steroidal agents (as OAG patients are at higher risk of steroid response).

- Stop hypotensive medications, allowing approximately 6–8 weeks from the date of surgery to reach a new steady state for IOP and the restart hypotensive medications as necessary.
- Ideally, gonioscopy should be performed at the Week 1 and Month 1 postoperative reviews to assess stent placement and ensure there is no blockage.
- Restart any antiplatelet or anticoagulant medications that have been stopped.

Complications of TM MIGS

Intraoperative

- Endothelial damage.
- Iridodialysis.
- Cyclodialysis.
- Hyphaema.
- Malpositioning.

Postoperative

- Transient IOP spikes.
- Hyphaema.
- Stent obstruction with PAS/iris tissue.
- Endothelial cell loss from malpositioned stent (Hydrus).

Procedures: ab interno dilating +/- excision

iTrack Advance Microcatheter

The iTrack Advance microcatheter (Ellex, Adelaide, Australia) consists of a 220-µm polymer shaft with lubricious coating for 360° cannulation of Schlemm's canal, a guidewire mechanism, an infusion pathway that connects to an OVD delivery system, and an optical fibre connected to a portable light source with an illuminated tip for transluminal visualization of the microcatheter.

Surgical steps

1. Sitting temporally, create an oblique limbal paracentesis 1–2 mm into the clear cornea, a separate wound from the main phacoemulsification incision, 2–3 clock hours away from the TM target.
2. Fill the anterior chamber with OVD.
3. Place the goniolens on the eye.
4. Pierce the upper portion of the anterior pigmented TM at a 15° angle with the cannula tip.
5. Release the forward pressure with the cannula tip and rest the tip against the scleral wall, remaining as static as possible.
6. Ensure the cannula is parallel to Schlemm's canal.
7. Intubate the canal by slowly advancing the microcatheter using the actuator. Verify the location of the microcatheter using the illuminated tip.
8. Advance the microcatheter 360° slowly around Schlemm's canal via a single intubation, maintaining the cannula tip parallel to the scleral wall.
9. After full intubation, slowly withdraw the microcatheter using the actuator and instruct the assistant to simultaneously deliver OVD, usually Healon GV via the Viscoinjector.
10. Remove all OVD.

OMNI Surgical System

The Omni Surgical System (Menlo Park, CA, USA) is a single-use device that integrates an access cannula, a microcatheter allowing 180° advancement into Schlemm's canal, an internal fluid reservoir, and a catheter advancement and retraction wheel mechanism all into a single disposable device. The device allows for viscodilation and trabeculotomy in one procedure.

Surgical steps

1. Sitting temporally, create an oblique limbal paracentesis 1–2 mm into the clear cornea, a separate wound from the main phacoemulsification incision, 2–3 clock hours away from the TM target.
2. Fill the anterior chamber with OVD.
3. Place the goniolens on the eye.
4. Insert the cannula through the incision and move it across the pupil, toward the iridocorneal angle.
5. Press the cannula tip against the TM to create a small opening in Schlemm's canal.
6. The microcatheter is then inserted by turning the small wheel located on the handle of the device.
7. The catheter is deployed within Schlemm's canal for 180° or one hemisphere at a time.
8. Upon retraction of the microcatheter, OVD is injected in a consistent and measured amount.
9. The microcatheter is then re-introduced into Schlemm's canal and a trabeculotomy is performed.
10. The same manoeuvre is repeated in the opposite hemisphere by removing the cannula from the anterior chamber, rotating the cannula 180°, and re-entering the anterior chamber to treat the remaining hemisphere.
11. Remove all OVD.

Complications of ab interno MIGS

Intraoperative

A steady injection of OVD and good coordination with the assistant helps in avoiding the following complications:

- Hyphaema.
- Descemet's membrane detachment.

Postoperative

- Hyphaema.
- Transient hypotony or IOP spikes.

Tips for success

- steady injection of OVD and good coordination with the assistant helps in avoiding the above complications.
- The OVD in the catheter can be used to push blood out of the way for a better view.

Procedures: tissue excision MIGS

Kahook Dual Blade or similar

The Kahook Dual Blade (New World Medical, Rancho Cucamonga, CA, USA) is a disposable dual blade knife designed to remove up to 120° of TM tissue. The Tanito Microhook (Inami, Tokyo, Japan) and bent ab interno needle goniotomy (BANG) are used for the same procedure.

Surgical steps

1. Create a main corneal incision for a cataract wound.
2. Fill the anterior chamber with OVD.
3. Place the goniolens on the eye.
4. The blade enters the canal and moves along the TM removing tissue with minimal collateral damage. The manoeuvre is then repeated in the other direction. The trabecular tissue is pulled out with a Kawai forceps.

