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Research Article

Fungal Keratitis – Epidemiology and Treatment Outcome - In North Costal Andhra Pradesh

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Abstract
Purpose: *To review the distribution, current trends, and response patterns for treatment of fungal keratitis isolates in costal districts over the last 2 years*
Methods
Design: *Retrospective, observational, case series.*
Participants: *Microbiology records of suspected fungal keratitis cases that underwent a diagnostic corneal scraping and cultures from March 1,2010, through April 31, 2012,at sankar foundation eye hospital, teritiary eye care and referral center, were reviewed. Culture results and medical and surgical management response were reviewed and analyzed.*
Results: *A total of 450corneal scrapings were taken during the 2years of the study. Pathogen was recovered in 380 samples (84.4%), with fungal keratitis accounting for 350 of the positive cultures (81.5%). Asperigillus 48.15%, Fusarium 43.15%, Yeast 0.2%, Paecillomysis0.52%, and Acremonium 0.52%, not able to grow in 7.63%. Out of 380 cases 315 cases responded for topical antifungals, 75 cases with deep infiltrates and endoexudates resistant to topical medication alone, 33cases posted for TPK , 42cases treated with intracameral Ampho-B 10-15 u and intrastromal 7.5microns at least 2-3 times along with oral anti fungals.*
Conclusions: *1. About 90% h/o of injury with vegetable matter,2.Pts who presented early are responded very well with Natamycin 5%e/d and Fluconazole e/d along with repeated superficial debridement . If not responding addition of Amphotericin B 0.2%e/d hrly is with good results, 3.Deep infiltrates and endoexudate cases those who were given intracameral and intra stromal along with oral azoles doing well than TPK patients after optical PKP. 6. Topical Voriconazole 20% e/d (aurolab) did not give any added advantage except in few cases. 7.Pts on steroids were refractory to maximum medical treatment ultimately going for surgical intervention.*
Keywords: *fungal keratitis, asperigillous, natamycin, vozole, intracameral Ampho-B, deep keratitis, TPK.*

According to the World Health Organization, corneal diseases are a major cause of vision loss and blindness, second only to cataract in overall importance. It is estimated that ocular trauma and corneal ulceration result in 1.5 to 2 million new cases of corneal blindness annually.

Objective

To review the distribution, current trends, and response patterns for treatment of fungal keratitis isolates in costal districts over the last 2 years (from March 1, 2010, through April 31, 2012, were reviewed).

Design

Retrospective, Observational, Case Series.

Participants

Microbiology records of suspected fungal keratitis cases that underwent a diagnostic corneal scraping and cultures from March 1,2010, through April 31, 2012, at Sankar foundation Eye Hospital, Teritiary Eye care center, North Costal Andhrapradesh. Referral center for Costtal Andhrapradesh, Costal districts of Orissa and Chattisghar, were reviewed. Most of the patients who attend the Hospital with corneal ulcer were working as agricultural Labourers.

Methods

Culture results and antifungal response profiles were reviewed and analyzed, Main Outcome Measures and distribution of the main isolated pathogens as well as treatment response patterns for antifungals and TPK were analyzed

Results

Microorganism Identification

- A total of 450 consecutive corneal scrapings were taken during the 2years of the study. Pathogen was recovered in 380 samples (84.4%), with fungal keratitis accounting for 350 of the positive cultures (81.5%). All cases fungus identified wether inKOH mount, or Gram's staining, (*Fig3)* Culture blood agar, SDA

Predisposing factors *(fig1)Table 1*

1. Local predisposing factors include trauma, topical steroids, and antibiotics.
2. Trauma , Injury to the cornea is the leading cause of particularly fungal keratitis. A history of corneal trauma with vegetable matter or organic matter is reported in327. (86.06%) of fungal keratitis.
3. Topical steroid use is reported in 7 (1.84%)patients of fungal keratitis
4. Cause is unknown in46 (12.1%)

