

Effects of Noncompliance with Multiple Drugs in the Treatment of Fungal Corneal Ulcer

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Abstract

A prospective, observational study was conducted in a tertiary level specialized institution in Bangladesh, between February and August of 2023, to assess the effect of noncompliance with multiple drugs in treating fungal corneal ulcers. A total of 100 patients with fungal corneal ulcers from the cornea outpatient department were enrolled in this study. They were checked in for study on the first week, second week, after one month and after two months. Visual acuity, size of the ulcer, grade of opacity, level of hypopyon, and compliance with drugs were recorded (measured by MMAS-8). All data were recorded on a predesigned data collection sheet and analyzed. Out of 100 corneal ulcer patients, 47 were found to have therapeutic failure. The patient's level of education, place of residence, kind of trauma, and patient compliance were identified as possible risk factors for treatment failure on bivariate analysis. The respondents identified the frequency and use of multiple drugs as the primary reasons for noncompliance. It was found that patients' willingness to cooperate significantly influenced the success of their medical treatment. Compared to medium-compliant patients, patients with lesser compliance had a 4.4 times increased risk of not receiving medical treatment (OR: 4.408; $p < 0.05$). One of the main contributing factors to treatment failure for corneal ulcers is noncompliance. Key components to improving compliance are reducing the frequency of doses, avoiding multiple medications, and improving the patient's awareness and comprehension of the illness.

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Introduction

Blindness caused by corneal diseases is a significant global health issue.¹ Among them, infectious keratitis is one of the predominant causes.²⁻⁸ Approximately 1.5 to 2 million people become blind due to ocular trauma and corneal ulceration, according to a report by the World Health Organization (WHO). Corneal diseases affect a significant number of people every year, particularly in developing countries. This poses a significant public health concern for these nations.⁹

A corneal ulcer is an infectious condition of the cornea, disrupting its epithelial layer with the involvement of the corneal stroma. The etiological and epidemiological pattern of corneal ulceration varies significantly with patient population, geographical region, and prevailing socioeconomic conditions.¹⁰ Many microorganisms cause infective corneal ulcers. These organisms are bacteria, fungi, viruses, protozoa, and chlamydia. Fungi cause 46.8% of all central corneal ulcers.¹¹ Filamentous fungi

cause more than 70% of fungal keratitis cases.¹² They are caused by trauma, particularly with vegetative matters, as well as chemical injury, contact lenses, and infections. Significant vision loss, eye pain, a sensation of a foreign body, watering, photophobia, redness, and occasional discharge are

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the main symptoms. Important signs include corneal ulcers, which appear as grey to yellow-white infiltrates with an elevated margin.

Treatment options for fungal corneal ulcers include both medical and surgical approaches. Medical treatment includes topical antifungal agents like natamycin 5%, amphotericin B 0.15%, econazole 1%, fluconazole 2%, clotrimazole 1%, miconazole 1%, and voriconazole 1 or 2 %.¹³ Almost always, both topical and systemic antifungal agents are needed.¹⁴ Fungal corneal ulcer is commonly associated with hypopyon and toxic iridocyclitis, irrespective of the size of the ulcer. Therefore, additional preparations are necessary, such as a broad-spectrum antibiotic to prevent bacterial co-infection, a cycloplegic to reduce pain from ciliary spasm and prevent the formation of posterior synechiae from secondary iridocyclitis, and sometimes anti-glaucoma medications to manage secondary glaucoma. In severe cases, subconjunctival injections and injections into the corneal stroma may also be required.¹

Fungal corneal ulcers are challenging to treat, as they often do not respond to standard treatments. Common reasons behind treatment failure are systemic corticosteroid users with compromised immunity, an ulcer caused by *Candida* species, an immunocompromised host and corneas with chronic erosions/ulceration from other causes, Diabetes mellitus that delays the healing process,¹⁰ corneal surgery (e.g., penetrating keratoplasty) and poor compliance of the patient with multiple drugs for the treatment of fungal corneal ulcer. Multiple reports have shown that the average healing time of fungal corneal ulcers after drug treatment was 1-2 months.¹⁵ Treatment failure measures unsuccessful disease management and procedures in individual cases.

