Recent Advances in OPHTHALMOLOGY–13

Salient Features
- Contains two editorials and 19 chapters on selected topics in ophthalmology
- Focuses mainly on endophthalmitis, its differential diagnosis and control
- Includes an interesting subject of intravascular intervention in neuro-ophthalmic disorders
- Discusses the text with the help of numerous illustrations in diabetic macular edema
- Opens new avenues for the treatment and progression of glaucoma through imaging.

HV Nema MS has a distinguished academic career and is well-known for teaching, researches and publications. He has served as a Consultant Editor/Advisory Editor to Indian Journal of Ophthalmology, Afro-Asian Journal of Ophthalmology and Indian Journal of Optometry. He has published more than 6 dozen papers in the national and international journals. He is an established author in the field of ophthalmology. Ophtalmic Syndromes (Butterworth; London, UK, 1973) and Textbook of Ophthalmology 6th edn, 2012, Jaypee Brothers Medical Publishers, New Delhi, India are some of his popular books. He has edited 13 volumes of Recent Advances in Ophthalmology and 3 editions of Diagnostic Procedures in Ophthalmology, which were well-received by readers and favorably reviewed in Indian and international journals. He has delivered guest-lectures in many universities.

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Recent Advances in Ophthalmology–13

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The year 2017 marks the 25th year of publication of *Recent Advances in Ophthalmology* (RAO). The main objective of the publication of RAO is to keep abreast the postgraduate students and practicing busy ophthalmologists of South East Asia with the recent development in ophthalmology. It is a tremendous task in which a galaxy of national and international ophthalmologists has been supporting us right from the inception of the book. We received thumbing response from readers and reviewers.

Like its predecessors, the 13th volume of RAO contains selected topics on cornea, uvea, glaucoma, retina and systemic diseases. Editorials on imaging in glaucoma and intravascular interventions in ophthalmic disorders are included to highlight the diagnostic treatment aspect of these diseases respectively.

Refractive lenticule extraction (ReLEx), small incision lenticule extraction (SMILE) is a bladeless and flapless procedure wherein a corneal lenticule is removed by femtoseconed laser. It is less invasive and does not cause dryness and is free of corneal flap complications. However, it is in an evaluation stage. SMILE has several limitations such as, it cannot treat hyperopia and takes longer time for visual recovery. On the other hand, laser-assisted in situ keratomileusis (LASIK) is an established technology which can provide good visual acuity in a short time. It has a versatile ablation profile and can correct all types of ametropia. Alio and coworker have presented a critical account of both types of refractive surgery.

Many patients with ocular tuberculosis may not present any evidence of primary tuberculosis. It is reported that only 1.4% of patients with primary tuberculosis develop ocular manifestations. Ocular tuberculosis is unilateral and asymmetrical. It may result from hematogenous spread. It may cause a wide spectrum of lesions ranging from ocular surface to optic nerve. Biswas and associates have described the ocular lesions of tuberculosis and summarized the ongoing research and development in the diagnosis and treatment.

Some cases of uveitis pose a challenge to the treating ophthalmologists because they are chronic, recalcitrant and sight threatening. They remain refractory to systemic corticosteroid and immunosuppressant therapy. Both these drugs cause unacceptable side effects; therefore, intravitreal administration of biologicals is considered relatively safer and effective. Majumder and Biswas described the importance of intravitreal therapy.

We know that diabetic macular edema (DME) is the leading cause of blindness in patients with diabetic retinopathy. A poor glycemic control, impaired blood retinal barrier integrity, release of vasoreactive substances and altered vitreoretinal interface play their complex role in the pathogenesis of DME. The control of metabolic factors, laser photocoagulation therapy, and vitrectomy are effective, sight-saving interventions. Das and associates have discussed DME in some details with the help of nice illustrations.

Classical case studies of postoperative endophthalmitis are presented by Verma and Chakravarti in the chapter on endophthalmitis. The pictorial case studies reveal not only
the mode of presentations but also their response to the given treatment. Management of endophthalmitis mainly comprises intravitreal antibiotics and pars plana vitrectomy. Authors have described prophylaxis, availability of newer intravitreal antibiotics, cluster infection and legal issues related to endophthalmitis also.

Toxic anterior segment syndrome (TASS) may be confused with blinding endophthalmitis. Hence, it is also included in the volume. The differentiating points between these two conditions are detailed.

Prevention of postoperative endophthalmitis is a joint responsibility of operating surgeons, staff of the theater and paramedical staff. Viewpoints of an experienced microbiologist are projected in the chapter on control of infection in ocular surgery.

Oxidative stress, chronic inflammation and genetic and environmental factors largely contribute to the occurrence of age-related macular degeneration (AMD). Chandra and Kulkarni have reviewed the role of anti-oxidative stress therapies, anti-inflammatory therapies, visual cycle modifying agents, choroidal blood flow enhancing agents and regenerative stem cell therapies in the prophylaxis of AMD and concluded that these therapies lack definitive evidence of benefit. Therefore, Age-related Eye Disease Study (AREDS) formulation remains the mainstay of prophylaxis. Anti-VEGF agents have a definite place in the treatment of wet AMD, but they need repeated intravitreal injections, and develop drug resistance and tissue atrophy from chronic use.