Trabectome (NeoMedix Corporation)

The Trabectome (Tustin, CA, USA) is a disposable 19.5-gauge handpiece with irrigation, aspiration, and electrocautery combined. The tip of the Trabectome removes TM tissue and coagulates at the same time.

Surgical steps

1. Create a main corneal incision for a cataract wound.
2. Fill the anterior chamber with OVD.
3. Place the goniolens on the eye.
4. The procedure if often performed prior to phacoemulsification.
5. The probe is inserted through the incision, targeting the nasal TM across the anterior chamber.
6. Approximately 90° of ablation is performed in one direction. The probe can then be rotated 180° and advanced in the opposite direction.

Gonioscopy-assisted transluminal trabeculotomy

Gonioscopy-assisted transluminal trabeculotomy (GATT) involves the removal of the entire 360° TM tissue using a 6-0 polypropylene or nylon suture after incising the TM wall.

Surgical steps

1. Create a main corneal incision for a cataract wound.
2. Fill the anterior chamber with OVD.
3. Place the goniolens on the eye.
4. Create a nasal goniotomy with a 27-gauge needle.
5. Blunt the 6-0 Prolene suture with heat from diathermy.
6. Place the suture into Schlemm's canal and advance circumferentially 360° using a microsurgical forceps.
7. Grasp the distal edge and retract the proximal end, thus shearing the TM and creating a 360° trabeculotomy.

Excimer laser trabeculostomy

Excimer laser trabeculostomy delivers 308 nm excimer laser energy via an intraocular fibre-optic probe to create permanent perforations over the iridocorneal angle, selectively ablating multifocal areas of the TM and Schlemm's canal inner wall, and thus creating direct communication between the anterior chamber and collector channels.

Surgical steps

1. Create a main corneal incision for a cataract wound.
2. Fill the anterior chamber with OVD.
3. Place the goniolens on the eye.
4. Direct the probe directed toward the pigmented TM and advance until the probe comes into contact with the TM.
5. Perform 10 to 20 trabeculostomies over a span of 90° to 120° of the nasal quadrant.

Complications of tissue excision MIGS

Keep a steady grip and avoid any upward or downward movement to avoid the following complications.

Intraoperative

- Hyphaema.
- Iridodialysis.

Postoperative

- Hyphaema.
- Transient hypotony or IOP spikes.
- Risk of cleft closure from residual TM leaflets and IOP reduction is limited by episcleral venous pressure and Schlemm's canal resistance.

Tips for success

- Keep a steady grip and avoid any upward or downward movement to avoid the above complications

SUBCONJUNCTIVAL MIGS DEVICES

This group of MIGS is sometimes referred to as minimally invasive bleb-forming surgery or MIBS.

PRESERFLO MicroShunt

The PRESERFLO MicroShunt (Santen Pharmaceutical Co., Ltd, Japan), previously known as the InnFocus MicroShunt, is a stent composed of SIBS material, 8.5 mm in length, with a 1-mm fin, external diameter of 350 µm, and an internal lumen of 70 µm.3 It is recommended to keep ocular pressure high with reinflation to ensure there is immediate flow through the PRESERFLO upon insertion.

Surgical steps

1. The surgeon is positioned superiorly
2. Create a superior fornix-based conjunctival flap over a circumference of 90°–120° (avoid 12 o'clock position) from near the limbus to at least 8 mm deep and apply sponges saturated with MMC (0.2–0.4 mg/mL) as in standard trabeculectomy. Higher doses of MMC for PRESERFLO MicroShunt surgery compared to trabeculectomy may be considered.
3. Perform a sclerostomy with a double step knife or in 2 steps using a 1-mm keratome and a 25-gauge short needle 3 mm behind the limbus.
4. Aim to have PRESERFLO parallel to the iris plane, but not touching the iris, keeping as far back from the endothelium as possible, with the bevel of the device upwards.
5. Ensure the PRESERFLO is flowing by inflating the anterior chamber with balanced salt solution and looking for flow. Flushing with a 23-gauge cannula may be necessary.
6. The PRESERFLO can be stented with 9 or 10-0 nylon suture to control flow using a buried releasable technique in patients with high risk for hypotony.
7. The conjunctiva and Tenon's capsule are closed at the limbus with 10-0 nylon or 9-0 vicryl.

Contraindications4

- Angle-closure glaucoma.
- Presence of conjunctival scarring, previous incisional ophthalmic surgery involving the conjunctiva or other conjunctival pathologies (*e.g.*, thin conjunctiva, pterygium) in the target quadrant.
- Active iris neovascurisation.
- Active inflammation (*e.g.*, blepharitis, conjunctivitis, scleritis, keratitis, uveitis).
- Secondary glaucoma (*e.g.*, post-traumatic, pseudoexfoliation or pigmentary).
- Vitreous in the anterior chamber.
- Anterior chamber IOL.
- Intraocular silicone oil.

