

Spectrum of bacterial keratitis in North India: A retrospective analysis of six years at a tertiary care eye center

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Purpose: To analyze the pattern of bacterial pathogens causing infective keratitis and their resistance to the recommended antibiotics over six years. **Methods:** It was a retrospective study of 9,357 cases of bacterial keratitis from January 2015 to December 2020, at a tertiary care ophthalmic center. A total of 9,547 corneal specimens were obtained from the study subjects. Demographic details of the patients, pathogenic bacteria isolated, and their antimicrobial susceptibility were noted and analyzed. **Results:** Bacterial pathogens were identified in 23.52% of the specimens. The most common isolates were coagulase-negative *Staphylococci* (60.75%), followed by *Pseudomonas aeruginosa* (14.23%), *Staphylococcus aureus* (13.92%), gram negative bacilli of the family *Enterobacteriales* (8.64%), *Streptococcus* spp. (1.72%), *Acinetobacter* spp. (0.13%), and other non-fermenting gram-negative bacilli (0.57%). In *Staphylococci*, 55–80% of isolates were resistant to erythromycin, and 40–70% to fluoroquinolones, while no resistance was observed against vancomycin. 40–60% of isolates of *P. aeruginosa* were resistant to cephalosporins, 40–55% to fluoroquinolones, and 30–60% to aminoglycosides. Also, 40–80% of isolates of *Enterobacteriales* were resistant to cephalosporins, and 50–60% to fluoroquinolones. Most gram-negative isolates were susceptible to carbapenems and polymyxin B. **Conclusion:** To the best of our knowledge, our study is the largest compilation of microbiological profile of bacterial keratitis from North India. It highlights the current trend of the bacterial pathogens that cause infectious keratitis. *Staphylococci* and *Pseudomonas* were found to be the most common pathogens. Increased resistance was seen against some of the commonly prescribed empirical antibiotics. Such evidence is useful for restructuring the empirical prescription practices from time to time.

Key words: Antimicrobial susceptibility testing, bacterial keratitis, bacterial pathogens, empirical antibiotics, seasonal variation

Bacterial keratitis is one of the most common causes of irreversible blindness due to corneal diseases.^[1,2] It is potentially a sight-threatening ocular emergency due to the possibility of its rapid progression with threat of corneal perforation and visual loss. Early diagnosis, which is primarily clinical and substantiated largely by microbiological data, and prompt treatment are needed to minimize the possibility of permanent visual loss and reduce structural damage to the cornea.^[3] Pending the reports of bacterial culture and antimicrobial susceptibility, empirical antimicrobials are started.^[4] An understanding of recent local epidemiological patterns of pathogens and their susceptibility profile can make empirical therapy evidence based. Hence, the present study was done with the objectives to know the recent epidemiological pattern of bacterial pathogens causing infectious keratitis, and to study the resistance pattern of the bacterial pathogens to recommended antibiotics.

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Methods

Study setting

The study was a retrospective analysis of the bacteriological profile and resistance pattern of the pathogenic isolates from bacterial keratitis cases from a tertiary care eye center. It was commenced after receiving clearance from the Institute Ethics Committee. Due to the retrospective nature of the study, ethics approval was given with a waiver for "Informed Consent of the patient".

Inclusion criteria

The samples from suspected keratitis cases from January 2015 to December 2020, which showed growth of ocular pathogenic bacteria, were included in the study.

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Exclusion criteria

Nonbacterial microbial keratitis such as fungal, viral, and parasitic were excluded from the study.