Idiopathic polypoidal choroidal vasculopathy (IPCV) is an ill-understood clinical entity that has some common features of AMD. Whether AMD and PCV represent two different and distinct entities or are variants of the same disease? Gopal and coauthors have tried to answer these queries. Presence of orange nodules, large hemorrhages, absence of drusen and typical indocyanine green (ICG) angiography picture helps to differentiate the two different disease entities.

Chapters on ocular sarcoidosis, retinoblastoma, ocular surface disorder, macular phototoxicity, herpes, nystagmus, Behcet’s disease, and cystinosis have also been included in this volume.

Recent developments in ophthalmology have significantly revolutionized the treatment of eye diseases and improved the quality of patient’s life. It is hoped that readers especially postgraduates, and residents and general practitioners will find the book useful in the examination and day-to-day care of their patients, respectively.

HV Nema
Nitin Nema
We express our sincere thanks and appreciation to all authors of *Recent Advances in Ophthalmology-13* for their very informative contributions. Dr Ronnie George and Dr Arun Gupta deserve our grateful thanks for writing the editorials on a short notice.

We are thankful to Shri Jitendar P Vij (Group Chairman), Mr Ankit Vij (Group President) of M/s Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India, and staff for their continued interest in the publication of the *Recent Advances in Ophthalmology Series*. 
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The past two decades have seen the availability of commercially available instruments that could image the optic head and nerve fiber layer. This was an exciting development as various reports had suggested that more than 20% nerve fiber layer loss occurred before the then available functional tests could detect visual field damage. Development of these techniques—the Heidelberg Retinal Tomograph (HRT) and GDx Nerve Fiber Analyzer gave rise to the possibility that it was now possible to image and detect the optic disc damage early. However, early studies demonstrated sensitivities and specificities in the mid-eighties—not really consistent with a paradigm shift in our ability to diagnose glaucoma in everyone earlier than would be possible with conventional perimetry.

This poor diagnostic performance is primarily a function of the huge inter-individual variability seen in optic disc morphology. Since, optic disc size itself shows an almost 600% variation. It is unlikely that any device would accurately classify optic discs as normal or glaucomatous with very high accuracies. This led to the realization that the true potential of imaging would be in the field of progression and reports demonstrated that imaging had the potential to detect change before it occurred on visual fields.

The advent of the GDx gave us the ability to actually measure the nerve fiber layer parameters and was a new clinical parameter entirely. It demonstrated extremely good diagnostic capability in the initial reports, subsequent reports however put its diagnostic ability on par with the other imaging devices. The GDx also had the misfortune of having three significant hardware changes during its lifetime. These were carried out as a way to minimize the effect that other birefringent structures had on the nerve fiber layer measurements. While this resulted in improved testing accuracy this came at the cost of no backward compatibility with earlier versions of the device. This effectively limited its utility in assessing progression since few patients had long-term follow-up on a single device. The advent of the spectral domain optical coherence tomography (OCT) effectively sounded the death knell for the GDx since you now had a device which could measure nerve fiber layer (NFL) at higher resolutions in addition to having retinal applications too.

While, the OCT revolutionized macular imaging, its impact on glaucoma was less dramatic with time domain technology. While, it was as effective as the HRT and GDx in detecting the disease there were concerns about the follow-up scans not being obtained from the same locations as the baseline scans because of poor image registration. This limited its utility in assessing progression as compared to the HRT where good image registration was available.

The resolution of the OCT was further enhanced with the spectral domain OCT. This was made possible by the improved hardware and the improved
computation power available. However, these generational changes were also backward incompatible rendering a lot of follow-up data useless. The HRT was in this respect an excellent tool because the hardware changes still permitted backward compatibility with earlier scans. The longest optic disc follow-ups for glaucomatous eyes is possibly available on the HRT because of the backward compatibility making it possible to use patient data from earlier devices for comparison. However, the HRT III will no longer be manufactured while support will be provided for existing devices. This has effectively limited the future utility of the HRT since most newly detected glaucoma patients would be imaged on the OCT.

The spectral domain OCT promised superlative resolutions. However, these resolutions are rarely seen in clinical practice partly because of issues with eye movements and scan artefacts. In spite of this, the level of detail available and measurement accuracies mean that it is better at detecting progression than earlier devices. However, the large number of device manufacturers is an issue since measurements between various devices are not the same and patients would have to be imaged on the same device for meaningful data on progression.

While the devices are helpful in classifying disease one must always remember that “abnormal” values on imaging are statistical abnormal and in the absence of corroborating clinical data should not be taken at face value as evidence of disease. The over diagnosis of glaucoma because of the so called “red disease” is very common and results in unnecessary medications and hardship to the patient. It is also worth keeping in mind that most normative databases include only eyes with “normal” optic disc morphology. There are very few macrodiscs or microdiscs. Tilted and otherwise anomalous discs are also not included. Using any imaging tool on such eyes will invariably result in abnormal results which do not necessarily indicate glaucomatous damage. It is also important to keep in mind that the imaging techniques perform better at detecting glaucoma progression early in the disease. In more advanced disease, perimetry is still more sensitive in detecting progression.

The adaptive optics devices promise almost cellular resolutions. They are currently limited by very small image windows which limit their utility in glaucoma detection.

