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Original article

MICROBIAL KERATITIS LEADING TO ADMISSION AT MAHARAJ NAKORN CHIANG MAI HOSPITAL

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Abstract

Objective To report the risk factors, microbiologic profile, therapeutic and visual results in patients with microbial keratitis in the tertiary eye care center setting in northern Thailand.

Methods New cases of microbial keratitis were retrospectively reviewed over a period of 36 months. Clinical features (demographics, risk factors, visual acuity), microbiologic studies and clinical outcome were analyzed.

Results Two hundred and fourteen eyes of 213 consecutive patients (mean age 44.4 (SD36) years) were studied. The common risk factors in this study were trauma including foreign bodies (44%), preexisting ocular diseases (14%), contact lens wear (11%), and undetermined cause (18%). Most of the patients (74%) had prior treatment from ophthalmologists, general practitioners and drug stores. Corneal scraping was performed in 190 eyes and 30% had positive culture results. Sixty percent of the offending organisms were bacteria and 40% were fungi. *Pseudomonas* (39%) was the most common bacteria isolated. The principal fungal species isolated were *fusarium* (14%) and *aspergillus* (7%). Sixty nine eyes required surgical interventions and 16 of these eventually underwent either evisceration or enucleation. One hundred and twenty seven eyes (60%) improved in unaided visual acuity of one or more lines after treatment.

Conclusion Antecedent ocular trauma is the main risk factor for microbial keratitis in northern Thailand. *Pseudomonas* is the predominant causative organism in bacterial keratitis, and filamentous fungi are the principal causes of fungal keratitis. A bacterial: fungal ratio in this setting is 3 : 2, which appears to be expected in the tropic. **Chiang Mai Med Bull 2004;43(3):93-103.**

Keywords Microbial keratitis, bacterial keratitis, fungal keratitis

Microbial keratitis is a serious ocular infection that can lead to severe ocular morbidity in all age groups, and is commonly encountered by ophthalmologists worldwide. In some developing country in the tropics, corneal infections are the

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second most common cause of blindness after unoperated cataract.[1]

Microbial keratitis is rare in the absence of predisposing factors. Most cases was associated with ocular trauma, pre-existing ocular surface diseases, or contact lens wear. Although a number of studies, both retrospective and prospective, have considered the etiology, management, and clinical outcome of microbial kerattis, the morbidity from severe keratitis remains high. Since there are regional variations in causative organisms for microbial keratitis according to local climate and occupation, an elucidation of factors that lead to its occurrence in different parts of the country is essential for the development of a strategy to prevent and treat of this important cause of blindness.[2-7]

The following study was conducted at a tertiary hospital in northern Thailand, which is a tropical country in which most people work in the agricultural field. This study aimed to identify risk factors, clinical features and microbiological profiles, and ascertain the visual results of patients with microbial keratitis that led to hospital admission.

Patients and methods

All new patients with suspected microbial keratitis, and were admitted at Maharaj Nakorn Chiang Mai Hospital over a 36-month period (1 April 2000 through 30 March 2002), were studied retrospectively. This study was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University.

Microbial keratitis was defined as a suppurative infiltrate with or without overlying corneal epithelial defect and anterior chamber reaction. Patients with suspected or proven active viral keratitis were excluded. Hospital records were reviewed for the patients' demographic data, predisposing factors, duration of symptoms before presentation to the hospital, history of prior treatment, clinical features including visual acuity (VA) at the time of the presentation and on discharge, microbiologic studies, and medical and surgical treatment during admission.

Eye examination was focused on the location and size (measured along the greatest dimension of the lesion), presence of associated clinical features including hypopyon, and complications such as corneal thinning, perforation, or intraocular extension.

After detailed examination of the affected cases, most eyes with suspected corneal infection were scraped for microbial culture and sensitivity tests before treatment was initiated. Following the instillation of topical anesthesia (benoxinate hydrochloride, Novesin 0.4%, Novar tis Ophthalmics, Hettlingen/Switzerland), a corneal scrape was performed. Specimens were routinely obtained by using a sterile 25-gauge needle, or flame-sterilized platinum spatula, and smeared onto slides to prepare wet mounts (KOH) and Gram stain for direct microscopic examination. Additional scrapes were performed and specimens were directly inoculated onto media for isolation of bacteria (blood agar, and chocolate agar)

and fungi (Sabouraud dextrose agar, Mycocel agar, and Littman Oxgall). All media were incubated at 37 ^{O}C in 5% CO_2 atmosphere.