Clinical and Microbiological diagnosis

Patients were clinically examined and corneal scrapings and other corneal specimens were collected by trained ophthalmologists. Corneal scrapings were obtained using a sterile, disposable surgical blade (No. 15) or kimura spatula. The samples were immediately inoculated on 5% sheep blood agar and chocolate agar plates (HiMedia, Mumbai, India) in a C-shaped streak and smeared onto a glass slide for Gram staining. The inoculated media and slides were received in the ocular microbiology section, and were processed using standard bacteriological procedures. Agar plates were incubated at 37°C; biological incubator and CO₂ incubator were used for blood agar and chocolate agar, respectively. The culture plates were observed for the presence of bacterial growth at 24 hours and 48 hours. Growth of bacteria was considered significant when it was confluent (more than 10 colonies) on the site of inoculation on solid media, or the bacteria were also seen in primary microscopy, or the same bacterium was grown on both solid media.^[5] Identification of the bacterial isolates was done conventionally, as per the standard microbiological procedures. Antimicrobial susceptibility testing for bacterial isolates was performed using the Kirby–Bauer disk diffusion method. The antibiotic discs were used as per the recommendations of the Clinical and Laboratory Standards Institute (CLSI) for a particular group of bacteria. Cefoxitin disc (30 µg) was used to categorize *Staphylococcus* isolates as methicillin-resistant. The results were interpreted according to the CLSI guidelines for the respective years.^[6] For the convenience of analysis of the antibiotic susceptibility results, intermediate category (I) was integrated with susceptible category (S).

Statistical analysis

Demographic and microbiological details of the cases were entered in Microsoft excel sheets. Statistical analysis was done using Pearson's Chi-squared test and Fisher's exact test; and a *P* value of <0.05 was considered significant.

Results

Demographic profile

A total 9,357 cases of bacterial keratitis were evaluated during the study period. Due to the COVID-19 pandemic, very few samples (*n* = 653) were received in the year 2020. These patients visited the center for some kind of emergency. Hence, the findings of the year 2020 may be different from the general denominator of all keratitis patients presented to the center.

Out of 9,357 cases, 6,174 (66%) were males (M), with a M: F ratio of 1.93. A wide-ranging age distribution was observed in our study: the youngest patient was eight months of age, and the eldest was 100 years old. The largest number of samples were received from patients of the age group 51–60 years (486, 21.63%), followed by 61–70 years (372, 16.56%), 21–30 years (327, 14.55%), 41–50 years (313, 13.93%), 31–40 years (306, 13.62%), and 11–20 years (192, 8.54%). The least number of samples were received from the age groups, 0–10 years (107, 4.76%) and >70 years (143, 6.36%).

Culture positivity

Out of 9,357 cases, 190 had bilateral keratitis (2.04%). Samples collected from the eyes of bilaterally affected cases were considered as different entities; thus, a total of 9,547 samples were collected from 9,357 cases. A total of 2,246 clinical samples showed bacterial growth, accounting to the culture positivity of 23.52%. Out of 2,246 samples, 9 had polybacterial growth (0.4%), with two types of pathogenic bacteria. Thus the total number of bacterial isolates was 2,255. The bacterial culture positivity in different years from 2015 through 2020 was 20.11%, 20.73%, 22.89%, 30.52%, 24.46%, and 26.64% [Table 1].

Primary microscopy using Gram staining was done for 6,480 out of 9,547 samples (67.87%), of which 1,426 showed presence of bacteria (22%). Concordant Gram stain and culture results (both positive and negative) were observed in 4,017 samples (61.99%).

Out of 2,255 bacterial isolates, 1,723 were gram positive (76.40%) and 532 were gram negative (23.59%). Coagulase-negative *Staphylococci* (CoNS) (1,370, 60.75%) were the most common, followed by *Pseudomonas aeruginosa* (321, 14.23%), *Staphylococcus aureus* (314, 13.92%), *Klebsiella* species (65, 2.88%), *Escherichia coli* (56, 2.48%), *Citrobacter* species (42, 1.86%), *Streptococcus* species (39, 1.72%), *Enterobacter* species (15, 0.66%), *Proteus* species (13, 0.57%), non-fermenting gram-negative bacilli (NFGNB) (13, 0.57%), *Providencia* species (4, 0.17%), and *Acinetobacter* species (3, 0.13%) [Fig. 1]. No significant difference was observed in the spectrum of bacterial pathogens over the study years except the difference in percentage of *S. aureus* isolates in 2016, which was significantly less in comparison to that of other years (*P* = 0.002).

