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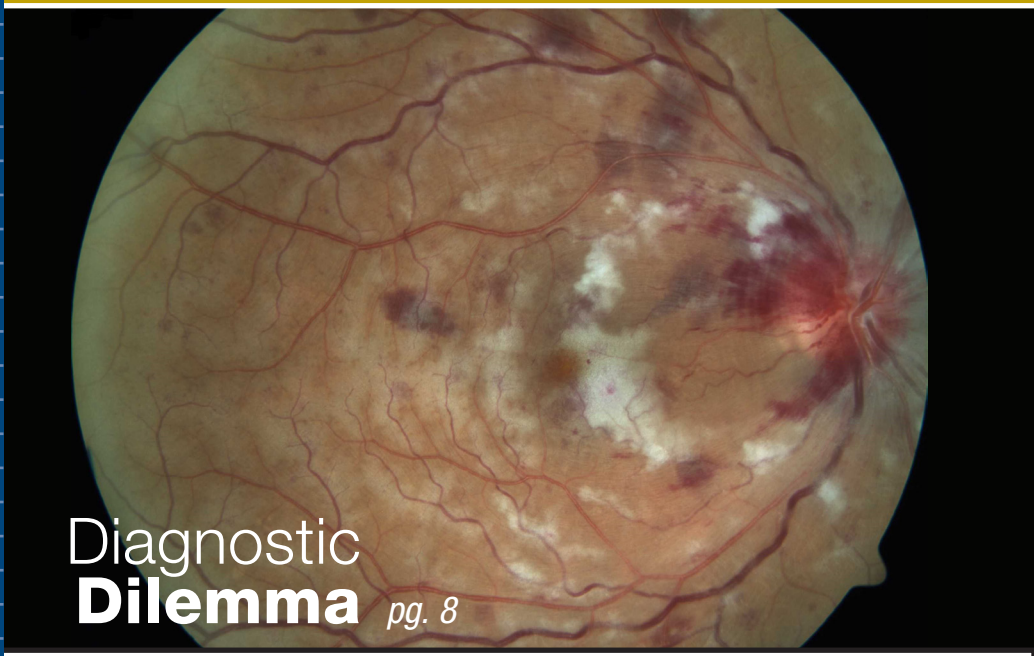
Spring 2014

the LIGHT PIPE



Diagnostic **Dilemma** *pg. 8*

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THE NEWSLETTER OF

GEORGIA RETINA

The next issue of the Light Pipe will be digital. If Georgia Retina does not have your current email on file, please go to garetina.com/light-pipe-newsletter and fill out the form or call us at 404-255-9096.

Contributing authors: Scott Lampert, Jay Stallman, Sean Koh, Krishna Mukkamala and Paul Lucas.

Idiopathic Central Serous Choroidopathy (ICSC)—
Not Always Clear Cut!

When speaking with a patient who has central serous it is important to remember that the textbook association with "stress" is very difficult to quantitate. Almost everyone says they have some degree of stress, and it's not really clear how much stress it takes to precipitate this condition, if it really does at all.

Certainly going through a death of a family member or a divorce or a house fire qualifies, but what about a stressful work environment, or just a "type A" personality. Any of these things could be related or unrelated, and may be difficult or impossible to modify.

The association with steroids is better defined and may be related not only to oral steroids as possibly used by body builders, but also topical creams and ointments as prescribed by the dermatologist, as well as nasal steroid sprays, which are prevalent during allergy season in Atlanta. Intra-articular steroid injections (eg. into a knee or shoulder bursa) may also exacerbate the condition. Some reports suggest that sleep apnea may be a predisposing factor. Occasionally other conditions that produce hypercortisolism may precipitate ICSC, and it could even be the presenting sign of an adrenal tumor, although this would be rare. Less well known is the possible association with helicobacter pylori infection.

The acute stage serous detachment in a young person with no drusen is easily identified as ICSC. Yellowish outer retinal deposits or subretinal fibrin are also consistent with the diagnosis. Blood or lipid exudate is generally not. However, the disease may present at later stages of partial or complete resolution, between episodes of exacerbation of leakage. Pigmentary deposits and RPE irregularity in that same young, healthy person is often an indicator of old, resolved central serous, one of the most commonly missed diagnoses in the retina. If you are looking at a fluorescein angiogram, everyone would recognize the typical "board exam description" of smokestack appearing leakage. Only about 10% of cases actually have this however. Broad areas of RPE mottling and low grade, poorly defined leakage may be present.

