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ORIGINAL RESEARCH

Ten-Year Analysis of Pathogenic Factors and Etiological Characteristics of Endophthalmitis from a Tertiary Eye Center in North China

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Purpose: To describe the etiology and spectrum of isolated pathogens in endophthalmitis over 10 years from an ophthalmic hospital in North China and report their antimicrobial susceptibilities.

Patients and Methods: The data covered the patients with endophthalmitis treated at Qingdao Eye Hospital from January 2011 to December 2020. Patients' medical history, pathogenic factors, bacterial and fungal culture results of intraocular specimens, and in vitro drug sensitivity test results were assessed.

Results: A total of 524 cases were counted in this study. Exogenous endophthalmitis was the main component, accounting for 94.66%, of which 49.62% of eyes had a history of ophthalmic trauma, intraocular surgery in 26.72% and suppurative keratitis in 17.37%. By comparison, endogenous endophthalmitis was found in only 5.34% of eyes. Among the 292 strains of pathogenic organisms obtained by co-culture, gram-positive bacteria accounted for 64.04%, with *Staphylococcus epidermidis* as the predominant pathogen (29.45%). Gram-positive cocci were identified in 76.77% of eyes with traumatic endophthalmitis, while 53.70% of keratitis-associated endophthalmitis was caused by fungi. The high susceptibility of bacteria to vancomycin (77.78%~98.33%) supported its continued use as empirical treatment. Among the fluoroquinolones, gram-positive cocci showed a higher susceptibility to gatifloxacin (94.83%), while there was a significant decrease to levofloxacin (51.67%). Gram-negative bacteria were less sensitive to cephalosporins (45.95%~66.67%) than fluoroquinolones (68.42%~78.05%) and aminoglycosides (75.00%~78.05%). Fungal susceptibilities to voriconazole and amphotericin B were 90.16% and 70.31% respectively. More than half of the 11 antibiotics were observed to exhibit a trend of reduced susceptibility.

Conclusion: Ophthalmic trauma was the primary pathogenic factor of endophthalmitis. Gram-positive cocci were the most common pathogens of traumatic and postoperative endophthalmitis, while suppurative keratitis-associated endophthalmitis often resulted from fungal pathogens. Levofloxacin as the preferred antibiotic in the perioperative period and cephalosporin as the first-line drug for the treatment of empiric endophthalmitis need to be vigilant.

Keywords: endophthalmitis, epidemiology, antibiotic sensitivity, microbiology

Introduction

Endophthalmitis is a serious blinding eye disease caused by microorganism infection. With advances in antimicrobial drugs and surgical techniques, the cure rate of endophthalmitis is increasing gradually, but there are still patients who cannot avoid visual impairment and even have to have the eyeballs removed. Endophthalmitis may be either exogenous, in which microbes on the ocular surface or from an external source are introduced into the eye, or endogenous, arising from hematogenous seeding of pathogens during bacteremia or fungemia.[1] Exogenous endophthalmitis is further divided into several categories mainly by pathogenic factors, such as post-trauma, post-cataract, keratitis-related, intravitreal treatment (vitrectomy or intravitreal injection)-related, and filtering bleb-associated.[1]

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The microbial profile and antibiotic sensitivity of endophthalmitis depend on the cause, geographic location, and population studied.[2] Empiric intravitreal antibiotics are the mainstay of treatment. Vancomycin and ceftazidime are recommended as the first-line antibiotics for intravitreal injection to treat bacterial endophthalmitis.[3] Numerous studies have evaluated the efficacy of third- and fourth-generation fluoroquinolones against endophthalmitis isolates and noted increasing bacterial resistance to these drugs.[4–6] Therefore, monitoring the causative organisms of endophthalmitis and their resistance has important guiding significance for the clinical treatment of the disease.

The purpose of the current study was to investigate the pathogenic factors and etiological characteristics of endophthalmitis and sensitivities of pathogens to commonly used antimicrobial agents at a tertiary eye center in North China in recent decade.

