Post operative Endophthalmitis [POE]

Endophthalmitis

- Endophthalmitis is the clinical term used to describe the inflammatory response of the eye to ocular infection.

Drugs 1996, 52(4), 526-540

Classification

Endophthalmitis can be classified according to the

- Mode of entry
- Type of etiological agent
- Location in the eye

Ind J Med Micro 1999, 17(3), 108-115

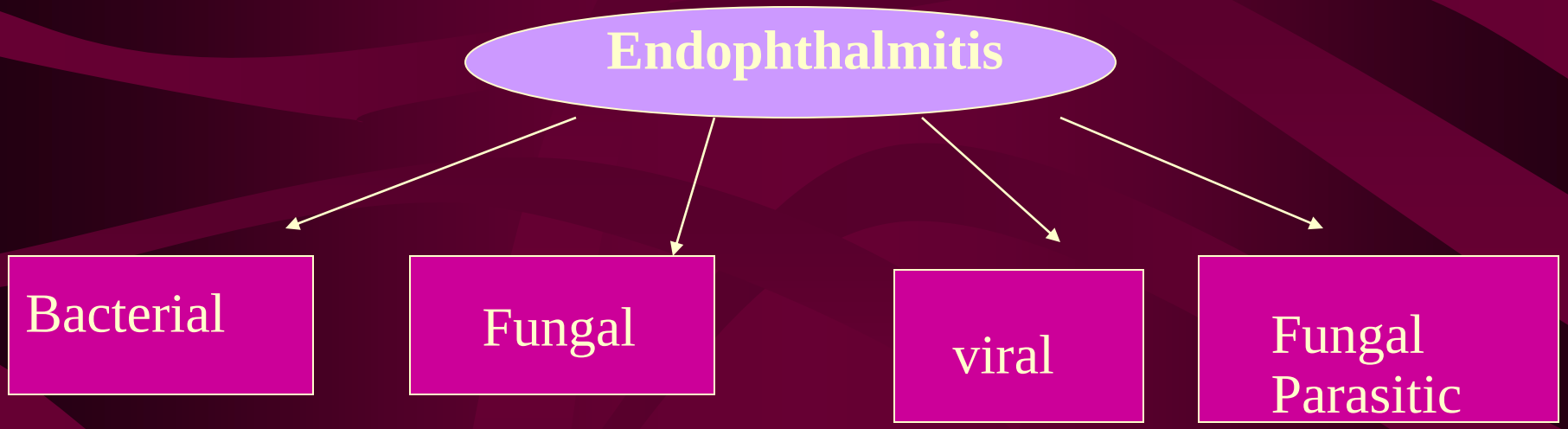
According to mode of entry

Exogenous	Endogenous
•Micro-org directly introduced from environment	•Haematogenous spread of organisms as a metastatic infection
•Usually occurs following surgery: i.e. **post-operative endophthalmitis** or trauma i.e. post-traumatic or keratitis	•Structural defect of eye is not necessary
•Mainly bacterial	•Common predisposing factors are immunocompromised status, septicemia or IV drug abuse
	•Mainly fungal

Ind J Med Micro 1999; 17(3): 108-115

Acc to aetiological agents

Based on aetiological agents



Ind J Med Micro 1999; 17 (3): 108-115

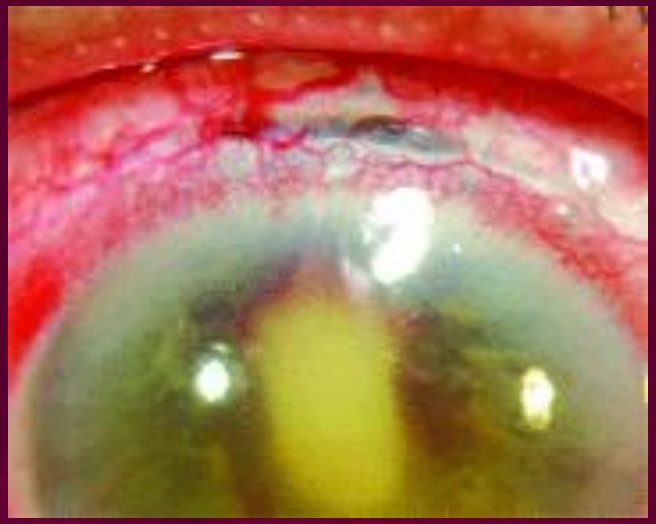
Based on location in the eye

- When sclera participates → **Panophthalmitis**

- Post-operative endophthalmitis is the most common form.
- It comprises 70% of infective endophthalmitis

Ind J ophthalmol 2000, 48: 123-128

Post operative Endophthalmitis (POE) is defined as a severe inflammation involving both the anterior and posterior segments of the eye secondary to an infectious agent.

