Infectious keratitis (IK) has increased to epidemic proportions in developing countries.[1,2] Fungi and bacteria are the most common organisms causing IK in these low- and middle-income countries.[3] In these regions, IK disproportionately affects the working population, leading to a significant financial burden in terms of lost wages and medical expenses.[4] More importantly, IK is an acute condition and hence the time window for arranging for finances is very less. A patient with IK has to bear the costs of numerous medications prescribed to him, the investigations required for accurate diagnosis, the frequent travel associated with the hospital visits, hospital admissions for close monitoring, and the lost wages associated with the loss of productivity during the disease period. In spite of appropriate and adequate therapy, a significant proportion of these patients fail medical treatment and may require therapeutic keratoplasty or end up with vision-threatening sequelae.[5]

In a study performed by our group in the year 2007, the costs to the patient to receive appropriate care for infectious keratitis were much higher than the average monthly wage of the patients.[6] With the emergence of newer antimicrobials, increased antimicrobial resistance, and a better understanding of the disease, the treatment of infectious keratitis has evolved significantly over the past decade.[7] At our institution, the patients who come to our non-paying section are offered free consultation and free investigations, including microbiologic investigations, and are then given prescriptions. The patients are expected to purchase the same and come for follow-up. Anecdotally, we noticed that the compliance of the patient to the treatment regimen was also not optimal because of the costs involved in the purchase of these medications.

To help support the costs of treatment to these patients, we reached out to Standard Chartered Bank who through the “Seeing is Believing” project; the bank came forward to support the medication costs and travel costs for this subgroup of patients who accessed our non-paying center. Understanding the costs of treatment of different infectious keratitis can help us in planning effective cost rationalization procedures. This study aims at studying the costs of medication and travel of patients with bacterial keratitis and fungal keratitis.

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Methods

This retrospective study included patients with IK who attended a tertiary care hospital in south India between April 2017 and March 2018 and whose costs of treatment and travel were supported by a humanitarian grant from Standard Chartered Bank. These included patients with corneal ulcers that were either smear-positive for bacteria or fungi. The case records were analyzed for the demographic factors, clinical and microbiological data, details of treatment provided, final outcome and the costs of treatment, and the travel expenses. The study adhered to the tenets of Helsinki and was approved by our institute’s review board (RET201700190). Patients who were lost to follow-up, smear-positive for acanthamoeba, mixed keratitis, smear-negative keratitis, and those who required therapeutic keratoplasty in the first visit were excluded from the study.

All patients with corneal ulcers were examined by a corneal specialist and underwent corneal scraping for microbial smear (gram staining and/or potassium hydroxide mount) and corneal culture (blood agar, potato dextrose agar) per the institutional protocol. The costs for the examination and the microbiological investigations were borne by the hospital. Every patient was prescribed appropriate treatment including topical antimicrobials, topical cycloplegics, and oral analgesics, as determined by the treating physician based on clinical diagnosis and microbiological results. Eyes from which smears revealed gram-positive bacteria received topical fourth-generation fluoroquinolones or fortified cephalosporins, while eyes from which smears revealed gram-negative bacteria received topical fortified aminoglycosides or fourth-generation fluoroquinolones. Topical antibiotics were modified based on the subsequent culture sensitivity reports and clinical response. Eyes with smear-positive fungal keratitis were treated with topical natamycin eye drops. Topical azoles, namely voriconazole or econazole or clotrimazole or itraconazole, were added for severe fungal keratitis and keratitis not responding to topical natamycin. The total number of antimicrobial medications prescribed to the patient (substitutions and additions) was documented from the case records. Visual acuity was documented in Snellens chart and was converted to logMAR for analysis. Conversion of low visual acuity such as counting fingers and hand motions were based previously reported protocols.

Standard Chartered Bank, through the “Seeing is Believing” project, supported the costs of medications, travel expenses for each visit, and the surgical costs of these patients. The patients had to present the actual bills of the travel costs so that reimbursements were made. The actual costs of the medication and travel of each patient provided by Standard Chartered Bank were documented for audit and were captured for this study. The endpoint for funding the follow-up visits of patients with corneal ulcers who resolved with medical management was corneal scarring. For the patients who underwent therapeutic keratoplasty without any immediate post-operative re-infection, a minimum of five post-operative visits were funded by the philanthropic grant. For patients with re-infection following TPK, the follow-up visits were funded till the resolution of graft re-infection. The distance travelled by each patient was calculated using Google Maps to calculate the distance from the patient’s native place to the hospital.