Materials and Methods

This research was carried out in accordance with the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of Qingdao Eye Hospital. This was a retrospective, laboratory-based microbiological study of 524 patients (524 eyes) who were clinically diagnosed with endophthalmitis at the Qingdao Eye Hospital of Shandong First Medical University between January 1, 2011 and December 31, 2020. Data on the patient demographics, pathogenic factors, date of specimen submission, pathogenic isolates, and antibiotic sensitivity tests were collected. As patient data were analyzed anonymously and maintained confidential, the patient consent was waived by the Ethics Committee of the Qingdao Eye Hospital.

Endophthalmitis cases were categorised into the following clinical types—post-trauma, postoperative, keratitis-related, endogenous, intravitreal injection-related. Postoperative endophthalmitis cases were then categorised into post-cataract endophthalmitis, postvitrectomy endophthalmitis, filtering bleb-associated endophthalmitis and postpenetrating keratoplasty endophthalmitis.

Antibiotic sensitivity testing of the isolates was performed using the automatic microbiological identification and susceptibility analysis system (Beckman Coulter WalkAway-96 plus, California, USA), which could identify both gram-negative and gram-positive organisms through a variety of biochemical reactions by colorimetry and fluorescence. Fungal identification was based on colony morphology, characters, and colors, combined with the size and shape of mycelia and spores, under a colony smear microscope. The anti-fungal susceptibility test was carried out in vitro.

Statistical Analysis

All statistical analyses were performed using SPSS 21.0 statistical software (SPSS, Inc., Chicago, IL, USA). To evaluate temporal trend in the distribution of antibiotic sensitivity, data were divided into two periods, 2011–2015 and 2016–2020. For bacterial susceptibility, intermediate sensitivity was also considered sensitive. Differences between the two groups were assessed using the Student's *t*-test. Post hoc multiple analyses were conducted to determine if the change for a certain organism was statistically significant. Two-tailed Student's *t*-tests were used to determine statistical significance ($P<0.05$).

Results

Endophthalmitis was exogenous in 496 eyes (94.66%) and endogenous in 28 eyes (5.34%). The mean age of patients was 47.19± 20.28 years, and 74.43% of patients were men.

There was a history of ophthalmic trauma in 49.62% of eyes (mostly male patients), intraocular surgery in 26.72% (cataract surgery in 11.5%), and suppurative keratitis in 17.37%, intraocular injection in 0.57%, and orbital cellulitis in 0.38%. Endogenous endophthalmitis was found in 5.34% of eyes (28 eyes) of 28 patients, including 3 patients with a fever of unknown cause, 1 with hepatapostema, 1 with pneumonia, 1 with enteritis, 1 with a recent dental surgery because of dental abscess, and 1 with a recent esophageal vein ligation surgery (Table 1).

A total of 292 strains of pathogenic organisms were obtained. Among them, bacteria accounted for 78.08% (228/292), including 187 gram-positive isolates and 41 gram-negative isolates, and fungi accounted for 21.92% (64/292). The most common bacterial isolates were *Staphylococcus epidermidis* (37.72%, 86/228), followed by *Bacillus* species (6.58%, 15/228) and *Staphylococcus aureus* (4.82%, 11/228). *Pseudomonas aeruginosa*, accounting for 4.38% (10/228) of the

Table 1 Predisposing Factors of 524 Patients by Endophthalmitis Etiology

Pathogenic Factors	Cases (n)	Sex (M/F)
Traumatic	260 (49.62%)	225/35
Postoperative (total)	140 (26.72%)	82/58
Post-cataract surgery	60 (11.45%)	30/30
Post-vitrectomy	23 (4.39%)	12/11
Post-keratoplasty	26 (4.96%)	21/5
Filtering bleb-associated	31 (5.92%)	19/12
Keratitis-related	91 (17.37%)	63/28
Endogenous	28 (5.34%)	17/11
Intravitreal injection-related	3 (0.57%)	2/1
Orbital cellulitis-related	2 (0.38%)	1/1

Note: The numbers in parentheses represent the proportion of pathogenic factors.

bacterial isolates, was the most frequently encountered gram-negative bacterial isolates (24.39%), followed by *Acinetobacter* (1.75%, 4/228), *Sphingomonas oligotinosa* (1.75%, 4/228), *Serratia* (1.75%, 4/228), and *Klebsiella* (1.75%, 4/228). The predominant detected fungal organism was *Fusarium* species (32.81%, 21 of 64 fungal isolates), followed by *Aspergillus* (26.56%, 17/64) and *Saccharomyces* (9.38%, 6/64) (Tables 2 and S1).

