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ORIGINAL RESEARCH ARTICLE

A Study of Various Factors and Laboratory Investigations in Non-Healing Corneal Ulcer

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ABSTRACT

Introduction: Corneal ulcers are a major cause of visual morbidity, particularly in developing countries. While most ulcers heal with appropriate therapy, a subset becomes non-healing or refractory, posing significant diagnostic and therapeutic challenges. These ulcers are often associated with systemic comorbidities, microbial resistance, and impaired corneal healing mechanisms. This study was undertaken to evaluate the ocular and systemic factors contributing to non-healing corneal ulcers and to assess the role of laboratory investigations in guiding effective management.

Material and Methods: A prospective observational hospital-based study was conducted in the Department of Ophthalmology, SRMS Institute of Medical Sciences, Bareilly, Uttar Pradesh, over an 18-month period (May 2023–October 2024). Patients of all ages and genders presenting with non-healing corneal ulcers were included after informed consent. Cases with endophthalmitis or complicated corneal ulcers, such as perforation and descemetocele, were excluded. Detailed clinical evaluation, microbiological investigations (corneal scraping, bacterial and fungal cultures, antibiotic sensitivity testing), and systemic assessments, including glycemic status, were performed. Statistical analysis was carried out using the Chi-square test, with $p < 0.05$ considered significant.

Results: The mean age of patients with non-healing corneal ulcers was 42.5 ± 10.4 years, with a higher prevalence in the 41 to 60 year age group. Diabetes mellitus was the most significant systemic risk factor (56.3%, $p < 0.001$), followed by steroid use (28.7%, $p = 0.001$) and ocular trauma (41.4%, $p = 0.037$). A history of previous corneal surgery was significantly associated with non-healing ulcers ($p = 0.006$). Microbiological analysis revealed fungal growth in 55.2% and bacterial growth in 43.7% of non-healing ulcers, both significantly higher compared to healing ulcers. Corneal sensation was absent or reduced in 81.6% of non-healing cases ($p < 0.001$), indicating neurotrophic involvement. Elevated or reduced intraocular pressure was also significantly more common in non-healing ulcers ($p < 0.001$). Tobramycin demonstrated the highest antibiotic sensitivity, while resistance to ciprofloxacin was noted.

Conclusion: Early identification of risk factors, comprehensive microbiological evaluation, strict metabolic control, and individualized targeted therapy are essential to improve healing outcomes and prevent vision-threatening complications.

Keywords: Non-healing corneal ulcer, Refractory keratitis, Diabetes mellitus, Microbial keratitis, Neurotrophic keratopathy, Antibiotic sensitivity

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INTRODUCTION

Corneal ulcers represent a significant ophthalmic concern worldwide, contributing substantially to visual morbidity and preventable blindness, particularly in developing regions. These lesions, characterized by epithelial disruption and stromal inflammation, can arise from a broad spectrum of causes, including infections, trauma, immune-mediated diseases, and systemic conditions. While many corneal ulcers respond well to appropriate medical intervention, a notable subset remains refractory—termed non-healing or persistent corneal ulcers—posing substantial diagnostic and therapeutic challenges.[1]

The etiology of non-healing corneal ulcers is multifactorial. Intrinsic factors such as diabetes mellitus, autoimmune disorders, and neurotrophic keratopathy, along with extrinsic contributors like microbial resistance, environmental exposure, and delayed treatment, compromise the cornea's natural regenerative capacity. Additionally, conditions like dry eye disease, improper contact lens use, and previous ocular surgeries can exacerbate the risk of ulcer chronicity.[2]

Refractory corneal ulcers demand a nuanced approach that integrates detailed clinical evaluation, robust microbiological diagnostics, and a keen awareness of systemic comorbidities. Laboratory investigations, including corneal scrapings, microbial cultures, sensitivity testing, and autoimmune serologies, are pivotal in guiding targeted therapy. Furthermore, imaging modalities such as slit-lamp biomicroscopy and anterior segment OCT enhance diagnostic accuracy and monitoring.[3]

