Less Than Perfect Outcomes After Uneventful Cataract Surgery
What Are We Missing?

Pseudophakic Cystoid Macular Edema (PCME)

Rapid Detection and Treatment
Improves Visual Outcome

Evidence points to a change in photoreceptor architecture in patients with Pseudophakic CME who have reduced CDVA.

Rapid detection and treatment of macula fluid is pivotal to mitigate visual sequelae.

Pseudophakic Cystoid Macular Edema (PCME)

Our Intervention caused the disease - by way of rendering the patient Pseudophakic

It is now our moral responsibility to:

- Diagnose Early
- Treat Early
- Refer Timely

Irrespective of cause of Temporary/Permanent Visual loss – Patient always attributes it to the Cataract Surgery & Surgeon

Cataract Surgeon’s interest in a Retinal disease

Spectral Domain OCT - Normal Resolved CME – Reduced CDVA

Ultra-High-Resolution OCT
Distortion of Cone Outer Segment Photoreceptor Tips (COST)
(Disruption of Verhoeff’s Membrane)
Pseudophakic Cystoid Macular Edema

AKA- Irvine-Gass Syndrome

- **Clinical CME** = 0.1 – 2.35 % \(^1, 2\)
  (Macular Edema associated with decreased visual Acuity)
- **Angiographic CME (Without Visual Loss)** = ICCE (60%), ECCE (15-30%) \(^3\)
- **OCT Incidence of PCME after Modern Phacoemulsification** = 4 - 41% \(^4\)
- **Permanently Reduced V/A after CME** = 8% \(^3\) to 26.8% \(^5\)
- **Total Ophthalmic payments (Medicare)** were 47% (US$1092) higher for those who developed PCME \(^6\)

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**Pseudophakic Cystoid Macular Edema**

- **Clinical Presentation**
  - Blurring of Vision (Watery Vision). *Need More Light Doc!*
  - Usually after 4 - 6 Weeks post operative.
- **Visual dysfunction to define Clinical CME varies**. \(^3, 7\)
  - Commonly cited level is 20/40 or worse, or
  - 2 lines less than the expected BCVA in a given eye
- **Classified as**: \(^1\)
  - **Acute** (occurring < 3 months lasting < 6 months)
  - **Chronic** (persisting more than 6 months)
  - **Late onset** (starting more than 3 months after cataract extraction)

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**Diabetic Retinopathy & Diabetic Macular Edema**

- **Medications:** PG analogs: Latanoprost, Bimatoprost, Travoprost
  - **Timolol**
  - **Preservatives (Benzalkonium)**
- **Uveitis**
- **Retinal Vein Occlusion, Retinal Degn, Radiation Retinopathy**
- **Intraoperative IOP Fluctuations & Post Op Hypotony**
- **Any Cause of Epiretinal Membrane, Vitreo Macular Traction**

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**Etiology**

- **Primary (Idiopathic)**
  - Irvine Gass Syndrome
  - Post Cataract Surgery CME

- **Multifactorial:**
  - Inflammation with the release of prostaglandins and leukotrienes
  - Vascular Instability, Vitreomacular Traction, Ocular Hypotony
  - Ultraviolet light damage

- **Inflammatory mediators** that are upregulated in the aqueous and vitreous humor 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.

- In **chronic CME**, lamellar macular holes and subretinal fluid may also form.

**Pathophysiology**


**Pathology**

- **'Dull' Foveal reflex** in an otherwise normal looking macula.
- **Retinal Thickening**
- **Yellow Spot at fovea**
- **“Cystic spaces seen at macula”**

**Clinical Diagnosis – Fundus Examination – 90D/78D**

- **Etiological Factors**
  - **Instability of Vascular endothelium**
  - **Breakdown of Blood retinal Barrier**
  - Extracellular and intracellular accumulation of FLUID.
  - Muller cell Breakdown
  - Collection of Fluid in Outer Plexiform and Inner Nuclear Layer

  **CYSTOID MACULAR EDEMA**
OCT - Optical Coherence Tomography

**Diagnosis**

OCT in PCME is characterized by:
1. Loss of the foveal depression
2. Retinal thickening
3. Cystic hyporeflective lesions

OCT also allows the detection of:
1. Vitreoretinal traction
2. Lamellar holes.

**Response to Treatment**

- Test to Find Integrity of Blood Retinal Barrier
- Test done to determine Retinal morphological Alterations

**F.F.A**

Test assessing the retinal function
- Macular Function test
- Contrast sensitivity Test
- Electroretinogram

**O.C.T**

- OCT in Mild Cystoid Macular Edema
  - Few Cystic Spaces
  - Relatively Preserved Foveal Contour

**OCT - Optical Coherence Tomography**

**OCT - Mild Cystoid Macular Edema**

- Hypo-reflective Cyst with clear fluid
- Loss of Normal Foveal contour
- Relation at Vitreo retinal interface
**Fundus Fluorescein Angiography**

- **Pre-OCT era**: Reduced visual acuity + no clear Fundus findings.
- **Still the ‘Gold Standard’** – Can rule out other causes of C.M.E. 4
- **“Angiographic macular edema”**, macular edema visible only angiographically.
- **Findings**:
  - **Early frames**: Retinal telangiectasis, capillary dilatation, and leakage from perifoveal capillaries – developing into
  - **Late frames**: Classic ‘petaloid’ pattern.
  - Optic nerve staining may also be seen

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Fundus Fluorescein Angiography

Minimal CME

Moderate CME

Typical CME
‘Flower Petal (Petaloid) Appearance’

Dye in Cystoid spaces

Progression

With Treatment Spontaneously
Etiological Cause Settles
RPE Functions with Muller cells
Fluid is withdrawn from EC Space
Normal Morphology Restored
Regain of Lost Function and vision (MOST COMMON)
Chronic CME (Non Resolving) OR
Coalescence of Cystic Space
Larger Cavities Formation
Lamellar Hole at Fovea
Visual loss
PCME - Treatment – Bad News!

