Multidrug-resistant keratitis: challenging yet manageable

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ABSTRACT

Purpose To study the incidence, clinical features and outcomes of multidrug-resistant (MDR) bacterial keratitis.

Methods All cases of MDR-bacterial keratitis presenting to our institute over a period of 2 years were retrospectively analysed. Details of risk factors, size and depth of infiltrate, treatment, and outcome were noted. Antibiotic susceptibility tests were done on the ocular isolates from the culture of samples obtained from ocular infections, and resistance or sensitivity of the organisms to the commonly used antibiotics was studied.

Results Forty patients were diagnosed with MDR-bacterial keratitis in the study period. The mean age of patients was 50.9±25.4 years. Most common risk factors were vegetative trauma (n=12, 30.0%), followed by corneal transplantation (n=7, 17.5%) and systemic comorbidities (n=7, 17.5%). Infiltrate was small (<6 mm) in 22 (55%) and large (>6 mm) in 18 (45%) patients. It involved the superficial, mid and deep stroma in 11 (27.5%), 9 (22.5%) and 15 (37.5%) cases, respectively. Gram-negative bacilli (n=18, 45%) were the maximum, among which *Pseudomonas aeruginosa* (15%) was the most common. Resistance to 3 (n=17, 42.5%) and 4 (n=17, 42.5%) classes of antibiotics was the most commonly observed. One (2.5%) patient showed resistance to all seven classes of drugs tested. Complete resolution of infection was seen in 15 (37.5%) MDR patients on medical management alone. Five (12.5%) patients underwent therapeutic penetrating keratoplasty. Size of the infiltrate was found to have a significant correlation with the outcome (p=0.002).

Conclusion MDR keratitis, despite being a challenge to treat, can be successfully managed by medical therapy alone, if appropriate therapy is started early in the clinical course.

INTRODUCTION

A global estimate of 36 million blind people and 216.6 million people with moderate/severe visual impairment has been reported by The Vision Loss Expert Group in the Global Burden of Disease Study.[1] Corneal opacities (non-trachomatous) are one of the leading causes of vision loss, comprising 3.21% of all cases. However, the role of corneal opacities to vision loss is more than two times the reported number, when causes of reversible vision loss such as cataract (35.2%) and uncorrected refractive error (20.3%) are excluded.[1] Corneal infections, caused by virus, bacteria and fungus, are among the most common causes of corneal scarring.[2]

Microbial keratitis requires urgent attention and prompt management. Risk factors commonly associated with microbial keratitis are contact lens wear, ocular surgery, trauma and ocular surface diseases. However, keratitis may develop even in the absence of any predisposing factor.[3–5] Identification of the causative microorganism accurately is essential for treating the disease. Culture is the gold standard in identifying the species of the offending organisms and initiating appropriate treatment.[6]

Antimicrobial susceptibility testing of significant pathogens, isolated from ocular samples in a microbiology laboratory, is important to confirm the susceptibility of the offending organisms to the various available antimicrobial agents. It is also imperative to detect resistance in individual bacterial isolates to make required modifications in the treatment. Empirical therapy can eliminate some bacterial pathogens, which commonly do not show resistance mechanisms. However, it is ineffective in species in which acquired resistance mechanisms have been observed (eg, members of the *Enterobacteriaceae*, *Pseudomonas* sp, *Staphylococcus* sp, *Enterococcus* sp and *Streptococcus pneumoniae*).[7] Susceptibility testing plays an important role in such pathogens.

The widespread use of broad-spectrum antibiotics is expected to result in a change in microbial spectrum and respective antibiotic susceptibility patterns, which may lead to an increased prevalence of resistant bacterial isolates causing disease.[8] Despite the burden of corneal ulcers, recent data regarding drug resistance are lacking. In this study, we intend to analyse the incidence, clinical features, microbiological profile and outcomes in multidrug-resistant bacterial keratitis seen at a tertiary care eye hospital in eastern India.

MATERIALS AND METHODS

Electronic medical records of all patients with bacterial keratitis from a tertiary eye care centre in eastern India from January 2018 to December 2019, who underwent diagnostic corneal scraping for direct smear and culture sensitivity, were retrospectively reviewed. Those cases where the organisms were found to be resistant to three or more classes of antibiotics were included in the study.

