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Research Article

Spectrum of Ocular Infections and the Emerging Epidemic of Resistance to Fourth Generation Fluoroquinolones

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Abstract

Purpose: To evaluate the spectrum of ocular infections and their sensitivity pattern to various antibiotics.

Methods: Retrospective analysis of the laboratory records of patients, clinically diagnosed with any ocular infection was undertaken. Variables studied include the sample source, type of ocular infection, pathogens isolated, overall sensitivity of isolates to antibiotics.

Results: Of the 324 samples analyzed, 312 (96.3%) were from ocular surface. A total of 177 (54.62%) were culture-positive. The commonest bacterial isolate was coagulase negative *Staphylococcus* and the commonest fungus was *Aspergillus flavus*. Overall sensitivity was 98.18% for cefazolin, 93.42% for tobramycin, 51.72% for moxifloxacin and 45.29% for gatifloxacin.

Conclusion: Emerging epidemic of resistance to fourth-generation fluoroquinolones such as gatifloxacin and moxifloxacin dictates the need for the use of fortified antibiotics such as cefazolin, tobramycin as empirical therapy in the treatment of ocular infections.

Keywords: *Fourth-Generation Fluoroquinolones; Ocular Infections; Epidemic; Resistance*

Introduction

The eye is protected from external infectious agents, primarily due to presence of protective mechanisms such as presence of enzymes like lysozymes, lactoferrin, defensin and various immunoglobulins in the tear film [1,2]. However, ocular infections can result from various inciting factors such as penetrating injury, intraocular surgery, and hematogenous spread from adjacent tissues or modification of normal ocular flora [3-5]. The spectrum of ocular infections varies from blepharitis, conjunctivitis, canaliculitis, and orbital cellulitis to endophthalmitis [6,7]. As aggressive antimicrobial therapy is needed for ocular infections, prompt isolation, identification and testing for susceptibility of the pathogens is necessary to treat these infections effectively. The emergence of bacterial resistance towards various antimicrobial agents raises the alarming concerns worldwide [8]. The etiological agent and the spectrum of antibiotic susceptibility varies with geographic locations and passage of time [9,10]. *Staphylococcus epidermidis, S. aureus* (methicillin sensitive and methicillin resistant), *S. pneumonia*, and *S. viridans* have been commonly reported pathogens in ocular infections [11]. Fourth-generation fluoroquinolones such as gatifloxacin and moxifloxacin have been proven to be efficacious in the treatment of ocular infections caused by these pathogens [11]. The fact that in recent times, ocular infections caused by microbial organisms are showing resistance to such fourth-generation fluoroquinolones makes it imperative to identify and report current patterns of emerging resistance.

Thus, the purpose of this study was to identify the spectrum of ocular infections, etiology and antibiotic susceptibility and resistance to the commonly used antimicrobial agents, especially fourth-generation fluoroquinolones. The changing spectrum of microbes involved in ocular infections and the emergence of acquired microbial resistance necessitates the need for continued surveillance to guide empirical antimicrobial therapy.

Materials and Methods

A retrospective analysis of case records of patients clinically diagnosed with any ocular infection and had undergone microbiological evaluation of various extraocular and intraocular isolates at Dr. R. P. Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi in the period of October 2016 to October 2017 was undertaken. Institute ethics committee approval was sought and taken. The laboratory records of all the clinically diagnosed ocular infections were retrospectively reviewed. Study variables included the microorganisms isolated, and their susceptibility to antibiotics such as ciprofloxacin, tobramycin, chloramphenicol, tetracycline, norfloxacin, gentamicin, cloxacillin, ampicillin, polymyxin B, ceftazidime, amikacin, vancomycin, cefazolin, moxifloxacin, gatifloxacin, and piperacillin-tazobactam. SPSS software version 17 was used for statistical analysis. The frequency of positivity of the culture reports and the frequency of their susceptibility to various antibiotics were analyzed. Pearson's Chi square test was used for analysis and a p value < 0.05 was considered statistically significant.