Results

In total, 1293 case records of patients with IK, presenting to our non-paying section, were analyzed during the study period, and 672 case records were included in this study after excluding patients with acanthamoeba keratitis (n = 13), mixed keratitis (n = 8), patients who did not undergo microbial investigations (n = 171), smear-negative keratitis (n = 231) who underwent therapeutic keratoplasty at first visit (n = 17), and those who were lost to follow-up (n = 181). The 672 case records included 177 smear-positive bacterial keratitis (BK) and 495 smear-positive fungal keratitis (FK).

The demographic profile and the clinical characteristics are provided in Table 1. Briefly, there was no significant difference in the mean age (54.5 ± 17 years for BK, 52.9 ± 15.7 years for FK, P = 0.77), male percentage (56.5% for BK, 61% for FK, P = 0.29), and the distance (km) traveled by the patient to reach our tertiary care hospital (124.6 ± 175.1 km for BK, 125.8 ± 156.4 km for FK, P = 0.73) between the two groups. FK had a significantly higher history of trauma (45.8% for BK, 59.6% for FK, P = 0.001), history of prior treatment (26.5% for BK, 50.1% for FK, P < 0.0001), and a median (IQR) duration of symptoms (5.3–10 days for BK, 7.4–10 days for FK, P = 0.0026). The mean logMAR uncorrected visual acuity at presentation was significantly worse in BK (1.79 ± 0.96 in BK, 1.52 ± 0.94 in FK, P = 0.0009) and the mean infiltrate size (mm) at presentation was significantly larger in FK (3.7 ± 2.1 mm in BK, 4.3 ± 2.2 mm in FK, P = 0.0016).

In the BK group, 67 (37.9%) patients received one antimicrobial, 98 (55.4%) received two antimicrobials, seven (3.9%) received three antimicrobials, and five (2.8%) received four antimicrobial medications. In the FK group, 124 (25.1%) received one antimicrobial, 336 (67.9%) received two antimicrobial, and 35 (7.1%) received three antimicrobial medications. Grams smear results of BK included 98 (55.36%) Gram-positive cocci, 25 (14.12%) gram-positive bacilli, 3 (1.69%) gram-positive cocci and bacilli, and 51 (28.81%) gram-negative bacilli. Cultures were positive in 127 (71.75%) of BK and 350 (70.7%) of FK. The most common bacteria isolated in culture in the BK group was Streptococcus pneumoniae in 47 (26.6%) patients followed by Pseudomonas aeroginosa in 35 (19.8%) patients. The most common fungi isolated in the FK group was Fusarium spp in 123 (24.5%) patients followed by Aspergillus flavus in 49 (9.9%) patients. Eighty one percent of BK (n = 143) and 71% of FK (n = 353) resolved with medication. The rate of TPK was 17% (n = 36) in BK and 26% (n = 139) in FK (P = 0.03).

The number of visits was higher in FK though the difference was not statistically significant (4.7 ± 3.1 for BK, 5.3 ± 3.6 for FK, P = 0.10) [Table 2]. The mean total medication cost (INR) was significantly more in FK (674.9 ± 463.7 for BK, 959.1 ± 675.2 for FK, P < 0.0001). The mean medication cost (INR) per visit was also more for FK (155.2 ± 84.1 for BK, 201.2 ± 109.4 for FK, P < 0.0001). The mean total travel cost (INR) (552.6 ± 624.6 for BK, 670.9 ± 738.4 for FK, P = 0.11) and the mean travel cost per visit (116 ± 109.1 for BK, 134.3 ± 195.5 for FK, P = 0.43) was higher in FK, though the difference was not statistically significant.
Table 1: Demographic and clinical characteristics of patients with bacterial keratitis and fungal keratitis