Clinical assessment

A detailed history was taken from all patients including that about possible risk factors and use of prior medications. This was followed by a detailed ocular examination, which included assessment

of the visual acuity, slit-lamp biomicroscopy, fundus evaluation wherever possible and ultrasound B scan when necessary. The size and depth of the infiltrate and presence or absence of hypopyon were noted.

Microbiological work-up

The patients presenting with clinical features of microbial keratitis underwent corneal scraping, and the samples were sent for microbiological evaluation as per our institute protocol. In the microbiology laboratory, smear preparation was done for Gram stain and potassium hydroxide with calcofluor white mount. Corneal scrapings were inoculated on various culture media (5% sheep blood agar, chocolate agar, Sabouraud's dextrose agar (SDA), potato dextrose agar (PDA), non-nutrient agar with *Escherichia coli*, thioglycolate broth, Robertson's cooked meat media and brain heart infusion broth). All media were incubated aerobically at 37°C except chocolate agar (incubated in 5% CO_2 at 37°C) and SDA and PDA (incubated at room temperature). The media were observed for 14 days for any growth. A culture was reported as significant when one of the following criteria was fulfilled: either there was growth of the same organism on two or more media, or confluent growth at the site of inoculation on one solid medium, or growth in one medium consistent with direct microscopy findings, or growth of the same organism on repeated corneal scrapings from the same site of infection. Cultured bacterial isolates were tested for antimicrobial susceptibility to seven classes of antibiotics including fluoroquinolones (moxifloxacin, gatifloxacin, ciprofloxacin, ofloxacin), aminoglycosides (amikacin, gentamicin, tobramycin, vancomycin), cephalosporines (cefazoline, ceftazidime), chloramphenicol, piperacillin–tazobactam, imipenem and colistin. Antibiotic susceptibility was done by Kirby-Bauer disc diffusion method, Epsilometer test and VITEK-2 system (BioMerieux, Marcy I 'Etoile, France) in all cases. Minimum inhibitory concentration was determined for each antibiotic and isolates were labelled resistant, intermediate or susceptible to a particular antibiotic by comparing the breakpoint values of each antibiotic for each pathogen with the cut-off values recommended by Clinical and Laboratory Standards Institute guidelines. Methicillin resistance in *Staphylococci* was tested by using cefoxitin as a surrogate marker with the help of VITEK-2 system. For analysis of antibiotic susceptibility, intermediately susceptible results were considered as resistant to that drug. Multidrug resistance (MDR) was defined as resistance to three or more different classes of antimicrobial drugs.[9]

Treatment protocol

According to the Institute protocol for the treatment of bacterial keratitis, topical antibiotics were prescribed as per the scraping report on the first day (gatifloxacin 0.5% or fortified vancomycin 5% or fortified cefazoline 5% for Gram-positive organisms; ciprofloxacin 0.3% for Gram-negative organisms; fortified amikacin 5% for Gram-positive filaments and mycobacteria) hourly, along with a mydriatic–cycloplegic eye drop and oral analgesics. All patients were reviewed weekly and observed for response to medications. In the absence of response or worsening, the treatment was modified based on the sensitivity report. For an impending perforation or a perforation less than 2 mm in size, tissue adhesive (TA) application along with bandage contact lens (BCL) placement was done. Therapeutic penetrating keratoplasty (TPK) was performed in cases where perforation was greater than 2 mm, and located either centrally or paracentrally, or if progression in the size or depth of the infiltrate was observed despite appropriate antibiotic therapy.

Data analysis

The following details were noted from the medical record: age, gender, occupation, eye affected, duration of symptoms, previous topical medications, risk factors, size of the epithelial defect and infiltrate, smear and culture results, antibiotic susceptibility profile of bacterial isolates, treatment received, surgical intervention, outcome, duration of follow-up, and presenting, and final visual acuity. For analysis, size of the infiltrate (along the longest dimension) less than 6 mm was referred to as small and greater than 6 mm as large. Complete success was defined as resolution of the infiltrate with scarring on medical treatment alone. Partial success was defined as resolution of infection following TA+BCL application. Failure was defined as progressive increase in size of the infiltrate, corneal melting, and/or perforation entailing TPK, or evisceration. χ^2 test was used for the comparison between two proportions. A p value of ≤ 0.05 was considered significant.