Xen Gel Stent

The Xen Gel Stent (Allergan, Irvine, CA, USA) is a 6-mm hydrophilic flexible tube with a 45-µm lumen made of porcine collagen-derived gelatine. The Xen decreases IOP by creating a permanent drainage shunt from the AC to the subconjunctival space through a scleral channel. The device hydrates within 1–2 minutes of contact with aqueous humour, bending and conforming to the surrounding tissue. The Xen allows for overhand or underhand insertion of the injector. The ab externo approach ensures the stent is less likely to be encased in Tenon's layer.[7]

Surgical steps

1. Surgeon usually positioned temporally to obtain a good gonioscopic view of the angle. (As previously described)
2. The intended area of placement in the supero-nasal quadrant is marked, which is approximately 3 mm from the limbus
3. 0.2 ml MMC (0.1–0.2 mg/ml) is injected with a 30-gauge needle in the superonasal quadrant and massaged over the area of anticipated Xen implant insertion
4. A cohesive viscoelastic is used to fill the AC through the paracentesis.
5. The inserter needle (double-beveled 27 gauge) is directed through the temporal incision and across the AC toward the superonasal quadrant.
6. The sharp tip is engaged at or slightly anterior to the trabecular meshwork and advanced through the sclera under gonioscopic guidance to exit subconjunctivally 2-3 mm from the limbus,
7. A sliding mechanism deploys the stent and retracts the needle
8. Ideally keep 2.0 mm in the subconjunctival space (preferentially in a more superficial layer than the sub-Tenon's space), 1.0 mm in the AC, and 3.0 mm tunneled through sclera.
9. Ensure that the stent is straight and not stuck in Tenon's layer
10. An ab externo approach similar to the PRESERFLO has also been described

Contraindications

- Angle-closure glaucoma where the angle has not been surgically opened.
- Previous glaucoma shunt or valve in target quadrant.
- Conjunctival scarring or other pathologies in the target quadrant (*e.g.*, pterygium).
- Active iris neovascularization or active ocular inflammation.
- Anterior chamber IOL.
- Intraocular silicone oil.
- Vitreous in the anterior chamber.

SUPRACHOROIDAL MIGS DEVICES

MINIject glaucoma drainage device

The MINIject (iSTAR Medical SA, Wavre, Belgium) is a supraciliary, minimally invasive, soft, flexible silicone implant that drains into the suprachoroidal space. Its dimensions are 1.1 x 0.6 mm x 5 mm in length. A 0.5-mm green ring from the tip of the device indicates the proper depth of placement.

Surgical steps

1. The surgeon is usually positioned temporally to obtain a good gonioscopic view of the angle.
2. The MINIject can be inserted ab-interno into the suprachoroidal space as a stand-alone procedure through a 2-mm clear corneal incision.
3. The device is then gently advanced between scleral spur and ciliary body until the green-coloured ring at the proximal end of the device at the level of scleral spur.
4. When the middle of the ring is at the level of the scleral spur, only 0.5 mm of the device projects into the anterior chamber.
5. The delivery system is then activated, retracting the sheath while leaving the implant in the suprachoroidal space.
6. Remove all OVD.

Complications

Intraoperative

- Endothelial damage.
- Iridodialysis.
- Cyclodialysis.
- Hyphaema.
- Malpositioning.
- Stent breakage.

Postoperative

- Transient hypotony (9.59%).
- Hyphema (5.53%).
- IOP spikes (2.11%).
- Choroidal effusion (1.31%).
- Implant occlusion (0.93%).
- Macular oedema (0.91%).
- Implant malposition (0.88%.)
- Device erosion and exposure of implant.
- Implant migration: Dislocation into the anterior chamber.
- Bleb leak or dehiscence (may be due to thin or ischaemic bleb with overfiltration).

Contraindications

- Angle-closure glaucoma.
- Traumatic glaucoma.
- Malignant glaucoma.
- Uveitic glaucoma.
- NVG.
- Discernible congenital anomalies of the anterior chamber angle.
- Patients with known intolerance or hypersensitivity to silicone.

FAQ

Is PRESERFLO a replacement for trabeculectomy?

Although both surgeries are similar, the PRESERFLO results in less tissue manipulation at the time of surgery such as fashioning of the scleral trapdoor, pre-placed buries releasable and iridectomy are avoided. Postoperatively, the patients require less follow-up as there is less bleb manipulation possible. The efficacy compared to trabeculectomy is less, even with the use of MMC. At present, trabeculectomy is still the gold standard for glaucoma drainage surgery.

How are failing MIBS managed?

