Kerala Journal Of Ophthalmology
VOL. XXV, ISSUE 4, DECEMBER 2013

The Kerala Journal of Ophthalmology is the official scientific publication of the Kerala Society of Ophthalmic Surgeons and 4 issues are published every year.

It welcomes original articles, interesting case reports, update articles, book reviews, journal abstracts and research papers in Ophthalmology. Original articles are accepted on condition that they have not been published in any other journal.

SUBSCRIPTION RATE
Annual : Rs. 600 (4 issues)
Single Copy : Rs. 150

Subscription should be sent by demand draft in favour of Kerala Journal of Ophthalmology payable at Ernakulam addressed to the Editor, KJO

ADDRESS FOR CORRESPONDENCE
Dr. Gopal S. Pillai, Editor KJO
Department of Ophthalmology
Amrita Institute of Medical Sciences
Kochi, Kerala - 682 041
Email: gopalspillai@gmail.com Mob: 094473 91266
KERALA SOCIETY OF OPHTHALMIC SURGEONS
(Registered under Societies Registration XXI of 1860, No. 387/2003)

President
Dr. Sahasranamam V
House No: 30
Vinayaka Nagar
Pappanamm P.O
Trivandrum - 695018, Kerala
Ph: 9846020421, 0471-2490421
Email: drsahasranamam@gmail.com

President Elect
Dr. K.V. Raju
Amruthareshmi, Chevayur P.O
Kozhikode - 673008
Kerala
Ph: 0495-2354906 9846071637
Email: rajukv4@gmail.com

Past Presidents
Dr. B.V Bhat
Asoka Hospital
South Bazar, Kannur - Kerala
Ph: 0497 - 2700715 9846139715,
9447110280, Email: drbhatbv@yahoo.com

Dr. Giridhar A
Giridhar Eye Institute
Ponneth Temple Rd, Kadavanthra
Cochin - 682020, Kerala

Dr. R.R. Varma
Ambikalayam, Warriam Road
Cochin-682 016
Ph: 0484-2352010 (H)
Mob: 9447152010
Email: 66varma@gmail.com

Dr. P. Rajagopalan Nair
Raj Bhavan, Palakkad-676 013
Ph: 0491-2535676 (H)
Mob: 9447645676
Email: dr.pr.nair@gmail.com

Dr. C.V. Antharyose
Medical Superintendent;
Jubilee Mission Medical College
Trichur - 680005 Kerala
Ph: 9447227826; 04872440809
Email: drcvandrews@gmail.com

General Secretary
Dr. S.J. Saikumar
Giridhar Eye Institute
Ponneth Temple Rd
Kadavanthra
Kochi - 682020, Kerala
Ph: 9847040840
Email: saikumarsj@yahoo.com

Joint Secretary
Dr. Thomas George T
Thazhiheli, A - 1, Aiswarya Nagar,
Kesavadasapuram
Trivandrum - 695004, Kerala
Ph: 9349318711
Email: thomasthazhethil@yahoo.co.in

Vice President
Dr. Charles K Skariah
Kakkuzhiyil House
Mundupalam, Kuriachira
Trichur - Kerala
Ph: 9447806303
Email: drckseye@vsnl.com

Web Site Editor
Dr. Unnikrishnan Nair
Chaitnya Eye Hospital and
Research Institute, Kesavadasapuram
Trivandrum - 695004, Kerala
Ph: 9947727020
Email: dr_unninair@hotmail.com

Treasurer
Dr. K Mahadevan
TC 15/2003, VRA-12,
Women’s college Lane,
Vazhuthakkad
Trivandrum - 695014, Kerala
Ph: 9387805076
Email: eyemahadevan@rediffmail.com

Scientific Committee Chairman
Dr. Thomas Cherian
F. Hospital, Angamaly
Angamaly - 683572, Kerala
Ph: 9388605608
Email: tcherian@rediffmail.com

Journal Editor
Dr. Gopal S Pillai
Dept of Ophthalmology
Amrita Institute of Medical Sciences
Kochi, Kerala
Ph: 9447391266
Email: gopalspillai@gmail.com

Immediate Past Secretary
Dr. Radha Ramanan
L.F.Hospital, Angamaly
Kochi - 683572
Kerala
Ph: 9447006421.
Email: rramanan@sify.com

Managing Committee members
Dr. Saju Joseph
Dr. S.J. Saikumar

Executive Committee Members
Dr. Vinod Kumar N.V
Dr. Bastin V.A
Dr. Anish M.R
Dr. Sreeni Edakhalon
Dr. Freddy T Simon
Dr. Simon George
Dr. Abdul Rasheed
Dr. Sarah Chirayath
Dr. Alex Baby
## Contents

291 **Editorial**

**Cover Story**

292 **Artificial Retina Project**  
Manoj Prathapan

**Special Feature**

296 **Retina - Past, Present & Future**  
Meena Chakrabarti, Sonia R John, Arup Chakrabarti

**Major Review**

319 **Retinal Vein Occlusion**  
Manoj S, Unni Nair, Sreelekha, Fazil Gafoor

335 **Proliferative Diabetic Retinopathy- Recent advances in management**  
Remya Mareeen Paulose, Ashok Nataraj, Thomas Cherian, Reesha K R, Faghima Benazir

342 **Diabetic Macular Edema**  
Anubhav Goel, Mahesh Gopalakrishnan

353 **Age Related Macular Degeneration**  
Shane Mathew

364 **Retinopathy of Prematurity**  
Natasha Radhakrishnan, Poornima R Pai

**Biostatistics Made Easy**

368 **Statistical Methods in Clinical Trials, Validity Analysis And Evidence Based Medicine & Meta-Analysis**  
K.R. Sundaram
Brief Reports

379 Management Of Choroidal Neovascularisation In Choroidal Osteoma
Manoj S, Unni Nair, Sreelekha

383 Nutritional anemia as a cause of vision loss in developing countries: A case report
Anusha Venkataraman, Bijnya B Panda, Anupam Dey

385 Outer lamellar hole with severe visual loss following High Tension Electric shock
A Saket, VR Sarvanan, V Narendran

Original Articles

Sandhya N, A. Giridhar, Mahesh G, Eliza Anthony, Jaihra P.G.

394 A study of Clinical, OCT and Fluorescein Angiographic Findings in Toxoplasma Retinochoroiditis.
Jayesh Thakkar, Prakash V S, Padmaja Krishnan, Suresh Puthalath

398 Long Term Intravitreal Bevacizumab (IVB) Safety Survey
Sonia Rani John, Meena Chakrabarti, Arup Chakrabarti

Surgical Corner

402 27-G Vitrectomy
S. Natarajan, Deepen Sheth, Shubhangi H.
Dorkar, Juhi Garg, Pandurang Kulkarni

403 Book Review

404 Journal Review

406 Instruction to Authors

408 Spot Diagnosis
I write this eighth editorial for the Kerala Journal of Ophthalmology with great happiness, pride, joy and with deep sense of satisfaction. This issue is completely devoted to retina and posterior uveitis. I am sure that the exam going postgraduates in the state will carry it and photocopy it many times over in the years to come.

Our journal has gone through vibrant leaderships from time to time and now we are celebrating the 40th year of KJO in 2014. It was started in 1974 by Dr KE Eapen and Dr K Narayanan Kutty. Dr T P Illtyearah (1978-83) and Dr N S D Raju (1983-88) had long stints of five years each. Dr K Krishnankutty of Trichur was editor for two years (1988-90). He converted it to bi-monthly in the first year and a monthly journal in the second year of his editorship. Not only was he successful in bringing out the journal regularly, but also raised the popularity of the journal among the ophthalmologist of Kerala and outside the state through his regular column on innovative techniques. The next editors, Dr P LMohan (1990-91), Dr K Mahadevan (1991-94), Dr A Giridhar (1995-99) reverted to the quarterly format and have strived hard to maintain the high standards of the journal. Dr Sasikumar (1999-2001) and Dr Saikumar (2001-03) were successful in publishing the journal in strict quarterly schedule. Dr Thomas Cheriyian, Dr Meena Chakrabarti and Dr Mahesh Gopalkrishnan in recent times got the journal to the high standards that it has achieved today. I have just continued on their footsteps and tried to maintain the high standards that were set before me by these giants in the field.

As usual, our issue starts with a cover story, a fairy tale about the success of artificial retina, a technology we have all been waiting for years together. The only thing which will surpass it next will be the artificial brain. The author has gone into the depths of this technology and in simple terms with a lot of pictures tried to explain the mechanism of the artificial retina.

Our next article is a very special feature by our new Chairman of Scientific committee, Dr Meena Chakrabarti and is a collectors article on Retina, Past, Present and Future. Through this most exhausting article in all my 8 issues, she takes us through a wonderful journey in what it was years back to what it will be in years to come in store for the retinal bandwagon.

Next I have a flurry of major reviews, which will be of special relevance to the postgraduates and practitioners alike. They are one stop areas where all information about these common diseases are dispensed. It starts with venous blocks, where the author has in detail discussed the pathophysiology to management paradigms. We go through proliferative diabetic retinopathy, diabetic macular edema, age related macular degeneration and retinopathy of prematurity, all important topics in the field of retina. All the authors have done a wonderful job in not only writing these articles, but showing the world, what a strong retinal faculty Kerala has produced over the last 10 years.

I should make a special mention about Prof Sundaram, who was the head of Biostatistics at AIIMS, New Delhi under whom, I did my thesis 15 years back. He is currently the head of Biostatistics at Amrita Institute and he has over the last 8 issues instilled in us, the sense of research methodology. His parting article is on testing the test, validity analysis, meta analysis and evidence based medicine. He gives an insight into how to conduct a clinical trial which will be a very important article to all people interested in doing research.

We have this time, three brief reports and three original articles, one of our original articles was all set to be presented in the 2013 KSOS conference by Dr Jayesh Thakkar from Comtrust hospital, Calicut, but before he could present, fate took him away in a road traffic accident while on duty. I have included that article which he was set to present in the conference. May his soul rest in peace.

Our surgical corner this time has a new surgical technique which will rock the present day retinal surgery options, the 27 gauge vitrectomy system is written by none other than Prof S Natarajan, our editor of the Indian Journal of Ophthalmology. The post operative comfort given after the smallest gauge surgeries is what makes it a success.

Journal review, book review and spot diagnosis brings up the rear end of the issue. I thank Dr Thomas Cheriyian and the post graduates of Little Flower Institute for supporting the journal review section in all my 8 issues. My special thanks to Dr Andrew Kakkanatt who has been instrumental in doing all the book reviews despite his very busy schedule of clinical work and administration. I thank my own postgraduates for providing me a continuous supply of tear sheets in which large amount of information was dissipated in a small piece of paer.

I thank Dr Mahesh G, my immediate predecessor who has given me a lot of advises on the go, all of which were relevant in the smooth turn around of issues. I thank my Associate editor Dr Natasha Radhakrishnan for hertireless reviews on the articles. I thank all the editorial board, contributors and authors who are the real substance of the journal and many of the senior members of the KSOS who has critically analyzed each of my issues to give me feedbacks. Their efforts have helped in maintaining the high standards of the journal.

We should all laud the efforts of Mr Ramachandran who is our designer, printer and publisher for the last 4 years and Mr Manoj from the week, who designs our cover. Their work has given the journal the finesse of an international journal.

I transfer the baton of responsibility to Dr Ashok Nataraj for the next 2 years, I wish him all success and hope that under his leadership our journal will still go higher.

Jai KSOS
Dr Gopal S Pillai
Editor
Artificial Retina Project

USA Department of Energy’s (DOE’s) Artificial Retina Project was a multi-institutional collaborative effort to develop and implant a device containing an array of microelectrodes into the eyes of people blinded by retinal disease. The ultimate goal was to design a device to help restore limited vision that enables reading, unaided mobility, and facial recognition.

The device is intended to bypass the damaged eye structure of those with retinitis pigmentosa and macular degeneration. These diseases destroy the light-sensing cells (photoreceptors, or rods and cones) in the retina, a multilayered membrane located at the back of the eye.

History
The DOE project builds on the foundational work of its leader, Mark Humayun at the Doheny Eye Institute of the University of Southern California. In a breakthrough operation performed in 2002, a team led by Humayun successfully implanted the first device of its kind—an array containing 16 microelectrodes—into the eye of a patient who had been blind for more than 50 years. Since then, more than 30 additional volunteers around the world have had first- or second-generation (60-electrode) devices implanted. These devices enable patients to distinguish light from dark and localize large objects.

Integrating revolutionary DOE technologies for useful vision
Achieving the quantum improvements in resolution needed for useful vision requires the integration of revolutionary technologies such as those developed at DOE national laboratories. In 1999, the Doheny group began collaborating with researchers at DOE’s Oak Ridge National Laboratory, who also were working on approaches for restoring sight to the blind. Shortly thereafter they began to evaluate technologies at several other laboratories as well.

To speed the design and development of better models, in 2004 Doheny and DOE (including six of its national laboratories), two additional universities, and Second Sight™ Medical Products, Inc. (a private-sector company), signed a Cooperative Research and Development Agreement. Under the agreement, the institutions jointly share intellectual property rights and royalties from their research. This spurs progress—freeing the researchers to share details of their work within the collaboration.

Three models in testing and development
Model 1 (Argus™ I)
The Model 1 device [developed by Second Sight™ Medical Products, Inc. (SSMP)] was implanted in six blind patients between 2002 and 2004, whose ages ranged from 56 to 77 at time of implant and all of whom have retinitis pigmentosa. The device consists of a 16-electrode array in a one-inch package that allows the implanted electronics to wirelessly communicate with a camera mounted on a pair of glasses. It is powered by a battery pack worn on a belt. This implant enables patients to detect when lights are on or off, describe an object’s motion, count individual items, and locate objects in their environment.

Model 2 (Argus™ II)
The smaller, more compact Model 2 retinal prosthesis (developed by SSMP with DOE contributions) is currently undergoing clinical trials to evaluate its safety and utility. This model is much smaller, contains 60 electrodes, and surgical implant time has been reduced from the 6 hours required for Model 1 to 2 hours.

Model 3
The Model 3 device, which will have more than 200 electrodes, has undergone extensive design and fabrication studies at the DOE national laboratories and is ready for preclinical testing. The new design uses more advanced materials than the two previous models and has a highly compact array. This array is four times more densely packed with metal contact electrodes and required wiring connecting to a microelectronic stimulator. Simulations and calculations indicated that the 200+ electrode device should provide improved vision for patients.

Synergies with others
Doheny also receives other federal funding to support and extend the work on the retinal and other neural prostheses. The National Eye Institute of the National Institutes of Health, for example, supports fundamental and applied research related to the prosthesis.

Additionally, the National Science Foundation provides funding for the longer-term goals of further enhancing the retinal prosthesis and adapting the technologies to treat a wide range of other neurological disorders.

Address for Correspondance: Associate Professor, Amrita Institute Of Medical Sciences & Research Centre, Cochin, India.
Email: manojprathpan@aims.amrita.edu
Worldwide projects
Other retinal prostheses projects are under way in the United States and world-wide, including Germany, Japan, Ireland, Australia, Korea, China, and Belgium. These programs pursue many different designs and surgical approaches.

How the Artificial Retina Works
Normal vision begins when light is focused on the retinal photoreceptor cells the rods and cones. These cells convert light signals to electric impulses that are sent to the optic nerve and the brain. Retinal diseases like age-related macular degeneration and retinitis pigmentosa destroy vision by annihilating these cells.

With the artificial retina device, a miniature camera mounted in eyeglasses captures images and wirelessly sends the information to a microprocessor (worn on a belt) that converts the data to an electronic signal and transmits it to a receiver on the eye. The receiver sends the signals through a tiny, thin cable to the microelectrode array, stimulating it to emit pulses. The artificial retina device thus bypasses photoreceptor cells and transmits electrical signals directly to the retina’s remaining viable cells. The pulses travel to the optic nerve and, ultimately, to the brain, which perceives patterns of light and dark spots corresponding to the electrodes stimulated. Patients learn to interpret these visual patterns.

Technological Challenges in Engineering a Retinal Implant
People with AMD or RP are blind because retinal photoreceptor cells degenerate and lose function. Rods and cones are specialized cells that capture light and translate it into electrical signals. These signals are passed through underlying retinal cells and down the optic nerve to the brain where visual images are formed. The Artificial Retina Project’s challenge is to replace the lost light-gathering function of the rods and cones with a video camera and to use the information captured by the camera to electrically stimulate the part of the retina not destroyed by disease. Stimulation is done with a thin, flexible metal electrode array that has been patterned on soft plastic material similar to that of a contact lens. Compounding this challenge is the fact that the delicate, electrical stimulation of the retina needs to be performed in the eye’s saltwater environment without shorting out any electronic circuits. Moreover, just as the resolution of graphic images on a computer screen improves with greater pixel density, researchers assume that increased electrode densities will translate into higher-resolution images for patients. However, the area of the retina being targeted for electrical stimulation is less than 5 mm by 5 mm. Consequently, as the number of electrodes increases, their size and spacing must decrease.

Preliminary Results
All of the patients implanted so far with the Argus™ II system had bare light perception or worse vision before the surgery. Averaging 56.8 years, their ages range from 28 to 77 years. The median surgery time for the implant procedure in the United States is 3 hours.

Ongoing 3-year feasibility studies are testing the safety and efficacy of the device. For the 17 patients implanted with the device in the first 6 months, there have been no device failures and few serious adverse events, all of which were resolved with treatment. Such events included conjunctival erosion, hypotony, and endophthalmitis.

All 17 patients have seen phosphenes—patterns of light produced by electrical stimulation—and many are showing statistically significant improvements in orientation and mobility, spatial localization, and motion detection. They all are using the device out-of-the clinical setting.

Preclinical testing of a retinal prosthesis with more than 200 electrodes (see story, DOE Technologies Drive Initial Success of Bionic Eye, p. 1) is under way and has the potential to significantly improve the visual acuity of people with RP and age-related macular degeneration. Additional research and development efforts by DOE laboratories are expected to produce artificial retinas with more than 1000 electrodes.

DOE role and funding
DOE supported the design, construction, and some preclinical (nonhuman) testing of the devices. Funding was for research in the following areas:

- Neuroscience imaging studies on Model 1
- Some preclinical animal studies of Model 2
- Design and fabrication studies of Model 3
Progress Metrics. The U.S. Department of Energy (DOE) has spent approximately $63 million to date (FY2009) on the Artificial Retina Project, with annual funding averaging ~$7 million between 2001 and 2009. During this time, 16- and 60-electrode devices have been developed and implanted, and major research is under way to develop a 200+ electrode device. "Increasing Resolution," to understand the level of vision each of these devices provides. DOE funding for the project ended in 2010.

Seeing Is Processing
The human retina is not just a detector of light that sends optical information to the brain. It also performs complex image processing to provide the brain with optimized visual information. Replacing diseased photoreceptors with the electrodes of an artificial retina thus not only reduces the number of pixels, it also disrupts this necessary image processing.

To restore that lost function, researchers at the California Institute of Technology’s Visual and Autonomous Exploration Systems Research Laboratory under the direction of Wolfgang Fink are developing software to pre-process the information from implant patients’ miniature cameras before it is fed to their retinal prostheses. Dubbed the Artificial Retinal Implant Vision Simulator (ARIVS), this software system provides real-time image processing and enhancement to improve the limited vision afforded by the camera-driven device. The preservation and enhancement of contrast differences and transitions, such as edges, are especially important compared to picture details like object texture.

Since predicting exactly what blind subjects may be able to perceive is difficult, ARIVS offers a wide variety of image processing filters. They include contrast and brightness enhancement, grayscale equalization for luminance control under severe lighting conditions, user-defined grayscale levels for reducing the data volume transmitted to the visual prosthesis, blur algorithms, and edge detection. These filters are not unlike what a person experiences in a regular eye exam during which a battery of tests is performed to determine the proper eyeglass prescription. In this case, retinal implant recipients can choose among these different filters to further fine tune, optimize, and customize their individual visual perception by actively manipulating parameters of individual image-processing filters or altering the sequence of these filters.

Increasing Resolution
These images approximate what patients with retinal devices ideally could see. It is hoped that increasing the number of electrodes will result in more visual perceptions and higher-resolution vision.
An incomparably greater challenge exists in predicting how to electrically stimulate the retina of a blind subject via the retinal prosthesis to elicit a visual perception that matches an object or scene as captured by the camera system that drives the prosthesis. This requires the efficient translation of the camera stream, pre-processed by ARIVS, into patterns of electrical stimulation of retinal tissue by the implanted electrode array. The Caltech researchers on the U.S. Department of Energy’s team are addressing this challenge by developing and testing multivariate optimization algorithms based on evolutionary principles. These algorithms are used to modify the electrical stimulation patterns administered by the electrode array to optimize visual perception.

To summarize DOE’s Artificial Retina Project shows great promise for the future. Though at present, still in its evolutionary stages this could very well be the next big revolution happening in ophthalmology.

Dr. Manoj Prathapan did his MS from Amrita Institute of Medical Science and is presently working as Associate Professor at Amrita Institute of Medical Science.
**Retina - Past, Present & Future**

**Introduction**

The retinal subspeciality is growing by leaps and bounds as evidenced by the explosion of treatment options for disease entities that were previously left to progress to irreversible blindness. Gone are the days when this specialty was taken up only by a choice few who were willing to have a special relationship with their perpetually dissatisfied patients with irrevocable retinal damage and the maximum that could be done was the prescription of a PLACEBO and needless to say a stiff dose of counseling. Most multidisciplinary hospitals thought twice before planning to finance and equip a retina vitreous clinic as the expenses incurred were far beyond the maximum returns that could be expected. The 3 factors that waved a magic wand over this barren area of ophthalmology were.

1. **Advancement in Imaging Technology**
2. **Advent of Intravitreal Phacomacotherapy**
3. **Availability of Small Gauge Vitrectomy**

These 3 advances in technology are not only available in elite institutions but are also available in each and every nook and cranny and their effects are translated into benefits in terms of anatomical and structural outcomes for our patients. Majority of the available treatment options are covered by insurance policies, a factor that increased their acceptability. To understand this magic let us take a journey through history…. visit the past, …live in the present and ……dream of an even brighter tomorrow!!!

**History of retinal imaging**

Imaging the retina has always been the most commonly performed diagnostic test for both vascular and non vascular retinal pathologies. Fundus photography and fluorescein angiography (FA) have long served to aid the retinal physician in the evaluation, management and documentation of these disorders. With technology advancing by leaps and bounds we are at present in the golden era of imaging where the retinal layers can be studied in microscopic detail, the vitreo-retinal interface analysed and an enhanced depth imaging of the choroid is possible. Our quest for perfection which began with a simple fundus camera providing a 20⁰ fundoscopic view, has been a highly successful journey. In its present state of evolution we have scaled a significant pinnacle of perfection where wide field 200⁰ imaging is the norm and the IS-OS function or External limiting membrane integrity can be studied. We still have miles to go……with no end of the road in sight, to a future that is brights with better prospects.

**Historical perspective**

The first reliable fundus camera¹, providing a 20⁰ field of view was developed by Carl Zeiss and J.W Nordensen in 1926 which was later developed further to give a 30⁰ field of view. Around the same time in 1961 Novotny and Alvis² discovered the technique of fluorescein angiography, a technique that was popularised by Gass (1962)³. Since then the diagnostic test of ‘Fluorescein Angiography’ has served to compliment fundus photography. This wonderful technique has with stood the test of time and is still done today albeit in fewer situation. Its indication have gradually shrunk to a mere few in comparison to its use when this technique topped the list of investigations for diagnostic confirmation of a retinal pathology.

While fundus imaging of the posterior pole became common place, obtaining more peripheral views became challenging due to restraints imposed by the physical properties of the eye. Improvisations to obtain a wider view occurred in the form of

1. **Equator plus camera** (1970;Pomerantzef)⁴ was a wide angle camera that utilized scleral trans-illumination and a contact lens to obtain a 148⁰ field of view of poor image quality thanks to the glare at the site of trans-illumination.

2. **Obtaining a mosaic of image** by performing multiple photographic sweeps and combining the images⁵, adding up to about a 100⁰ field of view.

3. **75⁰ Montage Images**⁶: The Early Treatment Diabetic retinopathy study (ETDRS) research group combined multiple 30⁰ fundus images to obtain a 75⁰ Montage which has served as the standard image used in the evaluation of most retinal vascular disorders.

Availability of digital imaging and improved computer software has made the creation of montages and mosaics easier, but this technology is not ideal for a dynamic imaging process such as a fluorescein angiography as the images from different phases of the angiogram have to be combined.
In addition to traditional film and digital cameras, another retinal imaging technology, the scanning laser ophthalmoscopy was developed in the early 1980s. When this technology was coupled with a confocal aperture, the combination provided an excellent performance compared to conventional systems. With this advancement in technology, evolved the techniques video angiography and simultaneous FA (fluorescein angiography) and ICG (Indocyanine green angiography) angiography.

4. **Using special lenses** in conjunction with a small angle camera: Accessorily contact and non contact lenses have been used to increase the field of view of both convolutional cameras and the SLO system since 1980s. Recently, the combination of the ocular Staurenghi 230 SLO retina lens (Ocular instrument, Bellevue, WA) and a SLO system has been used to provide a 150° field of view. When used with the Heidelberg Spectralis (Heidelberg Engineering, Dossenheim, Germany) it is possible to obtain wide field fluorescence images.

5. **The Retcam** first introduced in 1997 used a fibre optic light source and contact lens and with its widest angle attachment can provide a 1300° field of view. This technology is thus suited for neonatal and infants and it has been extensively used in the evaluation of paediatric disorders such as retinopathy of prematurity and familial exudative vitreo retinopathy. The Retcam has limited utility in adults because even a minor lens opacity can degrade the image quality.

6. **Panoret – 1000**: uses scleral trans-illumination similar to Equator – Plus camera, has less difficulty with lens opacity and is therefore suitable for use in adults.

7. **Another wide field imaging device**, the **Optos-Optomap** (Optos, Dunfermline, United Kingdom) developed in 2000 was the first camera capable of producing a 2000° field of view (roughly 82.5% of the total retinal surface area). Thus ultra wide field image is obtained in Optos device by utilizing an ellipsoid mirror and SLO technology. This device utilizes both a red and green laser. The Optos wide field device when combined with the Staurenghi lens is capable of obtaining fluorescein and indocyanine green angiography as well as fundus auto fluorescence. Let us take a look at how UWFA has expanded our treatment options in retinal vascular pathologies.

**The role of wide field angiography in the management of retinal diseases:**

1. Identifying peripheral proliferative diseases earlier, especially in patients with diabetic retinopathy and retinal vein occlusion which can be easily missed with small angle cameras and conventional FA.

2. Recent studies have significantly co-related peripheral retinal ischemia with macular oedema in eyes with DME and RVO. Studies have shown that patients with refractory macular oedema, who show minimal response to anti VEGF and steroids, may have peripheral ischemia. Treatment of these ischemic area with laser should improve treatment response in these patients.

3. WF-FFA is used to develop an “ischemic index” (amount of non perfused to total visualized retina) patients who develop proliferative disease have a significantly higher ischemic index. Hence if peripheral ischemia is diagnosed earlier with wide field angiography earlier initiation of laser coagulation could improve outcomes in these patients.

4. In retinopathy of prematurity, wide field imaging with the retcam shows co-relation with indirect ophthalmoscopy for treatment of ROP. Incorporating WF imaging with telemedicine in ROP management will reduce the cost of care.

**Indocyanine Green Angiography**

The main advantage of using Indocyanine Green Angiography (ICGA) is that it provides an additional imaging modality to access the choroidal circulation below the retinal pigment epithelium. ICG compliments fundus fluorescein angiography which images the retinal circulation above the RPE.

ICGA is not replacement for FFA, but it provides important adjunctive information that assists in defining the choroidal circulatory involvements in macular diseases. The commonest indications for the use of ICGA are:

1. In the diagnosis and management of a wet AMD like picture when an IPCV is suspected. ICGA is considered as a gold standard for diagnosing PCV.

2. In the diagnosis and management of retinal angiomatous proliferation and central serous chorioretinopathy.

**OPTICAL COHERENCE TOMOGRAPHY:**

**A RETINA ODYSSEY!!!**

The advent of optical coherence tomography in 1991 was associated with a prediction that this technology would never be commercially viable. The technology was developed by researchers of Massachussets institute of technology (MIT) headed by Fujimoto. Initial OCT technology licensed by MIT to Humphery systems (Now CARL ZEISS MEDITECH incorporated, Dublin, California) Although OCT
was developed in the early 90’s, it took more than 10 years before it became clinically accepted with the third generation technology — the ZEISS Stratus\(^\text{19}\). But this technology grounded in sound scientific principles withstood the test of time. Its acceptability both by the clinicians and the afflicted patients is so high, that it now occupies the coveted position “at the top”, in retinal diagnostics\(^\text{18}\)... a place were FFA was enthroned for years. We now routinely gazed deep inside the retina, the IS-OS junction and more recently the choroid without thinking twice about the “magic” that we are performing on our patients.

Initial devices utilized ‘Time Domain’ (TD) technology\(^\text{20}\) which was monopolized by Carl Zeiss Meditech. Their prototype machines Stratus III and later Stratus IV OCT were the only ones in the market for nearly 10 years.

This technology employed a mobile reference arm mirror that sequentially measures light echoes from time delays with acquisition speed of 400 A scans/second and axial resolution of 8 – 10 µm. The images obtained were described as an “OPTICAL BIOPSY” and was akin to a histopathological section of the retina.

The introduction of Fourier / Spectral Domain OCT\(^\text{21}\) improved imaging speed, which is now several times higher than in previous OCT technology. Resolution has improved and 3-D rendering imaging of selected layers and segmented 3-D images are now possible. More than seven companies have introduced OCT into the Ophthalmic market\(^\text{22}\)…The Indian market have 5 of them. The acquisition speed varies from 25000-52000 A scans/second, with an axial resolution of 3-7µm significantly improving the signal-to-noise ratio and allowing the detection of individual retinal layers and lesion components.

Thus spectral domain OCT represents a significant improvement over TD-OCT in axial resolution and image acquisition, reduction of motion artifacts, increased area of retinal coverage, and the ability to produce three dimensional data sets to create topographic maps with precise registrations.

Despite superior advantages, SD-OCT\(^\text{22}\) is still subject to some elements of motion artifacts, segmentation artifacts, and inter instrument comparability.

Known limitations of TD and SD-OCT include limited resolution due to infrared radiation absorption by the anterior segment structures and the ocular media, “speckle noise” due to image scattering from ocular structures and limited lateral resolution due to restricted numerical aperture of the optical system.

The last few years have witnessed mind boggling advances in imaging technology...we will take a look at these “impossible” advances. Some a never leave the work bench, but the few that will reach the clinical “bed side” will definitely change how we diagnose and treat retinal diseases in the future.OCT technology that is still under development includes:\(^\text{23}\)

1. **Swept-source OCT (SS-OCT)\(^\text{24}\)**, another form of FD-OCT uses a narrow band light source with central wavelength of 1,050 nm, and a short cavity-swept laser (instead of a super luminescent diode laser) that can emit light of different frequencies and can be rapidly turned over a broad band width. A high speed complementary metal oxide semi conductor (CMOS) camera and two parallel photo detectors are used to achieve 100,000 -400,000 A Scans/ second. With 5.3 µm tissue axial resolution over a 4 mm imaging range. Extensive B Scan averaging reduces speckle noise artifact. The small area, high density image allows imaging of individual photo receptors when coupled with adaptive optics. SS-OCT scores over SD-OCT in terms of reducing fringe wash out, better sensitivity with imaging depth, longer imaging range, higher detection effeminacy and dual balanced detection. Hence there is less patient introduced artifacts from movement and breathing, better penetration through media opacities and a longer imaging range (7.5 mm) that allows anterior segment imaging with ease.

2. **ADAPTIVE OPTICS – OCT (AO-OCT)\(^\text{25,26}\)** Adaptive optics corrects higher order ocular aberrations during image acquisitions, thereby allowing “near –cellular level” resolutions. AO-OCT limits motion artifacts, increases lateral resolutions, reduces speckle and enhances sensitivity. With a pupil diameter >6 mm, a lateral resolution of 2-3 mm and an axial resolution of 3.5µm enables imaging of individual cones on a 3- D basis.

3. **Full –Field OCT (FF-OCT)\(^\text{-}\)** is based on spatial coherence grating. A narrow band of illumination with high numerical aperture objectives and a liquid crystal retarder to minimize defocusing and dispersion effects are used to produce three dimensional ultra high resolution imaging\(^\text{27}\).

4. **Intra operative OCT (IO-OCT)\(^\text{28}\)** augments intra operative microscopy to help surgeons delineate tissues, reducing surgical time and excessive illumination as well as limiting the need for potentially toxic stains. IO-OCT can be microscope mounted (MM\(^\text{29}\)) or hand held (HH). Metallic surgical instruments are detected as highly reflective with sub total shadowing and silicone instruments are moderately reflective with minimal shadowing.
5. **Widefield OCT (WF-OCT):** employs ultra high speed SS-OCT technology. Using a 1050 – 1060 nm FD mode locked laser to collect 1900 * 1900 A Scan with roughly 70° angle of view in 3-6 seconds. The image acquisition speed varies between 684,000 – 1,368,700 A Scan /second. WF - OCT can achieve good choroidal and scleral interface penetration with an axial resolution of 6.7 to 19 µm.

In combination with Optical Microangiography technology (OMAG) vascular perfusion mapping down to the capillary level is possible. OMAG technology utilizes 840 nm wavelength with an A scan rate of 27000 Hz and axial resolution of 8µm to image a 7.4 * 7.4 mm² area of the posterior segment. A volumetric map acquisition comparable to fluorescein and indocyanine green angiography is possible.

6. **Doppler OCT** can be used to access blood flow velocity. In patients with perimetric glaucoma decrease, retinal blood flow access by Doppler OCT (840 nm wave length, axial resolution 5µm, and transverse resolution 20 µm) was evident even in the absence of RNFL changes.

**Functional OCT** is a method of functional tissue assessment by means of light polarization evaluation. PS-OCT allows individual retinal layer identification by measuring cross-sectional and volumetric birefringence, contrasting between birefringent layers and other retinal layers. PS-OCT simultaneously measures intensity (conventional OCT images), retardation, and optic axis orientation to distinguish polarization preserving tissue, birefringent tissue, and polarization scrambling tissue. Birefringent tissues include the RNFL, Henle’s layer, or any fibrotic tissue that increase phase retardation. The RPE is a polarization-scrambling layer. Light transmitted through the RPE maintains the same polarization state and degree of retardation as images below and above the RPE layer, allowing assessment of RPE damage, which is specially useful in the context of pigment epithelial detachments and pseudovitelliform dystrophy.

In summary, a variety of emerging OCT technologies are poised to expand significantly the scope of OCT imaging and to enhance significantly our approach to the diagnosis and management of patients with retinal disease. An in depth understanding of these technologies and their potential advantages and disadvantages will aid retinal specialists in using these new methods for optimum benefit.

THE USE OF MACULAR MICROPERIMETRY IN THE ASSESSMENT AND DIAGNOSIS OF MACULAR DISEASE

Although BCVA remains the gold standard assessment tool for measuring visual function, it is widely recognized that conventional tests of vision, such as high-contrast BCVA, underestimate the actual level of visual impairment, particularly in older patients. As a result, other clinical assessment tools, such as contrast sensitivity, macular recovery function, and reading speed tests, are often employed to assess visual function in an individual, particularly when changes occur in visual function after an intervention. Although the Humphrey Field Analyzer (HFA) can be used to measure central macular sensitivity, its role in monitoring macular disease has been limited by its inability to quantify retinal threshold accurately over small and discrete retinal lesions and to retest these areas accurately over time. In response to these limitations, **the scanning laser ophthalmoscope (SLO) microperimeter** was developed. The SLO integrates fundus imaging with computerized threshold perimetry to achieve an exact correlation between macular and corresponding functional defects. This device was, however, very time-consuming and cumbersome to use and did not easily facilitate automated follow up examinations. Consequently, its use remained the preserve of a few academic institutions, and it never gained widespread popularity as an assessment tool.

The desire for a more practical, user friendly alternative led to the development of the **Nidek MP1 microperimeter**. The later version of microperimeters incorporates a color fundus camera for image registration and an auto tracking system to facilitate the accurate measurement of retinal sensitivity within the central visual field, even in patients with unstable or extrafoveal fixation. Although the MP-1 has an array of test strategies, in clinical practice, it has two principle modes of use: fixation localization and threshold testing. By analyzing the relationship among MPI, OCT and autofluorescence data, we now know that, in the context of AMD at least, stable and central fixation correlates well with preservation of the outer retinal signal on OCT.

Conversely, the presence of fibrosis, RPE atrophy, and loss of fovea autofluorescence are associated with a much higher rate of unstable eccentric fixation.

Perhaps the most exciting potential with microperimetry is that it allows investigators to assess the relationship between functional and structural changes accurately. For example, recent data have revealed that progressive loss of macular function over time, which involves not only expansion of the absolute scotoma but also reduced sensitivity in the perilesional area and a loss of fixation stability. This loss of perilesional retinal sensitivity appears to be unrelated to progressive atrophy but is associated with progressive decreased fundus autofluorescence.
FUNDUS AUTOFLUORESCENCE: AN EMERGING WINDOW ON THE RETINA !!!

Fundus autofluorescence (FAF) has emerged in the past 10 years as an effective means of identifying lipofuscin distribution in the retinal pigment epithelium cell monolayer plus other fluorophores associated with disease in the outer retina and subneurosensory space. What makes FAF clinically effective is that excessive accumulation of lipofuscin granules within the RPE represents a common downstream pathological pathway in various hereditary and complex retinal diseases, notably AMD.

Common Ocular Fluorophores are
A: Lipofuscin in the retinal pigment epithelium (RPE) (A2E)
B: Extracellular vitelliform material
C: Crystalline lens
D: Optic nerve head drusen
E: Astrocytichamartoma
F: Sclera

HOW FAF WORKS:
FAF depends on the use of ultraviolet light to visualize lipofuscin with fluorescence microscopy. One difficulty in detecting FAF is that its intensity is about two orders of magnitude lower than the background of a fluorescein angiogram. Autofluorescent properties of structures anterior to the retina further confound the clinical picture. This means existing camera systems as well as new imaging devices must be adjusted to record FAF.

Confocal scanning laser ophthalmoscopy (cSLO) and fundus photography are the two chief clinical means of capturing the FAF signal.

SCANNING LASER OPHTHALMOSCOPY: Confocal SLO addresses the limitations of the low intensity signal of FAF and the interference of the crystalline lens. The confocal optics ensure the reflectance and fluorescence come from the same optical plane. Light originating in the light beam, but out of the focal plane, is greatly suppressed, which in turn reduces autofluorescence from structures anterior to the retina.

FUNDUS PHOTOGRAPHY: The fundus camera differs from a cSLO in that the former uses a single flash and captures the entire retinal area in a single frame. The fundus camera does not have confocal optics, which means the signal it detects comes from all tissue levels with fluorescent properties within that light beam. So also, light scattering both anterior and posterior to the plane of interest can disrupt the detected signal. These are serious drawbacks. What’s more, the fundus camera lens itself contributes significantly to the fluorescence signal. This is particularly the case with older patients who have yellowing of the lens with nuclear sclerosis. One way around this problem is to modify the fundus camera by moving the excitation and emission wavelengths toward the red end of the spectrum. Longer wavelengths are thought to exhibit much less contribution from nuclear sclerosis and macular pigment, compared with shorter wavelengths.

Because cSLO and fundus photography use different wavelengths, it stands to reason that the two techniques might record fluorescence from a different set of fluorophores. An example is that macular pigment absorption is observed at a much lesser extent and the signal is less decreased over blood, retinal vessels, and the optic nerve head using the fundus camera system compared with the cSLO. A head to head comparison of the two systems is lacking.

FAF’S CLINICAL CONTRIBUTION:
Fundus autofluorescence imaging allows topographic mapping of lipofuscin distribution in the retinal pigment epithelium cell monolayer as well as other fluorophores that may accompany disease in the outer retina and sub neurosensory space. FAF imaging yields diagnostic data otherwise unobtainable through fundus photography, FA, and OCT, and therein lies its special clinical value.

Fundus Autofluorescence Imaging in Clinical Practice
A: Detect and follow geographic atrophy
B: Follow hereditary retinal diseases
C: Monitor for drug toxicity (hydroxychloroquine)
D: Disease signatures (acute zonal occult outer retinopathy [AZOOR], A3243G, ABCA4, pseudoxanthomaelasticum, cuticular drusen, acute exudative polymorphous vitelliform maculopathy)
E: Distinguish vitelliform lesions from other material
F: Identify RPE tears
G: Identify optic disc drusen
H: Identify subretinal fluid
I: Diagnose and follow posterior segment inflammatory disease (MEWDS, PIC/MFC, AZOOR, acute posterior multifocal placoid pigment epitheliopathy)

Identifying Choroidal Pathology With Enhanced Depth Imaging OCT
Better imaging reveals new anomalies. What is their clinical significance?
The technique of enhanced depth imaging (EDI)-OCT, which involves placing the objective lens of the Spectralis SD-OCT device (Heidelberg Engineering) closer to the eye so that an inverted image is obtained. This maneuver allows deeper structures to be placed closer to the zero delay, thereby allowing for better visualization of the choroid. Combining high speed scanning, eye-tracking, image-averaging technology, reduced noise and greater coverage of the macular area, high-resolution OCT images of
the choroid can now be created. Due to the choroid’s chief functions of supplying metabolic support to the RPE and outer retina and the preliminary portion of the optic nerve, and because it contains melanocytes that absorb excess light and prevents damage to surrounding structures, it may be involved in several important diseases of the retina, RPE and optic nerve. With the development of EDI-OCT, the understanding of the choroid using noninvasive imaging techniques has grown significantly. Margolis and Spaide analyzed normal eyes and found that the choroid was thickest underneath the fovea, with a mean thickness of 287 µm. Given that the choroid is the most vascular structure within the eye and the fovea, is situated at the center of the macula, and has the highest photoreceptor density and metabolic activity, it is not unexpected that the choroid is thickest in this region.