RESULTS

Demographics

In the duration of 2 years, that is, between January 2018 and December 2019, 1036 cases of culture-positive microbial keratitis cases were observed, out of which 637 were bacterial in aetiology. MDR bacterial keratitis was found in 40 eyes of 40 patients during the study period. The mean age of patients was 50.9±25.4 (range: 2–97) years, and the male:female ratio was 4.7:1. The average follow-up of patients after the onset of keratitis was 5.4±4.6 months.

Risk factors, history of prior topical medications and clinical features at presentation have been summarised in table 1.

Microbiology

Gram-negative bacilli (GNB) (n=18, 45.0%) were found to be the maximum among the MDR group followed by Gram-positive bacilli (GPB) in 15 (37.5%), Gram-positive cocci in 6 (15.0%) and Gram-negative cocci (GNC) in 1 (2.5%) patient. Among the GNB, *Pseudomonas aeruginosa* (15.0%) and among the GPB, *Corynebacterium amycolatum* (12.5%) were found to be the most common MDR organisms (table 2).

Resistance to three, four, five and six classes of drugs was seen in 17 (42.5%), 17 (42.5%), 1 (2.5%) and 4 (10.0%) patients, respectively. One (2.5%) patient showed resistance to all seven classes of drugs. Resistance to moxifloxacin (n=33, 82.5%) and chloramphenicol (n=34, 85.0%) were highest and no resistance to tobramycin was observed (figure 1).

Among *Pseudomonas* keratitis (n=8, 20%), resistance to moxifloxacin and chloramphenicol was seen in all cases (100%) followed by ofloxacin (71.4%) and ceftazidime (71.4%). Among *Corynebacterium* keratitis (n=10, 25%), resistance to all fluoroquinolones and cefazoline was observed in all cases (100%) followed by resistance to chloramphenicol (80%). Two out of three cases of *Staphylococcus* sp were found to be methicillin resistant.

Medical management

After obtaining sensitivity reports, the prescription was changed to the drug to which the organism was sensitive in 16 (40.0%) cases. Ten (25.0%) patients were continued on the same medications as the prescribed drug was sensitive; while six (15.0%) were continued on the same medications since the lesion was

Table 1 History and clinical features at presentation (total eyes: n=40)

Risk factors	Number of patients (%)
Prior vegetative trauma	12 (30.0%)
Corneal transplantation	7 (17.5%)
Associated systemic comorbidities	
Postrenal transplantation	1 (2.5%)
Chemotherapy for renal carcinoma	1 (2.5%)
Vitamin A deficiency	2 (5.0%)
Other systemic diseases	3 (7.5%)
Poor ocular surface	
Post-Steven-Johnson syndrome	1 (2.5%)
Postchemical injury	2 (5.0%)
Decompensated cornea	1 (2.5%)
Previous history of ocular surgery	
Paediatric lens aspiration	1 (2.5%)
Postcorneal tear repair	1 (2.5%)
Nasolacrimal duct obstruction	1 (2.5%)
Total	33 (82.5%)
Prior topical medication	
Steroids	7 (17.5%)
Antibiotics	3 (7.5%)
Gatifloxacin 0.3%	1 (2.5%)
Ofloxacin 0.3%	2 (5.0%)
Moxifloxacin 0.5%	1 (2.5%)
Moxifloxacin 0.5% + tobramycin 0.3%	5 (12.5%)
Antifungal (natamycin 5%)	7 (17.5%)
Combination of topical antibiotics (gatifloxacin 0.3%: n=2; moxifloxacin 0.5%: n=5) and antifungal	8 (20.0%)
Cocktail of various topical medications (antibiotics, antifungal, antivirals, lubricants)	8 (20.0%)
Total	34 (85.0%)
Clinical features	
Mean duration of symptoms (days)	20.2±18.6*
Best-corrected visual acuity	
≥20/200	9 (22.5 %)
CF	8 (20.0%)
HM+	15 (37.5%)
PL+PR inaccurate	8 (20.0%)
Size of the infiltrate	
Small (<6 mm)	22 (55.0%)
Large (>6 mm)	18 (45.0%)
Depth of the infiltrate	
Superficial stromal	11 (27.5%)
Mid stromal	9 (22.5%)
Deep stromal	15 (37.5%)
>60% thinning	6 (15.0%)
Perforated	5 (12.5%)
Hypopyon	
Absent	20 (50.0%)
<4 mm	10 (25.0%)
>4 mm	3 (7.5%)
Could not be ascertained (near total/total infiltrate)	7 (17.5%)

