Outbreak of Gram-positive bacterial keratitis associated with epidemic keratoconjunctivitis in neonates and infants

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CLINICAL STUDY

Abstract

Objectives To report the clinical characteristics of bacterial keratitis associated with epidemic keratoconjunctivitis (EKC) and to evaluate the risk factors for bacterial keratitis development in eyes with EKC.

Methods After 108 patients diagnosed as EKC were retrospectively reviewed, clinical characteristics and incidence of bacterial keratitis-associated EKC were described. To analyse the effect of steroid use and the methicillin-resistant *Staphylococcus aureus* (MRSA) colonization in conjunctiva on developing bacterial keratitis, HCU-stayed children ($n = 43$) were divided into two groups: those with and those without bacterial keratitis. Other risk factors such as gestational age, duration of hospitalization, MRSA colonization rate of other sites, and interval between follow-ups were evaluated in neonates who stayed in a neonatal intensive care unit (NICU; $n = 29$).

Results Eight out of nine bacterial keratitis developed in HCU-stayed children. All the eight cases of bacterial keratitis occurred in neonates and infants. MRSA keratitis was found in seven hospitalized infants. The incidence of bacterial keratitis was significantly higher in HCU-stayed children than in outpatients ($P = 0.03$), although it never occurred in HCU-stayed adults. The culture-positive rate of MRSA in conjunctiva ($P = 0.047$) and topical use of steroid ($P = 0.01$) were significantly higher in HCU-stayed children who carried bacterial keratitis. The incidence of bacterial keratitis was significantly related with the longer interval of

follow-up in early EKC period in NICU in patients ($P = 0.009$).

Conclusions Infants and neonates show high tendency of MRSA keratitis accompanied with EKC, especially if they were in HCU, applied topical steroid or followed with long interval. *Eye* (2009) 23, 1059–1065; doi:10.1038/eye.2008.234; published online 1 August 2008

Keywords: conjunctival colonization; epidemic keratoconjunctivitis; health care unit; MRSA; neonate; steroid

Introduction

Epidemic keratoconjunctivitis (EKC), which is caused by adenovirus, presents as acute conjunctivitis and occasionally keratitis.^{1,2} Corneal superinfection with bacteria or acanthamoeba may occur; however, only one case each has been previously reported.^{3,4} There have been several cases of health care unit (HCU)-associated outbreaks of EKC, mostly in patients with critical condition, in paediatric sections, or in nursing homes.^{5–7}

Over a 2-month period from July 2007 to August 2007, there was an outbreak of EKC among inpatients referred for ophthalmology consultation and among patients from the outpatient clinics at Seoul National University Hospital. Interestingly, nine cases of clinical EKC were accompanied with Gram-positive bacterial keratitis and all of these cases were developed among young children, infants, and neonates. Eight out of nine patients who showed bacterial keratitis had had an experience of transient stay in an HCU or had been hospitalized. Although there were many

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yearly outbreaks of EKC, we had never experienced an outbreak of bacterial keratitis accompanied with EKC before. To the best of our knowledge, this is the first report to describe an outbreak of bacterial keratitis associated with EKC.

The objective of this study is to report the clinical manifestation of neonatal and infantile bacterial keratitis associated with EKC, to evaluate the risk factors for the development of Gram-positive bacterial keratitis accompanied with EKC, and finally to make paediatricians and ophthalmologists be aware that coinfection of methicillin resistant *Staphylococcus aureus* (MRSA)-associated keratitis is possible in neonates and infants with EKC who have a history of HCU stay.

Methods

Study design and population

Medical records of inpatients referred for ophthalmology consultation and patients from the outpatient clinics at Seoul National University Hospital, who were diagnosed as EKC from July 2007 to August 2007, were retrospectively reviewed. After identifying an outbreak of bacterial keratitis associated with EKC in neonate and infants, the clinical and epidemiological characteristics, and the causative organism of bacterial keratitis and risk factors were evaluated.