• No standardized treatment or prophylactic protocol for PCME, because:
  – No well designed large RCTs with long-term follow-up are available. 4, 8
• No FDA-approved therapy for the treatment of CME 9
• FDA approved Topical NSAIDs for Post Op inflammation (not PCME): 4, 9
  – Diclofenac 0.1%; Ketorolac 0.4% & 0.5%;
  – Bromfenac 0.09%; Nepafenac 0.1% & 0.3%
  – Used to decrease inflammation that may cause CME. 9
• Prophylaxis 4
  – Does it prevents chronic/late onset PCME? Uncertain
  – Any long-term visual benefits? Uncertain
  – High risk eyes may benefit


PCME - Treatment – Good News!

• CME even without treatment shows spontaneous resolution.10, 11
  But, would you like to take a chance?
• Off-label PCME prophylaxis has become widely adopted 8, 12
• Topical NSAIDs
• Topical Corticosteroids
• Combination - Topical NSAIDs & Topical Corticosteroids


Topical NSAIDs or Steroids

• Where does the drug act ?
  – PG inhibition - Anterior Uvea or Retina ??
• Side effects to be considered –for a non-FDA–approved indication – Co Haze, Delayed Healing, Melt
Topical NSAIDs

- Topical NSAIDs speed the recovery of the blood–aqueous barrier after Cataract Surgery
- Topical NSAIDs reduce inflammation after Cataract Surgery
- FDA approved NSAIDs for ophthalmic use (Pain & Inflammation): Diclofenac, Ketorolac, Nepafenac & Bromfenac
- No FDA-approved topical NSAID for the prevention or treatment of Pseudophakic CME.

PCME - NSAIDs Monotherapy

- NSAIDs may have greater effect on Retinal inflammation in comparison with corticosteroids, which do not inhibit COX
- Topical KETOROLAC and DICLOFENAC were found to be equally effective for the treatment of chronic PCME
- NSAID (Nepafenac) monotherapy effective in improving visual acuity & reducing retinal thickness in Chronic PCME in steroid responders. ¹³

PCME - Combination Therapy (NSAIDs + Corticosteroids)

- Pretreatment with an NSAID in combination with a corticosteroid significantly reduced the incidence of postoperative CME. ¹⁴, ¹⁵
- Combination Therapy (Corticosteroids and NSAIDs) - superior visual acuity outcomes compared with either monotherapy ¹⁶
- Rationale:
  - Both drugs affect different aspects of inflammatory cascade
  - May work synergistically.

Nepafenac for PCME (Off label)

- Nepafenac is a Prodrug
- Converted by intraocular hydrolases into its active form, Amfenac.
- Nepafenac reported to have superior corneal penetration and posterior segment activity in rabbit models. ¹
- Superiority compared to other NSAIDs has not been proven yet in clinical studies for macular edema.
- Bromfenac and Nepafenac have been detected in the rabbit retina after topical administration, but it is unclear whether this translates into superior clinical efficacy. ¹⁷, ¹⁸, ⁴

References:

**PCME - Other Treatments**

- **Periocular Steroids** – Sub – Tenon’s/ Retro bulbar – PCME refractory to Topical
- **Intravitreal Steroids** – IVTA – short acting/ Endophthalmitis & Glaucoma Risk
- **Intravitreal Sustained drug delivery systems (DDS)**
  - Ozurdex (Preservative Free Dexamethasone in Biodegradable DDS)
  - Retisert (Fluocinolone acetonide intravitreal implant)
  - Iluvien (Sustained release Triamcinolone Acetonide)
- **Anti-VEGF** – Bevacizumab (Avastin)
- **Carbonic anhydrase Inhibitors** – Acetazolamide
- **Immuno modulators** - subcutaneous interferon alpha & intravitreal infliximab
- **PP Vitrectomy** – (ILM Peeling no added benefit)
  - Vitreo macular Traction or
  - PCME unresponsive to Med Rx > 1 yr, < 2 yrs

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**PCME - Prophylaxis**

- **Meta-analysis (1998)** - PCME prophylaxis beneficial
- **Topical NSAIDs are effective in Prophylaxis of PCME**
- **No study has documented a long-term (more than 1 year) benefit of this prophylactic treatment**
- **Long-term benefit of prophylactic treatment - Unknown**

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**Pseudophakic CME (PCME) - Summary**

- **Occurs even in uneventful Cataract surgery.**
- **Onset 4 – 6 weeks Postoperative.**
- **Good Vision Followed by reduced vision.**
- **Co-morbidity** –
  - Diabetic Retinopathy
  - PG Analogues for Glaucoma
  - Retinal Vein Occlusion (BRVO)
- **Early Detection & Treatment affects Visual Outcome favourably.**
- **Combination of Topical Steroid & NSAID preferred.**
- **Postoperative Prophylactic NSAID for High Risk cases.**
- **If response to treatment not satisfactory - Consider timely referral to Retina Colleague.**

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**Refractory PCME - Treatment**

- **Chronic PCME - Refractory to** previous topical, periocular, systemic, and intravitreal treatments
- **Bevacizumab injections** resulted in improved visual acuity and CMT at 12 months.
- **Triple therapy** with intravitreal triamcinolone, intravitreal bevacizumab, and topical NSAIDs has been shown to be effective as well.

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