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Trends in bacterial and fungal keratitis in south India, 2002–2012

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Abstract

Objective: To assess the trends in microbiological organisms identified from corneal scrapings from patients with infectious keratitis at a tertiary care medical center in South India.

Methods: We reviewed the records of the Microbiology Laboratory at Aravind Eye Hospital in Madurai, India from 2002 until 2012. We identified the microbiologic cause of all corneal ulcers from the culture and smear results, and assessed for trends in bacterial and fungal keratitis over time.

Results: Of 23,897 corneal ulcer patients with a corneal smear from 2002–2012, a fungal organism was identified in 34.3%, a bacterial organism in 24.7%, and no organism in 38.3%. During this period, the annual number of keratitis cases due to bacteria decreased from 677 to 412, and the annual number due to fungus increased from 609 to 863. In analyses accounting for the total number of outpatients seen each year, the decline in number of smears positive for bacteria was statistically significant ($P<0.001$) but the increase in the number positive for fungus was not ($P=0.73$). The relative frequency of individual bacterial or fungal organisms remained relatively stable over this time.

Conclusions: At a tertiary eye care center in South India, there has been a reduction in the numbers of smear-positive bacterial keratitis over the past 11 years. This decline likely reflects economic development in India and increased access to antibiotics.

Keywords

corneal ulcer; bacteria; fungi; trends

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Introduction

Infectious keratitis remains a leading cause of blindness, especially in the developing world where rates of corneal ulceration far exceed those of industrialized countries.[1] The pathogens responsible for infectious keratitis vary regionally, with bacterial organisms more common in temperate climates, and fungal organisms more common in tropical climates. For example, a recent review found fungal pathogens caused 19–67% of corneal ulcers on the Indian subcontinent, compared to <10% of ulcers in North America, western Europe, and Australia.[2] Knowledge of the regional epidemiologic patterns of infectious keratitis is important, since treatments must often be started before the causative microbiological organism has been identified.

India is a tropical country that accounts for a large portion of the global burden of infectious keratitis. Therefore, trends in infectious keratitis observed in India are important not only for regional practitioners, but also for global public health planning. Recent studies have demonstrated a preponderance of fungal corneal ulcers in India, with fungal pathogens identified in approximately 35% to 40% of corneal ulcer scrapings.[3–6] One study from south India found that the percentage of positive cultures due to fungal organisms has been rising significantly in recent years. In this report, we analyzed the microbiological records of a different referral eye hospital in south India, and assessed for trends in the causative pathogens of corneal ulcers.

Methods

This is a retrospective cross-sectional study of corneal scrapings from eyes with infectious keratitis seen at Aravind Eye Hospital in Madurai, India from 2002 to 2012. Aravind Eye Hospital Madurai is the largest eye hospital in the state of Tamil Nadu in South India, and serves both a primary care and referral population. The Microbiology Laboratory at this institution was established in 1988 and has extensive experience processing specimens from corneal scrapings. For this study, we reviewed the Microbiology Laboratory registry for all patients who underwent corneal scraping from January 1, 2002 until December 31, 2012. During this period of time, there was a protocol in place in which all corneal ulcers presenting to Aravind Eye Hospital Madurai were referred to the Cornea Department, where corneal scrapings were performed. Per protocol, all corneal ulcers were scraped for a Gram’s and KOH smear, and additional scrapings were obtained for culture on blood, chocolate, and potato dextrose agar as requested by the cornea specialist. All microbiology procedures were done as per published protocol.[7] A higher proportion of corneal ulcers were cultured in the latter years of the study period because of the initiation of several randomized clinical trials for infectious keratitis during this time.[8 9]

We calculated the annual number of patients with bacterial, fungal, and mixed bacterial/fungal ulcers from the total population of patients who received a corneal scraping in the respective calendar year. Each patient was represented only once in the analysis. Because the proportion of corneal ulcers that were cultured changed throughout the study period, we used the smear results for the primary outcome, and assessed the culture results in secondary analyses. We assessed for temporal trends in the annual number of smears positive for

bacteria or fungus with Poisson regression, using the number of unique outpatients seen annually at Aravind Eye Hospital as the offset, and accounting for potential autocorrelation through a time series bootstrap with a fixed width of two (*tsboot* package in R; 10,000 repetitions). We performed similar analyses to assess for trends in individual organisms, except that we restricted the analysis to the years 2007 to 2012 (during which time cultures were routinely being performed on most patients), and we used the total number of patients with corneal cultures as the offset. We performed analyses with R statistical software, version 2.15.1 for MacIntosh (www.R-project.org). We obtained ethical approval for this study from Aravind Institutional Review Board.

