
Microbial Keratitis in the Developing World: Does Prevention Work?

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Ulcerative microbial keratitis remains a leading cause of blindness worldwide, even in the era of advanced treatment options.¹ The incidence is relatively high in developing countries whereas it is quite low in more developed countries. With the worldwide decrease in trachoma and other traditional causes of blindness such as onchocerciasis and leprosy, the World Health Organization (WHO) now recognizes that corneal blindness caused from microbial keratitis is emerging as an important cause of visual disability,¹ and that there is a “silent epidemic” of blindness that is occurring unnoticed worldwide.² In a study recently commissioned by the WHO South-east Asia Regional Office in New Delhi (WHO/SEARO), it was estimated that 6 million corneal ulcers occur annually in the 10 countries of South-east Asia Region encompassing a total population of 1.6 billion.³ These estimates are based on the data from 4 countries where the incidence of corneal ulceration ranged from a low of 113 per 100,000 in India⁴ to as high as 799 per 100,000 in Nepal.⁵ In contrast, in the United States, corneal ulceration was estimated at 2 to 11 per 100,000 over a 38-year study period in Olmsted County, Minnesota,⁶ and peaking in the last decade.

Risk factors for corneal ulceration vary markedly throughout the world. In the United States, the main risk is felt to be contact lens (CL) wear and changes in incidence reflect changes in CL use patterns.⁶ In contrast, in South-east Asia corneal abrasion was found to be the most important risk^{7,8} (Tables 1, 2). These corneal abrasions can be quite trivial and occur often in the course of agricultural work. In Nepal,⁷ patients with corneal ulcers usually presented for treatment only after the infection was well established, sometimes weeks to months later.⁵ This was especially the case with fungal ulcers that can be particularly

Table 1. *Predisposing Factors for Corneal Ulceration in Madurai District, South India January to March 1994*

Predisposing Factors	Patients (%)
Corneal trauma	284 (65.4)
Dacryocystitis	20 (4.6)
Neurotrophic keratitis	9 (2.0)
Climatic droplet keratopathy	9 (2.0)
Leprosy	8 (1.8)
CL wear	0 (0.0)
Miscellaneous conditions	18 (4.2)
No predisposing factors	86 (20.0)
Total	434 (100.0)

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devastating in countries where antifungal medications are unavailable or in short supply.

In South-east Asia, one quarter of all eyes with cornea ulceration undergoing standard medical treatment become blind because of perforation or other complications.³ All other patients had varying degrees of visual impairment secondary to corneal scars. In cases that are therapeutic “successes,” the eye is often functionally blind because of these sequelae. Unfortunately, rehabilitation with corneal transplantation and other surgical procedures is prohibitively costly in both time and money, and facilities providing such sophisticated eye care are frequently unavailable.¹ The conclusion was that the treatment of corneal ulceration in developing countries is currently unsatisfactory,³ and that corneal trauma has emerged as a clear risk factor for corneal

Table 2. *Agents Causing Corneal Trauma Followed by Ulceration in 405 Patients in Nepal 1985 to 1987*

Agent	Bacteria	Fungi	Mixed	No Growth	Total
Paddy	41	7	6	13	67
Dust	24	2	6	9	41
Maize	23	—	—	5	28
Grass	13	—	2	4	19
Wheat	13	—	—	3	16
Wood	8	—	2	3	13
Animal	4	—	1	—	5
Misc.	8	—	—	6	14
Unknown	7	1	2	1	11
Total (%)	141	10	19	44	214 (53%)

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ulceration.^{7,8} A study from South India⁸ indicated that the majority of both bacterial and fungal ulcers (65.4%) occurred after corneal abrasions usually associated with agricultural work (Table 1). CL wear was not a risk factor as it was in industrialized countries. The World Health Organization recommended that a series of studies be performed in the South-east Asia Region to determine whether corneal ulceration could be prevented at the village level where most corneal abrasions were occurring.

In Nepal, 53% of patients who presented with a corneal ulcer gave a history of prior corneal trauma.⁷ The agents responsible for the abrasion are documented in Table 2. Because of these findings and anecdotal reports of ophthalmologists in other countries of South-east Asia, it was decided by WHO/SEARO to initiate a series of studies to determine whether or not bacterial and fungal keratitis could be prevented in countries where there are different prevalences of pathogens causing ulceration, and where there are different health care systems providing health services at the grass roots village level.