The standard treatment consisted of topical fortified cefazolin (33 mg/mL) and gentamicin (14 mg/mL) given alternately every hour for the first 48 hours to offer broad-spectrum activity with gram-positive and gram-negative organisms. If fungal elements were shown clearly on smears or clinical features were compatible with fungal infection, antifungal agents of choice were administered. Filamentous fungi were treated topically with either hourly 1% ketoconazole or 5% natamycin suspension, whereas 0.15% amphotericin B was given for yeast. Oral itraconazole at 200 mg twice daily was given in cases with deep fungal infiltration or those with limbal involvement. Topical antimicrobial agents were progressively tapered and/or modified according to the clinical response and microbiologic results.

Results

A total of 213 patients (214 eyes) comprising 141 males (66.2%) and 72 females (33.8%) were included in this study (Table 1). Age of patients ranged from 6-94 years old (mean age 44.36 years, SD 36). The age distribution of the patients was in the normal curve, which was common in ages of 30 to 60 years (Fig. 1). The right eye was affected in 106 cases (49.53%), the left eye in108 cases (50.47%). One patient had bilateral corneal ulcer.

Table 1. Patients' demographic data

Demographic data	
Age, mean(range, SD)	44.36 (6-94,36)
Sex (cases)	
Male	141 (66.2%)
Female	72 (33.8%)
Laterality *(eyes)	
Right	106 (49.53%)
Left	108 (50.47%)
Prior treatment (cases)	
Ophthalmologists	112 (52.58%)
General practitioners	40 (18.78%)
Drug stores	3 (1.41%)
Health workers	3 (1.41%)
none	55 (25.82%)

*Bilateral corneal ulcers 1 case

Most cases (55.4%) presented after one week of symptoms, however 15 cases presented at 2 months after the onset of disease (Table 2). Prior treatment by 112 ophthalmologists, 40 general practitioners, 3 health workers and 3 patients who received medication from drug stores was reported in 158 of 213 patients (Table 1).

Predisposing factors

The majority of patients (82.24%) had at least one of the known predisposing risk factors, and antecedent ocular trauma was the most common (44.39%), due to injury, foreign bodies, and previous ocular surgeries in 39, 54, and 2 eyes, respectively (Table 3). In cases with a history of foreign bodies, vegetable materials (25.9%), dust (24%) and insects (18.5%) were common. Other common, local risk factors after ocular trauma were ocular surface diseases (14.48%), contact lens (CL) wear (10.75%), and chronic use of topical steroid (3.74%).

In the group with pre-existing ocular surface diseases, corneal anesthesia, due

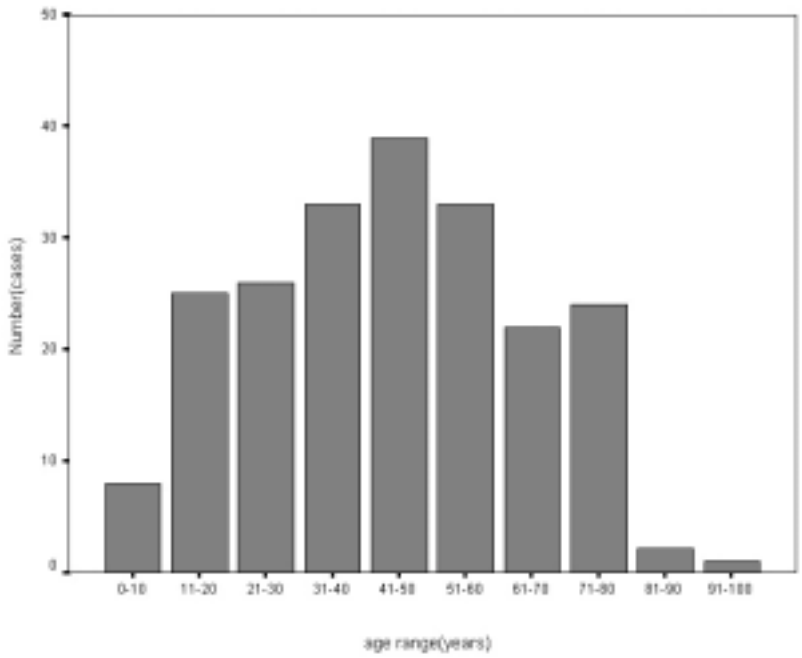

Figure 1. Patients' age distribution.