| Variables                           | Bacterial Keratitis (n=177) | Fungal Keratitis (n=495) | P     |
|-------------------------------------|-----------------------------|--------------------------|-------|
| Age, mean (SD)                      | 54.51 (17.01)               | 52.86 (15.7)             | 0.0776^d|
| Male, n (%)                         | 100 (56.5)                  | 302 (61.01)              | 0.293c |
| Mean Distance travelled (SD)        | 124.57 (175.12)             | 125.78 (156.39)          | 0.7376^d|
| Median (IQR) distance travelled     | 75.75 (43-130)              | 73.5 (43-144)            |       |
| Trauma, n (%)                       | 81 (45.76)                  | 295 (59.6)               |       |
| Prior treatment, n (%)              | 47 (26.55)                  | 248 (50.1)               | <0.001^m|
| Mean (SD) Duration of symptoms in days | 10.65 (20.16)             | 9.22 (9.3)               | 0.0026^d|
| Median (IQR)                        | 5 (3-10)                    | 7 (4-10)                 |       |
| Mean (SD) UCVA of affected eye      | 1.79 (0.96)                 | 1.18 (0.6-2.6)           | 0.0009^d|
| Mean (SD) Infiltrate Size           | 3.71 (2.1)                  | 4.32 (2.24)              | 0.0016^d|
| Mean (SD) Number of visits          | 4.69 (3.13)                 | 5.29 (3.58)              | 0.1042^d|
| Number of medications, n (%)        |                            |                          |       |
| 1                                   | 67 (37.9)                   | 124 (25.1)               | <0.001^c|
| 2                                   | 98 (55.4)                   | 336 (67.9)               |       |
| 3                                   | 7 (3.9)                     | 35 (7.1)                 |       |
| 4                                   | 5 (2.8)                     | 0                        |       |
| Final Outcome                       |                            |                          |       |
| Healed                              | 143 (80.79)                 | 353 (71.31)              | 0.033^c|
| Phthisical                          | 4 (2.26)                    | 11 (2.22)                |       |
| TPK                                 | 36 (16.95)                  | 139 (26.46)              |       |

M - Mann Whitney U test; C - Chi square test; UCVA - uncorrected visual acuity; TPK - therapeutic keratoplasty

Table 2: Costs of treatment and travel of all patients with bacterial keratitis and fungal keratitis

| Cost (INR), Mean±SD                  | Bacterial keratitis (n=177) | Fungal keratitis (n=495) | P     |
|-------------------------------------|-----------------------------|--------------------------|-------|
| Total Medication cost               | 674.9±463.66                | 959.12±675.22            | <0.0001|
| Medication cost per visit           | 155.2±84.05                 | 201.12±109.42            | <0.0001|
| Total Travel cost                   | 552.59±624.56               | 670.9±738.38             | 0.1078 |
| Travel cost per visit               | 116.0±109.06                | 134.32±195.47            | 0.4280 |

M - Mann-Whitney U test

For the patients who healed successfully with medications, the mean total costs of medications (611.6 ± 395.6 for BK, 801.5 ± 600 for FK, P = 0.0005) and the mean medication costs per visit (154.7 ± 82.2 for BK, 200.7 ± 110.9 for FK, P < 0.0001) were significantly high in patients with FK compared to BK. There was no difference in total travel costs, travel costs per visit, and mean number of visits between BK and FK of patients who healed with medications. The final visual acuity of patients who healed with medical treatment was better in FK than BK (1.36 ± 1.02 for BK, 0.96 ± 0.81 for FK, P = 0.0008) [Table 3].

For those who failed medical management and required therapeutic keratoplasty, the mean total costs of medications (INR 953.7 ± 653.1 for BK, 1374.6 ± 701.5 for FK, P = 0.0023) and the mean medication costs per visit (147.7 ± 74.2 for BK, 200.8 ± 105.2 for FK, P = 0.0036) were significantly high in patients with FK compared to BK [Table 3]. The total travel costs of FK was significantly higher than BK (682.1 ± 831.7 for BK, 904.3 ± 782.5 for FK, P = 0.0397) for patients who required TPK, though there was no statistical difference in the mean number of visits, travel costs per visit and the final visual acuity.