The diagnosis can be especially challenging in the 50-60 year old patient, who is a little bit old for the typical demographic of ICSC but a little young for age related macular degeneration.

Enhanced depth imaging (EDI) OCT is helpful in making the distinction, as the choroid may be thickened in patients with ICSC, suggestive of vascular congestion. Fundus autofluorescence (FAF) may show patchy increased autofluorescence in the macula. This may be from un-phagocytized photoreceptor outer segments containing a precursor of lipofuscin.

The usual recommendation for treatment is to observe, as data from the early 80's showed that the final visual outcome was the same whether

patients were treated with laser compared to observation alone. However, no studies were done on early treatment, which might have the potential to reduce photoreceptor disruption and permanent alterations of contrast sensitivity, color perception or distortion. If there is a very well defined punctate leak, gentle thermal laser treatment can be quite effective at accelerating the resolution of the subretinal fluid.

When central serous becomes chronic after multiple recurrences there can be widespread disturbance of the RPE with atrophy and pigment clumping. Broad areas of poorly defined leakage or multifocal leaks can occur (see Figures 1-3). In the absence of a focal, well defined leak, photodynamic therapy with Visudyne is often effective. ICG angiography may be useful to guide treatment with PDT. If the leaking areas are close to the foveal center, half fluence PDT (that is, reduced laser exposure compared to the standard

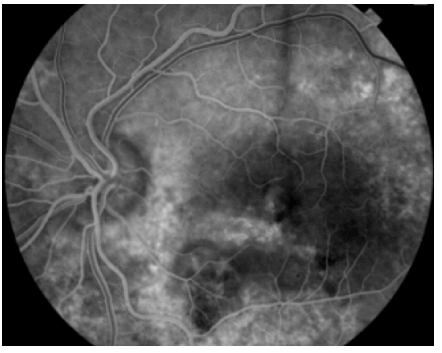


Figure 1: Early venous phase angiogram in a 60 year old patient with chronic, multifocal central serous choroidopathy in the left eye.

dose for AMD) may be used, and has been shown to produce less RPE atrophy than full-fluence PDT. More recently, pharmacologic therapy with compounds that have an anti-cortisol effect have been used.

These include Rifampin, an antibiotic normally used to treat tuberculosis, and spironolactone, a diuretic. Mifepristone, and eplerenone (other glucocorticoid antagonists) have been reported to be of benefit, but can be quite costly. Ketoconazole has been studied but the results were not impressive. Unfortunately, in our experience with Rifampin, the patient has to use the drug for at least three months, and the

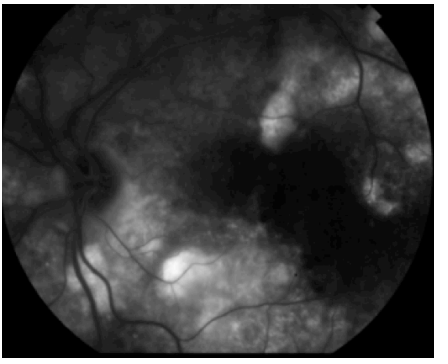


Figure 2: Late phase angiogram showing diffuse, poorly defined leakage.

effect often wanes when the drug is discontinued. Rifampin also has the annoying side effect of causing the sweat, urine and saliva to have an orange or purple color, and can have other side effects.

While the referral of central serous is not an

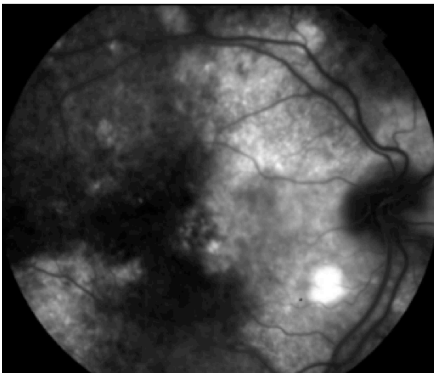


Figure 3: Late phase angiogram showing similar diffuse leakage in the right eye.

emergency, you would want to know that the facility to whom you refer has the capability to utilize enhanced depth imaging (EDI) OCT, fundus autofluorescence, ICG angiography and photodynamic therapy, as well as experience with therapies other than only thermal laser.

