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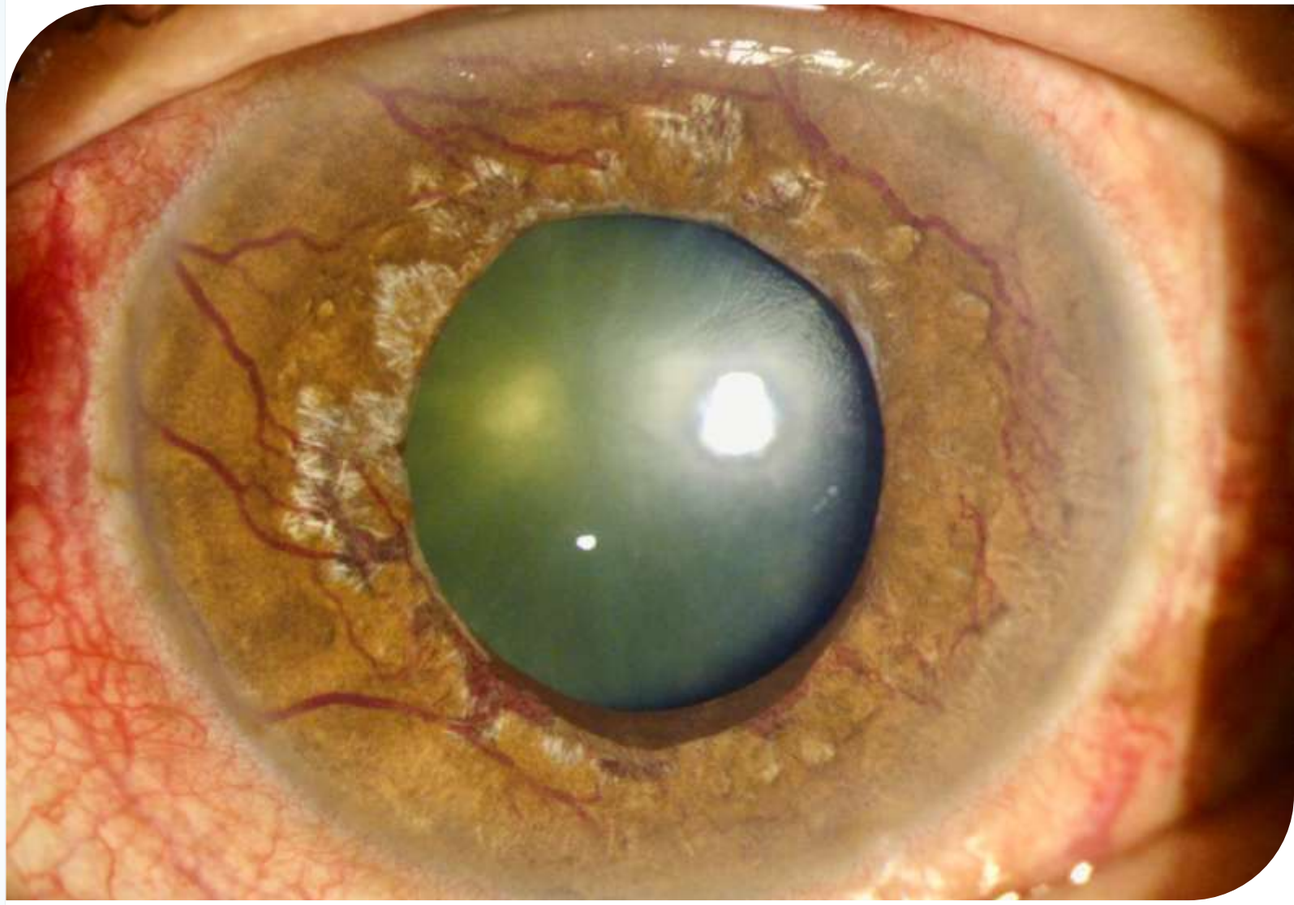

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FROM DARKNESS TO LIGHT

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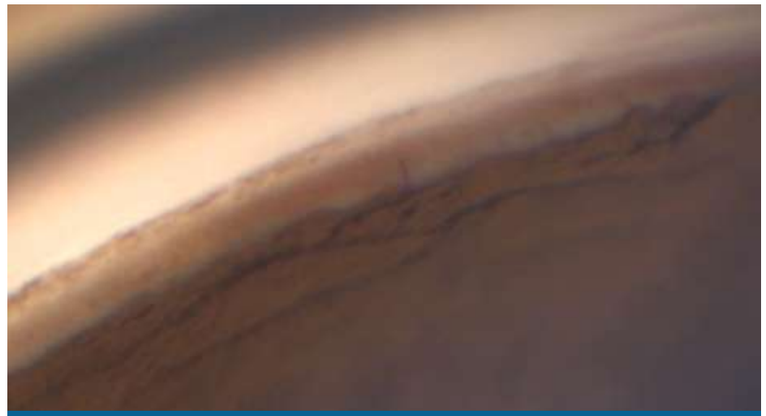

NEOVASCULAR GLAUCOMA

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Foreword

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Neovascular glaucoma remains one of the most challenging entities encountered by ophthalmologists with a high risk of vision threatening complications. These patients are often difficult to treat with multiple ocular and systemic issues and get referred from one hospital to another for the appropriate treatment. There is also an issue of treating glaucoma first or treating the retinal issues first and one often sees a tug of war between the glaucoma and retina surgeons.

There is an unmet need for standardization of medical, laser and surgical protocols for management of Neovascular glaucoma. The scientific committee of the All India Ophthalmological Society has taken this unique initiative to produce a manual on diagnosis and management of this dreaded disease with the top glaucoma and retina specialists of the country. I would like to thank Prof. Tanuj Dada & Dr. Saurabh Verma from RP Centre AIIMS, New Delhi and Dr. Vivek Dave & Dr. Sirisha Senthil from LV Prasad Eye Institute Hyderabad who have jointly undertaken the daunting task of producing this manual on Neovascular glaucoma with current practice patterns including surgical videos to facilitate video assisted skill transfer.

I am sure that this training module will help both trainee and practising ophthalmologists in better management of these difficult cases , improve the standard of care and help in alleviating blindness caused by Neovascular glaucoma through timely diagnosis and appropriate treatment strategies .

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Neovascular Glaucoma: Urgency, Coordination, and the Imperative of Early Intervention

Neovascular glaucoma (NVG) remains among the most devastating entities in contemporary ophthalmic practice. Its course is often rapid, presentation late, and visual consequences irreversible if not addressed promptly. Despite advances in medical and surgical therapy, NVG continues to test clinical judgment, interdisciplinary coordination, and health system responsiveness.

The disease is fundamentally ischemia-driven. Proliferative diabetic retinopathy, central retinal vascular occlusions, and ocular ischemic syndrome remain its principal antecedents. Retinal hypoxia stimulates vascular endothelial growth factor (VEGF) production, triggering neovascularization of the iris and anterior chamber angle. What begins as subtle neovascularization of the iris (NVI) or angle (NVA) progresses inexorably to fibrovascular membrane formation, synechial angle closure, uncontrolled intraocular pressure (IOP), and ultimately glaucomatous optic neuropathy.

The window for intervention is narrow. Early NVG is frequently under-recognized, particularly in patients with diabetes or vascular disease who present with asymmetric IOP elevation. Careful undilated slit-lamp evaluation of the pupillary margin and meticulous gonioscopy are not optional refinements—they are diagnostic imperatives. Yet, in many tertiary care settings, patients present only after synechial closure and severe IOP elevation have already occurred, underscoring persistent gaps in early detection and referral pathways.

Management of NVG rests on three interdependent pillars. First, the ischemic drive must be extinguished through timely anti-VEGF therapy and panretinal photocoagulation (PRP). Second, IOP must be controlled—initially medically, and surgically when necessary. Third, systemic disease must be aggressively optimized in collaboration with endocrinologists, cardiologists, and vascular specialists. NVG is not merely an ocular disorder; it is a manifestation of systemic vascular compromise.

In cases where media opacity precludes PRP, pars plana vitrectomy with endolaser provides an effective alternative, with adjunctive cyclodestructive procedures when indicated. Definitive glaucoma surgery—whether trabeculectomy augmented with mitomycin C or implantation of a glaucoma drainage device—should ideally be undertaken in a quiet eye after adequate retinal ablation and control of inflammation. Timing, in NVG, is not a technical detail but a determinant of outcome.

Equally important is vigilance toward the fellow eye, which may independently require prophylactic or therapeutic intervention. The systemic milieu that gives rise to NVG rarely confines itself to one eye.

Therapeutic decision-making must also remain individualized. Hyperosmotic agents such as glycerol are best avoided in diabetics, and carbonic anhydrase inhibitors used judiciously in those with renal compromise. Such considerations reinforce the necessity of interdisciplinary care.

Ultimately, preventing blindness in NVG depends not only on surgical expertise but on coordination, anticipation, and patient engagement. Education regarding systemic control, realistic visual expectations, and the risk to the fellow eye is central to comprehensive care. Lifestyle modification, metabolic optimization, and sustained follow-up are not adjuncts—they are integral to management.

This module synthesizes current concepts and collective clinical experience in glaucoma and retinal practice. Its purpose is not merely to review established strategies, but to reinforce an essential message: NVG demands urgency, collaboration, and decisive intervention. Where these converge, vision can still be preserved.

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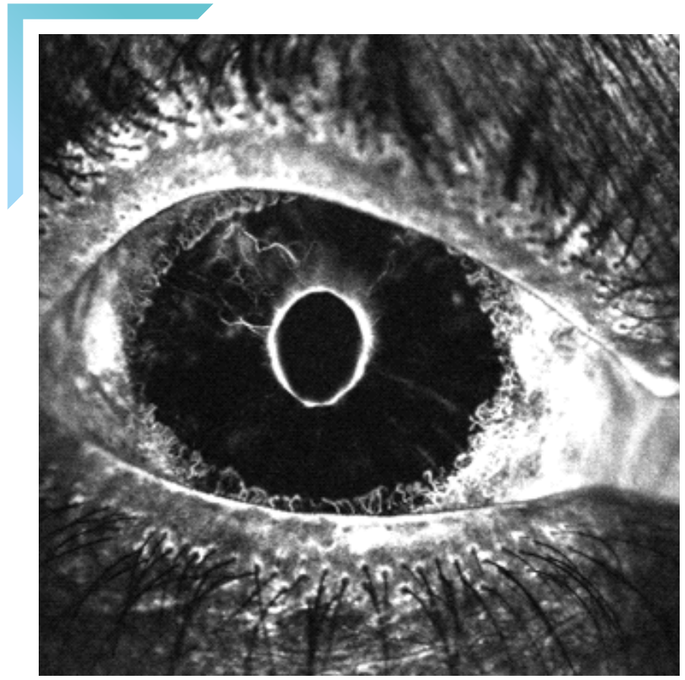
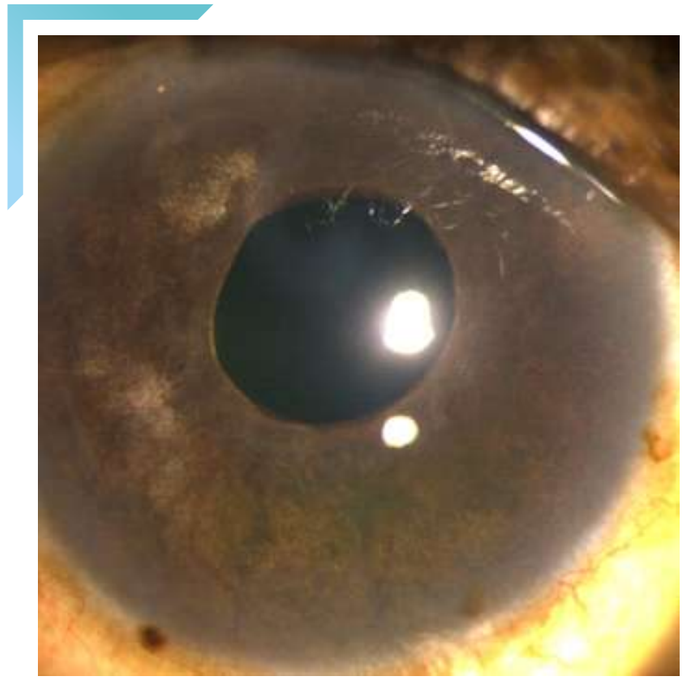
Index- Neovascular Glaucoma (NVG)





1 INTRODUCTION

Neovascular glaucoma (NVG) is an uncommon and aggressive form of glaucoma, characterized by the growth and proliferation of abnormal new blood vessels (neovascularization) on the iris (NVI) and in the angle (NVA) of the anterior chamber, consequently leading to progressive elevation of the intraocular pressure (IOP) and optic nerve damage.[1] It is a secondary glaucoma which causes a disruption in the balance between pro (e.g. antiVEGF) and anti-angiogenic factors, with the subsequent growth of new vessels in the anterior segment.[2]

1.1 Historical perspective.

Coats was the first to report new vessels on the iris in a patient with central retinal vein occlusion in 1906, terming it as rubeosis iridis. It has historically been called by various names such as hemorrhagic glaucoma, thrombotic glaucoma, congestive glaucoma, rubeotic glaucoma, and diabetic haemorrhagic glaucoma. The terminology NVG was coined much later, by Weiss et al in 1963.[3]

1.2 Epidemiology and global burden.

NVG has a relatively low prevalence, with studies quoting up to 0.12% in migrant Indians in Singapore and 0.01% in the Hooghly River Study (West Bengal, India). Among secondary glaucoma, the proportion of eyes with NVG is attributed to around 9–17.4%. However, it is a significant contributor to visual loss and morbidity amongst secondary glaucomas.[3] According to a metanalysis published in Lancet in 2022, about 3 million people in India are effected by vision threatening diabetic retinopathy.[4] The current trends demonstrate that prevalence of diabetes in the population is expected to rise rapidly, leading to an increase in the incidence of complications such as NVG.

1.3 Clinical relevance and challenges in management.

NVG is a vision-threatening condition with rapid progression, often reflecting severe underlying retinal or carotid ischemia, making early recognition critical for visual prognosis. Management is challenging due to aggressive disease process and the need to simultaneously control the ischemic drive (via retinal ablation/anti-VEGF) and the refractory IOP.

This module aims to give an in depth view of the current understanding of NVG, its management and prognosis in various scenarios, recent advances and possible future directions for improving functional outcomes in patients with this otherwise unforgiving disease. Management requires a co-ordinated team effort between retina and glaucoma specialists based on fundamental principles that are outlined in this manual. The underlying cause of NVG is often related to a systemic disease which must also be addressed to protect the fellow eye and improve the overall health related quality of life.

2 ETIOPATHOGENESIS

1.1 Role of retinal ischemia and angiogenic factors

The primary event in the pathogenesis of NVG is retinal ischemia, which disrupts angiogenic balance, triggering pathological angiogenesis. Key pro-angiogenic factors include VEGF, hepatocyte growth factor, insulin-like growth factor, tumor necrosis factor, and inflammatory cytokines such as IL-6, whereas inhibitory mediators include pigment epithelium–derived factor, TGF-β, thrombospondin, and somatostatin.

VEGF, produced by multiple retinal cells as well as the nonpigmented ciliary epithelium, is the principal driver, promoting endothelial proliferation, migration, increased vascular permeability, leukocyte adhesion, and breakdown of the blood–retinal barrier. TGF-β contributes by stimulating fibroblast proliferation and fibrovascular membrane formation.[3]

2.2 Common causative conditions

Proliferative diabetic retinopathy (PDR) is the most common cause of NVG, accounting for about 30% of all cases.[5] Other important causes are Ocular ischemic syndrome(OIS) and ischemic central retinal vein occlusion (CRVO). Without timely intervention and treatment, up to 65% of eyes with PDR, 68% cases of OIS, and 40% to 45% cases of ischemic CRVO can develop NVG.[5]

a) Proliferative diabetic retinopathy (PDR):

Diabetes mellitus, leading to PDR, is the most common cause of NVG (Figure 1). The risk of NVG is strongly correlated to longer disease duration. The risk of NVG can increase in some cases after vitrectomy and/or lensectomy in diabetic eyes, due to enhanced diffusion of vasoproliferative factors to the anterior segment. The presence of rubeosis iridis in non-proliferative diabetic retinopathy without marked retinal ischemia should arouse suspicion for coexisting pathology such as OIS.[6]

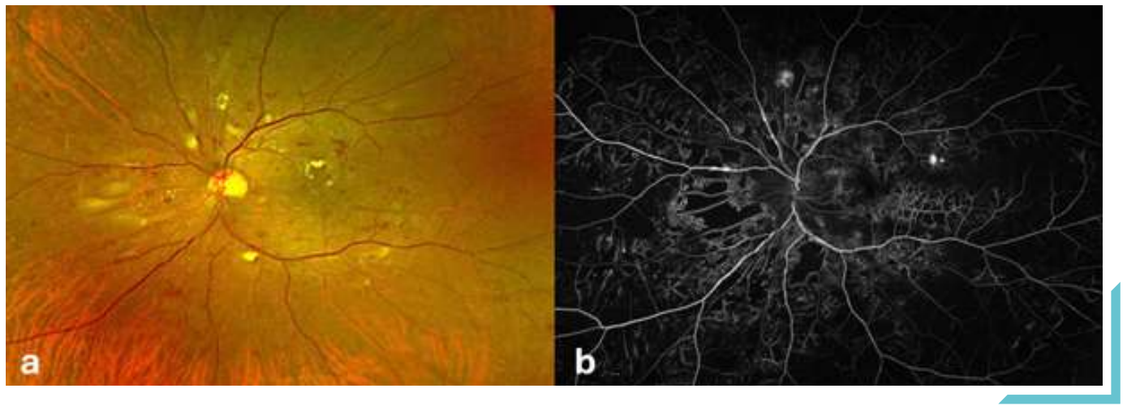


Figure 1-(a) Ultrawide field image of fundus showing hard exudates, soft exudates, blot haemorrhages and NVEs suggestive of PDR. (b) FFA highlights leakage from NVEs and extensive CNP areas.

b) Central retinal vein occlusion (CRVO):

NVG usually occurs in ischemic vein occlusions. It typically manifests 8–15 weeks after CRVO, giving rise to the term “90-day glaucoma”. In non-ischemic CRVO, NVG can develop in 10% of patients, usually with coexisting diabetic retinopathy or OIS. The cumulative incidence of NVG in untreated ischemic CRVO is approximately 40–45%. Approximately 30% of non-ischemic CRVO can convert to the ischemic form, particularly in the presence of extensive intraretinal hemorrhages.[6]

c) Ocular ischemic syndrome (OIS):

OIS represents a range of clinical manifestations caused by chronic ocular hypoperfusion, most commonly due to carotid artery occlusive disease, and is the third leading cause of NVG. Carotid atherosclerosis is the prime underlying pathology. Collateral circulation between the internal and external carotid vessels often limits the development of critical retinal ischemia. In eyes that develop OIS, retrobulbar blood flow is reduced with reversal of flow in the ophthalmic artery. Some eyes may present with paradoxically low or normal IOP despite advanced angle closure due to ciliary body ischemia and reduced aqueous production- which rapidly progresses to NVG with correction of carotid perfusion, a finding that strongly suggests carotid occlusive disease.[6]

d) Post-Traumatic NVG

Post-traumatic NVG stands as a unique clinical challenge because of mixed mechanism of ischemic triggers and mechanical structural damage. The pathogenesis of post traumatic NVG is outlined in the flow chart (Figure 2).