A comparison of costs incurred by the patients with gram-positive bacterial keratitis (n = 126) and gram-negative (n = 51) bacterial keratitis showed no significant difference in the number of visits, total medication costs, medication costs per visit, total travel costs, and travel costs per visit [Table 4]. Analysis of costs incurred by patients with Aspergillus keratitis (n = 67) and Fusarium keratitis (n = 123) showed that the total medication costs in patients with Aspergillus keratitis (1310.4 ± 990.2) were significantly higher than that of Fusarium keratitis (956.0 ± 624.1) (P = 0.017). The medication costs per visit and the total travel costs were higher in Aspergillus keratitis, though not statistically significant [Table 4]. There was no significant difference in the size of the infiltrate (5.18 ± 2.27 mm for Aspergillus vs. 4.55 ± 2.04 mm for Fusarium, P = 0.071), number of medication (P = 0.51), and the number of hospital visits (6.68 ± 4.47 for Aspergillus vs. 5.51 ± 3.74 for Fusarium, P = 0.1208) between Aspergillus and Fusarium.

Discussion

In our study, patients with fungal keratitis incurred significantly more costs on medications compared to patients with bacterial keratitis. More importantly, the number of patients failing medical treatment and requiring keratoplasty was also significantly more in the fungal keratitis group. This study deals only with the cost of medications and the follow-up costs. While the mean surgical costs of providing TPK would be similar to both fungal keratitis and bacterial keratitis patients, the increased number of fungal keratitis patients requiring TPK will significantly push up the total economic burden in absolute terms.

IK mainly affects people from a lower socioeconomic background and hence the knowledge about the costs involved
### Table 3: Comparison of medication costs (INR) and travel costs (INR) of patients with bacterial keratitis (BK) and fungal keratitis (FK) between those who healed with medications and those who required therapeutic keratoplasty

| Variables          | Healed BK (n=143) | Healed FK (n=353) | P*  | TPK BK (n=30) | TPK FK (n=131) | P*  |
|--------------------|-------------------|-------------------|-----|---------------|---------------|-----|
| Number of visits   | 4.1±2.19          | 4.2±2.54          | 0.8406 | 7.4±5.19      | 7.9±4.47      | 0.4563 |
| Total Medication cost | 611.6±395.6   | 801.4±599.9    | 0.0005 | 953.6±653.1  | 1374.6±701.5 | 0.0023 |
| Medication cost per visit | 154.6±82.1   | 200.6±110.8   | <0.0001 | 147.7±74.2   | 200.7±105.2  | 0.0036 |
| Total Travel cost | 524.7±577.8      | 586.2±702.1     | 0.7930 | 682.1±831.7  | 904.3±782.4  | 0.0397 |
| Travel cost per visit | 119.6±111.8  | 128.2±125.5   | 0.6959 | 97.3±97.1    | 154.3±318.3  | 0.1869 |
| Final Visual Acuity | 1.36±1.02       | 0.96±0.81       | 0.0008 | 2.46±0.6     | 2.34±0.73    | 0.4356 |

* M - Mann-Whitney U test; TPK - therapeutic keratoplasty

### Table 4: Medication costs (INR) and travel costs (INR) of patients with gram-positive bacterial keratitis vs. gram-negative bacterial keratitis and *Aspergillus* keratitis vs. *Fusarium* keratitis

| Variables          | Gram-Positive Keratitis vs. Gram Negative Keratitis | Aspergillus Keratitis vs. Fusarium Keratitis |
|--------------------|------------------------------------------------------|---------------------------------------------|
|                    | GPK n=126 | GNK n=51 | P* | Aspergillus n=67 | Fusarium n=123 | P* |
| Number of visits   | 4.6±2.65  | 4.92±4.14 | 0.8686 | 6.68±4.47      | 5.51±3.74     | 0.1208 |
| Total Medication cost | 651.5±460.1 | 788.8±474.6 | 0.1495 | 1310.4±990.2  | 956.0±624.1  | 0.0172 |
| Medication cost per visit | 148.6±77    | 174.9±99.2 | 0.1163 | 221.2±108.6   | 187.5±81.9   | 0.1087 |
| Total Travel cost | 562.7±622.9      | 510.7±612.9   | 0.6719 | 821.2±800.6   | 660.6±787.4  | 0.0595 |
| Travel cost per visit | 113.8±105.3 | 118.1±116.6 | 0.9496 | 124.9±106.1   | 126.7±133.7  | 0.2702 |

* M - Mann-Whitney U test

is of paramount importance. In an earlier study done almost 15 years back, we had documented that the economic burden of patients with an episode of IK was found to be more than the monthly wage of this population. In this study, we emphasize the cost difference between ulcers caused by bacteria and fungi in the current era.