Further improved resolutions and testing algorithms on the OCT will make it possible to perhaps detect progression earlier. This would require a rethink of our clinical strategies. Unfortunately, too rapid changes in technology are sometimes detrimental in glaucoma since in a slowly progressive disease our patients need to be tested for years before we can detect slow rates of progression. While highlighting the importance of imaging keep in mind its limitations and the need for clinical judgment before any major diagnostic or therapeutic decisions are made.

REFERENCES

Common orbital vascular lesions include cavernous hemangioma, lymphangioma, varix, arteriovenous malformation and vascular fistulas. A correct diagnosis is important because natural history and proper management are often dramatically different among no-flow, slow-flow, and higher-flow lesions.

Most of orbital lesions clinically present with proptosis, conjunctival congestion, chemosis, conjunctival bleeding, hemorrhage, pain, dropping of eyelids and restriction in eye movements. Due to these symptoms, patients come to the hospital early to seek the treatment.

For the patients with orbital lesions, a complete evaluation is essential to plan further diagnostic and treatment strategy. A complete high-resolution imaging with computed tomography (CT) or magnetic resonance imaging (MRI) has become most important investigations. Digital subtraction angiography has been considered the gold standard for vascular lesions including orbital lesions. Angiography can provide information about arterial blood supply, venous drainage, vessel caliber, collateral circulation, flow velocity, arteriovenous shunting, and presence of flow-related aneurysms which is essential for planning the interventions. CT and CT-angiography can provide excellent visualization of large and medium-sized blood vessels with dynamic information about blood flow to a vascular orbital lesion.

The various ophthalmic pathologies which can be diagnosed accurately and few of them can be treated using interventional radiological techniques are:

- Orbital vascular lesions
  - Arterial and arteriovenous lesions
  - Arteriovenous malformations
  - Arteriovenous fistulas: Congenital, spontaneous, post-traumatic
  - Ophthalmic artery aneurysms
- Arteriovenous fistulas
  - Carotid–cavernous fistula (CCF): Direct and indirect
    - Type A: Direct CCF—cavernous internal carotid artery (ICA) to cavernous sinus
    - Type B: Feeders from dural branches of internal carotid artery
    - Type C: Feeders from dural branches of external carotid artery
    - Type D: Feeders from dural branches of both internal and external carotid arteries.
  - A complex venous anomaly: Deep orbital varix
  - Highly vascular lesions and vascular tumors

Endovascular Interventions in Ophthalmic Disorders

Arun Gupta
• Miscellaneous: Coats disease
• Thrombolysis for central retinal artery
• Venous lymphatic malformations—capillary, cavernous, and cystic lymphatic malformations.

Surgery for these lesions is difficult due to high-risk of bleeding. The highest degree of success has been found when vascular malformations are treated by a multidisciplinary team. Image-guided therapy has proved highly effective with good to excellent results possible in 75–90% of patients.\(^4\) Interventional radiologists have taken a central role in the multidisciplinary team.

To treat vascular lesions of the orbit various routes had been tried with mixed results which are:
• Percutaneous
• Arterial
• Venous
• A combination of above.

**Percutaneous Treatment**

Various slow flow orbital vascular malformations can be treated via percutaneous route. Most of the malformations can be successfully punctured by needle under guidance of X-ray fluoroscopy, CT, duplex sonography, or MRI. The next step is sclerotherapy of the lesion with the volume estimation of sclerosing agent.\(^4\)\(^-\)\(^7\) The necessary steps for safe performance of sclerotherapy include precise preprocedural lesion visualization and characterization, accurate needle placement, determination of the correct volume of sclerosing agent for injection, and real time monitoring of venous egress during the injection procedure.

**Arterial Route**

- **Carotid-cavernous fistula (CCF):** Interventional radiology has changed the management of all types of CCFs. The direct CCFs are treated using balloons, coils, stent-assisted coiling or by covered stents with complete cure. The Onyx injection with coils also has been tried with good result.\(^9\)

  The other types of CCF are in reality dural AV fistulas and are treated either by arterial route or via venous route or a combination of it using the same materials. However, venous route using coils and Onyx gives good result and is popular among interventional radiologists.

- **Orbital arteriovenous malformation:** Orbital arteriovenous malformations are rare vascular lesions of the orbit. Endovascular treatment of these lesions is challenging and has to be planned in stages mainly via transarterial route embolization.\(^5\) Onyx and/or n-butyl cyanoacrylate (n-BCA) along with Lipiodol (Guerbet, Villepinte, France) is the choice of the embolic agent. However, there is a small-risk of embolization of the central retinal artery.

- **Arteriovenous fistula other than CCF:** These are rare lesions. Identification of site of fistula and embolization at the site of fistula cures the lesion.

- **Ophthalmic artery aneurysms:** Proper ophthalmic artery aneurysms are extremely rare. The carotid-ophthalmic artery aneurysms are more common but account for a small percentage of cerebral aneurysms. They arise at the origin of the ophthalmic artery from the supraclinoid internal carotid artery. Small aneurysms are asymptomatic but large ones can cause compression of the optic nerve and produce visual symptoms. They may rupture causing intracranial subarachnoid hemorrhage. Depending on the size, they are
treated either only by coils, or stent-assisted coiling or by flow diverters with good result.

- **Thrombolysis for central retinal artery:** Acute sudden vision loss may be due to occlusion of central artery of retina. It is treated as a case of local stroke. If patient reports in time, the thrombolysis can prevent the vision loss.