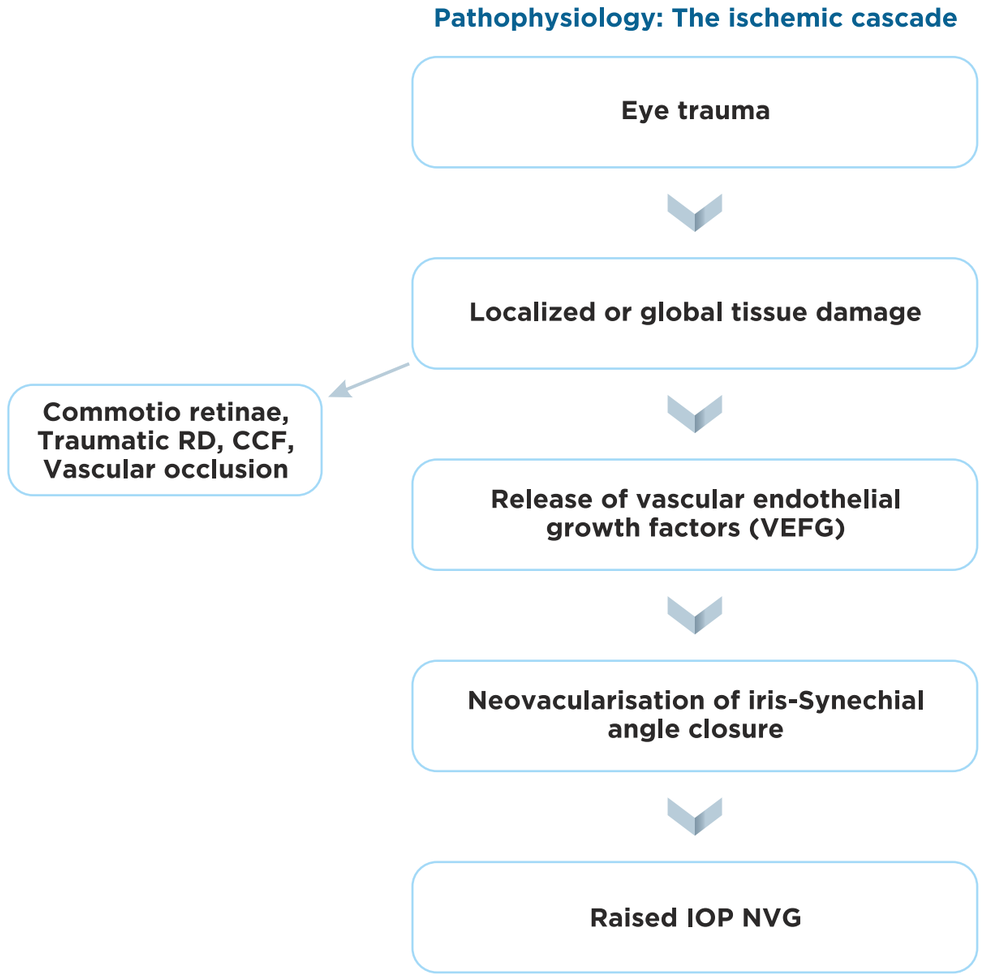


Figure 2: Flow chart highlighting the pathogenesis of post traumatic NVG

In those with severe trauma (like globe rupture or commotio) there occurs direct retinal hypoxia, triggering a rapid VEGF surge faster than chronic diabetes.

Specific to post- traumatic cases, ischemia results from:

- Commotio Retinae: Severe blunt trauma causing permanent damage to the outer retinal layers.
- Traumatic Retinal Detachment: Chronic detachment leads to hypoxia of the peripheral retina.
- Carotid-Cavernous Fistula (CCF): Trauma-induced fistulas increase episcleral venous pressure and decrease arterial perfusion, leading to global ocular ischemia.
- Vascular Occlusion: Direct trauma to the globe can cause traumatic central retinal vein occlusion or ophthalmic artery occlusion.

Diagnostic Challenges in Trauma: Evaluating a traumatized eye for NVG could be challenging due to the following conditions:

- Hyphema: Blood in the anterior chamber can obscure the view of rubeosis iridis.
- Corneal Edema/Scars: Limits the clarity of gonioscopy.
- Lens Subluxation: Can cause secondary angle closure that mimics or exacerbates NVG.

Gonioscopy is the gold standard for diagnosis. In the early stages, new vessels cross the ciliary body band and scleral spur, branching onto the trabecular meshwork in an arborizing pattern.

Trauma cases are unique because they often present with angle recession or cyclodialysis alongside neovascularization, complicating the gonioscopy assessment.

e) Special Situations

NVG in a child may rarely mask an underlying intraocular malignancy such as retinoblastoma, which must be excluded before any intraocular intervention. Advanced Coats disease may occasionally present with bullous exudative retinal detachment and NVG; globe salvage may be possible with external subretinal fluid drainage, intravitreal anti-VEGF, and subsequent laser or cryotherapy despite poor visual prognosis. Untreated advanced retinopathy of prematurity can also present with NVG and may require intracameral anti-VEGF followed by lensectomy and vitrectomy. NVG occurring after vitreoretinal surgery for PDR reflects ongoing retinal ischemia and should prompt intravitreal anti-VEGF therapy, prompt ablation of untreated ischemic retina, and evaluation for collateral causes such as OIS.

Recently long standing angle closure glaucoma has also been implicated in development of NVI and subsequent NVG. It is suggested that chronically elevated IOP can result in peripheral retinal ischemia resulting in increased production of VEGF and subsequent NVI formation.[7]

The various causes of NVG are listed in the table 1.

Table 1: Causes of NVG

Ischemic Causes	Inflammatory Causes	Ocular Tumors	Other Causes
Proliferative Diabetic Retinopathy	Post trauma	Retinoblastoma	Chronic Retinal Detachment
Retinal Vascular Occlusions	Uveitis	Iris/Choroidal Melanoma	Post vitrectomised eyes
Ocular Ischemic Syndrome	Retinal Vasculitis	Intraocular metastasis	Aphakia, Pseudophakia after eventful surgery
Radiation Retinopathy	Eales Disease	Medulloepithelioma	Neurofibromatosis
Sickle Cell Retinopathy	Endophthalmitis	Vasoproliferative Tumors of the retina	Sturge Weber Syndrome
Retinopathy of Prematurity	Sarcoidosis	Juvenile xanthogranuloma	Von Hippel Lindau Disease
Familial Exudative Vitreoretinopathy	Sympathetic Ophthalmitis		Primary Angle Closure Glaucoma
Persistent Hyperplastic Primary Vitreous			

3 CLINICAL FEATURES AND EVALUATION

3.1 Slit lamp examination and gonioscopy (table 2)

Slit-lamp biomicroscopy, along with meticulous gonioscopy, remains fundamental to the diagnosis and staging of NVG. Early identification of anterior segment neovascularization is critical, as timely intervention prior to synechial angle closure may significantly influence both IOP control and visual outcome.

The earliest clinically appreciable finding of anterior segment ischemia occurs at the level of the iris. In the prerubeotic stage, fluorescein angiography may reveal leakage from neovessels at the pupillary margin even in the absence of obvious neovascularization on slit-lamp examination. Once clinically evident, NVI most commonly originate at the pupillary ruff, although proliferation may occasionally arise from prior laser iridotomy sites.

On biomicroscopy, iris neovessels appear as fine, tortuous, irregular vascular channels distributed over the anterior iris surface.(Figure 3) Their disorganized orientation distinguishes them from normal radial iris vasculature embedded within the stroma. Early NVI may manifest as subtle vascular tufts and can be easily overlooked unless specifically sought. With progression, these vessels proliferate circumferentially, forming arborizing vascular networks that extend across the iris surface. Continued fibrovascular proliferation can lead to attenuation of normal iris architecture, stromal atrophy, pupillary distortion, and ectropion uveae as contractile membranes mature. (Figure 4,5)

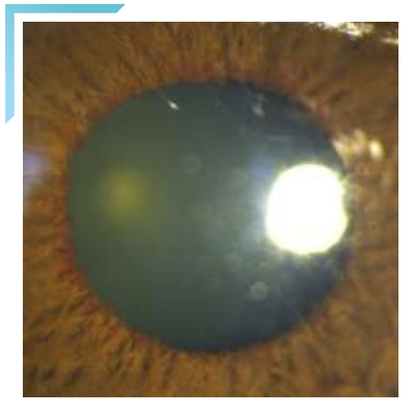


Figure 3- NVI along pupillary margin

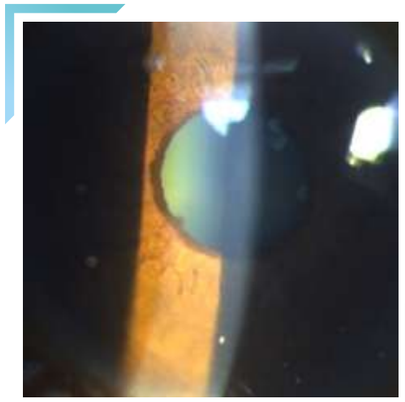


Figure 4- NVI with ectropion uvea

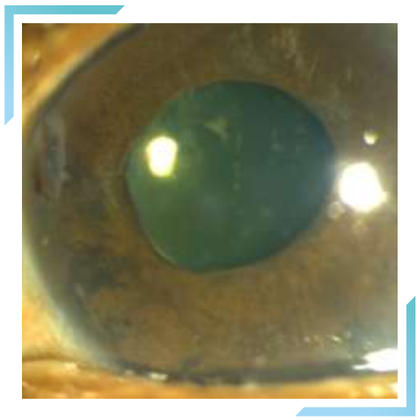


Figure 5- NVG with stromal atrophy secondary to raised IOP.

Gonioscopy is indispensable for detecting NVA, which may occasionally precede clinically evident iris involvement. Angle neovessels traverse the scleral spur and arborize over the trabecular meshwork, forming a fibrovascular scaffold that progressively obstructs aqueous outflow. Subsequent membrane contraction results in peripheral anterior synechiae, producing permanent synechial angle closure that advances in a circumferential “zipper-like” pattern. The extent of closure correlates with the severity of disease.

Associated anterior segment findings include markedly elevated IOP, often exceeding 40 mm Hg, corneal edema (Figure 6,7), conjunctival congestion, anterior chamber inflammation, and hyphema. Advanced disease may demonstrate relative afferent pupillary defect reflecting optic nerve compromise. Adjunctive imaging modalities such as iris fluorescein angiography and anterior segment OCT angiography may facilitate detection of subclinical neovascularization in high-risk eyes.

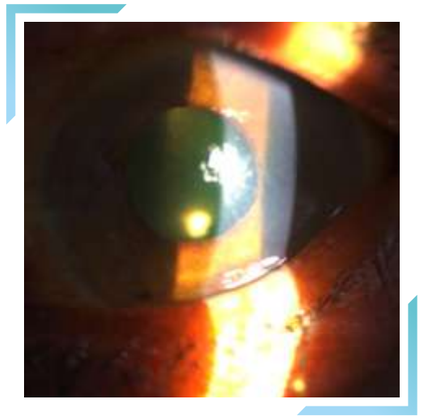


Figure 6- NVG showing NVI with corneal edema.

Figure 7- Corneal edema with ectropion uvea in NVG.

Ocular Test	What to evaluate
Slit lamp examination	• Slit lamp examination under high magnification and bright illumination in an undilated eye to identify NVI, especially at the pupillary border or margins of any pre existing iridectomy. • Ectropion uveae • Anterior chamber cells and flare • Microcystic corneal edema in NVG eyes with high IOP
Intraocular pressure	• IOP with preferably applanation tonometer
Gonioscopy Fundus examination	• Neovascularization of angle • Peripheral anterior synechiae • In a small proportion of eyes, NVA may precede NVI • Dilated fundus examination to identify the cause of the ischemia

Table 2: Showing the ocular examination required in eyes with NVG.

3.2 Retinal findings in NVG

a) Diabetic retinopathy

- Typical findings include intraretinal hemorrhages, cotton wool spots, hard exudates and neovascularization of the disc or elsewhere in the retina.

b) Central retinal vein occlusion (CRVO)

- CRVO features include intraretinal hemorrhages, cotton wool spots, venous dilation, and neovascularization of the disc or elsewhere in the retina (Figure 2-2).

c) Ocular Ischemic Syndrome (OIS)

- Mid peripheral haemorrhages with presence of vascular tortuosity without any dilation is noted in OIS.

d) Inflammatory diseases of the eye

- One may find cells or keratic precipitates in the anterior segment. Posterior segment can have vitritis or vascular sheathing with disc edema and intraretinal hemorrhages.

e) Radiation therapy

- Radiation retinopathy is a predictable dose dependent complication following radiation exposure especially brachytherapy for treatment of malignancies.
- Fundus features include retinal microaneurysms, hemorrhages, telangiectatic vessels, hard exudates, macular edema, cotton wool spots and retinal neovascularization. Vitreous hemorrhage and retinal detachment can be seen in later stages.

f) Ocular Tumours

- Retinoblastoma is a common primary intraocular malignancy of childhood that usually presents with leukocoria. It can present with variable features include strabismus, proptosis and NVG.
- Choroidal melanoma usually presents with elevated dome-shaped grey lesion of the choroid with irregular margins not sharply demarcated.

3.3 Systemic Investigations in Neovascular Glaucoma

The objectives of systemic investigations include identification of the ischemic stimulus responsible for neovascularization, detection of associated systemic vascular risk factors, and prevention of involvement of the fellow eye. The basic checklist of recommended investigations according to suspected underlying etiologies is summarized in Table 3.

Hypertension and diabetes mellitus are the most common systemic associations and should be assessed in all patients through blood pressure monitoring and evaluation of glycemic status using blood sugar levels and HbA1c. Poor systemic control contributes significantly to retinal ischemia and progression of proliferative retinopathy.

Evaluation for OIS due to carotid occlusive disease is particularly important in elderly patients, unilateral NVG, or cases where retinal findings appear disproportionate to the severity of retinopathy. Carotid Doppler ultrasonography serves as the first-line imaging modality. Color Doppler imaging of retrobulbar vessels may demonstrate dampened distal flow, and reversal of ophthalmic artery flow is highly suggestive of severe ipsilateral internal carotid artery stenosis or occlusion. Duplex ultrasound further allows quantification of stenosis using peak systolic velocity measurements. Magnetic resonance angiography and computed tomographic angiography are non-invasive imaging modalities which can confirm carotid stenosis or occlusion with high sensitivity and specificity. Intra-arterial digital subtraction angiography remains the gold standard for cerebrovascular imaging, however, it is reserved for doubtful cases or pre-interventional planning due to its invasive nature.

CT scan, MRI, MR venography, or PET imaging may be required in atypical presentations when clinically carotid cavernous fistula, orbital tumors, or metastatic disease are suspected. Younger individuals or those presenting with retinal vasculitis or uveitis with NVG- inflammatory infectious, and hematological disorders should be considered. Autoimmune screening, inflammatory markers, and hematological investigations help exclude vasculitis, hyperviscosity syndromes, and blood dyscrasias. Ancillary investigations may also be required to rule out tuberculosis, sarcoidosis, or other granulomatous diseases when clinically indicated.

A multidisciplinary approach involving physicians, diabetologists, cardiologists, and neurologists is often necessary. Early systemic diagnosis and management improve ocular prognosis and reduce the risk of serious systemic vascular complications.

Systemic Condition / Suspected Cause	Recommended Investigations	Purpose / Key Findings
Hypertension	Blood pressure measurement	Detect uncontrolled hypertension and vascular risk factors.
Diabetes Mellitus	Blood sugar (FBS/PPBS), HbA1c	Assess glycemic control and risk of proliferative diabetic retinopathy.
Ocular Ischemic Syndrome (Carotid Occlusive Disease)	Carotid Doppler ultrasound (retrobulbar, intra- and extracranial vessels)	Detect carotid artery stenosis or occlusion. Reversed ophthalmic artery flow suggests severe ICA stenosis.
	Colour Doppler imaging	Demonstrates dampened distal flow and reversed OA flow pattern.
	Carotid duplex ultrasound	Measures PSV, EDV, ICA/CCA PSV ratio to quantify stenosis severity.
	MR angiography (MRA) / CT angiography (CTA)	Confirm significant stenosis or occlusion; high sensitivity and specificity.
	Digital subtraction angiography (DSA) (selective use)	Gold standard imaging; reserved for doubtful or interventional cases due to complications.
Carotid Cavernous Fistula / Tumor Metastasis	CT scan, MRI orbit/ brain, MR venogram, PET scan	Detect fistula, orbital or intracranial tumors, and vascular abnormalities.
Uveitis / Retinal Vasculitis	HLA-B27, ANA, ESR, CRP, VDRL	Identify autoimmune or inflammatory causes.
Blood Dyscrasias / Hyperviscosity Syndromes	Hemogram, ESR, CRP, serum protein electrophoresis, immunoelectrophoresis	Detect leukemia, polycythemia, myeloma, or hyperviscosity states.
Infectious or Granulomatous Disease (TB, Sarcoidosis)	Ancillary investigations (Chest imaging, TB screening, serum ACE levels)	Rule out tuberculosis, sarcoidosis, and systemic granulomatous disease.

Table 3- Possible systemic investigations in a case of NVG

4 STAGING AND MECHANISM OF GLAUCOMA

The transition from a predominantly vascular process to a fibrotic one represents the critical turning point in NVG pathogenesis. While neovascularization alone may regress following appropriate treatment, fibrotic sequelae; particularly peripheral anterior synechiae; are largely irreversible and support the clinical staging of the disease.[8,9] Patients can present with ectropion uvea and hyphema.

The **pre-rubeosis stage (Stage 0)** represents the earliest phase in the pathogenesis of NVG and is defined by significant retinal ischemia in the absence of clinically evident anterior segment neovascularization. On slit-lamp examination, the anterior segment appears normal, with no evidence of iris or angle neovascularization, and IOP remains normal. Gonioscopy demonstrates open angles without abnormal vascularization.

In contrast, posterior segment examination and angiographic imaging reveal extensive retinal non-perfusion.[10,11]

Although clinically occult, this stage is biologically active and characterized by elevated intraocular levels of VEGF, reflecting the underlying ischemia. Persistent retinal hypoxia, if unaddressed leads to progressive upregulation of angiogenic mediators and subsequent neovascularization of the iris and angle.

Fluorescein angiography (FA) has traditionally served as the reference standard for detecting retinal ischemia in this stage, enabling dynamic visualization of capillary non-perfusion (CNP) and delayed arteriovenous transit. However, wide-field optical coherence tomography angiography has emerged as a valuable, noninvasive modality that provides depth-resolved, quantitative assessment of retinal microvasculature.

Importantly, stage 0 represents a crucial window for intervention, as timely treatment of the underlying retinal ischemia, most commonly with panretinal photocoagulation and/or intravitreal anti-VEGF therapy can significantly reduce the risk of progression and may prevent the development of overt NVG.[8,3]

Staging of NVG:

Stage 1: Neovascularization of the Iris (Rubeosis Iridis)

Stage 1 represents the earliest clinically apparent phase of NVG. Slit-lamp examination reveals fine, radially oriented neovascular tufts at the pupillary margin, which may extend across the iris surface and into the anterior chamber angle with disease progression. Gonioscopy typically demonstrates fine abnormal new vessels extending across the scleral spur and over the trabecular meshwork, while the angle remains anatomically open (Figure 8a). Intraocular pressure is usually normal or mildly elevated, and patients are frequently asymptomatic at this stage.

Analogous to the role of posterior segment imaging in Stage 0, anterior segment imaging plays an increasingly important role in the detection and characterization of early neovascularization in Stage 1. Anterior segment optical coherence tomography (AS-OCT) can identify subtle hyperreflective fibrovascular tissue along the iris surface or within the angle that may precede overt gonioscopy findings. Anterior segment OCT angiography (AS-OCTA) further enables non-invasive, depth-resolved visualization of abnormal iris and angle microvasculature.