Georgia Retina
Clinical Trials Update

Georgia Retina continues to play an active part in both NEI and industry sponsored clinical trials research. We are dedicated to the advancement of ophthalmic science and patient care through the active participation in well-designed, randomized, controlled clinical trials. Participation in clinical research trials helps to bring new and innovative therapies for many blinding conditions into clinical practice and to our patients.

Age-related macular degeneration is associated with irreversible vision loss in advanced cases. More than 10 million people in the United States and more than 120 million people worldwide are affected by AMD. Geographic atrophy (GA) is an advanced stage of dry AMD which can cause legal blindness. Currently, there are no approved therapies to prevent, slow progression or reverse geographic atrophy. Acucela Inc. is a clinical-stage biotechnology company that specializes in discovering and developing novel therapeutics to treat and slow the progression of sight-threatening ophthalmic diseases and is sponsoring a study to examine the safety and efficacy of Emixustat Hydrochloride (an oral agent) for the treatment of GA associated with dry AMD. The "SEATTLE" study is designed as a Phase 2b/3 multicenter, randomized, double-masked1, dose-ranging study comparing the efficacy and safety of emixustat hydrochloride with placebo for the treatment of geographic atrophy (GA) associated with dry age-related macular degeneration (AMD). The study is ongoing and achieved 100% patient enrollment in March 2014. Top-line 24-month clinical trial results are anticipated in mid-2016.

On the other end of advanced AMD, great strides have been made with regards to treatment of choroidal neovascularization. Currently, there are three intravitreal monoclonal antibodies (Avastin®, Lucentis®, and Eylea®) that are commonly used for the treatment for neovascular AMD - they all target Vascular Endothelial Growth Factor (VEGF). Despite maximal therapy with these agents, the majority of patients do not achieve significant visual gain (≥ 15 letters of vision), and approximately 20% to 30% lose additional vision from baseline.

It is known that both VEGF and Platelet Derived Growth Factor (PDGF) play important roles in the proliferation of neovascular tissues - which consist of a combination of endothelial cells, pericytes, and inflammatory cells. VEGF is an endothelial cell survival factor and a potent inducer of vascular permeability while PDGF is responsible for pericyte survival. Unlike current treatments that target VEGF alone, inhibition of both VEGF (with Lucentis) and PDGF (with Fovista) may have a more significant impact on inhibiting neovascular tissues.

The Fovista phase 2 trial results appear promising. In regards to mean visual acuity gain, at 24 weeks, patients who received combination therapy (Fovista + Lucentis) gained 10.6 ETDRS letters whereas patient who received Lucentis alone gained 6.5 letters (p=0.019). Fewer patients lost vision with combination therapy than with Lucentis alone. The side effect profile seemed consistent with the adverse events commonly seen with current intravitreal agents.

Georgia Retina is now enrolling patients in a new Phase 3 Study comparing intravitreal Fovista (anti-PDGF) in combination with Lucentis (anti-VEGF) compared to Lucentis alone for wet AMD. Patients that choose to participate in the 2 year study undergo a screening visit to include blood tests, an OCT, and a FA. All patients deemed to be candidates will receive Lucentis and either Fovista or a sham injection. Some basic inclusion criteria include subfoveal CNV, BCVA between 20/63 and 20/200, and age ≥ 50 years.

In a similar fashion to which the National Eye Institute compared Avastin and Lucentis for the treatment of neovascular AMD in the Comparison of Age-related Macular Degeneration Treatment Trials (CATT), the NEI is sponsoring the SCORE2 study to assess the non-inferiority of monthly Avastin to monthly Eylea for treatment of macular edema associated with CRVO/HRVO. The presence of macular edema is a common visually debilitating complication of a retinal vein occlusion. In the past, studies have shown that macular grid laser (BVOS, CVOS trials) and intravitreal triamcinolone (SCORE trial) can be used to this treat macular edema. More recently, anti-VEGF agents such as Lucentis (BRAVO and CRUISE trials) and Eylea (Galileo and Copernicus trials) have been shown to be very effective for macular edema secondary to CRVO.