### Venous Route

It is mainly used when lesion cannot be approached through arterial route.

For success of endovascular interventions of orbital lesion, detail knowledge of vascular anatomy, various materials used for procedure, embolic agents is very essential. Predicting the complications and their management is important to obtain good long-term results.

### REFERENCES

INTRODUCTION

Intraocular tuberculosis (IOTB) is a form of extra-pulmonary tuberculosis, which is caused by the bacillus *Mycobacterium tuberculosis* (MtB). It is noteworthy that a single organism produces such varied clinical features in a single organ and also that it is rarely isolated from samples which make a definitive diagnosis of this disease elusive in most of the cases.

EPIDEMIOLOGY

According to the WHO Global Tuberculosis Report 2015, out of the 9.6 million new tuberculosis cases in 2014, 58% were in the South-East Asia region and Western Pacific regions. India, Indonesia and China had the largest number of cases (23,10% and 10% of the global total respectively). The WHO has now moved from STOP-TB Strategy (2006–2015) to END-TB Strategy (2016–2035) and aims to attain a world free of TB. India’s TB control program is on track as far as reduction in disease burden is concerned. There was 50% reduction in mortality rate by 2013 as compared to 1990 levels. Similarly, there was also a 55% reduction in TB prevalence rate compared to 1990 levels.

PATHOGENESIS

*Mycobacterium tuberculosis* is an obligate, aerobic, non-motile, non-spore-bearing, slow-growing bacterium. Human beings are the only natural host for this organism. It spreads via inhalation of aerosolized droplets when infected patients cough or sneeze. It usually affects organs with high regional oxygen content like the apices of the lungs, kidneys, bones, meninges and the choroid. The choroid is known to have one of the highest blood flow rates in the human body.

IOTB has been postulated to have pathogenetic mechanisms similar to other forms of extrapulmonary TB. These include the following stages:

1. Bacterial dissemination

   *Mycobacterium tuberculosis* is engulfed by alveolar macrophages and transported to hilary lymph nodes leading to priming of T cells. Macrophages/dendritic cells carrying *Mycobacterium tuberculosis* or even free bacteria may disseminate to different parts of the eye.

2. Localization in ocular tissues

   Amongst various ocular tissues wherein the bacilli gets lodged, RPE is most suited among different cell types to harbor *Mycobacterium tuberculosis*
3. Bacterial reactivation and initiation of inflammation

*Mycobacterium tuberculosis* can remain latent for long periods of time. What factors can lead to reactivation is not known.

**Tuberculosis and Uveitis**

In patients with latent TB, antigenic mimicry between tubercular and retinal antigens could be a potential cause of uveitis. This hypothesis is supported by cytokine analysis of TB-associated uveitis that showed significantly increased interleukin-6 (IL-6) and other chemokines, but not IL-12, tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) that characterize active TB.⁴

**Clinical Features**

Ocular manifestations of tuberculosis are shown below (Fig. 4.1).

1. **Anterior uveitis**
   - Unilateral or bilateral
   - Usually granulomatous; can be non-granulomatous
   - Cornea- mutton fat keratic precipitates
   - AC–cells, flare, fibrinoid reaction
   - Iris nodules (Fig. 4.2) angle nodules
   - Posterior synechiae, peripheral anterior synechiae
   - Complicated cataract
   - Ciliary body granulomata.

2. **Intermediate uveitis**
   - Low grade, chronic uveitis
   - Vitritis
   - Snowball opacities
   - Snow banking
   - Peripheral vascular sheathing
   - Peripheral retinochoroidal granuloma.

3. **Posterior uveitis**
   - Choroidal tubercles
     - Unilateral or bilateral

---

**Fig. 4.1:** Various anterior and posterior segment manifestations of tuberculosis
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Tubercles measure between 0.5–3 mm in diameter
- Overlying serous retinal detachment
- Respond well to ATT
- Heal leaving behind pale atrophic areas with variable pigmentation.

- **Tuberculoma**
  - Large, solitary mass
  - Upto 14 mm in diameter (Figs 4.3A and B)
  - Overlying hemorrhages, retinal folds, serous retinal detachment
  - Respond well to ATT and corticosteroids.

- **Serpiginous-like choroiditis**
  - Important to differentiate it from serpiginoid choroiditis
  - Chronic inflammation of the retinal pigment epithelium, choriocapillaries

---

**Fig. 4.2:** A 21-year-old female patient with tubercular anterior uveitis showing mutton fat keratic precipitates, iris nodules, broad posterior synechiae and peripheral anterior synechiae

- Tubercles measure between 0.5–3 mm in diameter
- Overlying serous retinal detachment
- Respond well to ATT
- Heal leaving behind pale atrophic areas with variable pigmentation.

- **Tuberculoma**
  - Large, solitary mass
  - Upto 14 mm in diameter (Figs 4.3A and B)
  - Overlying hemorrhages, retinal folds, serous retinal detachment
  - Respond well to ATT and corticosteroids.