Interestingly, Margolis and Spaide found a statistically significant correlation with age and choroidal thickness, in which the choroid thinned with age. Using regression analysis they showed that the subfoveal choroidal thickness decreased 1.56 µm for each year of age or that, over the course of an 80 year lifetime, an eye would lose approximately one-third of its subfoveal choroidal thickness. This in vivo measurement of subfoveal choroidal thickness using EDI-OCT correlated with similar previous studies with eye bank and autopsy eyes, which found that choroidal thickness was correlated negatively with age and decreased by 1.1 µm per year of age.

On examination, individuals with ARCA (Age Related Choroidal Atrophy) demonstrate pigmentary changes, a tessellated fundus and a paucity of visible choroidal vessels. These clinical and EDI-OCT imaging observations may help explain the age related decrease in visual acuity and function commonly seen with aging.

The introduction of EDI-OCT has opened up a new world of imaging the choroid, using commercially available SD-OCT machines. Before the introduction EDI-OCT, SD-OCT imaging of the choroid was quite limited. Now, with this technology, noninvasive, in vivo measurements of this vascular structure can be repeatedly and reliably performed. EDI-OCT has allowed the identification of ARCA, which may explain certain macular pathologies, other possible pathophysiologic mechanism, such as peripapillary atrophy and glaucoma, and Focal Choroidal Excavations. ARCA and FCE represent two new choroidal entities that may provide more insight into the pathogenesis and management of retinal disease.

EDI-OCT of Choroid in Clinical Practice:

A: Quantitative analysis with EDI of the choroid is critical for baseline diagnosis and response to therapy of various retinal disorders. This type of analysis is unavailable with traditional modalities such as fluorescein and indocyanine angiography.

B: Diagnosis of CSR and differentiation from PCV and AMD is improved with EDI, and EDI is important for monitoring response to therapy of CSR.

C: Diagnosis of inflammatory disease is improved with EDI. A thick choroid is seen with VKH and thin choroid is seen with birdshot chorioretinopathy. EDI is helpful in assessing response to therapy of VKH.

D: EDI offers a higher resolution modality for analysis of choroidal tumors and potentially greater accuracy in measurement of choroidal tumors.

E: Qualitative analysis of each of the different layers of the choroid is possible with EDI and is evolving, and this may impact diagnosis, therapy, and understanding of retinal and choroidal diseases.

Future of Imaging

The Future of Imaging includes not only new OCT instruments and techniques but also innovations in other novel optical and non-optical technologies. These new technologies include:

1. Hyperspectral imaging for visualization of retinal oxygenation and other metabolites.
2. Multispectral imaging for measurement of rhodopsin concentration.
3. Photoacoustic imaging for visualization of melanin and blood vessels.
4. Magnetic resonance imaging (MRI) for characterization of retinal function in the setting of media opacity.

In addition to novel imaging technologies, one can expect new advances in imaging techniques. For example, wide-field imaging strategies, currently used for fluorescein angiography, fundus autofluorescence, and color imaging, will likely be expanded to new areas including indocyanine angiography, near infrared imaging, and OCT.

Indeed, OCT-related technologies can be expected to dominate the future of imaging in both research and clinical practice. The morphologic biopsy of the retina provided by OCT will likely be enhanced by the incorporation of robust, low-cost adaptive optics solutions, which should make commercial clinical application feasible. The improvements in resolution will enable better visualization and understanding of the various retinal bands. As a result, one can expect continued refinement of the classification of these structures over time.

A final expected advance in imaging is improvements in automation. Automated segmentation and classification of features on imaging data will increase with a more complete delineation and quantification of all disease findings. Automated diagnosis and monitoring of disease may
Availability of beautifully descriptive 3D imaging has definitely improved the diagnostic capabilities in retinal diseases and we will now move on to the vista of therapeutic option available for managing these conditions.

**Ischemia and VEGF in Different Retinal Diseases and Therapies: How does One Influence the Other?**

Retinal diseases have undergone a metamorphosis over the last seven years. Age related macular degeneration, retinal vein occlusion and diabetic macular edema, which were once primarily treated with laser, are now predominantly being treated with anti VEGF or corticosteroid based therapies. This switch to newer treatments is due to our better understanding of free intraocular VEGF levels and the role they play in retinal diseases. Currently, there are four different anti VEGF medications to choose from. If we include the three major corticosteroids – triamcinolone, dexamethasone and flucinolone, our armamentarium is significantly enhanced. There has been many studies in literature comparing one anti VEGF medication to another, yet there are many questions that remain unanswered.

The one year results of the CATT study showed that monthly injections of Bevacizumab vs Ranibizumab were equally efficacious when treating wet AMD. These findings although true for AMD, are not consistent with other retinal diseases, such as RVO and DME, which have much higher levels of free intraocular VEGF. Case reports in the literature have also suggested that persistent macular edema due to vein occlusions that are nonresponsive to one anti VEGF agent can have complete resolution if switched to another agent with a higher affinity for VEGF. In the coming years, studies such as CRAVE for RVO and the DRCR.net Protocol T for DME may answer these questions.

**VEGF LEVELS IN ISCHEMIA**

Why would there be differences among these diseases when they share abnormal VEGF levels as a basis for their pathology? The answer may lie in the degree of ischemia, as well as in the corresponding levels of VEGF expression. The levels of VEGF in central RVO are higher than in branch, RVO and are almost 100 times higher than the VEGF levels in wet AMD. This fact demonstrates that diseases with higher levels of ischemia result in higher intraocular levels of free VEGF.

**VEGF AND REBOUND EDEMA**

The exact duration of effect of these anti VEGF medications on any given retinal diseases is still unknown. The concept of rebound edema in RVO patients when occurring after injections with anti VEGF agents, tends to be much greater than on initial presentation. Prior experience have shown that nearly 41% of our patients who responded to bevacizumab at two weeks rebounded by four weeks. In many instances, the edema may be related to significant peripheral ischemia, which is often difficult to image. Using widefield fluorescein angiography, such as with the Optos device, may provide clues about some of these diseases, as well as potential therapies to block this cycle of rebound edema from going forward.

**Anti VEGF and drugs acting on the angiogenesis cascade :The future in the management of Exudative AMD and retinal vascular diseases**

The last decade has been a remarkable period for the treatment of neovascular AMD. We have gone from having no effective treatment and simply watching our patients go blind to providing anti VEGF monotherapy, allowing for some, albeit temporary, stabilization of vision.

Looking at present – day therapies for exudative AMD the role of VEGF in AMD has been well established and that blocking VEGF has been a good idea. Turning to the cascade of VEGF activity, we are aware of the fact that Macugen, Avastin, Lucentis, all block VEGF in the extracellular space and before it binds to its receptors. Thus till end of 2011 we had mainly 3 major players in the arena of VEGF inhibition.

**Year 2011 :Enter Eylea (Aflibercept, Regeneron)**

Eylea’s Roaring Rollout has taken the retinal world by storm.

By any fiscal reckoning, the launch of Eylea (Aflibercept, Regeneron) exceeded expectations. Wall Street forecasters initially predicted sales of the new anti VEGF agent for wet AMD would total $5 million in the final quarter of 2011. Instead, it took in $24 million. Enthusiasm is tempered by the second-year VIEW results and recent case reports of inflammation. Many had hoped Eylea would outperform Lucentis in its anti-VEGF punch, a point as-yet unresolved by the data available in the literature. Additionally, one of aflibercept’s main selling points, is its reduced dosing schedule. -just five injections in the first year of treatment -wasn’t maintained in the year 2 VIEW data submitted to the FDA. Finally, a cluster of post-injection inflammation events, though well within established incidence rates for intravitreal injections, prompted a company notification to the FDA to take a precautionary look at injection protocols.

Real-world testing will tell whether Eylea truly offers longer biologic activity. Furthermore, nine cases in the cluster of inflammation events occurred in a single physicians practice, a trend suggesting a localized problem and not a drug – specific issue. No other reports of such a cluster have since
kinase signaling pathways, and hence using Integrin proteins that help regulate and modulate the downstream to approach the problem.

Turning to the VEGF cascade downstream of the extracellular space to fix the “chronically leaking boat”. At first, we believed this led to blockade of VEGF induced angiogenesis, as was shown in the preclinical animal models. But as more and more data appeared, it seemed that anti-VEGF agents largely work by reducing vascular leakage and drying the retina, not by eliminating choroidal neovascularization. Therefore, we are just patching leaks, and not fixing the problem.

We are all well aware of the downsides of intravitreal Anti-VEGF pharmacotherapy ………. An overwhelming treatment burden, coupled with a suboptimal treatment response with little hope for a definite treatment end point. This has led to the exploration of newer anti-VEGF agents, and other molecules to target different areas of the angiogenesis cascade.

Some other VEGF related compounds under investigation. Among these VEGF related compounds was KH902, a VEGF-blocking fusion protein from China, which showed impressive results in phase 1 trials.

In addition, MP0112, a recombinant fusion protein based on DARPin technology, is important because it theoretically can prolong the durability of the chemical, providing a long intravitreal half-life. MP0112 is currently in phase 1 studies in the United States.

Another VEGF-related approach is to have body produce its own anti-VEGF therapy using genetics. For instance, AAV2-sFLT01 uses a viral vector to deliver a gene to the back of the eye, where “infected” cells then produce sFLT01. The drug’s effects lasted at least 12 months in animal studies. A phase 1 trial is currently under way.

Returning to the VEGF cascade, upstream of the extracellular space, there is a complicated series of events that result in VEGF production. Compounds that could be effective against VEGF in this part of the cascade include Sirolimus and Palomid 529. Palomid 529 is currently being investigated in a phase 1 trial.

Turning to the VEGF cascade downstream of the extracellular space, blockade of VEGF receptors is one way to approach the problem. Integrins are transmembrane proteins that help regulate and modulate the downstream kinase signaling pathways, and hence using Integrin antagonist may prove useful.

The drug being investigated along this route is an α5β1 integrin inhibitor, which via its blockade can lead to vessel regression, allowing for the destruction of choroidal neovascularization. In addition, volociximab, a monoclonal antibody against α5β1, showed inhibition of CNV on fluorescein angiography in a phase 1 trial.

Further downstream, once VEGF has bound to its receptors, another cascade of events occurs and targeting this area also could stop angiogenesis.

These chemicals include the Tyrosine Kinase Inhibitors (TKIs), which if blocked could stop the growth of vessels. Pazopanib, which is topically administrated, is a TKI that, in a phase 2 study, resulted in a mean 4.3 letter increase in VA, with patients with the CFHTT genotype exhibiting the best response.

Beyond the VEGF cascade: Can Anti-PDGF Drug Targets Heart of Angiogenesis?

Amid the justifiably positive excitement and fanfare surrounding the birth of anti-VEGF therapy, one important fact went largely unnoticed. In the pioneering ANCHOR and MARINA studies, which laid the foundation for anti-VEGF AMD therapy, patients in general did not experience neovascular membrane regression and a significant number (20% in ANCHOR and 15% in MARINA) saw their choroidal neovascular lesions grow over the course of the study, despite strict adherence to monthly injections.

At the time, visual acuity benefits were cause enough for celebration with angiograms clearly showing reduced vascular permeability, leakage, and edema. But the actual structures underlying exudative disease remained untouched by the treatment. Also worth remembering is that despite functional outcomes unimaginable at that time, most patients did not regain three or more lines of vision.

Then there is treatment burden, a more widely acknowledged anti-VEGF challenge. It is widely accepted that we get the best outcomes with a strict monthly injection schedule, and any deviation from that schedule resulted in decreased vision, even among patients who maintained disciplined monthly visits for years.

Angiogenesis involves hundreds of chemical factors of which VEGF is an important factor, but perhaps not the most vital. Angiogenesis occurs over many stages: initiation, progression, differentiation, maturation, and remodeling. Numerous cell types including pericytes, in addition to endothelial cells, contributes to vascular growth during these
stages.

In the initial stage of angiogenesis, a group of endothelial cells, known as tip cells, set the trail for this process, proliferating and expanding the size of the neovascular membrane. These cells shape the leading edge of the angiogenic sprout. They also secrete platelet-derived growth factor B (PDGF-B), which in turn recruits pericytes to proliferate and migrate along the growing neovascularization. The presence of pericytes is a hallmark of vascular maturation; pericytes protect and stabilize the endothelial cells that constitute to the vascular wall.

While this process is unfolding, the tip endothelial cells continue to build new sprouts. Pericyte attachment and maturation and endothelial cell protection lag behind endothelial cell proliferation. Throughout angiogenesis tip cells are the only endothelial cells unprotected by a shield of pericytes and this could be one of the main factors responsible for anti-VEGF resistance. Current anti-VEGF therapy only impacts the leading tip cells, temporarily reducing the vascular permeability, leakage, and edema that causes vision loss, but leaving the pericyte guarded neovascular complex intact. Soon after anti-VEGF therapy ceases or slows down, the pericyte protected endothelial lesions stand ready to sprout new vessels. Platelet derived growth factor (PDGF) is a key cytokine involved in this recruitment. Blockade of Platelet derived growth factor (PDGF) only blocks pericytes, it is not going to be successful as monotherapy but instead will need to be combined with anti-VEGF agents.

Ophthotech Corp, Princeton, NJ, recently developed an anti-PDGF aptamer, formerly known as E100300 and now called Fovista. The to using, dose-escalating, multicenter, uncontrolled, single and multiple-dose study included 22 patients who were given three monthly intravitreal injections of combination therapy, Lucentis (Ranibizumab, Genentech, South San Francisco, CA) with Fovista. No dose-limiting toxicities nor any adverse events were reported and all of the patients displayed some degree of neovascular regression, with an 86% average magnitude of regression.

Based on these results, a phase 2b clinical trial was designed involving 449 patients. Three groups received one of three treatments every four weeks: Fovista 1.5 mg combined with Lucentis 0.5 mg or a placebo combined with Lucentis 0.5 mg. Results for this phase 2 study mirrored the earlier trial results with a mean +10.6 letters of vision improvement at six months, or a 62% improvement over Lucentis monotherapy.

With any luck, we have here a combination therapy that inhibits pericyte recruitment, strips pericytes from the neovascular complex without negatively affecting host non cardiovascular vessels, and causes both inhibition and regression of the neovascular complex.

Combination anti-VEGF and anti-PDGF therapy offers hope that we may provide our patients with a more permanent and sustainable treatment model to combat the blinding effects of this common disease.

**ANTI VEGF THERAPY: Can Anti-VEGF Trigger GA?**

While anti-VEGF drugs have improved the vision and quality of life for hundreds of thousands of patients with retinal disease, these drugs do have some shortcomings. Patients and retinal specialists understandably chafe under the treatment burden that regular anti-VEGF intravitreal injections entail. In addition, some patients are not responsive to anti-VEGF therapy.

One of the most puzzling and controversial findings to come out of the 2 year CATT study data is the presence of geographic atrophy (GA) in 30% of patients who received monthly doses of Ranibizumab during the trial. Some patients who received Bevacizumab monthly or either drug on a PRN basis also showed signs of geographic atrophy, but not at the high levels seen in the Lucentis monthly arm of the trial.

The association of GA with the most potent arm of the trial has led to a concern that repeated anti-VEGF injectors can serve as a trigger mechanism for GA. Hence given the current lack of effective treatment for GA, Anti-VEGF therapy should be used judiciously following a “treat-and-extend protocol...a Goldilocks approval.” We don’t want too much or too little VEGF inhibition...we want just enough!!!

Given that opportunities exist to improve upon ant-VEGF monotherapy, numerous efforts are under way to find better drugs or less invasive delivery systems. In the investigational pipe line for wet AMD are such concepts as pills, eye drops, sustained-release delivery systems, radiation treatments and other innovative drug-development efforts too numerous to mention here.

But is terms of what new therapies are deemed most promising, early stage clinical trials have shown that combination drugs may have the best chance of early approval. Three combinations worth mentioning are:

1. **Ophthotech’s anti platelet derived growth factor (PDGF) drug Fovista in combination with ranibizumab** has shown excellent results in phase 1 clinical trials of 22 patients who were not responsive to anti-VEGF monotherapy. In a large phase 2 study encompassing 449 patients, investigator
PravinDugel, MD, reported a combination of Fovista and ranibizumab was 62% more efficacious than ranibizumab monotherapy.

2. Allergan’s DARP in (designed ankyrin repeat proteins) drug, developed along with partner Molecular Partners, showed efficacy in treating wet AMD as monotherapy in a phase 2a study. The priority now is to combine the DARP in with an anti PDGF in a dual acting combination therapy. The DARP in is also being tested in combination with ranibizumab.

3. Allegro Ophthamlc’s integrin peptide (ALG 1001) is designed to shut off VEGF production at its source. The drug showed good efficacy in a small study of DME patients and will be used in a phase 1b/2a trial as monotherapy to treat wet AMD.

The excellent results demonstrated thus far by Fovista, the DARP in and ALG-1001 appear to indicate that the next generation of combination drugs to combat retinal disease may be just over the horizon.

ADVANCES IN LASER TECHNOLOGY
New Breakthroughs in Laser Technology /Advances in Laser Technology for Photo coagulation: Delivering faster, safer and more accurate LASER treatment.

Laser photocoagulation has been the mainstay of retinal practice, having been validated as an effective treatment for clinically significant macular edema associated with Diabetic Retinopathy & retinal vein occlusion in landmark studies such as ETDRS & BVOS. The technology for laser photocoagulation has evolved through several prototype instruments. Important advances in laser photocoagulation technology has resulted in more accurate and effective treatment that is less painful to the patients. The xenon arc coagulator, the huge water cooled argon & krypton gas laser, solid state semiconductor diode red and frequency doubled 532nm Yag green laser have been in use till date. Dye laser, TTT and PDT lasers had only transient popularity and are rarely used in the present day scenario.

1. The Navilas is designed to improve the precision and efficacy of retinal photocoagulation by means of an integrated live imaging system that uniquely enables the surgeon to plan, “navigate” and execute the treatment. The Navilas device is a multifunctional system that combines fundus photography, fluorescein angiography and laser to effectively aid in the diagnosis and treatment of ocular pathologies in the posterior segment of the eye.

Throughout treatment, an LCD monitor provides live high definition color or IR images. The surgeon easily designs the treatment with the use of a mouse or touch screen. A joystick is utilized to position and control the device and provides a micromanipulator. The software allows the surgeon to place caution zones over the foveal avascular zone (FAZ) and the optic nerve area in order to highlight these sensitive regions during laser application. The surgeon is able to effectively plan a comprehensive treatment with the Navilas system targeting all microaneurysms and nonperfused areas with unprecedented accuracy due to this unique live imaging system.

To perform panretinal laser photoagulation, a PRP objective is utilized along with a specifically designed contact lens. The contact lens and Navilas optical head must be centered to each other with optical axes aligned. The image of the patient’s retina is brought into focus by moving the optical head axially using a joystick until a sharply illuminated image appears. Unlike a slit lamp microscope where only a small part of the aerial image can be sampled with narrow slit and microscope, Navilas instantly samples a static field of 630 X 500 (800 diagonal). By moving the Navilas optical head laterally, the full equatorial field may be sampled.

The PRP contact lens forms a real aerial image of the retina up to the equator. For covering the retina up to the equator, no or minimal tilt of the lens is required minimizing astigmatic changes of the image and of the projected laser spot. This leads to uniform and consistent laser uptake with round spots from the posterior pole to the periphery.

PRP using the Navilas Laser System appears to be safe, well tolerated and achieves a high rate of efficacy. Distribution of laser spots across the retina is even and very precisely placed due to the unique navigational capabilities of the Navilas device. Panretinal laser treatment can be efficiently completed with less pain than with the more traditional laser approach.

Why navigated laser?
The answer, is that navigated laser may offer increased accuracy and a lower retreatment rate. 91.5% of the treatment delivered vs 71.5% with conventional laser and the treatment rate was decreased by 50% when compared to conventional slit lamp laser.

The ability to utilize live imaging to plan, navigate and execute precise laser treatments with one multi-functional platform represents a tremendous technological advance. An entirely new level of safety, efficacy and stability is anticipated with expanded use of the Navilas Laser System as a stand alone treatment or in combination with anti-VEGF therapy.

Pattern Scanning Laser (PASCAL)
The launch of the pattern scanning laser technology by Topcon Medical Laser Systems, Inc in 2006 marked a major breakthrough in laser treatment for retinal diseases. By rapidly applying 532nm laser pulses (56 spots is approximately 0.6 seconds) in predetermined patterns, the PASCAL photocoagulator enables physicians to target specific pathologies with less scatter and to create multiple rapid, sequential burns. This results in reduced treatment duration and less pain for the patient. When compared to traditional single spot laser photocoagulation as well as less collateral damage. The Pascal photocoagulator features the following preset patterns for various pathologies.

1. Square arrays for proliferative diabetic retinopathy
2. Triple areas for retinal tears, lattice degeneration & PDR
3. Modified Macular Grid: for diffuse DME

Pattern specific controls such as spot spacing, enable further customization so that patterns can be matched to retinal disease states & anatomical features.

**SURGICAL RETINA**

**DOES SURGERY HAVE A FUTURE IN RETINA CARE?**

Advancements in medical treatments mean less time in the OR for retina specialists. It’s no secret that the treatment of retinal disease is changing. With the pharmacological advances that have been made, retina specialists face the choice of continuing to use the standard surgical techniques they have relied on for years, or the newer, less invasive medical treatments that are evolving at a rapid pace.

**MEDICAL TREATMENT NOW STANDARD FOR AMD:**

Surgical management of AMD, including vitrectomy and removal of sub retinal choroidal neovascular membrane, macular translocation, and RPE transplantation are rarely being done now.

Now for a patient with wet AMD, and with salvageable vision, anti VEGF injection is the first line of therapy, and treating a macular degeneration patient with laser or PDT has become rare in the past five years.

However, some retina specialists still find a place for PDT, and even thermal laser, in select AMD patients - PDT is a component of treatment for subtypes of macular degeneration, and occasionally laser is still performed for an area of choroidal neovascularization outside of the fovea itself. There still is an occasional surgical case, where someone comes in with a massive sub retinal hemorrhage that warrants surgery.

**TREATMENT OF RETINAL DETACHMENT:**

Retinal detachment, to a large degree, still requires a surgical treatment. The tendency has been more and more to go toward vitrectomy. In the past the sclera buckles were performed primarily in patients who were phakic. Or a combination of a buckle with vitrectomy was performed for rather extensive pathology in the inferior periphery. The exception to the rule were pseudophakic patients who have had previous cataract surgery and a lens implant. In this subgroup generally buckles were avoided.

Surgery for repair of retinal detachment is becoming less invasive. Some of the retinal detachments that were fixed with surgery in the past can now be done in the office with less invasive procedures such as pneumatic retinopexy. But pneumatic retinopexy is also being done less, mainly because of the reliance it places on the postoperative positioning.

**ADDITION OF Ocriplasmin:**

Ocriplasmin, (Jetrea, ThromboGenics, Iselin, NJ) recently received FDA approval for treating symptomatic vitreomacular adhesion (VMA). While it isn’t a treatment for retinal detachment, it might aid in helping to close macular holes and in the release to traction in VMA in some eyes that develop macular holes. Ocriplasmin could lead to fewer surgeries for symptomatic VMA and macular holes -just as the surgical volume was already dropping off when we began using anti VEGF agents for AMD.

The studies that were done with ocriplasmin certainly showed that patients who had relatively small macular holes or well defined VMAs responded favorably. Forty to 45% of cases had resolution of the abnormality with a single injection. However surgery has a 90% success rate or better for all conditions proposed for treatment with ocriplasmin. The drug has no application in retinal detachment and is rarely indicated for vitreomacular traction cases....

A select group of patients may be ideal for treatment with ocriplasmin especially patients with vitreomacular adhesions that focally elevate the posterior pole, resulting in the type of configuration more likely to progress to macular hole or already causing an early-stage hole. Those patients can be easily identified by the characteristic anatomic appearance on SD-OCT. It is very difficult to reliably determine if there is vitreous adherent to the margins of macular hole using OCT, the so-called stage 2 macular hole, said to be an indication for ocriplasmin. If there is no vitreous adherence, which is usually the case, the agent is not indicated.
The cost, expected to be around $4,000 in the United States, also is prohibitive. It is “Over twice the cost of Lucentis (Ranibizumab, Genetech, South San Francisco, CA) or Eylea (afibercept, Regeneron, Tarrytown, NY), and about the cost of surgery in an ASC.

A MATTER OF CONVENIENCE AND LESS INVASIVENESS:
What are the reasons for retina specialists moving in the direction of injection of pharmaceutical medications rather than a surgical procedure?

The greatest advantages is convenience for the patient and the retina specialist. If there is an agent that does the same job but in a less invasive way, or if the invasiveness is similar but the treatment is more effective, that option is always chosen.

Certainly in general, pharmacologic treatments are less invasive and is safer than a surgical procedure and can often be considered as an alternative at an earlier stage of disease to preserve or improve the patients vision.

TEACHING OUTGOING METHODS
As treatment evolve and older procedures are used less frequently, is there any need to continue teaching the old way to incoming students and residents? The need for surgery will never go away and the problem facing future generations is maintaining a certain level of expertise while the volume of a procedure may diminish. However if a newer, better approach replaces on older one the need to continue teaching the old method decreases.

ALWAYS A ROLE FOR SURGERY
Despite the advances in medical therapy and the discoveries certain to occur in the future, the need for surgery will continue. Looking at the future where stem cell research will be the next paradigm shift in retina therapy we may come full circle and may have to sharpen our surgical skills. Let us look at some of the newer indications for surgery.

Floatectomies: Should it Be a Routine Part of the Surgeon’s Armamentarium: Fact or Fiction
The management options for a patient with vitreous floaters were Observation (The treatment of choice in almost all cases - Efficacy: High patient satisfaction / Safety: No associated risks), and Nd: YAG laser vitreolysis / photodisruption (Procedure rarely performed / Efficacy: Most patients have no improvement; many patients report the continued presence of smaller floaters, moderately effective primary treatment conferring clinical benefit in one third of patients. Safety: Risks include retinal hemorrhage, retinal pigment epithelial damage, and choroidal hemorrhage) Vitrectomy surgery a procedure occasionally performed previously but is being advocated now as an out-patient procedure for vitreous floaters (27G vitrectomy)

a: Efficacy: High patients satisfaction; surgical removal of vitreous floaters is not expected to improve visual acuity.
b: Safety: Risks include those associated with vitrectomy for other conditions, such as cataract, vitreous hemorrhage, macular edema, retinal detachment, choroidal hemorrhage, and endophthalmitis.

Vitrectomy may be indicated in a select group of patients with visually disabling vitreous floaters, although objective assessment of visual dysfunction from vitreous floaters requires further evaluation. Vitrectomy, while offering superior results (compared to laser vitreolysis), should be reserved for patients who remain marked symptomatic following vitreolysis, until future studies further clarify its role.

Patients should be informed about the risk of cataract progression, unexpected inflammatory reaction and an increased risk for retinal detachment several years after vitrectomy (5.5%). The idea that vitrectomy for floaters is simple and less dangerous than vitrectomy for other indications should be banned. Despite these risks, a small section of patients with persistent and debilitating symptoms can consent to treatment by vitrectomy.

Endoscopy-assisted surgery
Current technology for ophthalmic endoscopy delivers undoubtedly advantages in certain surgical situations. Endoscopy allows for viewing in 3600 through nontransparent media, at a high magnification and tangential approach to the anterior “Zonular” vitreous base, involved in anterior posterior vitreoretinopathy and ciliary membranes. In facilitates excellent PRP in patients with peripheral ischemic retinopathies. It allows endoscopic cyclophotocoagulation in patients with glaucoma.

A long learning curve, absence of stereopsis and limited view with current 23G probes are the main drawbacks. In the future we can look forward to increased functionality of 23 G endoscopic probe. This reduced gauge probe may also be used for retinal vessel cannulation, delivery of stem cells or other therapeuctic agents.

The preferences & Trend Survey of ASRS (American Society of Retinal Specialists) showed that most surgeons are using 23G & 25G instrumentation for vitrectomy surgery. 72.5% for respondents perform 23G vitrectomy & 60% perform 25G Vitrectomy.

Concerns that were raised when 25G instrumentation was first introduced included...
Continuing Development of 27-gauge Vitrectomy Systems: Where Are We Now?

Since Eugene de Juan, MD, first introduced the concept of transconjunctival sutureless vitrectomy with a trocar-cannula system and 25-gauge instrumentation, microincision vitrectomy systems (MIVS) with 25 or 23 gauge instruments have evolved radically over the past several years.120,121

There is no doubt that MIVS has simplified the vitrectomy procedures and that it offers numerous potential advantages over traditional 20 gauge surgery, including shorter operating time, reduced corneal astigmatism, diminished conjunctival scarring, improved patient comfort, and in some cases, earlier visual recovery.122

Recent innovations and improvements seem to have settled several concerns that were raised in the early years of MIVS. Stiffer instruments and wide-angle viewing systems have eliminated the frustration with tool fragility. A more powerful light source combined with a chandelier system have improved the endoilluminating brightness through a small gauge optic fiber. The new generation of vitrectomy machines have dramatically improved the cutting efficiency of small-gauge vitrectomy probes.123, 124

CRITICISMS OF SMALL GAUGE VITRECTOMY

The most serious criticisms regarding the current 23 and 25 g systems have focused on complications related to wound sealing, such as leakage, hypotony, and postoperative infectious endophthalmitis. Although the recent refinement of trocar-cannula systems has ergonomically improved their self-sealing architectures, special techniques are still required. Complete self-sealing wounds are not yet achievable in every case, even with 25g systems, especially in patients who have thin scleras or who have had extensive peripheral vitreous shaving.125

On the basis of the above-mentioned aspects of modern MIVS, the gauge size for MIVS will likely decrease in the future. Recent innovations, such as the advent of powerful light sources, techniques for building up stiffer instrumentation, and high-performance vitrectomy systems, have also encouraged the development of a 27 g vitrectomy system over the past several years.126, 127

CURRENT STATUS OF THE DEVELOPMENT OF 27-G VITRECTOMY SYSTEMS

In 2008, reports on preliminary results using a first generation 27-g system were released. Although at that time it was used only in the selected cases, mainly macular disease and simple vitreous hemorrhage, both the anatomical and visual results were promising.

Remarkably, there was no need to transition to a larger gauge, no suturing was required, and no hypotony was observed in any of the study cases.128

Commercially available 27-gauge system packages include a 2,500-cpm high-speed pneumatic vitreous cutter, a wide-angle illuminating light pipe, an infusion tube with a trocar-cannula system, and a micro membrane forceps. The system from DORC is compatible with two vitrectomy machines, the Accurus (Alcon) and Associates (DORC). The system from synergetics can be used with the Accurus only.

When developing a smaller-gauge vitrectomy system, the most crucial concerns may be about reduced endoilluminating and cutting efficiency through smaller-gauge lumen. The introduction of powerful light sources, using xenon light and mercury vapor light, which have been featured in the new-generation vitrectomy machines as the standard illumination light sources, had fortunately enabled us to develop smaller gauge illumination tools.
Currently, not only the 27-g wide-angle illuminating light pipe packaged in the 27-g pack, but also the 27-g chandelier endoilluminating optic fibers, are commercially available from several manufactures for use with 27-g systems for more challenging cases, such as a 27-gauge twin light chandelier system (Dorc International, Zuidland, Netherlands) and a 29-/23gauge dual chandelier fiber system (Synergetics, O’Fallon, MO).129,130

Both types of 27-g chandelier fibers131 have maximum output reaching to more than 20 lumens, which is sufficient to endoilluminate the fundus. Development of a practical 27-g vitreous cutter is also a key step for establishing a 27-g vitrectomy system.

Very recently, the second generation spring/pneumatic 27 g cutter from DORC and Medical Instrument Development Laboratories, Inc., (San Leandro, CA) have become commercially available, featuring a normal shaft length (32 mm) and a maximum cutting rate of up to 2,500 cpm with higher duty cycles.

**TECHNIQUES, INDICATIONS, AND CLINICAL EXPERIENCE WITH 27-GAUGE SYSTEMS**

The most distinctive characteristic of the 27-g system that makes it superior to the larger-gauge MIVS systems is the simplicity of creating rigid, self-sealing wounds. The surgeon can begin 27-g vitrectomy immediately after creating sclerotomies at the paraplana by one-step vertical insertion. Complex techniques for creating a self-sealing wound, such as angled-insertion techniques or two step entry methods are no longer required.

Also, because of the small size and multifunctionality of the 27-g cutter, reducing the use of various instruments for manipulation in complex cases will minimize the time wasted in instrument exchanges and, as result, also contribute to the reduction of total operating time.

After simple removal of all instruments, surgeons can close at once, and all sclerotomies can self seal completely without the need for suturing, even in cases with thin scleras, extensive peripheral vitreous shaving, or multiple surgeries. It is no doubt feasible that this system will supersede the current 25 and 23-g systems, at least for treating macular diseases and simple vitreous hemorrhages.

The 27-gauge cutter can be much more easily inserted into the tiny space between the membrane and the retina. Through wide-angle fundus viewing, it is also easy to carry out bimanual membrane dissection with a 27-g system and it goes without saying that the 27-g cutter with a single hand is sufficient for several roles.

**FUTURE PERSPECTIVE**

The final goal of trans conjunctival surgery is to achieve perfect, self-sealing wounds with stable postoperative IOP from the first day after surgery, with tiny changes on the ocular surface-limited subconjunctival hemorrhages and scars and acceptable operating time with minimal intra and postoperative complications- as well as favorable anatomic success and early visual rehabilitation.

The 27-g system may have advanced one step closer to these final goals, compared with the current 23 and 25-g systems. Although the development of 27-g vitrectomy is an ongoing project, and it has not yet been established as a widely accepted system.

The new generation machines, featuring dual-pneumatic driven technology, allow for ultrahigh cutting rates with duty cycle control. The 27-g systems, with this new technology in the near future, will achieve much higher performance.

The recent evolution in 23 and 25-g systems, further development and refinement of 27-g instruments functionality are under way and will continue over the coming years, allowing us in the future to establish this system for ultra minimally invasive surgery for the full spectrum of vitreoretinal pathologies.

**Endophthalmitis after parsplana small gauge vitrectomy**

Several hypothesis have been put forward to explain the higher incidence of endophthalmitis after small gauge vitrectomies. These include

1. **Poor wound stability:** Unsutured wounds that lead to early post operative hypotony may allow intraocular influx of extraocular fluid and micro organisms.
2. **Infusion rate with reduced influx & efflux** of fluid may allow greater bacterial inoculum to remain in the eye.
3. **Residual vitreous skirt** may facilitate bacterial adherence and sequester bacteria from normal immunological factors &extraocular antibiotics.
4. **Vitreous wick prolapse** through sclerotomy sites may create a potentially open conduit through conjunctival and scleral wound, facilitating entry of bacteria into the eye.

Currently prevailing evidence emphasizes the importance of the following measures to reduce the risk of endophthalmitis.

1. **lid scrubbing**
2. direct povidone iodine application
3. conjunctival displacement and angled beveled incision
4. more complete vitreous removal adjacent to sclerotomies
5. air tamponade
6. repositing potential extra conjunctival vitreous wick
with light pipe assisted canula removal & subconjunctival antibiotic injection

7. extra insufflation of air/gas if necessary to stabilize IOP
With refinement of technology we can look forward to water tight sutureless closure and a lower complication rate

New Instrument Update: The list of new instruments released this year resembles science fiction components with ability to outperform older ones as well as make seemingly impossible procedures possible.A peep into the future will not be complete without a mention of these

1. Retidyne132: is a dye with low potential for phototoxicity due to the addition of small amounts of antioxidant Lutein to a low concentration of Brilliant Blue. This is an intense green dye which has affinity for both the posterior hyaloid and the ILM.(L/2 0.3% + BB 0.2%)
2. Rezzo Pocket Cryo with a small nitrous oxide canister.
3. UltravitProbe with 7500 cuts /min
4. 27 Gauge accessories
5. Edge Plus valved Trocar cannula
6. Versa Vit133 the small compact complete vitrectomy system
7. EVA Phacovitrectomy system with vacuum flow based vitrectomy mode, and LED light source with the first titratable colour source
8. Bausch & Lomb Stellaris with yellow green and amber filters
9. Ehab el Raes Suprachoroidal catheters
10. Tornabe “s temporary winged wedge scleral buckle for 2-8 wks
11. Disposable BIOM
The list goes on ………

GENE THERAPY IN RETINAL DISEASES
Gene Therapy: Where Are We Now?
A major misconception about gene therapy is that its application is limited to genetic disease. Gene therapy is simply a delivery system for drugs (bioactive substances). Any disease that would benefit by the local production of a genetically engineered protein, peptide, RNA, or RNA fragment would be a potential candidate for gene therapy.133

Proof of principle has been established in animal models for a variety of genetic and non-genetic retinal diseases. For example:

A: Acquired: retinal neovascularization, choroidal neovascularization134
1: Anti-VEGF strategies (eg, using RNAi, antisense RNA)
2: Production of pigment epithelium derived factor
B: Genetic: retinitis pigmentosa, Leber congenital amaurosis135,136, retinal/macular dystrophies
1: For recessive diseases, replacement with ‘wild-type’ gene or gene correction resulting in production normal enzyme:

eg, RPE-65, peripherin / RDS(Prph2)137
2: For dominant disease, neutralization of toxic “dominant” substance (eg, ribozyme therapy for rhodopsin mutants causing dominant RP)

Technique of Retinal Gene Therapy
As with any other drug, the gene therapy agent (ie, vector) has to somehow be applied in order to work. Systemic (eg, intravenous) administration of vectors increases toxicity by enhanced exposure to the immune system; furthermore, it will not result in any appreciable uptake in the retina. Vectors need to come in direct contact with their target cells as they do not cross tissue planes. They are engineered not to replicate and therefore do not spread beyond the field of administration. In addition, since retinal neurons do not replicate, the vector does not become diluted over time.

Administration procedures and the cells types that are transduced:

1: Subretinal injection: retinal pigment epithelium photoreceptors, Muller cells
2: Intravitreal injection: ganglion cells, optic nerve, Muller cells, ciliary body, anterior chamber structures
3: Ex vivo gene therapy can be used to create encapsulated implants; site of “drug” delivery depends on site of surgical implantation.

To date, the genes for some 35 ocular disorders have been identified, and a few of these diseases will be discussed below. The four ocular diseases that have received the most attention are Leber’s congenital amaurosis(LCA), wet AMD, Stargardt disease, and Usher syndrome.

Leber’s Congenital Amaurosis:
In treating LCA135,136, the majority of the work has been focused on RPE65, the RPE specific 65-kDA protein that is involved in the conversion of all trans retinol to 11-cis retinal during phototransduction and that has been implicated as a genetic defect in LCA. When loaded onto the AAV2 virus, the product becomes AAV2-RPE 65.

Wet AMD: Another major area of emphasis in gene therapy is treatment of wet AMD. Although anti-VEGF drugs are currently successfully treating wet AMD, the cost and time involved monthly or semimonthly injections can be troublesome. As a one time treatment the promise of gene therapy (the “for-ever fix”) is attractive. In wet AMD, VEGF plays a critical role because blockade of VEGF is sufficient to suppress the development of choroidal neovascularization. A variety of antiangiogenic proteins oppose the actions of proangiogenic factors, such as VEGF. Gene transfer to augment expression of these endogenous inhibitors or related engineered proteins is a potential alternative to
suppress CNV and avoid frequent intraocular injections. Considerable preclinical and emerging clinical data suggest this approach may be feasible.

The secreted extracellular domain of VEGF binding protein that consists of domain 2 of Flt-1 linked to a human immunoglobulin B1 (IgG) heavy chain Fc fragments (sFLT01). Intravitreous injection of AAV2.sFLT01 is being evaluated in a phase ½ clinical trial of wet AMD137,138.

**Stargardt Disease:**
The gene identified in the treatment of Stargardt disease is ABCA4139. This gene produces a protein involved in energy transport to and from photoreceptor cells in the retina. Mutations in the ABCA4 gene produce a dysfunctional protein that cannot perform its transport function. As a result, photoreceptor cells degenerate and vision loss occurs.

**PHARMACOGENOMICS AND TREATMENT OF NEOVASCULAR AMD**

**How genotype can affect response to treatment.**
Age related macular degeneration is a genetically heterogeneous condition in which the mainstay of local anti VEGF treatment also produces widely varied outcomes.