Results

The microbiological data of 324 samples (Table 1) from the clinically diagnosed ocular surface (keratitis), intraocular (endophthalmitis) and extraocular (blepharitis, conjunctivitis) infections were taken and were retrospectively reviewed. Among the collected data, 54.62% (n = 177) samples were culture positive for micro-organisms. Of these isolates, 128 samples (72.32%) were positive for bacterial growth, 26 samples (14.68%) were positive for fungal growth, 12 (6.78%) for Acanthamoeba growth and 11 (6.22%) for mixed growth. The organisms cultured from the ocular surface (cornea, conjunctiva) accounted for majority 96.30% (n = 312) followed by the intraocular (aqueous humor, vitreous fluid) which accounted for 3.70% (n = 12). When the culture-positive rates of different types of samples were assessed, the highest rate was found in corneal scrapings (63.55%; 136 of 214) followed by intraocular fluids (58.33%; 7 of 12) (Table 1). The commonest bacterial isolate responsible for the ocular infections in 45.76% (81 0f 177) was coagulase negative *Staphylococcus.* The most common pathogen was found to be *S. epidermidis* in conjunctivitis (56%; 15 of 25), blepharitis (44.44%; 4 of 9), and keratitis (44.85%; 61 of 136) while the commonest pathogen isolated from the intraocular fluids was found to be *Pseudomonas aeruginosa* in 41.66% (5 of 12) (Table 2). The most common fungal isolate was found to be *Aspergillus* in 61.54% (16 of 26) followed by *Fusarium* in 23.08% (6 0f 26) and *Candida* species in 15.38% (4 of 26) cases each. The antimicrobial susceptibility pattern of bacteria was done for fifteen antimicrobial agents the results of which are shown in table 3 and 4.

Sample source	Total number of samples	Number of Culture positive samples
Conjunctival swab	98	34
Corneal scrapings	214	136
Intraocular fluids (aqueous and vitreous)	12	7
Total	324	177

Table 1: *Details of sample source and culture positivity of ocular infections.*

Organism Isolated	Number (Percentage)
Staphylococcus epidermidis	81 (63.28)
Staphylococcus aureus	7 (5.46)
Diphtheroids	7 (5.46)
Pseudomonas aeruginosa	16 (12.50)
Escherichia coli	7 (5.46)
Klebsiella	2 (1.57)
Streptococcus viridans	1 (0.79)
Acinetobacter	1 (0.79)
Aerobic spore bearing bacilli	4 (3.12)
Non-fermenting gram negative bacilli	2 (1.57)

Table 2: *Type of the pathogens isolated from ocular infections.*

Antibiotic	No of sensitivity/No of samples tested								Overall sensitivity
	Coagulase negative Staph	Coagulase positive Staph	Non-fermenting gram negative bacilli	Pseudomonas aeruginosa	E. coli	Klebsiella	Strep. viridans	Acinetobacter	
Ciprofloxacin	49/81 (60.49)	4/7	1/2	11/16 (68.75)	4/7	1/1	1/1	1/1	72/116 (62.06%)
Tobramycin	56/57 (98.24)	5/5	NA	5/8 (62.5)	2/3	1/1	1/1	1/1	71/76 (93.42%)
Chloramphenicol	70/81 (86.41)	4/7	1/2	6/14 (42.85)	4/7	2/2	1/1	1/1	89/115 (77.39%)
Tetracycline	60/80 (75)	6/7	1/1	4/15 (26.66)	1/7	1/2	1/1	1/1	75/114 (65.78%)
Norfloxacin	4/4 (100)	1/1	1/2	1/ 1 (100)	4/7	1/2	1/1	0/1	13/19 (68.42%)
Gentamicin	68/74 (91.89)	4/6	2/2	7/14 (50)	4/6	1/2	1/1	1/1	88/160 (55%)
Cloxacillin	59/74 (79.72)	6/6	2/2	7/7 (100)	3/5	1/1	1/1	0/1	79/97 (81.44%)
Ampicillin	3/4 (75)	1/1	1/1	2/16 (12.5)	1/5	1/1	1/1	1/1	11/30 (36.66%)
Polymyxin B	1/1 (100)	0/7	1/1	12/16 (75)	7/7	2/2	0/1	1/1	24/36 (66.66%)
Ceftazidime	5/5 (100)	0/7	1/1	1/1 (100)	3/3	1/1	0/1	0/1	11/20 (55%)
Amikacin	7/7 (100)	0/7	2/2	2/5 (40)	4/7	1/1	0/1	1/1	17/31 (54.83%)
Vancomycin	74/74 (100)	7/7	2/2	1/4 (25)	1/7	1/1	0/1	0/1	86/97 (88.65%)
Cefazolin	58/81 (71.6)	6/6	1/1	1/13 (7.69)	4/6	1/1	0/1	1/1	108/110 (98.18%)
Moxifloxacin	36/81 (44.44)	3/7	1/1	8/16 (50)	1/7	1/2	0/1	1/1	60/116 (51.72%)
Gatifloxacin	38/81 (46.91)	3/7	1/2	8/16 (50)	1/7	1/2	0/1	1/1	53/117 (45.29%)