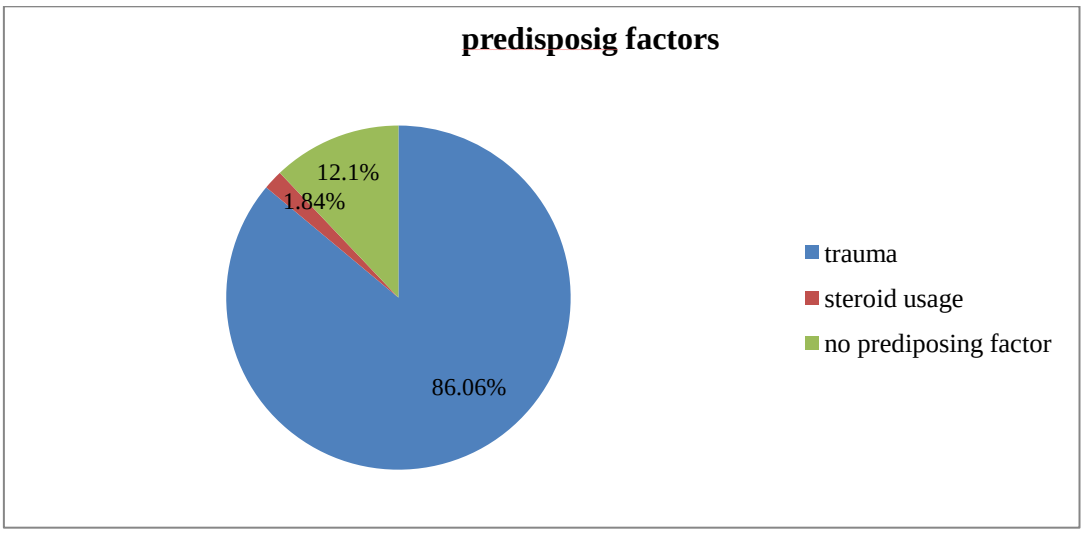


Figure 1

Etiologic agents *Fig 2, Chart1,*

- Filamentous fungi form the major etiologic agents of fungal keratitis.
- Asperigillus (*fig4,5,6*) 48.15%,
- Fusarium (*fig7*)43.15%,
- Yeast 0.2%,
- Paecillomysis (*fig8*)0.52%, and
- Acremonium (*fig9*)0.52%,
- 7.63%. organism not able to grow
- Most filamentous fungi associated with corneal ulceration in the tropics are found widely within the environment.

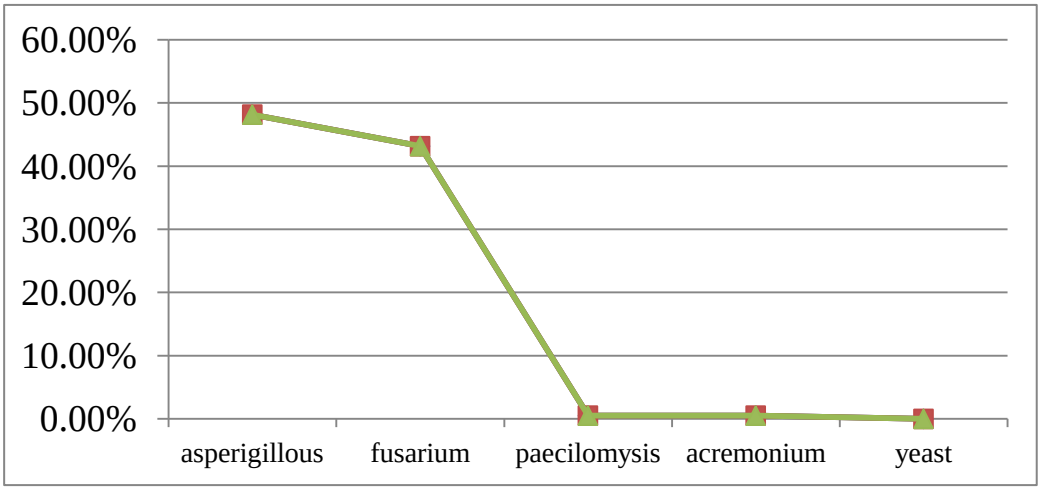


Figure 2

Out of 380 cases 101 cases are presented late with deep infiltrates and endoexudates resistant to topical medication alone. Cases with deep and large infiltrates and endo exudates posted for either TPK or intracameral and intrastromal Ampho-B 10-15 microns and, 7.5microns respectively given at 5-7 days interval at least 2-3 times along with oral anti fungal. Cases who are given injections are doing well than pts who underwent TPK after optical PKP.

Out of 380 cases 279 cases presented early 1-7 days of actual complaint started, 61 cases presented after 10-15 days, 33 cases presented after 15-20 days, 7 cases presented after more than 20days.