**GENETIC VARIATION TREATMENT RESPONSE:**
It has been long understood that there is a significant genetic component to AMD, based on family history studies. The advances in our ability to analyze the human genome have paralleled the advances in intraocular neovascular inhibitors. Single-nucleotide polymorphisms (SNPs), associated with AMD were first characterized in genes involved in the alternate complement pathway140. Subsequently, disease-associated SNPs have been associated with the genes that are involved in tissue remodeling, as well as oxidative and cholesterol metabolism.

By combining haplotype odds ratios of these multiple SNPs, smoking history, drusen size, our ability to predict the risk of individuals with AMD to progress to advanced sight-threatening AMD is so advanced that it approximates the level of correlation between tobacco smoking and the development of lung cancer, with an odds ratio >17.141

There was no correlation of overall risk score with response to anti VEGF treatment in terms of visual acuity change, OCT thickness change, or treatment number. There were no independent associations of SNPs within the CFH,C3 or ND2 genes with response to anti VEGF therapy based on these three parameters. However, at least one insertion/deletion polymorphic site, indel (NM_001099667.1:c.372_815del1443ins54), within the ARMS2 gene was found in 63 patients who had an average improvement in log MAR visual acuity, compared to a visual deterioration in those with the ancestral genotype which indicates both a clinically and statistically significant association.

This indel polymorphism in the ARMS2 gene did not appear to be related to a significant difference in the treatment number of anatomic response based on OCT thickness. Patients with or without deletions did not differ by age or presenting visual acuity. The positive treatment response related to this mutation was similar in patients who were treated with either bevacizumab or ranibizumab.

**ANTI VEGF RESPONSE AND ARMS2 GENE STRUCTURE**
Many groups have reported linkage of AMD markers that may predict response to anti VEGF treatment and photodynamic therapy, which include genetic polymorphisms CC(rs1061170,Y402H) in the complement factor H gene (CFH) and the APOE gene. Variable response to AMD therapy was initially studies for PDT, in which visual acuity change was linked to the Y402H SNP in complement factor H.142-146

First report of a relationship between treatment response and polymorphisms within the LOC387715/ARMS2 gene.147-150 The reported relatively strong association of the indel deletion of the ARMS2 gene with vision protection following 12 months of anti VEGF treatment, in a population that is representative of typical anti VEGF response, provides a framework for the development of confirmatory prospective studies and for the possible design of novel ocular antiangiogenic strategies.

Two of the central issues in the treatment of neovascular AMD remain optimizing the results of anti VEGF treatment with the lowest treatment burden. The next advances in treatment of neovascular AMD will likely be contingent upon the ability to predict the response of antiangiogenic treatment better and to develop neovascular inhibitors with novel mechanisms of action. Genetic analyses of patients undergoing anti VEGF treatment have the potential to help to accomplish these two advances.

Pharmacogenomics of AMD is therefore a rapidly evolving field, and initial studies of patients with neovascular lesions have provided both interesting results and the rationale for large studies to allow ultimately for better individualized patient care and the design of new therapies.

**Future Treatments for Retinal Degenerations: Neuroprotection**
Photoreceptor cell death is the ultimate cause of vision loss in many eye diseases, including AMD, retinitis pigmentosa, and retinal detachment (RD), which together affects tens of millions of people worldwide. While therapies exist for some of these eye diseases, there are currently no treatments...
that effectively prevent photoreceptor cell death. Much research has focused on the mechanisms of cell death in hopes of identifying therapeutic targets in degenerative retinal diseases. Apoptosis is the most characterized form of programmed cell death, and was previously thought to be the main mechanism of photoreceptor degeneration. Indeed, the caspase enzymes (which play a central role for inducing apoptosis) are activated in dying photoreceptor cells in experimental models of RD151. Paradoxically, inhibiting caspases does not sufficiently protect against photoreceptor cell loss. This suggests that other mechanisms of cell death are involved. Recent accumulating evidence demonstrates that non-apoptotic forms of cell deaths, such as autophagy and necrosis, are also regulated by specific molecular machinery, such as autophagy-related proteins and receptor-interacting protein (RIP) kinases,152 respectively. By identifying alternative cell death pathways and understanding how to inhibit them, we can prevent vision loss in multiple eye disorders.

Classification of Cell Death: Apoptosis, Autophagy, and Necrosis

The morphological features of apoptotic, autophagic, and necrotic cells are quite distinct and still the gold standard in distinguishing the various forms of cell death. Genetic / biochemical features have been now recognized, but there is a lot of interplay and cross talk.

Caspase signaling is initiated by either external death signals such as tumor necrosis factor (TNF)153 or Fas ligand (FasL) or intrinsic signals such as mitochondria damage and reactive oxygen species (ROS)154. First identified as the key player of cell death in development, apoptosis also has strong evidence supporting its central role in disease. Caspases are also involved in pyroptosis, a distinct mechanism of cell death associated with inflammation. The role of caspase-dependent apoptosis in photoreceptor cell death has been established in many models.

3: Apoptosis-Inducing Factor (AIF)-Mediated Mitochondrial Pathway

Apoptosis-inducing factor (AIF) is an intrinsic factor involved in initiating a caspase-independent pathway of apoptosis. It moves from the mitochondrion into the nucleus and has been shown to play a role in photoreceptor cell death after RD154.

RIP kinase (RIPK) signaling is closely connected to both the extrinsic caspase signaling pathway and the NF-KB survival pathway. Caspases inhibit RIPK signaling and limit necrosis. However, when caspases are blocked, the RIP kinases are activated, and increased necrosis compensates for the inhibition of apoptosis.

4: Autophagy-Related Protein (Atg) Family

Autophagy (from the Greek word auto meaning “self” and phagein meaning “to eat”) is a process/mechanism in which the cell degrades unnecessary or dysfunctional cellular components to ensure cellular survival during starvation by maintaining cellular energy levels. Depending on the system and the levels of activation autophagy can promote either cell survival or cell death.

5: Neuroprotection Strategies

A: Caspase inhibition

Early on it was shown in experimental RD that apoptotic photoreceptor cell death is associated with caspase activation. In addition, Zacks and colleagues155 have shown that the Fas-mediated apoptosis pathway becomes activated after RD, and inhibition of Fas activation (with anti-FAS-receptor antibodies) can decrease caspase-9 activity (Zacks, et al., 2004). However, when pan-caspase inhibition was tested as a neuroprotection strategy, caspase inhibitors were unable to prevent cell death. In contrast activation of the endogenous X-linked inhibitor of apoptosis (XIAP) 155as been shown to have protective qualities in rodent models of retinitis pigmentosa (Leonard, et al., 2007)156 and in RD Zadro-Lamoureux, et al., 2009)157, and it may be a useful strategy for neuroprotection.

B: Combined inhibition of apoptosis and necroptosis

We found that in photoreceptor degeneration after experimental RD, RIPK-mediated necrosis is also a significant mode of cell death; furthermore, when caspase are inhibited, RIP-mediated necrosis become the predominant form of death. (Trichonas, et al., 2010)158. This may explain why caspase inhibition has been unsuccessful in preventing photoreceptor cell death. RIPK-mediated programmed necrosis and apoptosis and redundant mechanism of photoreceptor cell death, and simultaneous inhibition of RIP kinases and caspase is essential for effective neuroprotection.

C: Ciliaryneurotrophic factor (CNTF)

CNTF159, which may act through the IL-6 receptor, is a potential neuroprotective treatment. Significant in vitro and animal studies have shown CNTF to be a potent survival factor for neurons and oligodendrocytes, and it may reduce tissue destruction resulting from inflammation. Neurotech has devised a technology using encapsulated human cells (NT-501) genetically modified to secrete CNTF. In the early stage clinical trials for retinitis pigmentosa and geographic atrophy secondary to AMD, this treatment appeared to be rather well tolerated with some hints of benefit.

D: Brimonidine: Brimonidine 160(Allergan; Irvine, Calif., USA) is a selective alpha 2-adrenergic agonist well known
for reducing aqueous production that has been shown to increase the production of neurotrophic factors, protecting cells from degeneration with unknown mechanism. Allergan is investigating a brimonidine intravitreal implant in patients with geographic atrophy in a Phase 2 clinical trial.

6: Pathway to Clinical Trials
To date, neuroprotection has been unsuccessful in ophthalmic clinical trials. Proof-of-concept studies could be undertaken in RD to test whether visual outcomes can be improved in acute settings. For chronic diseases like AMD and IRDs, slow-release formulation should be developed. The local delivery and tolerability to intravitreal injections will facilitate our efforts to easily integrate neuroprotective treatments into standard patient care.

Photoreceptor cell death is the ultimate cause of vision loss in RD and other retinal degenerative disorders, and apoptosis is the best-characterized form of programmed cell death. However, despite more than a decade of work, attempts to achieve neuroprotection by pharmacologically targeting apoptosis have largely failed. We and others have shown that not only apoptotic but also nonapoptotic pathways contribute to photoreceptor cell death and that simultaneously targeting key mediators in both pathways (e.g., inhibiting both caspases and RIP kinases) is effective in preventing photoreceptor cell loss. Further dissection of the complex molecular mechanisms of photoreceptor cell death will lead to novel strategies for preventing vision deficits in retinal degenerative diseases.

And more to come in future…………

Telemedicine’s Role in Posterior Segment Eye Care
Making eye care more accessible to patients and decreasing unnecessary visits

The advent of telemedicine heralds a new era in ophthalmology to bridge the gap between physician and patient and offering many benefits for the screening, diagnosis, monitoring and management of eye disease. Advances in computing and telecommunications technology enable ophthalmologists and optometrists to offer a higher standard of care despite geographic distance. Significant cost savings can be realized by using telemedicine instead of annual eye exams.

THE PROS OF TELEMEDICINE
Telemedicine provides a reliable, cost-effective means of screening diabetic patients and premature babies for retinopathy, which can lead to blindness. Since the number of diabetics in the United States is growing fast, and the supply of eye-care practitioners is not, healthcare resources are strained and becoming more so. Certainly, not every diabetic now receives the standard of care, an annual eye exam, but that situation will likely worsen unless alternative healthcare delivery systems are employed to address it. With new, easy to-use, non-mydriatic cameras, nurse and medical assistants without any ophthalmic training can learn to take excellent fundus photographs. These images can be transmitted to a reading center where they can be expertly assessed. This new methodology has already been adopted in a number of high profile institutions and also is part of the HEDIS standards for comprehensive diabetic care.

Two new technologies that work seamlessly together are the PRN Referral cloud based telemedicine software and the nonmydriatic fundus cameras.

References
17. Oh J, Kim SW, Kwon SS et al. Correlation of fundus autofluorescence grey values with vision and microperimetry in resolved central serous chorioretinopathy.

74. Peter K Kaiser Editorial. Retinal Physician 2012 OCTOBER.


76. Molecular partners report positive results from its clinical studies on MP 0112, its lead macular targeting VEGF-A. April 28, 2011, Eastern Daylight Time. Abstract ARVO Fort Lauderdale, FL (May 1st - 5th 2011)


119. Jorge G Arroyo. The role of endoscopy in vitreoretinal surgery today Retina Today. Jarrooy @ bidmc.harvard.edu


Retinal Vein Occlusion

Background
Retinal vein occlusion (RVO) is a common cause of visual loss. It is an obstruction of the retinal venous system by thrombus formation and may involve the central, hemi-central or branch retinal vein. Thrombus formation may be the primary cause but other possible causes are external compression or disease of the vein wall e.g. vasculitis. Retinal vein occlusions are the second commonest cause of reduced vision due to retinal vascular disease with BRVO occurring 2–3 times as common as CRVO. In the Australian population study the incidence was 0.7% at 49–60yrs and 4.6% at 80yrs. It is currently estimated from pooled data from 15 population studies from that there are about 520 new cases per million population of RVO. These include 442 and 80 per million of BRVO and CRVO respectively.

Aetiology and Risk Factors
Retinal vein occlusion is due to thrombosis within retinal veins (central, hemi or branch) although it remains unclear whether it is a primary or secondary effect. Established cardiovascular risk factors are the predominant medical associations for both central and branch vein occlusions and are summarised below.

Systemic vascular/atherosclerotic risk factors in RVO
Study design, patient characteristics, and risk factor definitions are seldom standardized across the various published papers in the literature. However accounting for this it remains probable that systemic hypertension is the strongest independent risk factor associated with all types of RVO, especially in the older (over 50 years) age group. Uncontrolled or newly diagnosed hypertension is common in this group, and recurrence of RVO in the same or fellow eye is also noted when hypertension is poorly controlled. In their meta-analysis of 21 studies, O’Mahoney et al12 report a significant association between hypertension and both CRVO (pooled odds ratio [OR = 3.8]) and BRVO (pooled OR 3.0). Accepting an inconsistent definition of hyperlipidemia across studies they also found hyperlipidemia to be twice as common in RVO cases (both CRVO and BRVO) compared to controls (pooled OR 2.5). Some studies also report hypertension and hyperlipidemia as independent risk factors for RVO12. The association of diabetes mellitus with RVO is weaker and has not been found to be consistent across all studies9-12. Its association with CRVO may be stronger than with BRVO10.

Hematological disorders and other systemic conditions.
Conditions that lead to increased blood viscosity such as myeloproliferative disorders are uncommon but known to be associated with CRVO. Similarly, a number of rare systemic inflammatory disorders causing systemic vasculitis (such as Behçet’s disease and polyarteritis nodosa) also cause retinal vasculitis leading to RVO, especially in the younger age group. The cause and management of the RVO here is closely linked to the underlying systemic disease and its management. Over recent years there has been great interest in the potential role of thrombophilia in the development of RVO and in particular CRVO. Thrombophilia refers to the propensity to develop thrombosis (usually venous) due to an abnormality in the coagulation system. This can be congenital (eg, Factor V Leiden, hyperhomocysteinemia or protein C, protein S and antithrombin deficiencies) or acquired (eg, antiphospholipid syndrome), and its importance is potentially greater in the younger age group. However Fegan’s review on CRVO and thrombophilia16 suggested that there was a lack of consistency between studies in showing a valid association between CRVO and protein C, protein S and antithrombin III deficiency, and factor V Leiden/activated protein C resistance. These natural anticoagulants are very labile with fluctuating physiological levels. It is recommended that they should be measured on at least two separate samples and if found abnormal confirmed with a third estimation. Most studies used single measurements and varying types of assays. The studies also lacked the statistical power to show a true difference either due to small sample size or lack of a suitable control group. In the antiphospholipid syndrome (APS) antibodies to phospholipid activate the coagulation cascade leading to both arterial and venous thrombosis. Tests can be done to either detect the antibody (using the anticardiolipin antibody assay) or its effect on coagulation using a test for lupus anticoagulant. Up to 8% of patients with APS have ocular manifestations and 4 of 8 studies reviewed by Fegan16 showed a significant association of APS in CRVO. Further studies are required to determine the strength of association between APS and RVO. Homocysteine is a naturally occurring amino acid not found in protein. There are many causes for hyperhomocysteinemia (including rare enzyme deficiencies leading to homocystinuria) which predisposes to both arterial and venous thrombosis. Several studies have questioned the validity of carrying out exhaustive tests for thrombophilia in RVO in the absence of a suggestive
Ischemic CRVO with extensive retinal hemorrhages

A- Nonischaemic CRVO with minimal retinal hemorrhages, B- Ischemic CRVO with extensive retinal hemorrhages

Glaucome/ocular hypertension

The association between RVO (CRVO in particular) and glaucoma/ocular hypertension has been widely reported with the Eye Disease Case-Control Study reporting an adjusted OR of 5.4 in CRVO for a history of glaucoma. The pathophysiology of this association is unclear, although deformation of the lamina cribrosa in glaucoma may distort the central retinal vein as it exits the eye.

Familial RVO

Familial clustering of RVO (CRVO in particular) has been reported but these reports have been few in number. It is interesting that such cases are more often bilateral, with a younger age at onset than sporadic cases. More data from existing and future familial clusters is required to establish if there is a genetic cause in these cases.

CLINICAL FEATURES OF CRVO

Non-Ischemic CRVO

Non-ischemic CRVO is the most common type, accounting for about 75%. Presentation is with sudden, unilateral blurred vision. Mild to moderate loss of acuity, usually 20/200 or better, and an absent or mild relative afferent pupillary defect (RAPD), characterize these patients. Funduscopy shows tortuosity and dilatation of all branches of the central retinal vein, dot/blot and flame-shaped hemorrhages, throughout all four quadrants and most numerous in the periphery, and optic disc and macular edema. Blood levels are often seen within the large retinal cysts in the foveolar area. Some cotton-wool patches, particularly in hypertensive patients, may be present. Transient retinal vessel wall sheathing may occur.

The acute signs resolve over 6-12 months, with disc collaterals and pigmentary changes at the macula as residual findings. In a clearly non-ischemic occlusion, initial follow-up should take place after 3 months. Conversion to ischemic CRVO occurs in 15% of cases within 4 months and 34% within 3 years.

A- Nonischaemic CRVO with minimal retinal hemorrhages, B- Ischemic CRVO with extensive retinal hemorrhages

Ischemic CRVO

Ischemic CRVO is characterized by rapid onset venous obstruction resulting in decreased retinal perfusion, capillary closure and retinal hypoxia. Patients with severe central retinal vein obstruction typically have severe visual loss, usually less than 20/200; a marked afferent pupillary defect; severe tortuosity and engorgement of all branches of the central retinal vein, extensive deep blot and flame-shaped hemorrhages involving the peripheral retina and posterior pole, severe disc edema and hyperemia. This may lead to profound vascular leakage, rubeosis iridis and raised intraocular pressure. The prognosis is extremely poor due to macular ischemia. Rubeosis iridis develops in about 50% of eyes, usually between 2 and 4 months (100-day glaucoma), and there is a high risk of neovascular glaucoma. Retinal neovascularization occurs in about 5% of eyes. Where possible, patients with ischemic CRVO should be seen monthly for 6 months to detect the onset of anterior segment neovascularization. Subsequent review should usually be for up to 2 years to detect significant ischemia and macular oedema.

Natural history data from the CVOS study and a systematic literature review demonstrated that visual outcome of CRVO depends on the visual acuity at presentation. Eyes with initial visual acuity of 20/40 (6/12) or better have a better prognosis for retaining good vision than those with worse vision. Only 20% of eyes with initial visual acuity of 20/50-20/200 (6/15 -6/60) improve spontaneously to 20/50 (6/15) while 80% of patients with baseline vision worse than 20/200 (6/60) remain at this level or worsen. Furthermore, the longer the duration of macular oedema, the more the structural damage at the fovea so it is justifiable that early treatment be initiated.

CLINICAL FEATURES OF BRVO

Major BRVO can be asymptomatic or with visual blurring usually involving the sector of visual field corresponding to the area of the retina involved. In macular BRVO, there is always a central visual disturbance with normal peripheral vision. Acute BRVO presents characteristic clinical features with flame-shaped, dot and blot hemorrhage, soft and hard exudates, retinal edema, and dilated, tortuous vein in a segmental distribution. Signs of old occlusion are vascular sheathing and venous collaterals. The diagnosis is based on clinical examination under slit lamp and funduscopy in artificial mydriasis; VA is of great importance for future visual prognosis. BRVO often leads to retinal non-perfusion zones in the occlusion area. Fluorescein angiography is particularly useful in determining the extent of ME and ischemia, although the ischemic areas are often obscured by the presence of intraretinal hemorrhage. Retinal neovascularization occurs in 36% of eyes with an area of non-perfusion greater than 5 disc diameter.
Natural history data from an evidence based systematic review of 24 studies by Rogers et al. indicated that VA was moderately poor (worse than 6/12) at presentation, and that although there may be some improvement in the follow-up period, such improvement was limited such that the average improvement did not result in VA better than 6/12. Macular oedema may develop in 5 to 15% of eyes over a 1 year period; however, of the eyes that had macular oedema at presentation, 18 to 40% may show some resolution. Approximately 20% of untreated eyes experienced significant vision deterioration over time. In the BVOS5, approximately 50% of untreated eyes with BRVO retain vision of 6/12 or better whilst 25% will have vision of <6/60.5 Fellow eye involvement by BRVO may occur in 10% of cases over time.

Clinical evaluation
The minimum assessments required before commencing treatments for CRVO include:
Clinical examination including...
a. Best corrected visual acuity (BCVA)
b. Pupillary reactions- the presence of a brisk afferent papillary defect (APD)
c. IOP
d. Gonioscopy
e. Slit lamp biomicroscopy of the anterior segment and fundus

**Retinal Imaging**
a. Colour fundus photographs (Whenever possible)
b. Optical coherent tomography (OCT)
c. Fundus fluorescein angiography (FFA) where the interpretation is not confounded by the presence of marked intraretinal haemorrhage or can be based on clinical judgement.

Electro-retinography: Is useful to differentiate nonischaemic CRVO from Ischaemic CRVO. Nonischemic RVO have normal b wave amplitude and b/a wave ratio. Ischemic type usually have reduced b wave amplitude and b/a wave ratio23,24

The minimum assessments required before commencing treatments for BRVO include:

Clinical examination including
a. Best corrected visual acuity (BCVA)
b. Pupillary reactions- the presence of a brisk afferent papillary defect (APD)
c. IOP
d. Gonioscopy if clinically indicated
e. Slit lamp biomicroscopy of the anterior segment and fundus

**Retinal Imaging**
a. Colour fundus photographs (whenever possible)
b. Optical coherent tomography (OCT)
c. Fundus fluorescein angiography (FFA) where the interpretation is not confounded by the presence of marked intraretinal haemorrhage or as per clinical judgement.

**FFA in RVO**
FFA in RVO shows dilatation and tortuosity of affected veins with retinal hemorrhages, cotton wool spots and edema in the areas of drainage. In all eyes there is a delay in the filling of the retinal circulation, dilated capillaries, microaneurysms and telangiectatic changes. Blocked fluorescence of the underlying retinal circulation occur if extensive intraretinal hemorrhages are present especially in the early part of the disease and therefore FFA may not reveal useful information.
CRVO is said to be perfused if capillary non-perfusion is less than 10 disc areas and non-perfused if capillary non-perfusion is more than 10 disc areas. BRVO is said to be perfused if capillary non-perfusion is less than 5 disc areas and non-perfused if capillary non-perfusion is more than 5 disc areas. Another main role of FFA is evaluation of macular edema. Macular edema can be of perfused type, if there is an intact parafoveal capillary network in arteriovenous phase followed by late accumulation of dye involving the foveal centre, non-perfused if there are areas of parafoveal and perifoveal capillary non-perfusion with no accumulation of dye seen in late phase. In other cases a mixed picture with combination of capillary dilatation and leakage, areas of capillary non-perfusion in the parafoveal region, with late phase showing some degree of accumulation of dye. Late staining and leakage from affected veins also occurs. Retinal capillary obliteration is a progressive phenomenon and it takes 3-4 weeks to obliterate; if FFA is done early, perfectly normal capillaries may be seen, despite retinal ischemia and may lead to wrong diagnosis of non-ischemic variety.

**OCT in RVO**

OCT delineates macular changes at a stage when fundus biomicroscopy and fluorescein angiography are not very informative. The various anatomical patterns of structural changes appreciated better on OCT are SRD, CME, epiretinal membrane, lamellar holes and subhyaloid or preretinal hemorrhages. OCT examination shows CME, if there were hyporeflective intraretinal cavities in cross sectional scans radiating from centre of macula and SRD, if there is retinal elevation over a nonreflective cavity with minimal shadowing of underlying tissues or if posterior surface of the retina is elevated above the retinal pigment epithelium. Non-ischemic maculae show an early and more rapid decline in macular thickness compared with ischemic occlusions. OCT is also useful to quantify macular edema and helps in follow up of patients with macular edema, in assessing treatment response especially to intravitreal pharmacotherapy and in explaining poor outcomes and has been part of all the recent trials in the management of macular edema of vein occlusions.

**MANAGEMENT**

There are two aims in the management of retinal vein occlusion: the identification of modifiable risk factors and their medical management and the recognition and management of sight-threatening complications.

**Central retinal vein occlusion (CRVO)**

The main management problem is to differentiate ischaemic from non-ischaemic central retinal vein occlusion. Patients with ischaemic CRVO are at risk of neovascular glaucoma. This risk of iris neovascularisation is higher if the area of retinal ischaemia (retinal non-perfusion as determined by FFA) is >10 disc diameters. Ischaemic central retinal vein occlusion is associated with one or more of the following characteristics:

1. Poor visual acuity (44% of eyes with vision of <6/60 develop rubeosis)
2. Relative afferent pupillary defect
3. Presence of multiple dark deep intra-retinal haemorrhage
4. Presence of multiple cotton wool spots
5. Fluorescein angiography showing greater than 10 disc areas of retinal capillary non-perfusion (CVOS)
6. Electrodiagnostic tests (ERG): reduced b wave amplitude, reduced b:a ratio and prolonged b-wave implicit time
7. Degree of retinal vein dilatation and tortuosity

There is no evidence as to which combination of the above characteristics best defines ischaemic CRVO. It is important to note that up to 30% of patients with initially non-ischaemic central retinal vein occlusion will develop ischaemic transformation. Ischaemic central retinal vein occlusion is usually heralded by further rapid visual deterioration and requires further assessment. CRVO especially of the non-ischaemic type needs to be differentiated from the ocular ischaemic syndrome and other simulating retinopathies.

**Medical Investigations for Patients Presenting with Retinal Vein Occlusion**

**ALL PATIENTS**
- Full blood count
- ESR
- Peripheral smear
- Random blood glucose (in non diabetics), FBS/PPBS,HBAIC (In known diabetics)
- Lipid profile
- ECG+ECHO heart
- Carotid Doppler study

**MORE SPECIALISED TESTS ACCORDING TO CLINICAL INDICATION**
- Thrombophilia screen
Medical Management
Medical management should be targeted at three areas:

1. **Restoring venous patency**
   **Clinical & Diagnostic Work-up:** This is applicable in a limited number of cases. Patients with ‘incipient’ retinal vein occlusion (consisting of the presence of dilated retinal veins and few widely scattered haemorrhages without any macular oedema in patients who are either asymptomatic or have transient episodes of blurring in the affected eye and may have slight increase in retinal circulation time on fluorescein angiography) should have medical investigation for underlying systemic risk factors and treatment urgently as there is the potential to prevent progression, or to reverse the existing occlusion.

The medical therapies explored to improve retinal venous flow include:
- **Anti-coagulants:** heparin
- **Fibrinolytic agents:** streptokinase, tissue plasminogen activator (intravitreal or systemic)
- **Anti-platelet drugs:** aspirin, prostacyclin, ticlopidine

These would seem to be logical treatments, but results from trials using heparin, streptokinase and warfarin have been disappointing with limited evidence of benefit owing to adverse effects of retinal and vitreous haemorrhage. Aspirin is not recommended for primary prevention of cardiovascular events. If aspirin is used in primary prevention, the balance of benefits and risks should be considered for each individual, particularly the presence of risk factors. Given that there is insufficient evidence to suggest that RVO is a risk factor for stroke or vascular mortality, the role of aspirin in RVO remains equivocal.

**Haemodilution:** The effects of haemodilution have been inconsistent in completed control trials in RVO and the treatment may have adverse affects on the patients’ general well-being.

2. **Ameliorate cardiovascular morbidity and mortality associated with retinal vein occlusion**
   **Manage underlying risk factors:** Although reports on the association of RVO with cardiovascular morbidity and mortality are conflicting, it is crucial that all cardiovascular risk factors be identified and treated in patients with RVO. Cardiovascular risk factors identified in patients with retinal vein occlusion should be managed according to the Joint British recommendations on prevention of coronary heart disease and the recent updates on the management of hypertension and the use of statins.

3. **To prevent the recurrence of retinal vein occlusion**
   Several series have demonstrated that recurrence of retinal vein occlusion may occur in the affected eye or in the fellow eye in up to 15% of patients over a five year follow-up period. Rates vary according to studies in differing countries from 9 to 15%. In view of the potential visual outcome of patients with recurrent retinal vein occlusion, this aspect has been studied, but not in controlled trials. Available data supports the concept that recurrence of retinal vein occlusion may be reduced by medical treatments of underlying cardiovascular risk factors.

**CRVO STUDY**

**Group M—Macular Edema:** Macular grid photocoagulation was effective in reducing angiographic evidence of macular edema but did not improve visual acuity in eyes with reduced vision due to macular edema from CVO.

**Group N—Panretinal Photocoagulation for Nonischemic CVO:** Prophylactic panretinal photocoagulation did not prevent the development of iris neovascularization in eyes with 10 or more disc areas of retinal capillary nonperfusion confirmed by fluorescein angiography. Rather, results of this randomized clinical trial demonstrate that it is safe to wait for the development of early iris neovascularization and then apply panretinal photocoagulation.

**Group I—Indeterminate:** Eyes with such extensive intraretinal hemorrhage that it is not possible to determine the retinal capillary perfusion status act as if they are ischemic or nonperfused.

**Management of nonischaemic central retinal vein occlusion**
An initial evaluation of risk factors and the appropriate treatment of the present risks must proceed alongside management of the ocular findings. These patients are managed conservatively till significant macular edema or features of ischaemic CRVO occur.

A useful algorithm is as follows
1. If VA is better than 6/12 + OCT < 250 microns, observe at monthly intervals for worsening in vision, increase in macular thickness, increase in IOP and onset of neovascularisation.
2. If VA is 6/12 or worse + OCT ≥ 250 microns (Stratus, or equivalent) consider pharmacotherapy with Ozurdex or anti-VEGF agents which is unlicensed but has robust evidence.

3. However, the presence of a brisk APD associated with VA < 6/96 indicates potentially poor treatment outcomes.
   a. As such no treatment would be recommended for such cases. Watch for NVI/NVA, and treat as ischaemic CRVO

Subsequent Follow-Up
1. Depending on baseline VA, OCT & FFA findings, and initial treatment options, monitoring will be required at varying frequencies during the first 6 months.
   a. Assessments at each visit include VA, IOP, gonioscopy, fundoscopy, and OCT
   b. From month 6 to 18 months, monitoring at monthly or 3 monthly, depending on the particular treatment of choice
   c. Based on the results of the clinical trials, treatment may be repeated unless
      a. VA > 6/7.5 (84 letters on LogMAR) OR
      b. Central Retina Thickness (CRT) on OCT < 250 microns OR
      c. Treatment is discontinued at the clinician’s discretion (See below)

2. Re-treatment with dexamethasone implant (OZURDEX) should take place at 4 to 6 month intervals. There is only limited case report data to support dosing intervals less than 6 monthly.
3. Based on the CRUISE study, consider following the monthly injection schedule for the first 6-12 months, and the PRN re-treatment criteria from the study should be used as the basis for a PRN dosing regimen.

Re-treatment Criteria
1. Based on the results of the clinical trials, treatment may be repeated unless
   a. VA > 6/7.5 (84 letters on LogMAR) OR
   b. Central Retina Thickness (CRT) on OCT < 250 microns OR
   c. Treatment is discontinued at the clinician’s discretion (See below)

3. In circumstances when regular follow-up is impractical, prophylactic treatment with PRP and anti-VEGF agent may be appropriate.

Posterior segment neovascularisation
This is an uncommon complication following ischaemic central retinal vein occlusion in eyes which have not developed neovascular glaucoma or who have been successfully treated for rubeosis by laser. There is anecdotal evidence that new vessels may be managed with a combination of anti-VEGF and PRP. Pan-retinal photocoagulation for CRVO with INV or ANV requires 1500 – 2000 of 500-micron burns at the retina. This is best applied with 0.05-0.1 second applications one burn width apart with sufficient energy to produce a pale burn in the retina. Treatment is usually placed in the periphery avoiding areas of retinal haemorrhage. Some cases require further treatment if the iris neovascularisation fails to regress. The pan-VEGF A blockers, ranibizumab and bevacizumab have been shown
to cause regression of new vessels of the iris, angle and retina when given intravitreally at the dose of 0.5mg/0.05ml and 1.25mg/0.05ml respectively. However, the effect is transient and recurrence of new vessels is common so repeated treatment, typically every six weeks with these agents supplemented with PRP may be required.

Management of established neovascular glaucoma
The aim of management of this condition in a blind eye is to keep the eye pain free. This is usually achieved by topical steroids and atropine. However, if the eye has any visual potential intraocular pressure should be controlled with topical pressure-lowering agents, cyclo-ablative procedures or filtering surgery. Intravitreal and intracameral bevacizumab has been shown to cause regression of iris new vessels and decrease angle obstruction. Comparative case series indicate that iris new vessels regress faster after intravitreal bevacizumab with PRP than with PRP alone. The reports also suggest that bevacizumab may reduce the need for surgical interventions and serve as a useful adjunct to filtering surgery.

Management of macular edema in CRVO
Macular oedema following central retinal vein occlusion results from leakage of perifoveal capillaries. It results in visual loss. Randomised controlled trials have failed to indicate benefit with grid laser photocoagulation, although a trend in favour of treatment has been observed in younger patients. Although there was significant reduction in the severity of macular oedema in treated eyes compared to controls there was no visual acuity benefit.

Triamcinolone acetonide: The rationale for the use of intravitreal triamcinolone acetonide (IVTA) to treat macular oedema is that corticosteroids reduce retinal capillary permeability and inhibit the expression of the VEGF gene and the metabolic pathway of VEGF. Evidence for the use of a specific preparation of triamcinolone in CRVO is from the SCORE-CRVO Study (SCORE Study Report 5). In this study, a
preservative-free form of triamcinolone (TRIVARIS, Allergan) given at different doses, 1mg and 4mg, at four monthly intervals and with pre-defined retreatment criteria, was compared to observation. Results showed that both doses of IVTA produced both anatomical and functional improvement of macular oedema due to CRVO, compared to observation. However, at month 12, the 1mg dose had a better safety profile compared to the 4mg dose in terms of a lower incidence of raised intraocular pressure (IOP) >35mmHg (5% vs. 8%), incidence of cataract formation or progression (26% vs. 33%, cf. 18% for observation) and need for cataract surgery (0% vs. 4%).

**Dexamethasone Biodegradable Implant:** The rationale for the use of intravitreal dexamethasone to treat macular oedema is similar to that of IVTA, although dexamethasone has been shown to be a more potent corticosteroid that IVTA but also is able to reduce retinal capillary permeability and inhibit the expression of the VEGF gene and the metabolic pathway of VEGF. However, dexamethasone when injected intravitreally in its free form, has a short half-life that limits its clinical utility as an injectable suspension. A pre-filled applicator single-use, sustained release biodegradable implant containing 0.7mg of dexamethasone (OZURDEX, Allergan) has been studied in the GENEVA study programme. In this study, OZURDEX and an alternative dose of dexamethasone implant (0.35mg) were compared to a sham injection, in patients with CRVO and BRVO in 2 parallel multicentre studies and published together as the GENEVA study. The percentage of eyes with ≥15 letter gain in BCVA was significantly higher in both implant groups compared with sham at days 30 to 90 with a peak effect at 60 days. Subgroup analyses of the BRVO and CRVO subjects showed a significantly greater number achieved ≥15 letter gain from 30 to 90 days than sham treated eyes, and that sham treated eyes in the BRVO subgroup were more likely to improve spontaneously than similar managed CRVO eyes. Anatomically, improvements in macular oedema as seen by OCT were also seen. In terms of safety, raised IOP peaked again at month 2 (3.2% of patients had an IOP>35 mmHg), but declined significantly by month 3 and was close to 0% by month 6, with 19% of patients requiring an IOP lowering agent at month 6 and 0.7% of patients requiring any IOP lowering surgical procedures. Similarly, rates of cataract progression were low with 7% progression at month 6, compared to 4% in the sham group. Based on the GENEVA study programme, OZURDEX has received approval for the treatment of macular oedema following either BRVO or CRVO. A post hoc analysis suggested that eyes treated within 90 days of CMO being present were more likely to improve than eyes commencing treatment after this time point.

**Ranibizumab:** The pan-VEGF blocker, ranibizumab (LUCENTIS, Novartis) when given in 2 doses (0.3mg and 0.5mg) every month for 6 months, in the CRUISE Trial, was shown to produce a 3-line gain of visual acuity and corresponding anatomical response. The mean gain in VA was 12.7 and 14.9 letters respectively with the 0.3 and 0.5mg compared to the sham treated group at 6 months. Following the first 6 months, all patients were enrolled into an open-label extension for an additional 6 months and the overall 12 months results suggest that the visual gain established in the first 6 months can be retained with a slightly less intensive pro re nata (PRN) therapy with ranibizumab (an average of 5.6 injections in 1st 6 months, vs. 3.3 injections in 2nd PRN 6 month phase). Early treatment may be preferable as confirmed from the earlier smaller observational studies , and a sham controlled study.

**Bevacizumab:** The pan-VEGF blocker, bevacizumab is unlicensed for intraocular use. Several case series (without controls) indicate that approximately 50% of subjects with non-ischaemic CRVO improve 2 or more lines with intravitreal bevacizumab, whilst 90% of eyes showed vision stabilization by 12 months. However, the dosing schedule is unclear and the long-term outcomes remain unclear.

**Pegaptanib:** A phase II trial, and prospective case series indicate that intravitreal 0.3mg pegaptanib sodium when given every 6 weekly for 6 months improved the visual acuity by approximately 7 letters at 6 months. The reported follow-up periods are short and so the treatment regimen and the response to treatment in the long-run remain unclear.

**Recommendations for Further Follow-up**
Follow-up after the initial 6 months of treatment will depend upon initiation of anti-VEGF agent or steroid treatment for macular oedema but will normally be required for up to 2 years in uncomplicated cases. The eyes should be monitored for ischaemia (>10DD non-perfusion) and for occurrence/recurrence of macular oedema. The development of disc collaterals +/- resolution of the macular oedema should lead to discharge from clinical supervision.

**Experimental treatments in CRVO**
Chorio-retinal anastomosis (C-RA) was recently evaluated in a small (n=113) randomised clinical trial. Of patients in whom the C-RA was patent (76%), VA improved by a mean of 11.7 letters compared to controls. Side effects included neovascularisation at the site of the anastomosis in 18% and vitrectomy was required in 9%, due to macular traction or non-resolving vitreous haemorrhage. The procedure requires a special high power laser and significant operator experience. It is only recommended in the context of prospective data collection by an ophthalmologist specifically trained in its
use. An Australian review of the technique concluded that there was only level IV evidence available. The procedure was therefore classified as experimental, with potential to cause serious side effects. Other studies have reported significant complications associated with the procedure e.g. choroidal neovascularisation, retinal and subretinal fibrosis or traction, and vitreous haemorrhage.

Trials of other treatments such as radial optic neurotomy (RON) with pars plana vitrectomy, and thrombolytic therapies are under way. RON is essentially a procedure in which a radial incision is made in the nasal segment of the scleral ring in order to decompress the presumed pressure within this compartment so as to relieve pressure on the CRV. These, however, are only experimental at present and are, therefore, not recommended except as part of clinical trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Regimen</th>
<th>Indication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCORE 1 year</td>
<td>Preservative free IVTA 1 mg</td>
<td>4 monthly injection</td>
<td>Atleast 3 month old CRVO Nonischaemic 20/40- 20/400 vision CFT &gt; 250 mic No ERM/ VMT</td>
<td>Atleast 25% improved by 15 letters 5% glaucoma 26% cataract</td>
</tr>
<tr>
<td>CRUISE 6 mths</td>
<td>Lucentis 0.5 mg</td>
<td>Monthly injection for 6 months</td>
<td>Atleast 3 month old CRVO Nonischaemic 20/40- 20/400 vision CFT &gt; 250 mic No ERM/ VMT</td>
<td>48% improved by 3 lines or more Average Vision gain of 14 letters</td>
</tr>
<tr>
<td>GENEVA 6 mths</td>
<td>Oxurdex 0.7 mg</td>
<td>Single injection</td>
<td>At least 6 wk old CRVO 20/50- 20/200 vision CFT &gt; 300 mic Nn ERM/VMT</td>
<td>Atleast 25% improved by 15 letters Effect best upto 90 days only</td>
</tr>
</tbody>
</table>

**Nonischaemic BRVO**

**Management of macular oedema secondary to BRVO with no or minimal evidence of macular ischaemia**

1. If patients with macular oedema secondary to BRVO are seen within 3 months of onset of BRVO, consider pharmacotherapy with Ozurdex which is licensed or Ranibizumab which is unlicensed but has robust clinical evidence of efficacy.

2. If patients are seen after 3 months from onset of BRVO, consider laser photoocoagulation or pharmacotherapy with Ozurdex which is licensed or Ranibizumab which is unlicensed but has robust clinical evidence of efficacy.

**Management in eyes with evidence of marked macular ischaemia**

No immediate treatment is recommended. Watch for conversion of the RVO to ischaemic type and subsequent neovascularisation.