Table 3: *Sensitivity of the pathogens to various antibiotics.*

No of sensitivity/No of samples tested			
Antibiotic	**Conjunctival swabs (%)**	**Corneal scrapings (%)**	**Intraocular fluids**
Ciprofloxacin	13/25 (52)	49/131 (37.40)	4/7 (57.14)
Tobramycin	16/17 (94.11)	54/124 (43.54)	1/2 (50)
Chloramphenicol	15/25 (60)	71/83 (85.54)	3/6 (50)
Tetracycline	14/25 (56)	57/82 (69.51)	4/7 (57.14)
Norfloxacin	3/3 (100)	3/3 (100)	0/0 (0)
Gentamicin	19/23 (86.36)	64/75 (85.33)	3/6 (50)
Cloxacillin	17/20 (85)	48/62 (77.41)	0/0 (0)
Ampicillin	2/4 (50)	4/19 (21.05)	3/6 (50)
Polymyxin B	1/2 (50)	14/19 (73.68)	4/6 (66.66)
Ceftazidime	1/3 (33.33)	4/101 (3.9)	0/0 (0)
Amikacin	2/2 (100)	5/9 (55.55)	0/0 (0)
Vancomycin	22/22 (100)	58/62 (93.54)	2/2 (100)
Cefazolin	16/20 (80)	48/121 (39.66)	1/5 (20)
Moxifloxacin	12/32 (37.5)	36/134 (26.86)	2/7 (28.57)
Gatifloxacin	12/34 (35.29)	38/134 (28.35)	2/7 (28.57)

Table 4: *Summary of sensitivity pattern of ocular pathogens from different sample source.*

Discussion

Out of 324 samples tested, 177 samples (54.62%) were culture positive for microorganisms. This culture positivity of 54.62% was comparable to that found by Bharathi., *et al.* (58.8%) [10] whereas significantly higher than that reported from China [11]. The most common organism was Coagulase negative *Staphylococcus epidermidis* (63.28%) followed by *Pseudomonas aeruginosa* (12.5%). This finding is in contrast to studies conducted from other parts of India [11-13] and also from other countries [14,15] where *Staphylococcus. aureus* was the most common isolate reported. The second common isolate in these studies was variable such as *S. Pneumonia* [10,13], *S. albus* [6], *E. coli* [16] different from our finding. 15 antibiotics were tested for resistance and the antibiotic susceptibility is being reported. The overall sensitivity was highest for cefazolin (98.18%) comparable to that reported by Ramesh., *et al.* [13] followed by tobramycin (93.42%), whereas Tesfaye., *et al.* [17] from Southwest Ethiopia reported maximum susceptibility to Ciprofloxacin (92.2%) and vancomycin (90.9%). These results are different from that reported from studies from both North [18] and South India [19] and United states [20] where maximum susceptibility to quinolone antibiotics was reported. Among the isolates from conjunctiva, susceptibility was maximum for vancomycin, amikacin and norfloxacin, but the number of isolates tested for amikacin and norfloxacin were very few. Among the samples from the cornea, maximum susceptibility was seen for norfloxacin followed by vancomycin where the isolates tested for norfloxacin were very few. Among the samples from intraocular fluids, maximum susceptibility was noted for vancomycin followed by Polymyxin B. Here again the number of isolates tested for vancomycin was very few. This variation in the susceptibility of intraocular and extraocular isolates is different from that reported from South India [19] and also, from China [11]. Coagulase negative *Staphylococcus epidermidis* showed maximum resistance to fluoroquinolones especially to the fourth-generation quinolones, moxifloxacin (55.56%) followed by gatifloxacin (53.09%) and ciprofloxacin (39.51%). This is in contrast to the results from a previous study from the same region as our study [18] where the susceptibility was 95.52% to gatifloxacin, 92.83% to moxifloxacin, 90.07% to tobramycin, and 83.56% to cefazolin. All the staphylococcal samples were susceptible to vancomycin. This finding is in agreement with studies from India [10,13], China [11], Iran [21] and United