- **Serpiginous-like choroiditis**
  - Important to differentiate it from serpiginoid choroiditis
  - Chronic inflammation of the retinal pigment epithelium, choriocapillaries

---

**Figs 4.3A and B:** A patient who was a known case of spinal tuberculosis presented with blurred vision in the left eye. (A) Fundus photograph of the left eye showing tubercular granuloma involving the macula; (B) MRI scan of the spine showing heterogenous, hyperintense signals from L1-L2 vertebrae with loss of intervening inter-vertebral disc morphology
Intraocular Tuberculosis

- Immune-mediated hypersensitivity reaction in the presence of a few acid-fast bacteria in the choroid or retinal pigment epithelium
- Seen in TB-endemic countries
- Significant vitritis
- Presence of multifocal lesions in posterior pole, juxtapapillary region—gray-white lesions with ill-defined edges, spread centrifugally with multiple recurrences
- FFA shows early hypofluorescence and late hyperfluorescence
- Responds well to combination of ATT and corticosteroids
- Can show paradoxical worsening when treatment is initiated with ATT.

- Subretinal abscess
  - Solitary, yellowish-white, circumscribed mass-like subretinal lesion
  - Often associated with overlying retinal hemorrhages
  - Vitritis
  - Can be diagnosed with the help of aqueous or vitreous samples subjected to PCR, microbial evaluation including smear, culture
  - Treatment must include ATT along with corticosteroids as this lesion responds very well to ATT.

- Retinal vasculitis
  - Cause remains speculative; infective or hypersensitivity response to tubercular antigens
  - Predominantly venular involvement; occlusive vasculitis
  - Vitreous infiltrates (vitritis)
  - Retinal hemorrhages (Figs 4.4A and B)
  - Neovascularization leading to recurrent vitreous hemorrhage
  - Tractional retinal detachment
  - Neuroretinitis
  - Treatment with ATT, corticosteroids, and panretinal photocoagulation to the capillary non-perfusion areas as determined on FFA.

- Eales’ disease: An idiopathic vasculitis; affects healthy adults, mostly men, in third to fourth decade of life, characterized by periphlebitis, capillary nonperfusion, neovascularization, recurrent vitreous hemorrhages, and fibrovascular proliferation. Absence of intraocular inflammation and

Figs 4.4A and B: Patient with tubercular retinal vasculitis, tested positive on Mantoux test and QuantiFERON TB Gold test with positive findings on HRCT-Chest. (A) Pretreatment fundus photograph of the left eye showing disc edema, cotton wool spots, hemorrhages, ILM folds; (B) Post-treatment with ATT and corticosteroids, vasculitis resolved leaving behind sheathing of the infer-temporal arcade vessel
absence of healed or active choroiditis lesions are important differentiating features from tuberculosis vasculitis. Biswas et al. detected the *Mycobacterium tuberculosis* genome by PCR detection in a significant number of vitreous fluid specimens with Eales’ disease, thus suggesting a possible association of *Mycobacterium tuberculosis* in the pathogenesis of Eales’ disease.

- **Optic nerve involvement**
  - Contiguous spread from choroid or hematogenous spread from the primary focus
  - Optic neuritis, ONH granuloma/tubercle, retrobulbar neuritis, neuroretinitis, opticochiasmatic arachnoiditis.

- **Endophthalmitis and panophthalmitis**
  - Patients with subretinal abscesses can develop endophthalmitis due to treatment with corticosteroids without ATT because of rapid multiplication of bacilli along with liquefaction necrosis.
  - Scleral involvement can lead to panophthalmitis ending in globe perforation.

**Pathology**

Various ocular structures have been noted to be involved in specimens obtained from enucleated eyes like sclera, cornea, conjunctiva, iris, ciliary body, vitreous adjacent to pars plana ciliaris, retina and choroid.

The histopathology of ocular involvement characteristically reveals granulomatous inflammation with central caseous necrosis, and shows occasional acid-fast organisms. The granulomatous response consists of abundant epithelioid, histiocytes, occasional giant cells of langhans type, and peripheral mononuclear cells, primarily made up of lymphocytes.

The disease should be differentiated from syphilis, leprosy, sarcoidosis, tumors, etc. (Table 4.1).

**Diagnostic Techniques (Table 4.2)**

- **Immunologic**
  - Tuberculin skin test (Mantoux test, PPD test)
  - Interferon-g release assays (QuantiFERON-TB GOLD or T-SPOT TB)

- **Radiologic**
  - Chest X-ray
  - Chest computer-assisted tomography
  - Positron emission tomography PET/CT.

**TABLE 4.1**: Showing differential diagnosis of tuberculosis

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Noninfectious</th>
<th>Neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis</td>
<td>Sarcoaidosis</td>
<td>Retinoblastoma</td>
</tr>
<tr>
<td>Leprosy</td>
<td>Serpiginous choroiditis</td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Sympathetic ophalma</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>Vogt–Koyanagi–Harada disease</td>
<td>Metastatic tumor</td>
</tr>
<tr>
<td>Borrellosis</td>
<td>Acute posterior multifocal placoid</td>
<td></td>
</tr>
<tr>
<td>Brucellosis</td>
<td>pigment epitheliopathy</td>
<td></td>
</tr>
<tr>
<td>Herpetic retinochoroiditis</td>
<td>Punctate inner choroidopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multifocal choroiditis and panuvelitis</td>
<td></td>
</tr>
</tbody>
</table>
**TABLE 4.2: Diagnostic modalities for intraocular tuberculosis**