*Range: 1–75 days; median: 14 days.

Table 2 Microbiological profile of multidrug-resistant organisms (total eyes: n=40)

Group	Number	Organism
Gram-positive cocci	6 (15.0%)	*Enterococcus faecalis* (n=2, 5.0%) *Staphylococcus hemolyticus* (n=1, 2.5%) *Staphylococuus* sp (n=1, 2.5%) *Streptococcus* sp (n=1, 2.5%) *Kocuria kristinae* (n=1, 2.5%)
Gram-positive bacilli	15 (37.5%)	*Corynebacterium amycolatum* (n=5, 12.5%) *Corynebacterium* sp (n=2, 5.0%) *Mycobacterium* sp (n=2, 5.0%) *Bacillus* sp (n=2, 5.0%) *Corynebacterium jeikeium* (n=1, 2.5%) *Pseudodiphtheriticum* (n=1, 2.5%) *Nocardia* (n=1, 2.5%) Atypical *Mycobacterium* (n=1, 2.5%)
Gram-negative cocci	1 (2.5%)	*Moraxella lacunata*(n=1, 2.5%)
Gram-negative bacilli	18 (45.0%)	*Pseudomonas aeruginosa* (n=6, 15.0%) *Sphingomonas paucimobilis* (n=3, 7.5%) *Hemophilus* sp (n=2, 5.0%) *Escherechia coli* (n=1, 2.5%) *Acinetobacter baumanii* (n=1, 2.5%) *Pasteurella pneumotropica* (n=1, 2.5%) *Rhizobium radiobacter* (n=1, 2.5%) *Aeromonas salmonicida* (n=1, 2.5%) *Pseudomonas stutzeri* (n=1, 2.5%) *Burkholderia pseudomallei* (n=1, 2.5%)

resolving, although the organism was intermediate or resistant to the prescribed drug. Two (5.0%) patients underwent evisceration due to rapid progression of infiltrate leading to perforation before switching the antibiotics. Six (15.0%) patients were lost to follow-up before the sensitivity report was obtained.

Outcomes

Complete resolution of infection was seen in 15 (37.5%) out of 40 patients on medical management alone. Eleven (27.5%) patients required TA+BCL application out of which six resolved (partial success), three required TPK, subsequently, one became phthisical and one was lost to follow-up. A total of five (12.5%) patients underwent TPK; graft failed in two eyes, one became phthisical, while two had clear graft at the last follow-up. One (2.5%) patient with graft infiltrate 7 days post-DSEK underwent lenticule explantation following which infection resolved on medical therapy (donor-related infection). Three (7.5%) patients underwent evisceration, two (5%) developed endophthalmitis and resolved with intraocular antibiotic injections. Six (15.0%) patients were lost to follow-up before complete resolution of the infiltrate.

Correlation of risk factors with drug resistance

History of previous corneal transplant (p=0.42), prior use of topical steroids (p=0.99), or prior use of topical antibiotics (p=0.53) did not correlate with the drug resistance profile of the organisms (table 3).

Correlation of duration of symptoms, size of the infiltrate and drug resistance with outcomes

Smaller infiltrates mostly resolved with medical management alone (p=0.002). Duration of symptoms at presentation (p=0.28) and pattern of drug resistance (p=0.12) surprisingly did not correlate with the success or failure of medical management in MDR keratitis (table 4).