The prolonged duration of the treatment and the costs associated with the medication and travel for follow-up makes these already financially vulnerable patients be less compliant with medications and fail therapy. A few studies in the past have captured the costs of treatment of IK. However, in these studies, the costs of treatment were calculated as estimates either from the hospital accounting system or by calculating the average wholesale pharmacy prices of each medication.

The data from our current study are more accurate because of the following reasons. The medications were provided to the patients from the pharmacy based on the prescription and the bills were accounted directly to the project. The travel costs were reimbursed to the patients on provision of the actual bus transport tickets provided. Thus, there is no recall bias in our study with regard to the costs associated with medicines and travel.

The total medications costs and the costs of medication per visit were significantly more in FK compared to BK. It is also interesting to note that the average cost of treatment per visit was also significantly more in FK than BK, implying the higher costs of antifungal medications compared to antibacterial medications. Also, unlike BK, the treatment options of FK are limited with non-availability of many antifungal medications in developing countries. Topical natamycin introduced in 1960s is still costlier than most brands of topical fourth-generation fluoroquinolones available in our country. Moreover, the addition of a topical azole in non-responsive cases increases the costs of treatment significantly. It is also interesting to note that patients with FK incurred significantly higher costs of treatment compared to BK irrespective of whether they had healed with successful medical treatment or failed medical treatment and required therapeutic keratoplasty. While there was no difference in the costs between different bacteria, ulcers caused by *Aspergillus* incurred more costs than ulcers caused by *Fusarium*, because of the prolonged treatment.

The total cost of travel was higher in fungal keratitis compared to BK though not statistically significant. Patients with fungal keratitis were scheduled for more follow-ups than BK (not statistically significant). The prolonged nature of the treatment of IK and the increased number of hospital visits play an important role in increasing the economic burden of patients with IK. Teleophthalmology-based locally available primary eye care centers reduce barriers to care by increasing the factors for accessibility and affordability for the patients. In a previous study, we found that patients with corneal disorders could save approximately INR 1200 by availing the treatment facilities in these teleophthalmology-based vision centers instead of traveling to the tertiary hospital. In that study, we also reported that 85% of the patients with corneal disorders accessing these teleophthalmology centers could get care in that facility itself and did not have the need to come to the base hospital. More importantly these centers would enable the patients to present early on with their symptoms and hence the costs associated with treatment would be significantly low.

The cost of the treatment of IK has been shown to be associated with the severity of the keratitis. It is important to note that though both the groups of IK had comparable demographic features in terms of age, gender, and the
distance traveled, they differed in the ulcer characteristics. The presenting visual acuity was worse in BK and the ulcer size at presentation was larger in FK. It is possible for these variations in the severity of the ulcers to be a confounding factor in the costs of medications. However, the large volume of the study and the consecutive nature of enrolment ensure that the patient population analyzed in this study resembles the natural presentation of a patient with IK to a tertiary care hospital. A prospective ulcer severity-matched study can provide a more accurate difference in the costs of treatment among the different causes of IK.

The major limitation of this study was its retrospective nature, because of which the reasons for lost to follow-up could not be captured. Our main aim was to compare the medication costs and travel expenses in this study. We did not capture the lost wages, costs of hospital admissions, costs of investigations, and the costs of food in this study. In an Australian study performed in 2003, the largest component of costs of treatment of IK was estimated to be from hospital visits and hospital bed days, whereas the costs of medications comprised less than 10% of total costs.10 Our study also captured only the number of hospital visits made by the patient and not the duration of treatment. Though the number of visits can be considered as a surrogate marker for duration of treatment, the duration of treatment between each visit can vary based on the changes in the severity of the ulcer and the response to treatment. This might also be the possible explanation for non-significant difference in number of visits among patients with BK and FK in our study.

