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Current Concepts in the Management of Unique Post-keratoplasty Infections

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Abstract

As corneal transplantation has evolved, the spectrum of post-surgical infection has changed and often presents a diagnostic and therapeutic challenge. Lamellar techniques hold the potential of improved outcomes and decreased post-operative complications, however, they create a lamellar interface, which is a potential space for sequestration of infectious organisms. In addition, while keratoprosthesis offers vision to patients who are poor candidates for traditional keratoplasty, infectious complications can be severe and sight threatening. Although antimicrobials remain the mainstay of treatment, definitive management often requires surgical intervention.

Keywords

Infectious keratitis; corneal ulcer; lamellar keratoplasty; keratoprosthesis

Introduction

Over the past decade, corneal transplantation has evolved rapidly. Newer lamellar techniques to replace only the diseased layer of the cornea hold the promise of improved outcomes and fewer complications. Deep anterior lamellar keratoplasty (DALK) replacing only scarred or ectatic stroma while preserving healthy endothelium, may lead to lower rejection rates and improved wound integrity[1]. Descemet's stripping endothelial keratoplasty (DSEK), and Descemet's membrane endothelial keratoplasty (DMEK) which replace only diseased endothelium, have led to faster recovery times, improved visual outcomes, and reduced post operative complications compared with traditional penetrating keratoplasty (PK).[2] The Boston Keratoprosthesis (KPro), an artificial cornea composed of

a hybrid of donor cornea surrounding a non-biointegratable optic, has provided vision for patients previously unable to receive corneal transplantation.[3]

With the introduction of new keratoplasty techniques there has been a change in the spectrum of post-surgical infectious keratitis. Lamellar techniques create an interface, which is a potential site for sequestration of infectious organisms. The KPro, which is never fully epithelialized, is at risk of both infectious keratitis at the border of the optic zone as well as endophthalmitis. This article will review diagnosis and management of infections after newer keratoplasty techniques including lamellar grafts and the KPro.

Anterior Lamellar Keratoplasty

Presentation and Diagnosis

There have been a number of reports on infectious keratitis after DALK and anterior lamellar keratoplasty (ALK) (Table 1). The organisms reported are predominately fungal, with only 4 reported cases of bacterial keratitis, including one case of mycobacterial keratitis. The majority of cases were reported within the first 30 days after the procedure, but some were described up to four months after surgery. Cases that presented early (within days) after surgery, including one *Aspergillus flavus* [4] and one *Klebsiella pneumoniae* interface keratitis[5], had a rapidly progressive course that worsened over hours to days and required emergent surgical intervention. The cases that presented later (weeks to months after surgery) were more likely to be *Candida* infections and have a more indolent course. Later-presenting cases tended to have a delay in diagnosis. In some of these cases, the infection was initially misdiagnosed as an episode of rejection[6] or epithelial down growth[7, 8]. Figure 1 shows a DALK with *Lecythophora* interface infection. DALK interface infection has been characterized by scattered interface deposits that are white or cream-colored with little overlying inflammation [6-10]. Although there are fewer reports of ulcerative keratitis after ALK in the literature, this is likely due to publication bias with the more interesting interface infections getting reported more often.

Treatment

Despite aggressive treatment with topical antibiotics, most reported cases required surgical intervention to eradicate infection. Nine out of twelve reported cases ultimately required PK. Of the three that did not, one improved after anterior lamellar graft exchange[4], one improved after irrigation of the graft-host interface[6], and in one case of anterior lamellar keratoplasty, the graft was simply removed and discarded[11]. While topical therapy can deliver a high concentration of antimicrobial to the site of infection, limitations include ocular penetration and achievement of steady-state drug concentration at the site of infection. This is likely to be particularly true when the infection is in the deep cornea, such as is the case with infections of the lamellar interface. Targeted anti-microbial therapy and consideration of early surgical intervention are required to treat cases of infectious lamellar keratitis after DALK.