As in Stage 0, this stage represents a critical therapeutic window. Prompt suppression of neovascular activity with intravitreal anti-VEGF therapy, combined with definitive reduction of the ischemic drive through pan retinal photocoagulation (PRP), can induce regression of iris and angle neovascularization and prevent progression to irreversible angle closure and glaucomatous damage.[8,9,12]

Stage2: Open-Angle NVG

Stage 2 is defined by sustained elevation of IOP due to **fibrovascular obstruction of the trabecular meshwork**, while the angle remains open. Persistent neovascularization of the iris and angle is accompanied by the formation of a **thin fibrovascular membrane** covering the trabecular meshwork, which functionally impairs aqueous outflow (Figure 8b). Clinically, IOP is often moderately to markedly elevated, and early corneal epithelial edema may be present. Progressive glaucomatous optic neuropathy can develop rapidly if pressure elevation is not controlled, even though gonioscopy may still demonstrate an open angle.[8]

Patients may experience ocular discomfort, a sense of pressure or heaviness, blurred vision, and halos around lights, reflecting rising IOP and corneal edema. Stage 2 represents the transition from a purely angiogenic process to a combined vascular-fibrotic pathology. Although synechial angle closure has not yet occurred, the risk of rapid progression is substantial, and medical therapy alone is frequently insufficient. Effective management therefore requires both IOP control and treatment of the underlying retinal ischemia to suppress ongoing VEGF-driven neovascularization.[8,9,13]

Imaging correlation:

- Anterior segment OCT/OCTA can detect fibrovascular membrane formation over the trabecular meshwork and early compromise of aqueous outflow pathways before synechial closure is visible.
- OCTA may reveal persistent flow in abnormal angle vessels, which can serve as a biomarker for disease activity and help monitor response to anti-VEGF therapy.

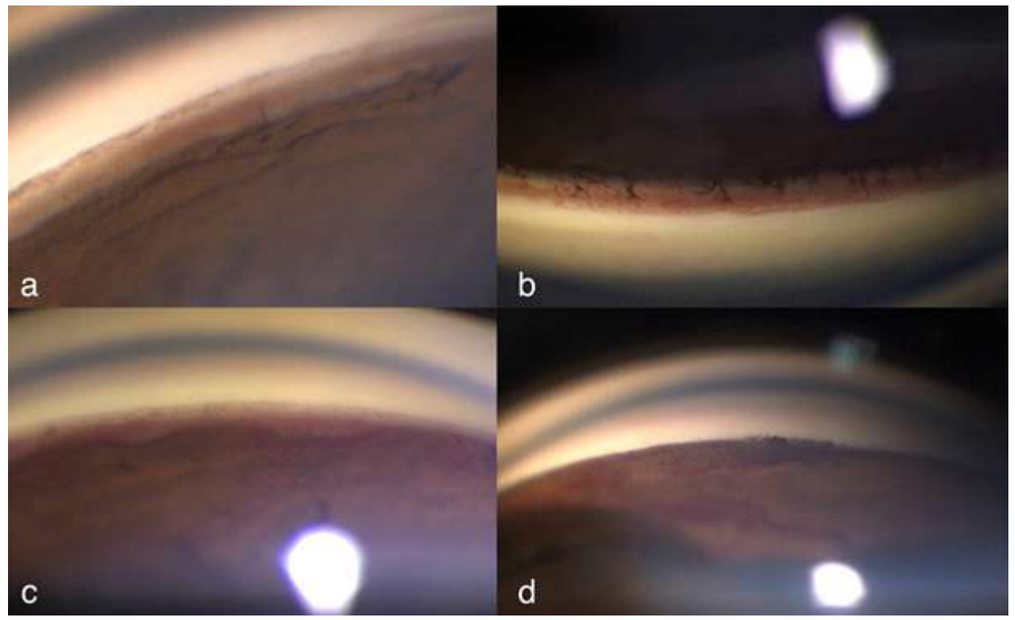


Figure 8: (a) Fine vessels over angle; (b) Extensive NVA over the angle but the angles are open; (c,d) Progressive synechiael closure of angles leading to uncontrolled rise in IOP along with thickening of NVIs.

Stage 3: Synechial (Closed-Angle) NVG

Stage 3 is defined by **permanent angle closure** resulting from contraction of fibrovascular membranes and the formation of extensive **peripheral anterior synechiae**. Clinically, dense neovascularization of the iris and angle is evident, and gonioscopy often reveals **broad-based synechial closure** that obscures angle structures (Figure 8c,d). IOP is typically markedly elevated, and corneal edema with epithelial bullae is common. Pupillary abnormalities, such as a fixed or poorly reactive pupil, may also be present. Patients usually report severe ocular pain, conjunctival hyperemia, rapidly progressive visual loss, and may experience systemic symptoms including headache, nausea, or vomiting.[8,14]

The visual prognosis in Stage 3 is poor due to **irreversible structural damage** to the angle. Conventional glaucoma surgeries have a high failure rate, driven by ongoing neovascular activity, inflammation, and aggressive fibrosis, making long-term IOP control challenging.[8]

Imaging correlation:

- **Anterior segment OCT** can demonstrate **extensive synechial closure** and loss of trabecular architecture, complementing gonioscopic assessment when angle visualization is limited.
- **Anterior segment OCTA** may show persistent abnormal vascular networks within the iris and angle, though flow may be reduced due to ischemic contraction of the fibrovascular tissue. These imaging biomarkers can guide surgical planning and monitor residual neovascular activity following anti-VEGF therapy

Stage 4: End-Stage NVG

Stage 4 represents the **terminal phase** of NVG, characterized by profound visual loss and either uncontrolled ocular hypertension or, paradoxically, hypotony due to **ciliary body ischemia and dysfunction**. Many eyes have no light perception and may exhibit **chronic corneal decompensation, recurrent hyphema, or persistent anterior segment inflammation**. IOP may remain markedly elevated or decline as ciliary body ischemia progresses, ultimately leading to phthisis bulbi in some cases.[8,9]

Management at this stage is primarily **palliative**, focusing on alleviating pain, preserving ocular comfort.

The difference between the various stages is documented in Table 4.

Table 4: Stages of NVG.

	Rubeosis Iridis	Secondary Open Angle Stage	Secondary Closed angle stage
Features	Only new vessels are clinically evident at pupillary margin and cross the Scleral spur	Fibrovascular membrane develops, obstructing aqueous outfow	Fibrovascular membrane undergoes contracture
IOP	Normal	Increased	Increased
Visual prognosis	Good	Good with early intervention	Guarded

Imaging correlation:

- **Anterior segment OCT** may show severe angle collapse, corneal edema, and ciliary body atrophy, confirming structural deterioration.
- **Anterior segment OCTA** is typically of limited value due to extensive ischemia and minimal residual perfusion, but it may demonstrate remnant or regressed iris vasculature in some cases.

5 MULTIMODAL IMAGING

5.1 Anterior Segment OCT (AS-OCT)

AS-OCT has revolutionized the objective assessment of the iridocorneal angle, offering a non-contact, high-resolution alternative to gonioscopy, especially when corneal edema or patient discomfort limits clinical examination.

Unlike older Time-Domain systems, the high scan speed in newer machines allows for rapid acquisition of the entire anterior segment architecture, providing several critical metrics (Figure 9) :

- **Irido-Trabecular Contact (ITC) Score:** This automated parameter quantifies the extent of the angle closed by appositional or synechial contact. In early NVG (the "Open Angle Phase"), the ITC score may be low. However, as the fibrovascular membrane contracts—the "zipper" effect—the ITC score increases significantly, reflecting the transition into the "Synechial Closure Phase."

- **Anterior Chamber Depth (ACD):** Early NVG often presents with a deep anterior chamber. However, as the disease progresses to the pupillary block stage (secondary to posterior synechiae or iris bombe), the ACD decreases.

- **Angle Opening Distance (AOD) and Trabecular Iris Space Area (TISA):** These measurements allow for the quantification of the degree of narrowing caused by NVA before it is clinically obvious on gonioscopy.

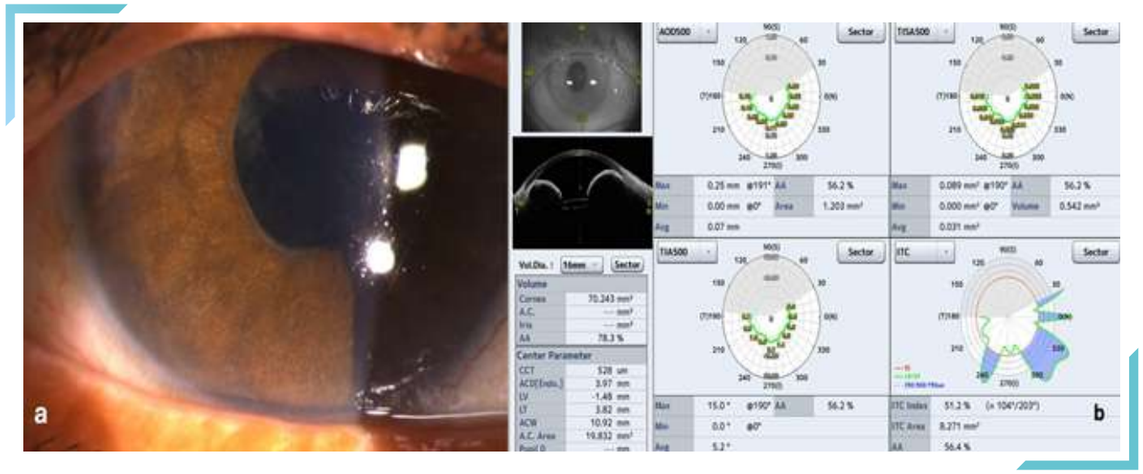


Figure 9.: (a) Anterior segment clinical picture showing NVI and peripheral anterior synechiae; (b) Corresponding ASOCT showing iris bombe configuration, extensive peripheral anterior synechiae and a high ITC index of 51.2% signifying that that greater than 50% angle has undergone synechial closure.

Changes Across Treatment Modalities

AS-OCT is an essential tool for longitudinal monitoring:

- **Post-Anti-VEGF:** Following intravitreal injections, AS-OCT can visualize the flattening or regression of rubeotic tufts. However, it often reveals that while the vessels have regressed, the structural ITC score remains high if permanent peripheral anterior synechiae have formed.
- **Post-PRP:** As the ischemic drive decreases, AS-OCT documents the stabilization of the angle architecture, preventing further synechial "zipping."
- **Surgical Intervention**: In cases where Glaucoma Drainage Devices (GDD) are implanted, AS-OCT confirms tube positioning and its relationship to the iris and cornea.

Anterior segment swept-source OCT has emerged as a useful modality for predicting bleb function. Thicker bleb walls, lower reflectivity, and microcyst formation early after surgery correlate with successful long-term IOP control. Early multilayered hyporeflective “striping” patterns are also associated with favorable outcomes.

5.2 Fluorescein Angiography (FA) of the Retina

While NVG manifests in the anterior segment, the pathology is almost always rooted in the posterior segment. FA remains the definitive tool for identifying the "ischemic drive."

Detection of Retinal Ischemia and Rubeosis

Retinal ischemia triggers the release of Vascular Endothelial Growth Factor (VEGF), which diffuses anteriorly.

- **Ischemic Threshold:** It is widely accepted in ophthalmic literature that a threshold of **10 to 30 disc areas of capillary non-perfusion (CNP)** on FA is required to generate enough VEGF to initiate rubeosis iridis. In CRVO, identifying "Ischemic CRVO" via FA is the primary predictor for the "100-day glaucoma." In Vasculitis ischemic areas are often peripheral and ultrawide field imaging (UWFA) is very useful in mapping such peripheral ischemic areas (Figure 10)

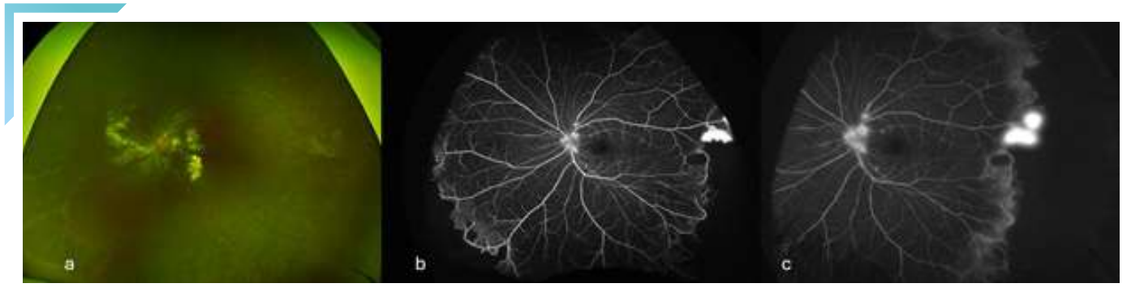


Figure 10(a): Left eye showing hard exudates at posterior pole, aneurysmal dilatation, peripheral vascular sheathing and sclerosis; (b and c) UWFA showing peripheral ischemic areas, peripheral NVE, NVD and aneurysmal arterial dilatations.

- **Adequacy of laser:** FFA can be used to visualize whether laser done to ablate CNP area is sufficient or not. Presence of NVE is a definite indication of laser augmentation of any CNP area even if laser spots have to be put inside the areas which are classically not lasered according to ETDRS protocol (Figure 11).

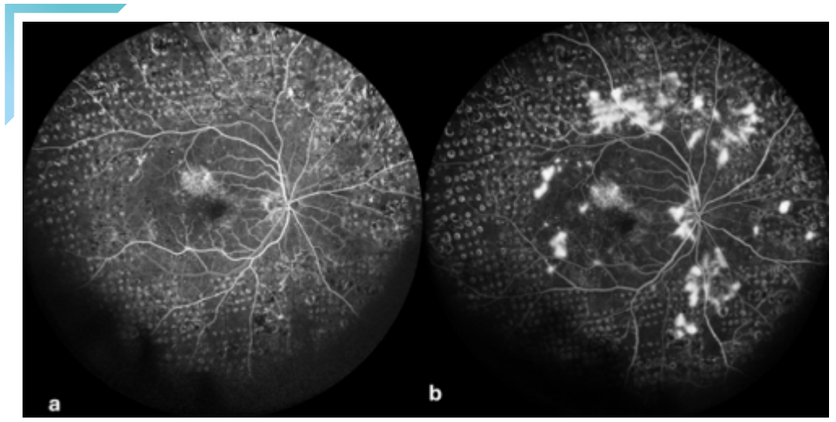


Figure 11: a) Lasered PDR with laser scars; b) Venous phase reveals extensive NVEs and unlasered CNP areas which need to be managed with laser augmentation.

5.3 Angiography of the Iris

While retinal FA is standard, imaging the iris specifically requires different considerations. In his seminal work, Sohan Singh Hayreh, noted that normal iris vessels are impermeable to fluorescein. He emphasized that any leakage seen on angiography is inherently pathological. Hayreh's studies demonstrated that in NVG, the breakdown of the blood-iris barrier precedes the formation of visible NVI, meaning "leakage" can often be detected before vessels are clinically visible via slit-lamp.

Phases of Angiography in NVG

1. **Early Phase:** Shows the first appearance of NVI. Detection of any vascular pattern over iris in heavily pigmented iris, as seen in the Indian context should be taken as pathological (Figure 12a-c). Normal iris stromal vessels can be picked up in light pigmented iris and in presence of stromal atrophy.
2. **Late Phase:** This is where the leakage becomes most apparent. In NVG, the "leakage" from rubeotic vessels often obscures the iris surface details, appearing as a bright, hyperfluorescent cloud(Figure 12d-f).

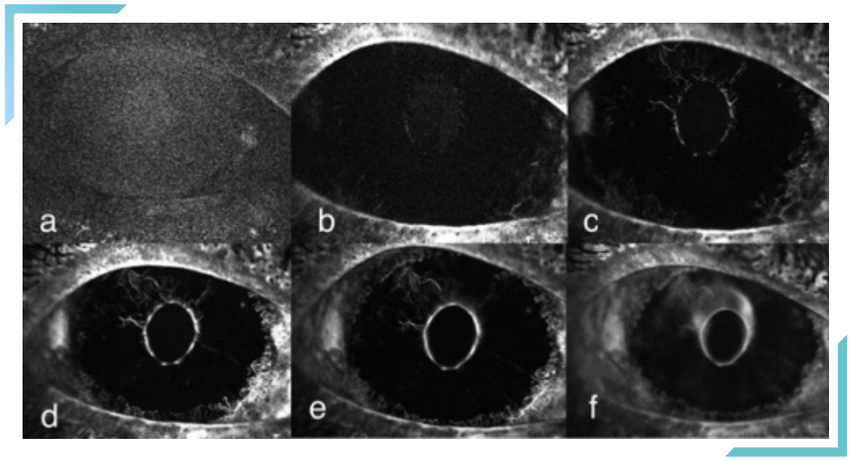


Figure 12- NVIs visible on fluorescein angiography of the anterior segment; a-c show progressive filling of the NVIs; d-f show progressive leak from these NVIs ultimately obscuring the vascular details.

While Fluorescein Angiography is commonly used, **Indocyanine Green Angiography** (ICGA) is technically superior for iris visualization. ICG is 98% bound to plasma proteins (albumin). This prevents it from leaking out of the leaky NVI as rapidly as fluorescein does. Consequently, the vascular architecture remains sharp and well-defined, whereas fluorescein quickly creates a "blur" of leakage that obscures the vessel morphology.

Circulation Timing and Delays

A notable clinical finding is that iris vessels become visible significantly later than retinal vessels.

- **The Path:** The retina is supplied by the central retinal artery. In contrast, the iris is supplied by the long posterior ciliary arteries and the anterior ciliary arteries, which must first form the major arterial circle of the iris.
- **Delayed Filling:** Because of this longer, more circuitous route and the lower flow rate of the ciliary system compared to the retinal system, the "Iris Transit Time" is delayed.

5.4 Ultrasound Biomicroscopy (UBM)

In many advanced NVG cases, the cornea is opaque due to high IOP or chronic bullous keratopathy, making optical imaging (like OCT) impossible. UBM, using high-frequency sound waves (35–50 MHz), is the "gold standard" for imaging in opaque media.

Evaluation of Ciliary Processes

The behavior of the ciliary body is a primary indicator of disease severity in NVG.

- **Anterior Displacement:** As the fibrovascular membrane in the angle contracts, it pulls the iris and the attached ciliary processes forward.
- **The Zipper Effect:** UBM can visualize the physical closure of the posterior chamber as the iris is pulled against the trabecular meshwork and even the peripheral cornea.

In a study by Gao et al., UBM based analysis of NVG patients provides critical insights into the morphological changes of the ciliary body during NVG progression :

1. **Progressive Atrophy:** As the disease reaches terminal stages, the ciliary body often undergoes **ischaemic atrophy**. The study highlights that a significant decrease in ciliary body thickness is a predictor of poor visual prognosis and eventual phthisis bulbi.
2. Ciliary Process Direction: In early stages, processes are pulled anteriorly. However, in late-stage NVG, especially following aggressive cyclodestructive procedures, the processes may appear **blunted, posteriorly rotated, or detached** due to the formation of a cyclitic membrane.
3. **Suprachoroidal Effusions:** UBM is vital for detecting occult effusions that can occur in NVG, which might be missed by other imaging modalities but are critical for surgical planning.

5.5 Optical Coherence Tomography Angiography (OCTA)

OCTA is a non-invasive, dye-free imaging modality that enables detailed visualization of retinal and anterior segment microvasculature and has become an important adjunct in the evaluation of change to NVG. The clinical utility is further enhanced with the advent of Widefield OCTA (WF-OCTA) which overcomes the limited field of view of conventional macular OCTA scans (3 × 3 mm, 6 × 6 mm, or 9 × 9 mm). Using larger 12 × 12 mm scans and montage facility, visualization of the mid-peripheral and peripheral retinal pathology, including areas of extensive capillary non-perfusion and peripheral neovascularization, is made possible with WF-OCTA. Unlike FFA, which produces a two-dimensional image without layer differentiation, OCTA generates high-resolution three-dimensional images extending from the inner retina to the choriocapillaris. It allows separate evaluation of superficial and deep capillary plexuses and demonstrates early ischemic changes such as foveal avascular zone (FAZ) distortion, CNP, macular ischemia, and neovascularization.