**Re-treatment criteria**

1. Based on the results of the clinical trials, treatment may be repeated unless.
   a. VA>6/7.5 (84 letters on LogMAR) OR
   b. Central Retina Thickness (CRT) on OCT<250 microns
   c. Treatment should be discontinued (See below)

2. Re-treatment with dexamethasone implant (OZURDEX) should take place with 4-6 months after first treatment.

3. Re-treatment with ranibizumab injections should occur monthly for the first 6 months followed by a PRN schedule based on re-treatment criteria from the BRAVO study.
4. Re-treatment with modified Grid Laser Photocoagulation should be considered at 4 monthly intervals

**Ischaemic BRVO**
1. Watch carefully for NV
2. Perform 3 Monthly follow, especially if the area of retinal ischaemia is > 4DD, and treatment is not required for macular oedema.
3. If NVE occurs, there is limited anecdotal evidence for the use of intravitreal bevacizumab in such cases and its use would be considered unlicensed, e.g.
   a. PRP+/- intravitreal bevacizumab 4-6 weekly until quiescent.
   b. bevacizumab
4. Follow-up 3 monthly to up to 12 months. Subsequent follow-up will be guided by the clinical findings and ongoing treatment

**Treatment of neovascularisation in BRVO**
Disc or retinal neovascularisation is an indication for photocoagulation to the ischaemic retina (sector photocoagulation), although available evidence suggests that waiting until vitreous haemorrhage occurs before laser treatment does not adversely affect the visual prognosis. New vessels occur only when there is at least a quadrant of capillary closure and commonly after six months following the occlusion. Follow up visits at 3- 4 monthly intervals are recommended in patients with one quadrant or more retinal ischaemia. It is recommended that sector laser photocoagulation is applied once retinal or optic disc neovascularisation occur. Fluorescein angiography is not usually necessary prior to laser because the area of ischaemia is visible clinically. Photocoagulation for neovascularisation is applied to the sector of retinal capillary closure. 600-micron burns at the retina are used and are applied in a scatter pattern to the affected sector, one burn width apart are appropriate with sufficient energy to create a gentle burn. A quadrant usually requires 400-500 burns.

**Laser treatment of macular oedema in BRVO**
Randomised clinical studies in the laser treatment of macular oedema have demonstrated that a grid pattern of photocoagulation in the distribution of leaking capillaries is beneficial but it is recommended only after a period of three to six months following the initial event and following absorption of the majority of haemorrhage.

Fluorescein angiography should be carried out prior to this therapy usually at > 3 months if visual acuity is 6/12 or less. This has two functions. Firstly it identifies the leaking capillaries and secondly will indicate the degree of macula ischaemia, which may limit the value of photocoagulation. It will also help to avoid laser to collaterals.

The optimal technique to administer laser photocoagulation for macular oedema requires gentle burns of 50 to 100um. The power depends on the individual patient. An average of between 20 to 100 applications (depending on the area of vascular leakage) are required in a grid pattern to the areas of vascular leakage but avoiding the foveal avascular zone (i.e. the burns must not approach the foveal centre by less than 1/2 DD). Collaterals should be avoided. Initial follow-up at three months following the occlusion. Subsequent follow-up at three to six monthly intervals will depend on complications and laser treatment, and will not normally be required after two years in uncomplicated cases.

**Other treatment options for macular edema**

**Triamcinolone acetonide:** Evidence for the use of a specific preparation of triamcinolone in BRVO is from the SCORE-BRVO Study (SCORE Study Report 6). In this study, a preservative-free form of triamcinolone (TRIVARIS, Allergan) given at different doses, 1mg and 4mg, at four monthly intervals and with pre-defined re-treatment criteria, was compared to laser photocoagulation. Results showed that both doses of IVTA produced both anatomical and functional improvement of macular oedema due to BRVO, but this was similar in magnitude to laser. In addition, at month 12, both the 1mg and 4mg doses had an inferior safety profile compared to laser in terms of a higher incidence of raised intraocular pressure >35mmHg (IOP) (2% and 14%, vs. 1%), incidence of cataract formation or progression (25% and 35%, vs. 13%) and need for cataract surgery (0% and4%, vs. 3%). As such, laser is considered to have a more favourable benefit:risk profile to IVTA in BRVO. Similar to the case in CRVO, there is no Grade A evidence to suggest that the visual and anatomical responses seen with TRIVARIS in SCORE-BRVO would be replicated with off-label IVTA preparations such as KENALOG.

**Dexamethasone Biodegradable Implant**
Based on the GENEVA study programme which has been discussed earlier, OZURDEX has received also approval for the 0.7 mg preparation for the treatment of patients with macular oedema following BRVO.
Ranibizumab: The pan-VEGF blocker, ranibizumab (LUCENTIS, Novartis) given in 2 doses (0.3mg and 0.5mg) every month for 6 months, was compared with sham, in the BRAVO study. At 6 months, the mean gain in VA was +16.6 and +18.3 letters (0.3 and 0.5 mg respectively) compared to +7.3 letters in the sham injection group. Sixty-one percent of the ranibizumab 0.5mg group achieved a 15 letter gain vs 29% in the sham treated group. However from months 3-5, a single application of rescue laser photocoagulation was also allowed in all study arms if hemorrhages had cleared sufficiently to allow safe application of laser, based on predetermined criteria. Approximately 20% of patients in both ranibizumab arms received adjunctive laser, versus 55% in the sham injection arm. Following the first 6 months, all patients were enrolled into an open-label extension for an additional 6 months and the overall 12 months results suggest that the visual gain established in the first 6 months can be retained with a slightly less intensive pro re nata (PRN) therapy with ranibizumab (an average of 5.7 injections in 1st 6 months, vs. 2.7 injections in 2nd PRN 6 month phase). However, as seen with the results of GENEVA & CRUISE studies, the visual acuity outcome never caught up in this delayed treated group compared to eyes treated earlier.

Bevacizumab: Currently, increasing short-term data support the fact that multiple intravitreal bevacizumab injections reduce macular oedema secondary to branch retinal vein occlusion including those that had failed previous laser treatment. The most common treatment regimen is two to three injections over the first 5-6 months. However, further randomized, controlled trials are required to assess longterm safety and efficacy of intravitreal bevacizumab.

Periocular triamcinolone: Periocular (orbital floor or retrobulbar) triamcinolone has been administered as treatment of macular oedema in BRVO. Although both routes of administration demonstrated efficacy, the results are short-lived.

### Intravitreal Drug trials in BRVO

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Regimen</th>
<th>Indication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAVO 6 mths</td>
<td>Lucentis 0.5 mg</td>
<td>Monthly injection for 6 months</td>
<td>Atleast 3 month old BRVO with no RAPD 20/40- 20/400 vision CFT &gt; 250 mic No ERM/ VMT</td>
<td>61% improved by 3 lines or more Vision gain of 18 letters</td>
</tr>
<tr>
<td>GENEVA 6 mths</td>
<td>Oxurdex 0.7 mg</td>
<td>Single injection</td>
<td>Atleast 6 wk old BRVO 20/50- 20/200 vision CFT &gt; 300 mic Nn ERM/VMT</td>
<td>Atleast 27% improved by 15 letters Effect best upto 90 days</td>
</tr>
</tbody>
</table>

Other Treatments

The evidence on the efficacy of surgical interventions in BRVO are limited to case reports and case series. Metaanalysis studies has reviewed the evidence of arteriovenous sheathotomy for this condition and recommended that this procedure be done only as part of a research study.

Management of younger patients (less than 50 years of age)

Central retinal vein occlusion in this age group has been thought to have a more benign outcome in a greater proportion of patients, with spontaneous regression of the central retinal venous occlusive event being more common. However, at least 20% of patients develop poor visual outcome with severe neovascular complications. Some authorities advocate the use of steroid therapy but this has not been tested in controlled trials. Patients in this age group with BRVO usually have underlying systemic conditions such as hypertension or hyperlipidaemia which should be managed appropriately. Those with CRVO present a particular problem in investigation and management. Many of these patients will have no identifiable underlying cause despite extensive investigation including the specialised investigations listed before. In females the contraceptive pill is the most common underlying association, and caution is advised in patients with retinal vein occlusion. There is debate as to the exact prevalence of thrombophilic disorders in this patient group as well as appropriate therapy. Identified inflammatory disease should be treated as appropriate to the condition and referred for specialist medical advice.

Hemisphere vein occlusion

The risk of rubeosis in ischaemic hemi-central vein occlusion is greater than that of BRVO but less than that of CRVO. The risk of disc neovascularisation appears greater for hemispheric vein occlusion than either ischaemic CRVO or BRVO. The management of hemispheric vein occlusion is similar to that described for branch retinal vein occlusion, the guidelines for treatment options being those described above for retinal branch vein occlusion.
REFERENCES
32. Lipid modification for prevention of cardiovascular disease - NICE Clinical Guideline 67 2010
Kerala Journal of Ophthalmology


Dr. Manoj S was trained at Aravind Eye Hospital. He is now the Senior Consultant, Vitreo Retinal Services, Chaithanya Eye Hospital, Trivandrum
Introduction
The word diabetes mellitus comes from Greek words “Diabetes” means “siphon” and mellitus which mean “honey tested urine”. It is a major risk factor of blindness in both developing and developed countries. It is estimated that diabetes mellitus affects 4 per cent of the world’s population, almost half of whom have some degree of diabetic retinopathy (DR) at any given time. DR occurs both in type 1 and type 2 diabetes mellitus and has been shown that nearly all type 1 and 75 per cent of type 2 diabetes will develop DR after 15 years duration of diabetes as shown in epidemiological studies. Visual disability from diabetes is a significant public health problem and if managed with timely intervention, the quality of life can be preserved. This article aims at providing an overview of proliferative diabetic retinopathy (PDR) and recent advances in the management.

Pathogenesis and course of Proliferative Diabetic Retinopathy (PDR)
Retinal neovascularization occurs in response to retinal ischemia. Angiogenic factors have been isolated from ocular tissues in proliferative diabetic retinopathy patients. Major factors have particular relevance in PDR: Vascular endothelial Growth factor (VEGF), basic Fibroblast Growth Factor (b-FGF) and Insulin like Growth Factor (IGF). They stimulate endothelial cell proliferation, migration and organisation into three dimensional collagen matrices to form capillary like tubes.

New vessels once formed progress along the routes of least resistance. The absence of a true internal limiting membrane on the disc explains the prevalence of new vessels at that location. Also, neovascularization seems to grow more easily on a preformed connective tissue framework. Thus, a shallow detached posterior vitreous face is a frequent site of growth of new vessels. The new vessels, initially naked, undergoes through a stage of further proliferation with connective tissue formation. The fibrous component becomes more prominent, with the fibrotic tissue being either vascular or avascular. The fibrovascular type is found in association with vessels that extend into the vitreous cavity or with abnormal new vessels on the surface of the retina or disc. The avascular variety usually results from organization or thickening of the posterior hyaloid face. These proliferations exert traction on the retina and may lead to retinal detachment. Finally, the end stage is characterized by regression of the vascular systems. No further damage may take place, but there may be contraction of the connective tissue components, development of subhyaloid bands, thickening of the posterior vitreous face, appearance of retinoschisis, retinal detachment and formation of retinal break.

Clinical signs of PDR
1) Neovascularisation- Proliferative diabetic retinopathy is characterised by new vessel growth or by fibrous tissue proliferation on optic disc, retinal vasculature elsewhere and along the partially detached posterior hyaloid. Proliferative diabetic retinopathy also includes rubeosis iridis or new vessels in the anterior chamber angle.

Severity of new vessels increases on a four step scale:
• None
• Neovascularisation elsewhere (NVE)
• Neovascularisation of disc (NVD)
• Neovascularisation of the anterior chamber angle with neovascular glaucoma (NVG)
2) Vitreous and preretinal haemorrhage- As long as the posterior hyaloid remains attached neovascular proliferation appears to be slightly anterior to retina and is usually asymptomatic. Small haemorrhages may occur at the growing tip of the new vessels, mostly remain subhyaloid. As the posterior hyaloids detaches, haemorrhages become less confined and symptoms appear. Contraction of the vitreous or fibro vascular proliferation can lead to avulsion of a retinal vessel, usually a vein and cause vitreous haemorrhage. Blood in the fluid vitreous behind the detached posterior vitreous face remains red until absorbed (over weeks to months). Haemorrhage into formed vitreous tends to turn white over time and may take several months to clear.

3) Rubeosis iridis / Neovascularisation of angle

Classification of PDR (ETDRS)

- Early PDR
  New vessels not meeting the criteria for high risk characteristic

- High risk PDR
  NVD > 1/3- ½ disc area
  NVE > ½ disc area and preretinal or vitreous haemorrhage

If both NVD & NVE count severity of NVD

Investigations in PDR

Fundus photography

Fundus fluorescein angiography (FFA) - Helps in identifying areas of capillary nonperfusion and occult/ invisible NVE if present. Areas of macular leak in FFA have to be treated prior to PRP as laser may worsen the edema. If associated with ischemic maculopathy the visual prognosis is generally poor. Fluorescein angiography also aids in the follow-up and evaluation of treatment.

Blood investigation and control of systemic factors - Glycemic control, Haemoglobin level, renal function including 24 hour urine protein, lipid levels and control of blood pressure

OCT (Optical Coherence Tomography) - to assess type and severity of macular edema
Ultrasound B scan – Done in cases where there is no fundus view for e.g.: vitreous haemorrhage

Clinical trials in proliferative diabetic retinopathy in a nutshell

1. Diabetic Retinopathy Study (DRS) 1972-1975
Patient eligibility criteria was presence of proliferative diabetic retinopathy in at least one eye or severe non proliferative retinopathy in both eyes. One eye of each patient was assigned randomly to immediate photocoagulation (scatter pan retinal treatment, direct local treatment to new vessels and focal treatment for macular edema). The other eye was assigned to follow up without photocoagulation. The eye chosen for treatment was then randomly assigned to either argon laser or xenon arc photocoagulation.

Conclusion
- Defined high risk characteristics (HRC) of PDR
- Scatter PHC decreases the risk of severe vision loss in patients with HRC by 50 %
The study however does not provide clear guidelines for laser treatment in eyes with less severe retinopathy without HRC.

2. Early treatment of Diabetic Retinopathy (ETDRS) 1980-1985
This study enrolled 3700 patients with bilateral Non proliferative diabetic retinopathy with or without macular edema.

Conclusion
- Focal photocoagulation should be considered for eyes with CSME
- Scatter treatment is not indicated for eyes with mild to moderate non proliferative diabetic retinopathy.
- As the retinopathy progresses to the severe non proliferative or early proliferative stage, scatter treatment should be considered, especially for patients with Type 2 diabetes and it should be performed without delay for virtually all eyes with high-risk proliferative retinopathy.

3. DRVS (Diabetic Retinopathy Vitrectomy Study)
Patient eligibility criteria were presence of recent severe vitreous haemorrhage (within 5 months) or very severe proliferative retinopathy with extensive active fibrovascular proliferations and useful vision in patients with Type 1 and Type 2 diabetes mellitus. Early vitrectomy 1-6 months after the onset of haemorrhage. Conventional management includes vitrectomy if haemorrhage fails to clear during a waiting period of 12 months or if retinal detachment involving the centre of the macula develops at any time.

Conclusion
- For eyes with recent severe vitreous haemorrhage, early vitrectomy provided a greater chance of prompt recovery of visual acuity although greater, is more pronounced for patients with Type 1 diabetes.

At the present time, it should be noted that the results of DRVS were obtained before the development of modern vitrectomy instrumentation, techniques and endolaser photocoagulation. With these techniques, the results are more favourable. Nowadays in general, the recommended timing of vitrectomy for severe diabetic vitreous haemorrhage is before 3 months for Type 1 diabetics and 6 months for Type 2 patients.

Treatment Strategies in PDR

1. Laser Photocoagulation 4,5,6
The classic and established indication of laser treatment in proliferative retinopathy is the presence of neovascularisation with high risk characteristics (HRC).
The recommended guidelines for treatment of PDR summarised in table 1

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Treatment recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDR with high risk characteristics (HRC)</td>
<td>Full scatter PRP (Pan retinal Photocoagulation) Avoid areas of tractional RD and fibrous proliferation Mild – moderate burns</td>
</tr>
<tr>
<td>Iris or angle neovascularisation</td>
<td>Early PRP irrespective of presence or absence of retinal HRC.</td>
</tr>
<tr>
<td>Consider systemic factors for decision - i.e. eyes with very severe Non proliferative diabetic retinopathy or eyes with PDR without high risk characteristics.</td>
<td>Role of PRP in such cases is uncertain 12, 13 and individual decisions are to be made</td>
</tr>
<tr>
<td>Severe ischaemia i.e. extensive retinal haemorrhages, capillary non-perfusion, multiple soft exudates (high risk of anterior segment neovascularisation)</td>
<td>consider PRP</td>
</tr>
<tr>
<td>Early PDR and maculopathy</td>
<td>macular treatment preferably done first followed by PRP 2-4 weeks later</td>
</tr>
<tr>
<td>Maculopathy + PDR with HRC</td>
<td>focal macular treatment can be combined with nasal half PRP, followed 2-3 weeks later with completion of PRP</td>
</tr>
</tbody>
</table>

Special situations for PRP 5,6
Various factors known to worsen the retinopathy may influence the decision to initiate treatment in eyes with severe Non proliferative diabetic retinopathy (NPDR) or PDR
without HRC. These factors include pregnancy, nephropathy, cardiac failure, carotid artery disorders, cataract surgery and yag laser capsulotomy, uncontrolled blood sugars, recent institution of Insulin in a patient of NIDDM with long-standing uncontrolled blood sugars, poor patient follow-up etc. This is important in our country where various social and economic factors reduce the follow up rate.

Hence the decision to treat or not to treat hence has to take into account all these factors, besides the guidelines provided in the randomized clinical trials.

**Technique of LASER treatment**

The commonest wavelengths used are Double frequency Nd Yag (532 nm), Argon green and blue-green using the slit-lamp delivery system or indirect ophthalmoscopic delivery. In case of hazy media due to cataract or vitreous haemorrhage, Krypton red or diode red laser (814 nm) can be used.

The initial limits of scatter laser are:
- Posterior: Superiorly & inferiorly - temporal vascular arcades
- Nasal: ½ DD from disc
- Temporal: 2 DD from fovea centre
- Anteriorly: Equator (recognized by ampulla of vortex veins)

General rule is to treat the inferior quadrant first (since if by any chance vitreous bleed occurs). A total of 1600-3000 burns are placed in two or more sittings, carefully avoiding the macular area and any areas of tractional elevation of the retina. Typical initial settings on the Nd Yag Laser would be 500 μ spot size, 0.1 second exposure and 100-150 mw power. The power is gradually increased till a whitish reaction is obtained on the retina.

**Table 2: Grading of retinal burns**

<table>
<thead>
<tr>
<th>Grading of burns</th>
<th>Reaction seen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light</td>
<td>Barely visible retinal blanching</td>
</tr>
<tr>
<td>Mild</td>
<td>Faint white retinal burn</td>
</tr>
<tr>
<td>Moderate</td>
<td>Opaque, dirty white retinal burn</td>
</tr>
<tr>
<td>Heavy</td>
<td>Dense white retinal burn</td>
</tr>
</tbody>
</table>

The lesions are placed one burn width apart. Local confluent treatment to small, flat NVE can be done in addition. Laser treatment should not be applied over major retinal veins, pre-retinal haemorrhages, darkly pigmented chorioretinal scars or within one disc diameter of centre of macula, so as to avoid risk of haemorrhage or large scotomas1.

**How does Laser photocoagulation (PHC) work?**

Under normal conditions, diffusion of oxygen from choriocapillaries to inner retina is limited because of high oxygen consuming photoreceptor RPE complex. PHC destroys photoreceptor RPE complex. By decreasing the oxygen consumption, more oxygen is available to diffuse in to the inner retina and vitreous. This reduces stimulus for angiogenesis and induces inhibitors of neovascularisation.

**Follow-up treatment after initial PRP**

ETDRS guidelines for follow-up treatment after initial PRP based on six factors
1. Change in new vessels since the last treatment/last visit
2. Appearance of the new vessels (calibre, degree of network formation, extent of accompanying fibrous tissue)
3. Frequency and extent of vitreous haemorrhage
4. Status of vitreous detachment
5. Extent of photoocoagulation scars
6. Extent of tractional retinal detachment and fibrous proliferation.

Assessment of laser treatment is generally done 2-3 months after the completion of scatter laser.

**Factors favouring additional photoocoagulation**

1. Lack of regression within 6-8 weeks of the initial treatment.
2. Active new vessels (tight networks, little fibrous tissue, rapid growth in size).
3. Recurring vitreous haemorrhage, whether the source is visible or not.
4. Extensive intraretinal lesions (venous beading, intra retinal microvascular anomalies (IRMA), blot haemorrhages, retinal edema).
5. Skip areas

2. Intravitreal Anti VEGF in PDR

Adjuvant agent to PRP for PDR
Substantial regression of new vessels may take weeks after completion of PRP, and in up to one third of cases, new vessels continue to grow despite initial PRP. In these cases, vitreous hemorrhage may induce visual loss and prevent complete laser. Moreover, macular edema may increase after PRP and cause transient or persistent visual loss. Intravitreal anti VEGF seems to be a useful treatment for PDR minimizing
a) Risk for exudative complications
b) Progression of retinal neovascularisation
c) Vitreous haemorrhage
d) Deterioration of vision caused by macular edema.

**Pre-treatment of diabetic vitrectomy**

Another important use of intravitreal anti VEGF is in the pre-treatment for diabetic vitrectomy. A recent metaanalysis of all randomised studies demonstrating effect of preoperative adjunct intravitreal bevacizumab (IVB) showed that the incidence of intra-operative bleeding and frequency of endodiathermy were statistically significantly less in the IVB pre-treatment group than in the vitrectomy alone group11. The IVB pre-treatment group took significantly less surgical
time than the control group. Postoperative results indicated that reabsorption time of blood was significantly shorter, incidence of recurrent vitreous haemorrhage was almost significantly less (p=0.05), and final best-corrected visual acuity was significantly better in the IVB group than in the control group.

3. Vitrectomy

Indications of vitrectomy in PDR

- Media opacity
- Surgical intervention for non resolving diabetic vitreous haemorrhage

Vitreo-retinal traction

- Cases of tractional retinal detachment involving or threatening macula, macular heterotopia, progressive fibrovascular proliferation without retinal detachment, and secondary rhegmatogenous retinal detachment.

Progressive fibrovascular proliferation

- Rapid progression seen in type 1 eyes and is associated with guarded visual prognosis after vitrectomy because of lack of posterior vitreous detachment.

Trabecular Retinal Detachment

Vitrectomy is generally reserved for cases in which the macula is involved or threatened. Chronic macular detachment is associated with poorer anatomic and visual prognoses due to thin, atrophic retina with more extensive and more tightly adherent fibrovascular membranes. Therefore, in cases of TRD involving macula of more than six months, surgery may not be recommended.

Combined Traction and Rhegmatogenous Retinal Detachment Diabetic Maculopathy

- Diabetic macular edema
- Traction-induced caused by the contraction of a taut, persistently attached posterior hyaloid.

Timing of vitrectomy in PDR

- Urgent
- Neovascularisation of iris in an eye with a recent vitreous haemorrhage and extensive pre macular haemorrhage
- Early surgical intervention
- No previous laser treatment
- More extensive and vascular fibrovascular proliferation
- Fellow eye with rapidly progressive visual loss/blind
- Surgical intervention deferred if presence of a complete PVD
- Extensive prior PRP
- Comorbidities contraindicating surgical procedure
- Such patients need to be monitored frequently with ultrasonography to rule out retinal detachment.

Surgical Techniques in proliferative diabetic retinopathy

When vitreous haemorrhage is present, a standard pars plana vitrectomy is performed first and the posterior hyaloid face (PHF) is identified; if there is a significant amount of blood behind the PHF, an opening in the PHF is created in order to aspirate the retrohyaloid blood and to gain adequate view of the retina. It is imperative to release any traction on the retina by existing membranes. Such membranes are almost always vascularized, and thus they cannot be simply peeled from the surface of the retina, as this would result in severe hemorrhage and/or tearing of the retina.

Segmentation, delamination, en-bloc delamination and bimanual dissection represent the main surgical techniques employed in diabetic vitrectomy.

Segmentation

Segmentation involves the vertical cutting of epiretinal membranes into small segments, and this can be accomplished either with vertically cutting scissors or a mechanized vitreous cutter. Segmentation is used to release circumferential traction when other methods, such as delamination, are made difficult by very mobile retina in the presence of a retinal break. When segmenting membranes, it is not necessary to remove the membranes completely, leaving small, circumscribed remnants centered on the neovascular pegs. The disadvantage of the segmentation technique is that the residual islands of fibrovascular tissue may encourage reproliferation and recurrent bleeding.

Delamination

The risk of postoperative bleeding may be reduced by a complete removal of fibrovascular tissue from the retina using horizontally cutting scissors to sever the individual neovascular pegs from the retinal surface. The aim is to cut rather than avulse the neovascular pegs, as this would lead to perioperative hemorrhage from the sidewall of a retinal vessel, which may prove to be difficult to control. Finding the correct plane between the posterior hyaloid and the retina near the vascular epicenter is crucial, in order to avoid iatrogenic tears.

En-bloc delamination

En-bloc delamination is preferable to segmentation because it enables us to completely remove all the fibrovascular tissue from the retinal surface. In this technique, the posterior hyaloid is kept partially intact in order to use the continuing antero-posterior traction to elevate the epiretinal membranes during dissection. A small window in the partially detached posterior hyaloid is made so that a horizontally cutting scissors can be introduced into the retrohyaloid space.
Gentle traction immobilizes the fibrovascular membrane and the underlying elevated retina exposing areas of adhesion between the membrane and the retina facilitating its excision. The light pipe or illuminated forceps can be used to turn the membrane over and facilitate the dissection. When the membranes have been completely separated from the retina the remaining posterior hyaloid complex can be removed with the vitreous cutter.

Techniques for vitrectomy in PDR require the combination of delamination and segmentation techniques, because of the difficulties in completely separating the fibrovascular membranes from a mobile detached retina.

**Bimanual surgical technique**

   This method can be employed in complicated cases using a separate light source, which allows the surgeon to use two instruments for dissection.19

**Advances in diabetic vitrectomy**

**Viscodissection**

Several adjunctive manoeuvres like visco-dissection of membranes involves injecting viscoelastic material in between the sheet of fibrovascular membranes and the retina and can be useful in thin, atrophic retinas. Viscodissection distributes the forces more broadly and evenly, better defines fibrovascular stumps.

**Vitrectomy with ILM (Internal Limiting Membrane) peeling**

Vitrectomy with or without ILM peeling is generally an effective procedure in retinopathy reducing diabetic macular edema and improving visual acuity. A prospective, comparative, nonrandomized study evaluating the efficacy of pars plana vitrectomy (PPV) with and without inner limiting membrane (ILM) peeling for persistent diffuse clinically significant macular edema showed structural improvement but with limited visual improvement after ILM peeling.22

**Tamponading agents in diabetic vitrectomy**

Intravitreal tamponading agents like silicone oil can be used as adjunctive measures in vitrectomy for proliferative diabetic retinopathy. This enables rapid visual recovery, fundus examination during postoperative follow up, reduces vascular proliferation and post operative bleeding. Silicone oil in addition also helps in long term tamponade of multiple retinal breaks and reduces the chance of proliferative vitreoretinopathy. Anterior segment neovascularisation regresses after vitrectomy in eyes with silicone oil, possibly via blocking diffusion of vasculoendothelial growth factor (VEGF).16

**Conclusion**

Awareness of diabetic retinopathy and prompt referral of diabetics play a crucial part in the management of this potentially vision threatening condition. Diabetic retinopathy screening camps have a long way to go for the early case detection. Every diabetic patient must be informed by their physicians/ opticians/ ophthalmologists about risk of retinopathy and need for periodic dilated eye retinal examinations. Proper treatment and follow-up of these patients is essential for preservation of vision in many of these patients. In eyes not amenable to laser treatment or where the retinopathy shows progression even after laser treatment, early and appropriate vitreoretinal surgery is successful in regaining some useful vision.

**REFERENCES**

3. Salmon WD, Daughaday WH. A hormonally controlled serum factor which stimulates sulphate incorporation by cartilage invitro. J Lab Clin Med. 1957;49 p 825-836
22. Pars Plana Vitrectomy With and Without Peeling of the Inner Limiting Membrane for Diabetic Macular Edema, Retina 2006 Jan 26 (1)5-13

Dr Remya Poulose after finishing her DNB from Little Flower Hospital is working as fellow in vitreoretinal services at Little Flower Hospital, Angamaly

Sparingly used
PHACO MACHINES
FOR SALE

1. QUANTUM - CES
2. MEGATRON - GEUDER - GERMANY

LUKE MEMORIAL EYE HOSPITAL
Email: lukesindia@gmail.com
Tel: +91 98470 52123
Diabetic Macular Edema

MACULAR EDEMA is clinically defined as any increase of water in the retinal tissue resulting in an increase in foveal thickness. Diabetic macular edema (DME) is the most common cause of visual impairment in patients with Diabetes Mellitus and affects approximately 75,000 new patients in the United States every year. The central foveal thickness was defined as the distance between the innermost foveolar surface and the outermost foveolar surface and was measured using the manually assisted technique of the program within the OCT system software. If it was difficult to point out the foveal center on the image, the fixation point was regarded as the foveal center. The diagnosis and the management of diabetic macular edema depend on traditional techniques such as stereoscopic biomicroscopy and fluorescein angiography.

PATHOGENESIS
The pathogenesis of DME is complex and multifactorial. It occurs mainly as a result of disruption of the blood--retinal barrier (BRB). The BRB consists of two major components: the outer barrier and the inner barrier. The inner BRB is a biological unit formed primarily by tight junctional complexes between retinal vascular endothelial (RVE) cells and a well-differentiated network of glial cells (astrocytes and Muller cells) that operates to maintain a low permeability environment. The outer BRB is formed by tight junctions between retinal pigment epithelium (RPE) cells and includes zonula occludens with prominent desmosomes. Disruption of both components of BRB leads to increased accumulation of fluid within the intraretinal layers of the macula.

Hyperglycemia is a major risk factor for development of diabetic retinopathy. It leads to high intracellular levels of glucose, formation of free radicals (oxidative stress), protein kinase C activation, and glycation end products, which may be the inciting event for diabetic retinopathy and maculopathy. Other factors such as altered vitreomacular interface, hypoxia, altered blood flow, retinal ischemia, and inflammation may contribute significantly to the progression of macular edema. Inflammatory processes, such as increased vascular endothelial growth factor (VEGF) levels, endothelial dysfunction, leukocyte adhesion, decreased pigment epithelium derived factor (PEDF) levels, and increased protein kinase C production, that cause breakdown of the BRB and increased vascular permeability are upregulated within the diabetic retinal vasculature.

EPIDEMIOLOGY
In one study, the incidence of DME over a 10-year period was 20.1% among patients diagnosed before age 30 years (younger onset) and 39.3% among patients diagnosed after age 30 (older onset). The Diabetes Control and Complications Trial (DCCT) reported that 27% of patients develop macular edema within 9 years of diabetes onset. The frequency of DME increases with the duration and the severity of diabetes.

Older onset diabetic patients have a tendency to develop macular edema earlier in the course of their disease (prevalence: 3--8% with up to 3 years of disease duration) compared to younger onset diabetic patients (prevalence: 0.5% with up to 10 years of disease duration). In the presence of macular edema, 50% of older onset diabetic patients have visual acuity worse than 20/40 compared to 20% of younger onset diabetic patients. Elevated diastolic blood pressure and abnormal lipid level are associated with increased risk of developing DME. Microalbuminuria and diabetic nephropathy have not been found to be significantly associated with an increased risk of DME.

Data from Klein et al.
CLINICAL DESCRIPTION AND CLASSIFICATION
The only indicator for the diagnosis of clinically significant diabetic macular edema is foveal thickening. It does not reflect the severity and the extent of edema, from where the fluid comes, and the retinal layer involved in thickening. The physiologic aspect of clinically significant diabetic macular edema can be assessed with fluorescein angiography, and the anatomical features of clinically significant diabetic macular edema such as the extent of thickening and the retinal layer involved can be assessed with OCT.

EARLY TREATMENT DIABETIC RETINOPATHY STUDY CLASSIFICATION
Clinically significant diabetic macular edema is diagnosed with ophthalmoscopy, stereoscopic biomicroscopy as defined by ETDRS. The Early Treatment Diabetic Retinopathy Study (ETDRS) defined DME as the term clinically significant macular edema (CSME). Macular edema is clinically significant if one of the following conditions is present: retinal thickening at or within 500 mm of the center of the macula; and/or hard exudates at or within 500 mm of the center of the macula if associated with thickening of the adjacent retina; and/or a zone or zones of retinal thickening 1 disk area in size, at least part of which is within 1 disk diameter of the macular center.

(3) Diffuse cystoids leakage type, predominantly diffuse leakage but with pooling of dye in the cystic spaces of the macula in the late phase. Furthermore, focal DME is responsive to focal laser photocoagulation, whereas diffuse DME represents a more challenging clinical situation and is refractory to laser photocoagulation in many cases.

OPTICAL COHERENCE TOMOGRAPHY CLASSIFICATION
Otani et al observed sponge-like swelling (88%), retinal edema with cystic spaces (47%), and retinal edema with subfoveal fluid accumulation (15%). Kang and coworkers described four patterns of OCT findings associated with CSME: foveal thickening with homogenous optical reflectivity throughout the entire thickness of retina (type 1); foveal thickening with decreased optical reflectivity in the outer layers of the retina (type 2); and foveal thickening with subretinal fluid accumulation with or without retinal traction (types 3A and 3B, respectively). The OCT type 3B with tractional membrane should be the best candidate for vitrectomy to resolve CSME. They also showed a significant correlation between these OCT categories and the FA findings: 58% of patients with type 1 pattern OCT had focal leakage on FA, and 92% of patients who had diffuse cystoid leakage on the FA had either a type 2 or type 3A OCT pattern.

DIAGNOSIS
The traditional methods of evaluating macular diseases, such as slit-lamp biomicroscopy and stereo fundus photography, are relatively insensitive in determining small changes in retinal thickness. Several additional diagnostic techniques for ocular imaging are available:

FLORESCEIN ANGIOGRAPHY
Fluorescein angiography is a standard method used to evaluate patients with DME that is sensitive for qualitative detection of fluid leakage. In patients with CSME, an
OPTICAL COHERENCE TOMOGRAPHY
OCT has been used for high-resolution imaging of the retina and detection of increased retinal thickness. OCT uses infrared illumination of the fundus to take images and thus is more comfortable and well tolerated by patients than more invasive techniques such as FA.

OCT studies of CSME, as defined by the ETDRS, have revealed three basic structural changes in the neurosensory retina: retinal swelling, CME, and serous retinal detachment. Otani and coworkers found that retinal swelling was the most common change in the structure of the retina (88%). Cystoid macular edema usually has four or five cystoid spaces located in the macula area within a diameter of 5 mm. Perifoveal cystoid spaces are located mainly in the outer retinal layers, and the inner retinal layers are relatively preserved. In eyes with well established cystoid macular edema persisting for more than 1 year, the cystoid spaces fused to form a large cystoid cavity involving entire retinal layers, remaining remaining retinal tissue as atrophic. The thickness of the subretinal space is the greatest at the central fovea and declined peripherally. Hard exudates are observed as spots of high reflectivity, located primarily in the outer retinal layers with low reflective shadows behind them. The external limiting membrane is not impermeable to fluid and albumin. So, with the disruption of inner blood retinal barrier, the excessive fluid might reach the subretinal space in large amounts, which cannot be removed properly by retinal pigment epithelium and may result in subfoveal detachment.

OCT has several advantages as a retinal imaging technique: 1) it is non-invasive (no injected dye involved) and well tolerated (especially important in children); 2) it provides quantitative information regarding retinal thickness with a high degree of accuracy and reproducibility; 3) it clearly reveals the presence and extent of vitreomacular traction; and 4) it serves as valuable teaching tool for fellows and residents and is easily understood by most patients. Moreover, OCT can be used to calculate the standardized change in macular thickness (SCMT) on various follow-up visits. Disadvantages of currently available OCT machines include the facts that image quality can be affected by media opacities, and the reliability of the data depends on the skill of the OCT operator.

TREATMENT
LASER PHOTOCOAGULATION
Many studies have demonstrated a beneficial effect of photocoagulation therapy for DME.

Another theory proposes that the beneficial effect of laser photocoagulation is due to restoration of a new RPE barrier. If the lesion is relatively small (<125 microns), the RPE defect can be filled by cell spreading; if the defect is relatively large, the cells can proliferate to resurface the area, and the RPE can produce cytokines which antagonize the permeability of VEGF. Complications associated with laser photocoagulation are full-thickness retinal break, choroidal neovascularization, subretinal fibrosis, or symptomatic scotoma.

The Early Treatment Diabetic Retinopathy Study Results
The ETDRS study was a prospective, randomized, multicenter clinical trial designed to evaluate the effects of argon laser photocoagulation for macular edema. Among the subgroup of eyes with mild to moderate non-proliferative diabetic retinopathy with macular edema, visual acuity improved in 16%, remained unchanged in 77%, and worsened in 7% of treated eyes after 2 years of follow-up. Whereas, macular thickening after 1 year follow-up was present in only 35% of eyes by immediate photocoagulation compared to 63% of eyes assigned to deferred photocoagulation. If macular edema involved the center of the macula, then the visual prognosis was worse, but the magnitude of the treatment benefit was greater. Standard guidelines for focal photocoagulation for DME by ETDRS were, direct treatment
to leaking microaneurysms and grid treatment of diffuse macular edema or nonperfused thickened retina suggested for mild and moderate NPDR, and combination scatter laser photocoagulation and focal laser photocoagulation has been suggested for DME in selected cases of severe NPDR and in eyes with PDR. The most effective strategy for reducing the risk of moderate visual loss in eyes with macular edema and less severe retinopathy was immediate focal photocoagulation with delayed scatter. The technique of focal laser involves placement of light, small (around 50 microns) laser burns only within thickened areas of the macula, including direct (focal) treatment of microaneurysms as well as spots scattered approximately two to three burn widths apart (grid) within other areas of edema not accounted for by microaneurysms. Focal/grid laser is used in conjunction with anti-VEGF therapy/ intravitreal steroids, typically when DME persists and is not continuing to improve after at least 6 months of monthly injections of anti-VEGF therapy. Because of its lower cost and less intensive management, focal laser is still a preferred therapy in developing countries. (Adam S Wenick 2012).

In addition to traditional argon or diode laser used for macular photocoagulation, newer navigated laser photocoagulator (NAVI-LAS) integrates a computer aided scanning laser slit camera with fluorescein angiography. This laser automatically marks the sites and is more accurate. Other newer laser technology include subthreshold diode-laser micropulse technology and selective retina therapy (SRT), which aim in minimizing retinal and RPE tissue damage. But these newer modalities are not directly compared to focal/grid laser by ETDRS or DCRN Network.

**Functional Outcome of the Eyes with CSME with less/more DR Treated with Different Techniques of Laser Photocoagulation (LP) in ETDRS**

<table>
<thead>
<tr>
<th>Type of Treatment</th>
<th>Severe Visual Loss (VA&lt;5/200)</th>
<th>Moderate Visual Loss (15 letters or more)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Focal LP / Delayed Full Scatter LP</td>
<td>1</td>
<td>22.4</td>
</tr>
<tr>
<td>Immediate Full Scatter LP / Delayed Focal LP</td>
<td>0.9</td>
<td>29.8</td>
</tr>
<tr>
<td>Immediate Focal LP / Delayed Mild Scatter LP</td>
<td>2.2</td>
<td>19.5</td>
</tr>
<tr>
<td>Immediate Mild Scatter / Delayed Focal LP</td>
<td>1.2</td>
<td>21.8</td>
</tr>
<tr>
<td>Defferal</td>
<td>2.9</td>
<td>30.2</td>
</tr>
</tbody>
</table>

Follow-up was 5 years

**VITREOUS SURGERY FOR DME**

Approximately 10–15% of laser treated patients for DME continue to experience moderate visual loss at 3-year follow-up. In patients with Vitreo-Macular Traction, induction of posterior vitreous detachment, removal of taut posterior cortex, removal of ILM, and a complete pars plana vitrectomy have been reported to resolve DME. Removal of vitreous gel can decrease the concentration of DME-promoting factors (e.g., AGEs, VEGF), inhibit activation of proinflammatory factors and also improve the fluid currents and thus oxygenation of the inner retina. Release of any tractional forces at the vitreomacular interface may further improve resolution of the macular edema and restore visual acuity. Yang reported that PPV with taut posterior hyaloid removal could be beneficial in eyes with DME with massive hard exudates that have poorly responded to conventional laser photocoagulation. The reported complications encountered with PPV for DME include cataract (10–7.5%), choroidal detachment (8%), epiretinal membrane (8–10.3%), fibrinoid syndrome (8%), glaucoma (1.7–8%), development of hard exudates (3%), macular ischemia (10%), neovascular glaucoma (3.4–8%), retinal detachment (10%), retinal tear (10–20.7%), tractional rhegmatogenous retinal detachment (1.7%), and vitreous hemorrhage (12.1–16%).

**INTRAVITREAL STEROID INJECTION**

In patients with DME, whose vision has failed to improve following laser photocoagulation, has prompted clinicians to seek more effective treatment with Intravitreal Triamcinolone Acetonide (1-4mg). The therapeutic effect of IVTA is typically seen within 1 week, but in many patients re-injections are needed every three to six months as the effect diminishes... Martidis and coworkers showed that macular thickness decreased by 55%, 57%, and 38% at 1, 3, and 6 months, respectively after intravitreal triamcinolone acetonide. Jonas and coworkers reported visual acuity increased by at least two lines in 68% of the treated eyes compared with 33% of the eyes in the control group (p < 0.001). The most common ocular side effects attributed to corticosteroids are glaucoma and cataract, endophthalmitis...
and retinal detachment may also occur\textsuperscript{74,75}.