Table 2. Duration of the patients' symptoms before admission.

Duration of symptoms (days)	Number of patients (%) N=213
1	20 (9.4)
2-7	98 (46.0)
8-15	39 (18.3)
16-30	30 (14.1)
31-60	9 (4.23)
>60	15 (7.0)
Unknown	2 (0.9)

Table 3. Frequency of predisposing risk factors in microbial keratitis

Predisposing factors	Number of cases (%) N=214
Trauma	95 (44.39)
Injury	39 (18.23)
Foreign body	54 (25.23)
Surgery	2 (0.93)
Ocular surface disease	31 (14.48)
Corneal disease	20 (9.34)
Lid/lash abnormalities	11 (5.14)
Contact lens wear	23 (10.75)
Steroid use	8 (3.74)
Underlying systemic disease	19 (8.88)
None	38 (17.76)

to previous herpes infection, was presented in 12 eyes, bullous keratopathy in 2 eyes, dry eye in 2 eyes, persistent epithelial defect in 2 eyes, and vernal keratoconjunctivitis in 1 eye. Lid and/or lash abnormalities were presented in 10 eyes including exposure keratitis in 9 eyes (4 had thyroid eye disease), and entropion in 1 eye. All patients with CL-related corneal ulcer wore soft lens.

Underlying general diseases were identified as leading factors in 19 cases including diabetes mellitus (5 cases), human immunodeficiency virus infection (7 cases), stroke (2 cases), systemic malignancy (4 cases) and myasthenia gravis (1 case).

Ophthalmic assessment

Considering VA at presentation, the initial VA of 20/80 or better, between

20/120 and 20/200, and poorer than 20/200 was found in 25.6%, 13% and 61.4% of patients respectively. Clinical features of all corneal ulcers were summarized as shown in Table 4. In most cases, ulcers were located at the central and paracentral area of the cornea (199 of 214 eyes, 93%) and 152 of 214 (71%) eyes presentation with a relatively large area of ulcer (2 mm or more). Sixty-nine eyes had hypopyon at presentation, 5 had descematocele, 21 had perforated ulcers and 5 eyes presented with either endophthalmitis or panophthalmitis.

Microbiologic study

Corneal scrapings were performed in 190 of 214 eyes, but the specimen of one eye was lost during processing to the laboratory. Sixty-four of the 189 (33.86%) eyes had positive results on smears. Bacteria were identified by Gram stain in 42 specimens and the most common found was gram positive cocci (21 eyes). Fungal elements were found in 22 smears on KOH preparation (hyphal element 18, mixed hyphae and yeast 4).

Significant growth of microorganisms was obtained in 57 (30.16%) of the 189 specimens. Of these, bacteria were isolated in 61% and fungi in 39% (Table 5). *Pseudomonas aeruginosa* was the most common isolated bacterium and half of the pseudomonas keratitis cases were due to CL wear (10 of 22 eyes). *Fusarium* (14.04%) and *Aspergillus* (7.02%) were the most common fungi isolated. All isolated bacteria were sensitive to antibiotic tests.

Table 4. Characteristics of the corneal ulcers

Clinical features of the corneal ulcers	Number of eyes (%) (n=214)
Location of ulcers	
Central	93 (43.46)
Paracentral	106 (49.54)
Periphery	14 (7)
Area of ulcers	
<2 mm	62 (28.97)
2-6 mm	112 (52.34)
>6 mm	40 (18.69)
Hypopyon	69 (32.24)
Desmatocele/perforation	26 (12.15)
Endophthalmitis/panophthalmitis	5 (2.34)