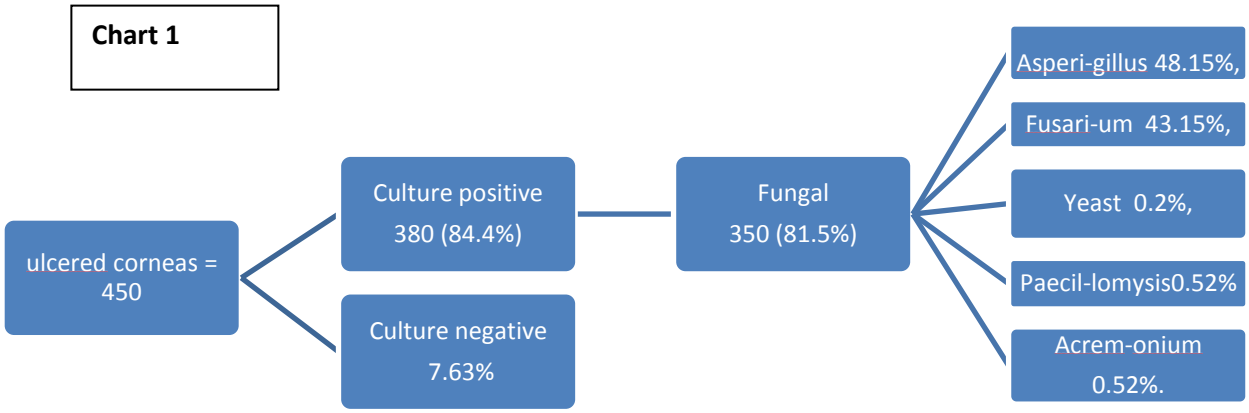


Fig 3 Fungal filaments on Gram staining

Figure 3

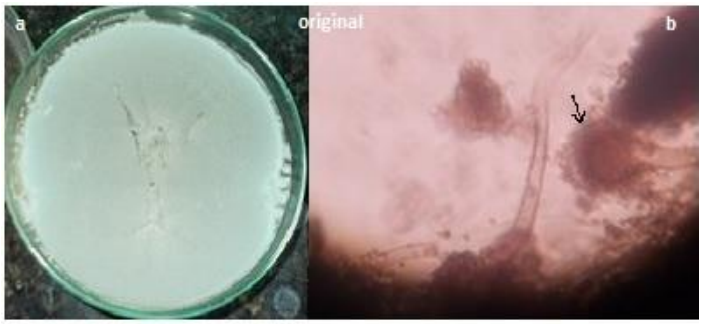


Fig :4 a: Asp. fumigatous on SDA plate, b: conidea on electron microscope

Figure 4

Association of injury and previous use of corticosteroids and anti- biotics with Organisms isolated from patients on presentation to the hospital Table 1

organism	Injury with vegetable matter	Use of corticosteroids	Use of antibiotics	No h/ predisposing factor
Aperigillus	171/183(93.4%)	6/183(3.27%)	2/183(1.09%)	3/183(1.63%)
Fusarium	164/174(94.2%)	0/174(0)	5/174(2.87%)	5/174(2.87%)
Acremonium	0/2(0%)	0/2(0%)	0/2(0%)	2/2(100%)
Paecilomyces	0/2(0%)	0/2(0%)	0/2(0%)	2/2(100%)
Yeast	0/1(0%)	0/1(0%)	0/1(0%)	1/1(100%)
Mixed infection gram+ve cocci	10/380(2.63%)	0/380(%)	0/380(0%)	0/380(0%)
Organism could not be isolated	12/13(85.2%)	1/13(7.67%)	0/13(0%)	0/13(0%)

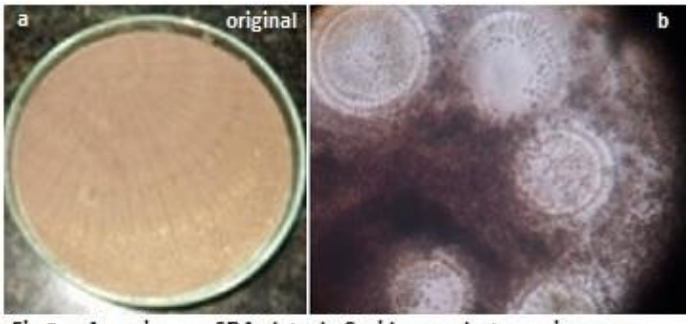


Fig:5, a:Asp. niger on SDA plate, b: Conidea on electron microscope

Figure 5

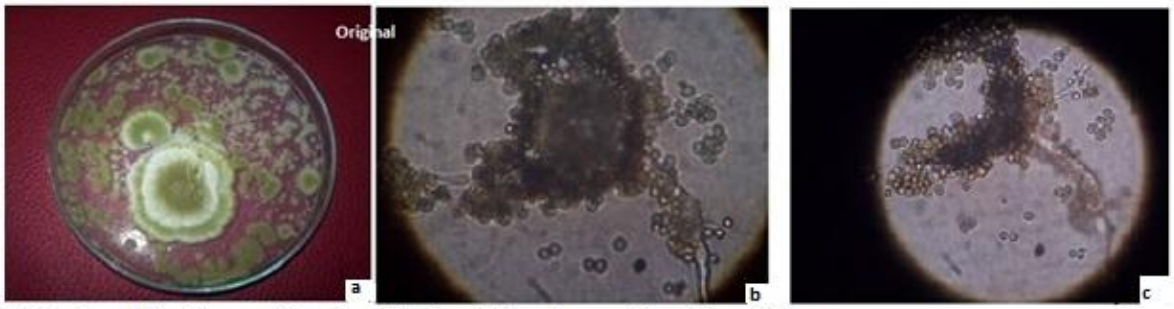


Fig:6 a, Asperigillous flavus on SDA culture, b&c Asperigillous flavus conidea with multiple spores

Figure 6

Fig :7 a fusarium on SDA culture plate, b; fusarium filaments on electron microscope