Anterior segment OCTA has enabled direct visualization of iris and angle neovascularization, facilitating early detection before obvious clinical recognition on slit-lamp examination or gonioscopy.[16] OCTA also provides quantitative vascular parameters such as vessel density and perfusion indices, allowing objective monitoring of disease progression and treatment response following anti-vascular endothelial growth factor therapy or panretinal photocoagulation[17]

Several studies have demonstrated the expanding clinical role of OCTA in ischemic retinopathies relevant to NVG. Roberts et al. demonstrated the feasibility of anterior segment OCTA in imaging iris vasculature and identifying abnormal vascular networks in pathological conditions.[18] Shiozaki et al. showed that swept-source anterior segment OCTA could successfully document regression of iris neovascularization following anti-VEGF therapy.[19]

In a prospective study by Parameswarappa et al., widefield OCTA demonstrated strong correlation between retinal vascular abnormalities and diabetic retinopathy severity. Enlargement of the FAZ and increasing capillary non-perfusion areas significantly correlated with disease progression and WF-OCTA detected subtle neovascularization of the disc and elsewhere that were not identified on widefield fundus photography. These findings highlight the superior sensitivity of WF-OCTA in detecting early neovascular changes and peripheral ischemia, which are critical drivers for the development of NVG in diabetic eyes.[20]

OCTA offers several advantages including rapid acquisition, repeatability, and avoidance of dye-related adverse reactions associated with FA. However, it does not demonstrate vascular leakage and may be limited by motion artifacts, media opacity, corneal edema, or poor fixation, particularly in advanced NVG. Despite these limitations, OCTA provides valuable structural and quantitative vascular information and serves as an important tool for early diagnosis, assessment of ischemic drive and monitoring treatment response in NVG.

5.6 B-scan ultrasound

It is helpful in the detection of lesions of the posterior segment in NVG eyes with poor media haze. Ultrasound B scan can detect the presence of vitreous hemorrhage, fibrous proliferation, and tractional or rhegmatogenous retinal detachment. Mass lesions like choroidal melanoma, ciliary body melanoma, and retinoblastoma can be detected. Ultrasound B scan can detect retinal detachment in the advanced stages of ROP with NVG.

Summary Table 5: Imaging Comparison in NVG

Modality	Primary Use Case	Key Measurement	Advantage
AS-OCT	Angle Anatomy	ITC Score, ACD	High resolution, non-contact
Retinal FA	Ischemic Drive	Disc areas of CNP	Confirms the "Why" of the NVG
Iris Angiography	Vessel detection and morphology	Iris Transit Time	Can pick up subclinical NVI
UBM	Opaque Media	Ciliary Process Direction	Works through edema/scars
OCTA	Retinal vasculature and NVI	Neovascularisation, CNP areas	Non invasive

6 MANAGEMENT OF NVG

6.1 Principle of management

1. **Rapid regression of neovascularisation**
   - Anti-VEGF, PRP, Anterior Retinal Cryopexy (ARC)
2. **Medical treatment**
   - **Usually of temporizing measure to optimize conditions for surgery**
     - Surgery is almost always required once IOP is uncontrolled.
3. **The choice of surgery depends on:**
   - Visual potential
   - Stage of NVG (open vs closed angle)
   - Ocular inflammation
   - Patient's systemic status
4. **Adjunctive anti-VEGF improves surgical success**, especially for trabeculectomy and glaucoma drainage device (GDD).
5. **Cyclodestruction is no longer "last resort only"**, especially with slow-coagulation or micropulse cyclophotocoagulation.

In end-stage disease with poor visual potential, management is largely palliative and aimed at pain relief, with cyclo-destructive procedures or, rarely, enucleation reserved for a painful blind eye refractory to other treatments. Careful long-term surveillance and prophylactic evaluation of the fellow eye remain critical components of comprehensive management.

6.2 Stage-Based Approach to the Management of NVG

NVG is dynamic, progressive and often aggressive, necessitating early recognition and timely intervention. A stage-based management approach enables targeted therapy at each phase of disease evolution, emphasizing early suppression of angiogenic drive, definitive treatment of ischemic retina, and appropriate surgical intervention when indicated. Across all stages, control of VEGF remains central to the management.[21]

Stage 1: Rubeosis Iridis (Pre-glaucoma Stage)

The primary therapeutic goal is prevention of disease progression by eliminating the ischemic stimulus driving VEGF production. Intravitreal anti-VEGF agents provide rapid regression of anterior segment neovascularization and are useful for immediate control of active disease.[13,22]

However, the effect is temporary and anti-VEGF therapy should not be considered definitive.

Early and complete PRP remains the gold standard intervention. By ablating ischemic retina, PRP results in sustained reduction of intraocular VEGF levels and long-term regression of neovascularization.[21] PRP should be instituted as soon as media clarity permits. Incomplete or delayed retinal ablation is a major risk factor for progression. UWFA–guided laser can help address peripheral ischemia missed during conventional PRP. Close follow-up with repeat gonioscopy is essential.

Stage 2: Open-Angle NVG

Progression of fibrovascular tissue over the trabecular meshwork leads to elevated IOP while the angle remains open. At this stage, NVG becomes clinically apparent. Management requires a combined medical and retinal approach. Intravitreal anti-VEGF therapy is administered early to induce regression of neovascular tissue, reduce inflammation, and improve the safety of subsequent laser or surgical procedures.[13,22] This is followed by urgent and complete PRP, which remains the definitive treatment of the ischemic drive.

Topical IOP-lowering medications, primarily aqueous suppressants, are initiated concurrently, although their efficacy is often limited.

GDD are preferred over trabeculectomy due to higher long-term success in eyes with active neovascularization.[23] Early surgical intervention is advised when IOP remains uncontrolled.

Stage 3: Angle-Closure NVG

Advanced NVG is characterized by contraction of fibrovascular membranes, extensive peripheral anterior synechiae, secondary angle closure and markedly elevated IOP. Medical therapy alone is inadequate.

Although PRP remains important to reduce ongoing VEGF production, it cannot reverse established synechial closure. Anti-VEGF agents play a supportive role by reducing neovascular activity and minimizing intraoperative bleeding.

From a retina perspective, anterior retinal cryoablation or pars plana vitrectomy (PPV) with endolaser is indicated in eyes with non-clearing vitreous hemorrhage, dense media opacity or tractional pathology precluding adequate PRP. Vitrectomy allows complete retinal ablation, improves intraocular oxygenation and enhances long-term disease control. In selected cases, combined PPV with GDD implantation may be performed.[24] Visual prognosis is guarded, and surgical goals focus on IOP control and pain relief.

Stage 4: Refractory or End-Stage NVG

End-stage NVG is characterized by uncontrolled IOP, severe optic nerve damage, poor visual potential, or failure of prior surgical interventions. Management is primarily palliative.

Cyclodestructive procedures are central to management. Micropulse transscleral cyclophotocoagulation has gained popularity due to its favorable safety profile and repeatability compared with continuous-wave cyclophotocoagulation.[25,26] Control of the ischemic retinal drive remains important to reduce recurrent neovascularization and inflammation. In eyes with no visual potential and intractable pain, more definitive palliative measures may be required.

6.3 Surgical Management - Retina Perspective

From a retinal standpoint, surgical management of NVG is directed at improving media clarity by removing vitreous hemorrhage, eliminating intraocular VEGF and addressing posterior segment ischemia responsible for sustained VEGF production and anterior segment neovascularization. Surgery also provides access to peripheral ischemic retina that may remain untreated after conventional PRP, a common cause of recurrent neovascularization. Intravitreal anti-VEGF agents serve as critical adjuncts by inducing rapid but temporary regression of iris and angle neovascularization, reducing intraoperative bleeding, and improving the safety of subsequent glaucoma procedures. Silicone oil tamponade and cyclophotocoagulation of the ciliary processes under direct visualization have been reported to be useful in selected cases.[27]

Silicone oil helps maintain retinal attachment, facilitates laser treatment of previously detached ischemic retina, and may promote regression of rubeosis by separating the anterior and posterior segments.

Anterior Retinal Cryopexy (ARC)

When the media is not visible, for example, due to vitreous haemorrhage, PRP is not possible. In these situations, ARC can be helpful. Cryopexy involves a probe than can be frozen to -70 to -80 degree Celsius and can be used to freeze the retinal pigment epithelium and underlying retina, when placed over the scleral surface. This can be helpful to cause the retinal necrosis and reduce the VEGF release. The probe is kept 8mm from the limbus and 4-8 spots are delivered per quadrant, using double-freeze thaw technique and the endpoint is the whitening of the retinal surface as visualised through the indirect ophthalmoscopy. The procedure is associated with high chances of inflammation and macular oedema and is usually reserved for patients in whom the other modalities of laser are not possible. Hseih et al showed that ARC, when combined with Anti-VEGF, resulted in faster clearing of visual field in patients with PDR, as compared to anti-VEGF alone.[28]

In advanced NVG with uncontrolled IOP, combined or staged surgical approaches involving pars plana vitrectomy and GDD implantation may be required, particularly in eyes with visual potential. Appropriate timing and sequencing of retinal and glaucoma surgeries are crucial, as definitive control of retinal ischemia significantly enhances the success of anterior segment interventions and long-term anatomical stabilization.

6.4 Glaucoma surgery

a) Trabeculectomy with Antimetabolites

Surgical intervention is indicated in these eyes when IOP is uncontrolled on maximal medical therapy or when there is progressive synechial closure of angle compromising trabecular outflow. Although trabeculectomy remains the gold standard filtration procedure, its success in these eyes is limited by intensive intraocular inflammation, recurrent hyphema, and subconjunctival fibrosis because of ischemia-mediated angiogenesis (Figure 13).

Figure 13: Failed trabeculectomy in an eye with NVG.

Adequate suppression of the proangiogenic environment with retinal ablation and/or anti-VEGF and reduction of inflammation is essential to improve the surgical outcome.

The use of antimetabolites- Mitomycin-C (MMC) and 5-Fluorouracil (FU) have significantly improved surgical outcomes. MMC, applied subconjunctival and/or subscleral inhibits fibroblast proliferation and improves bleb survival.

In a study of 101 eyes by **Takihara et al**., MMC-augmented trabeculectomy had success rates of 62.6%, 58.2%, 51.7% at one year, two years and five years respectively, showing progressive attrition despite favorable early outcomes.[29]

In a prospective study by **Obeidan et al**, MMC–augmented trabeculectomy demonstrated cumulative success rates of 86.5%, 74.7%, and 57.6% at 6, 12, and 24 months, respectively, with pseudophakia being the only significant predictor of failure. In the same They also reported 80% success rate in eyes that had received complete preoperative PRP, underscoring the importance of adequate ischemia control prior to filtration surgery.30

In a study by Hyung et al., MMC-augmented trabeculectomy the overall success rates at 1-, 3-, 6-, 9-, and 12-months after surgery were 71%, 58%, 50%, 29%, 29% respectively thus showing the impact of sustained angiogenic drive and postoperative scarring on surgical success.[31]

Kiuchi et al. demonstrated significant IOP reduction following MMC-augmented trabeculectomy in NVG eyes , although the extent of peripheral anterior synechiae and history of prior vitrectomy negatively influenced the outcomes.[32]

5-FU, has also been used to modulate postoperative fibrosis. Augmentation with 5-FU though improved early success to nearly 67% at two years; however, long-term survival declined to as low as 28% by five years.[33]

In a study by Katz et al. IOP control following trabeculectomy was better with MMC compared with 5-fluorouracil.[34]

Adjunctive anti-VEGF therapy to reduce ischaemic drive has is as an important perioperative strategy. In a study by **Higashide et al**., intravitreal bevacizumab administered prior to trabeculectomy resulted in regression of iris neovascularization, reduced intraoperative bleeding, and improved surgical success.[35]

Intraoperative use of releasable sutures or laser suturolysis post operatively improves aqueous outflow, prevents early postoperative hypotony.[5]

In a retrospective analysis by **Senthil et al**., trabeculectomy success was poorest in NVG secondary to PDR compared to CRVO and OIS, with complete success declining to as low as 8% by five years which can be because of ongoing inflammation in NVG eyes.[36]

Risk factors associated with trabeculectomy failure were older age, PDR, persistent NVI, higher number of anti VEGF injections, and long duration between diagnosis and surgery. Persistent NVI and a higher number of anti VEGF injections before trabeculectomy as they indicate severity of retinal ischaemia. GDD are a better surgical alternative in these cases. It may be prudent to perform implant surgery in the eyes with these risk factors. Young age was a risk factor for failure in a study by **Mermoud et al**.[37]

The prognostic factors for surgical failure in a study by **Takihara et al** were younger age and previous vitrectomy in all NVG patients, and having a fellow eye with NVG in patients with disease caused by diabetic retinopathy.[29]

Modifications of Trabeculectomy: Several surgical modifications have been proposed to improve filtration survival.

- **Releasable or adjustable sutures** allow postoperative titration of aqueous outflow and reduce early hypotony risk.
- **Polypropylene bed modification** maintains scleral flap elevation and reduces fibrosis.[38]
- **Trabeculectomy combined with limited deep sclerectomy** creates an intrascleral aqueous reservoir to maintain filtration and reduce the risk of early fibrosis.[39]
- **Anterior chamber proliferative membrane interception** aims to prevent fibrovascular membrane obstruction of the filtration site.[40]

b) Glaucoma drainage devices

The GDD - valved/flow restrictive implants (Ahmed glaucoma valve (AGV; Models- FP7, S2) and non valved implants (Bearveldt- (BGI; Models: 250 and 350 mm^2), Molteno, ACP, PGI, AADI. In eyes with NVG, valved implants are preferred to ensure immediate IOP reduction with lesser risks of hypotony, however long term outcomes are better with non valved implants. Implants with smaller lumen size of the tube such as ACP ST or PGI may be preferred to reduce risk of hypotony related complications.

The cumulative probabilities of success of AGV in a study by Yalvac et al were 63.2% at one year, that dropped to 25.2% at five years which suggests success rates of GDD in NVG are lesser compared to other indications.[41] In a systematic review by by Hong et al. visual acuity was better preserved in AGV group in comparison to other GDDs.[42] GDD surgery combined with vitrectomy could bring additional benefit in reduction of IOP and dependence on anti-glaucoma medications.[43,44]

GDD placement in anterior chamber vs sulcus vs pars-plana

The "tube" of these devices can be placed in three primary locations, each with a unique profile of risks and rewards.

1. Anterior Chamber (AC) placement

This is the most common and technically straightforward approach. The tube is inserted through a small track into the space between the cornea and the iris.

- **Advantage:** High initial success. It is the "gold standard" for patients with a clear natural lens or a stable intraocular lens (IOL).
- **Problems: Corneal Decompensation:** The primary risk. If the tube is too close to the cornea, it can damage endothelial cells over time, leading to corneal swelling and the need for a transplant.
    - **Tube-Iris Touch:** Can cause chronic inflammation or iris erosion.
    - **Tube Shifting:** More prone to migration if not anchored perfectly.

2. Ciliary sulcus placement

The tube is tucked behind the iris but in front of the IOL (Figure 14). This is an excellent "middle ground" option, often used in patients who have had cataract surgery (pseudophakic).

- **Advantage:** IOP control is comparable to AC placement in terms of IOP lowering, but often preferred for long-term "ocular surface" health.
- **Problems:**
    - **Lower Corneal Risk:** Since the tube is further away from the cornea, the risk of endothelial cell loss is significantly reduced.
    - **Uveitis-Glaucoma-Hyphema (UGH) Syndrome:** If the tube rubs against the posterior surface of the iris, it can cause bleeding (hyphema) and inflammation.
    - **Pigment Dispersion:** Friction against the iris can release pigment, which might paradoxically clog the drainage system.

3. Pars Plana placement

This approach places the tube in the vitreous cavity at the back of the eye (Figure 14). It requires a complete PPV performed by a retina specialist to clear the path for the tube.

- **Advantage:** Very high success rate, particularly in complex cases like NVG or eyes with extensive scarring in the front (anterior segment). It is often the preferred choice for patients with corneal grafts. A retrospective study by Samuel et al showed that IOP control was better in pars plana placement of the tube than anterior chamber or sulcus placement.[45]
- **Problems:**
    - **Vitreous Blockage:** If the vitrectomy isn't thorough, vitreous strands can clog the tube, causing immediate failure.
    - **Retinal Issues:** Higher risk of retinal detachment or vitreous hemorrhage compared to the other two methods.
    - **Cataract Formation:** In patients who still have their natural lens (phakic), this method almost guarantees cataract progression due to proximity.

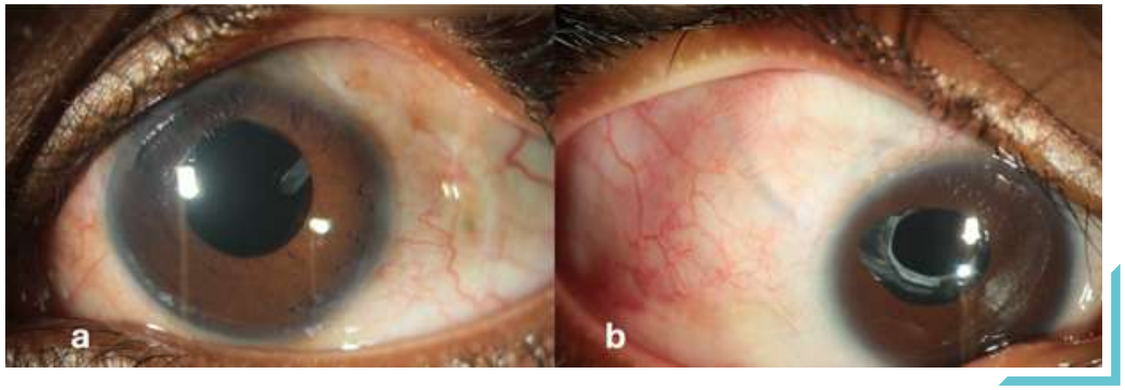


Figure 14: GDD tube placement- (a) pars plana and (b) sulcus.

c) Trabeculectomy versus Ahmed Glaucoma Valve Implantation

Given the high risk of failure of trabeculectomy in NVG eyes owing to extensive scarring, GDD—particularly the Ahmed glaucoma valve (AGV)—have gained popularity in NVG management for better IOP management and reduced risk of hypotony as their success is less dependent on control of intraocular inflammation and the failure of filtering bleb (Figure 15).

Figure 15: Postoperative inflammation in an eye with NVG and AGV implantation.

Success of trabeculectomy remains highly dependent on bleb survival. In contrast, the AGV provides an alternate aqueous outflow pathway that is independent of subconjunctival filtration. Its valved mechanism confers immediate flow resistance, reducing IOP and preventing early postoperative hypotony risk.

In a study by **Shen et al**., trabeculectomy with MMC and AGV implantation demonstrated success rates of 55% and 60% respectively at two years, with no statistically significant difference. Hyphema remained the most common postoperative complication in both groups.[46]

Similarly, study by **Rani et al**. NVG eyes with moderate visual potential- better than 20/200 at presentation reported comparable visual preservation and IOP control between trabeculectomy (performed in Indian cohort) and tube shunt surgery (performed in a UK cohort), suggesting that procedure selection should be individualized. Success was 70% and 65% at 1 year and 60% and 55% at 2 years after AGV and trabeculectomy, respectively.[47]

In eyes requiring concurrent PPV, implants may offer additional benefit. In a study by **Wang et al**., NVG eyes with vitreous hemorrhage undergoing pars plana vitrectomy combined with AGV implantation achieved greater IOP reduction than vitrectomy combined with trabeculectomy at 12 months, although absolute success rates were comparable in both the groups.[48]

Prior vitrectomy—recognized as a risk factor for trabeculectomy failure—appears less detrimental to tube survival.[31] Consequently, AGV implantation is often favored in post-vitrectomy eyes, extensive synechial closure, or persistent anterior segment neovascularization.