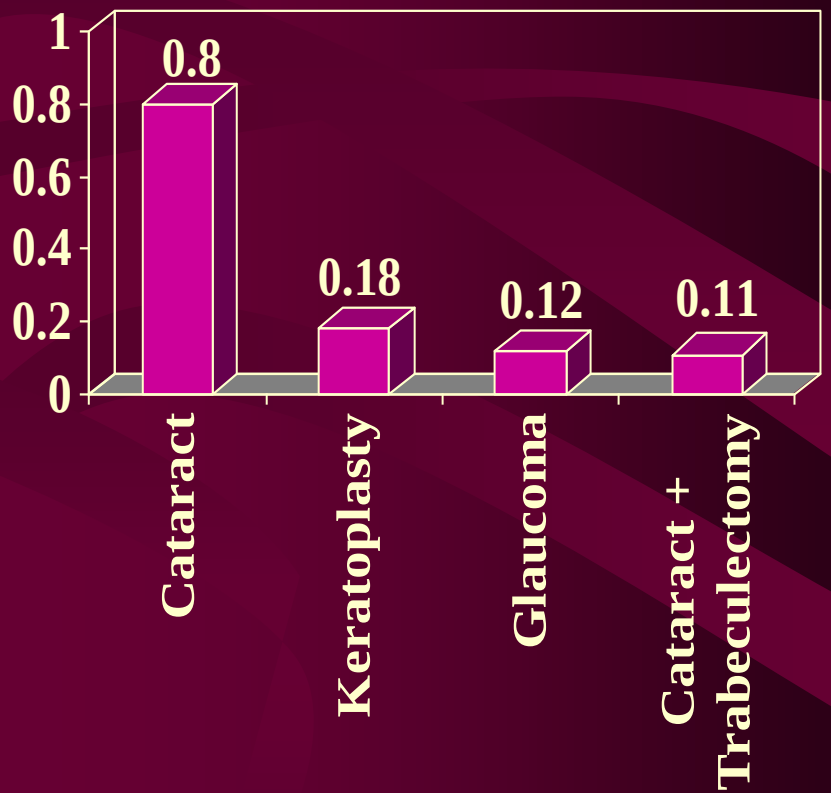


Ophthalmol 2004; 49 (2): S55-S61

Postoperative endophthalmitis

- May occur after any surgical procedure.
- Possibility must be considered after any surgical procedure that breaches the integrity of the corneo-scleral wall of the eye, no matter how ‘minor’ the breach may be

Incidence after various ocular surgeries (%)



Ophthalmology 1998; 105(6): 1004-1010

- Large majority follow cataract surgery, most common surgical procedure (approx prevalence 0.082%- 0.1%)

- Post- operative endophthalmitis is one of the most dreaded complications of cataract surgery and constitutes a true emergency.

CMR 2002, 15(1), 111-124

Incidence of postoperative endophthalmitis

- Worldwide, the reported incidence of post-op endophthalmitis is 0.04-4%.

In India,

Incidence varies from 0.07-0.3%

POE: A potentially blinding condition

- Though rare, it is potentially the most devastating complication of intraocular procedures and can lead to a permanent, complete loss of vision. (animal studies confirm that the retina begins to necrose very quickly in endophthalmitis)

- Endophthalmitis has been associated with severe visual loss in 20% of patients.

Surv Ophthalmol 2004, 49(2), S53-S54)

Post-op endophthalmitis: causes

- Periocular flora gain access into eye during surgery
- Organisms may be carried into the eye as surface fluid refluxes through the wound during surgery
- IOL contamination if it touches the ocular surface or with the air of the operating room
- Contaminated irrigation solutions

Risk factors

Bacterial

- Defects in sterilization of instruments.
- Contamination of tap water.
- Multiple dose fluids and drugs.

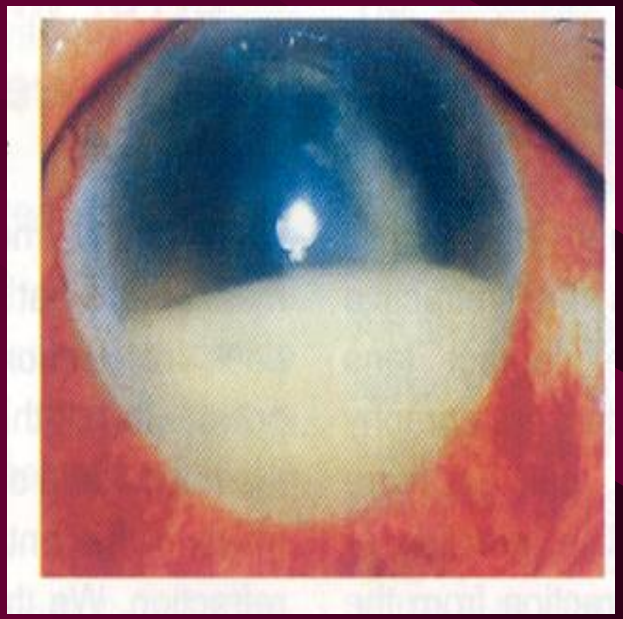
Fungal

- Contaminated irrigating solutions.
- Contaminated IOLs, viscoelastics, poor OT hygiene, hospital construction activity.