Speciation of CoNS is not done routinely in our center. However, in a few isolated studies done at the center, speciation of CoNS isolates of bacterial keratitis (*n* = 518) was done using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) method. *S. epidermidis* (218, 42%) was the most common CoNS isolated, followed by *S. hominis* (83, 16%), *S. haemolyticus* (62, 11.96%), *S. capitis* (47, 9.07%), *S. warneri* (40, 7.72%), *S. simulans* (37, 7.14%), and *S. cohnii* (31, 5.98%) (unpublished data).

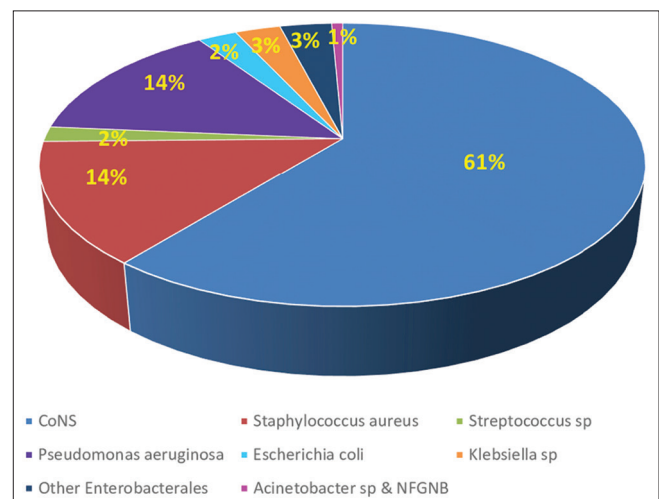


Figure 1: Spectrum of pathogens causing bacterial keratitis

Table 1: Spectrum of bacterial pathogens isolated from keratitis patients over the study years

Organisms isolated	2015	2016	2017	2018	2019	2020	Total percentage	P
Coagulase-negative <i>Staphylococcus</i> species	248	224	263	250	266	119	1,370 (60.75%)	0.681
<i>Staphylococcus aureus</i>	48	29	73	83	60	21	314 (13.92%)	0.002*
<i>Streptococcus</i> species	8	10	9	9	3	0	39 (1.72%)	0.165
<i>Escherichia coli</i>	13	12	8	10	11	2	56 (2.48%)	0.588
<i>Klebsiella</i> species	14	16	10	10	10	5	65 (2.88%)	0.499
<i>Citrobacter</i> species	8	9	5	14	5	1	42 (1.86%)	0.167
<i>Enterobacter</i> species	2	4	2	6	1	0	15 (0.66%)	0.256
<i>Proteus</i> species	2	0	3	2	4	2	13 (0.57%)	0.477
<i>Providencia</i> species	3	0	1	0	0	0	4 (0.17%)	0.083
<i>Pseudomonas aeruginosa</i>	57	65	60	66	50	23	321 (14.23%)	0.614
<i>Acinetobacter</i> species	1	1	0	1	0	0	3 (0.13%)	0.774
Non-fermenting gram-negative bacilli	2	4	2	2	2	1	13 (0.57%)	0.861
Total samples received	2,018	1,804	1,904	1,484	1,684	653	9,547	-
Total bacterial isolates	406 (20.11%)	374 (20.73%)	436 (22.89%)	453 (30.52%)	412 (24.46%)	174 (26.64%)	2,255 (23.52%)	-

*The difference in percentage of *S. aureus* isolates in 2016 was statistically significant in comparison to that in other years

Antibiotic susceptibility of pathogenic bacteria isolated from keratitis cases

Resistance pattern of *Staphylococcus* isolates

The percentage of methicillin-resistant *Staphylococci* (as indicated by cefoxitin resistance) varied from 18% to 44% over the six years. 40–70% of isolates were found to be resistant to fluoroquinolones and 50–80% to erythromycin. On an average, resistance of less than 30% was seen to aminoglycosides, tetracycline, and chloramphenicol. None of the isolates showed resistance to vancomycin [Fig. 2a].