Georgia Retina, having participated in the original SCORE trial, will also be participating in SCORE2-- a multicenter, prospective, randomized, phase III clinical trial in which all participants enrolled will be followed for 12 months. SCORE2 aims to determine if Avastin is non-inferior to Eylea for the treatment of macular edema associated with central retinal vein occlusion (CRVO), with the primary outcome of visual acuity measured at Month 6. Secondary objectives of SCORE2 are to:

- compare the Avastin and the Eylea groups with regards to central retinal thickness, as measured with spectral domain optical coherence tomography (SD-OCT;
- assess Month 12 visual acuity and SD-OCT outcomes associated with different dosing strategies after Month 6 in participants who respond well to treatment;
- assess Month 12 visual acuity and SD-OCT outcomes associated with alternative treatment strategies (e.g. steroid) after Month 6 in participants who respond poorly to treatment;
- compare area of retinal ischemia and rates of neovascular complications of CRVO in the Avastin vs. Eylea groups;
- add to our knowledge of the safety profile of these anti-vascular endothelial growth factor (VEGF) medications in the setting of eyes with macular edema secondary to CRVO;
- conduct a cost effectiveness analysis comparing intravitreal Avastin to intravitreal Eylea to assess the economic implications.

These two new studies are being conducted at Georgia Retina's Marietta location.

Georgia Retina also continues its active participation in the Diabetic Retinopathy Clinical Research Network (DRCRnet) and is actively following patients enrolled in a comparative trial studying the safety and efficacy of Avastin, Lucentis and Eylea in the treatment of diabetic macular edema (DME). This is a 2 year study with primary outcome data to be released at 1 year. We eagerly anticipate the results later this year.

If you have any questions regarding the Clinical Trials program at Georgia Retina, please contact Dr. Stoltz or our study coordinator, Leslie Marcus.

the "Admin Angle"

by **Paul Lucas**, Administrator/CFO – Georgia Retina

Call me Captain Obvious, but in the world of healthcare – things be a changing!

Seemingly everyday the delivery of medicine becomes a little more burdensome with added regulation and the threat of reduced reimbursement for noncompliance.

We've seen the Physicians Quality Reporting Incentives (PQRI) change its name to the Physicians Quality Reporting System (PQRS) – don't we wish that was the only change – and expand its reporting requirements. The year 2013 required compliance to avoid 2015 penalties, and now in 2014 we are at it again to avoid 2016 penalties – or in CMS vernacular, "payment adjustments". Granted there is a "carrot" in the form of an incentive bonus for compliance, so the added internal education, training and system adjustments do carry this offset (assuming successful reporting). Further, it would appear this "quality" reporting effort, is here to stay; or rather, expand. Multiple methods exist to report your chosen quality measures. Should your group need a refresher, information abounds at the site below:

http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/pqrs/index.html

Closely linked with these CMS quality initiatives are the CMS Electronic Health Record (EHR) incentives. Around since 2012, this requirement is loaded with both an incentive and a penalty. Most practices that plan to be around for the indefinite future realize the importance of automation and secured recordkeeping; however, getting there can be quite challenging as I'm sure many of you have experienced. Converting to an EHR is but one part of the equation as the requirement to avoid payment reductions is to "prove it" by successfully attesting directly to CMS online. This proof involves the adoption of Core Measures, Menu Measure and Clinical Quality Measures – some mandatory and some with selection options, but all required. Many systems exist, most of which have achieved their certification as an accredited EHR for CMS reporting purposes. In addition to Measures, this requirement has Stages – three at the moment, all of which build on successful achievement of each: Stage 1, 2 & 3. Changes have occurred fairly regularly with this program and will continue to as more Measures are defined and Stage 3 requirements become more clear. For now, Stage 1 and 2 is where most practices lie. The CMS details can be found at:

http://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/index.html?redirect=/ehrincentiveprograms/

Let's see, what else remains on the change docket?

