Original Article

Evidence based use of antibiotics in epidemic keratoconjunctivitis to prevent development of microbial resistance

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Abstract

Aim: It was thought that resistance acquired during treatment of systemic diseases can lead to resistant bacteria in eye infections. However, evidences are showing emergence of bacterial resistance owing to prior topical antibiotic usage. In the current study, we intended to promote evidence-based usage of antibiotics during outbreak of epidemic keratoconjunctivitis. **Methods:** A descriptive study was designed. First 50 patients who visited the outpatient department of ophthalmology with signs and symptoms of EKC during the outbreak in the months of July-August, 2023 in a tertiary hospital in northern India were included in the study. Prior usage of topical antibiotics during this epidemic outbreak was the exclusion criteria. Conjunctival swabs were taken and subjected to Gram staining and Culture and sensitivity, for any bacterial infection. **Results:** Only two slides of gram stain showed gram-positive cocci. These two samples were positive for Methicillin resistant Staphylococcs Aureus (MRSA). Rest of the 48 samples were negative for any bacterial growth. *P* value for no growth in bacterial cultures was <0.05, which is significant. **Conclusions:** Our study suggests restrain from overusage of topical antibiotics in outbreaks of EKC until microbiological outcomes suggest otherwise. In view of presence of MRSA in neo-natal sample, and its known serious complications, we suggest prophylactic use of topical antibiotic and its modifications once reports of culture and sensitivity are available.

Keywords: Antibiotic resistance, bacteria, epidemic keratoconjunctivitis, fluoroquinolones, ocular infections

Introduction

A growing area of concern is increasing antibiotic resistance among ocular pathogens, a challenge to the ophthalmologists. It leads to decline in the effectiveness of many commonly available topical antibiotics in the current era. It is thought that this rise in resistant ocular bacterial pathogens is linked to systemic resistant counterparts. However, recent evidence has linked this rise to prior usage of topical antibiotics. No significant change has been observed in the spectrum and diversity of ocular pathogens over a span of last 10 years. However, geographic region, climate, prior exposure to specific antibiotic and population characteristics are known to influence pathogens' *in vitro* susceptibility. Fluoroquinolone (FQ) monotherapy is considered standard for common ocular infections as it is effective against most common ocular pathogens all over the world. In Ophthalmology, Moxifloxacin and Gatifloxacin are the most commonly prescribed

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4th generation antibiotics. These are known to be used as first line monotherapy in corneal ulcer cases. Another commonest usage is as pre-operative topical medication in cataract surgery. A higher incidence of resistance has been documented and associated with systemic use of fluoroquinolones. Although resistance to this antibiotic is minimal, an alarming rising pattern has been observed for the same. *In vitro* efficacy of Fluroquinolones has declined. The factors contributing to this rising resistance may be misuse of antibiotics for viral and other nonbacterial infections, and improper dosing regimen.[1]

The need of hour is the formulation of strategy for judicious usage of currently available antibiotics and development of newer ones, with potential of low-resistance.

There was an outbreak of Epidemic keratoconjunctivitis (EKC) in the month of July-August, 2023 in India. These outbreaks of adenoviral keratoconjunctivitis are considered to be a major public health issue considering its rapid community transmission. Primary healthcare settings are often frequented by patients during outbreaks of epidemic keratoconjunctivitis. Patient's outcome can be improved upon if such cases are diagnosed accurately, early treatment is instituted, and promptly referred to an ophthalmologist as per requirement.

Epidemic keratoconjunctivitis (EKC) is caused by adenovirus serotypes 8, 19, and 37. Its manifestation ranges from conjunctivitis to occasional keratitis. The most common cause of red eye around the world is adenoviral conjunctivitis. The disease severity can range from mild to severely disabling. Mode of transmission of virus is both direct and indirect contact. Ocular and respiratory secretions can lead to transmission by direct contact, while contaminated instruments and objects are known to spread it by indirect contact. The most common presenting symptom are redness, photophobia, excessive tearing, and foreign body sensation. The most common clinical signs are conjunctival chemosis, hyperemia, follicular conjunctivitis, eyelid edema, epithelial keratitis and lymphadenopathy of preauricular glands. The severe form can manifest as pseudomembrane and symblepharon. The outbreak of EKC can be contained by accurate diagnosis and implementation of measures to prevent community transmission. The diagnosis is mostly clinical based on history, signs and symptoms. Cell culture in combination with immunofluorescence staining (CC-IFA) and PCR (Polymerase Chain Reaction) are the confirmatory laboratory diagnostic methods. However, unavailability of in-house testing facility, higher cost and time delay are the reasons behind the treatment based upon signs, symptoms and clinical experience in majority of clinical set-ups. Although EKC is a self-limiting disease, severity of symptoms can lead to ophthalmological consultation sought by patients. Cold compression and artificial tears are the commonest treatment prescribed. Topical corticosteroids are prescribed in acute EKC with persistent subepithelial infiltrates and pseudomembranous conjunctivitis.[2] Usage of topical Ganciclovir 0.15% ophthalmic ointment has been considered to be safe and effective in adenoviral conjunctivitis in one of the studies.[3] Another study has proved the efficacy of topical dexamethasone 0.1%/ povidone-iodine 0.4% (FST-100) in EKC on animal model.[4]

