·Clinical Research·

Corneal infection in Shandong peninsula of China: a 10-year retrospective study on 578 cases

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Abstract

• AIM: To determine the epidemiological characteristics, clinical signs, laboratory findings, and outcomes in patients with corneal infection in Shandong peninsula of China.

• METHODS: The medical records of 578 inpatients (578 eyes) with corneal infection were reviewed retrospectively for demographic characteristics, risk factors, seasonal variation, clinical signs, laboratory findings, and treatment strategy. Patient history, ocular examination findings using slit-lamp biomicroscopy, laboratory findings resulted from microbiological cultures, and treatment.

• RESULTS: Fungal keratitis constituted 58.48% of cases of infectious keratitis among the inpatients, followed by herpes simplex keratitis (20.76%), bacterial keratitis (19.03%) and acanthamoeba keratitis (1.73%). The most common risk factor was corneal trauma (71.80%). The direct microscopic examination (338 cases) using potassium hydroxide (KOH) wet mounts was positive in 296 cases (87.57%). Among the 298 fungal culture-positive cases, Fusarium species were the most common isolates (70.47%). A total of 517 cases (89.45%) received surgical intervention, including 255 (44.12%) cases of penetrating keratoplasty, 74 (12.80%) cases of lamellar keratoplasty which has become increasingly popular, and 77 cases (13.32%) of evisceration or enucleation.

• CONCLUSION: At present, infectious keratitis is a primary corneal disease causing blindness in China. With Fusarium species being the most commonly identified pathogens, fungal keratitis is the leading cause of severe infectious corneal ulcers in Shandong peninsula of China.

• **KEYWORDS:** keratitis; epidemiology; etiology; retrospective study
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INTRODUCTION

According to the World Health Organization (WHO), infectious keratitis is one of primary diseases causing blindness worldwide, particularly in developing countries[1-3]. China is a large agricultural country with higher incidence of infectious corneal disease than any other countries. Compared to the developed countries, the infectious keratitis in China has its own characteristics. To provide a useful clinical guidance, we retrospectively reviewed all the admitted infectious keratitis in Shandong peninsula, China between 2003 and 2012 in terms of epidemiology, clinical presentation, laboratory findings (etiology), and therapy.

SUBJECTS AND METHODS

Subjects In this hospital-based retrospective study, we reviewed the medical history of 578 patients (578 eyes) with infectious corneal ulcers hospitalized at the Affiliated Hospital of Medical College of Qingdao University from January 2003 to December 2012. The study was approved by the institutional review board of the Affiliated Hospital of Qingdao University, and written informed consent was obtained from all subjects. All procedures were in accordance with the tenets of the Declaration of Helsinki.

Data Collection The following clinical data were collected for all the cases of infectious keratitis. Epidemiology, clinical presentation, etiology, and therapies were received during hospitalization.

Collection, Separation and Culture of Pathogens Corneal scrapings were obtained aseptically from the base and edges of each ulcer, except those with corneal perforation. A portion of each scraping was examined for the presence of fungi, bacteria, or Acanthamoeba by using 10% potassium hydroxide wet mounts, smears stained with Gram's stain, and saline wet mounts, respectively. Another portion was inoculated onto Sabouraud glucose agar,

Table 1 Age distribution of infectious keratitis patients *n* (%)

Age (a)	FK	BK	HSK	AK	Total
0	0 (0.00)	6 (5.46)	4 (3.33)	0 (0.00)	10 (1.73)
10	0 (0.00)	4 (3.64)	8 (6.67)	0 (0.00)	12 (2.08)
20	0 (0.00)	10 (9.09)	8 (6.67)	0 (0.00)	18 (3.11)
30	35 (10.35)	20 (18.18)	14 (11.67)	0 (0.00)	69 (11.94)
40	69 (20.41)	24 (21.82)	12 (10.00)	4 (40.00)	109 (18.86)
50	128 (37.87)	32 (29.09)	40 (33.33)	4 (40.00)	204 (35.29)
60	76 (22.49)	7 (6.36)	22 (18.33)	2 (20.00)	107 (18.51)
≥70	30 (8.88)	7 (6.36)	12 (10.00)	0 (0.00)	49 (8.48)
Total	338	110	120	10	578

FK: Fungal keratitis; HSK: Herpes simplex keratitis; BK: Bacterial keratitis; AK: Acanthamoeba keratitis.