There's the conversion from ICD-9 to ICD-10, the new and improved coding initiative. That was put off a year and is now slated for becoming effective October 1, 2015. Much of this change will be system driven as EHR's and practice management systems adopt to the new and expanded coding requirements. That said, physicians and staff alike have a major learning curve ahead to bring this into the exam routine. Incentives here aren't carrot and stick oriented but rather comply or don't get paid at all!! Let's hope the added year allows for the much needed system testing and internal modifications to occur and stave off those dreaded line of credit draws.

Still hanging on as well is the Sustainable Growth Rate (SGR) factor used to calculate provider Medicare reimbursement. This one's been running for years, and thus far, only received lip service for a permanent fix or repeal. It bears to reason, one shouldn't hold their breath for a "fix" in the near future. Of course, this renders long term planning/budgeting to about six months. Again, adequate cash reserves (aka lines of credit sometimes) are a must to be prepared should future deferments for the cumulative 20%+ Medicare cut not occur. As for other temporary reductions that have morphed into seemingly permanent cuts, the 2% sequestration payment reductions are alive and well on most all Part B Medicare payments. 2022, I think, is the year this one is scheduled for removal. We'll see!

Many other external factors will shape our practice futures as well (ACO's, Pay-for-Performance measure to name a couple). Meanwhile, plenty of internal ones will continue, such as staff retention, provider succession plans, and the ever-present medical-legal environment to name a few.

All this said, the doctors at Georgia Retina and their eye care colleagues throughout the metro and state, everyday, deliver vision (and in some cases life) saving treatment as routinely as driving to work. This dedication to the patient is what makes the system work. Do right by them (patients), and the details historically have always sorted themselves out. Let's keep providing exceptional patient care, day in and day out, pay attention to the details of a changing environment, and hope this trend continues.

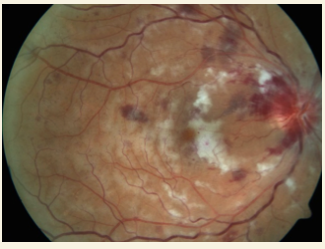
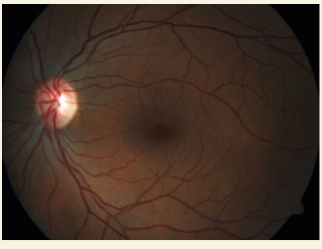
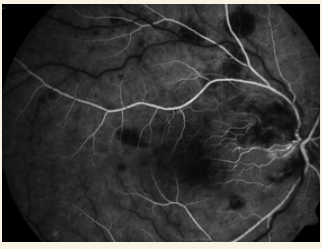
Please visit our website
to view our recently-added
Patient Education Videos!
www.garetina.com/education

Diagnostic Dilemma

L.T. is a 37 y.o. female with a history of previous deep vein thrombosis (DVT), who suffered sudden visual loss in the right eye 2 weeks prior to her exam at Georgia Retina. Because of the previous history, she was hospitalized by her hematologist and underwent numerous tests looking for other vascular problems. No new problems were found.

On her exam after the hospitalization, vision was 20/400 OD, with an afferent pupillary defect, and visual field loss. The anterior segment was quiet, with mild iris neovascularization. The anterior chamber angle was open and IOP was normal. In the left eye, vision, pressure, anterior segment, confrontation visual field and gonioscopy were normal. The right posterior segment showed disc edema and hemorrhage, many cotton wool spots, macular edema, venous tortuosity, and scattered peripheral hemorrhages. The left retina was normal.

Fluorescein angiography of the right eye showed normal arteriolar filling, with delayed AV transit in the right eye. The capillary bed was dilated, and there was evidence for capillary nonperfusion. The left eye had normal perfusion. OCT of the right macula demonstrated outer layer edema. The patient was started on antiVEGF therapy in the right eye with intravitreal Lucentis. Further treatment will be given based on her clinical response, and will probably include further anti-VEGF injections and panretinal laser photocoagulation. This clinically appears to be a typical, severe CRVO. However, L.T. is only 37 years old, and has an uncommon hematologic abnormality, hypofibrinolysis syndrome.