Resistance pattern of *Streptococcus* isolates

The percentage of isolates of *Streptococcus* species was very low (1.72%). Resistance in the range of 25–75% was seen to all groups of antibiotics except vancomycin, to which all isolates were susceptible [Fig. 2b].

Resistance pattern of *Enterobacteriales*

Amongst *Enterobacteriales*, 40–80% of isolates were resistant to cephalosporins and 50–60% to fluoroquinolones. Less than 40% of isolates were resistant to aminoglycosides and tetracycline. Even better susceptibility was observed against piperacillin/tazobactam and carbapenems, with 10–30% of isolates showing resistance. There was no antibiotic to which all the *Enterobacteriales* isolates were susceptible [Fig. 3a].

Resistance pattern of *Pseudomonas aeruginosa*

Amongst *P. aeruginosa* isolates, 40–60% showed resistance to cephalosporins, 40–55% were resistant to fluoroquinolones, and 30–60% to aminoglycosides. Better susceptibility was observed against other β -lactam antibiotics with 20–30% isolates being resistant to piperacillin, piperacillin/tazobactam and carbapenem. Around 20% or less isolates each year were resistant to polymyxin B. There was no recommended antibiotic to which all isolates showed susceptibility [Fig. 3b].

Resistance pattern of *Acinetobacter* species and other NFGNB

The percentage of *Acinetobacter* species and other NFGNB was very less (0.70%). The resistance varied between 20–100% against different groups of antibiotics over six years [Fig. 3c].

Trends of resistance pattern over six years

In general, the different groups of pathogens did not show any specific trend over the years in their resistance to β -lactams, fluoroquinolones, and macrolides. A decreasing trend in resistance over six years was observed in *Staphylococci* against aminoglycosides (P -value for gentamicin = 0.024, tobramycin = 0.033, amikacin = 0.002); and against polymyxin B in *P. aeruginosa* isolates (P = 0.017).

Season-wise distribution of bacterial keratitis cases

Based on different seasons defined by the Indian Meteorological Department,^[7] maximum numbers of bacterial isolates were reported in the monsoon season followed by the summer season. The least number of isolates were reported in the autumn season. In the year 2019, the highest percentage of isolates was reported in the winter season. The seasonal variation in bacterial culture positivity was found to be statistically significant [Table 2].