Results

Over the 11 years of the study, a total of 2,701,803 outpatients were seen at Aravind Eye Hospital, increasing from 179,158 in 2002 to 282,719 in 2012 (Figure 1). During this time, 25,097 patients with presumed infectious keratitis underwent corneal scrapings for microbiological testing. Of these, smear results were documented for 23,897 and culture results for 15,725. Smears were routinely performed for the vast majority of ulcer patients each year, ranging from a low of 2217/2395 (92.6%) in 2007 to a high of 2034/2057 (98.9%) in 2002. Overall, 14,738 of 23,897 (61.7%) smears revealed a causative organism, with 8,206 (34.3%) smears positive for fungus, 5,912 (24.7%) for bacteria, 515 (2.2%) for parasites, and 105 (0.4%) for mixed infections. As shown in Figure 1, the annual number of smears positive for bacteria declined over the 11-year study, from 677 to 412 per year ($P<0.0001$). The number of fungal smears increased, from 609 to 863 per year, though this was not statistically significant when the total number of outpatient visits was taken into account ($P=0.73$). The number of negative smears also increased, though this was likewise not statistically significant ($P=0.68$).

As an exploratory analysis, we assessed for trends in the most common organisms causing infectious keratitis over time, using only those 15,725 patients who were cultured. The most common bacterial cause of infectious keratitis was *Streptococcus pneumoniae* ($N=1102$; 7.0% of cultures), followed by *Pseudomonas aeruginosa* ($N=853$; 5.4%), *Nocardia spp.* ($N=244$; 1.6%), and *Staphylcoccus aureus* ($N=187$; 1.2%). The most common fungal causes of infectious keratitis were *Fusarium spp.* ($N=2274$; 14.5% of cultures) and *Aspergillus spp.* ($N=1390$; 8.8%). Note that in contrast to the proportion of patients who had a smear performed, the proportion of patients cultured rose during the 10 years of the study, from 657/2057 (32%) in 2002 to 1984/2579 (76.9%) in 2012. This increase corresponded with the initiation of several randomized clinical trials.[10 11] Because this change in clinical practice could bias the analysis, we focused only on the years 2007 to 2012 for these analyses, a time during which a consistently high proportion of patients were cultured each year (Figure 2). During this time, we were unable to detect any statistically significant temporal trends among *S. pneumoniae* ($P=0.17$) *P. aeruginosa* ($P=0.08$), *Nocardia spp.* ($P=0.53$), *Fusarium spp.* ($P=0.13$), or *Aspergillus spp.* ($P=0.24$)

Discussion

At a large tertiary eye care center in south India, the number of corneal ulcers with a smear positive for a bacterial pathogen has been decreasing. The number of smears positive for fungal pathogen has been increasing, although this change is not statistically significant when the increasing number of outpatients seen at the hospital is taken into account. There do not appear to be any significant temporal trends among the organisms that are the major causes of infectious keratitis.

India is experiencing rapid economic development. As a result, risk factors for infectious keratitis are changing. For example, increasing urbanization places relatively fewer people at risk for agricultural trauma and provides people with better access to health care. Economic development has likely made antibiotics more available, and indeed, increased antibiotic use in India over the past decade has been documented.[12] These changes would be expected to reduce the incidence of infectious keratitis. On the other hand, the rapid rise in incomes has likely also made contact lenses more available to a growing sector of the population, which could increase the risk of infectious keratitis.

The reason for the decline in bacterial keratitis is unclear. It is possible that this trend is simply due to changes in institutional referral patterns. However, Aravind Eye Hospital is the primary eye care provider for a substantial number of patients, suggesting that changes in referral patterns are not the only explanation. Moreover, a decline in bacterial keratitis was also found at our sister institution in Pondicherry, India from 2003 to 2009, which suggests that this finding may have broader generalizability to other areas in India, and not merely be a function of the specific referral patterns of our institution.[6] The most likely explanation for the decline in corneal smears positive for bacteria is an increasing use of antibiotics in India. Antibiotics taken for non-ocular diseases may reduce the burden of bacterial pathogens, making bacterial corneal infections less likely. Alternately, increased access to antibiotic eye drops may result in earlier successful treatment of bacterial keratitis, which could reduce the number of bacterial keratitis patients presenting for culture. Use of topical antibiotics prior to presentation could also result in clearance of the microorganism before corneal scraping, thus reducing the diagnostic yield of microbiological tests. Although our study cannot make firm conclusions, we did not find a significant increase in smears negative for a microorganism, which might suggest that patients who seek topical antibiotic therapy do not subsequently present at Aravind Eye Hospital for examination.