Endothelial Keratoplasty

Presentation and Diagnosis

There are multiple case reports of interface infection, ulcerative keratitis and endophthalmitis after endothelial keratoplasty (EK). The peak time for infectious keratitis after EK appears to be 1-3 months after surgery, but reports range from 3 days[12] to 16 months[13] post-operatively. Table 2 outlines reported cases of infectious keratitis after EK. There are relatively equal numbers of bacterial and fungal keratitis, as well as one report of a mycobacterial infection[14]. Corneal venting incisions may be a risk factor for infectious keratitis after EK[15]. When looking at only interface keratitis, fungal infection is much more common. Reported fungal interface keratitis cases after EK were all caused by *Candida* species[16-20]. Much like after DALK, white or cream-colored interface infiltrates, either solitary[20] or multiple[16, 18] are described. Because of the difficulty of obtaining a culture from the interface, the interface infections were diagnosed either after anterior chamber tap or explant of the donor lenticule.

Treatment

Six out of eleven cases of lamellar keratitis ended up ultimately requiring PK for eradication of the infection[12, 15, 17, 18, 21]. One case had an anterior chamber (AC) washout and graft exchange that was successful in clearing the infection,[20] one sustained a corneal perforation and underwent patch grafting[20], and one required AC washout with explant of the graft[16]. Two cases of presumed fungal interface keratitis were successfully treated with intrastromal injections of antifungals into the EK interface; both of these cases retained their original grafts.[22] Another case of *C. glabrata* endophthalmitis required explantation of the donor lenticule. [23] Although therapeutic keratoplasty is generally reserved for cases resistant to antibiotics, these reports suggest that early surgical intervention may be advisable for suspected infectious interface keratitis. Interestingly, surgical intervention short of PK, which has the potential to keep infectious organisms sequestered in the interface, may theoretically increase risk of spread of the infection.

Endophthalmitis after Endothelial Keratoplasty

Infectious endophthalmitis after keratoplasty is rare and has been reported to occur in 0.1% to 0.7% of PK cases[24]. In recent years, the number of cases has declined, in part due to the addition of broad-spectrum antibiotics, gentamicin and streptomycin, to corneal donor storage media[25, 26]. With the reduction of bacterial endophthalmitis, the importance of post-keratoplasty fungal endopthalmitis has grown. Preservation-to-surgery time greater than 4 days appeared to increase the odds of fungal compared with bacterial endophthalmitis by 3.4 in one study[26]. However, the benefit of adding antifungals to storage media remains undetermined at this time.

There have also been at least four reports in the literature of infectious keratitis after EK progressing to endophthalmitis. One case of *Bacillus cereus* interface keratitis presented on the 3rd post-operative day and rapidly progressed to panophthalmitis, resulting in evisceration[12]. Two cases of interface *Candida* keratitis progressed to endophthalmitis after initial misdiagnosis as epithelial down growth in one[19] and non-infectious keratitis in

the other (Table 2)[15]. One case of *Candida* endophthalmitis after transmission from the donor was diagnoses after the patient developed progressive pain and inflammation with vitreous involvement approximately four weeks after undergoing EK.[23]

The Role of Donor Cultures

There are a number of reports of cases of infectious keratitis after lamellar procedures that were from presumed graft-to-host transmission. Among these, there was one case of bacterial keratitis (*Klebsiella pneumonia*) after a DALK[5], one case of fungal keratitis (*Candida albicans*) after a DALK[9], and six cases of fungal keratitis after EK (five *C. albicans* and one *C. glabrata*) [16-18, 20, 21]. There is also a case of transmission of *C. glabrata* endophthalmitis after EK[23]. Given that there are only 33 reports of infectious keratitis/endophthalmitis after EK and DALK combined in the literature, a surprisingly large number (8/33) of them had positive donor cultures. It has been reported that a positive fungal donor rim culture represents a 247-fold increase in the odds of contracting fungal endophthalmitis in patients undergoing PK[27]. The Eye Bank Association of America, in its pooled data over the period of 2007-2010, reported an overall incidence of 0.022% of donor-related infectious keratitis and endophthalmitis in patients undergoing lamellar keratoplasty, which was not statistically different than patients undergoing penetrating keratoplasty[28]. Garg et al, in reporting their single-institution experience, noted one case of infectious lamellar keratitis in 12 positive donor culture results from 127 cases of EK total[18]. Overall, it would seem that a positive fungal culture result from a donor culture after EK should be taken seriously, and the patient monitored for signs of infection. Knowledge of the donor culture results may provide a guide to therapy, especially in the case of interface keratitis where cultures are not readily obtainable.