<table>
<thead>
<tr>
<th>Type</th>
<th>Principle</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunologic</td>
<td>Skin hypersensitivity test for mycobacterial antigens</td>
<td>Low cost</td>
<td>Not specific</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wide availability</td>
<td>Does not distinguish between latent and active TB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Larger induration-more specific</td>
<td>May be positive with BCG vaccination/exposure to atypical mycobacteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maybe negative in immunosuppressed states/children/extrapulmonary or military TB</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difficulties in test administration and interpretation may lead to false results</td>
</tr>
<tr>
<td>Interferon-γ</td>
<td>Interferon-γ release test after in vitro stimulation of patients' lymphocytes with <em>M. tuberculosis</em> specific antigens</td>
<td>More specific marker of <em>M. tuberculosis</em> infection/previous exposure</td>
<td>Higher cost</td>
</tr>
<tr>
<td>release assays</td>
<td></td>
<td>Not influenced by BCG vaccination or exposure to atypical mycobacteria</td>
<td>Not widely available</td>
</tr>
<tr>
<td>(QFT-G, T-SPOT</td>
<td></td>
<td>Not as subject to biases and errors of placement and reading as the TST</td>
<td>Possibly more sensitive to detect latent infection than TST but does not distinguish it from disease</td>
</tr>
<tr>
<td>TB)</td>
<td></td>
<td></td>
<td>May be negative or indeterminate in immunosuppressed states</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Problems in collecting or transporting blood specimen may decrease the accuracy</td>
</tr>
<tr>
<td>Radiologic</td>
<td>Look for evidence of pulmonary involvement, either active or healed infection</td>
<td>Low cost and wide availability</td>
<td>Not specific for tuberculosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Useful when a suggestive pattern is found (e.g. upper lobe infiltrates and cavitation, Ghon's focus, miliary disease)</td>
<td>Other infectious/granulomatous/lymphoproliferative/occupational disorders may lead to similar patterns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low sensitivity, especially for detection of lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A normal result does not exclude ocular tuberculosis</td>
</tr>
<tr>
<td>CT scan of chest</td>
<td>Look for evidence of pulmonary involvement, either active or healed (postinflammatory)</td>
<td>More sensitive than chest radiograph</td>
<td>Higher cost and greater radiation exposure than chest X-ray</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Modality of choice for detection of lymphadenopathy and for tuberculosmas</td>
<td>Not specific for tuberculosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A normal result does not exclude ocular tuberculosis</td>
</tr>
<tr>
<td>PET-CT scan</td>
<td></td>
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</tbody>
</table>
### Bacteriologic Smear
- Identify the presence of stained acid-fast bacilli in various clinical samples.
- Rapid and widely-available method.
- Useful especially in specimens with large bacillary load.
- Low sensitivity (e.g. for sputum, detection threshold is >5,000 bacilli/mL).
- Other acid-fast organisms are also identified through this method.

### Culture
- Detects growth of *M. tuberculosis* after seeding of clinical samples in culture media.
- Gold standard. Unequivocal proof of microorganism viability.
- Allows identification and drug sensitivity testing.
- Expensive and cumbersome needs long time for growth.
- May not be widely available.
- Results may take up to 6–8 weeks in solid media.

### Molecular Nucleic acid amplification tests
- Detects presence of *M. tuberculosis* genomic DNA in clinical samples after amplification (e.g. various PCR techniques).
- High specificity.
- Better sensitivity than microscopy.
- Fast results.
- Allows identification and investigation of genetic resistance patterns.
- Higher cost and limited availability. Variable sensitivity.
- Inferior sensitivity for non-respiratory specimens (not established for ocular samples). Does not allow ruling out tuberculous etiology.
- Detects only DNA (more prone to contamination and microorganisms may not be viable or may be dormant).

### LAMP
- Based on the novel loop-mediated isothermal amplification (LAMP) platform; for detection of *Mycobacterium tuberculosis* complex, *Mycobacterium avium*, and *Mycobacterium intracellulare*.
- Fast, easy operation without sophisticated equipment. Results visible to naked eye. Robust to inhibitors and reaction conditions that usually adversely affect PCR results. Simple enough to use in small scale hospitals, primary care facilities, and clinical laboratories in developing countries.

### Histologic Histopathology
- Stained tissue sections with evidence of granulomatous inflammation (especially with caseous necrosis) support the diagnosis. Finding of AFB in this setting is diagnostic.
- Allows the observation of the extent of tissue damage.
- Risks related to invasive procedure to obtain tissue specimen.
- Other microorganisms/noninfectious entities may also lead to granulomatous inflammation.
- Low sensitivity for AFB detection.

---

Intraocular Tuberculosis

- Bacteriologic
  - Smear
  - Culture.
- Molecular
  - Nucleic acid amplification tests.
- Histologic
  - Histopathology.

Ancillary Investigations

- **Fundus Fluorescein Angiography (FFA):** It is a very useful technique to study the various presentations of IOTB including Tb-serpiginous-like choroiditis, tubercles, tuberculomas, retinal vasculitis and inflammatory choroidal neovascular membranes. Active choroiditis lesions demonstrate hypofluorescence in early phases with hyperfluorescence in the late phases. Serpiginous-like choroiditis, shows an initial hypofluorescent active edge with late hyperfluorescence and diffuse staining of the active advancing edge. In cases of vasculitis, the presence of areas of capillary non-perfusion and neovascularization can be picked up on FFA determining the need and extent of panretinal photocoagulation. Inflammatory CNVM can be diagnosed by the classical appearance of early lacy hyperfluorescence and intense leak with fuzziness of borders in late stages.