Some clinicians prescribe antibiotics for prevention of secondary infection with bacteria.

One study reported cases of methicillin resistant Staphylococcus aureus (MRSA)-associated keratitis in neonates and infants with EKC. These neonates and infants had a history of hospital stay. There were no cases of bacterial keratitis-associated EKC in adults despite of hospital stay.[5]

MRSA has emerged as one of the most common causes of nosocomial infection in last few decades.[6-8]

In the current study, we intended to take conjunctival swabs from Epidemic keratoconjunctivitis (EKC) patients, visiting our outpatient department during recent outbreak, and processed these for gram-staining, culture and sensitivity for bacterial infection, in the backdrop of mass usage of topical antibiotics. There has been indiscriminate use of topical antibiotics in recent outbreak of epidemic kerato-conjunctivitis. It may lead to antibiotic resistance.

Methods

The study design was descriptive in nature. It was conducted during the outbreak of Epidemic keratoconjunctivitis in India. The outbreak of EKC occurred in the last week of July, 2023. It lasted around 2 weeks. The daily turn out of patients in ophthalmology outpatient department was in the range of 35-50, in the month of July-August, 2023 in a tertiary hospital in Northern India. Around 75-90%(range) of OPD patients on daily basis were diagnosed with EKC during this period. Around 20-30% (range) of opd patients, diagnosed with EKC, on each day reported prior usage of topical antibiotic, in the form of self-medication or dispensed by a chemist. Chloramphenicol containing capsules were the most commonly prescribed medication by chemists during this period.

First 50 clinically diagnosed cases of epidemic keratoconjunctivitis, attending outpatient department of Ophthalmology, were included in the study. Selection of patients for this study was done irrespective of age, sex, occupation and socio-economic status. Those who had prior history of topical antibiotics during this epidemic outbreak were excluded from study. Written consent was taken from each patient and ethical clearance was obtained from the institutional ethical committee. The study was conducted in accordance with the ethical principles mentioned in the Declaration of Helsinski (2013).

The most common presenting symptom were redness, photophobia, excessive tearing, foreign body sensation, and associated eyelid edema. After routine examination in ophthalmic outpatient department, each patient was examined on slit-lamp.

In each case, symptoms, duration, laterality, presence or absence of sub-conjunctival haemorrhage, Conjunctival follicles, Conjunctival chemosis, Severe lid edema, Pseudomembranes, Corneal filaments, Sub-epithelial immune infiltrates, and Discharge were noted. These first 50 patients were taken to microbiology department. Swabs moistened with sterile normal saline were rubbed over the lower conjunctival sac from medial to lateral canthus, and back again to the medial canthus. Two swabs were collected from each patient. One swab was used for microscopy. Direct smear was spread on glass slides and stained with Gram stain in each case. It was examined under oil emersion lens. The second swab was inoculated on blood agar, MacConkey's Agar and chocolate Agar. The medias were incubated at 37°C for 24 hours and cultures with no growth were incubated for further 48 hours. Bacteria were then identified on the basis of characteristics of culture, Gram staining and biochemical tests. Antimicrobial susceptibility test was carried out on pure, isolated colonies from 24-hour culture growth using disc diffusion method on Mueller-Hinton agar as per Clinical and Laboratory Standards Institute (CLSI) guidelines. Sensitivity was not done for micrococcus, which is a commensal. The organisms isolated were then tested for antibiotic sensitivity against Amoxycillin-Sulbactam combination, Penicillin, Ampicillin, Gentamicin, Tetracycline, Chloramphenicol, Erythromycin (only for staphylococcus), Cefoxitin (for MRSA screening), Azithromycin, Ciprofloxacin, Levofloxacin, Clindamycin, Linezolid, Vancomycin and Cotrimoxazole. The zone of inhibition was measured by using a ruler and compared with a table of zone diameter interpretative standards accepted by CLSI. Depending upon zone disc diameter of Cefoxitin, we decided upon MSSA (Methicillin sensitive Staphylococcus aureus) or MRSA (Methicillin resistant Staphylococcus aureus) strain. We treated all these cases to be of adeno-viral origin unless we got a bacterial growth. We treated culture-positive cases with appropriate antibiotic after getting culture and sensitivity result. In view of complications in neonate, prophylactic antibiotic was added which was modified after getting culture and sensitivity result.