There are many risk factors for venous occlusive disease in the retina. The most common are hypertension, diabetes, and glaucoma. All patients with a central retinal vein occlusion should be considered for screening for vascular and hematologic abnormalities. Ipsilateral carotid disease can be linked to CRVO, especially in older patients. Hypercoagulability can be caused by polycythemia, thrombocytosis, protein C or S deficiency, Factor V Leiden, Factor VIII, and antiphospholipid antibodies. Other clinical risk factors include immobilization, surgery, obesity, hormone therapy, pregnancy, and myeloproliferative disorders.

This patient has a different cause for the thrombosis, i.e., hypofibrinolysis, which means that when any clot forms, it does not degrade and liquefy normally. In the normal situation, when clots form, the enzyme plasmin liquefies the clot. Plasmin is produced from plasminogen when it is acted upon by tissue plasminogen activator, or tPA. tPA is commonly used as emergency treatment for stroke and acute coronary syndrome, and is also used in retinal surgery to help liquefy subretinal clots.

L.T. was on anti-platelet therapy prior to this event, and the treatment will certainly be continued.

Pseudophakic (Irvine-Gass) CME—
Still a Common Entity

Pseudophakic cystoid macular edema (CME), also known as Irvine-Gass syndrome, was first reported by A. Ray Irvine Jr., MD in 1953 and later shown with fluorescein angiography (FA) by J. Donald M. Gass, MD, in 1969. Small incision phacoemulsification has significantly reduced the incidence of pseudophakic CME, but because cataract surgery is the most commonly performed surgery in the United States, pseudophakic CME still remains a commonly encountered problem.

The detection of CME can be either through clinical examination, FA or optical coherence tomography (OCT) examination. Of the three modalities, optical coherence tomography has the highest sensitivity, followed by angiography and then clinical examination. The incidence of CME measured by OCT and FA after uneventful cataract surgery is up to 41 percent and 30 percent, respectively. Most patients with CME found via FA or OCT will not have visual changes. In the past, clinical pseudophakic CME was defined as reduced visual acuity in the presence of angiographic CME following cataract extraction, and the reported incidence was 1 percent to 2 percent.

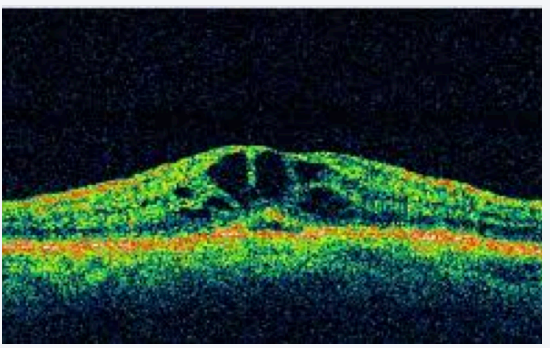


Figure 1: OCT demonstrating CME as well as subretinal fluid in a patient with pseudophakic CME following uncomplicated cataract surgery.

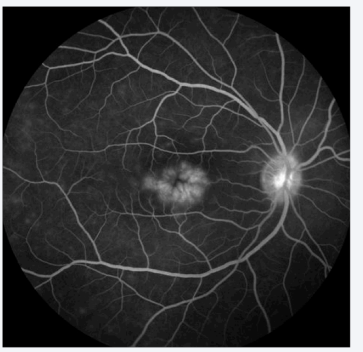


Figure 2: Late phase fluorescein angiogram depicting typical petalloid pattern of hyperfluorescence along with subtle late hyperfluorescence of the optic nerve head.

Pathophysiology

The pathogenesis of pseudophakic CME is thought to be multifactorial. However, the major etiology appears to be inflammatory mediators such as prostaglandins that are upregulated in the aqueous and vitreous humors after surgical manipulation. Inflammation breaks down the blood-aqueous and blood-retinal-barriers, which leads to increased vascular permeability. Eosinophilic transudate accumulates in the outer plexiform and inner nuclear layers of the retina to create cystic spaces that coalesce to form larger pockets of fluid.

Risk Factors

The development of pseudophakic CME is influenced by pre-existing systemic and ocular conditions, as well as complications during surgery. Surgical complications which increase the incidence of CME include vitreous loss, vitreous to the wound, iris incarceration in the wound, posterior capsule rupture, retained lens fragments and anterior chamber IOL.