New Techniques in Diagnosis of Infectious Lamellar Keratitis

Interface keratitis presents a diagnostic challenge given the difficulty in obtaining a specimen for culture. A number of authors have reported using confocal microscopy to help differentiate between infectious and non-infectious causes of interface keratitis after lamellar grafting. It is difficult to detect bacteria with confocal microscopy[29]. However *Nocardia*, a large filamentous acid-fast bacterium, has been visualized in one small case series as thin, extensively branching, beaded filaments[30]. There is still debate in the literature regarding the diagnostic accuracy of confocal microscopy in fungal keratitis. In one large series, confocal microscope had a sensitivity of 88.3% and specificity of 91.1% for 93 microbiologically confirmed cases of filamentous fungal keratitis[29].

The characteristic features on confocal of *Candida* keratitis are still being established. Two cases that have been culture positive for *Candida* species after DALK describe hyper-reflective deposits seen with confocal microscopy measuring 3 to 5 μm in diameter in the graft interface with no inflammatory cells[7, 8]. Another case from the same author that was culture positive for *Candida albicans* had high-contrast round structures that were 25-30 μm in diameter in the interface, and appeared to be epithelial cells[8]. This finding of epithelial cell-like deposits was also reported in another paper with culture-positive *Candida* interface

keratitis[19]. In addition to diagnosis, this modality may be used to monitor response to treatment.

Keratoprosthesis

Although multiple types of keratoprosthesis (Kpro) have been described, the predominant one in use currently is the Boston keratoprosthesis. The combination of the severe underlying diseases that necessitate KPro placement and lack of bio-integrated materials makes KPro patients very susceptible to infections. One series of 300 Kpro eyes with a mean follow-up of 17 months, found overall Kpro retention to be 93%, or an average of 1.42 years/implant[31]. In this series, nine were lost to infectious complications and fungal organisms caused 7 of these.

Two recent large studies on infectious keratitis after KPro placement have recently been published[32, 33]. One series by Chan and Holland reported an overall infectious keratitis rate of 7.9% (10/126 eyes), or 0.04 infections per patient-year[32]. All patients in this series were treated prophylactically with topical moxifloxacin and vancomycin (14mg/mL) twice a day after the initial postoperative period, and wore a bandage contact lens that was exchanged every 3 months. Of the seven culture-positive cases, five were fungi (3 *Candida* species, 1 *Fusarium* and 1 *Dactylaria constricta*) and two were unusual gram-negative bacteria (*Rhodococcus equi* and an non-specific gram negative cocci). Persistent epithelial defects and cicatrizing conjunctival processes were significant risk factors for the development of infectious keratitis. In this series topical vancomycin was not a risk factor for the development of resistant organisms. A second series by Kim, et al, reported an overall incidence of suspected infectious keratitis of 13.6% (15/110 eyes), or 0.073 infections per eye-year[33]. Patients in this study were managed with topical moxifloxacin indefinitely and vancomycin (25mg/mL) for four months after surgery. Six eyes were culture positive for gram-positive bacteria (5 cases of coagulase-negative *staphylococci* and one case of *S. aureus*); none of these were on topical vancomycin when the infection developed. Four cases were culture positive for fungi (3 *Candida parapsilosis*, 1 *Acremonium* species). A persistent epithelial defect was a significant risk factor for the development of presumed infectious keratitis, and the use of topical vancomycin was a risk factor for the development of fungal keratitis (p=0.01). Neither bandage contact lens use nor the presence of cicatrizing conjunctival disease were significant risk factors (p=0.5 and 1.0, respectively).

Endophthalmitis is a serious complication of the KPro, and has been reported to occur in as high as 12.7%[34] and as low as <1% of cases[3, 35]. A recent review examined all published cases of endophthalmitis after KPro placement up to September 2011 and found a pooled incidence of 5.4%[36]. The predominant organisms identified in this series were coagulase negative *staphylococcus* and *streptococcus*, comprising 49% of the total infections, followed by *S. aureus*, which caused 13% of the infections. The majority of the gram-positive infections occurred before topical vancomycin prophylaxis was instituted, or after it had been discontinued in individual patients. Ten percent of endophthalmitis cases were caused by fungus. There is some evidence that continuous use of topical vancomycin

alters the microbial flora of the eye and makes it more susceptible to fungal endophthalmitis in KPro patients[37].