Table 5. Micro-organisms isolated from corneal specimens

Bacteria	Number of eyes (%)	Fungus	Number of eyes (%)
Gram positive cocci		*Fusarium spp*	8 (14.04)
Streptococcus pneumoniae	4 (7.02)	*Aspergillus spp*	4 (7.02)
Streptococcus viridan	2 (3.50)	*Cuvularia spp*	2 (3.51)
Staphylococcus aureus	2 (3.50)	*Paecilomyces spp*	1 (1.75)
Coagulase negative staphylococcus	1 (1.75)	*Cladosporium spp*	1 (1.75)
Gram negative bacilli		*Exophiala spp*	1 (1.75)
Pseudomonas aeruginosa	22 (38.60)	Trichosporon spp	1 (1.75)
Serratia marcescens	1 (1.75)	Citrobactor freundii	1 (1.75)
Gram negative cocci		Unidentified septate hyphae	1 (1.75)
Moraxella spp	1 (1.75)	*Candida albican*	1 (1.75)
Norcadia	1 (1.75)	Pythium	1 (1.75)
Mixed *P. aeruginosa* and *S.saprophyticus*	1 (1.75)	Total	22 (38.60)
total	35 (61.37)		

Treatment and clinical outcomes

A combination of fortified cefazolin (33 mg/mL) and gentamicin (14 mg/mL) was the most frequently used initial antimicrobial treatment (131 of 214 eyes, 61.24%), whereas antifungal agents were administered in 53 eyes from which fungi were isolated from corneal scraping or clinical features were compatible with fungal infection.

Sixty-nine of 214 eyes underwent surgical interventions. Scleral patch graft (37.5%) was the most common surgical procedure performed for corneal perforation because of insufficient donor corneas in this region. Tissue adhesive glue was applied in 8 eyes (11.6%) with impending or small perforation. Sixteeen eyes (23.2%) eventually required either evisceration or enucleation. Among the patients who lost eyes, 15 presented with either poor initial VA or complications such as corneal perforation or endophthalmitis, and 5 had no perception of light at presentation. One patient with relatively good initial VA, lost his eye because of *Pythium insidiosum* infection which resisted medical treatment.

The length of hospital stay was up to 2 weeks, 1 month and more than 1 month in 54.9%, 28.6% and 15.5% of patients, respectively. When comparing the patients condition pre treatment with post treatment, unaided visual acuity had been improved in one or more lines, unchanged, and worsened in 59.35%, 13.55% and 14.48% of eyes, respectively.

Discussion

Corneal infection can occur if the cornea is damaged by injury or disease that may modify the local defence mechanisms or the flora of the ocular surface.[8] On a global level, leading factors vary tremendously with geographic location. While non-surgical trauma to the eye is the principle cause of corneal ulcers in developing countries,[1,3,4] pre-existing ocular disease and CL wear are common risk factors in developed countries.[6,7,9,10] Most patients (82%) in this study had leading risk factors; the most common being an antecedent ocular trauma (44%), as would be expected. Over half of these cases were caused by vegetable material. Other common risk factors after trauma were ocular surface diseases (15%) and CL wear (11%).

A bimodal age distribution of patients presenting with microbial keratitis was documented in previous reports, which may attribute to ocular traumas and CL-related keratitis in the younger group, and poor immunity and predisposing ocular disease in the older group.[2,4,6] The age profile of the patients in this study had a normal distribution, which was common in ages of 30-60 years. Males had a tendency to get corneal ulcer twice as much as females, which may be explained in part by males having more chance of accident or trauma than females, due to their work or outdoor activities.

When compared with our previous report,[11] CL-related corneal ulcers had increased, since the number of people wearing soft CL also increased over several years. Soft CL have greatly increased the risk of bacterial keratitis,

which is estimated to be 10-20 times higher with extended use of disposable CL.[12] Many pathophysiologic effects of CL wear have been reported, the most important of which is an induced hypoxia and microtrauma to the cornea[13-14] Recently, CL wear has become widespread and emerged as a common risk factor for microbial keratitis, subsequently, complications related with CL wear are now a matter of public health concern.