Statistical analysis

Continuous outcomes were presented as mean values accompanied by their standard deviations (SD), while categorical outcomes were expressed as frequencies along with corresponding percentages. The z-proportion test was employed to assess the statistically significant differences between the proportion of categorical variables under investigation, with a significant level of 0.05, *P* value. Pie charts, line diagrams, and bar diagrams were constructed to represent the bacterial culture, date of reporting with no of cases, and types of signs for all participants in the study. All analyses and graphical representations were performed using SPSS version 17.

Results

A total sample of 50 conjunctival swabs were collected from patients, diagnosed clinically as cases of epidemic keratoconjunctivitis, attending outpatient department of Ophthalmology. These samples were processed for Gram-staining, bacterial culture and sensitivity. Out of these samples collected, only 4% showed gram positive cocci (GPC) on gram-staining. [Figure 1] Rest 96% of samples showed occasional pus cells. Same 4% of samples showed growth on culture, which turned out to be methicillin resistant Staphylococcus aureus (MRSA). [Figure 2] Rest 96% of samples showed no growth. [Figure 3].

P value for no growth in bacterial cultures is <0.05, which is significant. [Table 1] One of the positive MRSA sample was of a 6-day-old neonate.

Table 1: Characteristics of participants included in the study

Variable	Mean (SD)/Frequency (percentage)	*P*
Age	36.32	
Gender		
Male	18 (36%)	<0.05
Female	32 (64%)	
Duration (Days)		
One	24 (50%)	<0.05
Two	5 (12%)	
Three	7 (18%)	
Four	6 (12%)	
Five	2 (4%)	
Seven	2 (4%)	
Bilateral or Unilateral		
Bilateral	38 (76%)	<0.05
Unilateral	12 (24%)	
Sub Conj. Hge		
Yes	23 (46%)	<0.05
No	47 (94%)	
Conjunctival follicles		
Yes	17 (34%)	0.002
No	33 (66%)	
Conjunctival chemosis		
Yes	2 (4%)	<0.05
No	48 (96%)	
Severe lid edema		
Yes	21 (42%)	0.16
No	29 (58%)	
Pseudomembranes		
Yes	1 (2%)	<0.05
No	49 (98%)	
Corneal filaments		
Yes	0 (0%)	<0.05
No	50 (100%	
Sub-epithelial immune infiltrates		
Yes	1 (2%)	<0.05
No	49 (98%)	
Discharge		
Mucoid	9 (18%)	0.01
Purulent	21 (42%)	
No	20 (40%)	
Gram Stain		
Gram positive cocci	2 (4%)	<0.05
Occasional pus cells	48 (96%)	
Bacterial Culture		
MRSA	2 (4%)	<0.05
No Growth	48 (96%)	

In our study, mean age of patients was 36.32 years. Female (64%) patients outnumbered male patients (36%). A total of 76% had bilateral involvement of eye. [Figure 4].

50% of patients reported with symptoms just for 1 day. Maximum no of samples, 15 in no, were collected on the 7 August, 2023 representing peak of outbreak of EKC. [Figure 5].

Sub-conjunctival haemorrhage (46%) was the most common sign in our study. [Figure 6] 1 case, 18-year-old male, presented with sudden onset unilateral secondary inflammatory mild ptosis.

The MRSA positive sample from 47-year-old female was resistant to 2nd and 3rd generation of Fluoroquinolone Group of antibiotics, while positive MRSA sample from 6 day-old-neonate was sensitive to these group. [Table 2].