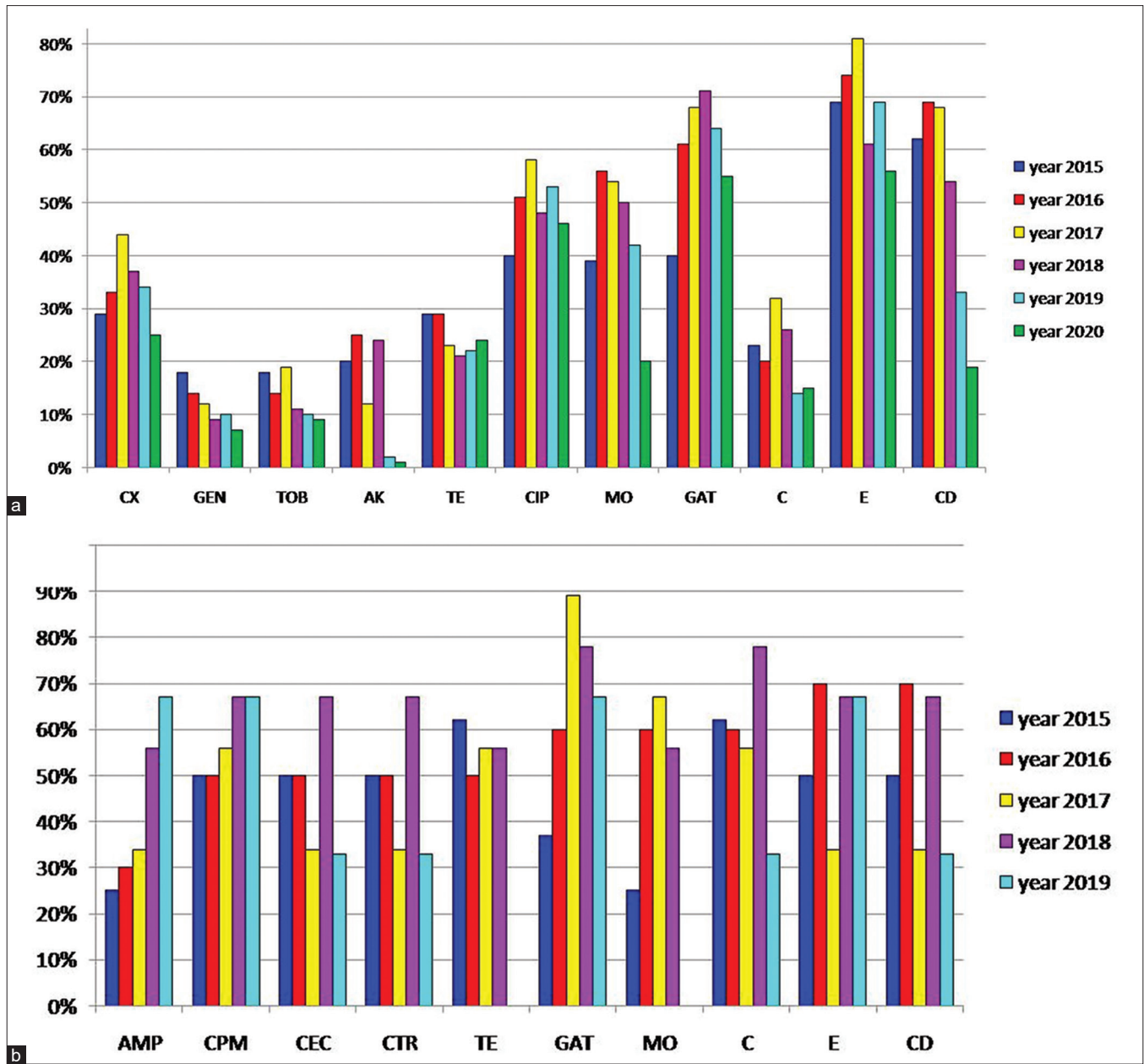


Figure 2: Resistance pattern for commonly prescribed antibiotics in gram-positive organisms; (a) *Staphylococcus* species; and (b) *Streptococcus* species

Table 2: Seasonal variation in the occurrence of culture positive bacterial keratitis

Seasons	Years					
	2015	2016	2017	2018	2019	2020
Winter (Dec-Feb)	162 (19.13%)	48 (12.83%)	82 (18.80%)	120 (26.49%)	130 (31.55%)	69 (39.65%)
Summer (Mar-May)	219 (25.85%)	58 (15.50%)	126 (28.89%)	122 (26.93%)	115 (27.91%)	28 (16.09%)
Monsoon (June-Sep)	349 (41.20%)	188 (50.26%)	178 (40.82%)	160 (35.32%)	112 (27.18%)	51 (29.31%)
Autumn (Oct-Nov)	117 (13.81%)	80 (21.39%)	50 (11.46%)	51 (11.25%)	55 (13.34%)	26 (14.94%)
P	<0.05*	<0.05 [†]	<0.05*	<0.05 [†]	<0.000 [‡]	<0.000

*All six P values of culture positivity in different seasons against all other seasons were <0.05. [†]P values of culture positivity in monsoon and autumn against all other seasons were <0.05. [‡]P value of culture positivity in autumn season against all other seasons was <0.000