The Diabetic Retinopathy Clinical Research Network reported 2-year results of a multicenter randomized clinical trial comparing preservative free intravitreal Triamcinolone (1mg and 4mg) and focal/grid laser for DME\textsuperscript{72}. The mean visual acuity and OCT-measured foveal thickness at 2 years after starting the treatment was better in the laser group compared to both 1mg and 4mg steroid-injected groups, though both improved more rapidly in the 4-mg triamcinolone group than in the laser group. But surprisingly, in a subgroup of patients who were pseudophakic at baseline, the triamcinolone plus laser appeared superior to the laser alone treatment and equivalent to the treatment utilizing anti-VEGF therapy\textsuperscript{77,78}.

Another long term intravitreal steroid implant used now-a-days is Dexamethasone. Haller and Callanan observed, at 90 days of intravitreal implantation, the 700 µm group showed a statistically significantly higher proportion of patients with 10 or more letter gain compared to no treatment. The 350 µm group showed a non-statistically significant improvement compared with laser alone. At 180 days, there was no statistically significant difference between either the dexamethasone group or no treatment group. The treatment effect appeared to peak at 3 months\textsuperscript{93,94}.

### Anti- VEGF THERAPY

The VEGF family is a sub-group of growth factors that include VEGF-A, B, C, D, E and placental growth factor (PIGF). VEGF-A in particular is most critical with regards to the pathogenesis of ocular disease and its signaling induces angiogenesis as well as increased vascular permeability. The VEGF-A165 isoform is the predominant isoform and appears to be the most important in the pathogenesis of ocular disease, including DME. VEGF is responsible for angiogenesis, mitogenesis and induction of vascular permeability. Triggering from pathological ischaemic stimulus, they promote collaterals which are essential for recovery following ischaemic events. VEGF-A is a major mediator of increased retinal permeability and is induced by hypoxia\textsuperscript{80,81}. The first anti-VEGF agent used in ophthalmology was pegaptanib (OSI Pharmaceuticals, Long Island, NY, USA), which is based on a 28-nucleotide ribonucleic acid aptamer that binds to the VEGF-A16 isoform and was initially approved for the treatment of neovascular age-related macular degeneration\textsuperscript{83}. Its use has largely been replaced by newer ranibizumab (Genentech, Inc., South San Francisco, CA, USA), a fragment antigen binding (Fab) anti-VEGF agent that neutralizes all isoforms of VEGF-A\textsuperscript{84}. Bevacizumab (Genentech, Inc., South San Francisco, CA, USA), a humanized monoclonal antibody that binds to all isoforms of VEGF-A, was developed in 1996 and first used for the treatment of human colon cancers\textsuperscript{84}. It is now-a-days popularly used as off-label treatment with effect similar to ranibizumab but with lot of systemic adverse effects, and is much cheaper than ranibizumab. But, IV ranibizumab is associated with greater improvement in BCVA, and the mean number of injections is higher in the IV bevacizumab group. (Antonio)

Several RCTs have evaluated ranibizumab as a potential new treatment for patients with DMO. READ-2 was the first large RCT. It compared ranibizumab (0.5 mg) alone, and ranibizumab in combination with laser and laser alone. At 6 months\textsuperscript{79}. BCVA had improved significantly in the ranibizumab alone group compared with laser alone or ranibizumab plus laser. RESTORE randomised similar groups as the READ-2 but outcomes were evaluated at 12 months\textsuperscript{85,87,88,92}. REVEAL compared ranibizumab (0.5 mg) with ranibizumab plus laser and laser alone\textsuperscript{86}. At 12 months, both ranibizumab arms resulted in a statistically significantly better improvement in BCVA compared to laser alone. Addition of laser to ranibizumab did not provide additional BCVA gain. RESOLVE compared two doses of ranibizumab (0.3 and 0.5 mg) with sham injection. The greatest

---

### Clinical Results after Viterectomy for Diabetic macular Edema

<table>
<thead>
<tr>
<th>Author</th>
<th>Resolution of Macular Edema (%)</th>
<th>Visual Acuity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete</td>
<td>Partial</td>
</tr>
<tr>
<td>Lewis et al (10 eyes)\textsuperscript{93}</td>
<td>none</td>
<td>80</td>
</tr>
<tr>
<td>Harbour et al (10 eyes)\textsuperscript{95}</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>Ikeda et al (3 eyes)\textsuperscript{92}</td>
<td>100</td>
<td>none</td>
</tr>
<tr>
<td>Pendergast et al (55 eyes)\textsuperscript{96}</td>
<td>81.8</td>
<td>12.7</td>
</tr>
<tr>
<td>La Heiji et al (21 eyes)\textsuperscript{97}</td>
<td>100</td>
<td>none</td>
</tr>
<tr>
<td>Yamamoto et al (30 eyes)\textsuperscript{98}</td>
<td>20</td>
<td>57</td>
</tr>
<tr>
<td>Otani and Kishi (7 eyes)\textsuperscript{95}</td>
<td>none</td>
<td>100</td>
</tr>
<tr>
<td>Tachi and Ogino (58 eyes)\textsuperscript{99}</td>
<td>98</td>
<td>none</td>
</tr>
<tr>
<td>Yang (13 eyes)\textsuperscript{99}</td>
<td>none</td>
<td>100</td>
</tr>
</tbody>
</table>
Improvement in BCVA at 12 months was in the 0.3 mg group (11.8 letter gain) compared to the 0.5 mg group (8.8 letter gain) or sham injection (1.4 letter loss). RISe and RIDe studies are similar to the RESOLVE study, 0.3 or 0.5 mg ranibizumab compared with sham. In the RISe study, the proportion of patients with 15 or more letter gain was greatest in the 0.3 mg group at 24 months, whereas in the RIDe study this was greatest in the 0.5 mg group. In the DRCR Net trial, Elman and colleagues compared ranibizumab (0.5 mg) plus prompt (within 3–10 days post ranibizumab) or deferred (≥24 weeks) laser with sham injection plus prompt laser, or triamcinolone (4 mg, Trivaris) plus prompt laser. At 1 year, both ranibizumab groups reported greater gains in mean BCVA change than triamcinolone or laser alone. Interestingly, at 3 years, the proportion of patients with 10 or more letter gain was not statistically significantly different between ranibizumab plus prompt laser and laser alone groups, but was statistically significant in the ranibizumab plus deferred laser compared with laser alone group.

**Comparative analysis of Ranibizumab Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Month</th>
<th>Letters gained</th>
<th>Percentage gaining</th>
<th>Mean CMT reduction (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESOLVE</td>
<td>12</td>
<td>9.4</td>
<td>98</td>
<td>2597</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>7.3</td>
<td>90</td>
<td>140</td>
</tr>
<tr>
<td>RISE</td>
<td>12</td>
<td>9.2</td>
<td>68</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>7.7</td>
<td>90</td>
<td>1892</td>
</tr>
<tr>
<td>DRCR Net</td>
<td>12</td>
<td>6.1</td>
<td>35</td>
<td>50.8</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>5.7</td>
<td>81</td>
<td>50.8</td>
</tr>
<tr>
<td>Rise</td>
<td>12</td>
<td>5.9</td>
<td>52</td>
<td>128.3</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>5.9</td>
<td>52</td>
<td>128.3</td>
</tr>
<tr>
<td>RIDE</td>
<td>12</td>
<td>6.1</td>
<td>21</td>
<td>61.3</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>5.9</td>
<td>21</td>
<td>61.3</td>
</tr>
<tr>
<td>NWSTON</td>
<td>12</td>
<td>6.1</td>
<td>21</td>
<td>61.3</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>6.1</td>
<td>21</td>
<td>61.3</td>
</tr>
<tr>
<td>AVISIN</td>
<td>12</td>
<td>6.1</td>
<td>21</td>
<td>61.3</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>6.1</td>
<td>21</td>
<td>61.3</td>
</tr>
</tbody>
</table>

**Potential adverse effects of blocking VEGF**

- Hypertension
- Proteinuria
- Impairment of wound healing
- Impairment of collateral vessel development
- Inhibition of bone growth
- Infertility
- Inhibition of skeletal muscle regeneration and cardiac remodelling

**Newer Anti-VEGF - Aflibercept has been evaluated in the Da Vinci study.** Four regimens of aflibercept (0.5 mg 4 weekly, 2 mg 4 weekly, 2 mg monthly for 3 months, then every 8 weeks, and 2 mg monthly for 3 months followed by treatment as required) were compared with laser. At 1 year, all aflibercept arms had a statistically better BCVA and CMT change than the laser arm. The regimen that resulted in the greatest BCVA gain and CMT reduction was 2 mg every 4 weeks. Because anti-VEGF treatment for DME is potentially required for years, chronic VEGF inhibition may cause adverse effects that are not immediately apparent.
REFERENCES


9. Witmer AN, Vrensen GF, VanNoorden CJ, Schlingemann RO. Vascular endothelial growth factors and angiogenesis in
glycation end products and its ligands: a journey from the
complications of diabetes to its pathogenesis. Ann NY
Acad Sci. 2005;1043:533—61
leukostasis and vascular leakage in streptozotocin-
induced diabetic retinopathy via intercellular
adhesion molecule-1 inhibition. Proc Natl Acad Sci USA.
1999;96:10836—41
on visual loss in patients with diabetic retinopathy.
Ophthalmology. 2006;113(12):2221—30
13. Klein R, Klein BEK, Moss SE, Cruickshanks KJ. The
Wisconsin epidemiologic study of diabetic retinopathy.
XV. The long term incidence of macular edema.
Ophthalmology. 1995;102:7—16
14. Intensive versus conventional treatment in the Diabetes
Control and Complications Trial. Diabetes Control
and Complications Trial Research Group. Ophthalmology,
1995;102(4):647—61
15. Klein R, Klein BEK, Moss SE. The epidemiology of ocular
problems in diabetes mellitus in SS F (ed): Ocular
problems in diabetes mellitus. Boston, Blackwell Scientific
16. Klein R, Klein BEK, Moss SE, Cruickshanks KJ. The
Wisconsin epidemiologic study of diabetic retinopathy.
XV. The long term incidence of macular edema.
Ophthalmology. 1995;102:7—16
17. Aroca PR, Espeso Sentis O, Del Castillo DD. Prospective
study of correlation between diabetic retinopathy and
microalbuminurian diabetes type 1 patients. Arch Soc
diffuse and focal macular edema. J Diabetes
Fluorescein Angiographic and Optical Coherence
Tomographic Features in Clinically Significant Diabetic
20. Early Treatment Diabetic Retinopathy Study R.
Photocoagulation for diabetic macular edema. Early
Treatment Diabetic Retinopathy Study report number 1.
Early Treatment Diabetic Retinopathy Study research
21. Early Treatment Diabetic Retinopathy Study R. Techniques
for scatter and local photocoagulation treatment of
diabetic retinopathy: Early Treatment Diabetic
Retinopathy Study Report no. 3. The Early Treatment
Diabetic Retinopathy Study Research Group. Int
22. Early Treatment Diabetic Retinopathy Study R.
Photocoagulation for diabetic macular edema: Early
[Comparative study of efficacy of focal photocoagulation in diabetic macular edema according to the wave length used]. J Fr Ophthalmol. 1989;12(11):785—9
51. Glaser BM, Campochiaro PA, Davis JJJ, Jordan JA. Retinal pigment epithelial cells release inhibitors of neovascularization. Ophthalmology. 1987;94:780—4
59. Evaluation of the Effects of Selective Photocoagulation for the Treatment of Diabetic Macular Edema (SRT) [cited in 2011].
60. Micropulse 577 nm Laser Photocoagulation Versus Conventional 532 nm Laser Photocoagulation for Diabetic Macular Oedema (UMDMO) [cited in 2011].
65. Lewis H, Abrams GW, Blumenkranz MS, Campo RV. Vitrectomy for diabetic macular traction and edema associated with posterior hyaloidal traction.


86. Ohji M, Ishibashi T Sr, REVEAL study group. Efficacy and safety of ranibizumab 0.5 mg as monotherapy or adjunctive to laser versus laser monotherapy in Asian patients with visual impairment due to diabetic macular edema: 12-month results of the REVEAL Study abstract]. Invest Ophthalmol Vis Sci 2012;53:E-Abstract 4664.


Dr. Anubhav Goel is working as a fellow in Vitreo Retinal Services at Giridhar Eye Institute, Cochin.
Age related macular degeneration is the leading cause of blindness among individuals 55yrs or older in developed countries. As the disease affects the central regions of the retina and choroid, central visual loss can ensue. Approximately 30 % of individuals who are aged 75 or older have some signs of maculopathy out of which 6 - 8 % have advanced AMD. By 2020 the prevalence of AMD is expected to be double of what is seen today. The increasing prevalence of AMD has led many investigators to search for factors that could be modified to prevent the onset of or delay the natural course of AMD. Recent advances in clinical research have led not only to a better understanding of the genetics and pathophysiology of age-related macular degeneration but also to new therapies designed to prevent and help treat it.

**PATHOPHYSIOLOGY**

With age, one change that occurs within the eye is the focal deposition of acellular, polymorphous debris between the retinal pigment epithelium and Bruch’s membrane. These focal deposits, called drusen, are observed during funduscopic examination as pale, yellowish lesions and may be found in both the macula and peripheral retina (Fig1). Drusen are categorized as small (<63 μm in diameter), medium (63 to 124 μm), or large (>124 μm) on the basis of studies that classified the grade of age-related macular degeneration. On ophthalmoscopic examination, the diameter of large drusen is roughly equivalent to the caliber of a retinal vein coursing toward the optic disc. Drusen are also categorized as hard or soft on the basis of the appearance of their margins. Hard drusen have discrete margins; conversely, soft drusen generally have indistinct edges, are usually large, and can be confluent. The clinical hallmark and usually the first clinical finding of age-related macular degeneration is the presence of drusen. In most cases of age-related macular degeneration, damage to the retinal pigment epithelium and a chronic aberrant inflammatory response can lead to large areas of retinal atrophy (called geographic atrophy), the expression of angiogenic cytokines such as vascular endothelial growth factor (VEGF), or both. Abnormalities in collagen or elastin in Bruch’s membrane, the outer retina, or the choroid may also predispose some people to this process. Consequently, choroidal neovascularization and the sequelae of choroidal neovascularization may extend anteriorly through breaks in Bruch’s membrane and lead to subretinal hemorrhage, fluid exudation, lipid deposition, detachment of the retinal pigment epithelium from the choroid, fibrotic scars, or a combination of these findings.

**CLASSIFICATION AND CLINICAL FEATURES**

According to the age-related eye disease study classification, early age-related macular degeneration is characterized by the presence of a few (<20) medium-size drusen or retinal pigmentary abnormalities. Intermediate age-related macular degeneration is characterized by at least one large drusen, numerous mediumsized drusen, or geographic atrophy that does not extend to the center of the macula. Advanced or late age-related macular degeneration can be either non-neovascular (dry, atrophic, or nonexudative) or neovascular (wet or exudative). Advanced nonneovascular age-related macular degeneration is characterized by drusen and geographic atrophy (Fig2) extending to the center of the macula. Advanced neovascular age-related macular degeneration is characterized by choroidal neovascularization and its sequelae.

In the early course of the disease visual loss will be mild or even asymptomatic. Visual symptoms include blurred vision, visual scotomas, decreased contrast sensitivity, need for higher magnification and brighter light to read small print and altered dark adaptation. Over the course of months to years central or paracentral scotomas develop in these patients. In cases of neovascular age-related macular
degeneration visual loss is usually abrupt and profound as a result of sub retinal fluid or hemorrhage secondary to choroidal neo vascularization. 80% of the cause of severe visual loss or legal blindness results from neo vascular AMD. However neo vascular AMD accounts for only 10 – 15 % of the prevalence of AMD. The risk of legal blindness in both eyes for a person with unilateral visual loss from neo vascular AMD may be approximately 12 % over a period of 5 yrs.

Non neovascular AMD is the most common form of AMD accounting for 80 – 90 % of overall cases. The clinical hallmarks of non neovascular AMD are drusen which are divided into hard, soft, crystalline, and cuticular or basal laminar according to their clinical appearance, histopathological differences as well as fluorescein angiographic pattern. Drusens are localised deposits noted between the basement membrane of the retinal pigment epithelium and the Bruch’s membrane, associated RPE changes, and mild loss in visual acuity. The advanced form of non neo vascular AMD, termed geographic atrophy (Fig 2), is characterized by outer retinal and RPE atrophy with loss of chorio capillaries. Loss of central vision is usually due to RPE atrophy or geographic atrophy in non neovascular AMD. Early stage AMD (or early ARM) is defined as presence of soft drusen(63 micro meter) alone, RPE depigmentation alone, or a combination of distinct/indistinct drusen with pigment irregularities. Late stage AMD is defined as geographic atrophy (both central and non central), signs of neo vascular macular degeneration, or a combination of both.

Neo vascular AMD (Fig 4) which was first recognised as early as 1875 by Pagenstecher who termed this condition “chorioidoretinitis in regione maculae luteae” is characterised by major clinical features which include subretinal fluid, subretinal hemorrhage, sub RPE fluid (PED) (Fig 3), sub RPE hemorrhage, RPE pigment alteration and hard exudates. Chronic neo vascular AMD is characterised mainly by presence of sub retinal fibrosis with or without other features of active exudation. The late manifestation of neo vascular AMD is a disciform scar (Fig 5) or geographic atrophy with or without subretinal fluid or subretinal blood. Sometimes the PED may rip resulting in an RPE rip which may be associated with active CNV. Spontaneous involution
of CNV may manifest as any of the above findings with RPE alteration and or scar formation.

Polypoidal choroidal vasculopathy (PCV) has been classified as a form of CNV that may occur in patients. Yannuzzi and colleagues in their study determined the frequency and nature of PCV in patients suspected of harbouring neo vascular AMD. Clinical features include direct visualization of orange coloured polyp in the sub RPE space to PED’s which were commonly seen in PCV with signs of serous or serohemorrhagic RPE and or sensory detachment. This entity needs to be clinically distinguished from AMD in which ICG angiography plays a major role.

Retinal angiomatous proliferation (RAP) is another distinct type of neovascular AMD which is characterised by anomalous retinal vascular complex which is most commonly associated with retinal and sub retinal neo vascularisation. Yannuzzi and colleagues classified RAP as stage 1 which is described as a nodular mass of intra retinal neo vascularisation which originates from deep capillary plexus in the para macular area. There is usually one or more associated retinal vessels which either perfuse or drain the vascular complex with intra retinal hemorrhages and edema. Stage 2 is characterised by subretinal neo vascularisation, which involves both retinal and subretinal vascular proliferation with tangential growth and minimal horizontal extension. Other common signs include increased intra retinal edema, neuro sensory retinal detachment, serous PED and pre retinal and sub retinal hemorrhages. Stage 3 is defined by stage 2 findings plus the clear presence of CNV. While its natural history is not fully understood, it is thought to progress ultimately to a disciform scar. Prior to recognition of this entity, it was often mis diagnosed as occult CNV.

RISK FACTORS
Several clear risk factors for the development and progression of age-related macular degeneration have been established. The molecular pathways leading to age related macular degeneration remain to be elucidated. The retina and its pigmented epithelium are unique among body tissues in their constant exposure to light energy and high oxygen concentrations, both of which are potent sources of free radicals—therefore, it has been suggested that the cumulative effects of oxidative stress over a lifetime may be the initiating stimulus for macular degeneration. Concordant with this hypothesis are the findings of epidemiological studies, which show that cigarette smoking and a high lifetime exposure to sunlight are risk factors. One recent cross sectional population based study in the European Union found that people with low levels of antioxidants in their serum combined with high cumulative lifetime sunlight exposure had a two fold increased risk of developing late macular degeneration. More recently, consistent associations between the clinical spectrum of age related macular degeneration and polymorphisms in genes encoding proteins involved in immune regulation have been observed and provide additional insights into how this condition may develop. Carriage of at-risk alleles at multiple complement loci confer additive risks and, when combined with information on lifestyle factors such as smoking, can account for as much as 80% of the risk. Ocular risk factors associated with increased risk of CNV include 5 or more large sized drusen, confluent drusen, and hyperpigmentation. The simplified AREDS scale predicts the risk of CNV over the next 5 yrs and 10 yrs based upon the presence of drusen and pigment abnormalities in each eye.

NATURAL HISTORY OF THE DISEASE
Early macular degeneration can progress to late manifesta-tions with sight loss in a proportion of people. The risk of progression is highly variable and depends on the severity and extent of the features of early macular degeneration. The age related eye diseases study has quantified this risk and showed that people with small drusen in both eyes have a very low risk of progression—between 0.4% and 3.0% over five years. However, if large drusen and pigmentary abnormalities are present in both eyes this risk increases to around 47.3%. Initially, geographic atrophy develops as focal areas of depigmentation. Eventually these coalesce or expand to involve the central macula causing progressive worsening of vision to legal blindness. Neovascular complications on the other hand have a more acute onset with sudden development of central blurring and distortion. Left untreated the area of neovascularisation expands rapidly and a large fibrous scar develops in the macula. A recent meta-analysis of data from several controlled clinical trials showed that within three years of the onset of neovascularization more than half of untreated eyes will have a level of vision of 20/200 (Snellen 6/60) or worse, which is within the WHO definition of severe visual impairment. The macular photocoagulation study (MPS) on extra foveal CNV showed loss of two or more lines in 50 % of the affected eyes or 6 or more lines in 10 % by 3 months after enrollment. Thus eyes with classic extra foveal CNV are at high risk for visual acuity loss. 13 % of patients with juxtapveal CNV in the natural history arm of MPS lost 6 or more lines of visual acuity by 3 months after enrollment which increased to 58 % by 36 months. The MPS sub foveal study is the largest study of the natural history of eyes with sub foveal CNV. In fact 77 % of the patients lost 4 or more lines of visual acuity at 24 months and 64 % lost 6 or more lines. When both eyes are affected with late stage age related macular degeneration sight can be markedly reduced and tasks that require visual discrimination, such as reading, driving, and recognising faces become difficult.
**DIAGNOSIS**

Often diagnosis is incidental especially in the early course of the disease as presence of small area of geographic atrophy may not hamper visual acuity. In cases where there is advanced disease in one eye sometimes may be detected by chance. The diagnosis is usually evident on clinical examination and fundus photography. Stereoscopic fundus examination is the best method for examining a patient with AMD. Visual acuity estimation and amsslers grid evaluation can also aid in diagnosing abnormalities.

**FLUORESCIN ANGIOGRAPHY**

Fluorescein angiogram (FA) has and continues to play an important role in managing patients with AMD. This investigation helped us in localising identifying and directing both laser and photo dynamic therapies as well as monitoring outcomes of treatment. With the advent of anti VEGF therapy the focus has shifted to where FA is useful in confirming the cause of exudative findings and identifying features that may limit visual benefits from the therapy. As newer therapeutic approaches are developed that may more selectively target the sub types and stages of neovascularisation, FA may once again be a critical tool in patient selection for these interventions.

**INDOCYANINE GREEN ANGIOGRAPHY ICG**

The role of ICGA in the treatment of AMD is in evolution. ICG Angiography has proven very useful in adding information to FA about lesion subtypes. The ability of ICG to identify subtypes of occult CNV, such as vascular PED, hotspots, plaques, and RCA allows targetted and sometimes effective therapy for these refractory types of CNV. It also helps us in differentiating polypoidal choroidal vasculopathy, retinal angiomatis proliferation, and recurrent choroidal neovascular membranes. Real time ICGA, wide angle ICGA and digital sub traction ICGA may improve our diagnostic ability in AMD.

**OPTICAL COHERENCE TOMOGRAPHY (OCT)**

OCT provides us with valuable information by giving in vivo cross sectional imaging of the affected macula. OCT can reproducibly track drusen morphology, volume and geographic atrophy. It is possible to directly visualise choroidal neovascular membranes and features of active neovascular tissue such as intra retinal fluid, sub retinal fluid or cystoid macular edema. High resolution and enhanced depth imaging helps us in finding new features such as ISOS abnormalities and choroidal vascular abnormalities. Qualitative and quantitative information provided by OCT may serve as the most important criteria in re treatment decisions.

**AUTO FLUORESCENCE IMAGING**

Fundus AF is a useful modality to image lipofuscin in retinal pigment epithelium cells and is a unique way to access RPE function in age related macular degeneration (AMD). Abnormal AF patterns are seen in patients with AMD. The normal homogenous fundus appearance is altered with areas of hyper or hypo AF. The international fundus auto fluorescence classification group (IFAG) described 8 distinct patterns of AF in early AMD namely normal pattern, minimal change pattern, focal increased pattern, patchy pattern, linear pattern, lace like pattern, reticular pattern, and speckled pattern. AF (automated imaging analysis) has been shown to be superior to other modalities in assessing the extent of atrophy. Increased AF especially at the edge of geographic atrophic area, may predict expansion. In neovascular AMD it helps us in assessing RPE health and consistently visualising RPE detachments. This is also a useful research tool to help validate and measure the efficacy of novel treatments for non neovascular AMD.

**MICROPERIMETRY AND PSYCHOPHYSICAL TESTING**

Microperimetry and a number of self monitoring tests including the time tested amslers chart are available for identifying AMD progression. Ongoing development of modern technologies allows detection of more subtle defects, quantitative analysis, and accurate follow up. Application of these tools in clinical practice and patient’s everyday life raises hope for earlier detection of disease progression and hereby better chances to preserve vision. Early detection and treatment of choroidal neovascularization is crucial for achieving better visual outcomes and avoiding permanent vision loss. Microperimetry offers a reliable method of visual field testing in patients with unstable or eccentric fixation due to macular disorders and provides correlation between retinal pathologies and functional defects. Self assessment with an Amsler grid frequently may fail to identify disease progression. The preferential hyperacuity perimeter is highly specific and sensitive in identifying new choroidal neovascularization.

**MANAGEMENT STRATEGIES**

The management of either type of AMD was a challenging task for the health care systems as well as the patients. The primary aim is to minimise visual loss and physical and emotional impairment and to optimise vision related quality of life. Increased comprehension and knowledge about basic pathological mechanisms in both type of AMD has led to novel developments in therapeutic strategies resulting in widening of available treatment and improved prognostic perspectives.

**PROPHYLACTIC TREATMENT (Prevention in intermediate and advanced AMD)**

Although data in the literature are mixed with regard to each of age related eye disease study (AREDS) and AREDS...
2 micronutrients, the AREDS results demonstrate the role of specific AREDS antioxidants with zinc formulation in the prevention of advanced AMD. This formulation is recommended as a treatment for non smokers with extensive intermediate drusen, large drusen, non central geographic atrophy, or unilateral advanced AMD. Observational data for macular xanthophylls and for omega 3 fatty acids are promising, but in the absence of data from a large, randomised clinical trial these supplements cannot yet be recommended for AMD. In addition to intake of vitamins and supplements described by AREDS study, stopping smoking and healthy diet are strongly recommended. The benefits and harms of taking supplements needed to be assessed for the individual.

**LASER PHOTO COAGULATION**

Thermal laser photocoagulation was first introduced in an attempt to halt the progression of neovascular AMD. The macular photocoagulation study (MPS) trials were conducted from 1979 -1994 and showed that laser photocoagulation was a preferable therapy to observation for several categories of well defined CNV based on the fluorescein angiographic location of the CNV with respect to geometric center of the fovea. The MPS studies also documented that laser treatment did not prevent the progressive vision loss associated with CNV. A significant vision loss occurred over time in most treated eyes. Thus MPS trial demonstrated an effective therapy for an extrafoveal CNV, visual results for subfoveal disease and the high rate of recurrence within the first year were disappointing to patients and to their physicians.

**PHOTODYNAMIC THERAPY**

Photodynamic therapy (PDT) with verteporfin (Visudyne) emerged as a welcome alternative to thermal laser because of its minimal collateral damage in the treatment of CNV. This technique employs intravenous administration of pharmacological photo sensitizer followed by physical activation of substance using a 689 nm laser light. The TAP22,23,24 and VIP25 studies provided evidence of the efficacy and safety of verteporfin therapy. This therapy reduces the risk of further loss in vision by 50%; however, an improvement in vision was still a rare event. Predominantly classic or purely occult lesions smaller than four disc diameters that showed recent progression were shown to have better outcomes. Considering the durability and need for fewer repeated treatments, in the pre- anti-VEGF era, PDT was an appropriate therapy for subfoveal CNV, new or recurrent, where the classic component is greater than 50% of the entire lesion (< 5400 μm; or in an occult CNV when the visual acuity is worse than 20/50 or greater than 20/50 with a lesion size less than a disc diameter). The VIMP trial 26 showed that PDT is beneficial in minimally classic CNV. ANCHOR trial 27,28 demonstrated that PDT with verteporfin can retard the rate of visual loss, but does not confer gains in visual acuity when compared to anti VEGF therapy. Combination therapy with IVTA and PDT helped only in prolonging the re treatment interval. The benefit of ranibizumab with PDT as combination therapy remains unclear. The study showed that ranibizumab and PDT (standard or reduced fluence) achieved inferiority to ranibizumab monotherapy as assessed by visual acuity. Combination therapy here lengthened the re treatment interval. Combination therapy with ranibizumab and standard fluence PDT was found to be non inferior to ranibizumab monotherapy with no difference in the proportion of patients with a treatment free interval of at least 3 months as evidenced in MONT BLANC study 29,30. On the contrary EVEREST Trial 31,32 showed that combination therapy is beneficial in polypoidal choroidal vasculopathy.

**ANTI VEGF THERAPIES**

Multiple studies have suggested that vascular endothelial growth factor increases vascular permeability and is involved in the pathogenesis of neovascularization in human eye disease. The current approach of Anti VEGF therapies are an important breakthrough in exudative AMD. The three Anti VEGF therapies currently approved by FDA for treatment of neovascular AMD are pegaptanib (macugen), ranibizumab (Lucentis) and afiblercept (Eylea). Pegaptanib an aptamer that specifically binds and inhibits VEGF isoforms containing at least 165 amino acids, was shown to delay the rate of vision loss in a large prospective randomised clinical trial. Visual acuity results are however limited. Ranibizumab an antigen binding fragment of a humanised monoclonal antibody directed against all the biologically active forms of VEGF-A, including the known active proteolytic breakdown products, effectively slows down the rate of visual loss and can improve vision as shown in prospective randomised clinical trial. Monthly injections provide superior sustained improvement in visual acuity and decreased central retinal thickness as compared with quarterly or as needed dosing. Overall intra vitreal ranibizumab is well tolerated and has a low rate of adverse ocular or systemic side effects. Bevacizumab is a full sized humanised monoclonal antibody with VEGF binding characteristics similar to ranibizumab; is approved by FDA for systemic treatment of metastatic colorectal cancer and lung cancer, but is an off label treatment for neovascular AMD. A large prospective randomised clinical trial (CATT) 33,34 showed that the visual outcome of bevacizumab was non inferior to ranibizumab. However the as needed therapy resulted in less visual gain than the monthly therapy of either drug. Bevacizumab was associated with a higher overall rate of systemic adverse events in the CATT trial, but most of the excess events have not been associated previously with systemic anti VEGF therapy. IVAN (randomised control trial of alternative treatments to inhibit VEGF in age related choroidal neovascularisation) 35 trial at one year; the comparison by
drug was inconclusive. Bevacizumab was neither inferior nor equivalent to ranibizumab using the pre determined 3.5 non inferiority letter limit. As needed treatment was found to be equivalent to monthly treatment. Fewer patients receiving bevacizumab had an arterial thrombotic event or heart failure and there was no difference between drugs in the proportion having a serious systemic adverse event. Fewer patients in the monthly treatment group had fluid on OCT and dye leakage on fluorescein angiography at one year but no difference was found between drugs. Afiblercept is a recombinant chimeric VEGF receptor fusion protein that inhibits all VEGF isoforms and placental growth factors and inhibits VEGF-A with high affinity. The FDA approved dosing regimen – 3 monthly injections followed by injections every 2 months has been shown to have clinical equivalent effects as monthly ranibizumab in two large prospective randomised controlled trials. Future anti VEGF therapies in the form of soluble fusion proteins, small interfering RNA’s receptor tyrosine kinase inhibitors are being tried.

Since untreated neovascular age related macular degenera–tion progresses to blindnness and previously available treat–ments did not achieve improvements on this scale ; anti-vascular endothelial growth factor therapy was hailed as the cure for neovascular age related macular degeneration. However there are drawbacks to anti-vascular endothelial growth factor treatment. Although initial worries that the eye might not tolerate repeated perforation or that serious adverse events (such as intraocular infection) might occur frequently have receded, the need for monthly monitoring and re-treatment, which creates a huge burden on resources, is a concern. There remains a theoretical possibility that long term inhibition of vascular endothelial growth factor could adversely affect the health of neural retina, the retinal pig–mented epithelium, and choriocapillaris, since these tissues constitutively express vascular endothelial growth factor and rely on it for maintained health. 20% of people with neo–vascular age related macular degeneration treated with anti-vascular endothelial growth factor therapy have been shown to lose vision over time. A further proportion (about a fifth to a third) may lose the initial improvements in visual acuity, which may be the consequence of attempts to decrease the frequency of drug administration or may result from underlying disease progression. Another issue is the resistance to anti-angiogenic therapy which cannot be dismissed. Small case series suggest an increased rate of RPE tears after an injection though there is no study suggesting that this is higher than the rate in untreated patients after one year of evolution. Finally, the long-term systemic safety above 2 years has not yet been addressed. It is unlikely, however, that we will have better results in terms of safety concerns given the reduced life expectancy of patients with AMD and concomitant systemic disease (mean 7 years). These findings have dampened the initial enthusiasm for biological treatment to some extent.

RADIATION THERAPY
The rationale for radiation therapy was based on the known effects of radiation therapy on tumour microvasculature and its ability to prevent proliferation of vascular tissue by inhibiting neovascularization. The macular epiretinal Brachytherapy in age related macular degeneration( MERITAGE) showed that epimacular Brachytherapy (EMB) is safe and effective method for neovascular AMD. A phase 3 multicenter prospective randomized non inferiority designd study called the CNV secondary to AMD treated with Beta Radiation EpiRetinal Therapy(CABERNET) demonstrated an acceptable safety profile for epimacular brachytherapy at the two year mark and identified a subgroup of patients who tend to respond well to the treatment and required fewer rescue injections. However the CABERNET study did not achieve its primary end point with a 10% non inferiority margin and is not yet known whether we can identify these sub group of patients. Stereo tactic radio surgery (Iray system) which uses external beam radio therapy have also shown in its initial results at one year follow up in a phase 1 trial that majority of the patients showed improved or stabilized visual acuity with a mean visual acuity gain of 8-10 ETDLS letters. The INTREPID trial is on its way to evaluate the safety and effectiveness of stereo tactic radio surgery in patients who have been previously treated with anti VEGF therapy thus epimacular brachytherapy and stereo tactic radio surgery may prove to be valuable adjuncts to anti VEGF therapy for neovascular AMD. Radiation therapy given in conjuntion with anti VEGF agents may reduce the number of intra vitreal injections required. The risk of radiation related adverse effects appears to be minimal with these radiation treatments.

STEM CELL THERAPY
AMD , the commonest cause of irreversible visual loss in the developed world is characterized by loss of the RPE and degeneration of the overlying photoreceptors. Therefore, transplantation of healthy photoreceptors and/ or RPE cells is an exciting option for future treatment of this disease. In the past, clinical studies employing this approach have involved autologous or allogeneic transplantation of retinal tissue. However, the former involves technical challenging surgery, while the latter involves use of fetal tissue, and thus both practical and ethical concerns. Moreover, both strategies have demonstrated only limited functional integration of transplanted tissue. In recent years, it has become clear that functional integration of transplanted retinal photoreceptors is possible, but is highly dependent on the differentiation stage of the cells in question. Since 1998, the advent of human embryonic stem cells offers the prospect of unlimited supplies of cells for transplantation, with tight control of...
their differentiation state. Since 2007, the development of human-induced pluripotent stem cells raises the prospect of retinal transplantation with all the advantages of embryonic cell technologies, but without fears regarding immunological rejection, or ethical concerns. In 2012, preliminary results from the first human clinical trial of embryonic stem cells were reported in a single patient with AMD, with larger trials under way. Therefore, it is clear that stem cell based therapies are at the cutting edge of new therapeutic interventions for AMD, with many exciting breakthroughs likely in the coming years.

**SURGERY FOR AMD**

Surgical removal of sub-foveal CNV, removal of sub-foveal hemorrhage, macular translocation, and transplantation of the pigment epithelium with or without choroidal graft are few of the surgical procedures evolved over the years in treating advanced AMD.

**Excision of CNV**

Removal of the CNV with submacular hemorrhage in AMD was first described by de Juan in 1988. The first visual result of membrane excision were disappointing with visual improvement in only 0% to 33% of the cases. The Sub macular surgery trial (SST) (1997 to 2003) evaluated removal of sub-foveal CNV compared with observation which showed that this surgical alternative therapy did not improve vision. A retrospective meta-analysis evaluating 647 cases of sub-retinal membrane excision in AMD subjects showed that improvement was achieved in about 33% and deterioration occurred in 27%. Recurrence rate of CNV was approximately 25%, and the progression of the atrophic scar size led to further visual loss. In a patient with recent macular hematoma secondary to CNV, different surgical options may be considered. The pneumatic displacement of the sub-macular hemorrhage with SF6 or C3F8. Vitrectomy, with TPA injection, hematoma removal, CNV excision, and gas tamponade have been proposed with variable functional and anatomical results. Despite these limited results, there are still some indications for sub-macular surgery, such as for patients with low preoperative visual acuity due to large hemorrhagic or fibrotic membranes.

**Retinal translocation**

Machemer in 1993 performed the first retinal translocation. The development of apical retinal rotation combined with scleral shortening has been tested for several years. Because of the very small angle of rotation, the high rate of recurrence (approximately 50%), and the availability of other therapies (PDT), this technique is no longer implemented. A complete 360° retinotomy, which allows a higher rotation angle of the retina, has been proposed in the second eye-affected patients. Long-term reports have shown favorable visual results with 52% of the subjects having one or more lines of improvement, specifically reading vision and contrast sensitivity after one year. A high rate of PVR (approximately 30% of the cases in inexperienced hands and between 8% and 18% in inexperienced hands) limits the use of this surgical technique. However, retinal rotation with 360° retinotomy may be an alternative in very large CNV, when it does not respond to new therapies when it is associated with large hematomas.

**RPE transplantation**

The disappointing visual results after CNV excision were explained by the simultaneous mechanical removal of the RPE layer and the transplantation of the RPE seemed to be a logical solution to restore vision. Currently, different techniques of autologous transplantation of the RPE are under evaluation. The iris pigment epithelial transplantation has been proposed, but this tissue is incapable of expressing crucial enzymes of the retinoid visual cycle. Investigators proposed the use of RPE suspension cells harvested through a nasal retinotomy at the beginning of the surgery and transplanted in the sub-retinal macular space after the excision of the CNV. A prospective trial was conducted with autologous suspension cell transplantation after membrane excision compared to membrane excision alone. At 12 months, visual improvement of two or more lines was achieved in 52.5% of the transplantation group (21.5% in the excision alone group), 32.5% remained the same, and 15% had a decrease of vision (21.5% in the excision alone group). The statistical analysis of far visual acuity showed just a trend in favor of the transplanted group, but the statistical analysis of the multifocal ERG showed a significant difference between the two groups, with better results in the transplanted group. Another transplantation technique using a full thickness RPE-choroid sheet has been proposed by some researchers with interesting results regarding the long-term survival and the revascularization of the transplanted tissue. This technique uses a RPE-choroid flap taken in the superior mid-periphery, which is directly introduced through the macular retinotomy into the subretinal space. This particular technique, however, seems to be traumatic and presents a high rate of PVR.

The two main limitations of “one-time” autologous transplantation techniques are the graft size and the quality of the RPE and the Bruch’s membrane. Culturing prior to transplantation may offer the potential to at least partially influence or reverse aging and the lipofuscin load per cell might be reduced by dilution during cell division. This “rejuvenation” process may also be combined with a potential gene defect correction. Unfortunately, the right surgical technique (with a prosthetic Bruch’s membrane) and a viable method of culturing are not yet available. RPE-like cells generated from embryonic stem cells, neural stem cells,
orbone marrow derived cells, however, may represent the future of the RPE transplantation in AMD.

VISUAL REHABILITATION
Patient success with low vision devices depend upon factors such as physical and mental status, level and stability of visual acuity, patient’s dependency on others, and the interval since vision loss. In cases of advanced macular degeneration vocational rehabilitation, occupational therapy and mobility training for routine activities should be considered. Support groups can play a pivotal role in coping up with the situation. Some of these patients are resistant to low vision devices especially the ones who have not accepted their visual loss. Success in visual rehabilitation is always based on identification and satisfaction of the visual requirements and goals of the patient. Apart from the older low vision devices exciting applications and devices are emerging such as the implantable miniature telescope, high resolution electronic video magnifiers which will no doubt be of great benefit to these visually impaired patients.

NON VEGF RELATED PATHWAYS FOR TREATMENT
Numerous molecular pathways are involved in angiogenesis, either by serving as angiogenic or antiangiogenic signals by facilitating or retarding endothelial migration or tube formation, by desensitizing vessels to regression through the process of vessel maturation, by inducing fibrosis, or by augmentation or diminishing VEGF or non-VEGF mediating signals. Thus potential treatment targets would be pigment epithelium derived factor, Notch family of receptors, platelet derived growth factor, transforming growth factor β, Angiopoietin and Tie, matrix metalloproteinases, intergrins, angioatin and endostatin, and placental growth factor. Therefore, all the important VEGF is far from the entire story in angiogenesis. Thus the future anti angiogenic therapy would be targeting multiple pathways in combination with VEGF which will help in maximising treatment outcomes.

