Original Research Article

Mixed Infective Keratitis - Truth or myth

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Abstract

Background: Infective keratitis is a leading cause of corneal blindness. A good microbiological workup in such cases is essential as it helps in delivering a targeted therapy for treatment. Mixed infections have been often reported in cases of infectious keratitis. This was a prospective study done to assess the incidence of mixed infections. **Methods:** 180 consecutive patients of suspected microbial keratitis presenting to the Cornea services of our hospital from September 2016 to August 2019 were considered for the study. A step wise microbiological workup was done as per the existing guidelines for establishing the causative organisms. The corneal scraping was done by the investigator themselves and all the microbiological specimens were examined by a senior microbiologist. **Results:** The organisms detected were bacterial (40%) followed by fungal (19.4%) and acanthaoemeba(0.5%). Surprisingly, no case of mixed infection was detected. All the cases where a causative organism could be established responded well to targeted therapy. No cases of partial response to therapy were seen. Bacterial fungal interaction may interplay with human host and immune system leading to dysbiosis in microbial keratitis resulting in infection with only a single kind of organism. Probable causes could be due to avascularity of cornea and nutrition and immunomodulation provided by aqueous humor and tear film. **Conclusion:** In the study, no case of keratitis was microbiologically established to have mixed infection.
Key words: Mixed infective keratitis, bacterial, fungal, corneal scraping.

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INTRODUCTION

Infective Keratitis is an infection of cornea due to invasion by microorganisms leading to inflammation and tissue destruction within the corneal tissue. It is a potentially sight threatening condition if not treated appropriately. Cornea is usually resistant to infection due to natural host defence mechanisms like protection by eyelids, tear film, corneal epithelium and normal ocular flora. Compromise with these natural defences can lead to microbial invasion.[1] The patient usually presents with pain, redness, watering and loss of vision. The infiltrate can spread to sclera or posterior segment leading to panophthalmitis or endophthalmitis. In such advanced cases the prognosis for visual recovery becomes very poor. A step wise approach becomes crucial in the management of keratitis. Microbiological assessment is imperative for identification and treatment of microbial keratitis. The benefit of culturing an organism from the infiltrate is in the form of target therapy that can be delivered. This therapy has the dual advantage of not only being specifically targeted against the causative organism but also avoiding unnecessary toxicity to the host cornea. However, a microbiological work up may not always yield an organism. There could be reasons for the same like improper scraping, plating and inappropriate culture media. It could also be due to prior antimicrobial therapy before presentation. It is also important to differentiate infective from non-infective causes of keratitis. In cases of negative microbiological work up, non-responsive patients, progressive keratitis or partial responders, patients are often started on broad spectrum anti-bacterial

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and antifungal drops. A cocktail of therapy is also attempted when mixed infection etiology is reported. A longitudinal, interventional, prospective study was designed to assess the probability of mixed infection in patients of microbial keratitis and justify the role of multiple drug regimen in these patients.

MATERIALS AND METHODS

180 consecutive patients of suspected microbial keratitis presenting to the Cornea services of our institute from September 2016 to August 2019 were considered for the study. Perforated corneal ulcers at the time of presentation were, however, excluded from the study. The Tenets of the Declaration of Helsinki were followed and informed consent was taken from all the patients. Data was collected for sociodemographic background of the patient, nature, mode and duration of injury if present, systemic risk factors like diabetes, malnutrition, measles, diarrhea, immunocompromised state, malignancy and connective tissue disorders, contact lens usage or any previous ocular surgery and use of long term systemic and topical medications including steroids. Routine blood investigations, baseline blood counts, sugar level and liver and kidney function tests were done. Specialist consultation was sought for any associated medical condition. Local examination was done to exclude local risk factors like lid abnormalities, dacryocystitis, dry eye and compromised ocular surface. Documentation was also done for corneal ulcer measurements, non-contact tonometry and posterior segment changes, if any. After complete clinical examination, corneal scraping and cultures were performed. These were repeated subsequently in case of inconclusive results. In all the cases the base and the edge of the ulcer was scraped after removal of any loose mucus or debris. The material was transferred directly on the slides for Gram's and KOH staining. It was also inoculated on Blood agar, Chocolate agar, MacConkey agar and two Sabouraud dextrose agar (SDA) which were incubated at 25 and 37 degree Celsius. The same was then evaluated by an experienced microbiologist.