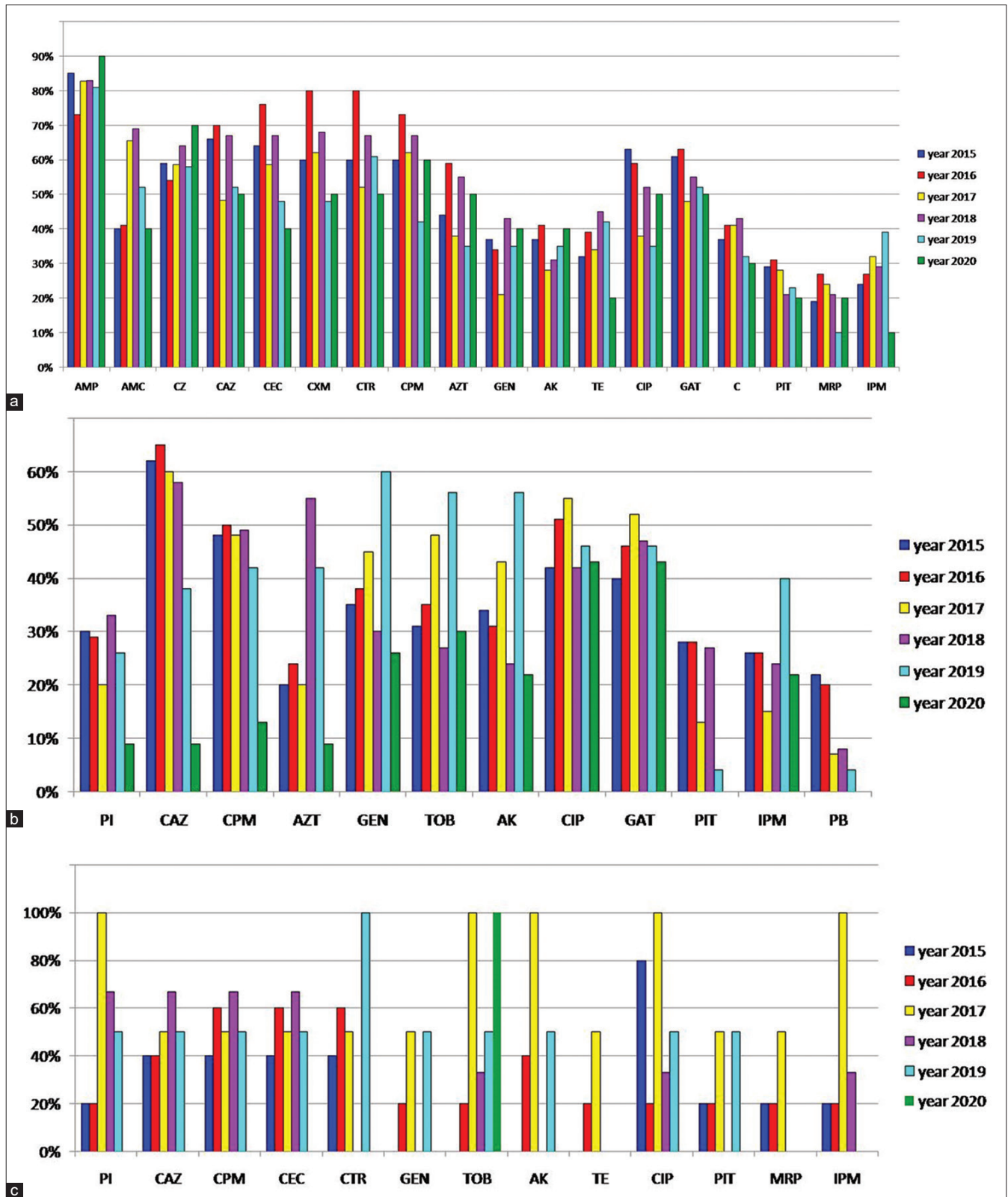


Figure 3: Resistance pattern for commonly prescribed antibiotics in gram-negative organisms; (a) *Enterobacteriales*, (b) *Pseudomonas aeruginosa*, and (c) *Acinetobacter* species and other non-fermenters

Discussion

Infective keratitis is a major cause of visual impairment worldwide, second only to cataract. The correct empirical treatment is important for a favorable visual outcome.^[8]

The pathogenic bacteria causing infectious keratitis, and their susceptibility to antibiotics varies with geographic region, population, and climatic factors. It is thus important to analyze the recent patterns of etiological agents and their resistance profile in a geographical region, and their variation over the years, for making an evidence-based decision and choosing the appropriate empirical therapy.^[9,10]

In this study, we have retrospectively analyzed the bacterial pathogens associated with bacterial keratitis and their antibiotic resistance patterns over a period of six years.

