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Medication burden for patients with bacterial keratitis

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Abstract

Purpose: To understand medication use and patient burden for treatment of bacterial keratitis (BK).

Methods: A retrospective study was performed examining medical records of adult patients with BK in an academic cornea practice. Data collected included medications used in the treatment of BK, dosing of medications, and the number and total duration of clinical encounters. Costs of medications were estimated using average wholesale pharmacy price. Linear regression analysis was used to investigate associations of medication use with patient demographics and corneal culture results and reported with beta estimates (β) and 95% confidence intervals (CI).

Results: 48 BK patients (56% female) were studied. Patients were treated for a median of 54 days with 10 visits, five unique medications, 587 drops, and seven prescriptions. Estimated median medication cost was $933 (interquartile range: $457-$1422) US dollars. Positive bacterial growth was significantly associated with more visits (β: 6.16, 95% CI: 1.75–10.6, p=0.007), more days of treatment (β: 86.8, 95% CI: 10.8–163, p=0.026), more prescribed medications (β: 2.86, 95% CI: 1.04–4.67, p=0.003), and more doses of medications (β: 796, 95% CI: 818–1,412, p=0.012), compared to patients without corneal scraping. For every 10 years older, patients were prescribed 132 more drops of medication (β: 132, 95% CI: 18.2–246, p=0.024). Gender and income were not associated with medication burden or treatment length.

Conclusion: Older patients and those with positive cultures incur the most medication burden in treatment of BK. Providers should be aware of medication usage and cost burden, as it may affect compliance with treatment.

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Keywords

bacterial keratitis; drops; medication; cost

Introduction:

One million annual medical visits in the United States result in a diagnosis of keratitis with 76.5% of patients receiving prescriptions for antibiotics.[1] The proportion of Americans with severe infectious keratitis is lower, estimated at 71,000 cases annually.[2] Bacterial keratitis (BK) is painful and vision-threatening. Therefore, BK requires immediate treatment to minimize or prevent vision loss and complications.

To treat BK, broad-spectrum or fortified antimicrobial medications are prescribed. For severe BK keratitis, cornea textbooks recommend initiating treatment with two separate fortified antimicrobial agents prescribed hourly to target different microbial species and minimize the risk of permanent vision loss.[3] Medication dosing is adjusted depending on how an eye responds to treatment. While practice guidelines exist for providers, patients' perspective on expected treatments for BK is less well captured. This study was conducted to understand the burden of medications used to treat BK, to explore if clinical factors are related to medication use, and to determine if the results of microbial scraping for organism identification alter medication use.

Materials and Methods:

Cohort:

The medical records of patients with microbial keratitis receiving care in the corneal clinic at the University of Michigan Kellogg Eye Center (KEC) between July 1, 2015 and August 7, 2018 were reviewed.[4] Participants were included if ≥18 years and diagnosed with culture-positive BK or presumed BK because of successful treatment with antibacterial medications. Participants were excluded if they had previous incisional corneal surgery, were pregnant, were hospitalized or institutionalized, or had only a single encounter with a cornea specialist for consultation purposes. All patients were followed until BK resolved or the patient underwent an urgent penetrating keratoplasty for corneal perforation. This study was approved by the University of Michigan Institutional Review Board and adhered to the Declaration of Helsinki.

Data collection:

Clinical and emergency department electronic health records for the cohort were retrospectively reviewed. Information was collected from all dates of clinical encounters related to BK. Demographic information collected on patients included age, sex, and zip code data. Zip code data was used to derive median household income based on 2010 United States census data and Zip Code Tabulation Areas (ZCTA).[5] Corneal scraping results, by Gram stain or culture, were extracted from microbiology laboratory records. Medications used in BK management, including those needed to treat intraocular pressure or inflammation, were recorded including name, strength, dosage frequency, and bottle size prescribed at each encounter (eTable 1, Supplementary Content). All medication prescriptions were converted to doses per 24-hour period. When medications were prescribed "as needed" or with a range of frequencies (e.g., every 4–6 hours), the maximum dose per day was recorded. For doses prescribed for use during waking hours, a 16-hour waking period was used. If a medication was prescribed, but not taken (e.g., not covered by insurance, pharmacy issues, etc.), the medication was noted, but dose was recorded as zero. The number of bottles used by each patient was calculated, using 20 drops per mL per the National Council for Prescription Drug Programs billing unit standard.[6] Specifically, the total number of medication prescriptions (i.e., bottles) used per participant was derived by combining the cumulative number of drops used and the estimate of drops per milliliter. Medication cost was estimated using the lowest of the average wholesale pharmacy prices listed in 2018 Redbook data for each medication. Generic pricing was used, when available. For fortified antibiotics, an average cost was calculated using prices from two local Michigan compounding pharmacies.