Often the first signs of failure are a deviated device caught in Tenon's, scar tissue, or the lack of a good drainage bleb. Needling with MIBS is often more difficult with these devices as there is the possibility of damaging the device or leaving it malpositioned. Nevertheless, it may be performed at the slit lamp with antifibrotics as per trabeculectomy needling. However, there is a need to break the scar tissue both above and below the device. Where needling has failed, it is necessary to take the patient to the operating room to revise the MIBS. This can involve flushing it and removing any scar tissue around the device. If excessive Tenon's is present, a tenonectomy may help reduce the risk of scarring.

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5.5. NON-PENETRATING GLAUCOMA SURGERY

Key messages

- ❖ Non-penetrating glaucoma surgery (NPGS) reduces IOP less effectively than penetrating surgery, but with lower complication rates.
- ❖ NPGS may reduce the hypotony risks of trabeculectomy in higher-risk patients, *e.g.*, high myopes, younger patients, previous vitrectomy, eye-rubbers.
- ❖ Further management with Nd:YAG goniopuncture may be required in up to 40% of surgeries to further lower the IOP in the longer term.

NON-PENETRATING GLAUCOMA SURGERY

Non-penetrating glaucoma surgery (NPGS) is a form of drainage surgery where Schlemm's canal is de-roofed underneath a scleral flap and deep corneoscleral lamellae are removed to create an intrascleral lake. The deep sclerectomy may be performed manually or assisted with CO_2 laser. Aqueous percolates through the remaining trabeculo-Descemet's membrane (TDM) into this area and thence into the subconjunctival space. Antimetabolites are applied and a shallow, diffuse filtration bleb can be seen. A collagen implant can be used as a spacer to keep the lake patent. Postoperatively, topical steroid is prescribed 3–4 times/day for 6–12 weeks. Pilocarpine 2 times/day for 2–3 weeks may be considered to reduce the risk of iris prolapse. The patient is followed up 1–3 weeks later. Further management with Nd:YAG goniopuncture may be required in up to 40% of surgeries to further lower the IOP in the longer term.

Viscocanalostomy modifies the above procedure by injecting hyaluronic acid into Schlemm's canal. This may increase outflow by widening and/or micro-rupturing the walls of Schlemm's canal and collector channels.

Although NPGS reduces IOP less effectively than penetrating surgery, it has lower complication rates (*e.g.*, postoperative hypotony, bleb-related infections) compared with trabeculectomy with antimetabolites. Developing the surgical skills to perform NPGS requires a steep learning curve.

Indications

- Failed medical and/or laser treatment, when there is a need for lower target IOP in eyes with an open and normal angle.
- May reduce hypotony risks of trabeculectomy in higher-risk patients, *e.g.*, high myopes, younger patients, previous vitrectomy, individuals who rub their eyes.

Complications

- Intraoperative perforation.
- Failure to control IOP.

- Cataract.
- Bleb-related complications.
- Iris prolapse following goniopuncture.

Points to note

- NPGS reduces IOP less effectively than penetrating surgery, but has lower complication rates (*e.g.*, postoperative hypotony, bleb-related infections) compared with trabeculectomy with antimetabolites.
- NPGS requires a steep learning curve.
- The deep sclerectomy may be performed manually or assisted with CO_2 laser.

LASER GONIOPUNCTURE

Laser goniopuncture may be utilised to convert NPGS to a penetrating drainage surgery in order to further reduce IOP.[1] Effectively, the laser is used to perforate the TDM. While laser goniopuncture can be performed early in the postoperative period (but preferably not in the first 4 weeks), the procedure may be effective even years later.

Steps in management

Pre-laser

- Explain the procedure and obtain the patient's consent.
- Instil 2% pilocarpine 2% to constrict pupil.
- Instil apraclonidine or brimonidine to lower the IOP and vasoconstrict the conjunctival vessels.
- Administer topical anaesthesia.
- Use a Latina SLT Gonio laser lens or similar.

Laser[1]

- Laser type: Nd:YAG
- Laser power: 3–6 mJ, starting at 3 mJ.
- Number of burns: Single bursts, 1–20 shots until TDM punctured.
- Location: Aimed at Descemet's portion of the TDM. Anterior placement minimises the risk of iris prolapse. The endpoint is a visible TDM hole, slit, or flap.

Complications

- Iris prolapse: Prevent with post-laser pilocarpine, pre-laser iridoplasty, iridotomy for pupillary block. Treat with pilocarpine +/- iridoplasty +/- YAG laser synechialysis +/- surgical iris sweep.
- Hyphaema: Usually minor, apply pressure with goniolens.
- Inflammation.
- Hypotony (rare): Treat with cycloplegia. However, it may require reformation of the anterior chamber.

FAQ

When do I perform NPGS versus trabeculectomy?

The indications for both surgeries are similar, *i.e.*, failed medical and/or laser treatment, when there is a need for lower target IOP in eyes with an open and normal angle. Generally, NPGS is regarded as less effective in terms of IOP reduction, but has lower complication rates such as postoperative hypotony and bleb-related infections.