Symptoms

Patient presents with symptoms most commonly on the second day after surgery

- Pain
- Red eye
- Decreased vision
- Hazy cornea
- Hypopyon

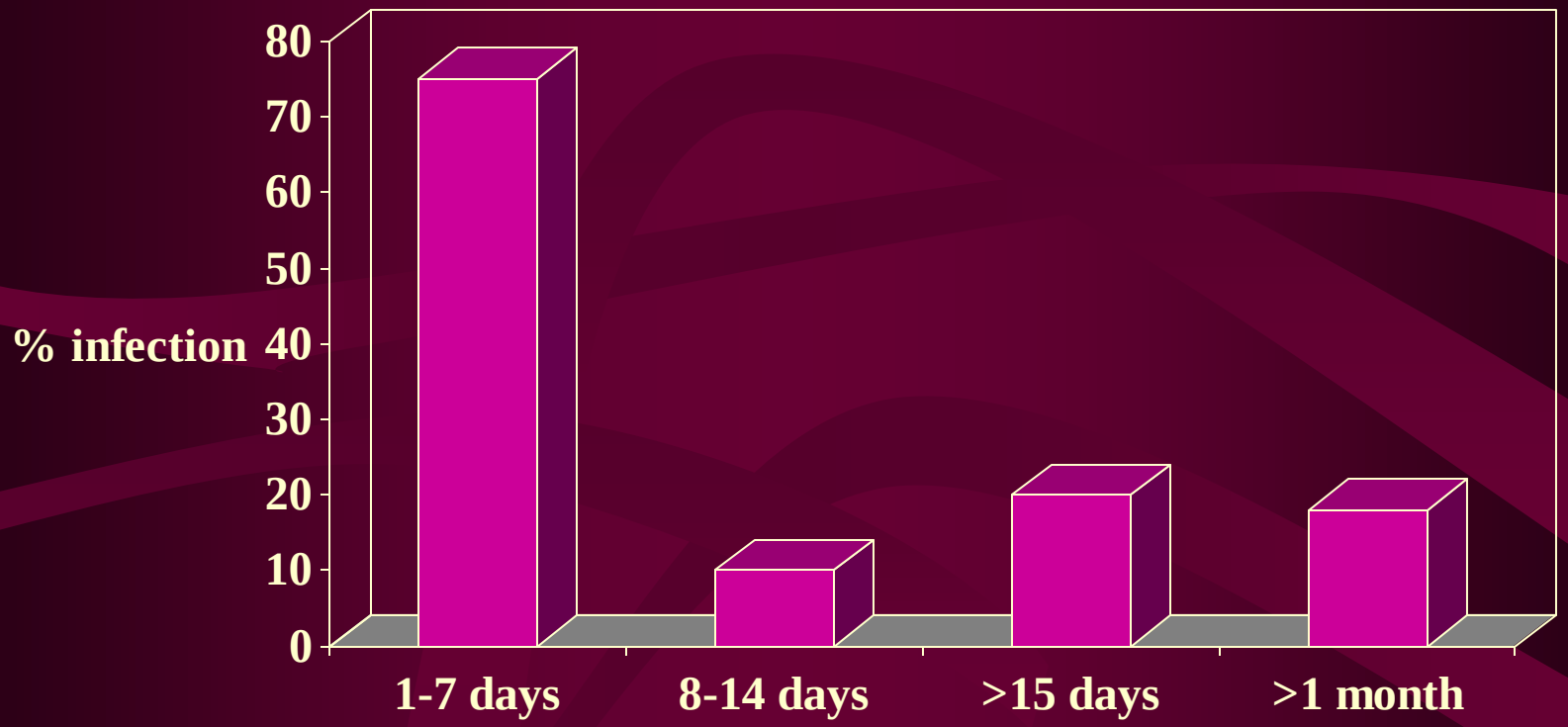


POE: Clinical aspects

- Three forms of clinical presentation can be distinguished
  - Acute form, usually fulminant, occurs 2-4 days post-op, most commonly due to *S.aureus* or streptococci.
  - Delayed form, moderately severe, occurs 5-7 days post-op, due to *S.epidermidis*, coagulase negative cocci, rarely fungal.
  - Chronic form, occurs as early as 1 month post-op, due to *P.acnes*, *S.epidermidis* or fungal.