Table 2 Risk factors in infectious keratitis patients *n* (%)

Risk factors	FK	BK	HSK	AK
Ocular trauma				
Trauma with vegetable matter	165 (57.29)	34 (21.38)	8 (8.42)	2 (25.00)
Physical injury	42 (14.58)	61 (38.36)	2 (2.10)	2 (25.00)
Others	54 (18.75)	30 (18.87)	11 (11.58)	4 (50.00)
Contact lens wear	0 (0.00)	4 (2.52)	0 (0.00)	0 (0.00)
Systemic disease				
Diabetes	13 (4.51)	17 (10.69)	16 (16.84)	0 (0.00)
Upper respiratory tract infection	6 (2.08)	11 (6.92)	52 (54.74)	0 (0.00)
Other	8 (2.78)	2 (1.26)	6 (6.32)	0 (0.00)
Total	288	159	95	8

FK: Fungal keratitis; HSK: Herpes simplex keratitis; BK: Bacterial keratitis; AK: Acanthamoeba keratitis.

brain-heart infusion broth, and chocolate agar, respectively, and cultured for potential growth of fungi, bacteria, or Acanthamoeba. The microbiological identification was performed by the Micro Scan AutoSCAN4 (DADE BEHRING INC, USA).

Therapies Surgical intervention was performed if a clinically diagnosed infectious keratitis was not improving or was worsening after 5-7d of medical management, including therapeutic penetrating keratoplasty (PKP), lamellar keratoplasty (LKP) and corneal lesion excision combined with conjunctival autograft valve covered or amniotic membrane covered. After consultation to determine visual function has been lost and the eye without reservation value, patients had evisceration or enucleation.

RESULTS

Epidemiologic Characteristics The 578 cases of infectious keratitis came from 8 cities. Four hundred and thirty-one cases were male and 147 cases were female with a ratio of approximately 3:1. Three hundred and forty-nine cases had infectious keratitis occurred in the left eye whereas 229 cases in the right eye with the ratio of approximately 3:2. The average age was 52.39±4.34y with the range from 60d to 82y (Table 1). Four hundred and five cases (70.07%) were farmers, 100 cases (17.30%) were labor workers, 43 cases (7.44%) were teachers and office clerks, 22 cases (3.81%) were children and students and 8 cases (1.38%) were unemployed.

The risk factors were studied retrospectively (Table 2). Definite history of ocular injuries was identified in 415 cases (71.80%). There were 561 cases (97.06%) having received topical drug therapy prior to being admitted to our hospital and 62 cases (10.73%) having received surgical treatment, which included 17 cases (2.94%) of PKP, 4 cases (0.69%) of LKP, 4 cases (0.69%) of lesion excision with conjunctival graft or simple amniotic membrane transplantation, 31 cases (5.36%) of lesion excision or cautery and 6 cases with unidentified surgical information (1.04%).

The duration from the onset of symptoms to presentation to our institution ranged respectively from 1.5 to 150d (fungal keratitis, FK), 3d to 55y (herpes simplex keratitis, HSK), 0.5 to 90d (bacterial keratitis, BK) and 3 to 90d (acanthamoeba keratitis, AK), particularly 16 to 30d (48.52 %) for FK, 3 to 10y (68.33%) for HSK, 0 to 15d (65.45%) for BK and 1 to 2mo (80.00%) for AK. Based upon the date of admission, the number of admission was the highest from October to December (47.93%) for FK, April to June (33.33%) for HSK, July to September (41.82%) for BK and April to June (60.00%) for AK. The number of annual admission showed rising incidences of infectious keratitis on the annual basis (Table 3).

Clinical Characteristics/Presentation Among the 578 cases of infectious keratitis, 120 (20.76%) had corneal perforation, 153 (26.47%) had hypopyon, 72 (12.46%) had

Table 3 Annual distribution of infectious keratitis

Cases	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
FK	22	26	34	30	35	36	38	33	47	37	338
HSK	12	7	10	15	17	11	14	13	10	11	120
BK	15	10	13	13	9	10	12	8	11	9	110
AK	0	1	1	0	1	2	2	0	2	1	10
Total	49	44	58	58	62	59	66	54	70	58	578

FK: Fungal keratitis; HSK: Herpes simplex keratitis; BK: Bacterial keratitis; AK: Acanthamoeba keratitis.

complicated cataract, 95 (16.44%) had secondary glaucoma, 35 (6.06%) had endophthalmitis, and 9 (1.56%) had panophthalmitis. Histopathology evaluation was positive in 382 of 403 cases (94.79%). Periodic acid-Schiff (PAS) staining was positive in 213 (95.09%) of 224 FK cases. Among the 90 (15.57%) cases that had white blood cells greater than 10.00×10^9/L, 55.56% were positive for BK and 33.33% were positive for Pseudomonas aeruginosa.

Etiology Among the 578 corneal samples collected from affected eyes with infectious keratitis, etiology was identified in 406 (70.24%) cases.