Epidemiology of EKC-associated bacterial keratitis was evaluated in adults and children during this outbreak. We conducted a retrospective case-control study with control subjects composed of children with a history of HCU stay who showed only EKC, and compared predisposing factors with the group who had bacterial keratitis associated with EKC. To analyse the incidence of steroid use and colonization of MRSA in conjunctiva as risk factors, children with a history of HCU stay ($n=43$) were divided into two groups; group 1 presenting bacterial keratitis ($n=8$)-associated EKC and group 2 presenting EKC only ($n=35$). Other risk factors such as gestational age, body weight, colonization of MRSA in other body sites, duration of hospitalization, and interval between the follow-ups were evaluated in neonates who stayed in a neonatal intensive care unit (NICU; $n=29$). The neonates were also divided into two groups: group 3 presenting bacterial keratitis ($n=6$)-associated EKC and group 4 presenting EKC only ($n=23$).

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Identification of organisms and clinical manifestations

The patients who had clinical signs including follicular hypertrophy, conjunctival exudative membrane accompanying epithelial defect, mucoid discharge or eye redness in one or both eyes, and no other identifiable cause of conjunctivitis were diagnosed as EKC in this period. When possible, conjunctival swabs were taken to be evaluated with direct immunofluorescence assay (IFA) and viral culture for human adenovirus.

Any solitary lesion of corneal epithelial defect with surrounding dense infiltration was suspected of bacterial keratitis. Gram or Giemsa staining and bacterial cultures were performed to confirm bacterial keratitis. The corneal specimens were sampled from the base or edge of the lesion and were cultured on culture media such as thioglycolate broth, blood, chocolate, and Sabouraud dextrose agar.

Clinical manifestations, including neovascularization, were examined using slit-lamp microscopy and the time from the detection of epithelial breakdown to full healing of the epithelium was measured.

Treatment

During the initial period of EKC, erythromycin eye drop was used for the prevention of secondary infection for children and levofloxacin eye drop was used for adults. Topical steroid was additionally applied when a pseudomembrane existed or severe conjunctival inflammation accompanying conjunctival epithelial defect was present.

When acute corneal epithelial defect and suppurative corneal infiltrate developed, topical use of steroid was immediately discontinued and topical 3.1% vancomycin and 2% amikacin eye drops were applied every hour in the suspicion of bacterial keratitis. In cases where the treatment induced the regression of cell infiltrations, or the corneal ulcer was localized and did not progress, instillations of 3.1% vancomycin and 2% amikacin were gradually reduced to prevent drug toxicity that may influence corneal epithelialization and vascularization. When keratitis was unresponsive to these therapies, antimicrobial therapy was changed by adding 5% vancomycin ointment⁸ or 0.5% moxifloxacin eye drops 4–6 times/day or as per culture and sensitivity reports, if available.

In cases of severe corneal stromal melt presenting as impending perforation, amniotic membrane was transplanted permanently in an emergency operation and oral vitamin C and topical terramycin ointment were additionally applied.

Assessment of the risk factor

For risk factor assessment, the history of topical steroid use in early EKC period, culture or IFA result of

adenovirus, and MRSA colonization in conjunctival swab were collected in the children with a history of HCU stay. Data of the following were collected from neonates in NICU; MRSA colonization of other parts of body (nares, tracheas, wounds, and inguinal areas), gestational age, body weight, duration of hospitalization, and interval between follow-up examinations in early EKC period.

Statistical analysis

χ^2 -test, Fisher's exact *t*-test, and Mann-Whitney *U*-test were used to evaluate the independent variables as risk factors. All statistical analyses were conducted using SPSS software (version 13.0; SPSS Inc., Chicago, IL, USA).

Results

Epidemiology of EKC and bacterial keratitis and microbiological features

During the 2-month period, there were 45 cases of EKC in adults and 63 cases of EKC in children. Bacterial keratitis accompanying EKC developed in nine patients (Table 1). Most of the bacterial keratitis occurred in children with a history of HCU stay. HCU-stayed patients showed significantly higher incidence of bacterial keratitis compared with outpatients ($P=0.03$, Fisher's exact *t*-test) and children presented high incidence of bacterial keratitis compared with adults ($P=0.01$, Fishers' exact *t*-test).