Br J O Oph 1997; 81:1006-15

Day of presentation of infection



In most cases, infection occurs in immediate post-op period,

Suppl. Ophthal Times 2003; 28(5), 1-15

POE: Aetiological agents

- Most common potential source of infection is the periocular flora of the patient
- 75% of conjunctival cultures from normal eyes harbour *S. epidermidis*, *S. aureus* and various *streptococci*
- Similar pattern has been found in eyes with post-operative endophthalmitis
- Role of external ocular bacterial flora in the pathogenesis of post-op endophthalmitis has been proven by DNA studies

Ind J Med Micro 1999; 17 (3): 108-115

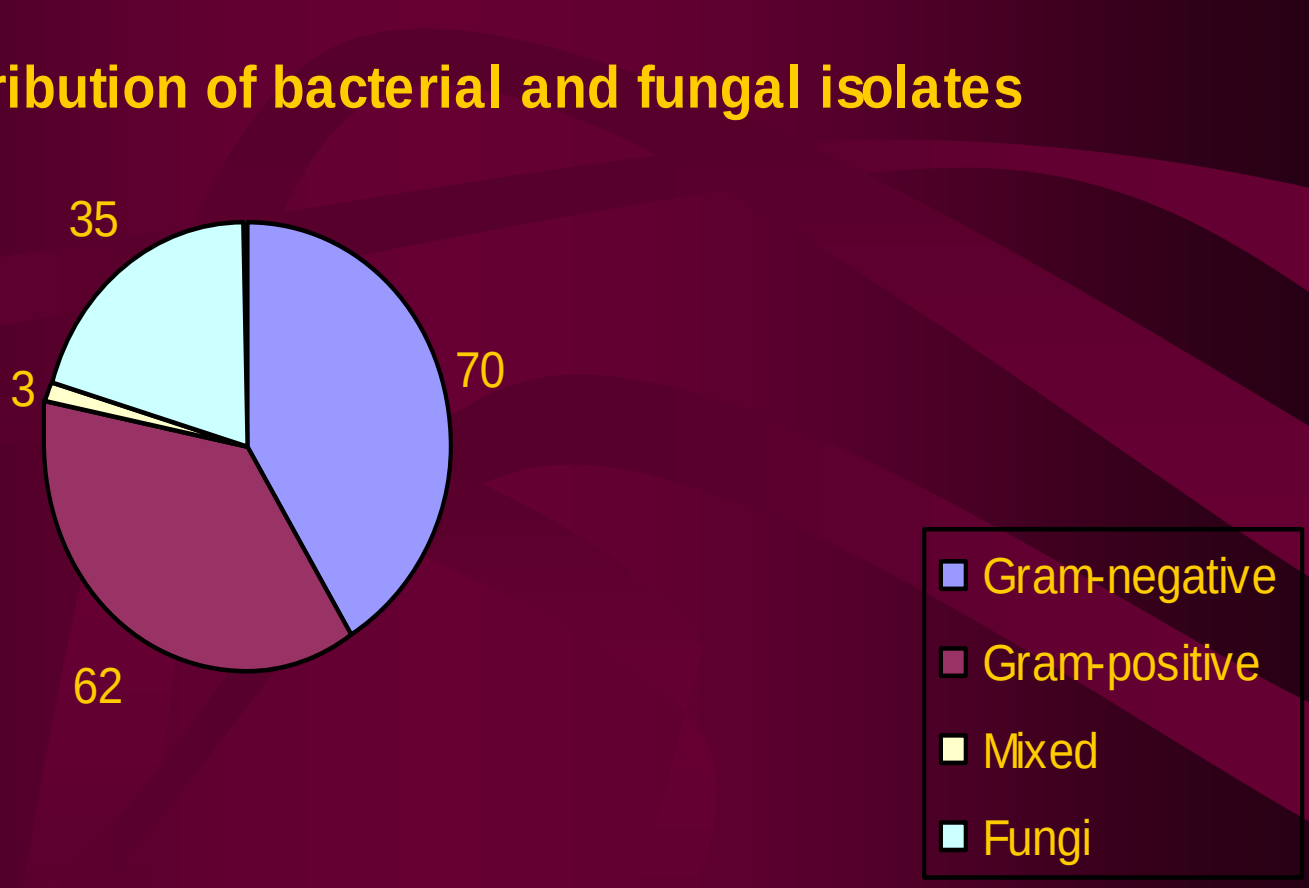
Most common organisms responsible for endophthalmitis

Gram positive bacteria 75%-85%	*Gram negative bacteria 10%-15%*
Staphylococcus epidemidis 43%	*Pseudomonas* 8%
Streptococcus spp 20%	*Proteus* 5%
Staphylococcus aureus 15%	*Haemophilus influenzae* 0-1%
Propionibacterium acnes 30 reports	*Klebsiella 0-1%*
Bacillus cereus 1%	*Coliform spp 0-1%*
Fungi (rare)	
Candida parapsilosis	
Aspergillus	
Cephalosporium spp.	