Surgeon preference based on training and experience determines the preferred procedure for the particular patient. Although NPGS skills are useful, trabeculectomy skills are essential for comprehensive glaucoma management.

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5.6. PHACO-GONIOSYNECHIALYSIS

Key messages

- ❖ Goniosynechialysis (GSL) is often performed with phacoemulsification to open the angle.
- ❖ Phaco-GSL is a good option to treat PACG with concomitant cataract due to its bleb-less nature.

PHACO-GONIOSYNECHIALYSIS

Goniosynechialysis (GSL) involves separation of the PAS with a spatula, microforceps, or needle under gonioscopic guidance. It is often performed with phacoemulsification to open the angle. Similar goniolenses to MIGS are used but a useful addition is the Mori goniolens, which has a lower magnification but means there is no need to tilt the head and microscope. Injection of a miotic helps to pull the iris away from the angle and viscoelastic maintains the anterior chamber deep. The chosen instrument is used to gentle peel away the adherent iris from the scleral wall to reveal the scleral spur without causing bleeding. Postoperative treatment is similar to that of other TM MIGS.

Phaco-GSL is a good option to treat PACG with concomitant cataract due to its bleb-less nature. Its capacity for lowering IOP seems superior to phacoemulsification alone and comparable to phaco-trabeculectomy in a recent meta-analysis.[1] For advanced PACG, since the TM and Schlemm's canal functions are impaired,[2] various TM MIGS and goniotomy (also call ab interno trabeculotomy) have shown early potential as add-on procedures.

Complications

- Hyphaema.
- Fibrinous uveitis.
- Iridodialysis.
- Corneal damage.
- Recurrence of PAS recurrence.

Contraindications

- Traumatic, malignant, uveitis or neovascular glaucoma.
- Discernible congenital anomalies of the anterior chamber angle.
- Cases where the PAS is known to be longstanding make be less likely to be successful.

Tips for GSL

- Proficiency with intraoperative gonioscopy is imperative.
- Postoperative management varies: miotics may help and some surgeons perform argon laser iridoplasty to maintain the angle opening.
- GSL can be performed either before or after the phacoemulsification.
- Diamox is useful postoperatively to prevent IOP spikes.

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ABBREVIATIONS

5-FU	5-Fluorouracil
ACD	Anterior chamber depth
ACG	Angle-closure glaucoma
ALS	Argon laser suture lysis
ALT	Argon laser trabeculoplasty
APGS	Asia-Pacific Glaucoma Society
CAI	Carbonic anhydrase inhibitor
CCT	Central corneal thickness
CDR	Cup-to-disc ratio
CI	Confidence interval
ECCE	Extracapsular cataract extraction
FAQ	Frequently asked questions
FDA	Food and Drug Administration
GAT	Goldmann applanation tonometry
GON	Glaucomatous optic neuropathy
ICE	Iridocorneal endothelial
IOL	Intraocular lens
IOP	Intraocular pressure
LASEK	Laser-assisted subepithelial keratectomy
LASIK	Laser in situ keratomileusis
LPI	Laser peripheral iridotomy
MMC	Mitomycin C
NA	Not applicable
Nd:YAG	Neodymium yttrium aluminum garnet
NTG	Normal-tension glaucoma
NVG	Neovascular glaucoma
OAG	Open-angle glaucoma
OCT	Optical coherence tomography
OHT	Ocular hypertension
ONH	Optic never head
PAC	Primary angle closure
PACD	Primary angle-closure disease
PACG	Primary angle-closure glaucoma
PACS	Primary angle-closure suspect
PAS	Peripheral anterior synechiae
PGA	Prostaglandin analogue
PI	Peripheral iridotomy
POAG	Primary open-angle glaucoma
PRK	Photorefractive keratectomy
PSD	Pattern standard deviation
PXF	Pseudoexfoliation
PXG	Pseudoexfoliation glaucoma
RGC	Retinal ganglion cell
RNFL	Retinal nerve fibre layer
SD	Standard deviation
SITA	Swedish Interactive Thresholding Algorithm
SLT	Selective laser trabeculoplasty
TM	Trabecular meshwork
VF	Visual field
YAG	Yttrium aluminum garnet

CONFLICT OF INTEREST

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Christopher Kai-Shun Leung
Code P (Patent): Carl Zeiss Meditec, Heidelberg Engineering; Code F (Financial Support): Carl Zeiss Meditec, Topcon, Heidelberg Engineering, Tomey; Code R (Recipient): Santen, Alcon, Janssen; Code C (Consultant/Contractor): Santen, Alcon, Janssen, AbbVie, Topcon, Carl Zeiss Meditec; Code O (Owner): AIROTA Diagnostics Limited, ACE VR Limited