Overall, with adequate preoperative control of retinal ischemia trabeculectomy and AGV implantation offer comparable results in terms of IOP control and dependence on anti glaucoma medications. However, glaucoma drainage devices offer better results in eyes with persistant neovascularization, extensive PAS, eyes in which trabeculectomy cannot be performed like with history of prior incisional surgery.

d) Ahmed versus Baerveldt Implants

Among drainage devices, the AGV and Baerveldt implant are most widely used. The surgical success rate of the BGI surgery group was significantly higher than that of the AGV group in a retrospective multicener analysis by Iwasaki et al with lower incidence of resurgery in BGI group.[49] AGV Baerveldt study suggested that both implants were effective in reducing IOP and there was similar need for post operative glaucoma medications. Although the Baerveldt group had a lower failure rate and a lower IOP on fewer medications than the AGV group, difference was not statistically significant but had a small risk of hypotony that was not seen in the AGV.[50] Yalvac et al. also suggested that outcomes of both AGV and single plate Molteno implant were successful for early and intermediate-term of IOP control.[41] Thus the long-term comparative evaluation in the AGV Baerveldt Study demonstrated no statistically significant difference in surgical success at five years on multivariate analysis, suggesting comparable durability of IOP control despite differing fluid dynamics

e) Cyclophotocoagulation: Transscleral and Endoscopic

Cyclodestructive procedures remain important therapeutic option particularly in eyes with refractory NVG, with limited visual potential(primary intervention) or those unsuitable for incisional/implant surgery or in eyes where filtration surgery and or tube surgery have failed (secondary modality).[51]

Cyclophotocoagulation (CPC) reduces aqueous production by ablating the ciliary body.

Transscleral CPC, most commonly performed using a diode laser, induces coagulative necrosis of the ciliary epithelium by delivering energy to the ciliary processes through sclera (Figure 16).

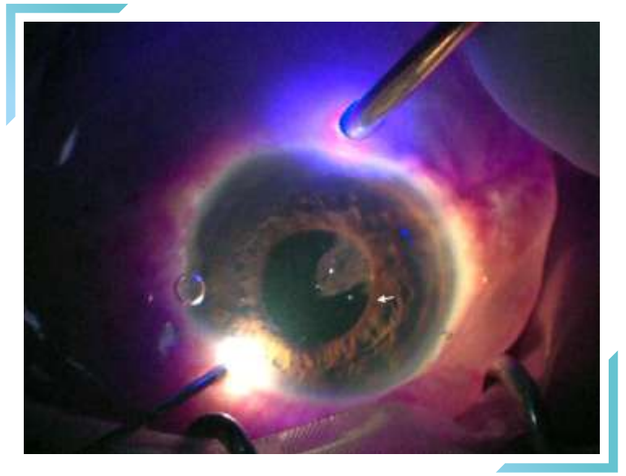


Figure 16: Illumination assisted cyclophotocoagulation in an eye with NVG; white arrow showing NVI and blue arrow showing hyphema.

It can cause collateral damage due to the extension of the cryoablated area to the neighbouring trabecular meshwork and corneal nerves. This may allow some patients with painful eyes to experience less pain, despite the IOP remaining high.[52]

Histopathologically, it results in destruction of both pigmented and non-pigmented ciliary epithelium along with vascular compromise of the ciliary processes, thus resulting in reduced aqueous secretion. In addition to suppression of aqueous production, transscleral CPC may also enhance uveoscleral outflow by increasing scleral and ciliary body permeability.[53,54]

Endoscopic CPC permits direct visualization and titration of laser delivery, minimizing collateral damage and thus is a safe and effective therapeutic modality for refractory glaucomas.[55]

ECP can be performed through a limbal approach in aphakic, pseudophakic or aphakic eyes through a clear corneal or scleral tunnel It can be combined with phacoemulsification in eyes with cataract or with vitrectomy in aphakic eyes. Another approach is through the pars plana that can be utilized in aphakia and pseudophakia.[51,5]

Uram et al reported the use of pars plana diode laser endoscopic CPC in ten eyes with intractable NVG, achieving IOP <21 mmHg in nine eyes at a mean follow-up of nine months, with three patients requiring adjunctive medication.[56]

Uram also described favorable outcomes with combined endoscopic CPC and phacoemulsification with intraocular lens implantation, where mean IOP reduced from 31.4 mmHg to 13.5 mmHg (57% reduction) over 19 months, with half of the eyes controlled without medications, suggesting combined procedure provided effective management of cataract and glaucoma with a minimum of postoperative care.[57]

In a prospective randomized trial of 58 eyes of 58 patients by Gayton et al. endoscopic laser cycloablation combined with cataract surgery was safe and effective(50-60% patients achieved qualified success in terms of IOP Control) compared to combined cataract and glaucoma surgery.[58]

Despite its utility, CPC has several limitations. The effect on the ciliary body is often difficult to titrate, and multiple treatment sessions may be required to achieve adequate IOP control as IOPs may revert after 6 months to 1 year due to ciliary process regeneration. Excessive laser application can lead to complications such as hypotony and phthisis bulbi. Severe postoperative inflammation may further contribute to these adverse outcomes. Other reported complications include hyphema, chronic iritis, and corneal edema.

The Ophthalmic Technology Assessment of the American Academy of Ophthalmology has suggested a framework of indications for CPC, which are not applicable to ECP as it is an intraocular procedure.[59]

Key Management Principles

Across all stages, early diagnosis, rapid VEGF suppression, and definitive treatment of retinal ischemia remain the cornerstones of NVG management. Anti-VEGF therapy should always be combined with adequate PRP or cryoablation. Surgical intervention should not be delayed once medical therapy fails. Optimal outcomes require close collaboration between retina and glaucoma services and an individualized, stage-based approach tailored to disease severity and visual potential (Figure 17).[60] Table 6 gives a review of literature comparing surgical modalities for the management options of NVG.

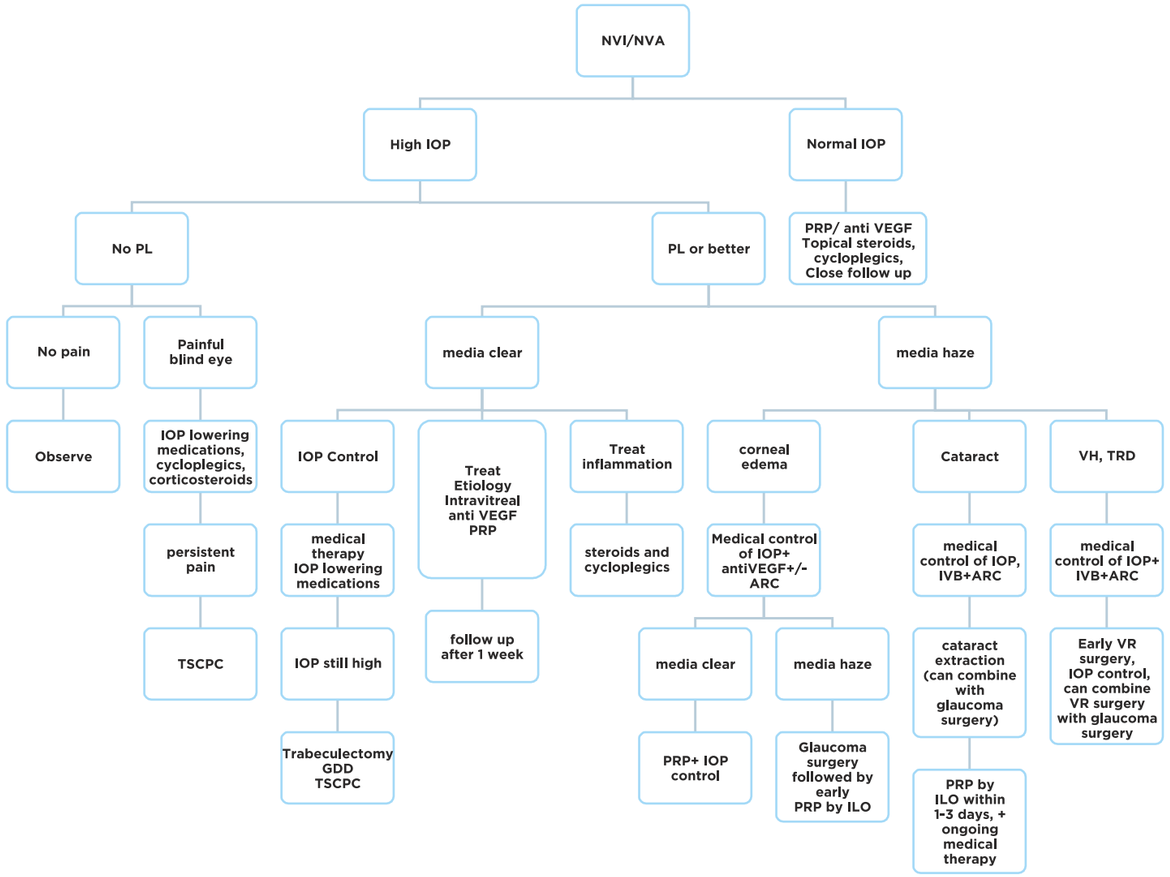


Figure 17: Flow chart showing the recommended treatment protocol of NVG (NVG):. NVD-Neovascularization of the disc; NVE- Neovascularization elsewhere; IOP- intraocular pressure; NVG- NVG; VEGF- vascular endothelial growth factor;IOP- Intraocular pressure; NVA-new vessels of the angle-; NVI-new vessels of the iris, PL-perception of light, TSCPC-transscleral cyclophotocoagulation, GDD-glaucoma drainage device, PRP: panretinal photocoagulation, ARC-anterior retinal cryopexy, VR-vitreoretinal, LIO-laser indirect ophthalmoscopy, VH-vitreous haemorrhage, TRD-tractional retinal detachment

Table 6. Review of literature comparing surgical modalities for the management options of NVG

Study	Authors	Aim	Success criteria	Results	Follow up
1. Trabeculectomy					
1. Trabeculectomy (Trab) with different anti-metabolites (RCT)	Sisto et al, Italy (2007)[1]	Trab + MMC vs Trab + 5-FU	IOP < 21 mmHg with topical treatment (qualified) or without topical treatment (complete)	54.5% (12/22) Qualified success 45.4% (10/22) Complete success 9.15 (2/22)Vs 55.5% (10/18)Qualified success 11.1% (2/18) Complete success 44.4% (8/18)	MMC group -18.6 ±17.2 months. 5-FU group- 35.8 ± 22.6 months
2.Trabeculectomy with and without anti-VEGF (meta-analysis)	Zhou et al, Japan (2023)[2]	Studies that compared trabeculectomy with or without anti-VEGF agents in patients with NVG	Difference of post operative IOP in 2 treatment groups	The difference in post operative IOP between the two groups- 1-week SMD, −1.36 (P =0.06) 6 months SMD −0.79 (P = 0.03) 12 months SMD −0.30 (P = 0.66)	6-12 months
3.Trabeculectomy (Trab) with different anti-VEFG agents (RCT)	Guo et al, China (2021)[3]	Trab +pan retinal photocoagulation (PRP) + IVC (intravitreal conbercept) – group 1 Vs Trab + PRP + IVR (intravitreal ranibizumab) – group 2	IOP > 8 mm Hg and < 18 mm Hg	Mean IOP 15 (group 1) vs 16 mm Hg (group 2) (p value 0.308) on 2 AGMs in group 1 vs 1 AGM in group 2 (p value 0.772)	1 year
4.Trabeculectomy (Trab) Vs Visco-trabeculotomy (VT) (RCT)	Elwehidy et al, Egypt (2019)[4]	Intravitreal ranibizumab (IVR) + pan retinal photocoagulation (PRP) + Trab MMC Vs IVR + PRP + Visco-trabeculotomy	IOP < 21 and > 6 mmHg with no further surgical procedures and no IOP lowering medications (complete) Above criteria but with IOP lowering medications (qualified)	Complete success 52% (13/25) Qualified success 28% (7/25) Vs Complete success 53.8% (14/26) Qualified success 30.8% (8/26)	18 months
2. Glaucoma Drainage Devices (GDD)					
1. Ahmed Glaucoma Valve (AGV) (RCT)	Choy et al., China (2018)[5]	Trans Scleral cyclophotocoagulation (TSCPC) vs AGV	Success - IOP < 21 mmHg with or without IOP lowering medication and preserved or improved BCVA	Success- 63% (TSCPC) (5/8) Vs Success- 42% (AGV) (5/12)	6 months

2. Baerveldt (RCT)	Tokumo et al., Japan (2021)[6]	Baerveldt vs trabeculectomy	Success - IOP < 22 mmHg or > 20% reduction in IOP with no further surgeries and no decrease in best corrected visual acuity	Success - 59.1% (Baerveldt) (14/23) Vs Success - 61.6% (trabeculectomy) (16/27)	12 months
3. Baerveldt (Retrospective clinical cohort study)	Iwasaki et al, Japan (2022)[7]	Baerveldt Vs Trabeculectomy	The criteria for failure were the following- IOP (with or without glaucoma medication) at ≥ 3 months after surgery: < 20% reduction in the preoperative IOP criterion A, IOP > 21 mmHg; criterion B, IOP > 17 mmHg; or criterion C, IOP > 14 mmHg on 2 consecutive follow-up visits. All others- success	The probability of success was significantly higher in the tube group than in the trabeculectomy group for criteria A (P < 0.01), B (P < 0.01), and C (P = 0.03). Criterion A, the probabilities of success at 1-, 3-, and 5-years post-surgery -85.3% vs. 67.8%, 83.2% vs. 50.3%, and 80.2% vs. 47.2%, respectively. Criterion B, the probabilities of success 1, 3, and 5 years after surgery in the tube and trabeculectomy groups were 79.3% vs. 54.6%, 66.1% vs. 41.6%, and 66.1% vs. 33.2%, respectively. For criterion C, the probabilities of success 1, 3, and 5 years after surgery in the tube and trabeculectomy groups were 67.4% vs. 43.3%, 41.7% vs. 31.8%, and 33.7% vs. 24.3%, respectively.	5 years
4. GDD, Trabeculectomy and Diode laser cyclophotocoagulation (DLCP) (meta-analysis)	Shchomak et al Portugal (2019)[8]	Comparison of GDD vs cyclophotocoagulation And AGV (Ahmed Glaucoma Valve) vs trabeculectomy	IOP reduction post-surgery	GDD vs cyclophotocoagulation -No statistically significant difference AGV vs Trabeculectomy- No statistically significant difference	6 months

5. GDD (AGV FP-7), trabeculectomy and TSCPC (Cross sectional study, retrospective)	Pegu et al, India (2024)[9]	Trabeculectomy with MMC (group 1) VS GDD (AGV FP-7) (group 2) VS TSCPC (group 3)	Complete Success - IOP < 22 mm Hg > 5 mm Qualified Success – above with ≥ 1 AGMs	complete success – 54.3% qualified success – 36.7% (group 1) vs complete success – 54.3% qualified success – 57.1% (group 2) vs complete success –33.3% qualified – 58.9% (group 3)	12 months
6. GDD (AGV) and ECP (Retrospective study)	Li et al, China (2023)[10]	ECP (PPV & PRP & ECP) (group 1) Vs GDD(Ahmed glaucoma valve) (group 2)	Complete success: (1) IOP within the range of 6–21 mmHg, and IOP reduced by more than 20% from preoperative IOP at least for two consecutive visits; AND (2) no loss of light perception; AND (3) no need of additional glaucoma procedure AND (4) no need of application of anti-glaucoma drugs after surgery. Qualified success - above with AGM's	Complete success rate 81.25% at 3-months, 75.00% at 6-months, 75.00% at 12-months Qualified success rate- 100.00% in each visit in group 1 VS Complete success rate- 64.30% 3-months to 12-months Qualified success rate -100.00% at 3-months, 85.71% at 6-months 78.57% at 12 months in Group 2.	12 months

Miscellaneous

1. Ex-PRESS vs TSCPC (RCT)	Wagdy et al., Egypt (2020)[11]	Ex-PRESS vs TSCPC	IOP < 22 mmHg and no further treatment (complete) Above but with medical treatment (qualified)	Complete success 50% (6/12) Qualified success 41.7% (5/12) Vs Complete success 44.445 (8/18) Qualified success 38.95 (7/16)	12 months

2. Different routes and types of ANTI VEGF (meta-analysis)	Wang et al, China (2024)[12]	simultaneous intravitreal and intracameral injection of conbercept (ICCIVC) vs intravitreal injection of conbercept (IVC) vs Intravitreal injection of ranibizumab (IVR) Vs intravitreal injection of bevacizumab (IVB) vs blank control group vs intracameral injection of conbercept (ICC),	IOP at 1 month	ICCIVC had the highest rank (82.0%) in terms of efficacy in reducing IOP after 1 month. Following this, ICC (65.8%), IVC (64.4%), IVR (51.7%), IVB (35.0%) and finally the Blank control (1.1%)	1 month

Abbreviations: MMC- Mitomycin C, 5 FU- 5 Fluorouracil, GDD- Glaucoma Drainage Device, TSCPC- Trans Scleral cyclophotocoagulation

7 ANTI-VEGF THERAPY IN NVG

VEGF plays a critical role in NVG pathogenesis by driving abnormal angiogenesis and fibrovascular membrane formation on the iris and iridocorneal angle. Elevated aqueous and vitreous VEGF levels correlate strongly with disease severity, which provides the rationale for anti-VEGF therapy as part of management.[3,8]

7.1 Rationale and Mechanism of Anti-VEGF Therapy

Anti-VEGF agents, such as bevacizumab, ranibizumab, aflibercept and conbercept, rapidly induce regression of NVIs and NVAs. This reduces vascular permeability, inflammation, and the risk of intraocular hemorrhage, improving short-term IOP control and stabilizing the eye before definitive treatment such as PRP.[61,48,62,63]

However, the therapeutic effect of anti-VEGF agents is temporary, typically lasting 4-6 weeks, since they do not address the underlying ischemic drive. Without PRP or surgical intervention, neovascularization frequently recurs.[62,63]

7.2 Anti-VEGF as Initial and Temporizing Therapy

Multiple studies have shown that anti-VEGF therapy is highly effective for rapid short-term suppression of anterior segment neovascularization. The VEGA randomized clinical trial found that intravitreal aflibercept produced clinically meaningful IOP reduction and significant regression of both NVI and NVA within one week compared with sham injection, although the primary endpoint narrowly missed statistical significance in the full analysis set. The majority of patients required only a single injection, with disease stabilization maintained up to 13 weeks.[24]

Similarly, prospective case series emphasize that early intravitreal bevacizumab allows rapid regression of neovascularization, facilitating completion of PRP and safer glaucoma surgery.[63] These findings support anti-VEGF therapy as a critical early intervention, particularly in eyes with open angles or incomplete synechial closure.