Br J Oph 1997, 81:1006-15

Aetiological Agents: Indian Data

N=170



Ind J Ophth 2000, 48: 123-128

Spectrum of bacteria from cases of post-operative endophthalmitis: Indian Data

Gram negative	
Organisms	72
P. Aeruginosa	29
Non-fermenters	18
Other Pseudomonas	15
Enterobacteriaceae	5
Miscellaneous	5

Spectrum of bacteria from cases of post-operative endophthalmitis: Indian Data

Gram positive	
Organisms	64
S. Epidermidis	22
S. Aureus	13
P. Acnes	10
Streptococc spp	7
E.faecalis	4
Micrococc spp	4
Coryne bacterium spp	2
Bacillus spp	2

Spectrum of fungi from cases of post-operative endophthalmitis: Indian Data

Fungi	
Fungi	37
Aspergillus spp	19
Unidentified fungi	12
Acremonium falciforme	2
Candida spp.	2
Fusarium spp	1
Paecilomyus spp	1

Ind J Ophthalmol 2000; 123-28

Diagnosis

- Clinical picture can be confirmed by culture of the organisms
- The most important samples to culture are aspirates from the aqueous and vitreous cavity
- Possibility of isolating an organism from vitreous 56-70% while from aqueous 36-40%

www.aios.org

Obtaining aqueous samples

- Aqueous fluid is obtained by paracentesis
- About 0.1 ml fluid is aspirated
- Innoculated on culture media

Obtaining vitreous samples

- Sample of vitreous is a very important source to know the causative organisms
- Aspiration may not provide adequate sample as vitreous is denser and contain inflammatory membranes in endophthalmitis
- There is also chance of retinal detachment.
- Safest method is vitreous biopsy (0.2-0.3 ml)
- Lost volume of vitreous replaced by saline

Management

Findings of the Endophthalmitis Vitrectomy Study (EVS) provide guidelines for management of POE.

ENDOPHTHALMITIS VITRECTOMY STUDY

Multicenter randomized trial carried out at 24 centres in U.S. (1990-1994)

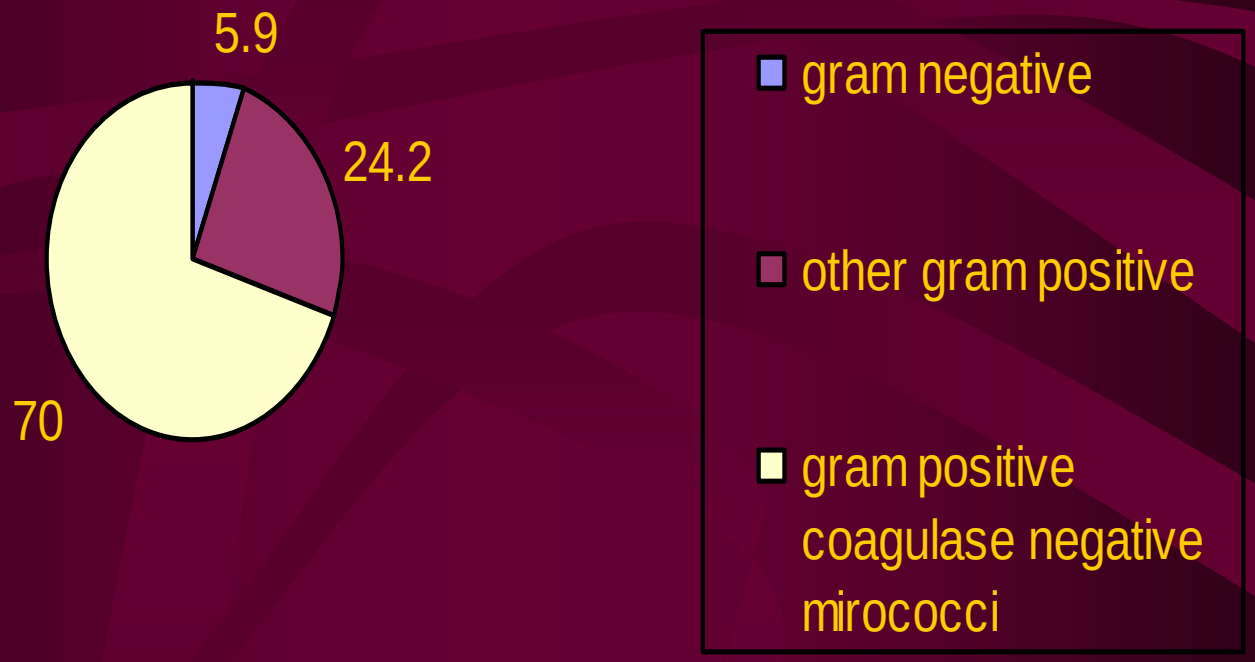
Purpose : To determine

- The role of IV antibiotics in the management of POE
- Role of initial vitrectomy in management.