The antibiotic sensitivities of the bacterial isolates are summarised in Tables 3 and S2. Sensitivities of the 187 gram-positive organisms isolated to vancomycin, gatifloxacin, and fusidine were 98.33%, 94.83%, and 80.12%, respectively. Sensitivities of the 41 gram-negative organisms isolated to vancomycin, levofloxacin, and tobramycin were 77.78%, 78.05%, and 78.05%, respectively. The sensitivity time trend analysis of six clinically used antibiotics showed that the sensitivity rates of all antibiotics decreased compare the 2011–2015 to 2016–2020. It is worth mentioning that the sensitivity of levofloxacin was significantly lower than 60% and ceftazidime, tobramycin and gentamicin decreased significantly in these two periods (Figure 1). Temporal trend in the distribution of susceptibility was shown in Figure 2, except vancomycin and moxifloxacin, all antibiotics involved exhibited a significant decrease in susceptibility with time.

As presented in Table 4, among the 64 fungal isolates, sensitivities to voriconazole, amphotericin B, ketoconazole, itraconazole, natamycin, and fluconazole were 90.16%, 70.31%, 61.02%, 55%, 43.33%, and 17.74%, respectively.

Table 2 Distribution of Pathogens Isolated from Endophthalmitis Patients by Clinical Setting

Pathogenic Factors	Gram-Positive	Gram-Negative	Fungus
Trauma	119 (76.77%)	20 (12.90%)	16 (10.32%)
Postoperative	52 (75.36%)	8 (11.59%)	9 (13.04%)
Keratitis-related	13 (24.07%)	12 (22.22%)	29 (53.70%)
Endogenous	2 (18.19%)	1 (9.10%)	8 (72.73%)
Intravitreal injection-related	1 (33.3%)	0	2 (66.67%)
Total	187 (64.04%)	41 (14.04%)	64 (21.92%)

Note: The numbers in the parentheses represent the pathogen detection rates.

Table 3 Overall Susceptibility Rate of Isolated Gram-Positive and Gram-Negative Bacteria to Different Antibiotics

Antibiotic	Gram-Positive	Gram-Negative
Vancomycin	177/180 (98.33%)	7/9 (77.78%)
Gatifloxacin	165/174 (94.83%)	28/39 (71.79%)
Moxifloxacin	88/123 (71.54%)	0/0 (0%)
Ofloxacin	121/178 (67.98%)	30/40 (75.00%)
Levofloxacin	93/180 (51.67%)	32/41 (78.05%)
Ciprofloxacin	95/178 (53.37%)	26/38 (68.42%)
Fusidine	129/161 (80.12%)	11/28 (39.29%)
Cefuroxime	104/140 (74.29%)	17/37 (45.95%)
Ceftazidime	63/94 (67.02%)	24/36 (66.67%)
Tobramycin	114/178 (64.04%)	32/41 (78.05%)
Gentamicin	105/175 (60.00%)	30/40 (75.00%)

Notes: The numerator represents the number of isolates sensitive to the listed antibiotic, and the denominator represents the number of isolates that underwent susceptibility testing with the listed antibiotics. The percentages in the parentheses represent the rates of antibiotic sensitivities.

Discussion

Endophthalmitis is a devastating complication that can have serious anatomical and functional consequences. To better reduce the incidence of endophthalmitis, an evaluation of pathogenic factors and etiological characteristics of the disease is of positive guiding significance. In this retrospective study, we investigated the pathogenic factors and major causative bacteria of endophthalmitis and the resistances of these bacteria to commonly used antimicrobials, aiming to guide the first-line empirical treatment.