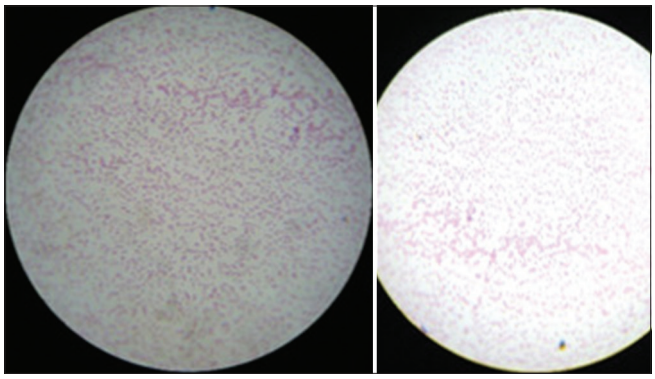

Figure 1: Gram-positive Cocci seen in 2 samples

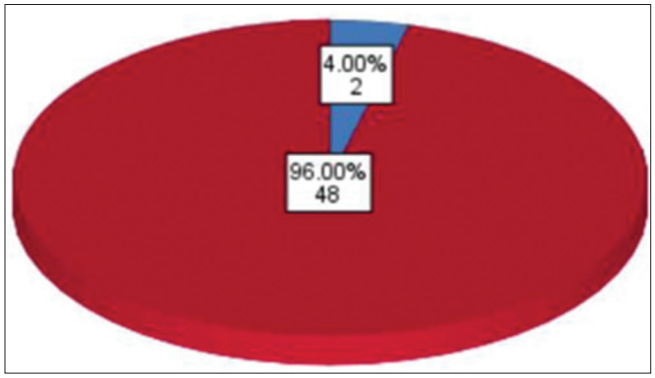

Figure 3: Proportion of Bacterial growth in our study

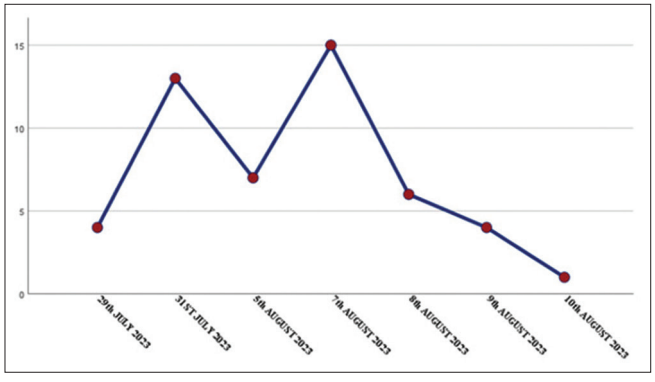

Figure 5: Graph depicting pattern of reporting for 50 microbiological samples taken during EKC in our out-patient department

Discussion

The development of antibiotic resistance is a matter of major concern due to its widespread use. True anti-infective resistance is defined as an acquired resistance that spreads to others, and has got no other anti-infective alternative treatment.[9]

There is an advantage while treating ocular infections, as topical and direct injections, routes of administration, ensures high concentration of anti-infectives in ocular tissue.[10] The resistance to antibiotics predicted by *In vitro* studies may not be accurately applicable to In vivo studies.[11] Systemic susceptibility standards are applied for interpretation of these resistances in ocular tissue as well.[9,12] Both the ARMOR (Antibiotic Resistance Monitoring in Ocular Microorganisms) and TRUST (Ocular Tracking Resistance in U.S. Today) studies are based on Systemic susceptibility

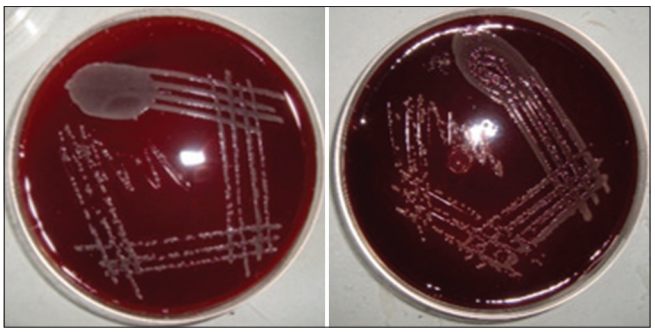

Figure 2: Culture showing growth of MRSA in 2 samples

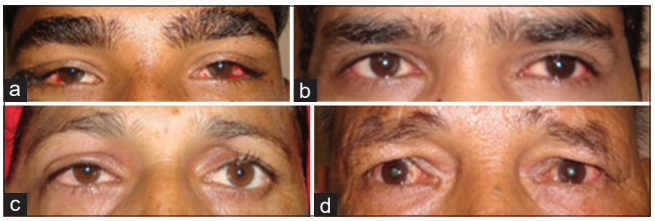

Figure 4: Pictures showing few signs of EKC in our patients; a: Sub-conjunctival Hge; b: conjunctival chemosis; c: lid edema; d: redness of conjunctiva