- **Patients :** N = 420 patients having clinical evidence of POE within 6 weeks of cataract surgery

Arch Oph 1995, 113; 1479-96

Spectrum of isolates from EVS



Am J Ophth 1996; 122: 1-17

EVS

Intervention

Random assignment to immediate vitrectomy (VIT) or vitreous biopsy (TAP). They were also randomly assigned to treatment with IV or no IV.

Study medications :After initial VIT or TAP, all patients received intravitreal injection of amikacin (0.4 mg) + vancomycin (1 mg).

Vancomycin (25 mg in 0.5 ml), ceftazidime (100 mg in 0.5 ml), dexamethasone (6 mg in 0.25 ml) were administered subconjunctivally.

IV treatment: ceftazidime (2 g every 8 hrs) + amikacin (6mg/kg every 12 hrs) for 5-10 days

Main outcome measure

Evaluation of visual acuity and clarity of ocular media at 3, 9, 12 months

Arch Ophth 1995; 113: 1479-1496

Results:

- Systemic antibiotics were of no benefit in this study.
- Initial Vitrectomy was only beneficial for patients presenting with a very poor visual acuity.

Management

- In established endophthalmitis, antibiotics when given oral or I.V. have poor penetration into the vitreous cavity.
- Hence, intravitreal injections are treatment of choice.
- Intravitreal injections bypasses the blood retinal barrier and rapidly achieves therapeutic levels at the sites of infection

Br J ophthalmol 1997, 81:1006-1015

For gram positive organisms

- Because most cases are caused by gram positive organisms, vancomycin- (broad-spectrum activity against most gram positive species) has become an agent of choice
- Thus vancomycin 1 mg in (0.1 ml) is given intravitreally
- Non toxic in recommended clinical dosage.

Arch Ophth 1999; 117: 1023-1027

- Studies have proved that intravitreal vancomycin is the most effective drug for treating endophthalmitis
- Administration of single intravitreal vancomycin dose results in adequate antibiotic concentrations for over one week

Time after Intravitreal vancomycin admin (h)	**Vitreal level mg/ml**
48	137.85
72	182.36

Arch. Ophthalmol 1999; 117: 1023-27

B J O 2001; 85: 1289-93

- Intravitreal concentration of vancomycin usually does not reach therapeutic concentrations after IV administration of a single dose

Arch Oph 1999, 117: 1023-27

For gram negative organisms

- Gentamicin (0.4 mg) was used, but was found to be associated with retinal toxicity
- Amikacin was used (4 times less retinal toxicity than gentamicin as shown by animal studies)
- Amikacin covers large number of gram negative organisms and those resistant to other aminoglycosides

Br J Ophth 1997; 81: 1006-15
Arch Ophth. 1986; 104: 367-371

- A survey of retinal specialists suggested that amikacin can also cause retinal toxicity
- Thus, Ceftazidine has emerged as on alternative to amikacin
- More effective than aminoglycosides
- Retinal toxicity studies in primates reveal concentration of 2.25 mg/0.1 ml to be safe.

Arch Ophthalmol 1994; 112: 48-53

Br. J. Ophth 97; 81: 1006-15

Vancomycin combined with amikacin or ceftazidime appears to be best association in treatment of POE.

Br. J Ophth 1997; 81: 1006-15

Pre-operative scrub

- Povidone-iodine (5%) has broad antibacterial, as well as antifungal & antiviral activity
- It decreases conjunctival flora growth to 91%
- Can destroy bacteria in 30 secs

Steroids

- Based on experimental studies in rabbits, an intravitreal injection of 0.2-0.4 mg of dexamethasone was recommended within first 10 hrs after inoculation (except when fungal infection is suspected)

B J O 1997; 81: 1006-51

Avoiding the blinding tragedy :

Role of prophylactic antibiotics

Role of prophylactic antibiotics

Studies have shown that prophylactic antibiotic reduces the number of conjunctival bacteria at the time of surgery

- Optimal choice of pre-operative topical antibiotic depends on spectrum of bacteria covered
  - Rapidity of killing
  - Duration of action
  - Penetration and toxicity of antibiotic
  - Antibiotic susceptibility pattern
  - Cost

Topical fluoroquinolones are commonly used prophylactic agents because of their broad spectrum of activity covering the majority of these pathogens found in endophthalmitis

3rd generation fluoroquinolones (Ciprofloxacin, Ofloxacin): widely used as prophylactic agents

When to begin prophylactic antibiotics?

Prophylaxis: On day of surgery

"I don't start preoperative antibiotics until the patient arrives on the day of surgery. The drops are given 15 mins apart, starting 2 hrs prior to surgery. An antibiotic is administered immediately at the conclusion of surgery, every hour while the patient is awake for the first day, and then 4 times per day afterwards for a week. The reason I don't use several days of pre-operative antibiotics is the potential risk of propagating resistant bacteria, which may then cause problems, including endophthalmitis."