The culture positivity of bacterial keratitis in the present study was 23.52%. Worldwide, bacterial culture positivity from keratitis cases shows great variation, with reported positivity ranging from 32% to 78% in different countries across the globe.^[11–18] In India, the reported percentages of culture-proven bacterial keratitis range from 11% to 72%.^[19,20] One study from a tertiary care center in South India reported a bacterial culture positivity of 20.1%,^[21] whereas another study from the same part of the country mentioned a high positivity of 72%.^[20] In another state from South India, a culture positivity of 51.9% was reported.^[10] Two studies from the eastern part of India observed a culture positivity of 14.1% and 21.4%^[22,23] whereas from western states, positivity of 19.31% to 42.08% (Maharashtra)^[24,25] and 26.5% (Gujrat) were reported.^[26] The culture positivity reported from Delhi and nearby states ranged from 11% to 54.2%.^[9,19,27,28] A single center from Delhi reported 38% and 54.2% bacterial culture positivity in adults and pediatric bacterial keratitis cases, respectively.^[9,27] As culture positivity largely depends on antibiotic treatment prior to sample collection, the positivity rates from tertiary care centers, where the patient reaches after non-response to outside treatment, are expected to be low.

In the present study, gram-positive bacteria were the predominant pathogens causing bacterial keratitis, which was in concordance with other studies.^[9,13,18,21] CoNS (predominantly *S. epidermidis*) were the commonest isolates followed by *Pseudomonas aeruginosa*. Similar findings were observed by other authors from Delhi and surrounding states.^[9,19,27,28] A few studies from South India have also reported comparable bacterial spectrum.^[10,21] However, a large study of 12 years duration from a tertiary care center in South India, and one study each from East and West India report *Streptococcus pneumoniae* as the most common etiological pathogen of bacterial keratitis in their region.^[21,23,25]

In the present study, high resistance rate was seen in all bacterial pathogens against commonly prescribed empirical antibiotics. In *Staphylococci*, 50–80% of isolates were resistant to macrolides and 40–70% to fluoroquinolones. Very few isolates (less than 30%) were resistant to aminoglycosides, and none were resistant to vancomycin. Amongst gram-negative organisms, high resistance of 40–80% and 40–60% were observed against cephalosporins and fluoroquinolones, respectively. A low resistance of less than 30% was observed against aminoglycosides, piperacillin/tazobactam, carbapenems, and polymyxin B amid *Pseudomonas* isolates; and

aminoglycosides, piperacillin/tazobactam, and carbapenems amongst *Enterobacteriales*. The resistance pattern was relatively stable over the studied years for all the tested antibiotics except for aminoglycosides and polymyxin B in *Staphylococci* and *Pseudomonas* isolates, respectively, where a decreasing trend in resistance was observed over the six years.

Very few studies have evaluated the antibiotic susceptibility pattern of ocular pathogens causing bacterial keratitis. A study from South India^[21] reported a high level of resistance to fluoroquinolones (46.7%) and aminoglycosides (51.7%) in *Staphylococci*. In the same study, resistance of 10–25% was reported to both fluoroquinolones and aminoglycosides in gram-negative bacterial isolates. Also, over the study period of 12 years, an increase in percentage of methicillin- and fluoroquinolone-resistance was reported by the same authors. Another study from South India reported 6% and 18% isolates, respectively, of *Staphylococci* and *Pseudomonas* to be resistant to fluoroquinolones; and 10% of *Pseudomonas* isolates as resistant to aminoglycosides.^[20] Two studies from one center in south Delhi looked for resistance to fluoroquinolones and amikacin in adult and pediatric cases of bacterial keratitis. They observed 54% of *Staphylococci* and 59% of *Pseudomonas* isolates to be resistant to fluoroquinolones, and 48% of *Pseudomonas* isolates to be resistant to amikacin in the adult population. In the pediatric age group, a lower resistance of 30% and 25% to fluoroquinolones in *Staphylococci* and *Pseudomonas*, respectively, and 15% to amikacin amongst *Pseudomonas* isolates was observed.^[9,21]