States [22]. Most of the isolates positive for *P. aeruginosa* was susceptible to Polymyxin B (75%). Gentamicin coverage for *Staphylococcus* species was 90% which is comparable to previous studies from India [10], Iran [21] Nigeria [6] and Ethiopia [17]. However, gentamicin coverage for *P. aeruginosa* was only 50% in our study which is much lower than that reported from Ethiopia [17]. The ciprofloxacin coverage for *Pseudomonas aeruginosa* was 68.75% which is lower than that reported from Nigeria [6], Ethiopia [17] and Saudi Arabia [23]. Multidrug resistance (MDR) organisms are defined as those which show resistance to at least one agent in each of three or more antibacterial categories according to the definition by the European Centre for Disease Prevention and Control in 2012 [24]. MDR bacteria in our study were 13.12% of which 27.72% were Coagulase negative *Staphylococcus epidermidis* and 11.67% were *Pseudomonas aeruginosa* which is comparable to that reported from Ethiopia [17]. Organisms showing resistance to fourth generation fluoroquinolones included CoNS, *S. aureus*, *P. aeruginosa*, *E. coli, Klebsiella* and *Streptococcus viridans*. This finding is in agreement with the previous study from our region [18]. Antibiotic resistance occurs due to various contributing factors such as the change in the pathogenicity and virulence of the organisms, improper dosage, use of cocktail therapy with antibiotics for viral infections, incorrect duration or prolonged duration of therapy [25]. The most important cause for poor isolation rates and emerging resistance in India is the misuse of antibiotics without prescription. The most common pathogen was found to be *S. epidermidis* in conjunctivitis (56%; 15 of 25), and blepharitis (44.44%; 4 of 9). This is different from the studies previously conducted in India [10]. and Nigeria [6,26]. which reported *S. aureus* as the most common pathogen in blepharitis and conjunctivitis. The predominant isolate in cases of microbial keratitis was again found to be *S. epidermidis* (44.85%; 61 of 136) which is comparable to the previous studies conducted in Australia [27] but was different from the studies conducted from Sudan [28] and India [29] which reported *P. aeruginosa* and *S. pneumonia* respectively as the predominant pathogen in microbial keratitis. In this study, the commonest pathogen isolated from the intraocular fluids was found to be *Pseudomonas aeruginosa* in 41.66% (5 of 12). This is in contrast to the study conducted in North-eastern United States, which reported Coagulase negative Staphylococcus as the most prevalent bacteria causing endophthalmitis [30].

Conclusion

To conclude, Coagulase negative Staphylococcus epidermidis was the most common isolate which is different from the rest of the world. The emergence of resistance to commonly used antibiotics, especially to the fourth-generation fluoroquinolones is alarming.

This dictates the need for use of fortified antibiotics as an empirical therapy to treat ocular infections.

Disclosures

There are no conflicts of interest and no financial disclosures to be made by author and the co-authors.

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Volume 9 Issue 6 June 2018