The model for this series of studies was the Bhaktapur Eye Study⁵ reported in 2001. In this large prospective study, a population of 39,000 villagers was followed over a 2-year period in south Bhaktapur, an agricultural area in the Kathmandu valley in Nepal. During that time period, there were 442 patients who reported with corneal abrasions and met the inclusion criteria. All were treated with 1% Chloramphenicol ointment 3 times a day for 3 days and 96% of the abrasions healed without sequelae. There were 18 “break through” ulcers, all culture-positive for bacteria and all in patients who came for prophylactic treatment more than 18 hours after injury. The absence of fungal ulcers was a curious finding because a previous prevalence study showed⁵ 79% of all culture-positive ulcers in Nepal were bacterial and 21% were fungal. It was expected that bacterial but not fungal ulcers, would be prevented. It was unexpected that no fungal ulcers occurred in any patients treated with Chloramphenicol prophylaxis. The number of ulcers was too small to prove this finding statistically.

The challenge was to apply the lessons of the Bhaktapur Eye Study to prevention of corneal ulcers in other developing countries where there is a diversity of health care delivery systems and diverse bacterial and fungal pathogens. Previous studies have shown the prevalence of pathogens causing microbial keratitis in 4 countries in South-east Asia (Table 3). In Nepal, as previously mentioned, the percentage of bacterial to fungal (or mixed bacterial and fungal) positive cultures in all corneal ulcers was 79% to 21%, in Bhutan it was 98% to >1%, in South India it was 47% to 52% (1% amoebic), and in Myanmar it was 34% bacterial and 66% fungal (or mixed fungal and bacteria). Fungal keratitis always overshadows bacterial keratitis, so all mixed infections were considered primarily as fungal from the point of view of prevention.

Table 3. *Prevalence of Bacterial and Fungal Organisms in Corneal Ulcers in South-east Asia as a Percentage of Pathogens by Country*

Pathogens	Nepal ⁵	Myanmar ¹	Bhutan ¹	India ⁸
Bacteria	79.0	33.8	98	47.1
Fungi	8.3	30.0	<1	46.8
Amoeba	None	None	None	1.0
Mixed*	12.7	36.2	1	5.1

*Mixed bacterial and fungal organisms.

■ Prevention of Corneal Ulcers in Bhutan

Even though fungal ulcers account for less than 1% of all corneal ulcers in Bhutan (Table 3), this country was selected for the first study in the WHO/SEARO group using the Bhaktapur Eye Study model. This was done in part to determine whether or not volunteer village health workers (VHWs) working at the grass roots level in remote mountain villages could achieve the same impressive results as those reported in Nepal. In Bhutan,⁹ 31 “volunteer” VHWs were trained to follow the inhabitants of 55 villages with a total population of 10,139 prospectively for 1.5 years. All corneal abrasions that met the study criteria were treated with 1% Chloramphenicol ointment 3 times a day for 3 days. There were 115 corneal abrasions in the 18-month period and all healed without sequelae. In 2 districts in the study area, Paro and Punakha, there were no corneal ulcers reported in the 18-month period, but in 3 surrounding districts the corneal ulcer incidence held constant at the reported incidence of 339 per 100,000 annually (Table 4). With modest variation, the incidence of corneal ulceration continued at this level in all the districts that were not part of the study before, during and after a 4-year period. As almost all ulcers in Bhutan are bacterial in origin (Table 3), it was concluded that this grass roots method using volunteer VHWs was extraordinarily effective in preventing corneal ulcers in this rural population.⁹

■ Prevention of Corneal Ulcers in Myanmar (Burma)

The second country in the WHO/SEARO group was Myanmar. Unlike Nepal and Bhutan, the southern part of Myanmar is a warm, humid delta almost at sea level with large densely populated villages each of which has several thousand inhabitants. In Myanmar,¹⁰ the health care system uses “government employed” VHWs to provide basic health care for the population. They work in village health centers that are very basic but are well stocked with medications to treat malaria, intestinal

Table 4. *Reported Incidence of Corneal Ulceration in 4 Countries in the South-east Asia Region¹*