Direct microscopic examination: the corneal scraping samples from 425 affected eyes showed positive findings in 263 cases (61.88%). The direct microscopic examination (338 cases) using potassium hydroxide (KOH) wet mounts was positive in 296 cases (87.57%). Gram staining was positive in 61 cases (55.45%). Corneal scraping examination revealed Acanthamoeba cysts were present in 4 eyes (40.00%).

Microbiology culture of infectious corneal tissue and/or scraping: corneal tissue and/or scrapings obtained from 425 eyes were examined. There were 377 pathogens identified with a sensitivity of 88.71%. Among the 298 fungal culture-positive eyes, Fusarium species were the most common pathogens (70.47%), followed by Aspergillus species (10.74%). Among the 70 bacterial culture-positive eyes, Staphylococcus species were the most common pathogens (48.57%), followed by Pseudomonas aeruginosa (42.86%).

Among the 338 eyes with FK, fungi alone were the etiological pathogens in 305 (90.24%) cases and bacteria were identified with fungi in 23 cases (6.80%) and virus were identified with fungi in 10 cases (2.96%). There were 83 (75.45%) cases that had bacteria as a single pathogen, while the rest had either multiple types of bacteria or mixed infection, including 12 cases (10.91%) of multiple bacterial infection, 15 cases (13.64%) of concurrent viral infection and 1 case (0.91%) of concurrent Acanthamoeba.

Effectiveness of the Treatments In this study, drug therapy was effective for corneal infection in 61 cases (10.55%). Surgical treatment was performed in 517 cases (89.45%), including 255 cases of PKP (44.12%), 74 cases of LKP (12.80%),111 cases of lesion excision with conjunctival graft (19.20%), 77 cases of evisceration or enucleation (13.32%). There were 30 cases (11.76%) of recurrent corneal infection after PKP and 17 cases (22.97%) of recurrence after LKP. Among 578 cases, 501 cases (86.68%) had the eyeballs saved with certain level of remaining vision.

DISCUSSION

Corneal diseases, especially infectious corneal diseases, are major causes of blindness worldwide[4-5]. The epidemiological features of infectious keratitis vary among different geographic regions, climate conditions, living environment, and economic status. The present study found that FK is the leading cause for severe infectious corneal ulcers, which is quite similar to the findings in Ghana and South India[6-7]. But it is quite different from the findings in a hospital in Taiwan, where fungal pathogens were identified in only 13.5% of 476 eyes (453 patients) with microbial keratitis, while bacterial pathogens were isolated from 82.1% of 476 eyes [8]. This discrepancy demonstrates that the incidence of different types of infectious corneal diseases has their own regional characteristics.

As reported in previous studies, corneal injury was identified as a major risk factor for infectious keratitis and subsequent corneal laceration repair and foreign body removal were the most important iatrogenic factors [9-10]. Among the current injury factors, vegetable matters were the most common pathogens responsible for FK and physical injury was the most common cause for BK. Many AK patients had history of some dirt splashing into the eye, which differs from many foreign reports noting that contact lens wear was the major risk factor in AK patients[8-11]. Furthermore, there was no case of contact lens wear in our FK, HSK, and AK series may because very few (0.40%) farmers wear contact lenses in China[12]. In this study, there were 52 (75.36%) cases of HSK among 69 cases with history of upper respiratory tract infection before corneal infection or recurrence. Similarly, Diabetes and bone marrow transplantation as a result of malfunction of self immune system may be the other potential risk factors of infectious keratitis [13]. In addition, 10.06% of FK patients had received topical corticosteroids before being admitted. Some of these FK patients had their infected eyes removed eventually, which are consistent with the findings from previous studies[13].

In the current study, the positive incidence of direct microscopic examination of corneal scraping samples with potassium hydroxide wet mounts was 87.57% , which is similar to the findings of Gopinathan *et al* [13] (91%). In consideration of its low cost, convenience, quickness, and high sensitivity and specificity, direct microscopic examination with potassium hydroxide wet mounts continues to be an ideal technique to assist in the diagnosis of FK. Although it is commonly used, Sharma *et al* [14] found microscopic Gram staining of corneal scrapings showed low sensitivity of 36% and 40.9% respectively during the early and intermediate stage of BK which were much lower than the sensitivity (88.7%) of KOH staining of fungal corneal scraping. In addition, the sensitivity of *in vitro* culture of corneal scraping and surgical corneal sample was only 37.37% and 36.90% respectively[9]. This is consistent with what we found in the present study. The potential causes of the low sensitivity were: 1) the patients had been treated with antibiotics prior to their admission to the hospital. The unnecessary overuse of antibiotics likely led to low sensitivity of laboratory testing; 2) the ulceration was covered by lysed and necrotic tissue which may interfere with deep penetration of commonly used antibiotics. Also, some clinical scenarios prohibited sampling at multiple locations of the corneal ulcer. Although a number of DNA probing analyses have been applied to clinical diagnosis, *in vitro* bacterial culture using standard bacterial culture medium is still the gold standard for diagnosis of BK. Therefore, how to achieve early, effective and reliable pathogenic diagnosis is still a challenge to ophthalmologists and microbiologists.

