



## Review article

## Challenges in the management of glaucoma in developing countries



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## ABSTRACT

Glaucoma is the most common optic neuropathy characterized by normal to raised intraocular pressure (IOP), visual field defects, loss of retinal nerve fiber layer, thinning of the neuroretinal rim, and cupping of the optic disc. IOP reduction by medical, laser, or surgical therapies remains the only clinically proven treatment of glaucoma. The challenges in glaucoma management are diverse. They include early detection and diagnosis, setting of appropriate target IOP, choice of treatment, monitoring of quality of life and sight, and compliance with the treatment. Early diagnosis can be made by assessing optic nerve structure using imaging devices and optic nerve function through perimetry. Reducing IOP and controlling its fluctuations are considered to be the most important factors in limiting progression of glaucoma. Selection of the best suitable therapy out of medical, surgical, or laser treatment options is yet another management challenge. Patients suffering from glaucoma experience poor quality of life owing to the diagnosis itself, functional visual loss, inconvenience and cost of treatment, and side effects of treatment. All these factors lead to poor compliance, adherence, and persistence to treatment, and further progression of the disease. It is, therefore, important that ophthalmologists keep all the aforementioned factors in mind when managing patients with glaucoma.

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## 1. Introduction

Globally, glaucoma is the most common optic neuropathy, the second common cause of blindness, and the most common cause of preventable visual disability.<sup>1</sup> Glaucoma includes a spectrum of progressive optic neuropathies characterized by pathological degeneration of nonmyelinated retinal ganglion cells, with structural damage at the level of optic nerve head. The common pathway in the pathogenesis of glaucoma is triggering of accelerated apoptosis of the retinal ganglion cells.<sup>2</sup> As a consequence of neuronal death within the central visual pathway, clinical signs of glaucoma start appearing. These signs include retinal nerve fiber layer defects, thinning of the neuroretinal rim, and excavation of the optic nerve head, commonly called cupping of the optic disc. These structural changes lead to functional defects in the form of irreversible visual field loss.<sup>3</sup>

In the currently published literature on glaucoma, intraocular pressure (IOP) is not considered to be a part of the definition of glaucoma; however, it is the most easily modifiable risk factor to

decrease the risk of disease onset and progression.<sup>4</sup> IOP reduction by medical, laser, and surgical treatments remain the only clinically proven treatment of glaucoma.<sup>5</sup> However, Collaborative Normal Tension Glaucoma study has exemplified that lowering of IOP alone is not entirely effective for all patients of glaucoma.<sup>6</sup> In some patients, sufficient IOP reduction to slow down or arrest the disease process may be either difficult or full of adverse effects of treatment.

## 2. Magnitude and burden of the disease

According to the World Health Organization estimates of 2002, the number of people blinded by glaucoma was 4.4 million (12.3% of the blind people worldwide). The majority of those with glaucoma remain undetected, and estimates of people afflicted by glaucoma and related blindness are made on the basis of data from epidemiological studies. From these studies, it has been understood that glaucoma affects all populations, but there is a disparity in distribution. This disparity is either because of a higher prevalence and racial predilection or because of a large population in these regions resulting in a larger absolute number of persons with glaucoma.<sup>7</sup>

The type of glaucoma also varies from region to region. Primary open-angle glaucoma (POAG) is the predominant glaucoma in

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North America, Europe, and European-derived populations of Australia. The highest prevalence of glaucoma in these regions is observed in the African and Caribbean origin population in the USA and the Caribbean. A study by Quigley<sup>8</sup> among Latin Americans revealed the prevalence of glaucoma to be intermediate between those of Caucasians and black people.

Nearly half of the population with glaucoma resides in Asia, which includes the three most populous countries—China, India, and Pakistan. Prevalence surveys in Mongolia, Singapore, China, and India have observed the prevalence of primary angle closure glaucoma to be equal to that of POAG, and is similar to that of Caucasians.<sup>9</sup>

The prevalence of combined glaucoma (primary and secondary) in Tanzanian and South African studies was reported to be 5%. The predominant type of glaucoma is POAG.