Country	Incidence/100,000	Reference	Comment
Nepal	799	3	Prospective study
India	113	2	Retrospective study
Myanmar	710	Country report	Retrospective study
Bhutan	339	9	Prospective study

disorders, and the other common infectious causes of disease. Fifteen “government” VHWS were trained to follow the inhabitants of 3 villages with a combined population of 16,986 prospectively for 1 year. Because two thirds of all corneal ulcers in the population are culture-positive for fungi (Table 3) and there is a high incidence of ulceration (710 per 100,000; Table 4), all corneal abrasions were treated 3 times a day for 3 days with both 1% Chloramphenicol ointment to cover bacteria and 1% Clotrimazole ointment to prevent fungal infections.

During the 12-month period, there were 126 abrasions. All were treated with both drugs and no corneal ulcers developed. Likewise, there were no adverse sequelae from the treatment. It seemed from this study that in Myanmar both fungal and bacterial keratitis could be effectively prevented by a relatively simple grass roots program at the village level of diagnosis and treatment of corneal abrasions by government employed VHWS, thereby effectively preventing all bacterial and fungal ulcers following corneal abrasion from occurring.⁹ This conclusion was supported by the continued high incidence of corneal ulcers in districts outside the study area. However, as in the previous studies in Nepal and Bhutan, there were no control patients. Because of the devastating visual outcome of most corneal ulcers, it was felt that a true control group (patients who received an ointment base or no ointment at all) would be unethical. This question was the genesis of the third study in Madurai, India.

■ Prevention of Corneal Ulcers in South India

The fourth site, and the coordinating center for the WHO/SEARO study, was Aravind Eye Hospital in Madurai, South India. Aravind supplied the medications, study forms, and logistical, and statistical support for the 3 studies in cooperation with the WHO Collaborating Center at the Proctor Foundation in San Francisco and WHO/SEARO in New Delhi.

In Madurai, more than half of all corneal ulcers are known to be culture-positive for fungi (Table 3). Of all those ulcers, 47% are positive for *Fusarium* spp., arguably the worst of all fungal corneal pathogens.

Medical treatment of severe bacterial and fungal ulcers at Aravind, and in most tertiary referral eye hospital in the world is often disappointing. Topical antibiotics are moderately effective, but topical antifungal medications penetrate the cornea poorly, the choice of medications is limited, and their effectiveness is poor compared with antibiotics in the treatment of bacterial keratitis. Even the best medical treatment often leads to severe corneal scarring and functional blindness that can only be corrected by corneal transplantation. Many severe fungal ulcers also lead to corneal perforation and loss of the eye. Because of these disappointing treatment outcomes, cost, and disappointing efficacy of antifungal medications, whether antifungal prophylaxis was actually necessary to prevent fungal keratitis became an essential question. The Myanmar study seemed to show that fungal ulceration could be prevented by applying antifungal ointment 3 times a day for 3 days to eyes with corneal abrasions. Although this outcome seemed to demonstrate that antifungals are efficacious, the question remained, “are they really necessary to prevent fungal ulcers after corneal abrasion in a high-risk population?” The lack of fungal “breakthrough ulcers” in the Bhaktapur study was an interesting and somewhat surprising outcome, and seemed to indicate that antibiotics alone might also prevent fungal ulceration after corneal trauma. Anecdotal evidence from clinicians at Aravind Eye Hospital suggested that “corneal abrasions treated with Chloramphenicol ointment almost never develop either bacterial or fungal keratitis” also raised this interesting question.

In Madurai,¹¹ 15 VHWS employed by Aravind Eye Hospital were trained to follow a population of 48,039 in 2 panchayaths for 18 months (a panchayath is approximately 25,000 individuals and comprises a number of different villages). Patients with corneal abrasions were randomized into 2 groups. One group received 1% Chloramphenicol ointment and 1% Clotrimazole ointment 3 times a day for 3 days and the other group received 1% Chloramphenicol ointment and a placebo ointment 3 times a day for 3 days. VHWs, physicians, and patients were all masked to the treatment. At an ulcer incidence of 113 per 100,000 in the population, 80 ulcers were expected in the 18-month period, half bacterial and half fungal. Therefore, 20 fungal ulcers were expected in each of the 2 treatment arms without intervention. In an adjacent untreated large village of 4000, the corneal ulcer rate during the same period was 165 per 100,000 annually, and in the study area of 48,039, 8 patients with corneal ulcers (11 per 100,000) were seen in the 18-month period who had not reported to have their abrasions treated.¹¹