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Alcon, Glaukos, Ivantis, Santen, Sun Pharma, Thea, Abbvie, Novartis, Leica

Harsha Rao
Santen (C), Abbvie (C), Viatris (C), iSTAR Medical (C)

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Alcon Laboratories, Inc.: Consultant/Advisor, Lecture Fees; Abbvie: Lecture Fees; Eye Care Box: Founder/Shareholder; Hoya: Research Grant, Lecture Fees; Johnson & Johnson: Lecture Fees; Kowa: Lecture Fees; Program Management Unit for Competitiveness (PMU-C): Research Grants; Santen: Consultant/Advisor, Lecture Fees

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NOTHING TO DISCLOSE

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KEY MESSAGES

SECTION 1: EPIDEMIOLOGY OF GLAUCOMA IN THE ASIA-PACIFIC REGION

- Glaucoma is the leading cause of irreversible visual impairment and blindness worldwide.
- Glaucoma currently affects 76 million individuals globally and an estimated 111.8 million people will be affected by 2040.
- Asia accounts for 60% of all glaucoma cases globally.
- Within Asia, East Asia has the highest prevalence of PACG, whereas South Central Asia has the highest burden of POAG.
- NTG accounts for 70–92% of POAG cases in in the Asia-Pacific region.
- Nearly 50–90% of individuals with glaucoma worldwide are undiagnosed.
- Targeting high-risk populations and implementing cost-reducing strategies can make glaucoma screening cost-effective.

SECTION 2: DIAGNOSTIC WORKUP

2.1. Intraocular pressure measurement

- GAT remains the gold standard for IOP measurement.
- One should be aware of the measurement errors associated with GAT and other types of tonometry.
- Further investigation is needed to determine whether home self-monitoring of IOP is cost-effective and leads to better clinical outcomes.

2.2. Anterior chamber angle assessment: gonioscopy versus anterior segment OCT

- Examination of the anterior chamber angle with gonioscopy is mandatory in the diagnostic workup of glaucoma.
- Gonioscopy is indispensable for assessing the pigmentation of the TM (*e.g.*, in pigment dispersion syndrome) and neovascularization of the angle (*e.g.*, in NVG).
- While angle assessment with gonioscopy can be confounded by inadvertent indentation and slit-lamp illumination, AS-OCT offers non-contact assessment of the anterior chamber angle width and iris trabecular contact in the dark.

2.3. Assessment of the optic disc, retinal nerve fibre layer, and ganglion cell-inner plexiform layer

- Clinical examination of the optic disc is essential to discriminate GON from non-GON.
- Widefield imaging with OCT covering the parapapillary region and the macula for RNFL and ganglion cell-inner plexiform layer (GCIPL) thickness measurement is more informative compared to circumpapillary RNFL thickness assessment in the diagnostic assessment and monitoring of glaucoma.
- Caution should be taken in interpreting the RNFL/GCIPL thickness deviation/probability maps in highly myopic eyes due to the increased false-positive errors. This is because the normative datasets in most OCT models contain RNFL/GCIPL thickness measurements obtained from eyes that are not highly myopic.

- Macular parameters may not be reliable for glaucoma assessment in eyes with macular disease.
- Change analysis of RNFL/GCIPL thicknesses for assessment of glaucoma progression requires event-based and trend-based analyses.
- The role of OCTA remains unclear in routine diagnostic evaluation of glaucoma.

2.4. Perimetry

- Standard automated perimetry (SAP) is usually performed using a Goldmann size III stimulus in the central 24° or 30°, although testing the central 10° is also important for patients with retinal nerve fibre layer (RNFL)/ganglion cell-inner plexiform layer (GCIPL) defects over the macula.
- Reliability indices should be checked before interpreting perimetry results.
- Test frequency should be tailored according to the stage of glaucoma and the rate of progression. Advanced glaucoma or rapid progression requires more frequent testing.
- Progression analysis of VF sensitivity requires event-based and trend-based analyses.

2.5. Risk factors for glaucoma

- Major risk factors for development of POAG include elevated IOP, small CCT, and increased age, CDR, and VF PSD.
- Risk factors for progression of glaucoma include older age, exfoliation/pseudoexfoliation, bilateral disease, higher IOP, worse VF mean deviation, small CCT, and disc haemorrhage.
- Major risk factors for progression of PACD include older age, small axial length, small ACD, and small anterior chamber angle width.

SECTION 3: MANAGEMENT APPROACH

3.1. Ocular hypertension

- The decision to treat OHT should be carefully discussed between ophthalmologist and patient after weighing the risks and benefits of treatment.
- The decision to treat OHT is suggested in patients who have higher risk of conversion to POAG, such as those with higher pre-treatment IOP, older age, thinner CCT, larger vertical CDR, and higher PSD in the VF.
- The Ocular Hypertension Treatment Study (OHTS)-European Glaucoma Prevention Study (EGPS) risk calculator serves as a good reference to categorize patients based on their risk of progressing from OHT to glaucoma.