Although bacterial keratitis was more common than fungal keratitis early in the study period, fungal keratitis became more common in 2004, and has been a more common cause ever since. This preponderance of fungal corneal infections is consistent with recent studies from other sites in tropical locations, including several from south Asia and China.[3 6 13–17] Fungal keratitis is difficult to treat and may result in worse outcomes than bacterial keratitis.[18 19] A recent clinical trial conducted in part at this hospital found that natamycin was more effective than voriconazole, likely due to its superior activity among *Fusarium* ulcers. However, even when treatment is successful in clearing the causative pathogen, patients are often left with a dense corneal opacity and severe vision impairment.[10] Visual

rehabilitation for these patients can only be achieved with corneal transplantation—an option not available to most in the developed world.

There are several strengths of this study, including the large sample size and long duration of time. Another strength is the high proportion of keratitis cases for which an organism was identified. In addition, we performed stringent statistical analyses that accounted for correlation of smear results over subsequent years. Such analyses should reduce the chance of type I error in this study. A potential limitation is the reliance on smear results of corneal scrapings, which may be more sensitive for fungus than for bacteria.[20] However, this should not affect the conclusions of the study, because there is no reason to think that the sensitivity of the smears changed over the duration of the study. The major limitation of this study is that it does not directly assess incidence rates of bacterial and fungal keratitis. Although Aravind Eye Hospital provides primary eye care to a considerable proportion of its patients, it is also a referral center, and is therefore subject to referral bias. Moreover, there are other eye hospitals in the district that provide care for corneal ulcers.

In conclusion, the proportion of infectious corneal ulcers due to bacterial pathogens decreased significantly over the past 11 years at a tertiary care medical center in south India. This decline could be due to increasing availability of antibiotics in India, likely as a result of economic development. Further research into the trends of incident corneal ulcers is warranted, especially given the global burden of corneal opacities as a cause of blindness.

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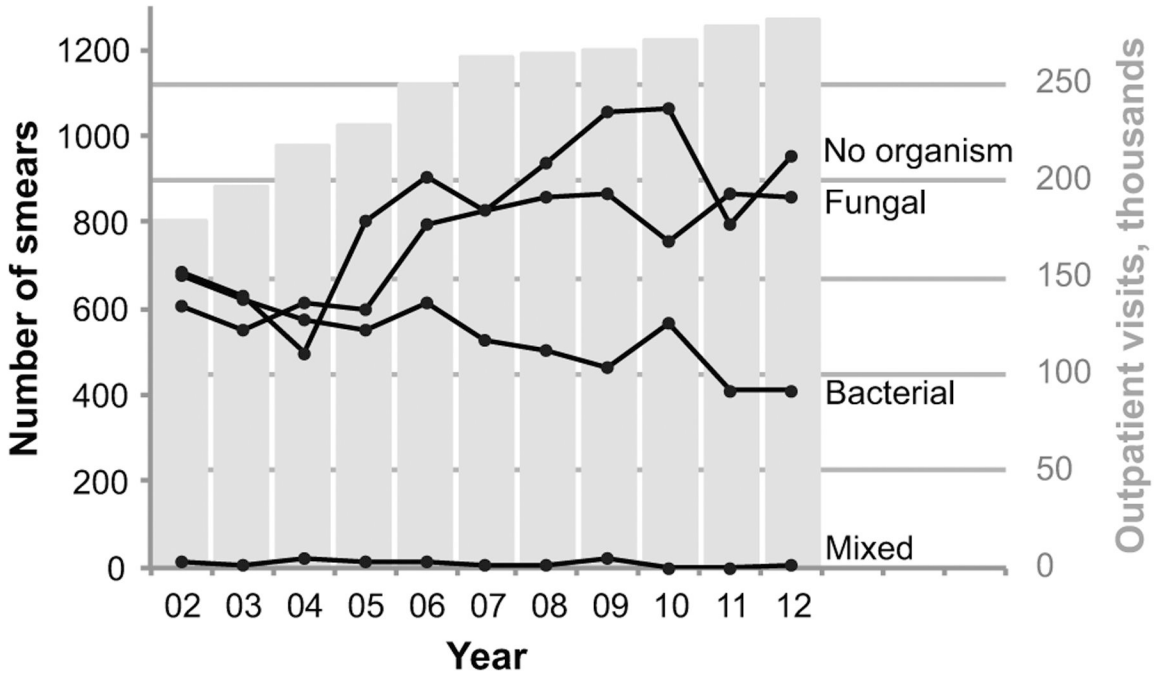