Figure 7

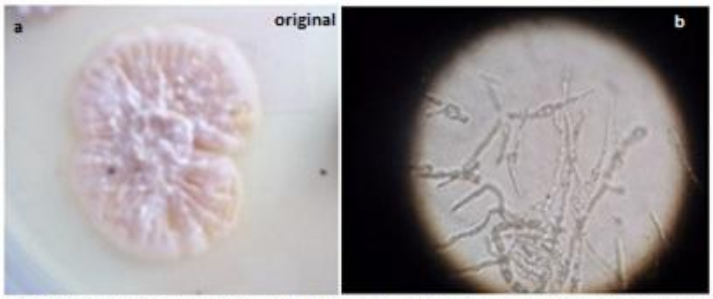


Fig :8 a, paecilomyces on SDA groth, b, paecilomyces filaments on electron microscopy

Figure 8

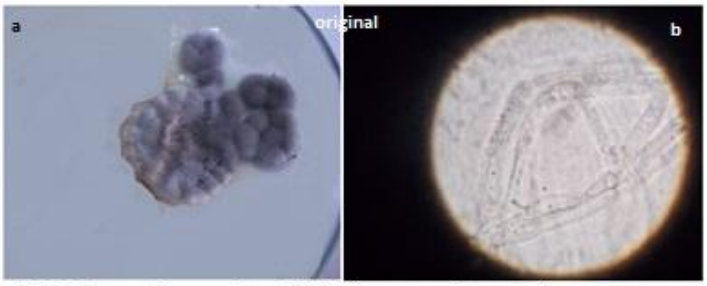


Fig : 9a:Acremonium growth on SDA,b: filaments on electron microscope

Figure 9

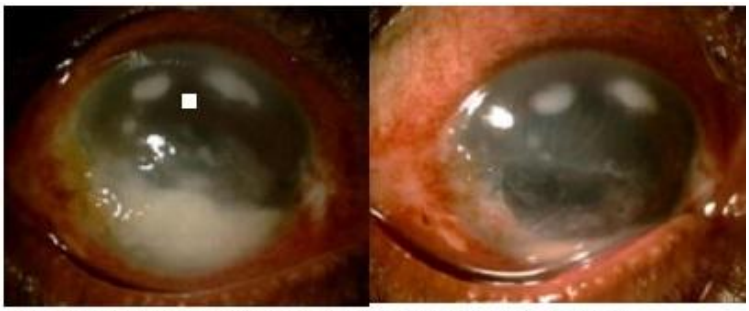


Fig :10a: central fungal infiltrate with hypopyon, b: After treatment

Figure 10

Fungal Keratitis Management and treatment outcome: Chart 1

- 279(73.2%)case out of 380 cases presented early within 5-7 days of symptoms.
- Teatment in KOH positive cases awaiting culture reports started on (*fig11*)
  - Natmycin 5%e/d hrly or Fluconazole e/d hrly
  - Fluroquinolonese/d 0.3% 4thhrly
  - Cycloplegic e/d 2times a day
  - Along with supported treatment like Vitamin C 2000mg/day, Vit B_{12} 1500 microns/day.
  - All cases reviewed after 48 hrs and
  - 248 out of 279 cases responded to above treatment. And topical Natamycin e/d 4 times a day continued for 2months after corneal scarring.
- IF not responding to above treatment
  - 31/279 cases Amphotericin- B e/d hrly 0.125% e/d /day added in the next visit. All cases responded to medical management.
- For those who responded with above treatment antifungal e/d continued for 2 months on minimum dose of 4times a day after corneal scarring.

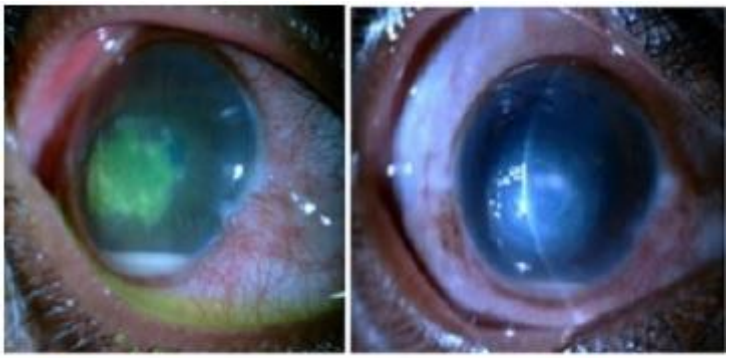


Fig:11a:Fungal ulcer with Hypopyon, b: After Treatment after 1week

Figure 11

Cases with deep and large infiltrates and endo exudates 101/380

posted for either TPK or intracameral and intrastromal Ampho-B 10-15 microns and , 7.5 microns respectively given at 5-7 days interval at least 2-3 times along with oral anti fungals tab fluconazole 200mg/day after liver function tests.

Topical voriconazole tried in 10 pts with no significant response.