Conclusion

To conclude, patients with fungal keratitis spent significantly more on medications compared to bacterial keratitis. Further, patients with fungal keratitis had a higher chance of failing medical treatment and undergoing therapeutic keratoplasty, further pushing up the costs. A better understanding of the economic burden of these patients will help us in planning a compliant treatment regimen for this vulnerable group. The use of telemedicine facility in vision centers closer to their home have proven to be a successful model in providing care for their corneal infection at their doorstep. Further thrust should be made to have more points of care treatment facilities closer to the vulnerable population with tele conferencing facility with the cornea specialists at the base hospital, thus addressing the concepts of early initiation of treatment and thereby potentially reducing the economic burden associated with the frequent travel visits needed for treatment of IK.

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Conflicts of interest
There are no conflicts of interest.

References

1. Whitcher JP, Srinivasan M. Corneal ulceration in the developing world—A silent epidemic. Br J Ophthalmol 1997;81:622-3.
2. Ung L, Acharya NR, Agarwal T, Alfonso EC, Bagga B, Bispo PJ, et al. Infectious corneal ulceration: A proposal for neglected tropical disease status. Bull World Health Organ 2019;97:854-6.
3. Lalitha P, Prajna NV, Manoharan G, Srinivasan M, Mascarenhas J, Das M, et al. Trends in bacterial and fungal keratitis in South India, 2002-2012. Br J Ophthalmol 2015;99:192-4.
4. Prajna VN, Nirmalan PK, Saravanan S, Srinivasan M. Economic analysis of corneal ulcers in South India. Cornea 2007;26:119-22.
5. Prajna NV, Srinivasan M, Lalitha P, Krishnan T, Rajaraman R, Ravindran M, et al. Differences in clinical outcomes in keratitis due to fungus and bacteria. JAMA Ophthalmol 2013;131:1088–9.
6. Austin A, Lietman T, Rose-Nussbaumer J. Update on the management of infectious keratitis. Ophthalmology 2017;124:1678-89.
7. Schulze-Bonsel K, Feltgen N, Burau H, Hansen L, Bach M. Visual Acuities “Hand Motion” and “Counting Fingers” can be quantified with the freiburg visual acuity test. Invest Ophthalmol Vis Sci 2006;47:1236–40.
8. Ballouz D, Maganti N, Tuohy M, Errickson J, Woodward MA. Medication burden for patients with bacterial keratitis. Cornea 2019;38:933-7.
9. Keay L, Edwards K, Naduvilath T, Taylor HR, Snibson GR, Forde K, et al. Microbial keratitis predisposing factors and morbidity. Ophthalmology 2006;113:109-16.
10. Keay L, Edwards K, Naduvilath T, Forde K, Stapleton F. Factors affecting the morbidity of contact lens-related microbial keratitis: A population study. Invest Ophthalmol Vis Sci 2006;47:4308-8.
11. Agrawal S, Arya N, Agrawal M. Cost analysis of various topical eye preparations currently available in Indian market. Int J Basic Clin Pharmacol 2019;8:1754-7.
12. Chandrappa S, Rajarathna K. Cost variation analysis of various brands of topical eye preparations currently available in Indian pharmaceutical market. Int J Basic Clin Pharmacol 2018;7:2364-7.
13. Kovai V, Rao GN, Holden B, Krishnaiyah S, Bhattacharya SK, Marmamulla S, et al. An estimate of patient costs and benefits of the new primary eye care model utilization through vision centers in Andhra Pradesh, India. Asia Pac J Public Health 2010;22:426-35.
14. Komal S, Radhakrishnan N, Vardhan S A, Prajna NV. Effectiveness of a Teleophthalmology Vision Center in Treating Corneal Disorders and Its Associated Economic Benefits [published online ahead of print, 2021 Jun 9]. Cornea. 2021;10.1097/ICO.0000000000002784. doi:10.1097/ICO.0000000000002784.