7.3 Anti-VEGF as an Adjunct to Panretinal Photocoagulation

PRP remains the cornerstone of long-term NVG management, as it reduces retinal ischemia and suppresses ongoing VEGF production. Anti-VEGF therapy complements PRP by bridging the delay before laser-induced ischemia reduction becomes effective.[8,5]

Combination therapy consistently produces faster and more complete regression of NVI/NVA than PRP alone. Large observational studies indicate that PRP combined with anti-VEGF may delay disease progression and reduce the need for urgent glaucoma surgery, though it does not reliably improve long-term visual outcomes once advanced disease is established.[64,65]

7.4 Anti-VEGF in Surgical Management of NVG

a) Adjunct to GDD

A recent systematic review and meta-analysis showed that combining anti-VEGF therapy with AGV implantation significantly improved postoperative IOP control at all time points up to and beyond 12 months, reduced postoperative hyphema, and lowered medication burden compared with valve implantation alone.[66]

Network meta-analyses further suggest that GDD surgery combined with intravitreal anti-VEGF achieves higher short-term success rates than surgery alone, although differences diminish at longer follow-up intervals.[67]

b) Adjunct to Trabeculectomy

Trabeculectomy in NVG is associated with high failure rates because of aggressive fibrovascular proliferation and postoperative hyphema. Preoperative anti-VEGF therapy improves surgical conditions by reducing neovascularization and inflammation. Long-term studies have shown that trabeculectomy following intraocular bevacizumab can achieve durable IOP control in selected eyes, though hypotony remains a significant risk, particularly in eyes with lower baseline IOP.[35]

Anti-VEGF agents, however, do not replace antimetabolites such as MMC for long-term wound-healing modulation and are best viewed as adjunctive rather than primary antifibrotic agents.[62]

7.5 Intracameral versus Intravitreal Delivery

Emerging evidence suggests that intracameral anti-VEGF delivery may offer faster regression of NVI and more rapid IOP reduction in advanced NVG compared with intravitreal injection. Stage-based treatment strategies propose intracameral anti-VEGF followed by early surgery for NVG with secondary angle closure glaucoma (stage III), while intravitreal anti-VEGF followed by PRP may suffice in earlier stages.[61]

A Bayesian network meta-analysis indicated that combined intravitreal and intracameral conbercept may offer superior short-term IOP reduction compared with other regimens, although long-term benefits remain uncertain, and overall evidence quality is low.[48]

7.6 Visual Outcomes and Limitations of Anti-VEGF Therapy

Despite improved short-term disease control, visual outcomes in NVG remain poor. Large real-world cohorts show that 75–90% of eyes progress to severe visual impairment or blindness.[65] High presenting IOP, advanced angle closure, delayed treatment and PDR are strong predictors of poor prognosis.[68] Anti-VEGF therapy alone does not significantly improve long-term visual outcomes and should not delay definitive ischemia-reducing or pressure-lowering interventions.[8,69]

8 SINGLE STAGE PROCEDURE OPTIONS IN NVG (IOP CONTROL AND LASER/ ANTI VEGF TOGETHER)

Patients presenting with advanced NVG with vitreous hemorrhage and high IOP pose a management dilemma whether to do glaucoma procedure first to control the IOP or proceed with PPV first along with PRP at the earliest which is the definitive treatment that addresses the primary retinal pathology.

In such situations a combined retinal and glaucoma surgical approach may be advantageous, as it simultaneously addresses both the primary retinal ischemia and the glaucoma. Recent literature suggests that giving intravitreal anti VEGF agents 3-7 days before the surgery significantly reduces iris and angle neovascularization, decreases intraoperative bleeding, and facilitates both vitrectomy and glaucoma surgery. Following which a combined PPV along with PRP and glaucoma like trabeculectomy or AGV or an endoscopic CPC can be performed at the same sitting.

Campagnoli et al. evaluated outcomes of combined PPV and Baerveldt glaucoma implant placement for refractory glaucoma in their retrospective review of medical records found a cumulative success rate of 79% in non-NVG group and 40% in NVG group at the end of 1 year (=0.038). Non clearing vitreous hemorrhage was the most common postoperative complication occurring in 16 (17%) eyes, and postoperative suprachoroidal hemorrhage developed in 5(5.4%) eyes in both groups combined. Serious complications like phthisis bulbi were seen in 12 out of 43 NVG eyes (28%) and only 2 out of 49 non NVG eyes (4%).[70]

Alabduljabbar et al. did retrospective review on CPC versus AGV in NVG with poor vision at presentation. Patients with NVG who had a visual acuity of 20/200 or less underwent one of the two procedures as a primary intervention: AGV or CPC. CPC and AGV procedures yielded good outcomes with similar IOP levels 12 months after the surgery. However, AGV demonstrated a higher overall success rate and a lower medication requirement than CPC. AGV implantation experienced a higher rate of complications than those treated with CPC. The main complications observed in the CPC group included inflammation, hyphema, and aqueous misdirection. On the other hand, the AGV group experienced complications such as the shallow anterior chamber, choroidal effusion, hyphema, hypotony, encapsulated bleb, tube obstruction, and aqueous misdirection and phthisis bulbi. As per their study the complications like phthisis bulbi were seen more in AGV group than in CPC group.[71]

In a pilot Randomized comparative trial conducted by Choy et al. 8 transscleral CPC and 12 AGV patients who had a minimum follow up period of 6 months with no previous glaucoma surgery were included in the study and they found that both procedures were equally effective in controlling the IOP and reducing glaucoma medications in NVG. However, eyes with AGV implant tended to have higher rates of visual loss and complications, as well as requiring more postoperative procedures, than eyes that were treated with transscleral CPC, although the difference was not statistically significant. But the sample size of the study was a major limitation to generalize their outcomes.[72]

Shalaby et al. in their study on outcomes of AGV and transscleral CPC in NVG in 121 eyes (70 AGV and 51 CPC) seen that both groups had similar IOP and medication number at 6 months but failure was significantly higher in the CPC group than in the AGV group. Serious postoperative complications were infrequent in both groups. Suprachoroidal hemorrhage occurred in three (4.3%) AGV eyes and no CPC eyes (P = 0.262). Hypotony and phthisis bulbi occurred in one (2.0%) CPC eye and no AGV eyes (P = 0.421).[73]

9 EMERGING THERAPIES THERAPEUTIC OPTIONS FOR MANAGING NVG

While the current standard of care has improved short-term outcomes, recurrence of neovascularization remains common. Accordingly, emerging long-term strategies focus on reducing the VEGF drive, including sustained-release anti-VEGF platforms, gene therapy, and disease agonist approaches that aim to restore vascular homeostasis rather than merely inhibit angiogenesis.

9.1 Sustained Release Anti VEGF agents

In NVG, the ischemic stimulus often persists for months, with VEGF levels rebounding as drug concentrations decline. Therefore, long-acting anti-VEGF agents may reduce recurrence and serve as effective adjuncts to retinal ablation.

Several sustained or long-acting anti-VEGF approaches have been explored in retinal disease and can possibly be effective in NVG.

a) Faricimab:

Faricimab is a bispecific antibody designed to bind and neutralise Ang-2 and VEGF-A.[74] The Ang-Tie2 signaling pathway maintains vascular stability; however, in nAMD, the elevated levels inhibit Ang-1 signalling. Such inhibition upregulates VEGF-A, leading to inflammation, vascular leakage, and neovascularization. By targeting both pathways, Faricimab has a more durable efficacy.

In the phase 3 non-inferiority trials YOSEMITE and RHINE, faricimab every 16 weeks was compared with aflibercept administered every 8 weeks in diabetic patients.[75]

b) Aflibercept 8 mg

Aflibercept 8mg (Bayer) was developed to achieve longer retreatment intervals by using a higher molar concentration of Aflibercept. High dose Aflibercept 8mg (q12w-q16w) was compared with Aflibercept 2mg (q8w) in a randomised controlled phase 3 trial PHOTON with extended dosing intervals.[76]

c) Susvimo

The Port Delivery System (PDS) has been designed to provide continuous intravitreal release of ranibizumab for approximately six months or longer. It comprises an ocular implant, a customized Ranibizumab formulation, and four dedicated ancillary devices for initial filling, surgical implantation, refill–exchange, and explantation when indicated.[77] The PDS with ranibizumab received approval in the United States for the treatment of neovascular age-related macular degeneration. However, due to a reported endophthalmitis incidence of approximately 2%, this novel drug delivery system has since been discontinued.[78]

d) Implantable Drug delivery System

Biodegradable intravitreal depots and hydrogels delivering small-molecule VEGF pathway inhibitors, as well as neuroprotective antiglaucoma agents, are under active investigation.[79] Multiple delivery platforms are being explored, including reservoir, capsule, nanosheet, nanofiber, microneedle, hydrogel, lens-based, in situ–forming biodegradable implants and triboelectric nanogenerator systems. Currently available sustained-release implants include Susvimo, Ozurdex, and Durysta, the latter providing prolonged delivery of bimatoprost.

Several factors limit the role of sustained-release anti-VEGF therapy in NVG:

- NVG eyes often have significant inflammation, synechial angle closure, and poor surgical tolerance
- Continuous VEGF suppression may impair wound healing, particularly in eyes requiring GDD or cyclodestructive procedures
- Sustained anti-VEGF therapy does not address the underlying ischemic stimulus and therefore cannot replace PRP

9.2 Gene Therapy

Gene therapy has achieved clinical success in inherited retinal dystrophies and is actively being studied in retinal vascular diseases, including neovascular age-related macular degeneration.

Micro RNAs (miRNAs) evaluated in animal models of ARMD exhibit different behaviour in human patients, leading to uncertainty regarding their role in the disease.[80]

Retroviruses and lentiviruses have been employed in gene therapy products, such as RetinoStat® (Oxford BioMedica, Oxford, UK, OXB-201) for nAMD (NCT01301443) and in stem cell therapy.[81] However, retroviruses and lentiviruses carry risks such as potential insertional mutagenesis and germline transmission.

AAVs are commonly used vectors for retinal gene transfer due to advantages like extended transgene expression, minimal risk of insertional mutagenesis, slight inflammatory responses, and low chance of germline transmission.[82]

An adenoviral vector containing the PEDF gene, an endogenous antiangiogenic factor, with deficient replication (achieved by deletion of E1, E3, and E4) was found to reduce the incidence of macular neovascularization in a phase 1 trial.[83,84]

An AAV2-derived vector, ixoberogene soroparvovec (AAV.7m8-aflibercept), named ADVM-22, was administered via intravitreal injection in nAMD aflibercept-responder patients. The Optic phase 1 multicentre randomised trial showed vision and CST remained stable throughout two years with annual anti-VEGF injections reduced by 80% (10.0 mean annual anti-VEGF injections to 1.9) in 2 × 1011 vg/eye and 98% (9.8 mean annual anti-VEGF injections to 0.2) in 6 × 1011 vg/eye cohorts.85 Intraocular inflammation responding to topical corticosteroids was observed in 60% of the patients with no systemic or long term ocular adverse effects at the end of 2 years. In the Diabetic Macular Edema patients (INFINITY trial) a Suspected Unexpected Serious Adverse Reaction (SUSAR) hypotony not responding to steroids was seen at 16-32 weeks after the administration of 6 x 1011 vg/eye high dose ADVM. This led to halting treatment in DME patients however no similar SUSAR was observed in nAMD patients.[86]

A gene encoding monoclonal portion of an anti-VEGF antibody structurally similar to ranibizumab called RGX-314 was studied in Diabetic retinopathy patients offering a one time therapy for the condition. Two routed of administration are being explored via subretinal injection and the suprachoroidal route (Phase 2 ALTITUDE trial).[87]

4D-150 is an investigational gene therapy engineered for multi-year sustained retinal delivery of anti-VEGF agents (aflibercept and anti-VEGF-C) via a single intravitreal injection using the proprietary R100 vector. In the phase ½ SPECTRA trial, which primarily evaluated safety, tolerability, and dose selection, 22 patients were enrolled across three dose cohorts, including the phase 3 dose of 3E10 vg/eye (n=9). Over 60 weeks, 4D-150 was well tolerated without intraocular inflammation or need for corticosteroid modification, and patients in the phase 3 dose group achieved a mean BCVA gain of +9.7 letters with a mean central subfield thickness reduction of 174 Qm on OCT.[88]

Gene therapy faces several important limitations when applied to NVG:

- **Irreversibility:** Once delivered, transgene expression cannot be readily stopped, posing risks in eyes that may later require surgery
- **Physiological VEGF suppression:** VEGF plays a role in endothelial survival and wound healing, particularly relevant in glaucomatous eyes
- **Inflammatory risk:** NVG eyes are already prone to inflammation, which may be exacerbated by viral vectors
- **Failure to address ischemia:** Like sustained-release anti-VEGF, gene therapy does not eliminate the primary ischemic drive

Despite advances in biological therapy, the core principles of NVG management remain unchanged:

1. Rapid regression of neovascularization with short-acting anti-VEGF
2. Definitive treatment of retinal ischemia with PRP
3. Timely and appropriate surgical IOP control

Sustained-release anti-VEGF therapies may improve disease stability and reduce recurrence but should be viewed as supportive rather than definitive treatments. Gene therapy, while promising, currently lacks sufficient safety and reversibility data to justify routine use in NVG. Disease agonist strategies represent a potential future direction, aiming to restore vascular homeostasis rather than aggressively suppress angiogenic signaling.

10 PROGNOSTICATING AND FOLLOW-UP PROTOCOL FOR NVG

Despite modern advances in anti-VEGF therapy, PRP, and glaucoma surgery, NVG continues to carry a guarded visual prognosis and high rates of surgical failure. Clinical outcomes are highly variable, reflecting differences in etiology, disease stage at presentation, baseline visual potential, and response to treatment.

10.1 Factors determining prognosis-

Etiology of Retinal Ischemia

The underlying ischemic etiology is one of the strongest determinants of prognosis. PDR generally confers a better prognosis than ischemic CRVO or OIS, provided adequate PRP and systemic metabolic control are achieved.[89,63,90] In contrast, ischemic CRVO is associated with extensive retinal non-perfusion, with NVG classically developing within approximately 90–120 days, however, it is postulated that the highest risk of developing NVG exists within the first 7-8 months of the disease.[21] OIS-related NVG carries the poorest prognosis, reflecting chronic hypoperfusion and limited potential for reversibility despite medical and surgical intervention.[91]

Stage of Disease at Presentation

Eyes presenting with early NVI and open angles demonstrate significantly better IOP control and visual outcomes compared with eyes that already exhibit NVA and peripheral anterior synechiae.[90,65] Advanced NVG presenting with corneal edema, very high IOP, and severe visual impairment is consistently associated with higher rates of surgical failure and vision loss.[92]

Baseline Visual Acuity and Visual Potential

Baseline visual acuity strongly predicts long-term outcomes. A large multicenter study has demonstrated that up to 50% of eyes presenting with visual acuity of 20/200(6/60) or better can achieve stable or improved vision with contemporary treatment algorithms.47 In contrast, eyes presenting with poor visual potential (visual acuity of worse than 20/100) are significantly more likely to require glaucoma surgery and further progress to blindness.[68]

IOP and Angle Status

Presenting IOP is one of the strongest predictors of outcome in NVG. Eyes presenting with very high IOP (>30–35 mmHg), and those requiring 2 or more topical glaucoma medication have a significantly increased risk of requiring glaucoma surgery and progressing to no light perception (NLP) vision.[89,75] Angle configuration is likewise an important determinant of prognosis. Open-angle NVG represents an earlier stage and is associated with better IOP control and outcomes compared with closed-angle NVG, which reflects advanced fibrovascular membrane contraction and peripheral anterior synechiae formation.[8,14,65] Once extensive synechial closure has occurred, medical therapy alone is rarely sufficient, and surgical intervention is usually required.

Response to Anti-VEGF Therapy and PRP

Intravitreal anti-VEGF therapy induces rapid regression of NVI and NVA, often within 4–7 days (Figure 18).[90] However, this effect is transient. Failure to consolidate neovascular regression with timely and adequate PRP is associated with recurrence of neovascularization and disease progression.[89] Eyes requiring repeated anti-VEGF injections without sustained regression frequently reflect an active and ongoing ischemic drive, carrying a worse long-term prognosis.

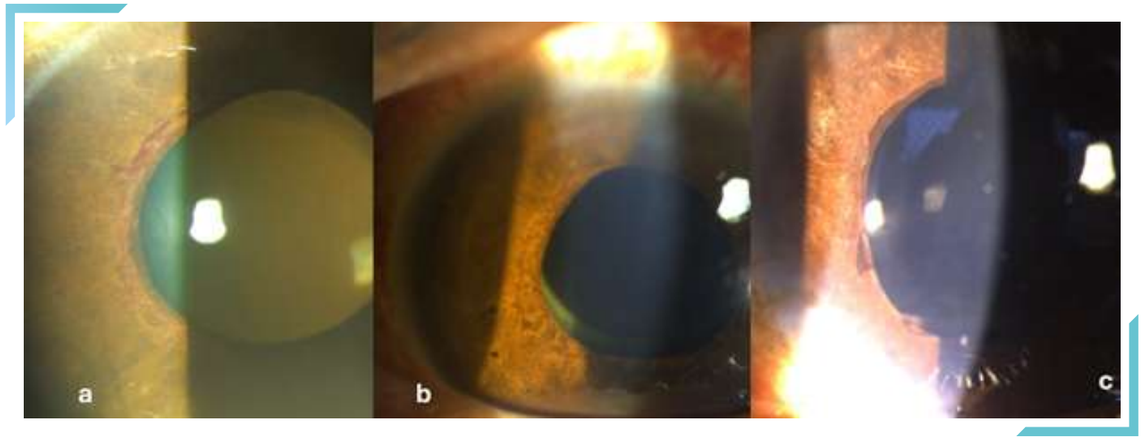


Figure18: Regression of NVI along with progression of ectropion uvea with anti-VEGF injections.

Surgical Prognostic Factors

NVG itself is a recognized risk factor for surgical failure. A meta-analysis comparing surgical modalities suggest similar IOP-lowering efficacy between trabeculectomy and GDDs.[93] Trabeculectomy augmented with anti-VEGF therapy has been shown to improve short-term IOP control, increase success rates, and reduce early postoperative complications compared with trabeculectomy alone, though these benefits may diminish beyond six months.[94] Cyclodestructive procedures remain an option for eyes with poor visual potential but are consistently associated with inferior visual outcomes.[47,93]

Risk Stratification in NVG

Based on current evidence, NVG may be stratified into three prognostic categories: (1) rubeosis iridis, where there is NVI with open angles, normal IOP, and good visual potential; (2) secondary open-angle glaucoma, with NVA, partial PAS, and elevated IOP; and (3) secondary angle-closure glaucoma, with closed angles, NVA, raised IOP, and usually with a guarded prognosis.[3]

10.2 Evidence-Based Follow-up Protocol

Acute Phase

Patients newly diagnosed with NVG require close monitoring. Review is recommended within 4–7 days following initial anti-VEGF injection to assess regression of neovascularization and IOP response.[90] Gonioscopy should be performed once corneal clarity allows. PRP should be initiated and completed as early as possible to suppress ischemic drive, ideally within 1-2 months.