Routine culture of corneal lesions before antimicrobial treatment is initiated, and is a key to the management of microbial keratitis.[15-16] Even though this information is less valuable for patients with small ulcers, a positive microbial culture provides prognostic information regardless of the organism isolated.[17] It is imperative that the quality and quantity of specimens are made essential for accurate laboratory diagnosis. In this study, the microorganisms were isolated in one third of the patients. The high proportion of culture negative rate might be due in part to the inclusion of sterile cases and the difficulty in obtaining sufficient corneal material for conventional investigation, particularly concerning severe ulcers with the risk of corneal perforation. The application of topical anesthetic with preservatives before corneal scraping, and prior administration of antibiotics, may affect the recovery of organisms in the culture.[18] In this study, most of the patients (75%) had some form of treatment before being presented to us.

Microorganisms were isolated in one third of our patients. Of those with positive culture results, bacteria had been isolated in 60% and fungi in 40%, giving a bacteria to fungal ratio of 3 : 2. This proportion was close to others reported from other centers in Thailand.[4,19,20] However, fungus was more common than bacteria in southern lndia and Ghana.[3]

We found that the most common causative bacterium was *Pseudomonas* (39%), while *Streptococci* accounted for 10%. *Pseudomonas* species was identified as the most common bacterial isolate in other parts of Thailand and in studies from India and Hong Kong.[3-5,19-21] It should be pointed out that nearly half of the *Pseudomonas* keratitis cases in our study were associated with soft CL wear. Even though multiple organisms have been reported from microbial keratitis associated with CL wear, there was a higher prevalence of gram-negative rods compared with that in the absence of CL wear.[6,22-23] A shift in predominant bacterial pathogens was observed, compared to our earlier report, in which *Streptococci* was the predominant causative organism.[11] This could be due to the ready availability of effective topical antibiotics such as new generation fluoroquinolone, and less severe degrees of microbial keratitis could be treated an an outpatient basis.[15,24]

In this study, *Fusarium* and *Aspergillus* were common fungal pathogens. This is compatible with other reports from the tropics,[3,4,11,19,20] where filamentous fungi are the principle cause of fungal keratitis. These kinds of fungi are saprobic, thermophillic moulds that are found

widely in a warm and humid climate. They are ubiquitous in the soil and vegetation. Patients with injury caused by vegetable matter should be considered for possible fungal infection.[25]

Visual prognosis after microbial keratitis depends on several factors including the size, location and depth of the ulcer, as the well as patient's risk factors and the virulence of the pathogen. In this study, 60% of patients gained one or more lines of unaided visual acuity after treatment. However, fifteen cases (7.5%) eventually lost eyes. Most of these patients had either very poor vision or complications such as corneal perforation or endophthalmitis at presentation. Only one case had relatively good initial visual acuity and *Pythium insidiosum* was isolated. This aquatic micro-orgainism is unusual in humans and recalcitrant to any medications.[26-28] It may be assumed that patients with very poor visual outcome are more likely to be associated with poor initial VA, complications at presentation or caused by virulent organisms.

It should be noted that the cases of microbial keratitis reported in this study may not be representative. There may be a bias towards more severe and complicated cases because only inpatients were studied and most cases had been referred to our center. The difficulty in accurate diagnosis may contribute to that in treating severe keratitis, since there was a high proportion of culture negative cases, as well as a high proportion of fungal keratitis in this study. In addition, many patients had a long duration of disease and some had developed complications such as corneal perforation and intraocular extension by the time they were referred. In this setting, treatment with antimicrobial agents may not be effective, particularly in fungal keratitis, because most antifungal agents have poor corneal penetration.[29-31] A study from China suggested that surgical management should be considered if infection is not responsive to medication. It concluded that penetrating keratoplasty was an effective method to not only cure the disease, but also rehabilitate useful vision if surgery is performed soon enough to preserve the eye.[32] However, cornea donors are insufficient in Thailand and most cases of corneal perforation have been managed by scleral patch graft.

Severe keratitis remains a leading cause of blindness and inflicts to social and healthcare costs. It is essential to optimize the prevention and management of this serious infection. Since most of the patients (82%) in this study had at least one leading risk factors, education is important in preventing some kinds of work-related trauma, and avoiding the chance of fungal infection. particularly in agricultural activity. In addition, people should be concerned about the side effects of eye drops because in Thailand many topical medications are sold over the drug store counter. The importance of lens hygiene and the duration of CL wear should be emphasized to all CL wearers. In addition, clinical guidelines for clinicians should include the appropriate manage-

ment and time for follow up in cases with suspected corneal infection.