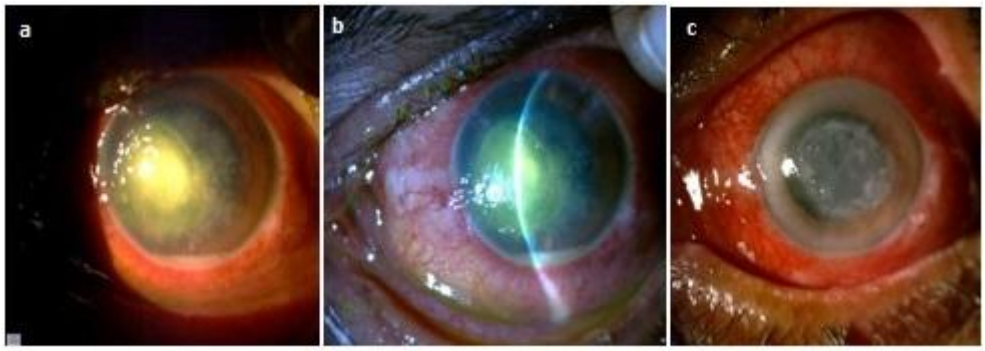


Fig:12 a,b: Deep fungal ulcer wth feathery edges &hypopyon, c: Scar after intra stromal injection

Figure 12

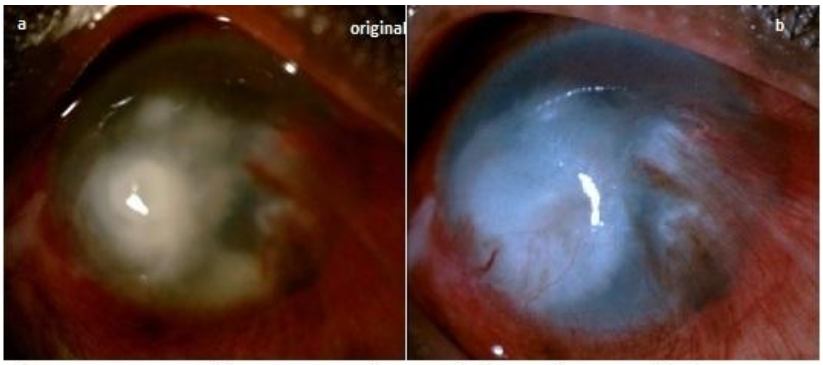


Fig:13 a, Deepfungal keratitis, b, corneal scar with vascularization after intrastromal injections

Figure 13

Fungal keratitis in those who were using steroids-

who were on topical steroids with fungal keratitis7/380 cases. Did not respond to maximum medical treatment *Fig 14.* All 7 cases posted for TPK

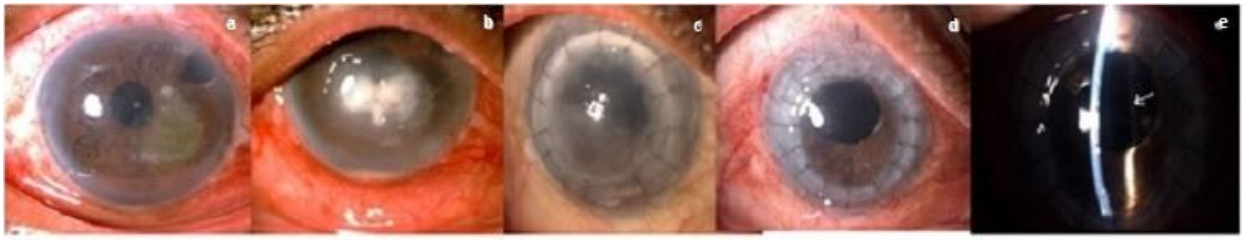
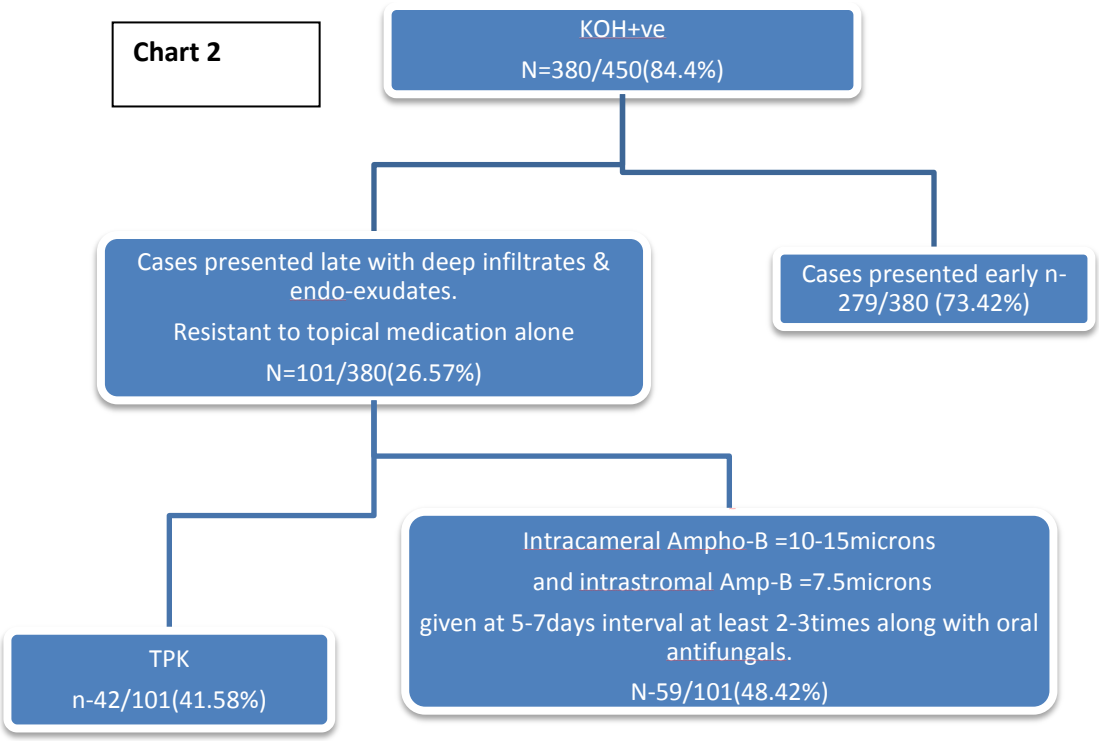