Prevention

The majority of the literature supports routine, lifetime use of topical antimicrobial prophylaxis, including vancomycin for the prevention of infectious complications in Kpro patients. However, a recent publication by the Massachusetts Eye & Ear Infirmary group recommended moving away from routine vancomycin use in binocular patients without an underlying autoimmune etiology, and suggested polymyxin-trimethoprim as a broad-spectrum, economical alternative[38]. The authors of this study suggest that the goal of antimicrobial prophylaxis should not be the complete sterilization of the ocular surface, rather to decrease the load of pathogenic bacteria. Some have suggested routine surveillance cultures, or periodic use of anti-fungal drops, particularly in regions with a high prevalence of fungal keratitis. There is some suggestion that the addition of topical 5% povidone-iodine, either as an ocular surface wash at clinic visits or as a daily application may be useful to prevent colonization by harmful pathogens.[38, 39]

The continuous use of topical antibiotics has raised the question of causing resistance in KPro eyes. Robert et al., looked at routine conjunctival surveillance cultures taken from KPro, post-PK, and control eyes and compared the culture positivity rate and the rate of resistance. In this series, patients with KPros were maintained on only moxifloxacin once daily for prophylaxis.[40] They found 44% of KPro patients had growth of bacteria resistant to 4th generation fluoroquinolones as compared to 20% of eyes that had undergone PK and 8% of controls.

Treatment

None of the measures described completely prevent infectious keratitis or endophthalmitis, and a significant proportion of patients develop these complications despite prophylaxis. A high index of suspicion and clinical vigilance must be maintained in eyes that have undergone KPro. Once infection has occurred, it can be difficult to treat medically for numerous reasons. These include the development of a biofilm on the prosthetic, as well as lack of penetration of topical medications under the optic flange.[41, 42] In the literature a high proportion of reported KPro infections required removal of all hardware for adequate control of the infection[32, 33]. Figure 2 shows *Candida* keratitis in a Boston Keratoprosthesis patient. Removal of the device resulted in complete resolution of the infection.

There is little evidence to guide the management of endophthalmitis in Kpro patients. It is unlikely that the recommendations of the Endophthalmitis Vitrectomy Study[43] apply. Some advocate inclusion of anti-fungal medications along with antibiotics for tap and inject given the higher proportion of fungal organisms compared with post-cataract endophthalmitis patients[44]. Others advocate consideration of earlier pars plana vitrectomy due to the poor visual prognosis[41].

Summary

Infectious keratitis remains a concern with newer corneal grafting techniques. The advent of lamellar keratoplasty has resulted in cases of interface keratitis that present a diagnostic and therapeutic challenge. Although antimicrobials remain the mainstay of treatment, definitive management often requires surgical intervention. Infectious complications following keratoprosthesis are common and may be vision-threatening. Prevention with measures such as bandage contact lens, antibiotic prophylaxis and surveillance cultures may reduce infection rates.