- **Indocyanine Green Angiography (ICG):** This angiography is useful in determining the extent of the choroidal lesion and the stage of disease and in evaluating treatment results. Herborst et al. suggested that hypofluorescent lesions seen in all phases of ICGA represent full-thickness choroidal granulomas or atrophic lesions. ICGA changes are reversible and therefore, help in monitoring the disease.

- **Wide-field Imaging (WFI):** It is especially useful in cases with vasculitis involving the peripheral vessels, usually veins in patients with Eales’ disease. Standard field FFA can miss the abnormalities in the peripheral retina. But with WFI, capillary non-perfusion areas in the periphery can be picked up earlier, preventing complications like neovascularization and bleeding.

- **Fundus Autofluorescence (FAF):** It is a novel, non-invasive technique which can help in differentiating active from inactive choroiditis. Gupta A and Biswas J described the serial FAF pattern of serpiginous choroiditis and reported that in the initial phases the lesion appears hyperfluorescent. Sharpening of the hyper-autofluorescent borders indicated healing of the lesions. Completely healed lesions showed hypo or absence of fluorescence (Figs 4.5A and B).

- **Optical Coherence Tomography:** OCT It helps in the assessment of macular complications like cystoid macular edema and inflammatory CNVM in these cases. Also, entities that may mimic tubercles like CSCR and choroidal tumors can be excluded. Enhanced-depth imaging-OCT (EDI) of active Tb-SLC lesions demonstrated infiltration of the choroid, elevation of the RPE-Bruch’s membrane complex and focal increase of choroidal thickness. These findings are not seen in non-infectious SC and can help in differentiating between the two entities.

- **Ultrasound (USG):** It is a helpful tool in diagnosis and follow-up of choroidal mass lesions like subretinal abscess, which characteristically show an anechoic space within the mass on A-scan. Tuberculomas can be
Differentiated from malignancies like retinoblastomas, malignant melanomas and metastatic tumors.

- **Ultrasound Biomicroscopy (UBM):** It is a useful tool to study eyes with hypotony in patients with chronic uveitis and poor media clarity to assess the pars plana region. It can also pick up granulomas in this region.

- **Fine Needle Aspiration Cytology (FNAC):** Samples can be taken for histopathology or for techniques like PCR in cases, which present with diagnostic dilemmas.

### Challenges in Diagnosis

The diagnosis of IOTB remains a challenging issue because each of the tests available has its strengths and weaknesses as discussed above and because TB infection can present with features of any type of extraocular or intraocular inflammation. Gupta A et al.11 have proposed the classification of IOTB (Table 4.3) comprising of confirmed IOTB, probable IOTB and possible IOTB. These guidelines offer a greater degree of “certainty” of diagnosis as IOTB largely remains a presumptive diagnosis, as unequivocal evidence of infection is often not available. There are some signs which are consistent with intraocular tuberculosis; they are:

1. Presence of cells in anterior chamber or vitreous along with:
   1. Broad posterior synechiae
   2. Retinal perivasculitis with or without discrete choroiditis/scar
   3. Multifocal serpiginoid choroiditis
   4. Choroidal granuloma
   5. Optic disc granuloma
   6. Optic neuropathy.

   Approach for the diagnosis of tuberculous uveitis in immunocompetent individuals12 is shown in a flow chart below.

   Showing diagnosis of tuberculous uveitis in immunocompetent individuals (Flowchart 4.1).12
TABLE 4.3: The proposed classification of intraocular tuberculosis

<table>
<thead>
<tr>
<th>Clinical diagnostic group</th>
<th>Case definition criteria</th>
</tr>
</thead>
</table>
| **Confirmed IOTB** (Both 1 and 2)         | 1. At least one clinical sign suggestive of IOTB  
2. Microbiological confirmation of MTB from ocular fluids/tissues                                                                                     |
| **Probable IOTB** (1, 2, and 3 together)  | 1. At least one clinical sign suggestive of IOTB (and other etiologies excluded)  
2. Evidence of chest X-ray consistent with TB infection or clinical evidence of extraocular TB or microbiological confirmation from sputum or EO sites  
3. At least one of the following:  
a. Documented exposure to TB  
b. Immunological evidence TB infection                                                                                                                      |
| **Possible IOTB** (1, 2, and 3 together)  | 1. At least one clinical sign suggestive of IOTB (and other etiologies excluded)  
2. Chest X-ray not consistent with TB infection and no clinical evidence of EOTB  
3. At least one of the following:  
a. Documented exposure to TB  
b. Immunological evidence TB infection  
4. Evidence of chest X-ray consistent with TB infection or clinical evidence of EO TB but none of the characteristics given in 3 |

**Flowchart 4.1: Uveitis in immunocompetent patient**

*Abbreviations:* TST, tuberculin skin test; IGRA, interferon-gamma release assay; CT, computer-assisted tomography; TB, tuberculosis. Anti-TB treatment for 8 weeks; presumed and definite TB require treatment for 6 months

 MANAGEMENT

Tuberculosis is a readily curable disease with highly effective treatment. The management of ocular TB includes medical management of the disease on the same lines as other forms of extrapulmonary TB and surgical management to treat complications developing due to chronic ocular disease.