At the end of 18 months, there were 374 patients with documented corneal abrasions that had been randomized to 1 of the 2 treatment groups. Two patients dropped out of the study for personal reasons, 2 had mild allergic reactions to the placebo ointment, and 368 of the abrasions (98.5%) healed without complications. Two patients in the

placebo group developed microscopic culture-negative subepithelial infiltrates at the site of the abrasion. They were treated empirically with 5% Natamycin for 1 week because of the risk of developing a fungal ulceration and both healed without sequelae.¹¹

■ Conclusions

Microbial keratitis creates devastating visual disability in millions of individuals every year worldwide but especially in the countries of the South-east Asia Region. The incidence of corneal ulceration in India of 113 per 100,000⁴ is 10 times the incidence of corneal ulceration in the United States as reported in the Olmstead County study,⁶ but the incidence in Nepal is 799 per 100,000⁵ or 70 times in the incidence in the United States. Fungal keratitis presents a special problem because the prevalence of fungal pathogens is so high in developing countries. The treatment outcomes are dismal, because there is paucity of effective antifungal medications commercially available, and they are often prohibitively expensive.

Can we prevent most bacterial corneal ulcers in developing countries? The answer is an unequivocal “yes.” Studies have shown bacterial keratitis can be drastically reduced at the grass roots village level where corneal abrasion is the main risk factor for a corneal infection, and corneal abrasion is the common risk factor in all the countries that have been studied in South-east Asia. It is possible to prevent bacterial corneal ulcers at the village level was first proven conclusively in the Nepal in the Bhaktapur Eye Study,⁵ and then a similar outcome was repeated in Bhutan⁹ where villages were more isolated and the health care delivery system was dependent solely on volunteer VHWs.

The key question that this group of studies has investigated, however, is whether or not we can prevent the development of fungal ulcers after corneal abrasion under the same village conditions. The answer to this question is surprising and somewhat counter intuitive. The noncontrolled study in Myanmar¹⁰ indicated that fungal ulcers that occurred after corneal abrasions could be conclusively prevented by adding an antifungal ointment, 1% Clotrimazole, to the antibacterial regimen, 1% Chloramphenicol. However, without a placebo control, we could not be absolutely certain that fungal ulcers were being prevented by the antifungal medication. This issue is more important than it may appear at first glance because of cost considerations, the complexity of using 2 different medications at the same time, the decrease in compliance as the treatment regimen becomes more complicated, and practical considerations of the lack of availability of antifungal medications in many developing countries. It would be much better all

around if we could use one inexpensive, readily available, well-tolerated medication. And Chloramphenicol certainly meets those requirements. It is the most widely used and one of the least expensive antibiotic eye ointments commercially available in the developing countries. It has a broad antibiotic spectrum, but presumably no antifungal properties. The South India study was designed to answer the question of whether or not an antibiotic ointment alone could prevent fungal ulcers and it was done primarily because of anecdotal observations of local ophthalmologists. They reported rarely seeing either bacterial or fungal ulcers develop after antibiotic prophylaxis for corneal abrasions. This observation was also given credence by the fact that no “break through” fungal ulcers were seen in the Bhaktapur Eye Study, even though 21% of all culture-proven corneal ulcers in Nepal are positive for fungal pathogens (Table 3). The South India study to our surprise proved conclusively that antifungal prophylaxis is not necessary for the prevention of fungal ulcers after corneal abrasion.¹¹ This was unexpected, but there may be a plausible biological explanation for this finding. There is one case report of *Fusarium* keratitis responding to treatment with tobramycin,¹² and a laboratory report of sensitivity of *Fusarium* in vitro to several antibiotics including Chloramphenicol.¹³ In the *Fusarium* keratitis outbreak recently reported from Singapore,¹⁴ it was interesting that 11 of the 68 eyes (16.2%) improved on antibiotics alone (cefazolin and gentamicin) before the cultures were read as positive for *Fusarium* spp. A more mundane explanation may be that the ointment base itself has antifungal properties or that it may simply act as a barrier to the establishment of an infection by fungal pathogens present in the environment. An antibiotic ointment may also enhance rapid epithelialization of an abraded cornea, although this has not been proven conclusively, thus reducing the length of time that the vulnerable corneal stroma is at risk for fungal colonization. A large prospective study is currently being carried out under the auspices of the WHO by Dr Srinivasan and coworkers from Aravind Eye Hospital in a District in Tamil Nadu to answer the question definitively of whether or not antibiotics alone definitely will prevent fungal keratitis in a population where more than half of all ulcers are fungal in origin.