CONCLUSION
Last two decades, a multitude of clinical trials have evaluated the efficacy of various treatment modalities for neovascular AMD. Thermal laser successfully prevented the proliferation of CNV; however, visual loss and recurrences impaired the treatment benefit. Using non-thermal laser energy through PDT appeared as a healthy alternative, but again, it was unsatisfying to both the patient and treating clinician given the inability to improve vision in a majority of patients. As we begin to better understand the pathophysiology of CNV and the role of VEGF in its development and persistence, newer pharmacologic interventions have led to previously unattainable results regarding improvements in vision. But again, we are faced with a new problem of repeated treatment. We are also now beginning to experiment with combination therapy in an attempt to discontinue the cycle of repetitive treatment. Although it appears promising, retrospective and small prospective studies are no substitute for large, randomized, controlled trials. As our understanding of the disease continues to grow at the molecular level, investigators are simultaneously exploring other treatment venues that may offer a more long-term solution, such as the inhibition of gene expression and signal transduction. So to conclude we are far ahead now in the treatment of AMD, but there is still a long way to go especially in prevention of this disease.

BIBLIOGRAPHY


[Epub ahead of print].
38. Bressler NM. Age related acular degeneration is the leading cause of blindness.DAMA 2004;291:1900-1.


Retinopathy of Prematurity

INTRODUCTION
Retinopathy of prematurity or retrolental fibroplasia is a proliferative vitreoretinopathy affecting premature infants of very low birth weight that can cause retinal detachment. Retinal detachment occurs as a result of tractional forces caused by neovascular proliferation and its presentation can range from mild peripheral tractional retinal detachment to total retinal detachment. In retinopathy of prematurity patients, retinal detachment that develop shortly after birth are usually due to mechanical traction or exudation from retinal vessels in the active stage of proliferation. Those that develop later in life are usually of rhegmatogenous type and may or may not be associated with cicatrical ROP changes.

PATHOPHYSIOLOGY
Retinal receives its blood supply from both choroidal and retinal circulation. The choroidal circulation is complete prior to 20 weeks of gestational age, and therefore prior to survivable premature birth. But retinal circulation arising from optic nerve head is just beginning to develop a vascular bed at this time and thus is involved in ROP pathogenesis.

There are 2 theories in ROP –
A classic theory by Ashton and Patz and a gap junction theory by Kretzer and Hittner.

The “classic” theory proposed by Patz and Ashton describes an initial hyperoxic phase of the disease which causes arteriolar constriction with subsequent irreversible vaso-obliteration. This is then followed by a second phase in which a vaso-proliferative response is induced by retinal ischemia as a result of retinal capillary closure. The “classical” theory has been followed by the “gap junction theory” of Kretzer and Hittner. Their theory of pathogenesis is based on the activity of mesenchymal spindle cell precursors of retinal capillaries. Accordingly, these cells migrate centrifugally from the optic disc toward the junction between vascular and nonvascularized retina, to form a new capillary network. Under hyperoxic conditions, abnormal gap junctions appear between adjacent spindle cells, and this interferes with normal cellular migration and vascular formation. The angiogenic factors secreted by these mesenchymal cells may in turn trigger a neovascular response.

RISK FACTORS
Systemic factors (1)
1) Younger gestational age
2) Multiple births
3) Out-of-nursery birth
4) Low birth weight
5) White race
6) More than 6 hours stage 3 labour

Ocular factors (1)
1) Lower PMA on ROP diagnosis
2) Zone 1 ROP in 1st exam
3) Rapid progression to prethreshold
4) Plus disease at 1st prethreshold exam
5) Iris vessel dilatation
6) Plus disease
7) Zone 1 ROP

Others (1)
1) Prematurity
2) High levels of supplemental oxygen
3) Mechanical ventilation
4) Multiple blood transfusion
5) Intraventricular hemorrhage
6) Concurrent illness
7) Anemia
8) Seizures and apnoea
9) Multiple prenatal maternal factors like diabetes, preeclampsia, smoking etc
10) Genetic polymorphism

SCREENING GUIDELINES AND PROCEDURES
According to American Academy Of Paediatrics the screening guidelines include:
1) Infants with birth weight ≤1500 g or gestational age of 30 weeks or less and selected infants with a birth weight between 1500 and 2000 g or gestational age of >30 weeks with an unstable clinical course, including those requiring cardiorespiratory support and who are believed by their attending pediatrician or neonatologist to be at high risk for ROP, should have retinal screening examinations performed after pupillary dilation by using binocular indirect ophthalmoscopy with a lid speculum and scleral depression (as needed) to detect ROP.

2) The initiation of acute-phase ROP screening should be based on the infant’s postmenstrual age. The onset of serious ROP correlates better with postmenstrual age (gestational age at birth plus chronologic age) than with postnatal age.
That is, the more preterm an infant is at birth, the longer the time to develop serious ROP.

### TABLE 1

<table>
<thead>
<tr>
<th>Gestational Age at Birth, wk</th>
<th>Age at Initial Examination, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Postmenstrual</td>
</tr>
<tr>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td>24</td>
<td>31</td>
</tr>
<tr>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>29</td>
<td>33</td>
</tr>
<tr>
<td>30</td>
<td>34</td>
</tr>
</tbody>
</table>

Older gestational age, high-risk factors: 4

Follow-up examinations should be recommended by the examining ophthalmologist on the basis of retinal findings classified according to the international classification (see Fig 1). The following schedule is suggested:

**FIGURE 1**

Scheme of retina of the right and left eyes showing zone borders and clock hours used to describe the location and extent of ROP. Diagrammatic representation of the potential total area of the premature retina, with zone I (the most posterior) symmetrically surrounding the optic nerve head (the earliest to develop). A larger retinal area is present temporally (laterally) rather than nasally (medially) (zone III). Only zones I and II are present nasally. The retinal changes discussed in recommendation 4 are usually recorded on a diagram such as this one. (2)

**1-Week or Less Follow-up**
- immature vascularization: zone I—–no ROP
- immature retina extends into posterior zone II, near the boundary of zone I
- stage 1 or 2 ROP: zone I
- stage 3 ROP: zone II
- the presence or suspected presence of aggressive posterior ROP

**1- to 2-Week Follow-up**
- immature vascularization; posterior zone II
- stage 2 ROP: zone II
- unequivocally regressing ROP: zone I

**2-Week Follow-up**
- stage 1 ROP: zone II
- immature vascularization: zone II—–no ROP
- unequivocally regressing ROP: zone II

**2- to 3-Week Follow-up**
- stage 1 or 2 ROP: zone III
- regressing ROP: zone III

Babies born with birth weight of less than or equal to 1500gm or gestational age of 31 weeks or less should be screened for retinopathy of prematurity. Screening should begin at 1-2 weekly intervals, depending on the severity of the disease and continue until retinal vasculature reaches zone 3. In the management of premature infants weighing less than 1200gm, the PaO2 level of blood from the umbilical artery should be monitored, levels of 50-100mmHg being regarded as unlikely to produce constriction of retinal vessels.

If minor signs of ROP are noticed, examination should be repeated at the ages of 1, 3 and 6 months and every 4 months up to the age of 4 years with the aim of diagnosing early retinal holes or localized detachment of the retina.

Screening conclusion done when:
1) Zone 3 retinal vascularisation attained without previous zone 1 or 2 ROP, assuming no examiner error. If there is doubt about the zone or if postmenstrual age is unexpectedly young, confirmatory exams may be warranted.
2) Full retinal vascularisation
3) Postmenstrual age of 45 weeks and no prethreshold ROP or worse presentation
4) Definite disease progression signs in compatibly aged infants.

According to Jalali et al (3), the screening criteria for ROP in the Indian scenario includes:

**Screening of all eligible babies to be started**

1. 31 weeks postconceptional age or 3-4 weeks after birth (whichever is earlier)
2. Infants weighing 1200gms at birth and those born at 24-30 weeks gestational age are screened early, usually not later than 2-3 weeks after birth
3. No examination needed in the first 2-3 weeks of life
4. Next examination date to be decided by ophthalmologist based on initial findings.
5. Complete one screening session definitely before ‘Day 30’ of infants life

**Frequency of examination is**

1. Further evaluation for ROP is not needed if the retina is fully mature (defined as retinal vessels seen up to nasal ora serrata, in the context of ROP). This usually occurs by 40 weeks post-conceptional age. These babies, however, need to see an ophthalmologist for refraction, vision assessment, and ocular alignment (squint) at 3-12 months of age. Preterm babies are at higher risk for developing ametropia, delayed visual maturation and squint. If there is no apparent squint or vision problem, the child can be seen at one year of age. If there is an obvious squint, nystagmus, tearing, discharge, photophobia, leucocoria or vision loss, then early evaluation is needed. Usually the eyes are well aligned, and have good ability to fixate and follow an object by three months of age.

2. If the retina is immature (retinal vessels are not seen up to nasal ora serrata) then baby must be screened every two weeks till the retina is mature.

3. In eyes with retinal vessels seen only up to the Zone I area at initial visit, weekly evaluation is needed. These eyes can develop fulminate ROP or Rush disease very quickly, and not necessarily the classical stages 1-3 before reaching threshold ROP.

4. If there are early signs of ROP then the child must be examined every week for any progression or regression of the disease.

5. If child develops pre-threshold ROP, then the child should be seen every 3-7 days for progression.

6. In case of threshold ROP, urgent peripheral retinal laser/cryo ablation should be done within 48-72 hours.

7. In eyes with ROP stage 4 or 5, early surgical treatment such as belt buckling or vitreous surgery can help save some vision, though the majority have a dismal prognosis.

8. In case of any doubt about the retinal findings (especially by beginners) it is a good practice to examine the baby again every 1-2 weeks, at least till the child is 38-40 weeks old

**NATURAL HISTORY AND SEQUELAE**

ROP is divided into acute and cicatricial phase. The inherent activity in the retina determines the timing of the disease expression. Youngest infants at birth develop ROP at a later chronologic age and infants with the oldest gestational ages at birth develop ROP at an earlier gestational age.

ROP progression has natural breakpoints between disease without risk of unfavorable outcome and disease with this risk. Escalating disease with very low risk includes:

- Stage 1, zone 2 or 3, no plus
- Stage 2, zone 2 or 3, no plus
- Stage 3, zone 2 or 3, no plus

Constants above are not stage, but absence of Zone 1 or plus disease. All of them have a less than one percentage chance of poor outcome.

Maximal observed disease with significant and increasing risk includes:

- Stage 3 plus, 1-4 sectors, Zone 2
- Stage 1 & 2, Zone 1
- Stage 3 plus, 5-8 sectors, Zone 2
- Stage 3 plus, 9-12 sectors, Zone 2
- Stage 3, Zone 1

According to CRYO ROP, above risks of unfavourable outcome from 8-60%. The greatest risk of poor outcome was Zone 1 threshold ROP. The unfavourable visual outcome in those patients was close to 90% whether treatment was given or not.

Regression or cicatricial disease is less well understood and includes fibrovascular proliferation, contraction, scarring, pigmentary changes and permanent traction. CRYO-ROP study developed a macular scoring system as the degree of macular damage was the most clinically relevant cicatricial event. They classified tractional damage as:

- MS 0 : Normal macula
- MS 1 : Macular heterotopia
- MS 2 : Macular fold
- MS 3 : Macular retinal detachment
INDICATIONS OF TREATMENT
The presence of plus disease (defined as abnormal dilation and tortuosity of the posterior retinal blood vessels in 2 or more quadrants of the retina meeting) in zones I or II suggests that peripheral ablation, rather than observation, is appropriate.3

Treatment should be initiated for the following retinal findings:
- zone I ROP: any stage with plus disease
- zone I ROP: stage 3—no plus disease
- zone II: stage 2 or 3 with plus disease

The revised International Classification of Retinopathy of Prematurity Revisited classification gives specific examples on how to identify zone I and zone II disease by using a 28-diopter lens with binocular indirect ophthalmoscopy.

The presence of plus disease rather than the number of clock hours of disease may be the determining factor in recommending ablative treatment. Treatment should generally be accomplished, when possible, within 72 hours of determination of treatable disease to minimize the risk of retinal detachment. Follow-up is recommended in 3 to 7 days after treatment to ensure that there is no need for additional treatment in areas where ablative treatment was not complete.

According to ETROP study(4), early treatment of high-risk prethreshold ROP significantly reduced unfavorable outcomes to a clinically important degree . Earlier treatment is defined as retinal ablation administered to the avascular retina when an eye reaches high risk prethreshold retinopathy of prematurity (ROP). Prethreshold indicates any Zone I ROP; or Zone II stage 2 with plus disease, or stage 3; or Zone II with less than 5 contiguous or 8 cumulative clock hours of stage 3 ROP with plus disease. High risk include birth weight, gestational age, ethnicity, singleton/multiple status, newborn status, Zone on first exam, severity of ROP and rate of progression of ROP.

TREATMENT
1] Laser photocoagulation-Recommended in infants with threshold disease. This is successful in 85% of cases, but the remainder progress to retinal detachment in spite of treatment. The visual and anatomical outcomes are better compared to cryotherapy as laser induces less myopia. The systemic adverse effects are significantly less, the ocular tissues are less traumatized, posterior zone 1 disease is treated easily, general anesthesia is not necessary, there is less incidence of late complications. Complications include corneal haze, burns of the iris, cataracts, and intraocular hemorrhages.

2] Intravitreal anti-VEGF agents- Bevacizumab has been used but the optimal timing, frequency and dose are yet to be established. According to BEAT ROP study(5) there was significant benefit with Intravitreal bevacizumab monotherapy, as compared with conventional laser therapy, in infants with stage 3+ retinopathy of prematurity for zone I but not zone II disease. Development of peripheral retinal vessels continued after treatment with intravitreal bevacizumab, while conventional laser therapy led to permanent destruction of the peripheral retina. But safety issues of using Bevacizumab in ROP still persists as the study trail was too small.

3] Lens-sparing pars plana vitrectomy – For tractional retinal detachment not involving the macula(Stage 4a). It has better visual and anatomical outcome. The visual outcome in stages 4b and 5, in which the macula is involved, is disappointing despite successful reattachment.

CONCLUSION
Retinopathy of prematurity is a disease that affects immature vasculature in the eyes of premature babies. It can be mild with no visual defects, or it may become aggressive with new neovascularization and progress to retinal detachment and blindness. Increasing awareness among general public, neonatologists and ophthalmologists and a mandatory screening protocol for all NICUs can go a long way in preventing visual morbidity due to this condition.

REFERENCES

Dr Natasha Radhakrishnan is Associate Professor, Vitreoretinal services at Amrita Institute, Kochi. Her areas of interest include medical retina and paediatric retinal disorders.
Statistical Methods In Clinical Trials, Validity Analysis And Evidence Based Medicine & Meta-Analysis

(A) PRINCIPLES & STATISTICAL METHODS IN CLINICAL TRIALS

CLINICAL TRIALS
The drug characteristics are generally assessed through animal experiments or laboratory tests before they are recommended for use. But, however successful these experiments may turn to be, the drug ultimately has to be tried on human beings to assess their efficacy as compared to the existing lines of treatment, their side effects and dosages. Such trials are called CLINICAL TRIALS. In a clinical trial the effect of exposure / intervention on the outcome on a group of subjects is studied:

Exposure / intervention: drug, surgery, diet, exercise or health education.
Outcome: recovery, improvement, survival, increase / decrease in the value of the variables etc.

EFFICACY
Is a measure of the benefit resulting from an intervention for a given health problem under the ideal conditions (under the control of the investigator) of an investigation. It answers the question, “does the intervention do more good than harm to people who fully comply with the recommendations?”

EFFECTIVENESS
Is a measure of the benefit resulting from an intervention for a given health problem under the usual conditions of clinical care for a particular group. Under this evaluation, in addition to measuring the efficacy of an intervention, it also measures its acceptance by those to whom it is offered. Thus, effectiveness answers the question, “does the practice do more good than harm to people to whom it is offered?”

FOUR PHASES OF TRIALS

PHASE - I : Toxicology, Pharmacokinetics, Safety etc. on human volunteers are studied.
PHASE - II : To study treatment effect on small number of patients.
PHASE - III : Randomized (multi-centric) controlled trials (RCT).
PHASE - IV : Marketing the drugs - strategies and modalities and to study long term side effects.

In this section statistical aspects to be taken care of in RCT are discussed:

STEPS IN STATISTICAL ASPECTS OF RCT

1) Estimation of minimum sample size based on the objective(s) of the clinical trial.
(Chapter on Sample size estimation and selection of sample from the population applying appropriate sampling method may be referred).

2) Selection of patients
(a) Exclusion & inclusion criteria
(b) Comparability of subjects in the different groups
(c) Control group (placebo / standard treatment)
(d) Method of selection of patients adopting appropriate sampling method - simple random method of allocation may be applied. Stratified sampling method of allocation may be applied if there is heterogeneity in the population of patients. For example, if the population consists of all age groups and age is a factor which affects the response to the treatment, stratified sampling method will increase the precision of the estimate of the response parameter.

3) Treatment specifications: dose, frequency, route, duration and other related aspects should be clearly spelt out.

4) Ethical considerations: It is very important that the study is approved in ethical angles by the Ethical Committee in the Institution following the accepted guidelines. Without the ethical clearance of the study the findings of the study are not acceptable.

5) Follow-up of patients: Recording of various information systematically in suitably designed proformae is very important in clinical trials. Since the clinical trial is carried out over a period of follow-up depending upon the requirement the records have to be kept systematically and carefully to rule out loss of data.

6) Drop out: Drop out of the patients over the study period may be a problem. The drop out rate has to be kept as low as possible for accepting the results scientifically.

7) Coding the treatment: Carefully coding the treatment, if it is feasible and de-coding it only after the results are available.
available is very important to maintain confidentiality of the trial and trial results. A third person will have to keep the code of drugs and it will be decoded only by him/her after the results are made available. Of course this will be possible only if the two or more treatment methods look alike (pills or capsules).

8) Data analysis applying appropriate statistical methods:
Appropriate statistical methods have to be applied to the data for the scientific validity of the results. Depending upon the type of variable, number of groups, design of the study and the objectives of the study, appropriate statistical methods should be applied.

9) Interpretation of the results validly and meaningfully, mentioning the drawbacks of the trial and cautioning the interpretations.

ALLOCATIONS OF PATIENTS IN THE DIFFERENT GROUPS
(1) Biased randomization (alternate, odd / even): This method can be biased due to the preference that may be given by the treating doctor due to the severity of the disease. By making double blind allocation this problem can be taken care of to an extent.

(2) Balanced randomization: (random number table from books or computer generated numbers). This is the ideal method of allocation. This can be done either by using the table of random numbers or by generating them through computer software

Stratification: If the study population is heterogeneous with respect to, say, age, severity, type etc. which could affect the outcome, stratified allocation would be better. The study population may be stratified according to the factor which makes the population heterogeneous and required samples can be selected from each stratum and allocated randomly to the different treatment groups. This method will make the estimate of the response parameter more precise (less standard error).

DESIGNS OF CLINICAL TRIALS: Basically there are two types of design used in clinical trials - Parallel & Cross-over designs

(1) PARALLEL DESIGN: Two or more independent groups with different treatments—Allocation of total patients is done to the independent groups randomly. For example, 40 patients may be randomly distributed to the two treatment groups (Treatment-A & Treatment-B) randomly. This is the most commonly used design.

(2) CROSS-OVER DESIGN: If the number of patients available for the study is limited and there is no carry over effect w.r.t. the treatments after a certain period, Cross-over design may be adopted. This design results in reducing the sample size since the same patients will be used in each group after a certain period of time. For example, out of a total of 20 patients, the first 10 patients may be given treatment-A and the second 10 patients, treatment-B. After a certain period the first 10 patients will be given treatment-B and the second 10 patients, treatment-A. This design is recommended provided there is no carry over effect of the drugs after a certain period which has to be ascertained statistically and clinically from earlier documented studies.

\[
\begin{array}{cccc}
\text{Type} & \text{Patient} & \text{Investigator} & \text{Evaluator} \\
\text{Single} & \text{Yes} & \text{No} & \text{No} \\
\text{Double} & \text{Yes} & \text{Yes} & \text{No} \\
\text{Triple} & \text{Yes} & \text{Yes} & \text{Yes} \\
\end{array}
\]

The most commonly and recommended blinding is the Triple blinding: The patient, the Investigator and the statistician who does the analysis are blinded and gives unbiased results.

SHORT AND LONG TERM CLINICAL TRIALS
In a trial to find out the efficacy of a new drug in comparison to the standard drug in the treatment of common cold or influenza, the outcome is expected within a short time but, in trials on cancer patients, the outcome will take long time to show. Specific practical problems may be faced in such trials.

PRACTICAL PROBLEMS IN LONG TERM CLINICAL TRIALS
1) Necessity of dedicated investigators because of the long period of study
2) Systematically maintained registers
3) Drop outs / withdrawals due to side effects / partial improvement
4) Patient consent & compliance
5) Necessity of change in treatment due to side effects or ethical reasons
6) If multicentric trial, problem of keeping uniformity in the methodology & execution of the trial and data analysis
7) Necessity of interim evaluation
8) In multicentric trials, coping with conflicting results
9) Specific statistical methods to analyze the end point results has to be applied for example—survival analysis

STATISTICAL METHODS FOR DATA ANALYSIS
1. Descriptive methods
2. Inference methods

For the details on the methods of Descriptive & Inference analysis, corresponding chapters may be referred in the earlier issues of this Journal. Some specific issues in clinical trials and the methods of analysis for the same are discussed below:

**INTERIM ANALYSIS**

It is always suggested that a certain number of interim analysis may be planned in the clinical trial. Number of interim analysis may be decided according to the requirement and convenience. Interim analysis helps to monitor the progress of the trial and to see whether all planned activities are going on as per the plan. Any aspect – like, selection of patients, criteria for giving treatments and recording of responses requires any modification due to any reason, that may be incorporated in the trial without affecting the design and conduct of the trial. Also, it helps the investigator to find out whether anticipated statistical significance has been achieved in the improvement rates between the treatment methods based on the patients already included in the trial. If anticipated statistical significance has been achieved based on the lesser number of patients, the trial may be stopped for ethical reasons to avoid treating the patients with the lesser effective treatment method. The only modification which has to be made in the analysis is that the level of statistical significance (p-value) has to be changed depending upon the number of interim analyses. If the p-value fixed for statistical significance is 0.05 and the number of interim analysis is 3, the p-value for statistical significance has to be fixed based on O’Brien formula. The p-value in the first interim analysis will be much lower than 0.05, for the second interim analysis, p-value will be slightly higher than the p-value fixed for the first interim analysis and for the final analysis p-value will be fixed as 0.05. For more details of finding out the p-value for each interim analysis, the paper given under Books for further reading may be referred.

**INTENTION TO TREAT ANALYSIS**

Drop-out, Withdrawal, change of Treatment (within or outside the CT Protocol) — due to serious side effects, general negligence etc. are ideally to be avoided, but, in practice, may not be possible. It affects the balance of Randomization and introduces bias in the Treatment comparisons. To avoid this, analysis may be done as per the original grouping itself. This analysis is called — INTENTION TO TREAT ANALYSIS.

Medication for unstable Angina pectoris may be an example. Medication may not be effective in some patients and for ethical reasons and keeping the treatment for the benefit of the patient, coronary by-pass surgery may have to be done in such patients. This will affect the randomization of patients. It is advisable to do the analysis in both ways — i.e; Original grouping & according to the grouping after the change over.

**STATISTICAL ANALYSIS FOR ADJUSTMENT FOR THE CONFOUNDING VARIABLES**

**PROGNOSTIC (CO) FACTORS—CONFOUNDING FACTORS**

Effect of the Treatment could be related to many variables: -- Sex, Age, Severity of disease, Duration of the disease, Personality Variables (Diet, Smoking habit, Use of Alcohol, Clinical & Laboratory variables (BP, Heart rate, Blood Sugar level) etc. These variables may be called — confounding factors or prognostic co-factors. While comparing the Response variable between the Treatment Groups, the effect of these Co-Factors on the Response Variable has to be studied and adjusted. Consider the following results obtained from a clinical trial:

<table>
<thead>
<tr>
<th>Response</th>
<th>Group</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ND (Standard drug)</td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>17(45.9%)</td>
<td>20(60.3%)</td>
</tr>
<tr>
<td>Not-improved</td>
<td>38</td>
<td>25</td>
</tr>
</tbody>
</table>

$\chi^2 = 1.41$ (p = 0.24) — The difference in the improvement rates between the two treatment groups (SD and ND) is statistically not significant. Assume that the investigator knows that age of the patient may affect the response to the treatment. Statistical significance of the difference in the age distribution between the two groups has to be tested before comparing the effect of the two drugs.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Group</th>
<th>SD</th>
<th>ND</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-30</td>
<td>20(36.4%)</td>
<td>30(66.7%)</td>
<td></td>
</tr>
<tr>
<td>31-60</td>
<td>35</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

$\chi^2 = 7.92$ (p = 0.005) — Significant

On comparing the age distribution between the two groups it was found that there is a statistically significant difference in the age distribution between the two groups. Hence the comparison of the treatment effect should be done separately in the two main age groups, assuming that the improvement rate might be the same, statistically, within each age group.
Response                         Group
                            SD    ND
Improved                   10(50.0 %)          10(33.3 %)
Not-improved              10                                       20
χ² = 0.78 ( p =0.38 ) – Not Significant. Though comparatively higher improvement rate was observed in the SD group compared to ND group, the difference was statistically not significant.

31-60
Improved                   07(20.0 %)             10(66.7 %)
Not-improved              28                                        05
χ² = 8.22 ( p =0.004) – Significant with 99% Confidence. Statistically significant difference was observed in the improvement rates between the two treatment groups in the age group 31-60 years. The effect of the ND was statistically better than that of SD. Statistical difference was not observed when the analysis was done for the combined age group.

However, if there are many confounding factors, say 5 factors, each having two sub-groups we will have 10 tables for analysis adjusting for only one variable at a time. If all the 5 confounding factors have to be considered together, there will be 2^5 (32) tables for which analysis has to be done for 32 tables and it will be difficult for interpretation of the results.

Mantel-Haenzel method of Chi-square may be applied to adjust for a few confounding factors and to get a p-value for statistical significance after adjusting for the confounding factors. However, the best method to take care of many confounding factors and to get a p-value for statistical significance after adjusting for all the confounding factors, Multivariate logistic regression analysis can be done. In this analysis the inter-associations among all the confounding variables and with the type of treatment will be taken care of in the comparison of treatment effects between the treatment groups. For example, comparing the improvement rates in vision between two treatment approaches, adjusting for the confounding variables such as age, gender, nutritional status, eye care, duration of watching TV etc. A description of this analysis is beyond the scope of this chapter and hence the books given under references may be referred for the details of this analysis.

(B) STATISTICAL METHODS IN SCREENING AND DIAGNOSTIC TESTS

In Epidemiological studies diagnostic tests play a very important role based on clinical observations or on laboratory techniques, by means of which individuals are classified as healthy or having the disease under investigation. This forms a part of the screening programme in Epidemiological studies for early diagnosis of the disease. The test should be as far as possible, simple one, which will be feasible in the field set-up. The suspected cases will be referred for further clinical and laboratory tests for more accurate diagnosis.

One of the principal goals in the practice of medicine or in a clinical trial or in an epidemiological study is to make as far as possible, as close as possible and as accurate as possible the correct diagnosis based on various clinical and laboratory tests. In this process care should be taken to avoid, again as far as possible to declare him/her as a case falsely or to declare him/her as a normal falsely. That is --- if it cannot be completely avoided, the efforts should be taken to minimise the probability of the wrong classification. The aim should be to minimise the magnitude of uncertainty as low as possible. Since the diagnosis based on the information obtained is a probabilistic computation, the process of making diagnosis is known as – diagnostic reasoning or clinical decision making.

The major criteria of the screening test are – Validity of the test, easy applicability, acceptability and less costly.

Validity of a screening test is measured by its ability to correctly categorize persons who have the disease as test positive and those without the disease as test negative. These are measured by the Sensitivity, Specificity and Predictive values of the positives and negatives and accuracy by the test.

Analysis
Type of variable
In most of situations the test under investigation could be of discrete type. For example, test is positive or negative. Some investigations are of continuous type such as cholesterol, hemoglobin, albumin, heart rate etc.

Discrete variable
For easy analysis and interpretation it is better to arrange the data in a 2 x 2 Contingency table.

Gold standard
The method / procedure that is used to define the true state of the person examined - the most accurate diagnosis for confirming the presence of the disease.

Example
For evaluating a certain serological test for diagnosis of pulmonary tuberculosis, the Gold standard could be the result of sputum culture for mycobacteria.

Index Test
The test whose validity / discrimination power is to be
investigated in comparison to the gold standard. Without a gold standard a new test cannot be tried upon and recommended for use.

**Table-1: 2 x 2 --- Contingency Table**

<table>
<thead>
<tr>
<th>TEST</th>
<th>GOLD STANDARD ( TRUE )</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>--</td>
</tr>
<tr>
<td>+</td>
<td>a (TP)</td>
</tr>
<tr>
<td>--</td>
<td>c (FN)</td>
</tr>
<tr>
<td>b (FP)</td>
<td>d (TN)</td>
</tr>
</tbody>
</table>

TP = True positives (both test & disease positive) = a
TN = True negatives (both test & disease negative) = d
FP = False positives (test positive, but, disease negative) = b
FN = False negatives (test negative, but, disease positive) = c

Total positives by the GS = a + c
Total negatives by the GS = b + d
Total positives by the Test = a + b
Total negatives by the Test = c + d

Validity of an index test is mainly judged in terms of FIVE parameters: 
Sensitivity, Specificity, Predictive values of the positives (P+) & the negatives (P-) and Accuracy

Sensitivity = Proportion of the diseased cases rightly detected as diseased by the test = TP / total positives by the GS = a / (a + c)
Specificity = Proportion of the non – diseased rightly detected by the test as non – diseased = TN / total negatives by the GS = d / (b + d)
P+ = TP / total positives by the test = a / (a + b)
P- = TN / total negatives by the test = d / (c + d)

Accuracy = Proportion of those correctly detected as diseased/ non – diseased by the test = (a+d)/(a+b+c+d)

Higher the Sensitivity, lower the false negatives will be. Similarly higher the Specificity, lower the false positives will be.

For a good test a careful analysis is required keeping in mind the importance of sensitivity over specificity or vice-versa, keeping the right balance between them and also keeping the predictivity of the test in mind.

If we don’t want to miss a case, sensitivity should be as high as possible. If we don’t want that unnecessarily a normal should not be declared as a case, specificity should be as high as possible. At the same time the test should yield high predictivity of positives & negatives.

Sensitivity is influenced by the severity of the disease. Any test result is more likely to be positive in advanced stages of the disease. Specificity is influenced by the state of heath in the non-diseased sample.

Predictive values of the Positives and Negatives by the test are very important in evaluating a screening test. Predictive values of the Positives (P+) measures the Probability that a person actually has the disease given that he/she tests positive. Predictive value of the Negatives (P_) measures the Probability that an individual is truly disease free given that he/she tests negative by the screening test. Predictive values are affected not only by the Validity parameters, but also by the population characteristics to which the test is applied. For rare diseases, the major determinant of P+ is the prevalence rate. In such a situation, the results that are positive will mostly be false positives. Predictivity of a test closely depends upon the prevalence of the disease, even if the sensitivity & specificity remain constant. As the prevalence increases, positive predictivity increases, But, negative predictivity decreases. If the P+ & P_ are low (false positives & false negatives are more ), the test will have lesser validity.

While Sensitivity and Specificity refer to the Accuracy of the test, P+ and P_ refer to the estimation of the Probability of the presence or absence of the disease.

The computation of the Validity parameters are explained for the following data:

**Table-2: Results of a simple & easy vision test for visually impaired (with confirmed test done in hospital) in school children are given below:**

<table>
<thead>
<tr>
<th>Simple field test (B)</th>
<th>Visual impaired (A)</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td></td>
<td>80</td>
<td>60</td>
<td>140</td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td>20</td>
<td>4840</td>
<td>4860</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>100</td>
<td>4900</td>
<td>5000</td>
</tr>
</tbody>
</table>

Sensitivity of B = 80/100 = 80.0 %
Specificity of B = 4840/4900 = 98.8 %
P+ of B = 80/140 = 57.1 % False positives = 42.9 %
Only 1 out of 2 children who had the test positive had Visual impairment.
P of B = 4840/4860 = 99.6 % False negatives = 0.4%

Virtual all children whose test was negative were free from Visual impairment.

Obviously, it would be desirable to have a screening test with high sensitivity and specificity. But, usually that won’t be possible and generally there would be a trade-off between these two parameters. The criteria for fixing acceptable values for these two parameters depend upon weighing the consequences leaving cases undetected (false negatives) against erroneously classifying those not having the disease as diseased (false positives). Sensitivity should be increased at the expense of specificity when the penalty associated with missing a case is high such as when the disease is serious and definitive treatment exists. Specificity should be increased relative to sensitivity when the costs of risks associated with further diagnostic tests are substantial, such as breast cancer for which definitive diagnostic evaluation is biopsy.

After the validity of the test has been evaluated, its reliability should be studied. Reliability of a test refers to consistency of results when repeat examinations are performed on the same persons under the same conditions. Four sources of variability can affect the reproducibility of the results of a test—biological variation (inherent in nature), instrument variability, intra-observer variability and inter-observer variability. While the biological variation cannot be manipulated, the other types of variation can be minimized by standardization of instruments and techniques and giving appropriate training for measuring and recording the information to the staff who are involved in doing and evaluating the screening tests.

Feasibility of the screening test is determined by many factors such as acceptability by the screenees, cost of effectiveness, time and transport and testing facilities available. While Pap smear test may be easier and acceptable for detecting cancer, sigmoidoscope for detecting colon cancer may be more difficult and non-acceptable and costlier.

Likelihood –Ratio (LR)

A simpler expression for measuring the results of Diagnostic tests is by computing the Likelihood Ratios (LR). LR is defined as follows:

\[
\text{LR} = \frac{P(\text{test is positive in diseased})}{P(\text{test is positive in non-diseased})} = \frac{\text{True positive rate}}{\text{False positive rate}}
\]

\[
\text{LR} = \frac{P(\text{test is negative in diseased})}{P(\text{test is negative in non-diseased})} = \frac{\text{False negative rate}}{\text{True negative rate}}
\]

LR is a very useful way to characterize diagnostic information. The clinician / epidemiologist needs to remember only one parameter value instead of two parameters and it is easy to interpret the meaning of this parameter.

Example: for the data given in Table-2

\[
\text{LR} + = \frac{\text{Sensitivity}}{1 - \text{Specificity}} = 0.8 / 0.012 = 66.7
\]

\[
\text{LR} - = \frac{1 - \text{Sensitivity}}{\text{Specificity}} = 0.2 / 98.8 = 0.2
\]

The test result would be expected to be positive in 66.7 children with visual impairment as compared to a positive result in a person without visual impairment.

The test result would be expected to be negative in 5 children without visual impairment as compared to a negative result in one child with the visual impairment.

Larger is the value of LR+, the stronger the association between having a positive test result and having the disease and thus better the diagnostic value of the test. Similarly, smaller the value of LR, stronger is the association between having the negative test result and not having the disease and thus better the diagnostic value of the test. It has been shown that a value of 10 or greater for LR+ and a value of 0.1 or less for LR can be considered as an indication of a test with high diagnostic value. Likelihood ratios do not vary according to the prevalence of the disease.

Continuous variables

Validity parameters can be computed for different cut-off points of the values of the continuous variable and a trade-off between sensitivity and specificity can be done to arrive at an ideal cut-off point. This is done by plotting a curve taking Sensitivity along the Y-axis and (1 – Specificity) along the X-axis. The resulting curve is called ---Receiver operating characteristic curve (ROC curve).

ROC curve is a graphical method for depicting the trade-off between True positive rate and False positive rate. A summary index of overall test performance can be computed as the area under the ROC curve. The greater the area, the better the test performance. The highest possible value for the area under the ROC curve is 1, which is equivalent to a perfect test. The area under the diagonal line corresponds to a test that does not distinguish between persons with & without the disease of interest. The closer an ROC curve is to the upper left hand corner of the graph, the more accurate it is, because the true positive rate is 1 and the false positive rate is zero. ROC curves are useful graphic methods for comparing two or more diagnostic tests.

Example:- Table:3

The validity parameters of a test variable for different cut-off
points are as follows:

<table>
<thead>
<tr>
<th>Cut-off Value</th>
<th>Sensitivity</th>
<th>(100 - Specificity)</th>
<th>LR +</th>
<th>LR -</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>95</td>
<td>90</td>
<td>1.05</td>
<td>2.00</td>
</tr>
<tr>
<td>10</td>
<td>90</td>
<td>60</td>
<td>1.50</td>
<td>4.00</td>
</tr>
<tr>
<td>15</td>
<td>80</td>
<td>40</td>
<td>2.00</td>
<td>3.00</td>
</tr>
<tr>
<td>20</td>
<td>75</td>
<td>25</td>
<td>3.00</td>
<td>3.00</td>
</tr>
<tr>
<td>25</td>
<td>60</td>
<td>10</td>
<td>6.00</td>
<td>2.25</td>
</tr>
<tr>
<td>30</td>
<td>50</td>
<td>5</td>
<td>10.00</td>
<td>1.90</td>
</tr>
</tbody>
</table>

The cut-off value 20, with a sensitivity and a specificity of 75%, could be a better cut-off value as compared to all other cut-off values, even though LR+ is much lesser than 3 and LR- is much higher than 0.1.

A summary index of overall test performance can be computed as the area under the ROC curve. The greater the area, the better the test performance. The highest possible value for the area under the ROC curve is 1, which is equivalent to a perfect test. The area under the diagonal line corresponds to a test that does not distinguish between persons with & without the disease. The closer an ROC curve is to the upper left hand corner of the graph, the more accurate it is, because the true positive rate is 1 and the false positive rate is zero. ROC curves are useful graphic methods for comparing two or more diagnostic tests.

(1) Proportion = a / (a+b)

Example:
- a: No of smokers who have lung cancer
- b: No of smokers who didn’t have lung cancer

\[
\text{a / (a+b) = Proportion of smokers with lung cancer}
\]

(2) Odds = \( \frac{a}{b} \)

Example: Ratio of lung cancer cases to non-cases in smokers.

Similarly, BENEFIT of an event due to a factor can be expressed in two ways

(1) Proportion = a / (a + b)

Example:
- a: No of patients who responded to the drug positively
- b: No of patients who didn’t respond to the drug positively

\[
\text{a / (a + b) = Proportion of patients who responded to the drug positively.}
\]

(2) Odds = a / b

Example: Ratio of responded to the non-responded in those patients who received the drug.

Combining these two measures-(proportion and odds), literature searching and gathering all available information (evidence) and applying formal scientific & statistical methods in evaluating the clinical literature.

Easy access to the computer and Internet facilities, literature search has become much easier and faster. This is a method which helps the clinicians in making decisions about the care of individual patients using the current best evidence concisely, explicitly & judiciously.

While reviewing the evidences in clinical trials and epidemiological investigations, several important questions need to be asked before taking a decision: similarity of the groups to be compared, at the start of the study, allocation of patients to different groups, whether random or not, validity of the diagnostic tests, drop out rate, the results on the treatment effect, its precision, its clinical importance and applicability etc.

**STATISTICAL METHODS IN EBM**

One of the important statistical method commonly used in EBM is the RISK ANALYSIS.

Risk of an event due to a factor can be expressed in two ways – Proportion or Odds

(1) Proportion = \( \frac{a}{a+b} \)

Example:
- a: No of smokers who have lung cancer
- b: No of smokers who didn’t have lung cancer

(a+b): Total no of smokers with or without lung cancer

\[
\frac{a}{a+b} = \text{Proportion of smokers with lung cancer}
\]

(2) Odds = \( \frac{a}{b} \)

Example: Ratio of lung cancer cases to non-cases in smokers.

Similarly, BENEFIT of an event due to a factor can be expressed in two ways

(1) Proportion = \( \frac{a}{a+b} \)

Example:
- a: No of patients who responded to the drug positively
- b: No of patients who didn’t respond to the drug positively

\[
\frac{a}{a+b} = \text{Proportion of patients who responded to the drug positively.}
\]

(2) Odds = \( \frac{a}{b} \)

Example: Ratio of responded to the non-responded in those patients who received the drug.

Combining these two measures- (proportion and odds),
META – ANALYSIS IN CLINICAL RESEARCH

Meta – analysis has been defined as the ‘Statistical analysis of a collection of analytic results for the purpose of integrating the findings’. The last few years have seen rapidly increasing interest in meta – analysis in the medical research literature. The results from a collection of independent randomized studies can be summarized in a systematic and quantitative way using a meta – analysis.

The main objective of such an analysis is to obtain information about treatment effects that cannot be ascertained from any of the studies taken alone. Any individual study may either be too small to detect moderate treatment effects, say on mortality, or too limited to allow generalization to other patient populations. We should like to know, overall, whether a treatment has a beneficial or harmful effect. Reviews of treatment or therapeutic areas are frequently carried out when new compounds are developed. They could perhaps benefit from such a quantitative approach in addition to qualitative and subjective summaries.