3.2. Primary open-angle glaucoma

- Target IOP should be individualized and reviewed at every follow-up visit based on disease severity, rate of progression, and life expectancy.
- SLT is a first-line alternative to medical topical treatment in achieving optimal IOP control.

3.3. Normal-tension glaucoma

- IOP reduction is the primary objective in the treatment of NTG.
- The choices of topical IOP-lowering treatment are similar to those used to treat POAG.

3.4. Primary angle-closure disease

- Not all cases of PACS require a prophylactic LPI.
- LPI is recommended for PAC.
- Early lens extraction instead of LPI can be offered to selected patients with PACG.

3.5. Acute angle closure

- Medical therapy including topical IOP-lowering medications, acetazolamide and hyperosmotic agents constitutes the initial therapy to reduce IOP and to clear corneal oedema.
- LPI should be performed when the cornea is clear to relieve pupillary block.
- Argon laser peripheral iridoplasty (ALPI) can be attempted in cases with shallow anterior chambers or severe corneal oedema when peripheral iridotomy is detrimental to the corneal endothelium.
- Cataract/early lens extraction is the definitive management to relieve pupillary block.

3.6. Neovascular glaucoma

- The use of anti-vascular endothelial growth factor (anti-VEGF) in conjunction with panretinal photocoagulation (PRP) is recommended for control of retinal or ocular ischaemia.
- Optimizing the management of the underlying systemic disease is crucial for controlling and preventing NVG.

3.7. Uveitic glaucoma

- Effective management requires addressing both the underlying inflammation caused by uveitis and the resulting elevated IOP.
- A collaborative approach involving ophthalmologists, rheumatologists, and primary care providers is essential for successful management.

SECTION 4: MEDICAL TREATMENT

4.1. Overview of medical treatment and recommendations

- Antiglaucoma medication is a widely available and effective modality to lower IOP for most patients.
- IOP-lowering eye drops are generally considered the first-line treatment for glaucoma.
- When choosing antiglaucoma medication for a patient, ophthalmologists should consider the drug's mechanism of action, systemic risk factors, other special considerations (children, pregnant, and breastfeeding women), potential side effects, ease of eye drop application and medication adherence.

4.2. Fixed-dose combinations

- Fixed-dose combinations (FDC) simplify medication regimens, which may improve medication adherence, provide synergistic IOP reduction efficacy, and reduce medication side-effects.
- The development of preservative-free FDC would further improve the advantages.

4.3. Novel medications for glaucoma treatment

- New medications and classes of drugs have been developed recently, broadening our treatment options.
- A selective EP2 receptor agonist and Rho kinase (ROCK) inhibitors have shown comparable efficacy to currently available medication, with different side-effect profiles.

4.4. Side effects of medical therapy

- IOP-lowering eyedrops may have a wide range of side effects.
- During medical treatment for glaucoma, ophthalmologists should be attentive to ocular surface disease (OSD) and prostaglandin-associated periorbitopathy (PAP) as they can affect quality of life, IOP measurement accuracy, and success rates of future surgery.
- Closing the eyes for three minutes directly after application of the eye drops may increase their ocular efficacy and decrease their systemic side effects.

4.5. Patient adherence and drug delivery systems

- Medication adherence is critical to prevent disease progression and visual impairment.
- Ophthalmologists and patients can overestimate medication adherence, which tends to be poor.
- Adherence can be improved by identifying the barriers and addressing them strategically.
- Novel drug delivery systems may help to improve overall adherence.

SECTION 5: SURGICAL AND LASER TREATMENT

5.1. Laser treatment

- In SLT, pre-laser treatment with topical alpha-2 agonists helps reduce post-treatment IOP spikes.
- Higher baseline IOP is associated with greater IOP reduction after SLT and ALT.
- A useful tip to reduce laser power for laser iridotomy is to choose a small iris crypt or thin iris area that is located peripherally as possible.
- Peripheral iridoplasty can help to break an attack of acute angle closure as initial treatment.

5.2. Trabeculectomy

- Trabeculectomy is the most performed glaucoma filtering surgery.
- Antifibrotic agents are applied to a large surface area of subconjunctival-tenon pocket to reduce the risks of bleb fibrosis and failure.
- Postoperative care during the first 12 weeks after surgery is critical to long-term outcome in IOP control.
- MMC and 5-FU are the 2 antifibrotic agents that are used intraoperatively and postoperatively, for their effectiveness in reducing filtering bleb scar formation.
- Care must be taken after 5-FU subconjunctival and MMC injections to avoid corneal toxicity resulting in epitheliopathy and thin blebs leading to blebitis. Copious irrigation after injection is recommended.