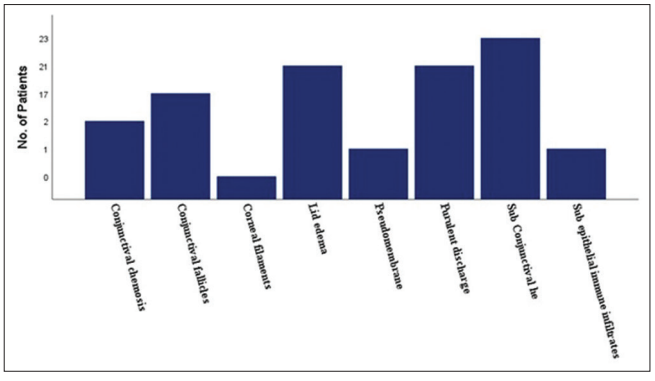

Figure 6: Distribution pattern of signs observed in 50 patients during EKC

Table 2: Pattern of sensitivity/resistance of MRSA strains in our study

MRSA	RESISTANT	SENSITIVE
Sample 23	Penicillin Ciprofloxacin Levofloxacin Ampicillin Sulbactam Cotrimoxazole Tetracycline Gentamicin Amoxyclav	Erythromycin Clindamycin Linezolid
Sample 28	Penicillin Cotrimaxazole Gentamicin	Erythromycin Clindamycin Levofloxacin Ciprofloxacin Linezolid Vancomycin

standards. Cefazolin, bacitracin, sulfacetamide, or other commonly used ocular anti-infectives are not included in these studies.[12]

Staphylococcus aureus is the commonest bacterial pathogen in conjunctiva. In total, 72% of pathogens sampled from conjunctiva are gram-positive. Among gram-negative isolates, Pseudomonas aeruginosa is the commonest one.[13] The cultures from microbial keratitis shows Staphylococci species and Streptococcus pneumoniae as major bacterial pathogens.[14]

Aminoglycosides, macrolides, polymyxin B combinations, and recently fluoroquinolones are the classes of topical antibiotics used for bacterial conjunctivitis treatment.[15]

Fluoroquinolone (FQ) is the most frequent antibiotic dispensed in bacterial keratitis, conjunctivitis and in prophylaxis of ocular surgeries. Fluoroquinolone group has Ciprofloxacin and Ofloxacin as 2nd generation, Levofloxacin as 3rd generation, and Besifloxacin, Moxifloxacin and Gatifloxacin as 4th fourth-generation antibiotics in its armamentarium. Moxifloxacin is the most potent fluoroquinolone against Gram-positive bacteria, and Ciprofloxacin is the most potent against Gram-negative bacteria in cases of keratitis, and conjunctivitis. Besifloxacin is the 1st fluoroquinolone specifically developed for ophthalmic use. The absence of any prior systemic use of Besifloxacin therapy is an advantage against development of resistance. The mechanism of development of resistance is different for 2nd, and 3rd-4th generation. A single mutation of DNA gyrase, topoisomerase and efflux pumps is required in 2nd generation, while double mutation of the same is required for 3rd- 4th generation. Resistance against ophthalmic usage of Ciprofloxacin has been reported. But, again basis of interpretation is systemic susceptibility standard.[15]

Reports have suggested association of *in vitro* resistance to FQ against S aureus ocular pathogen and prior ophthalmic usage.[1]

A commonly known resistance of penicillin and beta lactam anti-infective to Streptococcus pneumoniae is not of much significance in ophthalmic usage as these antibiotics are never used for bacterial conjunctivitis treatment.[16] In our study, similar resistance of MRSA to penicillin and beta lactam anti-infectives has been noted. [Table 2].