A meta – analysis can be viewed as an extreme form of multi – center study. There is a continuum from the true multi – center study, in which all centers follow an identical protocol, to a collection of studies addressing the same general therapeutic question but in results obtained from different independent studies caution has to be taken w.r.t. the design,objectives,inclusion & exclusion criteria of patients,drug delivery etc.This poses problems in getting similar studies for applying Meta-analysis.

OBJECTIVES OF META ANALYSIS

• To enhance power by increasing the size of sample which may not be large enough in individual studies especially in a rare medical condition.
• To restore uncertainty when the reports disagree.
• To improve estimates of effect size.
• To answer questions (not always possible) not posed at the start of individual trials.

These functions are particularly applicable to randomized control trials, because such trials are often too small to detect clinically important differences.

There are a number of reasons why Meta analysis is an important technique in Clinical Trials .It is now recognized that narrative reviews of a set of clinical trials can be misleading, being potentially distorted by the selection of evidence -mainly those providing positive results which might include small and large studies, randomized and non-randomized trials and inadequately analysed trials.

The human mind is not equipped to consider simultaneously a large number of alternatives.Confronted with the results from a large number of studies, giving different results, some significantly favouring one type of treatment, some favouring another treatment and some giving statistically non-significant results, it would be difficult to comprehend them and take a decision. Yet that is exactly the scope of the problem faced by a researcher attempting to integrate the results from a large number of studies.

Meta analysis will help us in reviewing systematically the available evidences,to provide quantitative summaries of the results from each study, to combine these results applying valid statistical analysis and to provide over all interpretation to help the clinicians and pharmacologists to take valid clinical decisions.Combining results will provide more statistical power and precision for detecting treatment effects.

Systematic reviews of articles on and related to the study variables is an important primary task the researcher has to do before attempting meta-analysis.Cochrane Library is the main source of gathering information on various clinical trials .There are many Centres of Cochrane Library at different Geographical sites such as New England Cochrane Centre, Australasian Cochrane Centre, Canadian Cochrane Centre, U.K. Cochrane Centre, French Cochrane Centre and so on.Various information related to several clinical studies have been stored systematically for the benefit of the researchers.

META ANALYSIS MODELS

While combining results from various studies we come across two types of variation viz; Within Study Variation & Between Study Variation. Fixed Effect Model is applied if only Within study variation need to be considered and the statistical analysis normally applied is Mantel-Haenzel method . Random Effect Model is applied if both within and between study variation has to be considered and the statistical analysis normally applied is :Dersimonian & Laird method.

If Between Study Variation is substantial relative to Within Study Variation larger studies will get more weightage under Fixed Effect Model than in Random Effect Model. In Random Effect Models,weights given to each Trial are more evenly distributed and small Trials get relatively more weight. Confidence Limits in Fixed Effect Model will be narrower than in Random Effect Model.Discussion on the details of doing the analysis applying these methods is beyond the scope of this article in the Journal.A typical way of presentation on the combined results based on the results from various studies is by drawing the Forest Tree as follows:

Suppose there are 9 studies considered for Meta-analysis and the study parameter is Odds of improvement in the condition
of the patient with drug-A as compared to the improvement in the condition of the patient with drug-B. Each line in the Forest Tree indicates the 95 % Confidence limits of Odds ratio which is marked by a dot. The diagram shows that odds of improvement is better with drug-A (left hand side of the Centre line) than drug-B (right hand side of the centre line) in most of the 9 studies except in the 8th study and to some extent in the first and 9th studies.

By applying both the Fixed effect & the random effect models, the combined Odds ratio, with 95 % Confidence limits, shows that drug-A is better than drug-B w.r.t. the improvement rate.

BOOKS FOR FURTHER READING


NOTE:
This is the last chapter in my presentation on "Biostatistics- Principles and Methods", applied to Medical Research. I hope that the readers are/will be benefitted from the presentation of various applications of Biostatistical methods described in the Eight chapters in planning their research projects/Thesis reports and in analysing their data applying appropriate statistical methods and thus helping them in conveying their research findings systematically with statistical & scientific validity. The readers may contact me through E-mail for any clarification or any query w.r.t. any aspect covered in the various chapters. Needless to mention I enjoyed writing these chapters with many examples in research in Ophthalmology and in that process I learned a lot in the field of Ophthalmology, especially the important terms and terminologies in this important branch of Medicine. Let me use this opportunity to express my Good Wishes to all the Ophthalmologists, especially the researchers, meaningful, scientifically and statistically valid and useful research for the benefit of the people, especially the patients.

Prof Sundaram was previously the Head of Biostatistics at All India Institute of Medical Sciences. Currently he heads the Department of Biostatistics at Amrita Institute of Medical Sciences, Kochi.
Management Of Choroidal Neovascularisation In Choroidal Osteoma

Introduction
Choroidal osteoma is believed to be first described at the 1975 Meeting of Verhoeff Society but the term choroidal osteoma was coined by Gass in 1978 when he described four healthy young women with characteristic ophthalmoscopic findings of slightly elevated, yellowish, choroidal tumour with sharp geographic borders. These tumours demonstrate evidence of bone formation in the choroid and are believed to be choristomatous in origin. It is commonly juxtapapillary or peripapillary, but may extend to the macula. It is rare that it would be found only in the macula. The shape is commonly oval or round with well defined scalloped or geographic margins. Occasionally decalciﬁcation can occur and is characterized by thin, atrophic, yellow-gray regions with associated RPE atrophy. Decalciﬁcation can occur spontaneously or as a result of laser photocoagulation or PDT. Choroidal neovascular membranes (CNVM) can also develop. The majority of patients with choroidal osteoma maintain good vision. Long term poor visual acuity in patients with choroidal osteoma is associated with subretinal ﬂuid, RPE alterations, and subretinal hemorrhage from choroidal neovascularization. In a follow-up study of 36 patients, the probability of loss of visual acuity (20/200 or worse) was more than 50% by 10 years. Choroidal neovascularization is the most frequent cause of visual loss in choroidal osteoma with more than half of the patients expected to develop choroidal neovascularization. Management of choroidal neovascularisation in this entity has been difﬁcult and various modalities of treatment have been reported with variable success. Combination therapy is likely to be an effective therapy in the management of this often resistant CNVM and very reports are available in the literature. This case report is on combination therapy in the management of CNVM in a young patient with choroidal osteoma.

Case report
A 25 year old male patient presented to us with complaints of metamorphopsia and defective vision in his left eye of two weeks duration. There was no associated pain or redness. He had no known systemic illness. On examination his best corrected visual acuity in the right eye was 6/6, N6 and in the left eye with -0.50 DCyl 900 was 6/12, N9. Colour vision was normal. Amsler grid examination of left eye revealed wavy gridlines infero-temporal to fixation. Anterior segment was unremarkable. Intraocular pressure was 16 mm Hg in right eye and 14 mm Hg in the left eye. Right eye fundus was normal. The left eye showed a well-circumscribed orange-red lesion around 5 DD in size, superotemporal to the optic disc with the inferior edge adjacent to the superior disc margin. Subretinal haemorrhage was present near the inferotemporal edge of the lesion just superior to the fovea with sub-retinal ﬂuid (SRF) spreading to the fovea (Fig 1).

Address for correspondence: Vitreo-retinal Consultant, Chaithanya Eye Hospital & Research Institute, Trivandrum, Kerala
Email: soman.manoj@gmail.com
Fig 3; HRA FFA showing the classic extrafoveal CNVM with early bright well defined hyperfluorescence (A) and intense late leakage (B).

Fig 4; HRA ICG imaging showing the relative hypofluorescence of the osteoma(A) with late staining (C) and the classic hot spot extrafoveally with an adjacent point of increased fluorescence (B) seen clearly in the late phases (D).
Spectral domain HRA OCT revealed thickening above the RPE at the site of CNVM and shallow subretinal fluid at the fovea (Fig 2). B Scan revealed highly echogenic lesion 7.52 mm in diameter and 1.94mm in thickness above the optic disc with significant back shadowing suggestive of calcification. A-scan ultrasonography showed a high spike corresponding to the anterior surface of the lesion suggestive of choroidal osteoma (Fig 5). Simultaneous FFA + ICG angiography was done. The lesion showed persistent hypofluorescence corresponding to the osteoma with an area of early well defined hyperfluorescence that increased towards the later phases in FFA suggestive of CNVM (Fig 3). The ICG showed another small hotspot in ICG near the inferior edge of the primary hyperfluorescent lesion (Fig 4). A diagnosis of Choroidal Osteoma with secondary predominantly classic extra-foveal choroidal neovascular membrane (CNVM) was made. Intravitreal bevacizumab 1.25 mg/0.05 cc was injected under sterile precautions and 2 weeks later focal laser was done for the extrafoveal CNVM. On subsequent follow up after one month, Fundus examination showed scarred CNVM and OCT revealed complete resolution of SRF and retinal oedema (Fig 6). Subsequently he was kept under observation with Home Amsler monitoring. The Vision remained stable at 6/6, N6 with correction, with regressed CNVM (Fig 7) and static osteoma until the completed 12 months follow up.

Fig 5; B scan showing the highly reflective lesion in the RCS complex with significant back shadowing (A), clearly seen at low gain (B).

Fig 6; HRA OCT through the CNVM showing regression (A) and dry fovea (B) at 1 month.

Fig 7; clinical photo showing scarred CNVM (A) and OCT showing dry fovea (B) at 12 months follow up.
Discussion

The etiology of the choroidal osteoma is unknown. Factors implicated in its development, however, include inflammation, trauma, hormonal state, calcium metabolism, environment, and heredity\(^1\)-\(^3\),\(^4\). None of these factors appear to be either a sole, or an established factor in causing patients to develop the condition. For instance, the hormonal hypothesis does not explain why males are affected by the condition or why these lesions can be observed in pre-pubertal patients. It has been postulated that choroidal osteoma is a choristoma\(^5\), i.e., normal tissue arising at an abnormal location, but this explanation begs the question of why females are affected more frequently than males and why there is continuous development and growth of the lesion in adulthood. No consistency has been established with serum calcium, phosphate, or alkaline phosphatase levels\(^6\). The reasons for vision loss from choroidal osteoma include CNV, subfoveal fluid, and photoreceptor degeneration\(^7\),\(^8\). The cause of CNV development is unknown. It has been hypothesized that the thinned, degenerated retinal pigment epithelium overlying the osteoma allows the growth of new blood vessels\(^8\).

Several treatments are tried but with limited success. Laser photocoagulation of CNV associated with choroidal osteoma was less effective owing to depigmentation of RPE that often reduces the absorption of laser energy\(^9\),\(^10\). The surgical removal of subfoveal CNV has been performed successfully, but the visual result has been poor\(^1\). Recently, PDT and transpupillary thermotherapy have been tried, but the visual result are variable\(^1\),\(^2\),\(^3\),\(^4\),\(^5\),\(^6\),\(^7\). Intravitreal bevacizumab has been given and improvement of visual acuity and regression of CNV was observed in a few reports\(^1\),\(^2\),\(^3\),\(^4\). Ranibizumab has also recently been been used successfully for the treatment of CNV secondary to choroidal osteoma either as monotherapy\(^5\),\(^6\),\(^7\) or as part of combination therapy\(^8\).

As monotherapy with antiVEGF agents have not been effective in all series and because these CNV are often extrafoveal and PDT is an expensive therapy in our part of the world, combination therapy of intraocular bevacizumab and focal laser in these resistant CNV. Also subfoveal CNV cannot be treated with conventional laser treatment and these patients may require photodynamic therapy.

References

Nutritional anemia as a cause of vision loss in developing countries: A case report

Anusha Venkataraman MD(AllIMS), DNB, FICO(UK), FRCS( Glasg)
Bijnya B Panda MS, FICO (UK), Anupam Dey MD

Abstract
We report the case of a 43 year old male patient who presented with sudden, non progressive loss of vision in the right eye. An ophthalmological evaluation revealed the presence of bilateral flame shaped hemorrhages, Roth’s spots with cotton wool spots with subhyaloid hemorrhage involving the macula in the right eye. Hematological evaluation revealed the presence of iron deficiency anemia with megaloblastic anemia. This case documents the occurrence of anemic retinopathy in dimorphic nutritional anemia and its rapid resolution following treatment with Vitamin B12 and iron.

Introduction
Anemia has varied ocular presentations that include conjunctival pallor, retinal flame shaped or white centred hemorrhages, sub hyaloid hemorrhages, cotton wool spots, dilated retinal veins, disc edema and cotton wool spots.1 We report a case of a patient with nutritional anemia who presented with decreased vision due to subhyaloid hemorrhage and showed rapid improvement in vision with signs of resolution within a week of correction of the underlying systemic condition.

Case Report
A 43 year old male patient presented to the outpatient department of a tertiary level hospital in Odisha with a complaint of sudden non progressive decreased vision in the right eye of three days duration. There was no history of trauma or long term intake of any systemic medication. The patient was a vegetarian by diet. He also gave a history of donation of 10 pints of blood over the last 10 years.

On examination, his Best Corrected Visual Acuity (BCVA) in the right eye was 6/36 and in the left eye was 6/6. His anterior segment findings were unremarkable, except for marked conjunctival pallor. Fundus examination showed the presence of flame shaped haemorrhages, with Roth spots and cotton wool spots in both the eyes. Macula of the right eye showed subhyaloid haemorrhage (Fig 1A&B). The intraocular pressure in both the eyes by non contact tonometry was 12 mmHg. Systemic examination revealed no organomegaly. A diagnosis of anemic retinopathy was entertained and he was further investigated for the cause of anaemia.

His haemoglobin level was 4.4 gm% with a hematocrit of 14.7%. He had an RBC count of 0.80 million / cumm, platelet count of 36,000 /cumm and a total leucocyte count of 4030/cumm. The MCV was 107 fl, MCH 29.7 pg and MCHC was 32.9 gms/dL. His bleeding time, clotting time and prothrombin time were normal. The peripheral blood smear report suggested features of dimorphic nutritional anaemia as evidenced by the presence of moderate hypochromasia with moderate to severe anisocytosis with microcytes and macroovalocytes, moderate poikilocytosis with tear drop cells, schistocytes, pencil cells and pessary cells, hypersegmented neutrophils and thrombocytopenia. S. A value of 179 pg/ml on serum Vitamin B12 assay confirmed the diagnosis of a co-existent megaloblastic anaemia with iron deficiency anemia.

He was treated with 2 pints of packed cell transfusion with intravenous vitamin B12 injection 1000 μg daily for 5 days, then every week intravenously for 1 month, then was advised to take injections once every 3 months for 2-3 years. Iron supplementation was also instituted. His haematological parameters improved. After one week of treatment, the laboratory parameters were as follows: haemoglobin 8.6 g/dL, total leucocyte count 5800/mm3, platelet count 100,000/mm3. The vision in the right eye had also improved to 6/18 with the subhyaloid hemorrhage showing signs of resolution. At one month follow up, his vision improved to 6/9 with resolution of the subhyaloid hemorrhage and stabilization of the hematological parameters (Figure 2)

Discussion
The pathogenesis of anemic retinopathy has been attributed to factors such as anoxia, venous stasis, angiospasm and increased capillary permeability with a higher prevalence in patients with Hb< 6g/dl.2,3 The co-existence of thrombocytopenia is known to be associated with a more severe manifestation.4 Thrombocytopenia in vitamin B12 deficiency, as noted in our case, is due to impaired DNA synthesis leading to ineffective thrombopoiesis. Vitamin B12 deficiency is also known to be associated with hemorrhagic
manifestations as bleeding from skin, subcutaneous tissue, epistaxis and even threatening haemorrhage from gut as well as intracerebral bleed, requiring emergency blood transfusion. The response to vitamin B12 in such cases is dramatic with rapid resolution of ocular hemorrhages and stabilisation of hematological parameters. The only source of vitamin B12 being of animal origin i.e, egg, fish and diary products, pure vegetarians are prone to develop this deficiency. The occurrence of iron deficiency anemia along with megaloblastic anemia in our patient was further worsened by repeated blood donations.

Very few cases of retinopathy due to megaloblastic anaemia have been reported from India. Megaloblastic anaemia induced retinopathy has also been reported from Africa and in alcoholics due to the combined deficiency of folate and Vitamin B12. The purpose of this report is to highlight the occurrence of anemic retinopathy due to nutritional deficiency in developing countries. This case, may represent just the tip of the iceberg, and hence calls for establishment of stringent screening protocols for the identification of nutritional anaemia in developing countries and mandatory fundus examination of the identified subjects for anemic retinopathy. This report also re-iterates the fact that ophthalmic manifestations of anemic retinopathy do not need any specific treatment other than systemic management.

References

Outer lamellar hole with severe visual loss following High Tension Electric shock

ABSTRACTS
The authors report a case of macular cyst following electric shock by high tension current with serial SD-Optical Coherence Tomography and its natural history to outer lamellar hole leading to irreversible loss of vision.

INTRODUCTION
Tissue damage from electric shock may occur through one or more mechanisms: transmission of electric current directly through tissues, conversion of electrical energy to thermal energy, which is subsequently absorbed by the tissues, or end organ ischemia caused either by generalized vascular constriction or cardiac arrhythmia. The extent of damage to the tissues depends on the intensity of the current, duration of the tissue exposure, and the tissues resistance to the current. Resistance is variable in different body tissues and is known to be the greatest in bones with decreasing resistance in fat, tendon, skin, muscles, blood vessels and nerves. For ocular tissues, retina and optic nerve have a low resistance and thought to be primarily affected by ischemia resulting from coagulation and necrosis of vascular tissues that feed them.

CASE REPORT
A 39 years old otherwise healthy male present to outpatient department with defective vision in both eyes following electric shock from high tension wire since 11 days. Visual loss typically started after day 3 following electric shock. He had grade 1 burns over both the hands. He had giddiness, headache, vomiting following the episode for which he was medically managed. Computerized tomography of brain was normal. There are was no history of sun gazing, exposure to welding arc or solar eclipse previous to this episode.

His best corrected visual acuity in right eye and left eye was 20/60 and 20/40 respectively. Anterior segment examination showed anterior capsular changes in both eyes (fig.1A and 1B). Fundus examination (2A & 2 B) showed cystic changes at the fovea which was confirmed on OCT (2C &2D), which also showed IS-O5 junction defect. There was no evidence of vitreomacular traction or posterior hyaloid separation. Fundus camera based autofluorescence (Topcon TRC 50 DX) imaging showed increased central hypoautofluorescence surrounded by decreased parafoveolar hypoautofluorescence (2E & 2F).

On his subsequent visit after 3 months, his BCVA was dropped to 6/24 in RE and 6/36 in LE, which is partly attributed to anterior and posterior diffuse subcapsular cataract (fig. 3A &3B).

OCT of both eyes showed outer lamellar hole(fig. 3C & 3D) on his last visit.

FIGURE 1
Figure (A) and (B) shows anterior segment imaging of both the eyes. Early anterior subcapsular changes (indicated by arrow) in right and left eyes respectively.
FIGURE 2 (For description see next page)

FIGURE 3
FIGURE 2

Figure (A) and (B) shows color fundus images of posterior pole demonstrating pale yellow spot at the center of the fovea in both the eyes. Spectral Domain Optical Coherence Tomography (horizontal 6 mm scan) shows outer lamellar defect with few cystoid changes just below internal limiting membrane and hyperreflectivity at the level of Retinal pigment epithelium in right eye (C) and cystoid edema with with cystic changes in inner nuclear layer along with interruption of external limiting membrane and inner segment and outer segment junction in the left eye (D). Central macular thickness was 206µin OD and 310µ in OS. Fundus camera-based autofluorescence images showed increased central hyperautofluorescence corresponding outer lamellar defects and decreased hypoautofluorescence in perifoveal region (E) and (F).

Discussion

Electric current can injure a tissue by several mechanisms. First, it can directly destroy cells and body structure. It can also damage retinal pigment epithelium by electrolysis. Second, melanin retinal pigment epithelium offers resistance to electric current which produces heat causing thermal injury.1,2 Localized inflammation in response to injury could contribute to pigment epithelium dysfunction. Third, damage to the posterior pole can occur by shock wave generated by lightning strike.3 The homeostasis of the retina could be compromised by mechanical, thermal, or inflammatory injury. Intraretinal edema could result from injury to Müller cells, which are involved in the active transport of fluid out of the retina.7

Cataract formation is the most common sequel of electric burn and can present in 5% cases of electric shock above neck region.8 Hinda JT et al reported a case of lightening maculopathy with cystic changes at the fovea along with diffuse posterior subcapsular cataract which progressed subsequently in both eyes. However, 14 month after injury and cataract extraction, visual acuity of 20/20 was noted in both eyes.8 Campo and Lewis reported a case of full thickness macular hole following lightning strike with visual acuity of 20/40, however, Watzke Allen test was not reported in the study and OCT was not available then.10 None of these reports of lightning induced macular cyst or macular hole have OCT documentation for confirmation.

Shukla et al have reported a case of lightning maculopathy following visualization of distant lightning strike. SD-OCT images showed central hyperreflective echoes with disruption of inner segment and outer segment junction in each eye. Fundus autofluorescence images showed bilateral increased hypoautofluorescence and decreased parafoveal hypoautofluorescence.11 However, by 12 months visual acuity returned to 20/20 with IS-OS disruption on SD OCT findings.

We believe the damage to outer retina at the fovea was caused by thermal reaction to resistance posed by retinal pigment epithelium to passage of electric current. We don’t know that why it was concentrated only on the fovea.

References


Abstract
Novel spectral Domain optical coherence tomography findings leading to new insights into the pathogenesis of Acute Posterior multifocal placoid pigment epitheliopathy.

Purpose
To analyze the spectral Domain optical coherence tomography (SD-OCT) findings in acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and to correlate it with the pathogenesis of the disease.

Methods
Prospective observational case series of 8 eyes of 5 consecutive patients diagnosed with acute posterior multifocal placoid pigment epitheliopathy. All patients underwent complete ophthalmic examination, fundus photography, fluorescein angiography (FA) and SD-OCT at initial visit. During the course of the disease and after resolution, ophthalmologic examination and SD-OCT were repeated. The SD-OCT scans were taken through the lesions seen clinically and on FA.

Results
In the acute stage all the 8 eyes had Inner Segment-Outer Segment (IS-OS) junction abnormalities in the form of undulations, thickening and irregularity at the edge of the lesion which got separated from the retinal pigment epithelial (RPE) layer towards the centre of lesion. The IS/OS junction was elevated as a dome in 4 eyes where there was significant sub-retinal pooling of dye on FA. 5 eyes had retinal pigment epithelial (RPE) changes in the form of irregularity, thickening or undulations. All the 8 eyes had involvement of outer plexiform layer (OPL) with splitting of the same at the edge of dome shaped elevation in two eyes. On resolution all eyes had prominent changes in the IS/OS junction in the form of irregularity, discontinuity and thinning at the site of lesion. There was decrease in thickness of outer nuclear layer (ONL) in all cases. Significant RPE abnormalities were seen only in 2 eyes. Eyes with significant thinning of outer retinal layers showed falling of inner retinal layers into the area of thinning.

Conclusion
In the acute and healed stages of APMPPE most significant changes appeared in the IS/OS junction of the retina in all 8 eyes. RPE changes were less significant compared to that of photoreceptors pointing to the primary involvement of photoreceptors in the pathogenesis of disease. Based on these we conclude that in APMPPE early and primary insult may occur in the photoreceptors.

Acute Posterior multifocal placoid pigment epitheliopathy is an idiopathic bilateral self limiting inflammatory disorder of the retina and choroid affecting young healthy adults as described originally by Gass1. Visual disturbances are caused by multiple round to oval yellowish white placoid lesions located at the posterior fundus. This is usually associated with a viral prodrome and typically resolves in 2-3 weeks leaving discrete pigment epithelial scars. Recently a few case reports have described atypical features like serous retinal detachment, unilaterality and papillitis which are intermediate between APMPPE and Haradas disease2. The purpose of this article is to describe the SD-OCT findings in APMPPE in the acute stage and after resolution.

Material and Method
This was a prospective observational study of 8 eyes of 5 consecutive patients diagnosed with APMPPE. The patients were evaluated at the uveitis service of Giridhar Eye Institute between July 2011 and March 2012.

Reduction of vision was the chief complaint in all patients. Multiple cream colored placoid lesions were present in the deep retina in all patients at the posterior pole. 2 patients had subretinal fluid at the macula and one patient had significant disc edema with hemorrhages. All patients at presentation underwent complete ophthalmic examination including best corrected visual acuity, slit lamp examination, fundus examination, color fundus photography (FF450 plus IR fundus camera; Carl Zeiss Meditec, Inc, Jena, Germany), fluorescein angiography(FF450 plus IR fundus camera; Carl Zeiss Meditec, Inc, Jena, Germany) and Heidelberg Spectralis.
SD-OCT (Heidelberg Engineering, Heidelberg, Germany).

All patients were treated with oral prednisolone which was tapered according to the clinical response over a period of 4 to 6 weeks. Fundus examination and SD-OCT were repeated at 1 month follow up. The retina was first scanned with fast macular line scanning protocol. Single high resolution scans were taken along the vertical and horizontal axis through the center of the fovea and on the affected retinal areas. For OCT after resolution, follow up acquisition mode was used which automatically placed the follow up scans in exactly the same location as that of initial scan.

**Results**

Table 1 shows patient’s demographic and clinical characteristics. Of the 5 patients 3 were males and 2 were females. Average age at presentation was 36 yrs. The disease was unilateral in 2 and bilateral in 3 cases. Preceding fever was present in 2 cases and 1 patient had head ache. All the patients were otherwise healthy. Laboratory examination included negative titers for Toxoplasmosis, a negative quantiFERON TB Gold for tuberculosis and a negative fluorescent treponemal antibody absorption test. There was no associated anterior uveitis or vitritis in any patient. Multiple cream colored placoid lesions were present in the deep retina at the posterior pole in 3 patients (patients 1, 2, 3) (typical APMPPE) and 2 patients in addition had sub retinal fluid (patients 4, 5) (atypical APMPPE) and one patient had significant disc edema with hemorrhages similar to Vogt-Koyanagi-Haradas Disease (VKH) (patient 5).

<table>
<thead>
<tr>
<th>Serial No</th>
<th>Age</th>
<th>Sex</th>
<th>Associated symptoms</th>
<th>Affected Eye</th>
<th>Initial VA</th>
<th>Final VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>F</td>
<td>Fever, Head ache</td>
<td>RE</td>
<td>20/30,N6</td>
<td>20/20,N6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LE</td>
<td>20/30,N6</td>
<td>20/20,N6</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>M</td>
<td>-</td>
<td>RE</td>
<td>20/20, N6</td>
<td>20/20,N6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LE</td>
<td>20/30,N6</td>
<td>20/20,N6</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>F</td>
<td>-</td>
<td>LE</td>
<td>20/30,N6</td>
<td>20/20,N6</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>M</td>
<td>-</td>
<td>RE</td>
<td>20/120,N36</td>
<td>20/30,N6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LE</td>
<td>20/200,N36</td>
<td>20/20,N6</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>M</td>
<td>Fever</td>
<td>RE</td>
<td>20/400,N36</td>
<td>20/80,N6</td>
</tr>
</tbody>
</table>

LE-left eye; RE-right eye; VA-visual acuity; M-male; F-female.

**Case Report (patient 1; Representative of typical APMPPE)**

This was a 35 yrs old female patient with history of decrease in vision of LE of 3 days duration. She had a viral prodrome 5 days prior to this. Her best corrected visual acuity (BCVA) in BE was 20/30,N6. Fundus examination showed multiple cream colored placoid lesions in the deep retina at the posterior pole (figure-1A). FA showed the classic pattern of initial hypo fluorescence with late phase hyperfluorescent staining of the placoid lesions (figure-1B&C). Patient was diagnosed to have APMPPE and was treated with oral prednisolone (1mg/kg) which was tapered over a period of one month.

SD-OCT demonstrated similar characteristic features in the acute stage in all 3 patients (patients 1, 2, 3). At the edge of the placoid lesions the IS-OS junction was irregular with undulations which got separated from the RPE layer more

Figure 1.Images of patient 1 at presentation. Fundus photograph of RE showing typical placoid lesions (A). FA pictures showing early hypo and late hyperfluorescence of the lesions (B&C). Black on white OCT image passing through the edge of the placoid lesion showing IS-OS irregularity and thickening (D). OCT section more towards the centre showing hyper reflectivity of the ONL and OPL (E). OCT through the centre of placoid lesion showing elevation of IS-OS junction and hyper reflective echoes within and at the roof of the dome (F).
towards the centre of the lesion (figure-1D). Then this layer became thickened and more hyper reflective with increase in hyper reflectivity of the overlying ONL. There was increase in reflectivity and irregularity of the OPL as well (figure-1E). As the lesion progressed more towards the centre the thickened IS-OS line got elevated partly from the underlying RPE and formed a dome shaped elevation that had a hyper reflective membrane lining all around it. Roof of the dome had a few hyper reflective points like echoes hanging down (figure-1F). At all levels changes in photoreceptors were more prominent than that of RPE.

Figure 2. Fundus picture of RE(A). Early FA picture showing hypo fluorescent lesions and large area of submacular hypo fluorescence(B). Late FA showing hyperfluorescence of the initial hypofluorescent lesions and macular dye pooling(C). Black on white SD-OCT image at the edge of the lesion with IS-OS irregularity and undulations and separation from the RPE layer(D). Hyper reflectivity of ONL and OPL(E). Dome shaped elevation of partly separated IS-OS junction with splitting of OPL at the edge and hyper reflective echoes from the roof are seen clearly(F). The fluid collection is above the partly separated IS-OS junction(F). RPE elevation and undulations(G).

Figure 4. Disc edema, peripapillary hemorrhages and large area of subretinal fluid collection in the RE of patient 5(A). Mid FA picture(B). Late FA picture showing disc leakage, large area of sub retinal pooling of dye and pin point hyper fluorescent dots within the area of dye pooling(C). Black on white SD-OCT image showing 3 compartments of fluid with more hyper reflective elements in the central one(D).
SD-OCT after resolution (1 month) showed changes mainly in the IS/OS junction and photoreceptor layer in the form of irregularity, discontinuity and thinning at the site of lesion. There was decrease in thickness of ONL. RPE layer showed undulations, irregularity, thinning and focal increase or decrease in reflectivity in the area of the lesion. The area of involvement of RPE was much less compared to the involvement of photoreceptor layer in healed lesions also. Irregularities in the OPL were also seen at 1 month.

Case Report (patient 4)

This 28 yrs old gentle man complained of blurring of vision of both eyes of 1 day duration. His BCVA in the RE was 20/120, N36 and LE was 20/200, N36. Fundus examination showed sub macular fluid in addition to the typical placoid lesions (figure-2A). Both the eyes had macular pooling of dye on FA along with the typical features of placoid lesions (figure-2B&C). SD-OCT through the area of sub macular fluid showed a large dome shaped elevation which had a similar pattern of progression from the edge towards the centre as in patient 1 (figure-2D&E). There was accumulation of fluid with hyper reflective material beneath the dome (figure-2F&G). There was splitting of OPL at the edge of the dome. At few places within the dome there were changes in the RPE layer in the form of irregular reflectivity, undulations, thickening and thinning which were much less significant compared to the involvement of photoreceptor layer (figure-2G). These changes did not happen at the edge of the lesion but more towards the centre.

SD-OCT findings of healed lesions were similar to patient 1 but the IS-OS junction and RPE layer abnormalities were much more prominent. The IS-OS junction was irregular and thinned with few undulations trough out the extent of the lesion with no area showing restoration of original architecture except at the edge (figure-3A). The IS-OS line and RPE layer were discernible as two separate layers only at few places within the area of initial dome shaped elevation (figure-3A&B).

Case Report (patient 5)

30 yrs old male patient presented with gross reduction of vision of RE of 2 days duration, 5 days following an episode of viral fever. His BCVA in the RE was counting fingers at 2 meters 20/400, N36. His LE was normal. There was a large area of subretinal fluid at the posterior pole and disc edema (figure-4A). Few placoid lesions were seen temporal to macula and below the major vascular arcade. FA showed pooling of dye in the area of subretinal fluid and a few pin point hyper fluorescent dots within this area. He also had disc leakage on FA (figure-4B&C).

SD-OCT showed large accumulation of fluid beneath the elevated IS-OS junction in 3 loculi. In the middle loculus corresponding to the yellowish area seen on fundus photograph, accumulation of hyper reflective material was significantly denser compared to the temporal and nasal compartments which had relatively clear fluid. In all the 3 compartments fluid collection was beneath the elevated IS-OS junction (figure-4D). The pattern of progression of the lesion was similar to patient 1 but the changes were more dramatic.

Healed lesions had features similar to patient 4. Area with significant thinning of outer retinal layers showed falling down of inner retinal layers into the area of thinning.

Discussion

In our study we analyzed the retinal structural changes in the acute and healed stages of APMPPE using Spectralis OCT. Based on our results we put forward a new proposal into the pathogenesis of the disease.

In all eyes structural alterations were seen in and external to the OPL with maximum changes occurring in the photoreceptor layer. SD-OCT findings of patients with typical...
APMPPE showed similar characteristic features. At the edge of the placoid lesions the IS-OS junction was irregular with undulations which got separated from the RPE more towards the centre of the lesion. Then this layer became thickened and more hyper reflective with increase in hyper reflectivity of the overlying ONL. As the lesion progressed more towards the centre the thickened IS-OS line got elevated partly from the underlying RPE and formed a dome shaped elevation that had a hyper reflective membrane lining all around it. At the roof of the dome there were a few hyper reflective points like echoes hanging down. In the 2 patients with subretinal fluid, fluid was located beneath the elevated IS-OS junction. Patient 5 had accumulation of fluid beneath the elevated dome of IS-OS junction in multiple loculi. Presence of hyper reflective material beneath the dome points to an inflammatory pathology. Changes in the RPE layer were more prominent towards the centre of lesion than at the edges. We postulate that there is an initial inflammatory insult to the photoreceptors which produced some morphological alteration at the IS-OS junction which led to an increase in reflectivity and thickening of this layer. With further changes inflammatory materials and fibrin would have got attached to this resulting in further thickening and eventual partial separation and elevation of this layer. The OCT findings of RPE layer points to the involvement of this also in the disease process but to a lesser extent compared to photoreceptors as indicated by the less frequent and less area of involvement of RPE and by the appearance of these changes more towards the centre than edge of lesions. The origin of fluid is most probably from the choroid because the inner retinal layers were intact on OCT and all the retinal vessels were normal on FA. The changes in the photoreceptors would have produced initially functional and later morphological changes in the RPE and that the subretinal fluid would have swept across the functionally deranged RPE from the choroid (the changes in the RPE may be functional initially and not picked up by the OCT). Also changes in the RPE layer were more prominent in the eyes with subretinal fluid collection (patient 4 & 5) favoring our suggestion. The IS-OS junction and photoreceptor changes on SD-OCT after resolution were much less significant compared to the initial OCT pictures which favor the inflammatory etiology rather than a vascular one which would have produced more permanent changes. Residual IS-OS junction and RPE changes were more prominent in eyes with subretinal fluid collection indicating more extensive damage in these eyes.

Patient 5 in addition to disc edema and pin point hyper fluorescent dots on FA and loculated subretinal fluid collection on SD-OCT pointing to the overlapping nature of APMPPE and Vogt-Koyanagi-Harada disease (VKH). Hyper reflective material in the central subretinal loculus seen in OCT in this patient was much more (corresponding fundus photo showed more yellowish discoloration of subretinal fluid) than in the temporal and nasal loculi (fundus photo showing clearer fluid collection). This may be because there is more inflammatory material and fibrin in the central loculus compared to the other two.

The hyper reflective dots seen hanging from the roof of the dome shaped elevation, not described earlier may represent the separated outer segments of photoreceptors. The splitting of OPL and falling down of inner retinal layers into the area of thinning were also not reported earlier and to the best of our knowledge this is the first report of an SD-OCT analysis from the edge towards the centre of the lesion in a systematic way.

We have measured the choroidal thickness of 3 patients (5 eyes) in the acute stage. The average choroidal thickness of RE (3 eyes) was 328 μm and that of the LE (2 eyes) was 302 μm which was not much higher than that of normals. Also there was no significant correlation between the choroidal thickness and presence or absence of subretinal fluid.

There are only a few published case reports on OCT findings of APMPPE in literature. Earlier reported OCT findings in APMPPE include increased reflectance of outer retinal layers without much increase in the retinal thickness at the site of placoid lesions, presence of subretinal fluid, focal disruptions of RPE and IS-OS junction. To the best of our knowledge there are only three case reports on SD-OCT findings in APMPPE to date. Lee et al. has described presence of compartmentalized sub retinal fluid lined with septae at the macula and in the peripapillary retina in his patient at the time of presentation who had features similar to VKH. Two of our patients (patient 4, 5) had similar features. The fluid was not seen when OCT was repeated 5 days later in his patient. Our repeat scans were taken much later (1 month) and hence the time of disappearance of fluid would have been earlier. Partial reappearance of IS-OS junction and re organization of OS/RPE region was demonstrated in the 3 month OCT in Lee’s series but similar changes were seen much earlier in our cases (1 month). Montero et al has described the location of fluid as intra retinal but the presence or absence of macular detachment was not specified. We could clearly demonstrate the location of fluid beneath the elevated IS-OS junction. Cheung et al demonstrated relatively well preserved RPE when changes occurred in the ONL and IS-OS junction in the early stages of the disease. Our cases had similar early changes in the IS-OS junction occurring before changes in the RPE layer.

**Conclusion:**
SD-OCT features in acute and healed stages of APMPPE...
suggest primary insult of photoreceptor layer which may be triggered by an inflammatory mechanism rather than a vascular one. However more extensive studies with newer imaging modalities and larger number of patients and longer period of follow up are needed to confirm this hypothesis.

**References**

A study of Clinical, OCT and Fluorescein Angiographic Findings in Toxoplasma Retinochoroiditis.

AIM
To determine the clinical, OCT and angiographic findings in Toxoplasma retinochoroiditis and whether these can be used to diagnose Toxoplasma retinochoroiditis.

METHODS
Retrospective chart review of all patients diagnosed and treated as Toxoplasma retinochoroiditis in the period April 2008 - March 2012. All patients had typical active retinochoroiditis patches suggestive of Toxoplasmosis. Anti Toxoplasma antibody titers were analyzed in available cases. FFA and OCT features were analyzed in available cases.

RESULTS: Of a total of 86 cases, 53 (61.63%) were primary and 33 (38.37%) secondary. 36 out of 86 (41.86%) were in children under the age of 16 years. Macular involvement occurred in 49 (56.98%). Vasculitis (63.95%) followed by Kylaeriasis arterialis (58.1%) were the most common lesion seen. Single or multiple segmental periphlebitic patches around posterior pole and frosted branch angiitis were significant clinical findings. Multiple spike like protrusions of inner retinal layers on the surface of the lesion were the typical and most characteristic OCT feature observed in 100% of cases tested. Seropositivity was obtained in 91.18 % of cases tested.

CONCLUSION
As clinical features together with angiographic and OCT findings have a better predictive value in the diagnosis of Toxoplasma retinochoroiditis, these rather than serology could be used for the diagnosis and treatment of Toxoplasma retinochoroiditis.

Transmission to humans occur mainly by three mechanisms viz. Ingestion of undercooked meat containing bradyzoites, ingestion of sporozoites from contaminated food or water and transplacental spread of parasite from infected mother.

Classically, Toxoplasma retinochoroiditis appears as a focus of inner retinitis. Healing of the lesion occurs with control of the acute infection and scar formation. The cyst may remain inactive in the scar or adjacent to it for a period of years. Ultimately, the cyst wall may rupture, releasing organisms into the surrounding retina and resulting in recurring retinitis. As a result, the initial lesion can cause damage to the inner retinal layers adjacent to an old chorioretinal scar and can be accompanied by vitritis.

However, considerable variation exists in the clinical features of this disease. Additional clinical insights into the disease may have important implications for the understanding of tissue damage mechanisms, with implications for the management and prognosis, as well as help future research efforts.

This is a study of the clinical, OCT and angiographic findings in Toxoplasma retinochoroiditis and their reliability as compared to serology.

Materials And Methods
Case records of patients who presented to Medical Trust Hospital from April 2008 – June 2011 & Comtrust Eye Hospital from July 2011 – March 2012, diagnosed and treated as Toxoplasma retinochoroiditis were included in the study. All patients had typical active retinochoroiditis patches suggestive of Toxoplasmosis.

The retinochoroiditis was classified as primary or secondary depending on the absence or presence of associated hyper pigmented chorioretinal scar.

All posterior segment findings were noted. Anterior chamber reaction if any was also noted.

Anti Toxoplasma antibody titers were analyzed in available cases.
cases (n=68).

Fundus photos available were reviewed in all cases. Type and location of lesion, associated Vasculitis and its extent, other features like hemorrhages were careful looked for and noted. Kylaeriasis was noted if intra vascular exudates like material were seen in fundus photo. FFA (n=24) features were analyzed in available cases.

Cirrus 4000 spectral OCT was used. 5 line HD scans and macular cube scans done were reviewed (n=36) in available cases. All available scans in macular cube were analyzed in advanced visualization software of Cirrus OCT.