Statistical analysis:

Descriptive results for medication and disease burden were summarized for continuous variables using means and standard deviations (SD) and for categorical variables using frequencies and percentages. Multivariable linear regression analyses were performed to investigate associations of patient demographic factors and diagnostic results with measures of medication and disease burden. Outcome measures of burden included the number of visits, the total doses of a medication prescribed to be dispensed in the eye, the number of unique drugs, the length of treatment (days) until the active ulcer resolved and a corneal scar formed, maximum doses in any given day during the course of the treatment, and average doses per day. The independent variables investigated for associations with burden included sex, age, median household income, and corneal scraping results. Model results are reported with beta estimates (β) and 95% confidence intervals (CI). A separate factor analysis was performed to explore collinearity between the six burden measures and to determine if a latent "burden" measure existed. Statistical analysis was performed using STATA version 15.1 (STATA Corp LLC, College Station, TX).

Results:

A total of 48 participants with BK met inclusion criteria for study. Participant characteristics and medication use are described in Table 1. Briefly, participants were on average 50.6 years old (SD=20) at the time of BK diagnosis, 56% were female, and had an average household income of $61,600 (SD=$23,200). Four participants underwent emergency keratoplasty for corneal perforation. Four participants in the sample were lost to follow-up during active management. Culture or gram staining showed positive bacterial growth in 54% (n=26) of cases and no growth in 29% (n=14) cases. Of the 26 eyes with positive growth on culture, 11 participants received antibiotic treatment prior to corneal scraping. Of the 14 eyes with no growth on culture, eight participants received antibiotic treatment prior to corneal scraping. Corneal scraping was not performed in 17% (n=8) cases.

Participants were treated for a median of 54 days (interquartile range, IQR: 20,110) and 10 visits (IQR: 6,13) to manage their infection. Participants were prescribed a median of 5 unique medications (IQR: 3,6) and told to administer a median of 587 drops (IQR: 227,1052). Based on the number of drops prescribed and the number of drops in a bottle, specific to each bottle size, patients filled 7 medication prescriptions (IQR: 4,12). Patients had an estimated median cumulative cost for their medications of $933 (IQR: $457, $1422) United States dollars.

Most patients were prescribed non-fortified antibiotic medications (94%). Patients were also prescribed fortified antibiotic medications (69%), corticosteroid medications (58%), and mydriatic medications (50%) (Table 2). A low percentage of patients (12.5%) were prescribed corticosteroid medications within seven days after presentation, not including those on corticosteroid-antibiotic combination drops.

Linear regression analyses showed associations of two predictors with individual outcome measures of burden (Table 3). Compared to participants who were not cultured, participants with positive bacterial growth had 6.16 more eye visits (β: 6.16, 95% CI: 1.75–10.6, p=0.007), 87 longer treatment duration (β: 86.8, 95% CI: 10.8–163, p=0.026), 2.86 more unique medications prescribed (β: 2.86, 95% CI: 1.04–4.67, p=0.003), and 796 more medication doses (β: 796, 95% CI: 818–1,412, p=0.012). Patients with negative culture results had 5.17 more eye visits (β: 5.17, 95% CI: 0.33–10.0, p=0.037) compared to patients who were not cultured. In addition, older age was significantly associated with more prescribed eye drops. For every additional ten years of age, patients were prescribed 132 more medication drops (β: 132, 95% CI: 18.2–246, p=0.024). Gender or income were not associated with burden (treatment length or medication use). When compared independently, no statistically-significant differences were observed between the number of unique medications in participants with positive versus negative culture results.