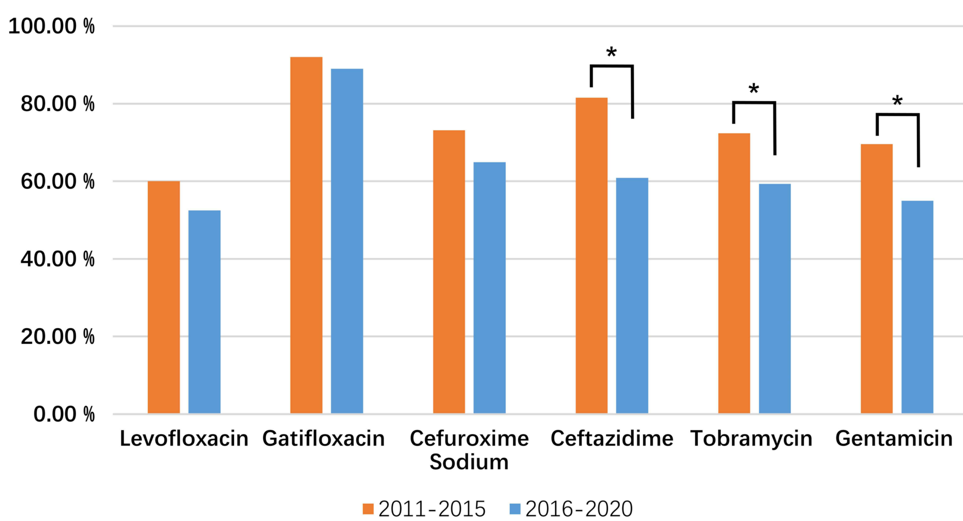

Figure 1 Time trend of overall antibiotic susceptibility rate from 2011 to 2020 in Qingdao Eye Hospital. Some antibiotics were omitted as the numbers of isolates that underwent susceptibility testing were not comparable between periods. The overall susceptibility rate for Ceftazidime decreased significantly from 81.58% in 2011–2015 to 60.87% in 2016–2018 (P<0.05). Similarly, Tobramycin decreased from 72.36% to 59.37% (P<0.05) and Gentamicin from 69.56% to 55.00% (P<0.05).
Note: *P<0.05.

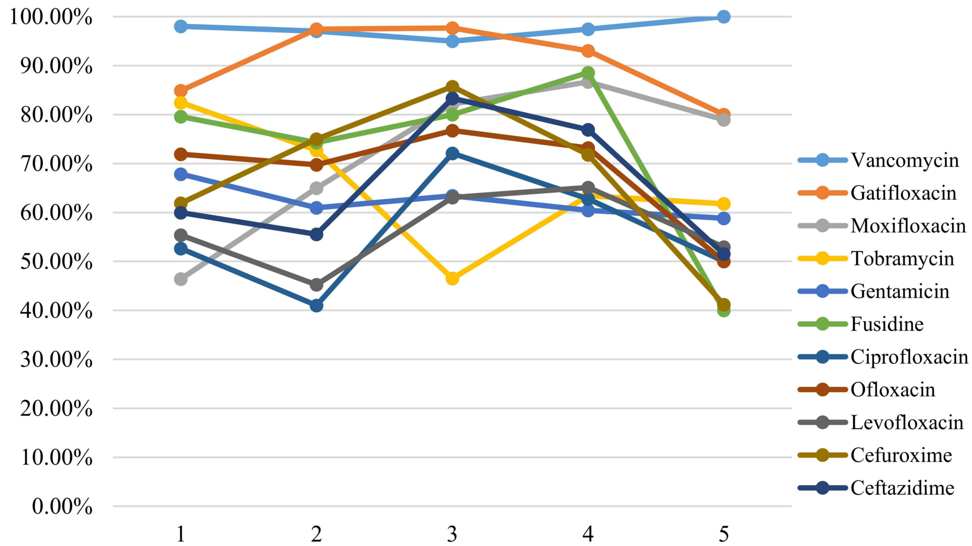

Figure 2 Time trends of bacterial susceptibilities. 1, 2010 to 2012; 2, 2013 to 2014; 3, 2015 to 2016; 4, 2017 to 2018; 5, 2019 to 2020.