In conclusion, microbial keratitis remains clinically challenging and although the outcome can be favorable with appropriate management, there is potential for significant and permanent visual impairment, particularly in severe cases. Regarding management, it is imperative to know the “local” etiology of keratitis in a particular region. This important information can be a guide, particularly if the diagnosis is reliant on clinical signs alone. In addition, continual education for both health personnel and patients is required to minimize the incidence and severity of microbial keratitis.

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โรคกระจกตาติดเชื้อในผู้ป่วยที่เข้ารับการรักษา ในโรงพยาบาลมหาราชนครเชียงใหม่

นภาพร ตนานุวัฒน์, พ.บ., สุรารักษ์ เซี่ยงหลิว, พ.บ., สมสงวน อัษญคุณ, พ.บ.

ภาควิชาจักษุวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

บทคัดย่อ

วัตถุประสงค์ เพื่อรายงานถึงปัจจัยเสี่ยง เชื้อที่ทำให้เกิดโรค และผลการรักษาในผู้ป่วยโรคกระจกตาติดเชื้อที่เข้ารับการรักษาในโรงพยาบาลมหาราชนครเชียงใหม่ ซึ่งเป็นโรงพยาบาลตติยภูมิในเขตภาคเหนือ

วิธีการ เป็นการศึกษาย้อนหลังในผู้ป่วยรายใหม่ที่เป็นโรคกระจกตาติดเชื้อ ที่เข้ารับการรักษาในช่วงเวลา 36 เดือน โดยนำข้อมูลทางด้านลักษณะทางคลินิก เชื้อที่เป็นสาเหตุ และผลการรักษามาวิเคราะห์

ผลการศึกษา มีผู้ป่วยที่ศึกษาทั้งสิ้น 213 ราย (214 ตา) อายุเฉลี่ย 44.4 ปี ปัจจัยเสี่ยงต่อการเกิดโรคที่พบบ่อย ได้แก่ การบาดเจ็บทางตา (ร้อยละ 44) โรคของผิวตา (ร้อยละ 14) การใส่เลนส์สัมผัส (ร้อยละ 11) และไม่ทราบสาเหตุ (ร้อยละ 18) ผู้ป่วยส่วนใหญ่ (ร้อยละ 74) ได้รับการรักษาเบื้องต้นมาก่อนจากจักษุแพทย์ แพทย์ทั่วไป และได้ยาจากร้านขายยา มี 190 ตา ได้รับการตรวจหาเชื้อโดยการขูดกระจกไปตรวจ และพบว่ามีร้อยละ 30 ที่เพาะเชื้อขึ้น ในจำนวนนี้เป็นเชื้อแบคทีเรีย ร้อยละ 60 และเชื้อราร้อยละ 40 เชื้อแบคทีเรียที่พบบ่อยที่สุดคือเชื้อ *Pseudomonas* (ร้อยละ 39) ส่วนเชื้อราที่พบบ่อยได้แก่ เชื้อ *Fusarium* (ร้อยละ 14) และ *Aspergillus* (ร้อยละ 7) มี 69 ตาได้รับการรักษาโดยการผ่าตัด และมีผู้ป่วยที่สูญเสียตาจำนวน 16 ตา พบว่ามี 127 ตา (ร้อยละ 60) ที่มีการมองเห็นดีขึ้นหลังการรักษา

สรุป การบาดเจ็บทางตาเป็นปัจจัยเสี่ยงหลักสำหรับการเกิดโรคกระจกตาติดเชื้อในผู้ป่วยในเขตภาคเหนือ โดยพบว่า เชื้อที่เป็นสาเหตุหลักในกลุ่มแบคทีเรีย คือเชื้อ *Pseudomonas* ส่วนเชื้อราได้แก่ เชื้อ ราสายดังนั้นสัด ส่วนของเชื้อแบคทีเรียต่อเชื้อราในการศึกษานี้เท่ากับ 3 : 2 **เชียงใหม่เวชสาร 2547;43(3):93-103.**

คำสำคัญ : กระจกตาอักเสบจากการติดเชื้อ กระจกตาอักเสบจากเชื้อแบคทีเรีย กระจกตาอักเสบจากเชื้อรา