In the etiology study, fusarium species were found to be the most commonly isolated pathogens of FK which is consistent with a number of investigations in both northern and southern China during the past 2 decades[15]. Similar findings were also seen in southern India, whereas Aspergillus species were the most common cause of FK in northern India [6,14]. Although Candida species were most commonly reported in a few developed countries [16], Fusarium species and Aspergillus species were the most common pathogens for FK in other parts of the world [14]. Because of conditioned pathogens in normal conjunctival sac, mixed infection of two or more pathogenic microorganisms in infectious corneal disease is relatively common. Although they are not pathogenic under normal circumstances, these micro-organisms can lead to corneal infection with the malfunction of self immune system and damage of corneal epithelial barrier. Compared with concurrent fungal infection (2.96%) or Acanthamoeba infection (0.00), BK is more commonly present with HSK infection (13.64%) and opportunistic pathogens (Gram positive Cocci) occurred at the original lesion. The incidence of corneal perforation was as high as 33.33% which was consistent with the report from Xie *et al*[17]. It was speculated that the higher incidence of corneal perforation was resulted from the specific and nonspecific immune reactions to the concurrent viral infection [18]. This study still found that 15.57% of keratitis cases showed higher than average white blood cell counts with 33.33% being Pseudomonas aeruginosa positive. Hazlett *et al* [19] reported that removal of neutrophilic granulocyte in the laboratory could lead to lethal septicemia of Pseudomonas aeruginosa in the mice within 48h, which has been reported due to its high virulence by releasing exotoxin such as proteoglycan and lipopolysaccharides *etc*. through blood-eye barrier to systemic circular system which in turn led to serious systemic infection. This finding also indicated that systemic administration of antibiotics may be necessary based upon the results of blood work of patients with keratitis in addition to topical application of antibiotics.

Currently the effectiveness of drug therapy of BK still needs to be improved [20]. Among the patients having surgical intervention due to keratitis, this study demonstrated that 44.12% received PKP surgery with a success rate of 88.24% and recurrence rate of 11.76% which was lower than findings reported by Ti *et al* [21]. The potential reasons for the higher incidence of surgery and lower incidence of recurrence were as follows: 1) the majority of the keratitis patients had received prolonged and high dose of antibiotics or had prolonged course of keratitis, serious condition and low sensitivity to antibiotics prior to their admission to our hospital; 2) the PKP has been well established in our hospital, which is one of the major treatment centers in China for corneal infection; 3) our state-of-the-art eye bank ensured the high success rate of PKP surgery. In particular, we were among the first few eye centers in China being able to perform therapeutic LKP with clinically accepted outcomes [17,22]. The fungal recurrence rate after LKP in patients with hyphae growing horizontally is much lower than that in those with hyphae growing vertically. Considered as the most important pathogens, fusarium hyphae (91.2%) lay parallel to the corneal stromal lamellae[17]. In clinical practice, we found LKP is effective for treating FK that is not resolved by antifungal therapeutics. In addition, LKP can provide useful vision with fewer complications. Furthermore, corneal tissue used in LKP may be more readily available than that required in PKP. With careful screening for indications, rational use of drugs during perioperative period, and improved surgical techniques, the popularity of LKP has increased year by year, while the rate of recurrence after surgery has been showing a downward trend[17,23]. Although the recurrence rate (22.97%) of LKP was twice as much as that of PKP (11.76%), the LKP is a procedure of choice due to its excellent long term outcome and lower likelihood of immune-rejection reaction.

In this study, the incidence of corneal perforation was 32.73% in BK whereas only 13.61% in FK which may be related to the unique proteinase produced by pathogenic bacteria which in turn caused lysis of corneal tissue. In a similar vein, it also explained that patients with BK had higher incidence (42.86%) in evisceration or enucleation. Among 36 cases corneal perforation in patients with HSK, 14 cases (38.89%) had bacterial or/and fungal infections, which had been reported by our group[17]. It was obvious that the likelihood for patients who were treated timely based upon the results of pathogen/microbiology testing was much less than that for patients who did not have pathogen/microbiology testing done among all the patients receiving evisceration or enucleation. The percentage of testing of corneal samples was only 23.11% prior to 2000 whereas 94.43% post 2000. Correspondingly, the incidence of evisceration or enucleation was much higher prior to 2000 (35.03%) compared with that post 2000 (17.87%) (data not shown). Therefore, systematic and effective early treatment to patients with corneal infection is very important for better outcomes and prevention of vision loss.

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