Medical Management

Anti-tubercular therapy has been known to eliminate latent TB and decreases a person’s lifetime risk of developing active TB by 90%.\textsuperscript{13}

Majority of patients with uveitis secondary to presumed Tb have underlying latent TB so treatment with timely ATT helps in reducing recurrences. In a study by Bansal et al.\textsuperscript{14} the addition of ATT significantly improved the 5-year probability of no recurrence of inflammation in their cohort.

Treatment is instituted in two distinct phases—the first intensive phase involves the use of 4 drugs—isoniazid, rifampicin, pyrazinamide and ethambutol. After use for 2–3 months, only isoniazid and rifampicin are continued for another 6–9 months. The CDC recommends prolonged therapy for tuberculosis of any site that is slow to respond and thus, patients with intraocular TB may require prolonged therapy.\textsuperscript{15}

Along with the initiation of ATT, low dose oral steroids are also commenced for a period of 4–6 weeks as they help in reducing the damage to ocular tissues, which can happen due to, delayed hypersensitivity.

Essential first-line anti-TB drugs:

1. **Isoniazid:** It is a prodrug; activation of isoniazid produces oxygen-derived free radicals (superoxide, hydrogen peroxide, and peroxynitrite) and organic free radicals that inhibit the formation of mycolic acids of the bacterial cell wall, causing DNA damage and, subsequently, the death of the bacillus. It has a bactericidal effect on rapidly growing bacilli, but has a limited effect on slow-growing (generally intracellular) and intermittently growing (generally extracellular) bacilli.

2. **Rifampicin:** It inhibits the gene transcription of mycobacteria by blocking the DNA-dependent RNA polymerase, which prevents the bacillus from synthesizing messenger RNA and protein, causing cell death. It is a bactericidal drug that kills growing, metabolically active bacilli, as well as bacilli in the stationary phase, during which metabolism is reduced.

3. **Pyrazinamide:** It is a prodrug; enters the bacillus passively, is converted into pyrazinoic acid by pyrazinamidase, and reaches high concentrations in the bacterial cytoplasm due to an inefficient efflux system. Pyrazinoic acid decreases the intracellular pH to levels that cause the inactivation of enzymes—such as fatty acid synthase I, which plays a fundamental role in synthesizing fatty acids—and, consequently, the impairment of mycolic acid biosynthesis. It is also bactericidal and is particularly potent in elimination of persistent bacilli in the sporadic multiplication phase which are responsible for bacteriological relapse.

4. **Ethambutol:** It interferes with the biosynthesis of arabinogalactan, the principal polysaccharide on the mycobacterial cell wall. It acts on intracellular and extracellular bacilli, principally on rapidly growing bacilli.

Side effects of anti-tubercular drugs are well documented. Dose associated hepatotoxicity can be prevented by regular monitoring of liver-function tests. Other commonly seen side effects include cutaneous reactions, gastrointestinal intolerance, hematological reactions and renal failure.
Side effects caused by these drugs are listed in Table 4.4.

A baseline ophthalmic examination including visual acuity, visual fields and color vision should be documented for all patients before starting ethambutol. In case of any ocular side effect the drug should be stopped immediately. Vision improves spontaneously in many cases. Parenteral hydroxocobalamin can be considered for a 10–28 week period for those who do not improve spontaneously.

The emergence of MDR-TB (multidrug resistance) and XDR-TB (extremely drug resistant) entails the use of next generation drugs for extended periods. About 8–10 drugs have to be used for 18–24 months. Additional agents include ethionamide, kanamycin, cycloserine, rifabutin, fluoroquinolones, interferon-γ and linezolid.

### Surgical Management

Complications may arise due to longstanding ocular disease leading to non-clearing vitreous hemorrhage, tractional retinal detachment, etc. Both the conditions need surgical intervention—vitrectomy.

### Research and Development

- A diagnostic platform called the GeneXpert Omni is in development. It is meant for testing for TB and rifampicin-resistant TB using XpertMTB/RIF cartridges. It is supposed to be smaller, lighter and less expensive than current platforms.
- A next generation cartridge called Xpert-Ultra is in development and intends to replace the XpertMTB/RIF cartridge. It could potentially replace culture as the primary diagnostic tool for TB.
- Eight new or re-purposed anti-TB drugs are in advanced phases of clinical development. For the first time in six years, an anti-TB drug (TBA-354) is in Phase I trials.
- Several new TB treatment resistant regimens are being tested for use in drug-susceptible and/or drug-TB in Phase II or Phase III trials.
- Fifteen vaccine candidates are in clinical trials; emphasis has shifted from children to adolescents and adults.

### REFERENCES

1. TB India 2015-RNTCP-Annual status report; page 22.

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**TABLE 4.4:** Ocular side-effects of antitubercular drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side-effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Optic neuritis, optic atrophy</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Optic neuritis, acquired red-green dyschromatopsia, central scotomas, disk edema, peripapillary splinter hemorrhages, optic atrophy, retinal edema pigmentary changes at fovea (rare)</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Severe acute anterior uveitis (hypopyon uveitis), corneal endothelial deposits, inflammatory vitreous exudates and opacities</td>
</tr>
</tbody>
</table>