In summary, the answer to the question of whether or not we can prevent both bacterial and fungal keratitis in developing countries is an unequivocal yes. It definitely can be done, and we can do it with the grass roots public health structure that is currently in place even in the poorest countries. It also seems that antifungal medications are not essential for the prevention of fungal ulcers, although further studies are needed to confirm this surprising finding. If this observation proves to be irrefutably correct, as we think it will be, it has very important implications for the initiation of cost-effective ulcer prevention programs at the village level in all developing countries where health care

resources are limited and corneal abrasion is the main risk factor for developing a corneal ulcer. In Nepal, a countrywide ulcer prevention program is currently being initiated to address this silent epidemic, and it is our hope that similar programs will be adopted in other countries where the problem of microbial keratitis is a major cause of blindness and visual disability.

■ References

1. Resnikoff S, Pascolini D, Elya'ale D, et al. Global data on visual impairment in the year 2002. *Bull World Health Org.* 2004;82:844–855.
2. Whitcher J, Srinivasan M. Corneal ulceration in the developing world—a silent epidemic. *Br J Ophthalmol.* 1997;81:622–623.
3. Guidelines for the Management of Corneal Ulcer at Primary, Secondary, and Tertiary Care health facilities in the South-East Asia Region. SEA/Ophthal/126. World Health Organization Regional Office for South-East Asia, 2004:1–3.
4. Gonzales CA, Srinivasan M, Whitcher JP, et al. Incidence of corneal ulceration in Madurai District, South India. *Ophthal Epidemiol.* 1996;3:159–166.
5. Upadhyay MP, Karmacharya PC, Koirala S, et al. The Bhaktapur eye study: ocular trauma and antibiotic prophylaxis for the prevention of corneal ulceration in Nepal. *Br J Ophthalmol.* 2001;85:388–392.
6. Erie JC, Nevitt MP, Hodge DO, et al. Incidence of ulcerative keratitis in a defined population from 1950–1988. *Arch Ophthalmol.* 1993;111:1665–1671.
7. Upadhyay MD, Karmacharya PC, Koirala S, et al. Epidemiologic characteristics, predisposing factors, and etiologic diagnosis of corneal ulceration in Nepal. *Am J Ophthalmol.* 1991;11:92–99.
8. Srinivasan M, Gonzales CA, George C, et al. Epidemiology and etiological diagnosis of corneal ulceration in Madurai, South India. *Br J Ophthalmol.* 1997;8:965–971.
9. Getshen K, Srinivasan M, Upadhyay MP, et al. Corneal ulceration in South East Asia. I: a model for the prevention of bacterial ulcers at the village level in rural Bhutan. *Br J Ophthalmol.* 2006;90:276–278.
10. Maung N, Thant CC, Srinivasan M, et al. Corneal ulceration in South East Asia II: a strategy for the prevention of fungal keratitis at the village level in Myanmar. *Br J Ophthalmol.* 2006;90:968–970.
11. Srinivasan M, Upadhyay MP, Priyadarsini B, et al. Corneal ulceration in South East Asia III: prevention of fungal keratitis at the village level in South India using topical antibiotics. *Br J Ophthalmol.* 2006;90:1472–1475.
12. Chodosh J, Miller D, Tu E, et al. Tobramycin-responsive *Fusarium oxysporum* keratitis. *Can J Ophthalmol.* 2000;35:29–30.
13. Mehta A, Chopra S, Mehta P. Antibiotic inhibition of pectolytic and cellulolytic enzyme activity in two *Fusarium* species. *Mycopathologia.* 1993;124:185–188.
14. Khor W, Aung T, Saw S, et al. An outbreak of *Fusarium* keratitis associated with contact lens wear in Singapore. *JAMA.* 2006;295:2867–2873.