Dr. Francis S. Mah

Asst. Prof. Of Ophthalmology

Co-director of the Charles T. Campbell Ophthalmic Microbiology Laboratory

Prophylaxis: 3 days pre-op

"What I am trying to accomplish with 3 days of preoperative antibiotics is 2-fold: first, to minimize the inoculum, have the fewest number of organisms on the field (including the conjunctiva, lids, and lashes); second, I try to get the maximum penetration into the eye so that in case any pathogens were inoculated at the time of surgery, there were bactericidal levels ready to kill them. With gatifloxacin, there is enough drug to treat both, beginning 3 days preop and continuing 1 week postop."

Dr. Calvin W. Roberts, MD

Professor, Dept. of Ophthalmology, Joan and Sanford T. Weill Medical College of Cornell University, New York

3 days vs 1 hr pre-op use of fluoroquinolones

Aim: To determine the efficacy of reducing conjunctival bacterial flora with topical fluoroquinolone (Ofloxacin) when given for 3 days compared to 1 hour before surgery.

Methods

89 patients (92 eyes)

Study group (44 eyes)

1 drop q.i.d for three days + 1 drop every 5 mins, 1 hour prior to surgery

Control group (48 eyes)

1 drop every 5 mins, 1 hour prior to surgery

All patients: a scrub of 5% povidone iodine for a minute + 2 drops of 5% povidone iodine

Conjunctival cultures obtained and inoculated

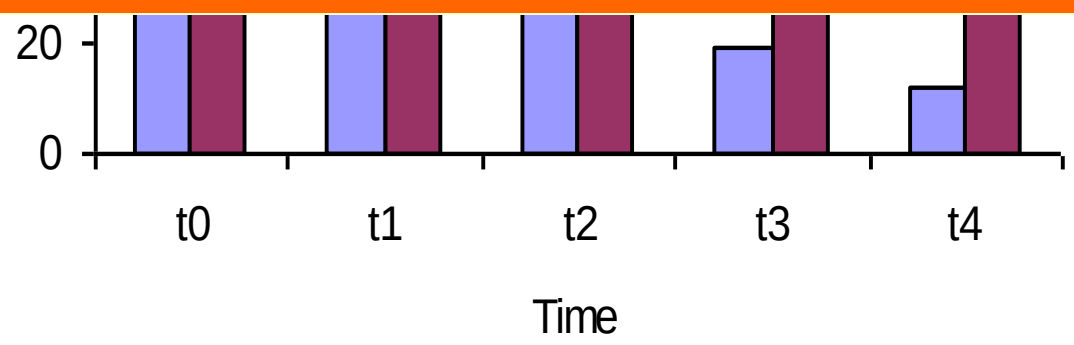
Ophthalmol 2002; 109: 2036-41

Description of time points when cultures were taken

Time points	Description
t0	5 days pre-op before topical antibiotic
t1	Before topical ofloxacin on the day of surgery
t2	After 1 hr pre-op antibiotic, before scrub
t3	After povidone iodine scrub, immediately before surgery
t4	Conclusion of surgical procedure

Percent of positive conjunctival culture

The application of topical fluoroquinolone for 3 days before surgery appears to be more effective in eliminating bacteria from conjunctiva than application 1 hour before surgery



Emerging resistance

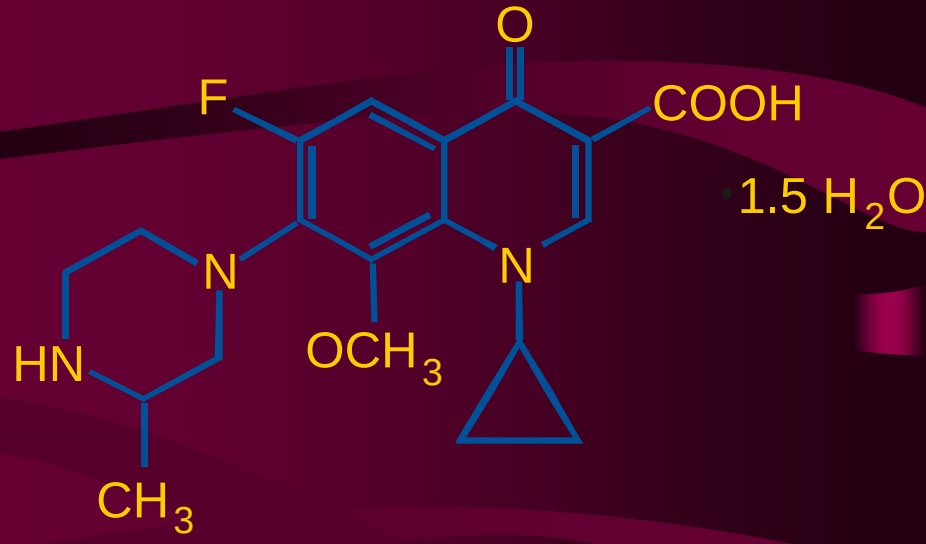
- Although fluoroquinolones have traditionally been chosen for topical prophylaxis resistance has been emerging to this class of antibacterials, particularly among gram-positive organisms.