DISCUSSION

Multidrug-resistant strains of microbes are increasing worldwide. The emergence of extremely drug-resistant and pandrug-resistant strains are more worrying. The excessive and inappropriate use of antibiotics, both systemic and topical, including use for

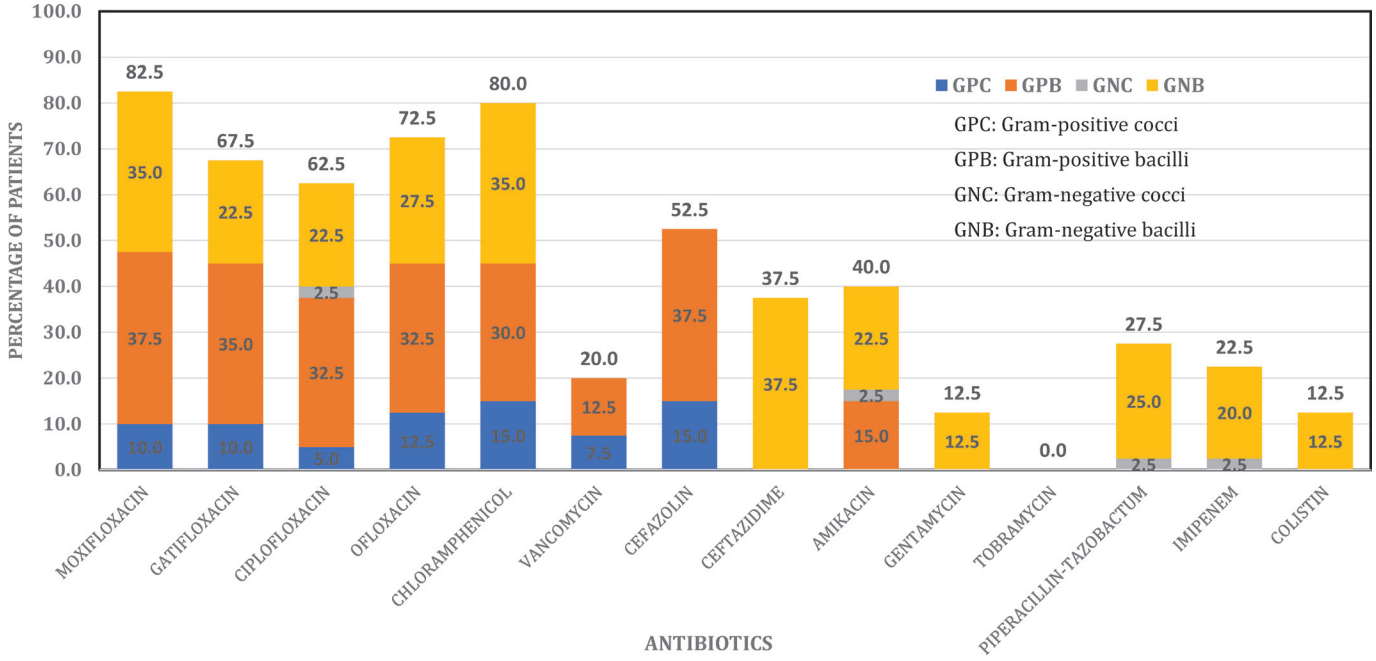

Figure 1 Resistance to antibiotics in study patients.

prophylaxis, is considered to be one of the leading factors for the emergence of antibiotic resistance.[10 11] There are numerous reports in the literature demonstrating that indiscriminate use of ophthalmic antibiotics has led to increasing antibiotic resistance.[12 13] Fluoroquinolone is widely used as monotherapy for presumed bacterial keratitis since it has a broad spectrum of action. However, this has led to gradual development of resistance towards this group of drugs.[11 14] Lalitha *et al* reported a significant increase in resistance to fluoroquinolone (ofloxacin/moxifloxacin) among *Staphylococcus aureus and Pseudomonas aeruginosa* isolated in south India over a period of 12 years (ofloxacin resistance increased from 11.1% in 2002 to 66.7% in 2013 in *S. aureus*).[15]