Diabetes mellitus, even in the absence of diabetic retinopathy, has been shown to increase pseudophakic CME incidence rates. The incidence has also been reported higher in eyes with diabetic retinopathy. Furthermore, a postoperative CME usually develops in those with a prior history of diabetic macular edema (DME). If the patient actively had DME at the time of surgery, it rarely resolves on its own. For these reasons, DME and severe diabetic retinopathy should be well treated before having cataract surgery. Patients with uveitis have a higher incidence of pseudophakic CME than non-uveitic patients. Eyes treated perioperatively with oral corticosteroids had a 7-fold reduction in CME, while those with active inflammation within 3 months of surgery had a 6 fold increased risk of developing CME. Such studies indicate that Strict control of ocular inflammation for at least three months is imperative for successful cataract extraction.

Other ocular conditions associated with a higher incidence of pseudophakic CME include epiretinal membrane, vitreomacular traction, and retinal vein occlusion. Patients with these vitreoretinal diseases should be advised to consult a retina specialist to find out whether or not they need any prophylactic treatment prior to cataract surgery.

Treatment for Pseudophakic CME

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the production of prostaglandins by their effect on the cyclooxygenase enzyme. Corticosteroids inhibit phospholipase A2, which also reduces arachidonic acid metabolites, particularly the leukotrienes that attract inflammatory cells and are potent mediators of inflammation. Therefore, NSAIDs and corticosteroids act synergistically at different sites in the inflammatory cascade to reduce the production of inflammatory mediators.

The current recommended regimen for treatment of CME is a combination of corticosteroids and NSAIDs. Initial treatment usually consists of topical administration of those medications.

For pseudophakic CME refractory to topical therapy, periocular corticosteroids given sub-Tenon's or subconjunctivally provide more sustained drug release and a higher concentration of the drug to the treated tissue. Intravitreal triamcinolone acetonide, dexamethasone implant (Ozurdex, Allergan) and fluocinolone acetonide implant (Retisert, Bausch + Lomb) have also been used in refractory cases. The literature reporting their efficacy in macular edema is mainly in diabetic or retinal vein occlusion eyes. Their efficacy in pseudophakic CME is unknown.

Vascular endothelial growth factor causes breakdown of the blood-retinal barrier and increased vascular permeability, contributing to the development of macular edema. Anti-VEGF with intravitreal bevacizumab (Avastin, Genetech) has been shown effective in refractory pseudophakic CME in some studies. Although a theoretical role may be considered for VEGF inhibitors, there is no definite evidence to recommend anti-VEGF agents as routine treatment for pseudophakic CME.

Oral carbonic anhydrase inhibitors (CAIs) may be considered in refractory pseudophakic CME. CAIs are thought to improve the pumping action of the retinal pigment epithelium, to decrease intraretinal fluid. They have been reported effective in treating macular edema due to retinitis pigmentosa and aphakia but CAIs have not yet been investigated in pseudophakic CME.

It is evident that the prevention and treatment of pseudophakic CME has been evolving over recent years. With approximately 3 million cataract surgeries performed in the United States per year and heightened patient expectations, it is important for retinal specialists to understand the varied pathogenesis, risk factors and proper management of this condition. New technology has and will continue revolutionize the diagnosis, prognosis and treatment of this condition.

Participating Insurance Plans:

- Aetna U.S. Healthcare
- BCBS of Georgia
- Beech Street
- Blue Choice
- CCN PPO
- Choice Care Network
- Cigna
- Coventry Healthcare
- Evolutions Healthcare System
- First Health
- Great-West
- Humana
- Kaiser Permanente
- Medicaid
  - -Peach State Medicaid
  - -Wellcare Medicaid
  - -Amerigroup Medicaid
- Medical Resource Network
- Medicare
- Medicare Railroad
- Multiplan PPO
- National Preferred Provider Network
- Novanet
- Private HealthCare Systems
- Southcare PPO
- TriCare PPO, HMO
- State Health
- United Healthcare
- USA Managed Care Organization
- WellCare Medicare HMO

Other plans are pending; please call to check specific participation.

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