INCREASING FLUOROQUINOLONE RESISTANCE

- A number of recent studies have reported emerging resistance to fq's among ocular isolates particularly among gram positive organisms
- In recent years, up to 30% or more of *S. aureus* strains are found to be fluoroquinolone resistant

Surv Ophth 2004; 49(2): 579-583

A new generation to treat infection



- The fourth generation fluoroquinolones like gatifloxacin, moxifloxacin have enhanced activity against gram positive pathogens.
- Organisms resistant to earlier gen FQs are susceptible to fourth gen FQs
- Secondly they are less prone to encourage development of resistant strains

Surv Oph 2004,49 (2),S55-61

Potential role of 4th gen FQs

- In terms of forestalling the development of resistance, primary use of 4th gen FQs may actually be a better strategy than initial use of older FQs
- Conventional strategy of reserving the use of newer anti-microbial only when older anti-microbial fails may not be a wise strategy if applied to FQs

Dr. Francis S. Mah, MD

Asst. Prof. Of Ophthalmology

Co-director of the Charles T. Campbell Ophthalmic Microbiology Laboratory

"Use of these currently-available, weaker agents (i.e. ciprofloxacin, ofloxacin, and levofloxacin) will only facilitate the continued development of resistant strains. Immediate use of the fourth generation should eradicate the more resistant bacteria along with those that have yet to develop resistance."

Aim : To study *in vitro* potency of 2nd, 3rd, 4th generation fq's for: bacterial endophthalmitis isolates

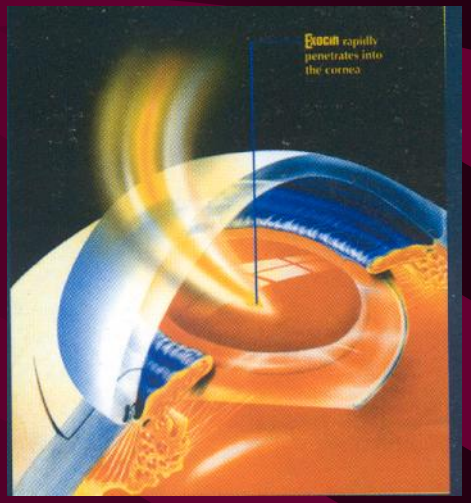
Results	CIP	OFX	GAT	MOX	Potency by Rank (p=.05)
2nd Gen FQ-Res SA	64	64	3.5	1.75	mox>gat>cip =ofx
2nd Gen FQ-Sen SA	.32	.63	.11	.06	mox>gat>cip >ofx
CoagNeg Staph FQ	64	64	2.0	2.5	mox=gat>cip =ofx
CoagNeg. Staph FQ	.13	.38	.09	.05	mox>gat=cip > ofx
Strep. pneumoniae	.75	2.0	.22	.09	Mox>gat=cip >ofx
Gram-negatives	.06	.19	.06	.08	Cip=gat=mox > ofx

Conclusion

In vitro study suggests that the 4th generation FQ are more potent than the 2nd and 3rd generation FQ for gram-positives and equally as potent for gram-negatives. The 4th gen FQ appear to cover 2nd and 3rd generation FQ resistance.

Gatifloxacin penetration

- In animal models gatifloxacin was proven to have superior ocular penetration than Ciprofloxacin.
- Another animal study has shown gatifloxacin to have equivalent ocular penetration to Ofloxacin.



Penetration of Gatifloxacin Ophthalmic Solution 0.3% into Human Aqueous Humor of Patients Undergoing Cataract Surgery

Purpose : To evaluate the penetration of gatifloxacin ophthalmic solution 0.3% into the aqueous humor of patients undergoing standard cataract surgery.

Methods : single center, open-label clinical study.

N=10.

Dosing regimen: Gatifloxacin 0.3%, 1 drop 4 times/day for 2 days, and then 1 drop every 10 minutes for 1 hour on the day of surgery.

Anterior chamber fluid was withdrawn during surgery and gatifloxacin concentration was quantified by HPLC.

- **Results :** The mean concentration (± SD) of gatifloxacin in aqueous humor was 1.26 ± 0.55 mcg/mL.

Conclusions

- The mean aqueous humor concentration of gatifloxacin achieved in this study meets or exceeds MIC values against commonly found bacterial ocular pathogens, including species of *Staphylococcus* and *Streptococcus.*

Conclusion

- POE is a devastating complication of ocular surgery.
- Certain measures and precautions can be taken to help reduce the risk of POE.
- Primary use of topical 4th gen FQs as prophylactic agents is beneficial.
- The newer 4th gen FQs are indeed interesting agents that will provide efficacy and may help control evolving resistance
- They offer a possible alternative to POE prophylaxis in an era of emerging resistance