Post-Anti-VEGF / PRP Consolidation Phase

Following completion of PRP and stabilization of neovascularization, follow-up every 2–4 weeks during the first 6-8 months, with visual field perimetry every 2 months.21 The following should be documented: IOP trend, recurrence of NVI/NVA, angle status, and optic nerve evaluation. Recurrence of neovascularization warrants repeat anti-VEGF therapy and reassessment of PRP adequacy.[62,61] Persistent IOP elevation despite maximal medical therapy should prompt early surgical planning rather than prolonged observation.[47,95]

Post-Surgical Surveillance

After trabeculectomy or GDD implantation, patients should be reviewed on postoperative day 1, at week 1, week 4, and then monthly for at least six months. NVG eyes are at increased risk of postoperative hyphema, inflammation, hypotony, and bleb failure, necessitating close surveillance. Adjunct perioperative anti-VEGF therapy may reduce early complications and improve short-term surgical outcomes.[61,66]

Evidence-Based Surveillance Protocol

Phase	Timing	Clinical Actions	Critical Checkpoints
Acute phase	**Day 0**	Diagnosis, Anti-VEGF #1, Medical IOP lowering	Check Fellow Eye (Dilated)
	Day 3-7	Confirm IOP response Initiate PRP Consider Glaucoma Surgery in high risk eyes	If no IOP drop: Check for angle closure or OIS High risk: IOP > 35 mmHg, Pain, >2 meds, PAS > 180°
	Week 4	Anti-VEGF #2 Continue PRP	If NVI persists, consider repeat intravitreal agent, combination with intracameral Anti-VEGF
	Month 2-3	Monthly Reviews Complete PRP (1500+ burns)	**Complete PRP:** Crucial to prevent recurrence
Consolidation Phase	**Month 4-6**	Every 4 weeks	Monitor for "Rebound" NVI
Maintenance Phase	**Year 1+**	Every 3-4 months	Watch for late bleb failure or Ghost Cell Glaucoma

11 INTEGRATION OF ARTIFICIAL INTELLIGENCE FOR RISK PREDICTION AND EARLY DIAGNOSIS OF NVG

The most important limitation in the appropriate management of NVG is delayed diagnosis. By the time the signs of NVG like rubeosis iridis and angle neovascularization become apparent, the patient already develops irreversible damage to optic nerve head. This is where Artificial Intelligence (AI) will emerge as a powerful ally. AI, with its ability to detect subtle patterns in large complex datasets, offers us a unique opportunity to shift NVG management from a reactive to a predictive and preventive strategy.

This article explores the current landscape, opportunities, and challenges in integrating AI for risk prediction and early diagnosis of NVG.

11.1 Understanding the burden and predictability of NVG

The course and risk magnitude of this sequence of events is highly variable. Some eyes with ischemic posterior segment pathology develop NVG within weeks, while others remain stable for months to even years. Currently, ophthalmologists rely on periodic slit lamp examination, gonioscopy, and imaging systems to detect signs of NVG when they become clinically apparent. What is lacking is an effective system to answer three clinically crucial questions:

1. Which patients are at higher risk of developing NVG?
2. When is NVG likely to develop?
3. Can intervention be timed before irreversible damage due to NVG occurs?

Currently, NVG risk stratification relies on clinical judgement, interpretation of diagnostic images, and biochemical markers. All of these can be subjective and may not accurately reflect subtle microvascular changes. On the other hand, AI models are inherently capable of detecting subtle patterns invisible to the human eye. These models can detect patterns hidden in OCT), OCTA, fundus photographs, FFA and longitudinal clinical variables

11.2 Artificial Intelligence for Ophthalmologists

Ophthalmology is particularly suited to AI because of its high reliance on high resolution imaging and structured clinical parameters. AI in ophthalmology predominantly involves:

- Machine learning (ML): Algorithms that learn patterns from structured clinical data.
- Deep learning (DL): Neural networks, particularly convolutional neural networks (CNNs), that analyse imaging data.
- Multimodal AI: Integration of imaging, clinical, systemic, and temporal data.[96,97]

11.3 AI for risk prediction of NVG

1. Imaging-Based Risk Stratification

Retinal imaging in modern times contains far more digital information than what is routinely interpreted in clinical practice. Deep learning models can analyse subtle features predictive of ischemia and angiogenic drive, including:

1. Ultra-widefield fundus photographs: Quantification of peripheral non-perfusion, venous beading, microaneurysm density, and hemorrhage patterns.[98]
2. Fluorescein angiography: Automated ischemic index calculation, leakage maps, and dynamic flow analysis.
3. OCT and OCTA):
    - Capillary non-perfusion in superficial and deep plexuses
    - Foveal avascular zone enlargement
    - Vessel density loss
    - Structural markers such as hyperreflective foci and inner retinal thinning[97]

Training AI systems on longitudinal imaging datasets can identify biomarkers of ischemia that precede clinically detectable NVG signs.

2. Clinical and Systemic Data–Driven Models

Beyond ocular imaging, the risk of development of NVG is influenced by several systemic and ocular factors. AI algorithms can integrate:

- Duration and control of diabetes (HbA1c trends)
- Presence of nephropathy or cardiovascular disease
- Type of CRVO (ischemic vs non-ischemic)
- Prior pan-retinal photocoagulation or anti-VEGF therapy
- Baseline IOP and angle configuration
- Follow-up adherence patterns

ML models can generate individualised risk scores, providing a more robust basis for risk stratification in NVG development.[99,100]

3. Multimodal and Temporal AI Models

The most powerful predictive systems combine imaging, clinical, and temporal data. For example, a multimodal AI model may analyse:

- Serial OCTA scans
- Changes in ischemic burden over time
- Response to previous treatments
- Systemic disease control[101]

Such systems continuously update risk as new data become available, mirroring real-world clinical practice.

11.4 AI for early diagnosis of NVG

Early diagnosis does not necessarily mean detection of visible neovascularisation. Instead, it refers to identifying the pre-neovascular stage, when intervention can even prevent disease progression. AI can assist in:

- Detecting subclinical angle or iris vascular changes on anterior segment imaging
- Flagging high-risk eyes for intensified surveillance

Integration of AI systems in Indian clinics, where time constraints may limit detailed evaluation at every visit.

11.5 Clinical applications in Indian context

1. Optimized resource allocation and follow-up plans:

   AI-driven risk stratification can help prioritise high-risk patients for closer follow-up, laser, or early anti-VEGF therapy, especially in resource-limited settings.

2. Preventive strategy

   Clinicians can intervene earlier in selected high-risk eyes, rather than waiting for anterior segment vascular signs, potentially reducing the incidence of refractory NVG.

3. Teleophthalmology and Vision centres

   AI models embedded in screening programs can identify patients at risk of NVG even before referral to tertiary centres.

4. Education

   AI systems can act as clinical decision-support tools, assisting young ophthalmologists and trainees in recognising high-risk patterns.[100]

11.6 Challenges and Limitations

Despite being a promising prospect, AI still faces few challenges:

1. Data heterogeneity: AI models trained on a limited dataset or non-Indian datasets may not fit well.
2. Black box phenomenon: Clinicians need to interpret the outcomes and the process involved in it.
3. Workflow Integration: Seamless integration of the AI models with the existing imaging platforms and EMRs will be a big challenge.
4. Ethical and medico-legal concerns: Careful communication and informed clinical judgement is required for AI based predictive diagnosis.

AI should be viewed as an adjunct, not a replacement, for clinical expertise.

11.7 Conclusion and future direction

The future of NVG care lies in personalized and predictive care. Prospective multicentric Indian datasets, robust learning models, effective integration of AI systems into imaging platforms and EMRs will likely define the next decade of NVG management. Importantly, collaboration between retina specialists, glaucoma experts, data scientists and governing bodies will be essential.

For ophthalmologists, AI represents not just a technological advancement, but an opportunity to move from late-stage management to true prevention of NVG-related blindness.

12 NVG IN PEDIATRIC EYES

Paediatric NVG is uncommon and can arise from any untreated systemic or ocular condition associated with retinal ischemia. Young children often present late due to an inability to recognize or report unilateral visual loss, and delayed diagnosis or treatment may culminate in complete vision loss and severe ocular pain, occasionally requiring evisceration after exclusion of malignancy and enucleation if malignancy is suspected or cannot be eliminated. In adults, NVG most commonly results from PDR, CRVO and OIS.. Since, these underlying conditions are infrequent in children, paediatric NVG is rare and arises from a diverse range of ocular and systemic disorders.[8,102]

12.1 Etiology

A. Retinal ischemic disorders

- Retinopathy of prematurity (ROP)
- Familial exudative vitreoretinopathy (FEVR)
- Coats disease
- PHPV

Retinopathy of prematurity (ROP)

It is characterised by abnormal development of retinal blood vessels in premature infants and glaucoma is a major vision-threatening complication in severe disease, with 1.36% of ROP eyes developing secondary glaucoma, due to advanced pathology or following surgical intervention. NVG occurs in 10% of cases, more frequently in stage IVA than stage V, likely due to higher VEGF levels.

Management includes retinal ablation and/or intravitreal anti-VEGF therapy. Stage IV ROP requires close, regular follow-up for early detection and prompt management of vision-threatening complications.

Familial exudative vitreoretinopathy (FEVR)

Familial exudative vitreoretinopathy (FEVR) is a hereditary retinal vascular disorder caused by Wnt pathway defects, leading to peripheral avascular retina and ischemic complications. Unlike ROP, it affects full-term infants and may remain undetected until later. NVG is rare but can present in advanced untreated cases, with glaucoma occurring in 6% of eyes, mostly as angle-closure, either neovascular or non-neovascular.[103]

Coats disease

Coats disease is a rare, usually unilateral retinal disorder in young males, marked by retinal telangiectasia with intra or subretinal exudation in the absence of significant retinal or vitreous traction (incidence ~0.09/100,000). NVG occurs in 8% of cases, typically in advanced stages, and historically predicts poor prognosis and enucleation.[104]

PHPV

Twisting of a persistent hyaloid artery can disrupt central retinal artery flow, causing secondary venous stasis and severe retinal ischemia, which may lead to NVG and permanent vision loss.

B. Inflammatory causes

- Chronic uveitis - Juvenile idiopathic arthritis–associated uveitis (JIA)
- Trauma
- Postsurgical anterior segment ischemia

C. Ocular tumours

- Retinoblastoma
- Medulloepithelioma
- Optic nerve tumours
- Uveal melanoma
- Ocular metastasis
- Retinal vaso-proliferative tumor
- Congenital melanocytoma

About 5% of eyes with intraocular tumors present with tumor-related elevated IOP, making tumors an uncommon cause of secondary glaucoma in children, most often seen with retinoblastoma, medulloepithelioma, or iris melanoma.[106,107]

Medulloepithelioma

Ciliary body medulloepithelioma is a rare embryonal tumor of the inner layer of optic cup epithelium, typically affecting children aged 2–5 years and occasionally linked to DICER1 syndromes.[108,109]

It often presents with unilateral NVG (37%) and retrolental cyclitic membrane (51%), findings that should raise strong suspicion for this tumor (Figure 19).[110]

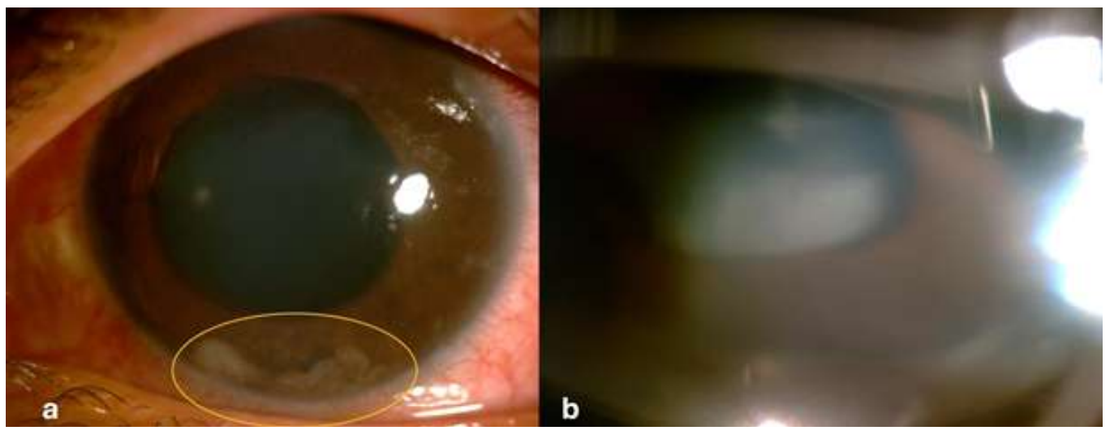


Figure 19: (a) Fluffy exudates in anterior chamber (tumor cells) in an eye with cilliary body medulloepithelioma; (b) In the same eye, gonioscopy showing mass behind the iris.

Retinoblastoma

NVG occurs in 12% of retinoblastoma cases, mainly in advanced tumors.[111] The predominant mechanisms of glaucoma are **iris neovascularization** (74%) followed by angle closure (27%) **from forward displacement of the iris–lens diaphragm**, while direct trabecular invasion is rare.[112]

Elevated IOP may also occur in anteriorly located tumors, which can be easily missed on B-scan ultrasonography, where findings may appear normal; ultrasound biomicroscopy can be valuable in such cases. These presentations are frequently misdiagnosed as congenital glaucoma, and incisional glaucoma surgery such as trabeculectomy can result in catastrophic complications. While initial glaucoma in retinoblastoma may respond to medical therapy, NVG usually indicates poor prognosis and often requires enucleation.[113]

Uveal melanoma

Secondary elevation of intraocular pressure occurs in 3% of uveal melanomas, with higher rates in ciliary body (17%) and iris (7%) than choroidal melanomas (2%), with mechanisms varying by location.

Mechanisms : Iris melanomas - angle invasion

Ciliary body melanomas - pigment dispersion and angle infiltration

Choroidal melanomas- iris neovascularization

In choroidal melanoma, NVG causes 56% of cases, and angle closure from lens–iris displacement accounts for 34%.[106]

Ocular metastasis

In a reported series of uveal metastatic cases, secondary elevation of intraocular pressure occurred in about 5% overall, with markedly higher rates in iris and ciliary body metastases compared with choroidal involvement. Elevated IOP was most often due to direct tumor invasion of the angle in iris and ciliary body lesions and angle closure either from choroidal detachment or retinal detachment in choroidal metastases, while NVG was an uncommon mechanism in metastatic disease.[106]

Retinal vaso-proliferative tumor

Retinal vasoproliferative tumors are benign proliferative vascular lesions that typically appear as red-pink to yellowish retinal masses, most often in the inferior retina, and are associated with prominent feeder vessels, retinal telangiectasia, subretinal exudation, macular edema, and epiretinal membrane formation. NVG can develop secondary to these tumors.[114]

Optic nerve tumours

NVG is a rare complication of optic nerve glioma, usually from retinal or anterior segment ischemia, where tumor growth disrupts circulation, causing venous stasis, iris neovascularization and subsequent NVG.[115]

D. Systemic diseases

- Juvenile myelomonocytic leukaemia
- Neurofibromatosis type 1
- Juvenile xanthogranuloma
- Systemic lupus erythematosus

Neurofibromatosis

- NF-1 may be associated with retinal vascular abnormalities predisposing to iris neovascularisation and NVG. VEGF-driven anterior segment neovascularization arises from retinal ischemia, vasoproliferative lesions, or choroidal neurofibromas, with chronic detachment worsening outcomes, especially in children.[116]

12.2 Pathophysiology

- Retinal ischemia and VEGF upregulation (either due to abnormal retinal vascular development, vascular occlusion or from tumor cells)

12.3 Clinical features

A. Symptoms

- Redness, pain, photophobia
- Increase in the size of the eye
- Excessive watering
- Decreased vision
- Irritability in infants

B. Signs

- Strabismus
- Buphthalmos
- Elevated IOP
- Corneal edema
- Angle neovascularization (on gonioscopy)
- Hyphema
- Psuedohypopyon or fluffy exudates in anterior chamber (tumor cells)
- Localised pigmentary changes in the iris
- Iris neovascularization
- Xanthocoria
- Sectoral cortical cataract
- Mass in the posterior segment

Coats

Coats disease may present vision loss, strabismus, xanthocoria, nystagmus or pain, with advanced cases showing features of NVG with anterior chamber cholesterolosis and heterochromia.

Diagnosis relies on the classic triad: exudative detachment, telangiectatic vessels and peripheral nonperfusion.

Medulloepithelioma

While most causes paediatric iris neovascularization is clinically identifiable, unexplained cases may signal early ciliary body medulloepithelioma and require thorough evaluation with gonioscopy, scleral depression, and ultrasound imaging (Figure 20).

Early mismanagement of ciliary body medulloepithelioma is common, often delaying diagnosis. Lesions are hard to visualize until tumor growth causes secondary signs like glaucoma, cataract, lens subluxation, pupillary masses or extraocular extension.

Figure 20: (a) Fine new vessels observed at the pupillary border and extending onto the peripupillary iris surface in an eye of 9yrs old girl with cilliary body medulloepithelioma and NVG; (b) In the same eye, there is peripheral iridocorneal adhesion inferiorly, corresponding to the location of the mass situated behind the iris in that region; (c) Gonioscopy showing mass behind the iris; (d) UBM of the same eye showing, heterogenous acoustically dense ciliary body mass at 6 & 7 clock hour measuring 3.45 x 2.27mm thickness (e) Extraocular extension of the tumor in the same eye in a child who was lost to follow up for 2yrs after advising enucleation.

12.4 Evaluation & Investigations

- Paediatric glaucoma assessment is challenging; EUA is needed if cooperation is poor, with serial EUAs for follow-up when required.[107-117]
- Intraocular pressure measurement by perkin's tonometer, gonioscopy assess the angle neovascularisation, synechial closure, reveal ciliary body mass behind the iris through a dilated pupil, which can be aided by UBM or anterior segment OCT, when visualization is limited.
- In suspected medulloepithelioma, UBM and AS-OCT effectively detect ciliary body masses with intratumoral cysts, which sometimes seen in the aqueous or vitreous.
- Anterior retinoblastoma, which can be missed because of absence of obvious intraocular mass can be detected, with the help of UBM which shows thickening of cilliary body. High suspicion in the presence of NVI without obvious cause is very important in such cases.
- Fundus evaluation via indirect ophthalmoscopy is essential but may be limited by media opacity, making multimodal imaging, including ultrasonography, critical to assess retinal detachment, haemorrhage, or masses.
- In Coats disease, diagnosis is primarily based on classic triad. In advanced cases, it is crucial to differentiate it from retinoblastoma which may require USG, CT, or MRI to detect calcification, invasive procedures are generally avoided if malignancy cannot be excluded.
- Wide-field fluorescein angiography is useful for detecting peripheral retinal nonperfusion and guiding therapy.
- Overall, identifying and addressing the underlying ischemic drive-whether retinal nonperfusion, tumor-related VEGF secretion, anterior segment ischemia, or chronic detachment-is fundamental to guiding management and prognosis in paediatric NVG.

12.5 Management Strategies

(Multidisciplinary and aggressive)

- There are no studies specifically addressing the treatment of NVG in children and management is therefore guided by treatment of the underlying cause.
- In cases secondary to intraocular tumors, primary treatment of the tumor is essential, as tumoral regression alone may lead to resolution of NVG.
- The gravest error in management of paediatric glaucoma is operating on an eye with an unrecognized intraocular tumor, as surgery may spread tumor cells and increase morbidity. Conversely, failing to identify the cause of raised IOP can allow tumor progression, reducing globe salvage.
- Glaucoma in young children—especially unilateral & atypical cases—should raise suspicion for tumors, which should always be ruled out, even though primary congenital glaucoma is more common.
- In the management of intraocular tumors associated with secondary glaucoma, the foremost priority is survival, followed by preservation of the globe and, where possible, maintenance of visual function.
- Treatment options includes local therapies(transpupillary thermotherapy, plaque brachytherapy, partial lamellar sclerouvectomy) or enucleation, the latter for large/advanced tumors.
- In eyes with prior inadvertent intraocular surgery, enucleation should include the previous surgical site to reduce residual tumor risk. If globe salvage is feasible, careful IOP control and close long-term follow-up are essential for tumor management and visual rehabilitation.

- In NVG caused by retinal ischemia or vasoproliferative tumors, anti-VEGF or intravitreal steroids with laser or cryotherapy can control retinal and iris neovascularization.[108-118]
- If IOP raise persists despite above measures, surgery may be needed. Glaucoma drainage devices are preferred in refractory NVG, while trabeculectomy has high failure rates even with antimetabolites.[109-119]
- In eyes without visual potential, less invasive measures like transscleral cyclodiode laser therapy may be used to control pain and avoid evisceration or enucleation when possible. In the past, advanced Coats disease often required enucleation due to difficulty distinguishing it from retinoblastoma, but modern imaging now allows safer differentiation, reducing the need for such radical intervention.