Conjunctival swab samples of 30 neonates or infants with EKC revealed positive results for either adenoviral IFA or culture in 11 cases without any significant difference in detection rate between groups 1 (216, 33%) and 2 (9124, 37.5%) ($P=1.00$, Fisher's exact *t*-test).

Table 1 Epidemiology of EKC and bacterial keratitis in adults and children

Patient no.	Adult [‡]		Children [‡]	
	HCU-stayed [†]	Outpatients [†]	HCU-stayed [†]	Outpatients [†]
EKC only	11	34	35	19
EKC + BK	0	0	8	1
Total	45		63	

BK = bacterial keratitis; EKC = epidemic keratoconjunctivitis; HCU = health care unit; HCU-stayed = the patients who had stayed transiently in hospital or nursery or who had been hospitalized when the bacterial keratitis was developed.

Most of bacterial keratitis-associated EKC occurred in HCU-stayed children. HCU-stayed patients showed significant increase of bacterial keratitis compared with outpatients ($P=0.03^{\dagger}$, Fisher's exact *t*-test) and children presented high incidence of bacterial keratitis compared with adult ($P=0.01^{\ddagger}$, Fishers' exact *t*-test).

Eight cases of bacterial keratitis developed in neonates and infants. A 3-year-old child also presented bacterial keratitis. There was no patient with bilateral bacterial keratitis. Surprisingly, there was no case of bacterial keratitis-associated EKC in adults, even though they stayed in HCU.

Of nine cases in which the causative organisms were identified, MRSA was the most frequently found (seven cases), one case was coinfection of *Staphylococcus epidermidis* and *Pseudomonas aeruginosa* and another case involved *Streptococcus pyogenes* (Table 2).

Clinical manifestation of bacterial keratitis

Table 2 shows the clinical course and characteristics of nine patients. In the case of MRSA keratitis, instillation of 3.1% vancomycin and 2% amikacin eye drops by the hour were the first line of therapy. When keratitis was unresponsive to these therapies, topical antimicrobial therapy was changed by adding 5% vancomycin ointment and 0.5% moxifloxacin eye drops 4–6 times per day. In cases 7 and 9, which showed isolation of *P. aeruginosa* and *S. pyogenes*, antibiotics were changed according to the reported sensitivity test.

Two patients showed shallow infiltrations with epithelial defect. Mean healing time was 9 ± 5.6 days (range: 5–13 days), scarring was minimal and corneal clarity increased after the antibiotic therapy (Figure 1a). Six cases presented dense stromal infiltrates underneath epithelial defects (Figure 1b and c). However, ulcerative lesions were shallow in most of the patients. Mean healing time of these patients was 25.6 ± 16.7 days (range: 10–51 days). Four out of six cases showed diffuse stromal new vessels and five out of six cases showed corneal opacity as a late corneal sequela (Figure 1d). A healthy 3-year-old boy needed an amniotic membrane transplantation, because *S. pyogenes*-associated keratitis was unresponsive to medical treatment, resulting in impending perforation of the cornea (Figure 1e). His corneal surface was stabilized; however, it became very thin and opaque (Figure 1f–h). Though bacterial keratitis eventually resolved in all these patients, unfortunately, four out of nine cases required corneal transplantation at 3 months follow-up due to dense central opacity.

Predisposing factors

In children with a history of HCU stay, the culture-positive rate of MRSA in conjunctiva ($P=0.047$, Fisher's exact *t*-test), and the incidence of topical steroid use in early EKC period ($P=0.01$, Fisher's exact *t*-test) were significantly higher in bacterial keratitis patients (group 1) than EKC patients (group 2; Table 3). In NICU patients,

Table 2 Characteristics of the patients who showed bacterial keratitis associated with EKC