Reports have suggested resistance of Streptococcus pneumoniae ocular pathogen, recovered from cases of acute conjunctivitis in children, to gentamicin, tobramycin and polymyxin B in significant number of cases.[17] It clearly states that no resistance was seen in Streptococcus pneumoniae against gentamicin and tobramycin during 1989-1992. There has been a rise in resistance of gentamicin against S. pneumoniae from 42.3% to 56% from year 1997 to 2000. While a similar rise in resistance of tobramycin has been reported from 43.6% to 46% during the same period.[18]

Another 10-year study suggests resistance of Staphylococcus aureus isolated from bacterial conjunctivitis cases to gentamicin. It also claims a moderate to very high resistance of H. influenzae, S. aureus, S. epidermidis and S. pneumoniae pathogens recovered from bacterial conjunctivitis to azithromycin.[15] Similar resistance of both MRSA samples was reported in our study against gentamicin. [Table 2].

In our country, India and countries like United States and Brazil, reports have suggested resistance percentage as high as 70% for both MRSA and MSSA (methicillin resistant and methicillin sensitive staphylococcus).[15,19,20]

Another study confirms continued rise in resistance of staphylococci (both methicillin susceptible and resistant) to fluoroquinolone group. It also highlights phenomenon of associated multidrug co-resistance.[14] Our study also showed resistance to FQ antibiotics in one of MRSA sample. [Table 2].

Another troublesome emerging trend is of alpha hemolytic streptococci developing resistance to fluoroquinolone, and *P. aeruginosa* to ceftazidime.[14]

One positive report suggests that there is no true Vancomycin resistance to S. aureus and/or S. epidermidis ocular pathogens in the United States so far.[14]

Another positive report claims successful treatment of MRSA ocular infection with moxifloxacin, which was previously considered resistant.[16]

One study claims that all MRSA and MRSE (Methicillin-resistant Staphylococcus Epidermidis) resistant to ciprofloxacin, 2nd generation FQ are also resistant to 4th generation FQ, i.e., gatifloxacin and moxifloxacin. But these are susceptible to besifloxacin, an antibiotic meant for only ophthalmic usage.[21] Our study used only 2nd and 3rd generation FQ antibiotics for susceptibility testing in MRSA. [Table 2].

A newly recognized ocular isolate, Corynebactrium Macginleyi, associated with conjunctivitis and keratitis, was earlier described

to be sensitive to large number of antibiotics, including FQ. In subsequent report, 11 out of 16 conjunctival isolates of this species was found to be resistant to FQs, i.e., ciprofloxacin, levofloxacin andnorfloxacin, in year 2008.[22-24]

Another alarming trend of rising resistance is seen with *Pseudomonas aeruginosa ocular* isolates to ciprofloxacin. It has increased from less than 1% in 1991-1994 to 29% in 2002-2003. Multidrug resistant *P. aeruginosa* isolates, associated with keratitis and endophthalmitis are also seen.[25-29]

A positive ray of hope is a well-known phenomenon of rebound susceptibility. It suggests a resistant organism develops disadvantages for survival if that particular class of antibiotic pressure is taken off. An example is a decline in resistance of S. pneumoniae to azithromycin, after its oral usage for trachoma was discontinued. Another example is rebound susceptibility seen in Salmonella typhi strain to chloramphenicol, once it was discontinued for typhoid therapy.[30]

Based on above observation, we suggest to restrain from over usage of topical antibiotics in outbreaks of EKC. Antibiotics to be used once result of microbiological strains are available. However, we also advocate use of prophylactic antibiotics in neonates and infants during EKC for containing complications in view of immune immaturity in this age group.

There are several limitations to our study. Small sample size is one of them.

Second, Clinical Laboratory Standards Institute antibiotic susceptibility breakpoints for serum and tissues may not be accurately applicable to ocular tissues and fluids. Thirdly, susceptibility testing of antibiotics has been performed only *in vitro*.

One more important drawback is that our center is a tertiary referral center. Its ocular isolates and susceptibility profiles may not be applicable to population in general.

Further research will be important to validate our findings.

Conclusion

Ocular infections in general are treated with anti-infectives in formulations as topical drops and direct injections. This ensures its very high effective levels into the ocular tissue. Still, empirical treatment should be adjusted for continued success, and to prevent the development of anti-infective resistance. This can be done by identification of causative agent by culture, and sensitivity testing.

Our study suggests restrain from the over usage of topical antibiotics in outbreaks of EKC until microbiological outcomes suggest otherwise. In view of the presence of MRSA in neo-natal sample, and its known serious complications, we suggest prophylactic use of topical antibiotic and subsequent modifications, once reports of culture and sensitivity are available.

Declaration of patient's consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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