A factor analysis to explore latent constructs showed that 77% of the variance within the six measures of burden was explained by four of the measures of burden: number of visits, total doses, number of unique medications, and treatment length (eTable 2, Supplementary Content). The four measures had roughly equivalent contributions to the latent construct. Results of a linear regression analysis for associations of this latent burden measure with the same predictors is shown in the rightmost column of Table 3. The associations observed with the individual outcome measures of burden remained significant in this second regression analysis. Participants with positive bacterial cultures had the highest predicted burden and participants in whom scraping was not performed had the lowest. There was a small, but statistically significant association of higher burden with increasing age.

Discussion:

Patients with BK were prescribed a median of five unique medications and administered 587 drops of those medications. Almost all participants (94%) were prescribed non-fortified antibiotic drops. Patients also received fortified antibiotics (69%), topical corticosteroids (58%), and dilating drops (50%). Patients with severe BK were more likely to have diagnostic corneal scrapings performed, which may explain the observed association between corneal scrapings and greater medication burden. No statistically-significant differences were observed between the number of unique medications in patients with positive versus negative culture results. The lack of an association between number of unique medications and culture results is consistent with research demonstrating no differences in outcomes between culture-positive and culture-negative keratitis.[7]

In this study, older age was associated with greater medication use. This association is consistent with prior work showing older age is associated with worsening keratitis severity.[8] Both older age and greater eye medication use have been shown, in the glaucoma literature, to each negatively impact drop compliance and patients' ability to afford medications.[9–12] In our study, older age was associated with more visits and more eye drops prescribed for treatment, but no longer treatment duration. The relationship with age and adherence was not explicitly explored in this study.

Although BK is an acute, short-lived medical condition, the burden of treatment has been documented. In one Australian study of microbial keratitis from 2006, severe keratitis of any etiology (e.g., acanthamoeba, fungal, and bacterial) had high costs and treatment burden.[13] In our study, the average wholesale price of medications to treat BK approached $1,000 United States dollars for the duration of disease, an estimate similar to the Australian study. In studies able to assess direct patient payments, patients with chronic dry eye syndrome paid, on average, $300 per year for medications.[14] Patients with severe, end-stage glaucoma paid, on average, $2511 per year, including visits, surgeries, and medications.[15] Patients with acute BK incur additional costs for diagnostic testing, procedures, and surgeries that were not evaluated in this study. Patients hospitalized for BK have more expensive hospital admissions and major surgical procedures compared to patients hospitalized for any other ophthalmic disease.[16]

Measures of medication use and treatment duration have overlapping characteristics, as shown by factor analysis. The combined factor was associated with the same predictors of burden as the individual outcome measures, namely culture results and age. A combined burden factor could be used as a patient-centered outcome measure in future studies of BK.

There are limitations to the study. Treatment burden is related to keratitis severity. The lack of a published definition of keratitis severity restricted our ability to use severity as a predictor in our models. Not all predictors of higher medication burden were examined, such as prior contact lens wear or predisposing ocular surface disease. Medications were not recorded after an urgent penetrating keratoplasty, if one occurred. Our rationale was, since data collection occurred at an academic medical center, more patients required urgent keratoplasty than would occur in the general US population. Twenty drops per milliliter was used to estimate drop bottle volumes. Glaucoma researchers debate the best estimate of drop quantity per milliliter.[17–20] Redbook data was used for the lowest price available for medications. The average wholesale price of fortified antibiotics may not accurately represent patients' costs. The team was not able to obtain patients' true costs from individual pharmacy data. Income data was used based on median income data for the participants' zip code as participants' personal household income was not available. To test if the income data altered the co-variates that were statistically significant in the multivariable regression models, the models were re-run without income as a covariate. With income co-variate excluded, the predictor variables found to be significant in our models did not change.

Like many patients with complex eye conditions, patients with BK require many medications. The intensity of treatment for BK likely means that much of the burden is incurred in a short time duration compared to other chronic eye conditions. It is likely that this complicated regimen is not possible for many patients. Providers should be mindful of the number and quantity of prescribed medications. Decreasing medications and dosing has been shown to improve health-related quality of life.[20] Even in microbial keratitis, quality of life differs between medication regimens, as shown in a randomized control trial comparing two anti-fungal medications.[22] Development of methods to personalize microbial keratitis treatments and tailor medications more effectively could reduce medication burden, improve compliance, and increase health-related quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Characteristics of participants with bacterial keratitis and medication use