Fig: 14 a: Early Fungal ulcer-in pt who is on steroid e/d for Post cataract surgery, b, progressed to deep fungal keratitis inspite of maximum medical treatment after 2wks, c: posted for TPK with failed graft , d&e: Repeat PKP with SFIOL after 1YR

Figure 14

Out of 380 cases 101 cases presented 2-4 wks after the starting of symptoms/or treated elsewhere, with deep keratitis.

- KOH+ve -N=380/450(84.4%)
- 101 /380 cases (26.57%) presented late with deep infiltrates, endoexudates with large hypopyon.
- 42 /101(41.58%)cases posted for TPK(group-1),
- 59/101(58.41%) cases treated with topical and intracameral/intrastromal Ampho-B(*fig 12,13*)
  - 5% Natamycine/d, hrly for 1wk followed by 6-8times a day
  - 0.125% Ampho-B e/d for 1st wk followed by 6-8 times a day
  - Cycloplegics e/d 2times a day
  - Intracameral 10µ or intrastromal 7.5µ Ampho-B at 5-7days interval 2-3times along with
  - oral Fluconazole 200mg/day for 2 months(group-2).
  - Depending on improvement with treatment antifungal e/d continued for 4times a day for 4months.



Treatment out come in Deep keratitis

- Group-1
- 38 cases (90.47%) presented with graft failure, more than 4 clock hrs vascularization, anterior synaechea, retrocorneal membrane and corneal melting. 4 cases (9.52%) with clear graft with anterior synaechea>270dgrees and secondary glaucoma.

- TPK group final out come as follows-
  - 38/42 (90.47%) presented with graft failure,
  - 30/42 (71%) vascularization more than 4 clock hrs ,
  - 28/42 (66%) anteriorsynechea,
  - 38/42 (90.47% retrocorneal membrane and
  - 5/42(11.9%) corneal melting.
  - 4/42(9.52%) with clear graft with anterior synaechea >270dgrees and secondary glaucoma.
- Pts who were on topical steroids with fungal keratitis7/380 cases
  - Did not respond to maximum medical treatment *Fig 14*
  - All 7 cases posted for TPK
- In Injection Group II 59/101(58.41%) (*Fig12,15)* post treatment results are as follows

by the end of the treatment 50(84.74%) cases infection resolved with corneal opacity, 9 (15.25%) cases posted for TPK. In 40 cases (68.9%) anterior synaechea with vessels 2-3 clock hrs, 10 cases (16.94%) adherent leucoma with >3 clock hrs vessels, 9(15.25%) cases posted for TPK.

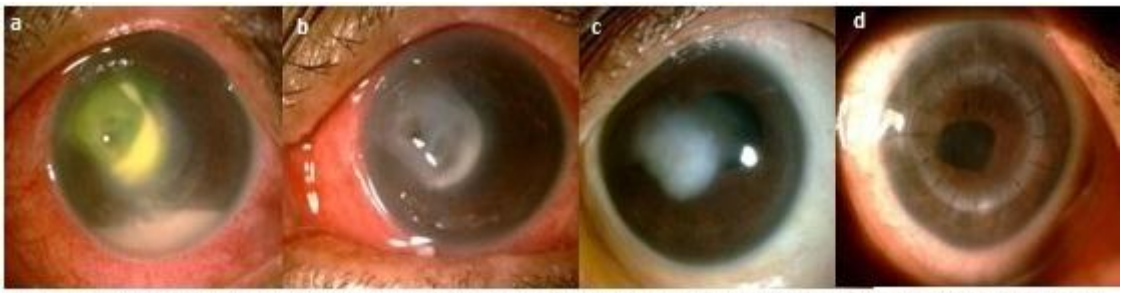


Fig:15 a:deep ulcer with hypopyon, b:after treatment absorbed hypopyon with central perforation, c: Adherent luecoma. d. Post PKP with clear graft after 6months