The total global estimate of POAG and PACG for the year 2020 was considered to be 60.5 million and 79.6 million respectively in year 2010.

### 3. Challenges

#### 3.1. Early detection and diagnosis

The anatomical and functional changes from glaucoma are largely irreversible; therefore, early disease detection remains an important strategy to prevent visual impairment. This has been achieved by assessing optic nerve structure using imaging devices and optic nerve function through perimetry. Imaging and perimetry techniques have improved considerably, and new strategies are emerging to complement these established techniques.<sup>10</sup> These include retinal nerve fiber layer analysis and detection of retinal ganglion cells apoptosis *in vivo*. Spectral-domain optical coherence tomography in glaucoma offers the opportunity of objectively measuring the retinal nerve fiber layer and its associated changes with time. Although it can achieve a resolution of 3–6  $\mu\text{m}$ , it is dependent on establishing structural and functional relationships. The ability to detect pre-perimetry glaucoma has been a goal in clinical management of glaucoma for several decades.<sup>11</sup> A technique termed as “detection of apoptotic retinal cells” has been developed, which utilizes nonradioactive fluorescent-labeled annexin V and high-resolution imaging to enable real-time detection of apoptosis in retinal ganglion cells. The technology has been demonstrated well in animal models but has to undergo Phase I clinical trials for its safety assessment.<sup>12</sup>

#### 3.2. Setting of IOP targets

IOP has been identified as the only modifiable risk factor, and lowering of IOP to prevent progression of glaucoma is now the backbone of glaucoma management. A growing body of evidence shows that not only the mean IOP reduction is important, but also control of fluctuation of IOP plays a major role in the preservation of vision and visual fields.<sup>13</sup>

European Glaucoma Society has defined the target IOP as the mean IOP obtained with treatment that prevents further

glaucomatous damage. Formulation of the target IOP is one of the most important steps in treatment. It is generally assumed that aiming to achieve at least a 30% reduction from the initial pressure at which damage occurred is a useful arbitrary way to achieve the initial target IOP. The target IOP is the IOP range at which the clinician decides that progressive disease is unlikely to affect the patient's quality of life (QOL). Besides, the target IOP can be explained as the upper limit of a stable range of measured IOPs deemed likely to retard further optic nerve damage.<sup>14</sup>

The target IOP is determined on the basis of the following factors: amount of glaucoma damage; the IOP at which the damage has occurred; life expectancy of the patient; status of the fellow eye; and family history of glaucoma.

It is recommended that the target IOP be recorded so that it is accessible on subsequent patient visits. The target IOP is not a static value; rather, it requires periodic re-evaluations. When setting the target IOP, each eye is staged into one of four severity groups: suspect, early, moderate, or advanced glaucoma based on the following factors: assessment of the optic nerve and visual fields; patient factors especially IOP; age; life expectancy; quality of life; risk factors for progression; and patient's own input (Table 1).<sup>15</sup>

However, it should be remembered that there is a fine line between setting an appropriate goal to prevent optic nerve damage and being overly aggressive in IOP lowering.

#### 3.3. More target IOP recommendations

Stage each eye of the patient as normal, suspect, early, moderate, or advanced glaucoma based on optic nerve and (or) visual field examination.

Set the upper limit of the initial target IOP range for each eye at the first visit and then re-evaluate at each visit based on stability/change in structure and function of the optic nerve (i.e., Optic nerve head (ONH) examination with or without additional imaging information as well as visual field data). The suggested upper limit of the target IOP as described by various studies is given in Table 2.<sup>15</sup>

IOP telemetry is done through a device called telemetric strain gauge contact lens (Sensimed Triggerfish).<sup>16</sup> The device measures the changes in corneal curvature with fluctuation in IOP. Variation of 1 mmHg produces a change of central corneal curvature radius of  $\sim 3 \mu\text{m}$ . A reading of 30-second duration is taken every 5 minutes over a 24-hour period.<sup>17</sup>