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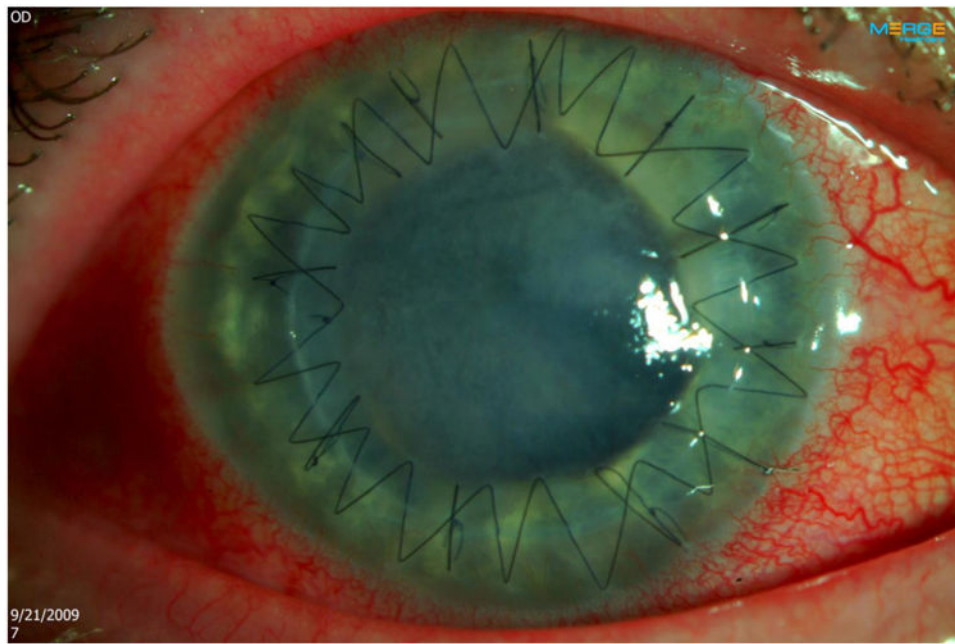
Figure 1.
Deep anterior lamellar keratoplasty with the ascomycete fungus *Lecythophora* interface
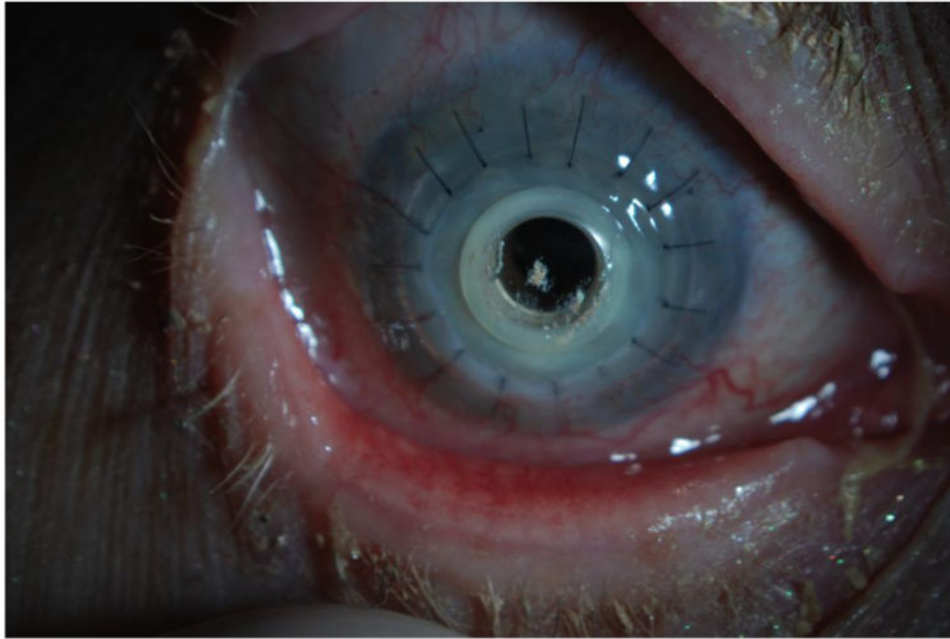infection. Photo courtesy of Bennie H. Jeng, MD.

Figure 2.
Boston keratoprosthesis complicated by *Candida* keratitis, requiring removal of the device.
Photo courtesy of Bennie H. Jeng, MD.

Table 1

Infectious keratitis cases reported in the literature after anterior and deep anterior lamellar keratoplasty.

Procedure	Diagnosis	Time to Presentation	Treatment	Organism
DALK[4]	Lamellar keratitis	4 days	Topical natamycin, oral fluconazole Graft exchange	*Aspergillus flavus*
DALK[5]	Lamellar keratitis	2 days	Topical vancomycin, ceftazadime, PK	*Klebsiella pneumoniae*
DALK[6]	Lamellar keratitis	4 months	Corticosteroids, topical vancomycin, ceftazidime, topical natamycin, interface irrigation	*Candida albicans*
DALK[7]	Lamellar keratitis	4 weeks	PK, topical amphotericin, oral itraconazole	*Candida Albicans*
DALK[8]	Lamellar keratitis	2 months	Irrigation of the interface, PK	*Candida glabrata*
DALK[8]	Lamellar keratitis	2.5 months	PK	*Candida albicans*
DALK[9]	Lamellar keratitis	4 weeks	Topical/IV amphotericin B, graft exchange, PK	*Candida albicans*
ALK[10]	Lamellar keratitis	7 days	Medical treatment, PK	*Actinomyces*
ALK[11]	Lamellar keratitis	4 months	Removal of ALK graft, Cefuroxime and gentamycin drops	*Gram + cocci*
DALK[45]	Lamellar keratitis	5 days	Irrigation of interface, anti-mycotics PK	*Candida orthopsilosis*
DALK[46]	Lamellar keratitis	3 months	Antimicrobials, Repeat DALK, PK	*Mycobacterium cheloniae*
DALK[47]	Lamellar keratitis	7 days	Topical Voriconazole, anterior chamber voriconazole, PK	*Lecythophora mutablis*