Patient no.	Sex	Age at birth (weeks)	Age at infection (weeks)	Microorganism	Health care association	Steroid before BK	Onset of BK after the onset of EKC (days)	Time to full epithelialization (days)
1	M	39	43	MRSA	NICU	-	7	13
2	M	38	54	MRSA	NICU	-	12	5
3	M	29	35	MRSA	NICU	+	7	26
4	M	29	35	MRSA	NICU	+	7	11
5	M	29	34	MRSA	NICU	+	13	30
6	M	36	37	MRSA	Nursery	+	10	10
7	M	39	40	<i>S. epidermidis</i> + <i>P. aeruginosa</i>	Nursery	+	3	51
8	M	27	42	MRSA	NICU	+	12	35
9	M	Term	3 years	<i>S. pyogenes</i>	—	NA	5	16

BK = bacterial keratitis; EKC = epidemic keratoconjunctivitis; M = male; MRSA = methicillin-resistant *Staphylococcus aureus*; NICU = neonatal intensive care unit; *P. aeruginosa* = *Pseudomonas aeruginosa*; *S. epidermidis* = *Staphylococcus epidermidis*.
Health care association: hospital or other health care units where the patient stayed before EKC.
Time to full epithelialization: days from the detection of epithelial breakdown to full healing of the epithelium.

the mean interval of follow-up examinations in the early EKC period was significantly longer in bacterial keratitis patients (group 3) than EKC patients (group 4) ($P = 0.009$, Mann-Whitney test; Table 3). Other factors did not show any significance between those groups.

Another interesting finding is that the incidence of topical steroid use in early EKC period was not significantly different between patients with and without a history of HCU stay (16/54 vs 25/54, $P = 0.07$, χ^2 -test).

Discussion

In this study, we found that EKC could accompany bacterial keratitis in neonates or infants who had experience of staying in HCU.

EKC compromises the ocular surface and provides access of bacterial pathogen through the broken epithelial barrier. However, in adults, bacterial keratitis is very rare even in compromised cornea by EKC. Neonatal immune responses are functionally immature having small number of immune cells and neonatal antibody responses are also delayed in onset, and reach lower peak levels with shorter duration.⁹ This may explain why infants are easily infected with bacteria when they have EKC compared with adults.

MRSA has been one of the most common causes of nosocomial infections since the late 1970s.^{10–12} Colonization of MRSA has been found in 1.5% of the general population, but it increased to 9.4% when the patients were exposed to a healthcare facility.^{13,14} Consequently, about 85% of MRSA infections are health care associated.¹⁵ Because 88% of our patients who showed bacterial keratitis were involved with HCU stay, it was expected that MRSA could be a common pathogen in our patients. In fact, there is a report that 10.4% of neonates in an NICU of Korea became usually colonized with MRSA and they could acquire MRSA colonization in a day (mean: 17days, range: 1–471 days).¹⁶ However, in our study, the mean colonization rate of the conjunctiva and other parts of body were 53 and 48.5% at that time, respectively. This higher colonization rate might be a possible contributing factor for MRSA-associated bacterial keratitis development. Besides, MRSA colonization can persist for prolonged periods. A significant percentage fails to decolonize before hospital discharge after 30 months.¹⁶ Our present study demonstrated that healthy neonates who had been discharged from the nursery 2 days after birth also developed MRSA keratitis after discharge. Considering the fact that the colonization can be established even with 1 day of HCU stay, it is quite possible that healthy neonates with EKC are at a higher risk for the

Figure 1 Photos showing clinical characteristics of bacterial keratitis associated with EKC, examined by slit-lamp microscopy. Mild MRSA keratitis (a) show multiple scattered epithelial infiltration (arrow) and overlying epithelial defect (from patient 2). Severe MRSA keratitis presents severe stromal infiltrations with overlying epithelial defect at the centre of cornea (b and c; from patient 3 and 6). After epithelial defect healed, diffuse stromal new vessel and corneal opacity were remained (from patient 8, d). Healthy 3-year-old child (patient 9) showed rapid corneal melting and impending perforation of cornea (e). The photo (f) presents the surface immediately after the permanent amniotic membrane transplantation (AMT) in patient 9, and the surface was stabilized (g and h) 10 days after AMT.