Figure 15

Final out come

- There is significant graft survival and visual prognosis in Group II (*Fig 11)* than Group I pts.(*Fig14).* In Group-1 As the steroids are not able to start graft failure in >90%cases.
- After optical PKP in 25 cases at a later date graft rejection noticed with in 4months due to corneal vascularization in Group I .
- In group-2 able to postpone TPK. After 4months 35 cases posted for optical PKP with visual outcome 6/36 to 6/12, no graft rejection up to 8 months post PKP.
- There was a very good response to medical treatment when pts report early in the 1st week than late reported cases.
- The most common fungal species isolate is Asperigillous. Next common isolate is fusarium.
- 90% of patients giving h/o of injury with vegetable matter.
- Pts who presented early are responded very well with Natamycin 5%e/d and Fluconazole e/d,hourly along with repeated superficial debridement .
- If not responding to this treatment after 5days addition of Amphotericin B 0.2%e/d hrly is showed good response.
- Among deep infiltrates and endoexudate cases those who were given intracameral and intra stromal along with oral azoles doing well than TPK patients after optical PKP.
- Topical Voriconazole20%e/d(aurolab) did not give any added advantage except in few cases.
- Fungal keratitis in pts with steroid treatment were refractory to maximum medical treatment even though they presented early, ultimately going for surgical intervention.
- Pts who presented early are responded very well with Natamycin 5% e/d or

Fluconazole e/d,hourly along with repeated superficial debridement . If not responding to this treatment after 5days addition of Amphotericin B0.2%e/d hrly has showed good response.

- Deep infiltrates and endoexudate treated with intracameral /intra stromal along with oral azoles doing well than TPK patients after optical PKP.
- Fungal keratitis in pts on steroids were refractory to maximum medical treatment even though presented early, ultimately going for surgical intervention.

Discussion

In our study h/o trauma with vegetable matter was the predisposing factorin 90% of fugal keratitis, 10 yrs review at referral eye center in south india at LV Prasad eye hospital presents the epidemiological features and laboratory results of the largest series of fungal keratitis[2]. Keratomycosis is predominant in young adults with trauma as the major predisposing factor.

1) In our study Asperigillus is the most common organism isolated and fusarium is the second common organism, which is correlating with P.A. Thomas observation[11], *Where as Aspergillus is reported as first common organism in* Riyadh, Saudi Arabia[8], fusarium is the second common organism isolated. But many studies reported fusarium is the most commonest organism isolated in ocular infections. In Bankok, thailand[3] , Bascom Palmer Eye Institute, Florida[5], Shandong, China[7], Aravind Eye Hospital, South India[4],LV Prasad eye hospital, south india[2] most common agents implicated in fungal keratitis is fusarium and second most common is *Aspergillus.* Candida is the first common in Willis Eye Hospital, Philadelphia[6], Melbourne, Australia[9], asperigillus is the second common organism.
2) Medical management is sufficient in Pts who presented early and are responded very well with Natamycin 5%e/d and Fluconazole e/d along with repeated superficial debridement . If not responding addition of Amphotericin B 0.2%e/d hrly shown with good results.
3) But in deep keratitis topical natamycin5% e/d not able to penetrate the corneal tissue, intrastromal injection or intracameral injection of Ampho-B7.5 to 10 microns helped to increase the drug load in the tissues to arrest and control the fungal load[10,11] along with oral Ketoconazole 200mg for a period of 2-3 months with liver function tests(Table 2). We are able to postpone theraputic PKP in these pts. For a period of 4months and after complete resolution of infection PKP done for Optical PKP at a later date. Topical Voriconazole20%e/d did not give any added advantage except in few cases is also observed by PA Thomas[14].Table 2

TABLE 2. Antifungal drugs to treat mycotic keratitis[10,11]

1. Natamycin (Pimaricin)

a. Commercially available as topical 5% suspension for ophthalmic use in some countries, where it constitutes first-line therapy for mycotic keratitis

b. Ophthalmic preparation is well-tolerated, stable and can be sterilized by heat

c. Relatively high levels reportedly achieved in cornea after topical application

a. Not commercially available as an ophthalmic preparation in many regions

b. Effective only when applied topically

c. Natamycin therapy may not be effective when keratitis is associated with deep stromal lesions

d. Only about 2% of total drug in corneal tissue is bioavailable

2. Amphotericin B

a. Good in vitro activity against Aspergillus spp. and Candida spp.;