5.3 Glaucoma drainage devices

- Non-valved glaucoma drainage devices (GDDs) result in greater postoperative hypotony than valved devices.
- Postoperative hypertensive phase is common with any shunt and may require medical therapy for management.
- Similar rates of surgical success were observed with both the valved Ahmed and non-valved Baerveldt implants at 5 years.
- Before implanting a GDD, its tube should be primed with irrigation for valve function in valve type and patency in the non-valve.

5.4. Minimally invasive glaucoma surgery

- Minimally invasive glaucoma surgery (MIGS) initially referred to ab interno devices and procedures usually targeting Schlemm's canal. However, the term has currently broadened to include ab externo bleb-forming procedures with little or no scleral dissection.
- Blood reflux from the stent or transient blanching of the episcleral vessels are indicators of correct stent placement.
- Gonioscopy should be performed postoperatively to assess stent placement and ensure no blockage.
- MIGS procedures in all forms have limited use in angle closure, given that open angles and a visible TM are necessary for performing the procedure.
- Subconjunctival MIGS devices are sometimes referred to as minimally invasive bleb-forming surgery (MIBS).

5.5. Non-penetrating glaucoma surgery

- Non-penetrating glaucoma surgery (NPGS) reduces IOP less effectively than penetrating surgery, but with lower complication rates.
- NPGS may reduce the hypotony risks of trabeculectomy in higher-risk patients, *e.g.*, high myopes, younger patients, previous vitrectomy, eye-rubbers.
- Further management with Nd:YAG goniopuncture may be required in up to 40% of surgeries to further lower the IOP in the longer term.

5.6. PHACO-GONIOSYNECHIALYSIS

- Goniosynechialysis (GSL) is often performed with phacoemulsification to open the angle.
- Phaco-GSL is a good option to treat PACG with concomitant cataract due to its bleb-less nature.

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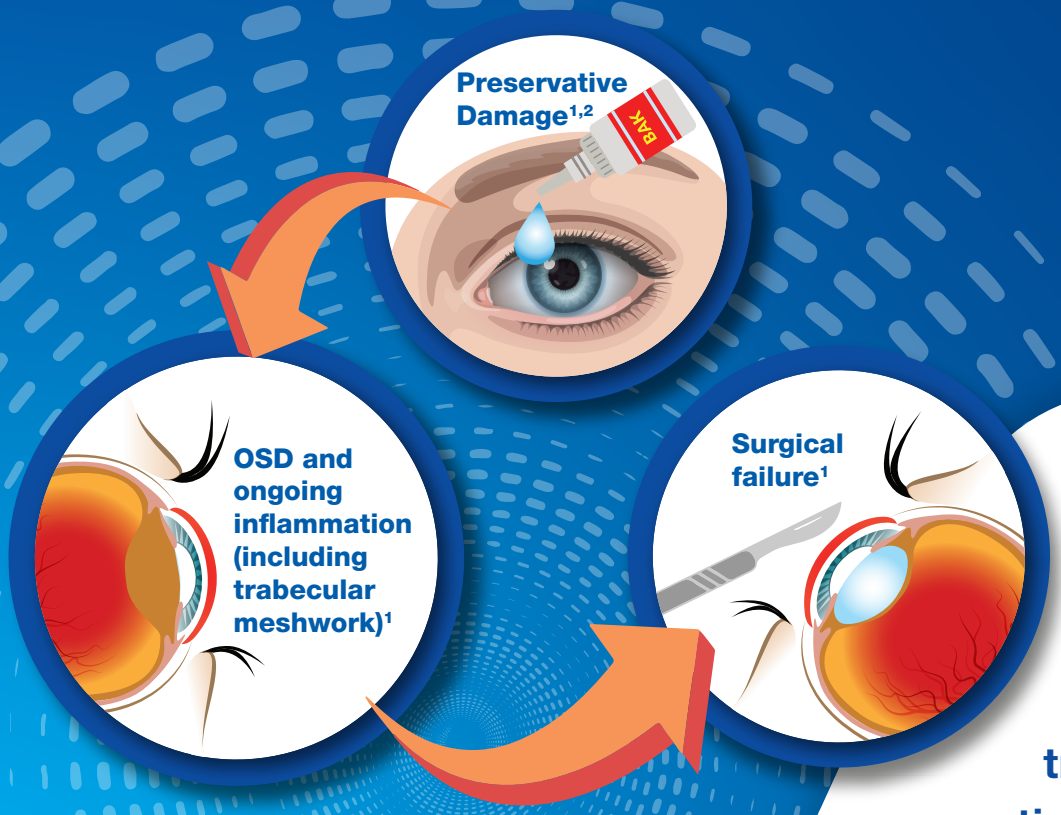

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