Table 3 Predisposing factors of bacterial keratitis in HCU-stayed in patients or in NICU

Predisposing risk factors	BK + (group 1, n = 8)	No BK (group 2, n = 35)	P-value
Number of patients with steroid use	6	9	0.01 ^a
Number of patients with positive conjunctival MRSA	7	11 ^b	0.047 ^a
	BK + (group 3, n = 6)	No BK (group 4, n = 23)	P-value
Number of patients with MRSA colonization at other sites	3	11	0.64 ^a
Mean gestational age (weeks)	32.85	31.33	0.418 ^c
Mean body weight (mg)	3108	2241	0.216 ^c
Mean duration of hospitalization (days)	46.37	41.14	0.732 ^c
Mean interval of follow-up (days)	5.8	2.9	0.009 ^c

BK = bacterial keratitis; EKC = epidemic keratoconjunctivitis; MRSA = methicillin-resistant *Staphylococcus aureus*.

The conjunctival colonization rate of MRSA, the incidence of using topical steroid in early EKC period, and the mean interval of follow-ups were significantly different between two groups.

Group 1: patients presenting bacterial keratitis associated with EKC in HCU stayed children.

Group 2: patients presenting EKC only in HCU stayed children.

Group 3: patients presenting bacterial keratitis associated with EKC in NICU-hospitalized neonates.

Group 4: patients presenting EKC only in NICU-hospitalized neonates.

^aFisher's exact *t*-test.

^bThe data of conjunctival MRSA were available in 25 patients.

^cMann-Whitney *U*-test.

development of MRSA keratitis even after discharge from nursery.

It is well known that corticosteroid can suppress the immune system and can increase the chance of infection

in eyes with corneal surface disease.^{17–24} Although there are controversies, most clinicians agree that the use of topical corticosteroids is justified for acute EKC in cases of incapacitating visual loss, pseudomembranous

conjunctivitis, and iridocyclitis.^{1,25} In our study, no adult who used steroid developed secondary bacterial keratitis including some patients who had systemic immune deficiency due to chemotherapy for cancers (data not shown). Therefore, it is likely that the treatment of EKC in infants should be different from those in adults. However, the role of steroid as a risk factor could raise some arguments. The cases treated with topical steroids might have more severe EKC and therefore might have developed bacterial keratitis due to severe inflammation and not the effects of steroids. Nonetheless, based on our findings, the use of topical steroid should be considered very carefully in infants even if they show severe conjunctival inflammation.

On the other hand, we found that a long interval of follow-up examinations may also be a risk factor. Because we all know that EKC is very contagious and would be propagated easily to other patients in the clinic, initially, we followed patients who carried EKC in a 4- or 5-day interval to prevent further outbreaks. After we learned about the outbreak of bacterial keratitis accompanying EKC, we followed all inpatients with EKC everyday and aggressively treated them with topical vancomycin when early corneal infiltrations were found with culture-positive result of MRSA. With these methods, we were able to finally control the outbreak of bacterial keratitis.

We believe that our study revealed a very clinically relevant message that both pediatricians and ophthalmologists should pay attention to the possibility of MRSA keratitis development when neonates or infants with a history of HCU stay are presenting EKC. Thus, immediate conjunctival swab is necessary to identify conjunctival colonization of MRSA in EKC-involved infants who have a history of recent staying in HCU even if the period is very short. When such patients are referred to the ophthalmology consultation service, ophthalmologists should know the risk of MRSA coinfection, and special attention should be given to close follow up examination and to the use of steroid.

In our study, there is a limitation that EKC was diagnosed in most patients based on clinical findings and clinical situations, though 37% of cases showed direct IFA or viral culture-positive results. Nevertheless, we believe that it is worthy of clinical relevance to demonstrate that EKC compromises cornea, resulting in bacterial keratitis in infants.

In conclusion, HCU-stayed infants show high tendency of MRSA-associated keratitis accompanied with EKC. Our study suggests that the use of topical steroids should be reserved in infants carrying EKC who have experience of HCU stay and that close follow-up examination is needed.

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