### 4. Choice of treatment

The choice of treatment is multifactorial and depends on the level of IOP, fluctuation of IOP, stage of disease, pace of progression, current treatment, and past treatments. Medical, laser, and surgical treatments are available in almost all parts of the world, with variations and preferences according to local populations. All the currently available treatments are targeted toward IOP control, which is a risk factor for glaucoma but not necessarily the sole cause of disease progression. Recent exciting developments in glaucoma management address these concerns. These include the development of a new class of IOP-lowering medications known as

**Table 1**  
Classification of eyes based on severity of glaucoma.

Severity group	Characteristics
Suspect	1 or 2 of the following: IOP >21 mmHg; suspicious disc or C/D asymmetry of >0.2; suspicious 24-2 (or similar) VF defect
Early	Early glaucomatous disc features (e.g., C/D* <0.65) & (or) mild VF defect not within 10° of fixation (e.g., MD better than -6 dB on HVF 24-2)
Moderate	Moderate glaucomatous disc features (e.g., vertical C/D 0.7–0.85) & (or) moderate VF defect not within 10° of fixation (e.g., MD from -6 dB to -12 dB on HVF 24-2)
Advanced	Advanced glaucomatous disc features (e.g., C/D* >0.9) & (or) VF defect within 10° of fixation (e.g., MD worse than -12 dB on HVF 24-2)

C/D = cup-to-disk ratio; HVF = humphrey visual fields; MD = mean deviation; VF = visual field.

**Table 2**  
Target intraocular pressures based on stage of glaucoma.

Stage	Suggested upper limit of target IOP (Modified based on longevity, QOL, & risk factors for progression)	Evidence
Suspect in whom a clinical decision is made regarding treatment	24 mmHg with at least 20% reduction from baseline	OHTS EGPS
Early	20 mmHg with at least 25% reduction from baseline	EMGTS CIGTS
Moderate	17 mmHg with at least 30% reduction from baseline	CNTGS AGIS
Advanced	14 mmHg with at least 30% reduction from baseline	AGIS Odberg

AGIS = Advanced Glaucoma Intervention Study; CIGTS = Collaborative Initial Glaucoma Treatment Study; CNTGS = Collaborative Normal Tension Glaucoma Study; EGPS = European Glaucoma Prevention Study; EMGTS = Early Manifest Glaucoma Treatment Study; OHTS = Ocular Hypertension Treatment Study.

Rho-kinase inhibitors, newer and safer techniques for surgically reducing IOP, and the development of non-IOP-dependent therapies such as neuroprotection.<sup>18</sup> Brimonidine and memantine are the prototype medicines that are in clinical use for neuroprotection. The conventional treatment includes groups of drugs such as beta-blockers, prostaglandin analogues, carbonic anhydrase inhibitors, alpha agonists, and parasympathomimetics.

For longer than the past two decades, the paradigm of the drug of first choice has shifted from beta-blockers to prostaglandin analogues. In case of poor IOP control, the add-on therapy is in the form of fixed combinations of two drugs available in almost all parts of the world.

For patients who cannot tolerate medications or are inadequately controlled with medications, laser treatment continues to be an excellent alternative in the developed parts of the world. The laser may also be used as a primary treatment option in case of pre-existing ocular surface disorder. The most common laser treatment for glaucoma is argon laser trabeculoplasty. A new type of laser, called micropulse laser trabeculoplasty, is currently being studied as yet another option for effectively increasing drainage of eye fluid to lower IOP.

Trabeculectomy with or without adjuvants is still considered the procedure of first choice, especially in the developing world. Modified procedures with variable outcomes include viscocanalostomy, nonpenetrating glaucoma surgery, shunts or tube implants, collagen matrix implants, and high-frequency deep sclerectomy.

All these procedures demand specialized training, expertise, and equipment, which vary from region to region.