12.6 Prognosis and outcomes

- Paediatric NVG generally has a poor prognosis, often resulting in severe vision loss or even loss of the eye. Early counselling of caregivers is essential to set realistic expectations and guide treatment decisions, which may be palliative rather than aimed at vision preservation.

12.7 Conclusion

- The diagnosis and management of NVG in children are particularly challenging due to its rarity and its frequent association with systemic disease or advanced ocular pathology, such as stage 4 Coats disease or group E retinoblastoma.
- In children with NVG, evaluation should include both ocular and systemic assessment to identify the underlying cause.
- Accurate diagnosis and careful assessment of visual potential are crucial, particularly in young children, to guide appropriate management for each individual case.

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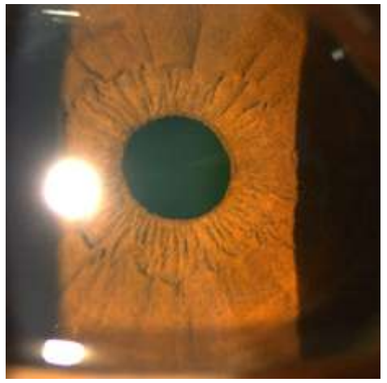
CASES

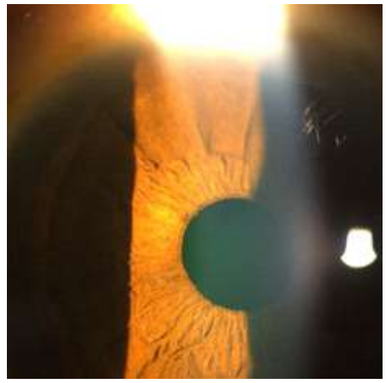
Case1:

A 54 year old female came for regular checkup. On examination both eyes had 6/6 vision with IOP being 14 mm Hg OD and 13 mm Hg OS. OD slit lamp examination showed NVI along pupillary margin (a,b). Fundus examination showed midperipheral microaneurysms and dot hemorrhages(c). Iris angiography confirmed presence of NVI (d). Fundus fluorescein angiography confirmed presence of midperipheral microaneurysms without any gross retinal ischemia (e).OCT showed no macular edema (f). Carotid doppler of neck confirmed presence of 60 % occlusion of common carotid artery on the right side clinching the diagnosis of Ocular ischemic syndrome.

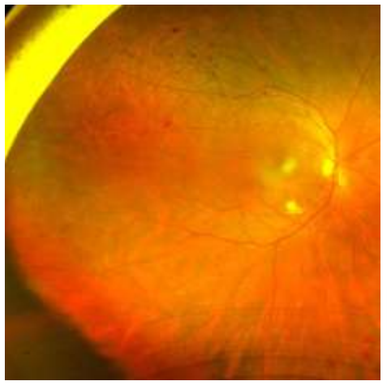
a)



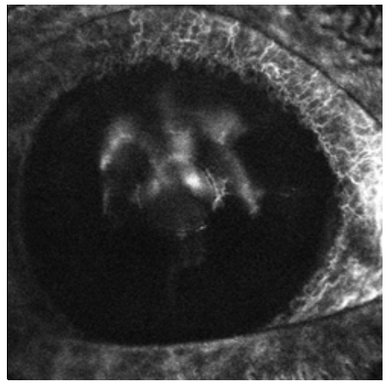
b)



c)



d)



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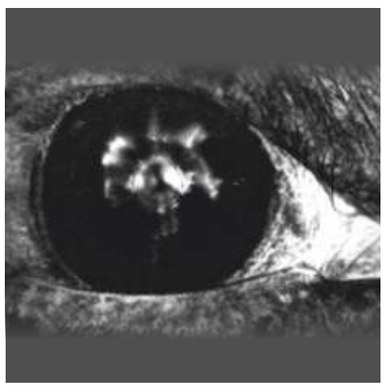
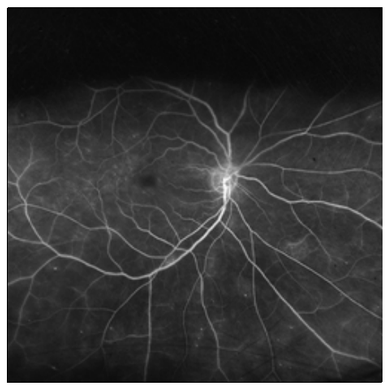
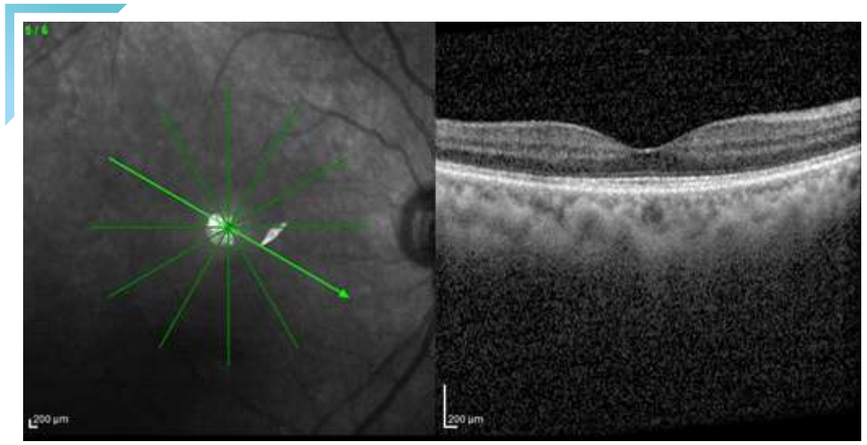


f)

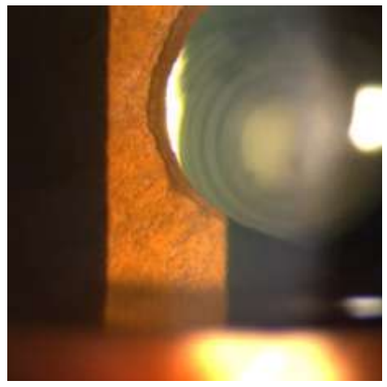




Case 2:

A 62 year old male with history of sudden vision loss OS about 6 months back and history of pan retinal photocoagulation presented with complain of pain. Presenting visual acuity was finger counting at 6 metres and IOP was 48 mmHg. Slit lamp examination showed ectropion uvea and NVI (a). Fundus examination showed advanced cupping with laser spots and blot haemorrhages in all quadrants suggestive of lasered central retinal vein occlusion (b). Iris angiography showed NVI along the pupillary margin (c). FFA showed enlarged foveal avascular zone, extensive capillary non perfusion area with unlasered area in temporal macula (d). OCT showed np macular edema. Patient underwent antiVEGF injection under cover of maximum torelable antiglaucoma medications, followed by laser augmentation and finally trabeculectomy to control IOP.

a)



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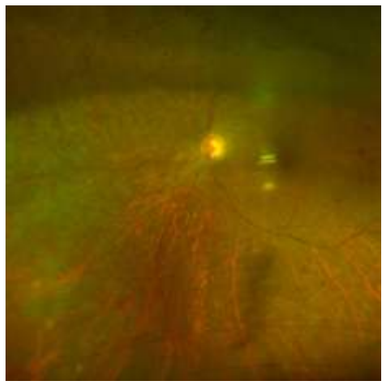
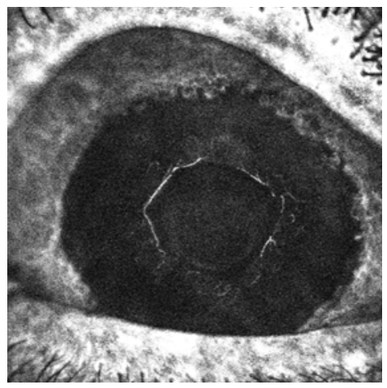
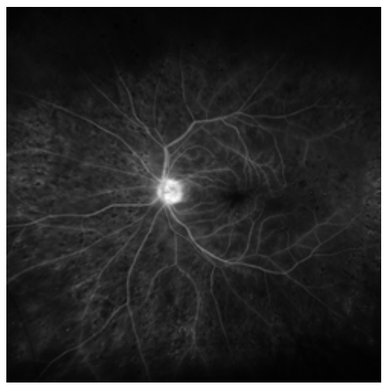


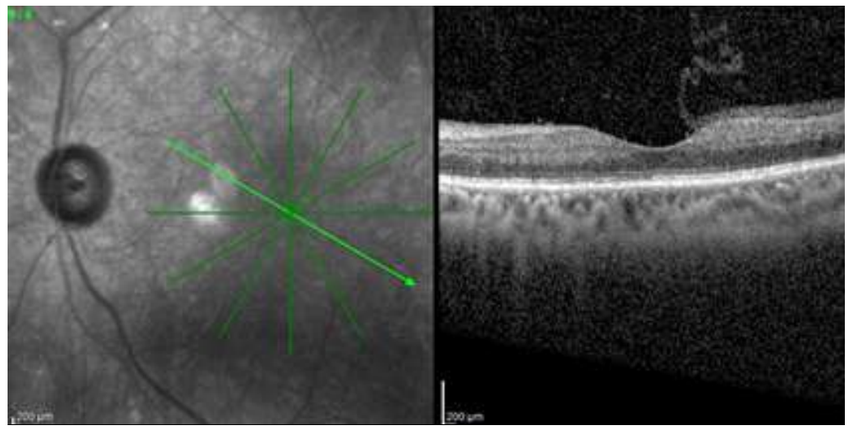
c)



d)



e)

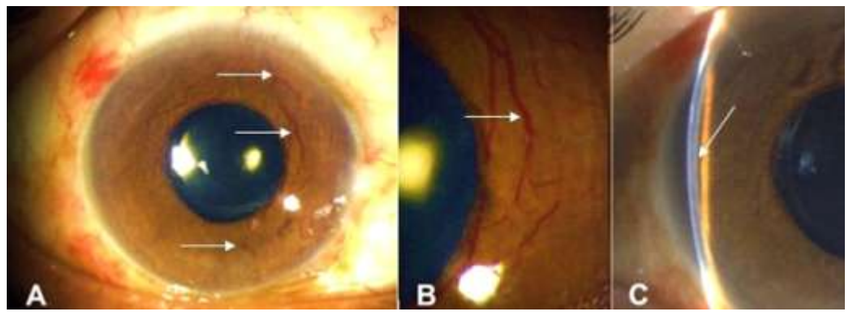


Case3:

A 60-yr-old male presented with diminution of vision in both eyes for 4 months, which was insidious in onset and associated with pain, redness, and watering. He had uncontrolled diabetes mellitus for the last 7 years and hypertension for the last 2 years, which was diagnosed incidentally after an episode of right sided hemiparesis. He underwent cataract surgery with IOL implantation in both eyes 2 years back followed by good visual gain. Visual acuity started deteriorating after 1.5 years of surgery for which he consulted at a local hospital where he diagnosed with Proliferative Diabetic Retinopathy (PDR) with clinically significant macular edema in both eyes. Pan-Retinal Photocoagulation (PRP) was done in both eyes in 3 sittings and referred for further management. On presentation his best corrected visual acuity (BCVA) was counting fingers in the right eye and perception of light in the left eye. The intraocular pressure (IOP) was 46 and 40 in the right and the left eye respectively off anti-glaucoma medications (AGMs). Anterior segment examination revealed extensive neovascularization of iris (NVI) in both eyes (more in the right eye), with closed angles in both eyes on gonioscopy (Figure 1-2).

Posterior segment examination revealed lasered PDR with a cup disc ratio of 07-0.8 (Fig 3) in both eyes. He was diagnosed with NVG (angle closure glaucoma stage) with Proliferative Diabetic Retinopathy (s/p Pan Retinal Photocoagulation).

He was started on oral and topical AGMs. Anti VEGF injection was given in the right eye followed by implantation of AGV within the next week. On first post-operative day the tube was visible in sulcus with a hyphema of 2 mm with an IOP was 16 off. The hyphema decreased on the third post operative day and gradually cleared in the next week. The left eye was planned for diode laser cyclophotocoagulation (DLCP). The patient could not follow up for the next 4 months. After 6 months, anterior segment examination revealed regressing NVIs in the right eye, no hyphema, and tube in the sulcus (Fig 4). The IOP was 22 and 52 in the right and the left eye respectively. Two AGMs were added in the right eye and the left eye was planned for DLCP.



Case 3.1:

A – Anterior segment photograph of the right eye under diffuse illumination showing florid NVIs (white arrows). B – Magnified view of the NIVs in the nasal quadrant (white arrow) C – Slit photograph of the anterior segment showing shallow peripheral anterior chamber (white arrow).

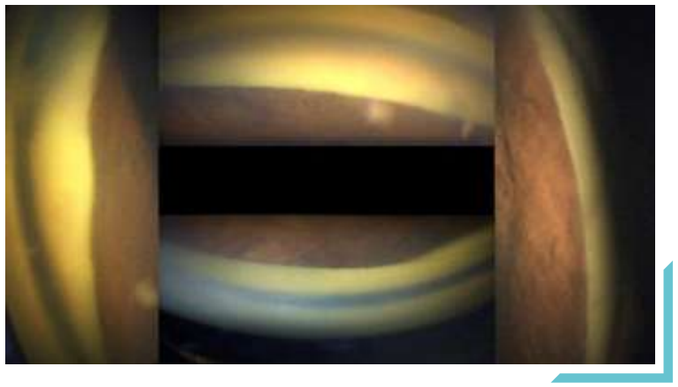
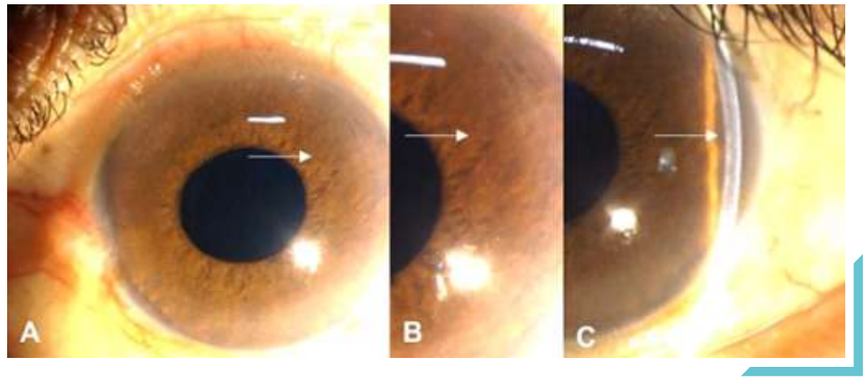


Figure 3.2- Gonioscopy photographs of the right eye showing closed angles in all quadrants

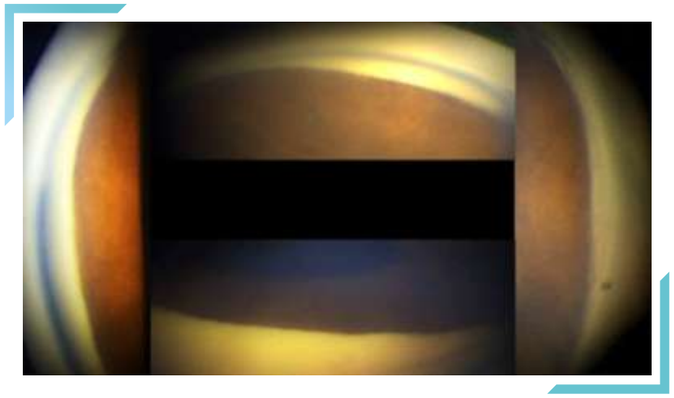


Case3.3:

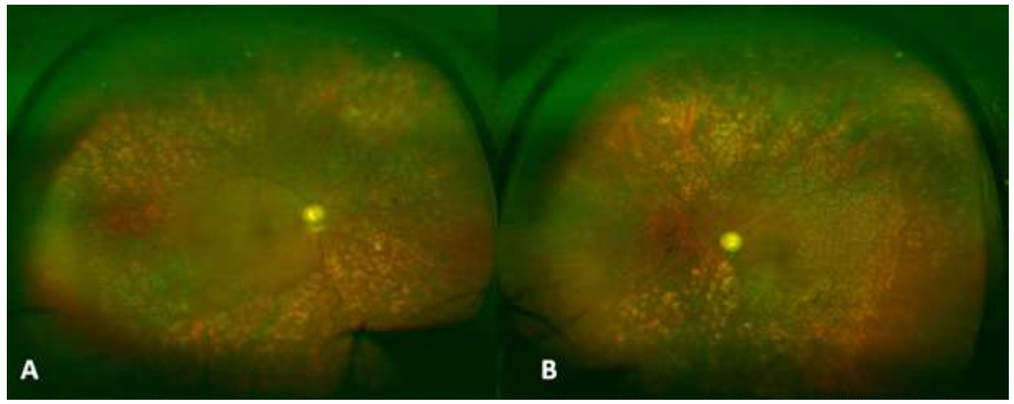
A: Anterior segment photograph of the left eye under diffuse illumination showing NVIs in the temporal quadrant (white arrow)

B: Magnified view of the NIVs in the temporal quadrant (white arrow)

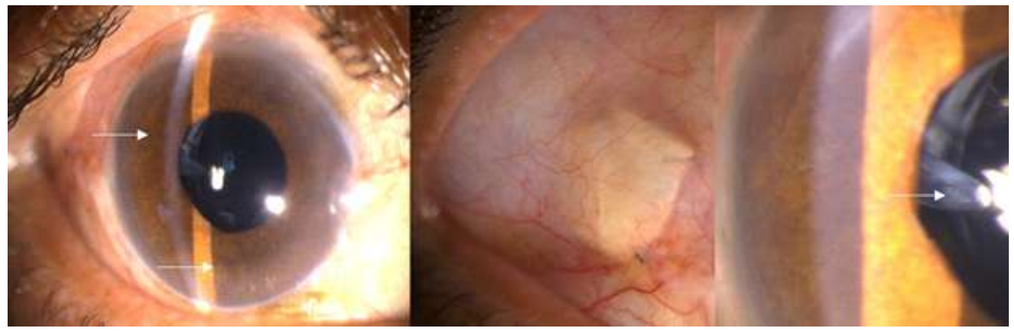
C: Slit photograph of the anterior segment showing shallow anterior chamber



Case 3.4: Gonioscopy photographs of the left eye showing closed angles in all quadrants



Case 3.5: Wide field fundus photograph of both the eyes (A-right eye, B left eye) showing extensive laser scars



Case3.6: Six months post-surgery

A: Anterior segment photograph of the right eye showing regressing NVIs, no hyphema

B: Magnified view of the scleral patch covering the tube and a formed capsule in the plate area

C: Slit photograph of the anterior segment (magnified view) showing regressed NVI's and tube in sulcus.

VIDEO LEGENDS

Video 1:
Iris angiography in NVG highlighting the leakage from NVI

Video 2:
Ahmed Glaucoma Valve in NVG

Video 3:
Ahmed Glaucoma Valve in Post retinal detachment NVG

Video 4:
Single step approach to manage NVG-Pars plana vitrectomy with retinal endolaser with diode laser cyclophotocoagulation

Video 5:
Single step approach to manage NVG-Pars plana vitrectomy with retinal endolaser with cyclocryo with anti-VEGF injection

Video 6:
Endocyclophotocoa-gulation of ciliary processed using vitreo-retinal laser probe

Video 7:
Endocyclophotocoa-gulation of ciliary process

Video 8:
Diode laser cyclophtocoagulation in a patient of NVG

Video 9:
Trabeculectomy with releasable suture in NVG

Video 10:
Glaucoma drainage device with sulcus tube placement in phakic NVG eye

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