Changes in Pathogenic Factors of Endophthalmitis

The results of our series revealed that ophthalmic trauma was the primary pathogenic factor of endophthalmitis (49.62%), followed by intraocular surgery (26.72%), which is consistent with previous reports from China[7–9] but different from studies in developed countries, which described that endophthalmitis mainly occurred after internal eye surgery, especially after cataract surgery.[2,10] The reason may be the relatively poor awareness of occupational protection among the large population engaged in industry and agriculture in China. Although cataract surgery-associated endophthalmitis accounted for 11.45% in this study, the incidence of endophthalmitis after cataract surgery in our hospital was 0.076% in the past 12 years.[11] Our previous studies have been proven that preoperative use of povidone-iodine and antibiotics to clean the bacteria in the conjunctival sac and intraoperative cefuroxime irrigation (1500 μg/mL) could greatly reduce the incidence of endophthalmitis after cataract surgery.[12,13] In fact, since September 2018, there has been no case of endophthalmitis after cataract surgery in our hospital. Relevant data have been collated and not published. Suppurative keratitis-related endophthalmitis accounted for 17.37%, which is lower than our previous report[7] but higher than the result reported by Henry et al.[14] This may be related to the fact that our hospital is a major referral

Table 4 Susceptibility Rate of Isolated Fungus to Different Antibiotics in Fungal Endophthalmitis

Fungus	Voriconazole	Amphozone	Ketoconazole	Itraconazole	Natamycin	Fluconazole
Fusarium sp	16/18 (88.89%)	13/21 (61.90%)	5/19 (26.32%)	5/19 (26.32%)	4/11 (36.36%)	3/20 (15.00%)
Aspergillus sp	15/17 (88.24%)	12/17 (70.59%)	12/16 (75.00%)	12/17 (70.59%)	4/8 (50.00%)	3/17 (17.65%)
Saccharomyces	6/6 (100%)	4/6 (66.67%)	4/5 (80.00%)	4/5 (80.00%)	2/3 (66.67%)	0/6 (0%)
Alternaria sp	5/5 (100%)	5/5 (100%)	5/5 (100%)	4/5 (80.00%)	2/3 (66.67%)	2/5 (40.00%)
Sedospora apical	3/4 (75.00%)	3/4 (75.00%)	3/4 (75.00%)	1/4 (25.00%)	0/1 (0%)	1/4 (25.00%)
Cladosporium	3/3 (100%)	3/3 (100%)	3/3 (100%)	2/3 (66.67%)	0/0 (0%)	0/3 (0%)
Others	7/8 (87.50%)	5/8 (62.50%)	4/7 (57.14%)	5/7 (71.43%)	1/4 (25.00%)	2/7 (28.57%)
Total sensitivity	55/61 (90.16%)	45/64 (70.31%)	36/59 (61.02%)	33/60 (55.00%)	13/30 (43.33%)	11/62 (17.74%)

Notes: The numerator represents the number of isolates sensitive to the listed antibiotic, and the denominator represents the number of isolates that underwent susceptibility testing with the listed antibiotics. The percentages in the parentheses represent the rates of antibiotic sensitivities.

center for diagnosing and treating corneal disease in China. Endogenous endophthalmitis occurred in 5.3% of eyes, which is similar to previous studies.[15,16]

Causative Pathogen Spectrum by Clinical Setting

The overall culture-positivity rate of the 524 patients with endophthalmitis from 2011 to 2020 was 55.73%, of which bacteria accounted for 78.08% and fungi accounted for 21.92%. Most of the isolates were gram-positive bacteria (64.04%), among which *Staphylococcus epidermidis* was most common (29.45%), which agrees with the findings of previous studies.[17–19] The major gram-negative bacterial isolate was *Pseudomonas aeruginosa* (3.42%), similar to a report from China.[20] However, *Pseudomonas aeruginosa* accounted for a high proportion of culture-positive isolates in Southern India, ranging from 13.1% to 25.9%,[21,22] which may be because *Pseudomonas* spp. prefer warm and moist environments. Gram-positive cocci were the most commonly detected pathogens in post-traumatic and postoperative endophthalmitis. Infectious keratitis-associated endophthalmitis was mainly caused by fungi (53.70%) and gram-negative bacilli (22.22%) in the present study. Progression of infectious keratitis to endophthalmitis is relatively uncommon. In a study from Germany of 3773 patients with diagnosed microbial keratitis, only 0.29% developed endophthalmitis, and the pathogen was found only to be bacteria.[23] Similarly, a report from the United States of 9934 patients with keratitis disclosed that only 0.5% progressed to endophthalmitis, with fungi as the predominant pathogens.[11] However, a study from Thailand showed that the incidence of keratitis-related endophthalmitis was as high as 20%, with *Pseudomonas aeruginosa* as the most common pathogen.[24] It is indicated that the risk of infectious keratitis progressing to endophthalmitis varies across geographic regions and climatic conditions.