## 5. Quality of life and quality of sight

Patients suffering from glaucoma can lose QOL for several reasons: the diagnosis itself, functional loss, inconvenience of treatment, side effects of treatment, and cost of treatment.<sup>19</sup> Glaucoma therapy, whether medical or surgical, can directly influence a patient's QOL. Health-related QOL is an important outcome in glaucoma, and it can be measured using either generic or vision-specific instruments. Generic instruments include the Medical Outcomes Study Short Form 36, sickness impact profile, Euro QOL Health Questionnaire, and utility values among others.<sup>20</sup> The most commonly used vision-specific instrument is the 25-question version of the National Eye Institute Visual Functioning Questionnaire.

Ocular surface disease is a group of disorders that affect various components of the ocular surface tissues. It has become increasingly common with growing age.<sup>21</sup>

Glaucoma primarily affects patients in the 5<sup>th</sup>–7<sup>th</sup> decades of their lives; therefore, ocular surface disease poses an increased risk to them, and more than 50% of patients with glaucoma and receiving antiglaucoma medications have ocular surface disease in at least one eye.<sup>22</sup> This is of serious concern because ocular surface disease results in dysfunction of the ocular tear film with wide-ranging symptoms and signs, including discomfort, grittiness, burning, foreign body sensation, dryness, ulceration, and even scarring. All these symptoms and signs negatively affect the QOL of these patients.

Topical antiglaucoma medications have been associated with ocular surface disease because they are instilled as drops into the tear film, where they interact with ocular surface tissues.

This interaction can involve the active agents themselves or preservatives used to keep the bottles sterile and to stabilize the active agents in solutions. Benzalkonium chloride is a detergent-like preservative common to most antiglaucoma medications. Studies<sup>23,24</sup> have shown that benzalkonium chloride can damage corneal and conjunctival epithelial cells and decrease conjunctival goblet cell density, thereby reducing tear film stability and promoting dry eye.

Since antiglaucoma treatment is long term and often involves multiple medical therapies, the potential for adverse interactions increases with time. The negative effect of dry eye on QOL cannot be overestimated. The reasons for nonadherence to treatment regimens are multifactorial, but they at least partly depend on discomfort of the eyes.<sup>25</sup>

## 6. Compliance, adherence, and persistence

Traditionally, compliance has been defined as the extent to which patients' behavior corresponds to physician's recommendations.<sup>26</sup> However, in recent literature, the term compliance has been replaced by adherence and persistence. Adherence is the measure of the degree to which a patient follows prescribed instructions during a defined time period, and persistence, by contrast, is a criterion that evaluates the time until the patient first discontinues the use of medications.

Patients routinely overestimate their adherence to eye drops. In fact, 95% of patients claimed in one study (Glaucoma Adherence and Persistency Study)<sup>27–30</sup> that they never missed taking drops, despite clear evidence that adherence of these patients was dramatically lower.

Persistence with glaucoma medications has been found to be low in several studies, varying from 20% to 64%.<sup>31</sup> Glaucoma suspects beginning latanoprost or a beta-blocker drop had persistency rates of 39% and 25%, respectively, at 1 year.<sup>32</sup>

Clinical implications of nonadherence and nonpersistence are serious. Determining, maintaining, and adjusting a target pressure range for patients are important in glaucoma care. A patient who resumes medication shortly before an office visit after a gap in therapy may appear to have an optimal pressure, yet visual field progression may have occurred. In this situation, it becomes impossible to decide whether the pressure goal needs to be further lowered or whether the pressure goal is appropriate but the patient is progressing because of nonadherence to therapy, as the IOP is above the goal for the period of nonadherence.

Medications work only for patients who take them.<sup>33</sup> Glaucoma patients may have variable clinical courses of the disease itself, which this is further confounded by improper or irregular medication use. Greater awareness among physicians of the widespread nature of nonadherence is a very important component of patient care.<sup>34</sup>

There are certain ways by which patients' compliance can be improved. The most important of them appears to be good

counseling of patients and their families regarding the nature of the disease, and an explanation of the role and importance of the medications advised. It is equally important to simplify the prescribed regimen by giving fixed combinations wherever possible, to limit the number of eye drops being used by the patient. If a patient admits that the cause of poor compliance is the cost of the medicine, then the treating physician should consider prescribing equally efficacious drugs with a lower cost or consider surgical or laser treatment for the patient.

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