Results
There were a total of 86 cases in this study. Of these 36 (41.86%) were children under the age of 16 years; 55 (63.95%) were male and 31 (36.05%) were female.

All patients presented with unilateral involvement except one, who had bilateral symmetrical involvement. Out of a total of 86 cases, 53 (61.63%) were primary and 23 (38.37%) were secondary. Macular involvement was seen in 49 (56.98%) whereas 37 (43.02%) were having extra macular involvement.

Vasculitis (63.95%) followed by Kyaraeriasis arterialis (58.54%), anterior chamber reaction (40.70%) and vitritis (39%) were the commonest clinical findings.

Neuroretinitis (8.34%) as well as frosted branch angitis (5.83%) were seen. These findings as well as pars planitis (32.14%) were seen always in patients with active retinochoroiditis. Intraparetinal hemorrhages (5.83%) were seen in few eyes in the absence of CNVM but sub retinal bleed when present was always associated with CNVM.

FFA was available in 24 cases. Mainly two types of angiographic patterns were seen. One was the early hypo fluorescent lesions followed by late hype fluorescence. The other pattern was very early hyper fluorescence followed by late further increase in hyper fluorescence. 14 of 24 (58.33%) showed early hypo fluorescent lesions followed by late hype fluorescence whereas 9 (37.5%) showed very early hyper fluorescence followed by late further increase in hyper fluorescence. 1 (4.17%) patient had cystoid macular edema. CNVM was present at presentation along with active disease in 3 cases. All were classic CNVM. One patient developed CNVM on follow up.
OCT was available in 36 patients. Characteristic finding of toxoplasmosis on OCT was Multiple spike like protrusions of the inner retina overlying the lesion. This was found in 36 (100%) out of 36 patients where OCT was analyzed. The other OCT findings were vitreous cells in 33 (91.66%) and sub retinal fluid in 5 (13.88%) cases. The commonest site of lesion was Inner & Outer retina in 17 (47.22%) (some view of outer retinal layers present); followed by Inner retina, outer retina and choroid in 12 (33.33%) and predominantly Inner retina in 7 (19.44%) cases (hyper reflectivity of inner retinal layers complete shadowing of outer retinal layers and choroid).

Of 68 patients in whom serology was done Ig G titer for Toxoplasma antibody was positive in 62 (91.18%), whereas Ig M Toxoplasma antibody titer was positive in only 7 (10.29%). Rest 6 (8.82%) didn’t show seropositivity.

Confusion arises when it comes to aid the clinical diagnosis and to start the specific treatment. Serology, including Ig G and Ig M Anti Toxoplasma antibody, is till now the most widely used test to aid the diagnosis. In our study we found Ig G Anti Toxoplasma antibody titer was positive in 91.18% of cases tested whereas Ig M Anti Toxoplasma antibody titer was positive in 10.29% cases only. The study by Juliana et al also showed a nearly similar result of Ig G titer positivity in 100% and Ig M in 13.33% of tested cases. From our study as well as reported literature we see that Ig M has very low sensitivity in ocular toxoplasmosis. This is possibly because eye is a very small organ affected and antibodies produced are probably less to be detected on routine serology. IgG even though has high sensitivity has low specificity as it can be high in normal population without ocular disease also, especially in endemic population like ours.

Although PCR of vitreous and aqueous tap can be used having both high sensitivity and specificity in these cases but being invasive and costly, is not popular as other methods.

Mainly two types of angiographic patterns were seen in our series. One was the early hypo fluorescent lesions followed by late hype fluorescence. The other pattern was very early hyper fluorescence followed by late further increase in hyper fluorescence. Early hyper fluorescence in toxoplasma retinochoroiditis is unusual when compared to other inflammatory lesions where we expect early hypo fluorescence. This is probably due to more severe involvement of inner retinal layers. In these eyes OCT also showed more profound inner retinal involvement with backscattering of all outer layers.

Further we have analyzed the entire surface of the lesion with advanced visualization of macular cube in cirrus OCT. Spike like protrusion of inner retina somewhere over the lesion were seen in 100% of cases. This retinal spikes are actual protrusions of very superficial retina, into the vitreous and are not due to vitreous traction or vitreous adhesions. Vitreous adhesions and overlying vitreous debris/ cells
were seen as separate findings. Though such findings not reported before in literature, we have observed it in each case analyzed. Study by Juliana et al have mentioned “Hairy appearance” over lesion in 20% of cases but no other detail regarding it had mentioned. OCT finding of retinal spikes has not been reported for any other macular inflammatory or non-inflammatory lesions. We feel this finding alone can be diagnostic in macular toxoplasmosis.

Vitreous cells/strands in OCT overlying the lesion was second most characteristic finding seen in 91.66% of patients. These thought to be appeared earlier than clinically visible cells on fundus examination.

Our study showed most common location of lesion was inner & outer retina followed by involvement of choroid. Exact location and involvement of layers is difficult by OCT since once inner retina is involved, it tends to cause severe shadowing preventing further visualization of outer retinal layers. But an approximate assessment can be made if entire lesion is scanned or as lesion is healing when inner layer reflectivity decreases. We have made such an attempt but it may be far from accurate.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Present study</th>
<th>Monnet et. al</th>
<th>Juliana et. Al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of study</td>
<td>Retrospective</td>
<td>Prospective</td>
<td>Prospective</td>
</tr>
<tr>
<td>Number of cases (n)</td>
<td>86</td>
<td>25 (16 Active and 9 Scarred)</td>
<td>15</td>
</tr>
<tr>
<td>Mean age of study group</td>
<td>25.08 (± 15.37)</td>
<td>25.5 (± 9.9)</td>
<td>25.7 (± 11.3)</td>
</tr>
<tr>
<td>Male</td>
<td>63.96%</td>
<td>56%</td>
<td>73.33%</td>
</tr>
<tr>
<td>Female</td>
<td>36.05%</td>
<td>44%</td>
<td>26.67%</td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>61.63%</td>
<td>40%</td>
<td>NR</td>
</tr>
<tr>
<td>Secondary</td>
<td>38.37%</td>
<td>60%</td>
<td>NR</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macular</td>
<td>56.98%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Extra macular</td>
<td>43.02%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Clinical findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td>63.95%</td>
<td>18.75% (A)</td>
<td>33.33%</td>
</tr>
<tr>
<td>Kylaeriasis</td>
<td>58.14%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Arteritis</td>
<td></td>
<td>81.25% (A)</td>
<td>100%</td>
</tr>
<tr>
<td>A/V reaction</td>
<td>40.70%</td>
<td>62.5% (A)</td>
<td>100%</td>
</tr>
<tr>
<td>Vitritis</td>
<td>39%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>OCT</td>
<td></td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Inner retinal spikes</td>
<td>100%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hairy appearance</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Vitreous cells</td>
<td>91.66%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>SRF</td>
<td>13.88%</td>
<td>12.5%</td>
<td>13.33%</td>
</tr>
<tr>
<td>Serology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ig G positivity</td>
<td>91.18%</td>
<td>NR</td>
<td>100%</td>
</tr>
<tr>
<td>Ig M positivity</td>
<td>10.29%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>NR = Not Revealed. (A) = Active lesions, SRF = Sub retina fluid</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion

Being non invasive and having more sensitivity and specificity, OCT together with clinical features and angiographic findings, can be considered superior in the diagnosis of Toxoplasma retinochoroiditis. These rather than serology could be used to aid the diagnosis and guide treatment of Toxoplasma retinochoroiditis.

References:


2. Garcia CA, Orefice F., Lyra CO, et al. Socioeconomic conditions as determining factors in the prevalence of systemic and ocular toxoplasmosis in northeastern Brazil.


Dr. Jayesh Thakkar et al. - OCT and Fluorescein Angiographic Findings

Dr. Prakash V S Did MBBS from TD medical college Alleppey (1997), and MS from Regional Institute of Ophthalmology, Minto Eye Hospital, Bangalore (2002). Completed research (2003) and clinical fellowships (2005) in VR surgery at Medical research Foundation, Sankara Nethralaya Chennai. Passed FRCS (Glasg) in 2009. Did ICO fellowship in Uveitis and Ocular Immunology at New York Eye and Ear Infirmary in 2011
Long Term Intravitreal Bevacizumab (IVB) Safety Survey

Aim: To assess the procedure related and possible drug related adverse events following IVB.

Methods: 360 S. Indian patients who had received off label IVB injection for neovascular and exudative ocular diseases since Jan 2007 were included in a survey for long term ocular or systemic adverse effects. Patients who had no follow up were contacted and medical reports screened.

Results: Reported adverse events included subconjunctival hemorrhage (4 patients -1.1%), and transient blood pressure elevation (2 patients- 0.05%). Death occurred after 1 year due to varying causes in 4 (1.15%).

Conclusion: Survey for adverse events after IVB did not show an increased rate of potential drug related ocular or systemic adverse effects. Theselong term result suggests that IVB is safe.

Background Statement: Long term follow up of patients receiving Intravitreal Bevacizumab injection did not show any increase rate of potential drug related ocular or systemic events in South Indian patients.

Précis: This study was conducted to ascertain the safety profile of Bevacizumab which is a commonly used anti VEGF agent in South India.

Introduction
Vascular endothelial growth factor (VEGF) plays an important role in many diseases of the posterior pole that are characterized by macular edema and/or intraocular neovascularization [1, 2]. Such diseases include proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), neovascular glaucoma, retinopathy of prematurity, choroida neovascularization (CNV) and retinal vein occlusions [1, 2]. VEGF inhibition in experimental models of diabetic retinopathy and CNV have shown promising results [3, 4]. Recently pegaptanib sodium (Macugen®, Eyetech, NY, NY), an aptamer against VEGF165, has been shown to be beneficial in the treatment of CNV secondary to age-related macular degeneration (ARMD) and DME [5, 6]. Ranibizumab (Lucentis®, Genentech, San Francisco, CA), a fragment of a humanized monoclonal antibody against all VEGF isoforms, also appears to be beneficial in the treatment of CNV secondary to ARMD [7]. However, in most parts of the world, both pegaptanib sodium and ranibizumab are not readily available and are not financially viable options. A humanized, recombinant monoclonal IgG antibody that binds and inhibits all VEGF isoforms, bevacizumab (Avastin®, Genentech, San Francisco, CA), is readily available. It has been approved by the United States Food and Drug Administration as an adjuvant agent in the treatment of metastatic colorectal carcinoma. In these patients with metastatic colorectal carcinoma, there was an increased rate of thromboembolic disease in patients receiving an intravenous infusion of bevacizumab 5 mg/ kg of body weight every 2 weeks. In addition, systemic hypertension was seen in a fair number of patients [8]. Michels and colleagues reported on the benefits of systemic bevacizumab administration in eyes with CNV secondary to ARMD. The most common side effect reported by them was systemic hypertension[9]. Rosenfeld et al. proposed the administration of intravitrealbevacizumab as an alternative to minimize the systemic risks associated with systemic anti-VEGF therapy [10, 11]. The purpose of this study is to report on the systemic and ocular safety of intravitreal injections of 1.25 mg of bevacizumab.

Materials and methods
This is an open label, uncontrolled single center interventional case series of all patients that were injected
Dr Sonia Rani John et al - Intravitreal Bevacizumab (IVB) Safety Survey

from 1st January 2007 to 31st January 2011 with 1.25 mg of intravitreal bevacizumab for a variety of retinal disorders characterized by intracocular neovascularization and/or macular edema including proliferative diabetic retinopathy, diabetic macular edema, retinal vein occlusions, and CNV of several etiologies including ARMD. A total of 360 consecutive patients were identified at a single institution in South India. Prior to injection, all patients were given an informed consent and offered alternative treatments. All patients were made aware of the off-label use of this medication, possible systemic and ocular complications. Patients underwent a complete ocular examination at baseline and then monthly. Additional examinations were scheduled according to the clinical decision individually. In addition, patients underwent fluorescein angiography and optical coherence tomography at different time intervals at baseline and several time points during their follow-up. Monitored systemic conditions included myocardial infarction, stroke, systemic hypertension, thromboembolic diseases and death. Blood pressure was measured prior to bevacizumab injection and at 2 weeks following each injection. Other systemic conditions were assessed by a thorough review of systems. All patients were contacted in December 2011 and January 2012 and asked to return for a check-up. If the patients were unable to attend, a telephone interview was conducted to assess for possible systemic complications. Bevacizumab was stored under refrigeration. All injections were performed in the usual sterile fashion with a sterile lid speculum and 5% topical povidone-iodine [12]. Topical antibiotics were prescribed for 5 to 7 days after the injection.

Results
A total of 360 intravitreal injections of bevacizumab in 250 eyes were reported from a single center in South India. The baseline demographic characteristics are summarized in Table 1. The most common indications for intravitreal bevacizumab were diabetic retinopathy and CNV of several etiologies. These are listed in Table 2. The patients have been followed for an average of 13.2 months (Range: 12–15 months). For the patients missing their 12-month appointment, telephone contacts were made. Thus, at the 12-month follow-up visit, all patients had been accounted for. Reinjections were reported in 84 eyes after an average of 8 weeks (Range 4–14 weeks). In average each eye received 1.8 injections (Range: 1–4 injections). Reported adverse events included subconjunctival hemorrhage (4 patients; 1.1%), and transient blood pressure elevation (2 patients; 0.05%). Death occurred after 1 year due to varying causes in 4 (1.15%) and cerebrovascular accidents resulting in two deaths. One developed myocardial infarction with fatality. Two (0.17%) diabetic patients underwent toe amputations at 2 and 6 weeks following injection. All the systemic adverse events are summarized in Table 3. Table 4 lists the reported ocular complications. The most common ocular complication was subconjunctival hemorrhage, which was seen in 4 cases. Seven (2%) cases of a transient increase of intraocular pressure (< 26 mm Hg) were reported. These were managed with topical medications. No case of severe uveitis or of bacterial endophthalmitis was reported. Two (0.05%) eyes with PDR characterized by extensive intraocular neovascularization despite extensive panretinal photocoagulation were injected with 1.25 mg of Bevacizumab and developed tractional retinal detachment within a period of 2 weeks after the injection.

Table 1: Baseline characteristics of patients receiving Intravitreal Bevacizumab

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - 45 to 80 years</td>
<td></td>
</tr>
<tr>
<td>Male: Female - 1:1</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus-250</td>
<td></td>
</tr>
<tr>
<td>Systemic arterial hypertension- 130</td>
<td></td>
</tr>
<tr>
<td>Prior history of cerebrovascular accident - 2</td>
<td></td>
</tr>
<tr>
<td>Prior history of myocardial infarction - 10</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Indications for Intravitreal Bevacizumab

<table>
<thead>
<tr>
<th>Indications</th>
<th>Number of patients- 360</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNV 20 to ARMD - 97</td>
<td></td>
</tr>
<tr>
<td>Diabetic macular edema - 128</td>
<td></td>
</tr>
<tr>
<td>Proliferative diabetic retinopathy - 23</td>
<td></td>
</tr>
<tr>
<td>CRVO - 20</td>
<td></td>
</tr>
<tr>
<td>BRVO - 22</td>
<td></td>
</tr>
<tr>
<td>CNV20 to myopia - 20</td>
<td></td>
</tr>
<tr>
<td>CME - 5</td>
<td></td>
</tr>
<tr>
<td>Neovascular glaucoma - 9</td>
<td></td>
</tr>
<tr>
<td>Idiopathic CNV - 3</td>
<td></td>
</tr>
<tr>
<td>Chronic CSR - 2</td>
<td></td>
</tr>
<tr>
<td>ROP - 2</td>
<td></td>
</tr>
<tr>
<td>Others - 49</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Reported ocular complications

CNV=choroidal neovascularization, ARMD=age-related macular degeneration, CRVO=central retinal vein occlusion, BRVO=branch retinal vein occlusion, CME=cystoid macular edema, CSR=central serous retinopathy, ROP=retinopathy of prematurity.

At a mean of 1 week (range: 4 to 13 days), it was noticed that the neovascular membranes had regressed, but the resulting fibrous tissue led to the development or progression of tractional retinal detachment. Both patients underwent pars plana vitrectomy with satisfactory anatomic results.
Table 3: Systemic adverse events following Intravitreal Bevacizumab

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Gender</th>
<th>Adverse event</th>
<th>Time from last injection</th>
<th>No. of injections(dose)</th>
<th>Ocular condition</th>
<th>Medical history</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>M</td>
<td>CVA</td>
<td>7 months</td>
<td>2</td>
<td>AMD CNVM</td>
<td>HT,DM</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>M</td>
<td>CVA</td>
<td>5 months</td>
<td>1</td>
<td>AMD CNVM</td>
<td>HT,DM</td>
<td>Death</td>
</tr>
<tr>
<td>3</td>
<td>74</td>
<td>F</td>
<td>MI</td>
<td>10 months</td>
<td>1</td>
<td>AMD CNVM</td>
<td>HT, DM, Asthma</td>
<td>Death</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>M</td>
<td>Bronchopneumonia</td>
<td>12 months</td>
<td>1</td>
<td>AMD CNVM</td>
<td>Asthma</td>
<td>Death</td>
</tr>
</tbody>
</table>

Table 4: Ocular complications following Intravitreal Bevacizumab

Ocular complications:
- Subconjunctival hemorrhage : 4 (1.1 %)
- Raised IOP: 7 (2 %)
- Endophthalmitis: 0 %
- Uveitis : 0 %
- Tractional retinal detachment (TRD) : 2 (0.05 %)
- Vitreous hemorrhage: 0 %

Discussion

Anti-VEGF agents gain access to the systemic circulation following an intravitreal injection [11, 13–15]. Systemic VEGF blockade can give rise to complications such as systemic hypertension, thromboembolic diseases or even death [8, 16]. In a cancer trial, hypertension was noted in [9]. In our study, a transient mild rise in systemic blood pressure was seen in 2 patients (0.05%) a few hours to 2 weeks after an intravitreal injection of bevacizumab. In contrast in a smaller series of 45 patients, Kert et al. reported significantly lower diastolic blood pressures at 1 and 6 hours following an intravitreal injection of 1.25 mg of bevacizumab compared to baseline. They attributed these changes to normal physiological diurnal variations or alternatively to easing of surgery-related stress [17]. As many as 5% of all patients using systemic bevacizumab in combination with chemotherapy may be at an increased risk of developing a serious or fatal thromboembolic event [8, 18]. Fung and associates designed an internet-based voluntary survey to assess the adverse events associated with intravitreal bevacizumab. In this survey, 7,113 injections were reported on 5,228 patients. They reported 2 deaths, 5 cerebrovascular accidents and 15 blood pressure elevations in this cohort of patients [19]. Other smaller series have also confirmed a lack of systemic complications following an intravitreal injection of 1.25 mg of bevacizumab [20]. In our series of 360 patients, 4 (1.15%) developed systemic adverse events, including 4 (1.15 %) deaths. Several clinical trials examining different pharmacologic agents against exudative age-related macular degeneration have reported a mortality rate of 2% to 4% in both experimental and control groups [6]. In addition, the rates of thromboembolic disease have ranged from 1.3% to 6%. There were no statistically significant differences between anti-VEGF treated eyes and controls [6]. Spaide and colleagues conducted a retrospective study of 266 patients that underwent an intravitreal injection of 1.25 mg of bevacizumab for exudative ARMD. They reported transient ischemic attacks in two patients, a non-fatal myocardial infarction and two deaths. Alternatively, the difference in ethnicity between the study and control groups may be accounted for the different ethnic background of our population from that of the aforementioned clinical trials could explain differentiates of mortality in different populations. In any event, there did not seem to be an increased number of deaths. Another concern has to do with the fact that bevacizumab is not manufactured or labeled for intravitreal injection. Several electrophysiologic and histologic studies have shown the lack of ocular toxicity of intravitreal bevacizumab in cell cultures, animal and human eyes at least in the short term. Bacterial endophthalmitis is an expected and dreaded complication of any intravitreal injection. Sterile technique and antisepsis with instillation of topical povidone iodine 5% into the conjunctival fornix prior to an intravitreal injection may reduce the risk of endophthalmitis [12]. Therapeutic strategy for bacterial endophthalmitis for intravitreal injections of a variety of substances such as pegaptanib sodium, ranibizumab, gancyclovir, fomivirsen, cidofovir, triamcinolone and gas is 0.1% to 0.6% [6, 7]. Interestingly in our study, the rate of bacterial endophthalmitis was 0.0% in subjects who were injected from a single multi-use vial. Intraocular inflammation has been shown to be the doselimiting toxicity of intravitreal ranibizumab [11]. In fact, the manufacturer switched from a lyophilized formulation to an liquid formulation. Given that bevacizumab and ranibizumab are derived from the same molecule, it is somewhat surprising that in our study no cases of severe anterior uveitis were reported. However, this is consistent with the findings of Ziemssen and colleagues that showed that the aqueous flare in 60 patients injected with 1.25 mg of intravitreal bevacizumab for age-related macular degeneration had a slight increase only in the first post-injection day as measured by the flare meter. Two eyes with progressive proliferative diabetic retinopathy despite aggressive panretinal photocoagulation underwent adjuvant bevacizumab injections. In a matter of days, the neovascularization regressed, but the resulting fibrous scar tissue led to the development or progression of tractional retinal detachments. Both eyes underwent pars planavitrectomy with satisfactory anatomic results. Therefore, caution should be exercised when injecting these eyes, and the patients should be warned that vitrectomy might be...
warranted after all.

Conclusion:
In summary, an intravitreal injection of either 1.25 mg or 2.5 mg of bevacizumab appears to be safe and well tolerated during the 1st year. Limitations of our study include its short term, its lack of randomization, its lack of controls and its retrospective design, which preclude any estimation of the long-term safety of intravitreal bevacizumab. Furthermore, the detection of systemic adverse events such as myocardial infarction was based solely on a thorough review of systems. Patients did not undergo routine cardiac examination. Therefore, our rate of adverse events probably underestimates the true rate of events as clinically silent events went undetected. Continued monitoring of the adverse side effects in these patients is essential to determine if chronic inhibition of VEGF by bevacizumab remains safe.

References

Sonia Rani John completed postgraduation from RIO Trivandrum, and Comprehensive Ophthalmology and medical retina training from Chakrabarti EyeCare Centre. At present Senior Consultant at Chakrabarti EyeCare Centre.
27-G Vitrectomy

http://vitreousurgery.in/index.php?option=com_allvideoshare&view=video&slg=bb-assisted-erm-peeling&orderby=latest&Itemid=105 - EOM

- The 27-G sx was first introduced in 2007, when Oshima et al. introduced a 27-G chandelier light.¹
- Later Sakaguchi et al. published their experience performing 27-G nonvitrectomy for epiretinal membranes.

Advantages of 27 gauge Nonvitrectomized surgery

- To do as less invasive as possible
- Less conjunctival trauma
- Less scleral trauma
- Less astigmatism
- Less inflammation
- Less postoperative discomfort
- Early visual recovery

Smaller wounds are more likely to self-seal and prevent hypotony. They are less prone to vitreous prolapse, which may act as a wick and promote endophthalmitis.²

These benefits, on the other hand, must be weighed against the drawbacks of increased instrument flexibility and limited aspiration capacity — drawbacks that may make some tasks difficult or impossible to perform, like removal of Foreign body, etc.¹

Recent advances

- Stiffer instruments
- Wide angle viewing systems
- Wide-angle illuminating light pipe, using xenon/mercury vapour light
- Chandelier endoilluminating optic fibres
- One step vertical insertion – trocar cannula, instead of 2 step / angled sclerotomies
- Self sealing sclerotomies
- 27G cutter easily passes between the membrane and the retina.
- Wide-angle fundus viewing – makes it easy to carry out bimanual dissection with a 27G system.

Indications

- Macular holes
- Macular puckers
- Vitreomacular traction
- Vitreous hemorrhage and focal tractional retinal detachment
- Macular edema associated with diabetic retinopathy, retinal vein occlusion, uveitis
- Persistent pseudophakic cystoid macular edema 3
- Subintimal limiting membrane hemorrhage
- Simple vitreous hemorrhage
- Vitreous biopsy
- Primary rhegmatogenous retinal detachment
- Moderate PDR w/ or w/o focal tractional retinal detachment 4
- Subretinal hemorrhage

The 27-gauge Instruments

Chandelier endoilluminator

- The tip is introduced about 3 mm into the vitreous cavity, so the reflected glare from the tip is mostly blocked by the iris during surgery.
- The tip of the light fiber is shaped-like a cone for wide-angle illumination.
- A polyamide sleeve (arrow) covers the microfiber to prevent thermal burn-induced scleral damage.
- Panoramic fundus view under 27-gauge chandelier endoillumination.
- Sufficient illumination and wide-angle view of the fundus are obtained without reflecting glare into the surgeon’s eyes
- Intraoperative view of the mercury vapor illuminator combined with a 27/29-gauge light fiber in a variety of vitreoretinal disorders.

Instruments for epiretinal membrane removal

Shaft of the microforceps: 0.40 mm in diameter, is rigid and thin enough for intraocular manipulation.

- The shape of the grasping end is asymmetric
- The distance between the two tips is 750 microns when opened-grasp tough and thick proliferative epiretinal tissue

VITRECTOR

Recent advances of new vitrectomy systems have allowed for increased rates from 1,500 cuts per minute (cpm) to 5,000 cpm.

- Faster cut rates allow for safer peripheral vitreous dissection with less likelihood of creating a peripheral tear.¹

References


Padmasree Prof Dr S Natarajan is senior Vitreoretinal surgeon and director of Aditya Jyot eye hospital, Mumbai. He is the current editor of the Indian journal of Ophthalmology

Address for Correspondence: Aditya Jyot Eye Hospital Pvt Ltd., Plot No. 153, Road No. 9, Major Parameswaran Road
Opp. SIWS College Gate No.3, Wadala, Mumbai - 400 031. Email: ajehpatient@gmail.com
Hospital Infection Control
Author: Dr. Sanjay Singhal, Professor of microbiology
ESIC Post graduate institute of medical science,
New Delhi.
Publisher: CBS Publishers & Distributors PVT Ltd,
New Delhi, Kochi
First Edition 2013, 198 pages, Rs 1250/

Hospital acquired infections are one of the major health management problems faced by the hospitals world wide. The development of multi-resistant organisms has further complicated the task of controlling nosocomial infections. It is now essential that all hospitals have Infection Control Committees, which perform the task of surveillance and take measures to prevent nosocomial infections as per the policies and guidelines.

Healthcare – associated infection is a major issue in patient safety as it affects millions of people worldwide and complicates the delivery of patient care. Infections contribute the patient deaths and disability, promote resistance to antibiotics and generate additional expenditure to those already injured by the patients underlying disease. At any given time, more than 1.4 million people worldwide become seriously ill from such infections. Between 5% and 10% of patients admitted to hospitals in developed countries acquire these infections. In such developing country settings, the proportion of patients affected can exceed 25%.

In this 21st century, doctors, nurses, and other healthcare practitioners are faced with vast amount of healthcare information, constantly changing database, and burgeoning technology. With advancements in knowledge and medical technology and emergence of difficult to treat infections, an updated infection control manual become a requirement for controlling these infections.

With advancement in knowledge in understanding the mode of spread of infectious agents and in the field of infection control, need was felt to prepare an updated manual which will provide up-to-date guidelines for proper surveillance and effective control of nosocomial infections. Dr. Sanjay Singhal has taken a good initiative to compose this handbook.

Dr. Sanjay Singhal has done an excellent job in compiling and editing the recent information available to prepare this handbook and shall fulfill its purpose of guiding healthcare workers to effectively control hospital acquired infections.

This handbook, therefore, has been prepared by adopting current guidelines and policies regarding infection control. The handbook focuses on the science of surveillance, control and preventive management during period of infections and episodes of endemic and epidemic outbreaks in the hospital. Relevant clinical content and guidelines are presented in a logical and simple format for monitoring the changing status of patients so that infection and their complications can be prevented or their effects minimized.

The handbook is intended to provide guidelines rather than rules, expecting that the healthcare workers of the hospital will incorporate these guidelines in their routine and all of them shall work together in surveillance and prevention of nosocomial infections.

The book has 5 parts with 26 chapters
1. General principles – nosocomial infection surveillance programme, Outbreak management, hand hygiene, isolation precautions in hospital.
2. Infection Control in ICU, neonatal ICU, dialysis unit, burn unit
3. Common nosocomial infections- UTI, surgical site infections, pneumonia, blood stream infections, infections of immunocompromised host, antimicrobial resistant microorganisms
4. Hospital services-disinfection, sterilization, CSSD, waste management, laundry, hospital food services.
5. Infection control and healthcare personnel-employee health, prevention of nosocomial transmission of selected infections, pregnant health care workers

Emergence of difficult to treat infections caused by multidrug-resistant organisms has now made it essential that infection control policies should be prepared and followed. The handbook, therefore, has been prepared by adopting current guidelines and policies regarding infection control from WHO, CDC, APIC and other organizations. It focuses on the science of surveillance, control and preventive management during episodes of endemic and epidemic outbreaks in the hospital.

It will be useful for hospitals, hospital administrators, planners and managers, as well as doctors, nurses and medical students. It will help hospitals to plan infection control programs and policies and will be useful for clinicians by demystifying many myths about infection control.

In addition, the handbook will be useful for nurses and medical students as ‘infection control’ is already a part of curriculum being proposed by the medical Council of India.
Fluorescein angiographic observations of peripheral retinal vessel growth in infants after intravitreal injection of bevacizumab as sole therapy for zone I and posterior zone II retinopathy of prematurity

Sjakon G Tahija, Rini Hersetyati, Geoffrey C Lam, Shunji Kusaka, Paul G McMenamin

The study aimed at evaluating the vascularisation of the peripheral retina using fluorescein angiography (FA) digital recordings of infants who had been treated with intravitreal bevacizumab (IVB) as sole therapy for zone I and posterior zone II retinopathy of prematurity (ROP). Recently, there have been several encouraging reports of the use of intravitreal bevacizumab as an off-label first line of treatment in neonates with severe ROP. One of the reported benefits of intravitreal bevacizumab as treatment for zone I and posterior zone II ROP is that the development of peripheral retinal vessels continues after treatment, whereas conventional laser therapy leads to permanent destruction of the peripheral retina. This study gives a report on the results of fluorescein angiography (FA) performed on 10 neonates (20 eyes), who had been treated up to 5 years previously with intravitreal bevacizumab as sole therapy for zone I and posterior zone II ROP. The authors have evaluated the extent of peripheral retinal vessel growth and remaining avascular retina after a single injection of intravitreal bevacizumab.

The study group comprised of 20 eyes of 10 neonates who had achieved regression of posterior disease in both eyes with a single injection of bevacizumab and had a minimal follow-up period of 24 weeks after IVB. At time of IVB, 7 of these 10 cases had been diagnosed as having AP-ROP and 3 cases as having posterior zone II ROP without plus disease. In all cases, regression of posterior disease was documented by RetCam fundus photographs. The interval between treatment with IVB and FA ranged from 27–224 weeks.

All eyes had initial resolution of posterior disease after IVB injection as documented by RetCam colour fundus photographs. Using a distance of 2 disc diameters from the ora serrata to vascular termini as the upper limit of allowable avascular retina in children, the FA of these infants demonstrated that 11 (55%) of 20 eyes had not achieved normal retinal vascularisation. In addition, there was fluorescein leakage at the vascular–avascular junction in 9 of these 11 eyes with avascular peripheral retina (82% of total).

The authors concluded that although bevacizumab appears effective in bringing resolution of zone I and posterior zone II ROP and allowing growth of peripheral retinal vessels, in the study group normal peripheral retinal vascularisation was not achieved in half of the patients. Ophthalmologists should remain cautious as infants may remain at risk due to avascular peripheral retinas even many years after treatment. Careful examination using FA allows accurate visualisation of risk factors such as the extent of avascular retina and the presence of dye leakage.

Injection frequency and response to bevacizumab monotherapy for diabetic macular oedema (BOLT Report 5)
Sobha Sivaprasad, Roxanne Crosby-Nwaobi, Ling Zhi Heng, Tunde Peto, Michel Michaelides, Phil Hykin

The aim of this study was to examine the dosing frequency profile of patients with diabetic macular oedema (DMO) treated with intravitreal bevacizumab (IVB) in the prospective randomized trial of A intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) that compared repeated IVB and focal/grid macular laser therapy in 80 patients with persistent centre-involving diabetic macular edema (DMO) following previous laser treatment. Since the re-treatment was guided by optical coherence tomography (OCT), studying the dosing profile of this study would help explore the parameters that influence injection frequency and thereby factors that are associated with persistent or recurring oedema.

BOLT study was a prospective randomised 2-year trial at a single centre that enrolled patients with persistent centre-involving DMO after at least one prior macular laser treatment and compared the efficacy of 6 weekly IVB (1.25 mg) treatments with 4-monthly laser at 12 and 24 months based on pre-specified re-treatment criteria. In the IVB arm, patients received three mandatory IVB injections at 6-weekly intervals followed by an OCT-guided re-treatment protocol. In brief, if the thinnest recorded Central Macular Thickness (CMT) was less than 270 μm at 18 weeks, then treatment was continued only if macular thickness was not ‘stable.’ If CMT was greater than 270 μm at 18 weeks and subsequent visits, then IVB injections were administered until a ‘stable’ macular thickness was attained. ‘Stable macular thickness’
was defined as three consecutive visits with the CMT within 20 μm of the patient's thinnest recorded CMT. A total of 42 patients completed the 12 months follow-up and 37 completed the 24 months endpoint in the IVB arm of the BOLT study and were included in this analysis.

Despite a median of nine injections in the first year, only 10/42 (24%) patients were dry at 12 months. This proportion increased to 14/37 (38%) in the second year despite the need for fewer injections (median=4). The median number of injections given to the patients with dry maculae at 24 months was not significantly different to those that continued to be thickened. The visual acuity outcomes of the dry group were also not significantly different from the persistently thickened macula group. Eyes with better baseline visual acuity less frequently had persistent oedema and had fewer recurrences in the second year. All eyes with baseline subretinal detachment showed persistent macular oedema at 24 months. None of the other factors assessed influenced injection frequency or response in the first or second year.

The study concluded that good long-term response is predicted by resolution of macular oedema by 4 months. However, approximately 20% of patients with persistent oedema at 12 months achieved a dry macula and 50% gained more than 15 letters at 24 months with sustained treatment, suggesting that oedema at 4 or 12 months should not be used as a stopping criterion for treatment.

Objective of the study was to determine the efficacy of 1 intravitreal bevacizumab injection followed by pro re nata (PRN) injection in cases of subfoveal myopic choroidal neovascularization (CNV). It also aimed to identify the clinical pre-treatment prognostic factors that associate with final visual acuity, myopic CNV recurrence, and the total number of intravitreal bevacizumab injections.

This was a retrospective observational study conducted in 103 eyes of 89 consecutive naive patients who had subfoveal myopic CNV and had been followed-up for at least 2 years. Of those eyes, 24 had recurrences. The remaining eyes were stable after the initial treatment. The recurrence rate during follow-up was 23.3%. The BCVA improved by 0.2 logMAR after 2.7 injections in the eyes without recurrence but by only 0.08 logMAR after 6.9 injections in the eyes with recurrence. In univariate analysis, recurrence was associated with older age, more myopic refraction, thinner choroid, larger CNV lesions, and subfoveal hemorrhage at baseline. In multivariate analysis, only baseline CNV lesion size associated significantly with CNV recurrence. Recurrence, baseline BCVA, choroidal thickness, and CNV size associated significantly with final BCVA. Baseline choroidal thickness, CNV size, age, and presence of lacquer cracks associated significantly with injection number.

In conclusion, the 1 + PRN intravitreal bevacizumab monotherapy effectively stabilized naive subfoveal myopic CNV. In addition, CNV size, baseline BCVA, and choroidal thickness were the main factors that shaped the prognoses of naive subfoveal myopic CNV after intravitreal bevacizumab injection. These clinical prognostic factors in patients with subfoveal myopic CNV who are scheduled to receive anti-VEGF treatment should be evaluated carefully before the first treatment because this will facilitate the prediction of myopic CNV progression.
The Kerala Journal of Ophthalmology (KJO) is a quarterly, peer reviewed, one, devoted to dissemination of the latest in ophthalmology to the General Ophthalmologists as well as to specialists in the various subspecialties of this discipline. It invites submission of original work dealing with clinical and laboratory materials.

Authors submitting materials to this journal are requested to adhere STRICTLY to the norms laid down below. The matter must be typed on one side of the paper. A margin of 1” must be left all around and the material must be double spaced. A page should contain not more than 25 lines. Two copies of the text in paper and one copy in a CD must be submitted to the Editor and the corresponding author is advised to keep another copy with him. The corresponding author must give it in writing in his covering letter that the same matter will not be submitted elsewhere if accepted. He must also enclose the copyright transfer of his work to this journal. The papers sent will be subjected to peer review. The accepted manuscripts become the permanent property of this journal. The author is informed that, if his work is returned to him for correction / clarification after peer review, he should effect the same and send the manuscript back to the Editor within one month. Each manuscript component mentioned here under must begin with a new page and the pages are to be numbered at the right tip corner starting from the Title page.

1. TITLE: The title of the work must be brief and precise. It should not exceed two lines and 40 characters (including comma, period) Author(s) full name(s) must be given along with his (their) degree and the affiliations. Corresponding author’s name, correct address (including e-mail and Fax, if available) and phone number must be mentioned at the bottom left hand corner of the first page.

2. ABSTRACT: The abstract is to be given in the beginning itself. It should not exceed 200 words. It must contain the aim, methodology, results and conclusion. For case report, summary / conclusion alone is to be given.

KEY WORDS: (maximum five) in capitals are to be included at the end of Abstract.

3. INTRODUCTION: Describe the aim of the study, along with the hypotheses that were tested. Only necessary references are to be given.

4. METHOD: Give in detail the materials used and the methods employed. Describe the type of study. Pharmacological names only must be mentioned for the drugs used and, if proprietary name is used, then the manufacturers name must be given in parentheses. Except for standard, well-accepted abbreviations (including SI Units), all others must be introduced in parentheses when the full term is used for the first time in the article.

5. RESULTS: Give only the results obtained by the study under discussion. State the statistics in the correct scientific form (P value, mean etc). Results based on assumptions must not be given. Indicate in the text the place where the tables have to be inserted.

6. DISCUSSION: The discussion should be to the point and relevant to the subject under discussion. This section can be combined with the previous one if the author desires. Avoid speculations. Use only standard abbreviations or the abbreviations already introduced.

7. ACKNOWLEDGEMENT: This is to be made only to those who were directly and scientifically involved with the preparation of the paper. Permitting authorities, technicians, photographers who assisted in the work need not be mentioned.

8. REFERENCES: The references should be given in numerical order in which they first appear in text and not in alphabetical order (Citation Order System). It should be numbered consecutively in the text. The references will not be checked by the Editor or by the Peer reviewer and hence the author is solely responsible for its completeness and the accuracy. Period should not be employed anywhere in the references. Personal communications, unpublished data and poster references, if mentioned, should be in the text itself and the source mentioned in parentheses. References should be in the following form:

   Journal reference: Author(s) full title, Journal name (as abbreviated in Index Medicus), volume number, pages and year. If there are more than three authors, then mention the first three authors and then ‘et al’.

   Book reference: Author(s) (& Editor, if any), title of book (and chapter), publisher, place of publication, page number(s) of the cited portion and year.

9. THE LEGEND: The legend for the illustrations (and tables, if necessary) must be given in a separate sheet of paper and should be typed double-spaced.
Name the enzyme defects which cause this condition

Send your answers to gopalspillai@gmail.com

Answer for last time is Chronic Canaliculitis, The microscopy is Gram Stain of Actinomyces Israeli
The winner was Dr. Deepa C., Damodarans Eye Hospital, Kuthuparamba
Illustrations: The photos and figures should be prepared in glossy prints with good contrast and of the size 6” x 4”. Only salient details should be included. On the back of the illustration, the figure number in text, title of the paper, the first author’s name and the top side (marked with an arrow) must be specified. Except for arrows, no text is to be on the photos. It is the duty of the author(s) to get the patient’s written permission when the subject is identifiable in the photo. Submit two sets of illustrations. Illustrations from other Journals and books are usually not accepted. If used, it rests with the author(s) to get the copy right permission from the original author / publisher and this permission letter must be sent to the Editor at the time of submitting the manuscript. For Histological figures the stain and magnification used should be noted e.g.: H & E Stain x 70.

10. TABLE: It should be in double space. Each table must have an Arabic numeral (except for single table) and a title both in a single line. Each column in the table must have a short heading. If a table is large, then it must be continued in a second page, which also must have the table number and the title. Avoid vertical lines in the tables. Two sets must be submitted.

11. All manuscripts are subjected to editorial board review.

12. Other Categories of Manuscript

a) Original Articles should generally not exceed 3,000 words or 12 double – spaced pages.
b) Review Articles: can be on topics of relevance to clinical practice, research methodology, community ophthalmology or investigative work, of relevance to visual science. These articles should include up to date review of existing literature, and summarize the current status / preferred practice for that particular topic.

Brief reports are short communication of new instruments, new laboratory techniques or surgical techniques as well as interesting case reports with unique findings. These should not exceed 1000 words with a maximum of 2 illustrations. They should follow the format – introduction, case, and discussion. No more than 8 references should be cited. Each brief report must begin with a 75-100 word summary that highlights the significance of the articles.