Figure 1. Trends in bacterial and fungal corneal ulcers from 2002 to 2012 at Aravind Eye Hospital, Madurai, India.

Points represent the annual number of smears that were positive for bacteria, fungi, mixed bacterial and fungal organisms, or did not show an organism (left y-axis). The grey bars depict the number of annual outpatient visits at Aravind Eye Hospital (right y-axis).

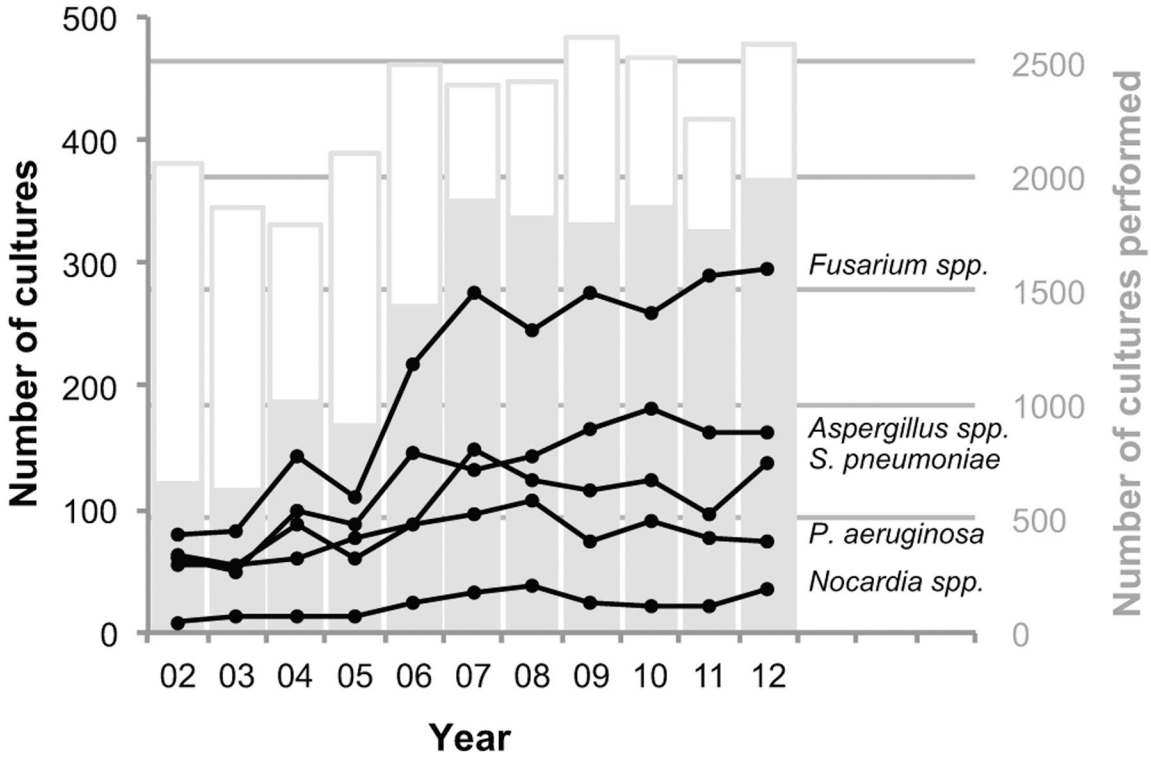

Figure 2. Trends in the major bacterial and fungal organisms isolated from corneal cultures from 2002 to 2012 at Aravind Eye Hospital, Madurai.

Points represent the annual number of cultures positive for each organism (left y-axis). Stacked bars depict the fraction of corneal ulcer patients who were cultured, with the grey portion representing the number who received a culture and the white portion representing the number who did not (right y-axis).