RESULTS

The Age and Sex distribution of the cases of microbial keratitis is shown in Table 1. Almost 75 percent of the patients were in the active age group of 20-60 years with male preponderance. Table 2 (A,B,C)shows organisms detected in corneal scrapings. Out of 108 positive isolates, 66.7% (72/108) were bacterial, 32.4% (35/108) were fungal and One case was (0.9%) Acanthamoeba. More than 65% of cases were from low socio-economic group 36 cases (20%) had a history of trauma. 29 cases out of these turned out to be fungal, 6 bacterial and 1 Acanthamoeba. Culture was positive in 108 cases (60%). The patients were started on treatment based on the results of Gram's and KOH. Treatment was modified on subsequent visits as per clinical response and culture and sensitivity reports when available. In cases where microbiological work up was negative the patient was started on therapy as per the clinical suspicion. Patients treated on the basis of clinical suspicion were 72(40%). Out of these 38 cases responded to anti-bacterial therapy or a change in antibiotic regime.10 cases responded only after shifting to antifungal therapy. 24 cases required therapeutic keratoplasty. The recipient cornea was sent for routine histopathological analysis and microbiological examination. Nine of these cases yielded positive results in the corneal button which was sent after keratoplasty. Of these 2 were Staphylococcus, 1 Streptococcus, 5 Aspergillus and 1 Acanthamoeba. Two of these cases could not be salvaged. No organism could be established in either of them. Both these patients were more than 60 years of age. Final visual outcome at 3 months follow up (Best corrected visual acuity-BCVA) is shown in Table 3. Seventy five percent of the patients gained useful vision of 6/60 or better. Out of these 36 cases had vision of 6/12 or better.

Table 1: Age and sex distribution

Age	No. of patients	Percentage	Male	Female
<20years	25	13.89	15	10
20-40 years	75	41.66	48	27
40-60 years	60	33.33	33	27
>60 years	20	11.1	8	12

Table 2: Organism detected in corneal scrapings

(A)

Bacteria(n = 72)	Number of cases	Percentage
Staphylococcus	35	48.6
Streptococcus	25	34.7
Psuedomonas	10	13.89
Enterobacteriacae	2	2.78

(B)

Fungus (n=35)	Number of cases	Percentage
Aspergillus	18	51.4
Fusarium	14	40
Candida	1	2.8
Dematiaceous	3	8.57

(C) Acanthamoeba (n=1)

Table 3: Final BCVA of all cases

Final BCVA	Number of cases	Percentage
6/6-6/12	36	20
6/18-6/24	79	43.8
6/36-6/60	22	12.2
6/60-FC 3mtr	20	11.1
< FC 3mtr	21	11.6
Loss of perception of light	02	1.1

DISCUSSION

In the study, initial microbial yield was seen in 60% of cases. All of them were either bacterial or fungal. 26.7% of cases responded to either bacterial or fungal treatment in situations where microbial assessment was negative. 13.3% cases which underwent therapeutic keratoplasty again failed to elicit mixed microbial infection in cases where yield was obtained. It was surprising to know that none of the 180 cases showed mixed etiology. It is known that fungi do have antibacterial properties.[2] It brought us to the question whether mixed etiology really exists as commonly as reported. All the cases in our study responded to a single class of drugs whether antibacterial or antifungal. A few cases which responded to addition of antifungal goes further to emphasize their etiology as fungal although the microbiological work up was negative. A large data has been published on bacterial fungal interactions.[3] These interactions may interplay with host immune system and can be both synergistic as well as antagonistic.[4] An interaction between the two organisms can lead to dysbiosis and modification of the physico-chemical environment.[5,6] The physico-chemical environment may thus become more acidic or alkaline prohibiting the growth of certain micro-organisms which need a particular pH for their survival.[7] There can also be contact based interactions between organisms leading to hypersensitivity and dysbiosis.[8] A nutritional interaction has also been well established wherein trophic competition between two organisms can lead to deficiency of essential nutrients like carbon, nitrogen or iron and serve as a biocontrol mechanism against the pathogens.[9,10] These observations may explain the findings observed in our cases where a single organism was detected. This may be further enforced by the fact that cornea is an avascular tissue and derives its nutrition from aqueous humor and tear film.[11] In our study all the culture positive patients responded completely to either antibacterial or antifungal drugs. Combination therapy of antibacterial and antifungal drops can reduce antimicrobial killing and clinical efficacy, increase potential for drug interaction and drug toxicity and carry much higher cost without proven clinical benefit. Most drug–drug interactions involving systemic antifungals have negative consequences.[12] Interaction can be additive dangerous. Pharmacokinetics of antifungal drugs are modified by other drugs and vice versa leading to serious complications. Thus, it is important to critically evaluate the role of combination therapy and unless microbiologically proven, combination therapy should be avoided. The strengths of this study are that this was a prospective, longitudinal cohort study where consecutive cases of infective keratitis were taken. The sample size was adequate. The scrapings were done by the investigators themselves and examined in detail with proper methodology by an experienced microbiologist. The importance of this study lies in the fact that unnecessary medications in the treatment of Infective keratitis can be avoided thus reducing the toxicity to the patient, better response and lesser burden on the economy. Although studies in the past have demonstrated the presence of mixed infection, we could not find even a single case of mixed infective etiology. A multicentric double blind study with adequate number of cases may be required to ascertain whether mixed infection is a myth rather than reality.

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