Table 2

Infectious keratitis cases reported in the literature after endothelial keratoplasty.

Procedure	Diagnosis	Time to Presentation	Treatment	Organism
DSAEK[12]	Lamellar keratitis progressing to panophthalmitis	72 hours	Topical cefazolin, amikacin, limbus-to-limbus PK, IOL explantation, evisceration within 48 hours of diagnosis	*Bacillius cerus*
DSAEK with vent incision[13]	Ulcerative keratitis at vent incision	16 months	Topical antibiotics, therapeutic PK	*Pseudomonas aeroginousa*
DSAEK with vent incision[13]	Ulcerative keratitis	3 months	Topical antibiotics, therapeutic PK	*Streptococcus pneumoniae*
DSAEK with vent incision[13]	Ulcerative keratitis at vent incision	7 weeks	Topical antibiotics, oral moxifloxacin, therapeutic PK	*Enterococcus faecalis*
DSAEK[15]	Lamellar keratitis progression to endophthalmitis	First seen 2 days, treated at 3 months	Topical antibiotics, AC washout, oral voriconazole, PPV, IOL explant, therapeutic PK	*Candida parapsilosis*
DSAEK[16]	Lamellar keratitis	34 days	Topical/IV voriconazole, 0.1% micafungin, explant of lenticule, with AC washout	*Candida albicans*
DSAEK[17]	Lamellar keratitis	1 month	Medical therapy, PK	*Candida albicans*
DSAEK[17]	Lamellar keratitis	1 month	Medical therapy, PK	*Candida glabrata*
DSAEK[18]	Lamellar keratitis	1 month	Topical voriconazole, intracameral voriconazole, PK	*Candida albicans*
DSAEK[19]	Chronic endophthalmitis	3 months	Topical and systemic antibiotics, explant of DSAEK with PPV, topical and systemic voriconazole	*Candida albicans*
DSAEK[20]	Lamellar keratitis	39 days	Topical amphotericin B, oral fluconazole, graft exchange with AC washout with amphotericin B	*Candida albicans*
DSAEK[20]	Lamellar keratitis	41 days	Topical and intracameral amphotericin B, oral fluoconazole, corneal perforation with gluing, patch graft	*Candida albicans*
DSAEK[21]	Lamellar Keratitis	7 days	Topical moxifloxacin, explant of the donor lenticule, topical and oral anti-fungals, therapeutic PK	*Candida albicans*
DSAEK[22]	Lamellar Keratitis	3 months	Oral voriconazole, intrastromal voriconazole	No culture, presumed fungal infection
DSAEK[22]	Lamellar Keratitis	3 months	Intrastromal amphotericin B, oral fluconazole	No culture, presumed fungal infection
DSAEK[23]	endophthalmitis	4 weeks	Explant of donor lenticule, intravitreal, intracameral and topical amphotericin B	*Candida glabrata*
DSAEK[48]	Ulcerative keratitis	5 weeks	Topical cefazolin/tobramcyin	*Staphylococcus aureus*
DSAEK[48]	Ulcerative keratitis	4 months	Topical cefazolin, topical tobramycin, biopsy of the posterior lamella, topical	*Aspergillus fumigatus*

Procedure	Diagnosis	Time to Presentation	Treatment	Organism
			natamycin, oral voriconazole, PK	
DSAEK[49]	Ulcerative keratitis	4 months	Topical antibiotics	*Methicillin-resistant Staphylococcus aureus*
DSAEK[50]	Ulcerative Keratitis	6 weeks	Topical antibiotics	*Pseudomonas aeruginosa*
DSAEK[50]	Ulcerative Keratitis	7 weeks	Topical antibiotics	*Pseudomonas aeruginosa*