Resistance to antibiotics in bacteria occurs by one of the following four mechanisms: modification of drug-binding target, efflux pumps in the cell membrane to flush out drugs from cells, secretion of enzymes to deactivate the drugs and/or formation of biofilms (which are impermeable to drugs) around bacterial colonies. These mechanisms are expressed by various drug-resistance genes, which are either transferred vertically (inherited resistance) or horizontally (through plasmids).[16] Bacteria may develop MDR by one of the two mechanisms. The bacteria may accumulate multiple genes, each coding for resistance to a single drug, which occurs usually on the resistance plasmids. Also, it may be due to increased expression of genes that code for multidrug efflux pumps, extruding a wide range of drugs.[16]

Gram-positive organisms have been reported as more common aetiological agents of microbial keratitis compared with Gram-negative organisms.[3 17 18] In our institute also, Gram-positive organisms are isolated more commonly from corneal scraping samples. On the other hand, we found Gram-negative bacteria to be the maximum multidrug resistant, which were consistent with one of our previous studies[19] and another study by Grandi *et al*[20]. Among them, GNB were most commonly seen. The emerging drug resistance of *Pseudomonas* was consistent with studies by Grandi *et al*[20] from Italy, Lalitha *et al*[15] from south India and Ng *et al*[21] from Hong Kong. Also, among the Gram-positive bacteria, *Corynebacterium* was found to be the most common MDR organism, which is different from other studies where *Staphylococcus* was found to be the most common drug-resistant organism, with increasing resistance to methicillin.[15 19 22]

Table 3 Correlation of risk factors with drug resistance

Sl.	Risk factors		Classes of antibiotics 3; n (% of total eyes: 40)	Classes of antibiotics >3; n (% of total eyes: 40)	P value
1.	(a)	Previous corneal transplant	2 (5.0)	5 (12.5)	0.42
	(b)	No transplant	15 (37.5)	18 (45.0)	
2.	(a)	Prior steroid use	3 (7.5)	4 (10.0)	0.99
	(b)	No steroid use	14 (35.0)	19 (47.5)	
3.	(a)	Prior antibiotic use	5 (12.5)	9 (22.5)	0.53
	(b)	No antibiotic use	12 (30.0)	14 (35.0)	

Table 4 Correlation of duration of symptoms, size of infiltrate and antibiotic resistance with outcome

Sl.	Risk factors	Outcome: Complete success; n (% of total eyes: 40)	Outcome: Partial success+failure; n (% of total eyes: 40)	P value
1.	Duration of symptoms			
	≤15 days	11 (27.5)	14 (35.0)	0.28
	>15 days	4 (10.0)	11 (27.5)	
2.	Size of infiltrate			
	Small	13 (32.5)	9 (22.5)	0.002
	Large	2 (5.0)	16 (40.0)	
3.	Resistance to antibiotics			
	3 classes	4 (10.0)	13 (32.5)	0.12
	>3 classes	11 (27.5)	12 (30.0)	

The most common risk factor in our study was ocular trauma (30.0%) followed by previous corneal transplantation (17.5%) and associated systemic comorbidities (17.5%). Similarly, ocular trauma has been found to be the most common risk factor for infectious keratitis in other studies by Xu *et al*[22] and Oliveira-Ferreira *et al*[23]. For MDR *Pseudomonas* keratitis, contact lens usage has been found to be the most common predisposing factor in studies by Fernandes *et al*[24] and Vazirani *et al*[25].

Antibiotics, to which the maximum bacteria were resistant, were fluoroquinolones, and the least resistance was seen towards aminoglycosides, imipenem and colistin. This is consistent with the hypothesis that the indiscriminate use of fluoroquinolones is leading to its increasing resistance.[26] Resistance to three (42.5%) and four (42.5%) classes of drugs was observed to be the most common.

The study has its limitations due to its retrospective nature and small sample size. A case–control study looking at MDR versus non-MDR keratitis might help us to understand the relationship between risk factors and drug resistance in a better manner. Overall, this study gives an insight into the microbiological profile of MDR bacteria causing keratitis. Regular monitoring of response to treatment with close follow-up is required in such cases. Inappropriate usage of topical as well as systemic antibiotics should be discouraged to prevent the further spread of MDR organisms.

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