Patient Characteristic (n=48)	**Frequency (percent)**		
Sex (female)	**27 (56%)**		
	Median (IQR)	**Mean (SD)**	**Range**
Age (years)	49.5 (36, 63)	50.6 (20)	19 – 88
Income (USD)	$58,049 ($46703, $78,197)	$61,554 ($23,193)	$17,667-$113,542
Number of visits per patient	10 (6, 13)	10.6 (5.9)	3 – 27
Length of treatment per patient * (days)	54 (20, 110)	90 (96.5)	9 – 373
Number of unique medications	5 (3, 6)	5.2 (2.6)	1 – 14
Cumulative medication doses	587 (227, 1052)	837.2 (850.1)	48 – 4149
Maximum daily dose	48 (20,51)	39.6 (20.2)	6–96
Average doses per day	8.2 (5.8–12.9)	10.6 (8.0)	2.7–52.7
Number of bottles of medications prescribed per patient	7 (4, 12)	10.5 (11.2)	1 – 49
Wholesale price per patient (USD)	$933 ($457, $1422)	$1344 ($1607)	$10 - $8232

IQR, interquartile range; SD, standard deviation; USD, United States dollars

* length of treatment defined as length on medications until corneal scar formation

Table 2:

Medication categories prescribed for managing bacterial keratitis

Medication Categories	Percent (n) of patients prescribed, by category (n=48)	Days on medication Mean (SD)	Total doses prescribed Mean (SD)
Fortified antibiotics	68.8% (33)	63.3 (72.2)	401.9 (235.0)
Non-fortified antibiotics	93.8% (45)	60.0 (83.6)	287.1 (372.8)
Antiviral medications	20.8% (10)	96.3 (130.0)	347.1 (397.8)
Glaucoma medications	12.5% (6)	111.5 (173.9)	311.7 (457.8)
Corticosteroids	58.3% (28)	102.7 (111.6)	237.3 (265.0)
Pain medications	16.7% (8)	16.3 (28.0)	10.3 (14.0)
Dilation drops	50% (24)	35.8 (44.0)	72.0 (91.2)

SD, standard deviation

Table 3:

Individual regression analyses for each measures of medication use and treatment course

Covariate	**Outcome Measures** **Covariate beta coefficients (95% Confidence interval) P value**						**Burden Factor*** **Beta coefficients (95% Confidence intervals) P values**
	Number of Visits	**Length of Treatment**	**Number of Unique Medications**	**Cumulative medication doses**	**Max Daily Dose**	**Average Doses Per Day**	
Positive Growth *(compared to no-culture reference)*	6.16 (1.8, 10.6) 0.007	86.8 (10.8, 163) 0.026	2.86 (1.1, 4.7) 0.003	796 (181, 1412) 0.012	19.8 (5.1, 34.5) 0.009	2.17 (−1.9, 6.2) 0.28	1.11 (0.4, 1.8) 0.002
Negative Growth *(compared to no-culture reference)*	5.17 (0.3, 10.0) 0.037	57.2 (−26.4, 141) 0.175	1.75 (−0.3, 3.7) 0.085	449 (−228, 1125) 0.188	25.3 (9.1, 41.4) 0.003	2.58 (−1.8, 7.0) 0.245	0.80 (0.03, 1.6) 0.041
Age (in 10-year increments)	0.70 (−0.1, 1.5) 0.09	10.0 (−4.0, 24.0) 0.16	0.19 (−0.1, 0.5) 0.25	132 (18.2, 246) 0.024	1.1 (−1.6, 3.8) 0.41	−0.06 (−0.8, 0.7) 0.88	0.013 (−0.001, 0.03) 0.051
Median Household Income (in thousands)	−0.02 (−0.1, 0.1) 0.65	−0.19 (−1.4, 1.1) 0.76	−0.03 (−0.1, 0.003) 0.07	−3.67 (−13.7, 6.4) 0.46	−0.08 (−0.3, 0.12) 0.51	−0.02 (−0.1, 0.05) 0.62	−0.005 (−0.02, 0.01) 0.36
Female (versus male)	1.43 (−1.90, 4.76) .392	10.6 (−46.9, 68.1) .711	0.56 (−0.82, 1.93) .418	203 (−263, 669) .383	9.20 (−1.92, 20.3) .102	1.71 (−1.33, 4.75) .262	0.26 (−0.26, 0.79) .32
R^2	.257	.174	.315	.290	.297	.083	.325

* Burden factor was created by factor analysis