The clinical outcome of a case of bacterial keratitis depends on several variables. Amongst them, the patient-related factors are age, occupation, presence of systemic or ophthalmic comorbidities, trigger of infection, compliance with medical advice, etc; the pathogen-related factors include type of bacteria (gram-positive or negative, or genus, or species), presence of mixed infections, antimicrobial susceptibility, presence of virulence factors like biofilm formation, etc., Due to the retrospective nature of our study, the clinical outcome of the participants could not be co-related with such variables. A prospective study of 131 bacterial keratitis cases from Ethiopia had reported outdoor occupation, ulcer depth, use of traditional medicine, poor adherence to medications, ocular comorbid conditions, and perforation or thinning at admission to be significant independent predictors of poor treatment outcome.^[29] Similar findings were reported by authors of a study from USA, who had found in 193 bacterial keratitis cases age more than 60 years, large ulcers (more than 5 mm), and ocular comorbidities, like previous surgery and ocular surface defect, to be the statistically significant predictors of a major complication in bacterial keratitis.^[30] In a multicenter prospective study of three years duration from United Kingdom, a linear association between clinical outcome and minimum inhibitory concentration (MIC) of causative bacteria was reported for *Enterobacteriaceae*, *Pseudomonas*, *S. aureus* and *Streptococcus* spp.^[31] In another multicenter study from USA, it was observed that patients in whom the bacterial isolate had a ciprofloxacin MIC exceeding 1 mg/L improved significantly more slowly than those with a more susceptible isolate. Also, 74.5% of patients with isolates having a ciprofloxacin MIC less than 1 mg/L had successful epithelial healing compared with 57.7% of patients with a less susceptible isolate.^[32] A study from a pediatric population in North India reported a better course of recovery in bacterial ulcers caused

by gram-positive bacteria.^[27] Authors from South India, in their analysis of the relationship between the causative bacteria, moxifloxacin MIC, and clinical outcome have observed that a higher MIC was predictive of a worse three-week visual acuity in bacterial keratitis.^[33]

Seasonal variation in bacterial keratitis was reported by very few studies. In the present study, maximum numbers of bacterial keratitis cases were reported in the monsoon, followed by summer and winter months. A study from South India reported a higher isolation rate in summer and monsoon seasons.^[10] However, two other studies from the same region found that bacterial keratitis occurrence was independent of seasonal variation.^[34,35]

The present study has many strengths and a few limitations. There is a dearth of recent literature on bacterial keratitis, especially on addressing the resistance of pathogenic isolates to the recommended antibiotics. Our tertiary care center caters to Delhi and nearby states; therefore, the spectrum of pathogens and their resistance profile reflects the trend from a larger area in northern India. Another major strength is the large sample size spanning over a duration of six years. Also, the antibiotic susceptibility testing in our study was carried out against all the antibiotics recommended by CLSI guidelines, and the interpretation was done following its updated version for each year.

The limitations of the study include the retrospective analysis of available medical records, as a result of which the predisposing factors and clinical outcome of the investigated cases could not be ascertained. Also, ours is a tertiary care center; hence the results, mostly of referred cases, may not be directly applicable to the cases of bacterial keratitis in the general population.

Conclusion

This is a very large compilation of microbiological features of bacterial keratitis from a tertiary eye center of North India. Coagulase-negative *Staphylococci* and *P. aeruginosa* were found to be the foremost bacterial pathogens causing bacterial keratitis. Increased resistance to a number of the commonly prescribed empirical antibiotics was seen. Good susceptibility was seen for now less-prescribed aminoglycosides and chloramphenicol, and also for polymyxin B, carbapenems, and vancomycin. The information was important for restructuring the empirical prescription practices. Such evidence-based medical management can go a long way in improving patient outcome in infectious keratitis; also it reduces the overuse of antibiotics, thus preventing resistance to antibiotics.

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Conflicts of interest

There are no conflicts of interest.

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