Treatment failure can be clinical, immunologic, mycologic, or a combination of factors, such as drug resistance, toxicity, and poor compliance, which can lead to treatment failure. Factors that can contribute to treatment failure include drug resistance, drug toxicity, or poor treatment compliance.¹⁶⁻¹⁸

Compliance or adherence can be defined as “persistence in a practice or tenet; steady observance or maintenance”, which appropriately conjures up the tenacity patients need to adhere to a therapeutic regimen.¹⁹ There are no stable (i.e., trait) factors that reliably predict compliance. However, questionnaires that assess specific behaviours that relate to specific medical recommendations may be better predictors of adherence behaviour.²⁰ In this study, we made an effort to determine the effect of noncompliance with multiple drugs in treating fungal corneal ulcers.

Methods

This prospective, observational study was conducted in a tertiary level specialized institution in Bangladesh, between February and August of 2023. A total of 100 patients with fungal corneal ulcers attending the cornea department who were taking three or more medications were included in the study.

The sampling technique was nonrandom and purposive. Patients suffering from other coexisting ocular diseases, taking topical or systemic medications for another systemic or ocular disease, who had undergone ocular disease in the preceding six months, and who were enrolled in another study group were excluded from the study. Selected patients underwent detailed ophthalmological and systemic examinations, as well as relevant investigations, including Gram stain, KOH stain, culture, and sensitivity tests. They were followed up

on days 7, 15, 1 month, and 2 months after enrollment. Visual acuity, grading, level of corneal opacity, ulcer margin and hypopyon were recorded during each visit and scored according to preset criteria.

Patients with persistent or deteriorated diagnostic parameters in the subsequent two-month follow-up periods were considered treatment failure cases. Non-compliant patients were defined using the Morisky Medication Adherence Scale (MMAS), a validated scale for estimating compliance based on questionnaires.^{22,23} All items of the questionnaire were scored as either zero (No) or one (Yes) except for item five, which scored as zero (Yes) or one (No), and the last item, which scored zero (Never) and one for other answers. The total score was calculated by adding up all the individual scores. A higher total score means lower adherence/compliance to prescribed medications. Ranking the total score of the Morisky scale, 0 means high adherence, 1 or 2 means moderate adherence, and more than 2 means poor adherence. The information was documented on a predesigned sheet for data collection.

Data was checked, coded and analysed using the Statistical Package for Social Sciences (SPSS) version 17.0 for Windows. Data was expressed as frequency and percentage. Determinants of noncompliance for corneal ulcer treatment was sought by binary logistic regression analysis. Reference group was noted, β was identified for standardised regression coefficient, $p < 0.05$ was considered as statically significant, level of CI (confidence interval) was set at 95%.

Results

A total of 100 patients with fungal corneal ulcers were included in the study. Table-I shows the causes of

noncompliance among the study patients – frequent and multidrug therapy was notified by the most of the patients (40%).

Table-I: Causes of noncompliance according to respondents (N=100)

Causes	Total (N=100)	Treatment failure group (n=47)	Responded with treatment (n=53)
Costly	5(100)	2(40)	3(60)
Frequency	24(100)	15(62.5)	9(37.5)
Multi drugs	12(100)	7(58.3)	5(41.7)
Frequent and multi-drug	40(100)	21(52.5)	19(47.5)
Illiteracy	2(100)	1(50)	1(50)
Not applicable	17(100)	9(52.9)	8(47.1)

Figures in the parentheses indicate percentages.

Table-II shows the distribution of responses to MMS-8 by the patients. Table-III shows the determinants of noncompliance for corneal ulcer treatment by binary logistic regression analysis. After adjusting for all possible confounders, the multiple logistic regression analysis revealed that patients' compliance had a strong impact on the medical treatment outcome of corneal ulcer cases. Patients with lower compliance had a 4.4 times higher chance of treatment failure than those with medium compliance ($p < 0.05$).