emergence of resistant mutants rare
b. Can be administered by topical (0.15–0.30% solution), intracameral (7.5–30 lg/0.1 mL), intravenous (0.5–1 mg/kg BW/day) or intravitreal (1–5 lg/0.1 mL) routes
c. Penetrates deep corneal stroma after topical application; bioavailability sufficient for susceptible fungi Exerts direct fungicidal effect and exhibits immunoadjuvant properties
a. Intravenous administration frequently associated with renal tubular damage, due to use of deoxycholate as vehicle
b. Subconjunctival injection causes marked tissue necrosis at the site of injection
c. Topical application of concn > 5.0 mg/mL may cause ocular irritation (solutions of 1.5–3.0 mg/mL better tolerated)
d. Not commercially available as topical ophthalmic preparation; needs to be reconstituted from powder or intravenous preparation
e. Poor intraocular penetration after intravenous administration
3. Miconazole Reported routes of administration in mycotic keratitis: topical (1%), subconjunctival (10 mg/0.5 mL), intravenous (600–1,200 mg/day); topical and subconjunctival administration generally well-tolerated
a. Use of intravenous preparation occasionally associated with toxicity due to the vehicle used
b. Undetectable concentration of drug in rabbit corneas and vitreous after intravenous administration
c. Generally considered useful in Scedosporium apiospermum ocular infections, but treatment failures have occurred
4. Ketoconazole
a. Given by oral (200–400 mg/day) or topical (1–2% suspension) routes in ophthalmic mycoses
Well-absorbed and good tissue distribution after oral administration. Peak serum concn of 2–3 lg/mL 2–3 hours after 200 mg oral dose
a. Oral doses >400 mg/day may cause transient rise in concn of serum transaminases
b. Acid pH required for absorption
c. Prolonged administration of high doses may cause impotence, gynaecomastia or alopecia or papilloedema. No commercially available solution of ketoconazole for topical or subconjunctival administration in ophthalmic mycoses
5. Itraconazole
a. Synthetic dioxolane triazole
b. Given by oral (200–400 mg/day) or topical (1% suspension) routes in ophthalmic mycoses.
Oral solution and intravenous formulation recently developed; no reports of use in ophthalmic mycoses
c. Peak serum concn 0.3 lg/mL after single oral dose of 200 mg; increased to 3.5 lg/mL after 200 mg/day orally for 14 days
a. Commercially available capsule (100 mg) should be taken with meal; difficult to give in infants and children
b. May be poorly absorbed after oral administration in certain groups of patients.
Caution needed in patients with previous hepatic disease
c. Absorption after oral dosing affected by antacids and H2 receptor antagonists; may interact with other drugs
d. Poor penetration into rabbit ocular tissue, compared with fluconazole and ketoconazole, after oral dosing
e. Intravitreal injection (>10 lg) causes focal retinal necrosis in rabbits
f. No commercially available solution of itraconazole for topical or subconjunctival administration
6. Fluconazole
a. Synthetic bistriazole
Soluble in water, hence excreted through kidney; 10–20% protein
bound in serum; long half-life
b. Given by oral (50–100 mg/day), topical (0.2 to 2% solution) or intravenous routes
c. High bioavailability, low toxicity, good stability
d. Commercially available for oral and intravenous use
a. May interact with cisapride, oral antidiabetic drugs and phenytoin after oral administration

b. Less active against Candida glabrata and Candida krusei than against C. albicans

c. May not be effective in treatment of filamentous fungal keratitis

7. Voriconazole (Azole)

a. Potent activity against a broad spectrum of yeasts and moulds

b. Oral (200 mg twice daily), topical (1%), intravenous and intravitreal (100 μg/0.1 mL) routes of administration have all been described

c. Achieves 53% and 38%, respectively, of plasma levels in aqueous and vitreous following oral administration

d. Has been used successfully to treat keratitis

Voriconazole monotherapy may sometimes not effect cure; caspofungin may need to be added

4) Fungal keratitis in pts on steroids were refractory to maximum medical treatment even though presented early, ultimately going for surgical intervention eventhough pt presented early due to immunosu-ppressin locally fungus did not respond to maximum medical treatment, and ulcer progessed to deep fungal keratitis finally planned TPK in all 7 patients(fig14) .
5) In our study results of surgical treatment for deep fungal keratitis, where as in TPK as the steroids are not able to start graft failure noticed in >90%cases. Where as *Xie L* etal study[1], out of 108 grafts, 86grafts survived, 32 graft reactions, 15rejected grafts, 8recurrence of infection. We are able to postpone theraputic PKP in Group II (intrastromal or intracameral injection of Ampho-B 7.5 to 10 microns in 0.1ml) patients for a period of 4months and after complete resolution of infection PKP done for Optical PKP at a later date with good visual outcome and less chances of graft failure due to rejection as able to start topical steroids immediately after PKP, where as TPKP patients Topical steroids not able to start with the fear of recurrence of infection in the graft.

Conclusions

1. About 90% h/o of injury with vegetable matter, 2.Pts who presented early are responded very well with Natamycin 5%e/d and Fluconazole e/d along with repeated superficial debridement. If not responding addition of Amphotericin B 0.2%e/d hrly is with good results,3.Deep infiltrates and endoexudate cases those who were given intracameral and intra stromal along with oral azoles doing well than TPK patients after optical PKP. 6.Topical Voriconazole20%e/d (aurolab) did not give any added advantage except in few cases. 7.Pts on steroids were refractory to maximum medical treatment ultimately going for surgical intervention.

There is no financial interest.

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