The diagnosis of fungal endophthalmitis is relatively difficult. *Fusarium* and *Aspergillus* species accounted for a large proportion as pathogens in fungal endophthalmitis in this study. Our previous studies have shown that the recurrence rate of corneal ulcers caused by *Aspergillus* spp. after corneal transplantation is higher than that of ulcers caused by *Fusarium* spp., which is considered to be related to the vertical growth in the human cornea of these species.[25,26] Thus, in theory, *Aspergillus* infection may be more likely to develop into endophthalmitis. It was reported that *Aspergillus* was the most frequently isolated fungus, followed by *Candida* species.[17] However, in the current study, *Fusarium* spp. (32.8%) predominated among the isolated fungal pathogens, followed by *Aspergillus* spp. (26.56%), similar to a report from South China.[9] The different findings of studies can be attributed to the time period, geographic and climatic factors, urban versus rural settings, ethnicity, outpatient versus inpatient populations especially in tertiary care centers, and the small size of many reported series.[27]

Profile and Time Trends of Antibiotic Sensitivities

Antibiotic sensitivities and empirical antibiotics are topics of global concerns. Notably, more than half of the antibiotics were observed to exhibit a trend of reduced susceptibility in our series (Figure 2). Previous studies on endophthalmitis demonstrated that the susceptibilities of Gram-positive organisms to vancomycin were about 97.7–100%.[9,22,28] The high susceptibility rate of Gram-positive bacteria to vancomycin supports its continued use as empirical therapy. On the other hand, ceftazidime is often considered to be the first choice for the empirical treatment of gram-negative bacteria. Moloney et al reported that the sensitivity of gram-negative organisms to ceftazidime was 100%.[2] Recent studies from southern China reported that gram-positive cocci showed a relatively higher susceptibility to cephalosporins (~90%),[9,20] while the sensitivity of gram-negative bacteria to cefotadine was 66.67% and cefuroxime was 45.95% in our study. Hence, cephalosporins as first-line agents in the empirical treatment of endophthalmitis need to be vigilant.

At present, topical fluoroquinolones have been used widely as the first-line eye drops for prevention and treatment of infectious eye disease because of their broad spectrum of activity and low toxicity. The sensitivity of levofloxacin to gram-positive bacteria was disclosed to be as high as 82.3%-96.8%[19,20] in southern China and 77.5% in Miami.[22] In this study, however, it was only 51.67%, which was much lower than gatifloxacin. Therefore, levofloxacin as the preferred antibiotic in the perioperative period should be considered for replacement.

Moreover, a number of new antimicrobial formulations, such as essential oils, povidone-iodine and hexamidine diisethionate,[29–31] have shown potential antibacterial effects in the treatment of eye diseases and deserve further investigation. These studies also provide more possibilities for us to find new antimicrobial strategies in the future.

This study has some limitations. Detailed clinical features and visual outcomes were not presented because the patients included were from all over the country, and the long distance hindered many follow-up visits. In addition, young subjects cannot cooperate well with visual testing, leading to incomplete follow-up data. Moreover, the original cause of endogenous endophthalmitis in some patients were not been traced since it is out of the medical care provided in an eye hospital.

Conclusion

We described the pathogenic factors, etiological characteristics, and antibiotic sensitivities in culture-proven endophthalmitis with relatively large samples. Ophthalmic trauma was the primary pathogenic factor of endophthalmitis. Gram-positive cocci were the most common pathogens of traumatic and postoperative endophthalmitis, while keratitis-associated endophthalmitis was mainly caused by fungi. Levofloxacin as the preferred antibiotic in the perioperative period and cephalosporin as the first-line drug for the treatment of empiric endophthalmitis need to be vigilant.

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Disclosure

The authors report no conflicts of interest in this work.

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