Table-II: Distribution of responses to MMS-8 by the patients (N=100)

Response to the MMS-8	Treatment failure (n=47)	Responded to treatment (n=53)
1. Do you sometimes forget to take your medicine?		
Yes (43)	20 (46.5)	23 (53.5)
No (57)	27 (47.4)	30 (52.6)
2. People sometimes miss taking medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?		
Yes (25)	25 (44.6)	31 (55.4)
No (44)	22 (50.0)	22 (50.0)
3. Have you ever cut back or stopped taking your medication without telling your doctor, because you feel worse when you take it?		
Yes (20)	9 (45.0)	11 (55.0)
No (80)	38 (47.5)	42 (52.5)
4. When you travel or leave home, do you sometimes forget to bring your medication?		
Yes (37)	17 (45.9)	20 (54.1)
No (63)	30 (47.6)	33 (52.4)
5. Did you take your medicine yesterday?		
Yes (64)	30 (46.9)	34 (53.1)
No (36)	17 (47.2)	19 (52.8)
6. When you feel like your condition is under control, do you sometimes stop your medicine?		
Yes (20)	7 (35.0)	13 (65.0)
No (80)	40 (50.0)	40 (50.0)
7. Taking medicine every day is a real inconvenience for some people. Do you ever feel pressured to stick to your treatment plan?		
Yes (100)	47 (47)	53 (53)
No (0)	0 (0)	0 (0)
8. How often do you have difficulty remembering to take all your medicine?		
Never / Rarely (26)	14(53.8)	12(46.2)
Once in a while (4)	2(50.0)	2(50.0)
Sometimes (58)	27(46.6)	31(53.4)
Usually (10)	3(30.0)	7(70.0)
All the time (2)	1(50)	1(50)

Figures in the parentheses indicate percentages.

Table-III: Determinants of noncompliance for corneal ulcer treatment by binary logistic regression analysis

Variables	β	P value	Odds Ratio (OR)	95% CI	
				Lower	Upper
1. Gender					
Female	Reference				
Male	0.893	0.119	0.416	0.140	1.235
2. Education status					
Graduate	Reference				
Primary school education	1.475	0.32	0.229	0.059	0.883
Secondary school	0.906	0.228	0.404	0.092	1.766
Higher Secondary	2.144	0.056	0.117	0.013	1.045
Illiterate	0.854	0.001	5.67	2.456	17.059
3. Place of residence					
Urban	Reference				
Rural	0.445	0.521	0.641	0.164	2.498
4. H/O of Trauma					
No H/O trauma	Reference				
Agricultural trauma	1.919	0.010	6.816	1.576	29.483
FB impaction	0.604	0.425	1.830	0.415	8.074
5. Causes of Noncompliance					
Costly	Reference				
Frequency	1.142	0.171	3.134	0.610	16.102
Frequency+ Multi Drugs	3.06	0.001	21.356	3.881	117.50
Multi drugs	1.11	0.290	3.047	0.387	23.99
Illiteracy	2.250	0.202	9.484	0.299	300.90
6. Compliance Status of patients					
Medium compliance	Reference				
Lower compliance	1.483	0.008	4.408	1.466	13.255

Reference group was noted, β for standardised regression coefficient, $p < 0.05$ was considered as significant, level of confidence interval 95%.



Fig. 1: Patient having fungal corneal ulcer with hypopyon..

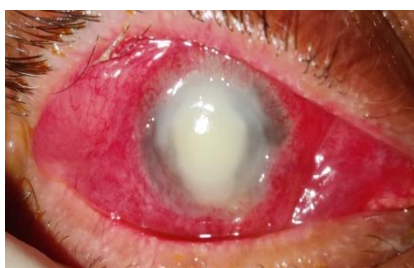


Fig. 2: Patient having fungal corneal ulcer with total corneal involvement.



Fig. 3: a) suppurative fungal corneal ulcer at presentation, b) at healing stage after treatment.

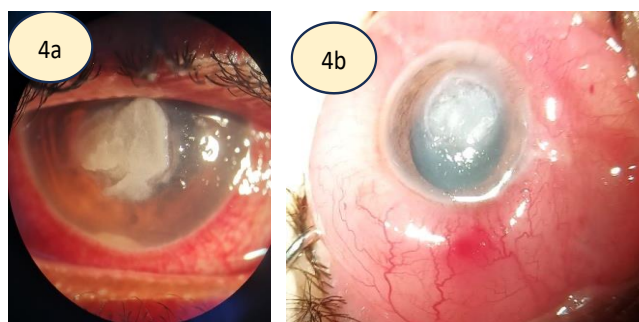


Fig. 4: a) fungal Corneal ulcer with plaque formation using natamycin drug, b) same patient with a fungal corneal ulcer in the healing stage, with a clear margin and no hypopyon.



Fig. 5: Fungal corneal ulcer, impending to perforation.

Discussion

Our study found that the percentage of fungal keratitis in men is comparatively higher than in females. The male-female ratio was 1.94:1.00, almost twice that of females. A similar result was found in the study done by Bharathi *et al.*¹⁰, where the calculated odds were 1.47 times higher in males (95% confidence interval (CI) 1.26-1.71). The reason behind this ratio is that most earning members of the family in our country are male, so the chance of injury is higher in this group. The female group is comparatively neglected, and they come late or do not even come to seek treatment.

Srinivasan *et al.*¹¹ studied 434 patients with fungal corneal ulcers. Among them, 8.1% were business people, 56.4% were farmers, 12% were homemakers, 2% were unemployed, 9% were students, and 3% were labourers. In our study, we found some differences. Here, 21% were business people, 26% were farmers, 32% were homemakers, 7% were service holders, 2% were unemployed, 9% were students, and 3% were labourers.

In our study, the leading cause of fungal corneal ulcers was ocular trauma. Among them, the most common cause was agricultural trauma (50%), and the treatment failure rate was 66% among this patient group. Bharathi *et al.*¹⁰ also identified the main cause

as an injury involving vegetative matter, which was 23.6 times (95% CI, 6.12-9.85) more likely. As an agricultural country, it is quite natural to be affected by vegetative matter. Both males and females are involved in agriculture-dependent work in rural areas. This may be the reason behind the high incidence of agricultural trauma, as well as the high incidence in rural areas. This causes an economic and social burden for an agriculture-dependent country like ours. Hence, proper attention should be paid to this population, and preventive measures should be taken. The treatment failure rate was 52.6% among patients treated with three drugs, and for patients treated with more than four, the rate was 43.5%. There was no significant difference between the person who instilled the drop – whether it was himself or other family members ($p>0.05$).

In this study, according to respondents, the most common causes of noncompliance were the frequency of medication use and the use of multiple medications (76%). A previous study showed a positive association between a dose frequency of more than twice a day and a dose frequency of twice a day or less.²¹ Studies conducted to validate the 8-item MMAS by showed excellent test-retest reliability scores.^{22,23} The study showed patients with multiple medications had the lowest compliance. Taylor *et al.*²⁴ revealed that switching medications less frequently is a factor that influences patient compliance. The study sample of Plakas *et al.*²² demonstrated intentional non-compliance, as the study population reported that they found taking their prescription inconvenient. A total of 97% of low-compliant patients feel that it is an inconvenience having to adhere to medications, while 77.6% choose not to take them, and 79.1% forget to take them. In the same way, 95.8% of people who adhere to medications feel that it's a trouble having to adhere to

them, 4.2% choose not to take them, and no one forgets to take them. Therefore, both in medium and low compliance (according to Morisky sub-scales) the most prevalent answer was that they feel it is a hassle to adhere to a medication plan. Dabaghian *et al.*²⁵ showed that 90% of participants had low or moderate compliance, and only 10% of patients reported high medication compliance. In our study, 33% of patients were found to be medium-compliant, and 67% were low-compliant; the treatment outcome significantly differed ($p=0.001$) between them.

In bivariate regression analysis, in the present study, level of education, place of residence, causes of noncompliance, type of trauma, and compliance were found to be associated factors for treatment failure among fungal corneal ulcer patients. In our study, after adjusting for all confounders, through multinomial logistic regression, patients' compliance and education status were found to be strong determinants of the treatment outcome for fungal corneal ulcers. Lower compliance patients were 4.4 times more prone to failed response to the drugs (OR: 4.408; CI: 1.47–13.26). According to the patients, multiple drugs and frequency of use were the main causes behind their noncompliance. Therefore, these factors should be given special consideration during management of fungal corneal ulcer.

Conclusion

As Bangladesh is an agriculturally dependent country, fungal corneal ulcers from plant injuries are common. Noncompliance with multiple medications leads to treatment failure. Compliance can be improved by reducing the frequency of other drugs, except for antifungal drugs, avoiding multiple unnecessary medications, educating patients properly about the significant necessity of compliance, especially, and

counselling them regarding the consequences of noncompliance. However, large-scale controlled studies with a pharmacometrics approach are needed to establish the clinical relevance of future research.

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