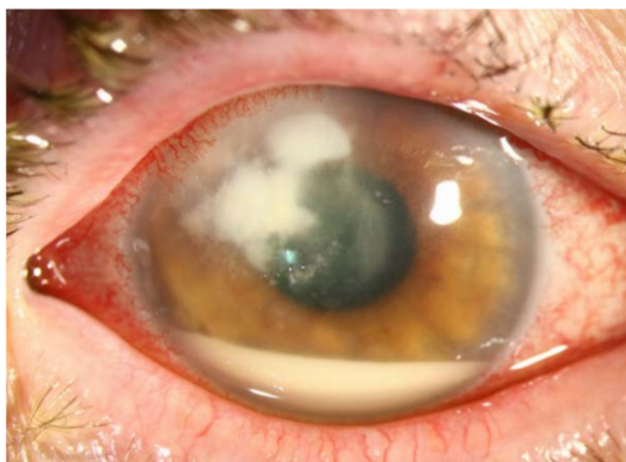

Figure 1: Fungal corneal ulcer

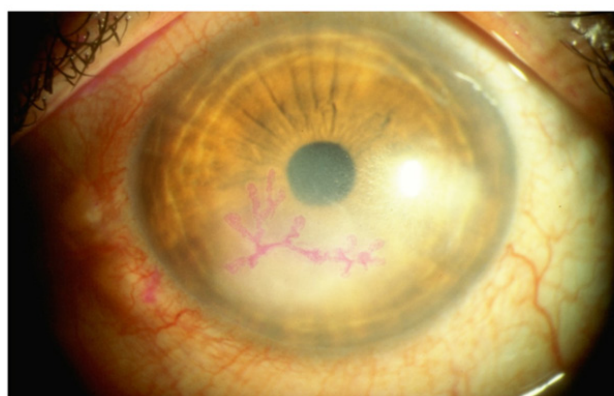

Figure 2: Viral corneal ulcer

Despite advances in antimicrobial therapies and supportive care, the outcomes in non-healing ulcers remain guarded due to the risk of complications such as scarring, neovascularization, secondary glaucoma, and corneal perforation. Therefore, understanding the diverse underlying mechanisms and contributing factors is essential for improving prognostic outcomes.[4,5]

This study aims to evaluate the various ocular and systemic determinants implicated in the persistence of corneal ulcers and assess the role of laboratory investigations in facilitating accurate diagnosis and effective treatment planning.

MATERIALS AND METHODS

A prospective observational hospital-based study was conducted in the Department of Ophthalmology, SRMS Institute of Medical Sciences, Bareilly, Uttar Pradesh, over a period of 18 months (1st May 2023–31st October 2024). Patients with non-healing corneal ulcer, irrespective of gender, age and socioeconomic background. Patients with corneal ulcer with or without affected visual acuity, consenting for the study and with a corneal ulcer, even if already on medications, were included.

Patients who were initially diagnosed with a case of endophthalmitis and with a complicated corneal ulcer, like perforation or descemetocele, were excluded.

Prior to commencing the study, approval was obtained from the institute's ethics committee. (SRMSIMS/ECC/2023/119)

RESULTS

Table 1 shows that the mean age of patients with non-healing ulcers (42.5 ± 10.4 years) was significantly higher than that of patients with healing ulcers (36.6 ± 6.1 years, $p < 0.001$). While healing and non-healing ulcers were nearly equal in the 21 to 30 age group, healing ulcers predominated at 31 to 40 years, and non-healing ulcers were more common above 50 years, suggesting older age as a risk factor for delayed healing.

Table 2 shows the association between risk factors and ulcer type. Smoking was not significantly associated ($p = 0.087$), while alcohol use ($p = 0.017$), steroid use ($p = 0.001$), diabetes ($p < 0.001$), and trauma ($p = 0.037$) were significantly linked to non-healing ulcers. Overall, smoking (8.0%) and alcohol use (9.2%) were uncommon, whereas steroid use (28.7%) and diabetes (56.3%) were more prevalent.

It also shows that a history of previous corneal surgery was significantly associated with non-healing ulcers (77.3 *vs*. 46.1%, $p = 0.006$). Overall, 12.6% of participants reported a history of surgery.

The use of contact lenses was not significantly associated with ulcer type ($p = 0.224$), with 60% of users having non-healing ulcers compared to 48.7% of non-users. The overall prevalence of contact lens use was 11.2%.

Microbial growth was significantly more frequent in non-healing ulcers. Bacterial growth was observed in 43.7% of non-healing vs. 27.6% of healing ulcers ($p = 0.027$), while fungal growth was found in 55.2 *vs*. 34.5%, respectively ($p = 0.006$).

Levered IOP was significantly more common in non-healing ulcers (36.8%) than in healing ulcers (16.1%), while normal IOP predominated in healing ulcers (66.7 vs. 28.7%). Reduced IOP was also more frequent in

Table 1: Age-wise distribution of patients with non-healing corneal ulcers

Age group (In Years)	*Frequency*	*Percent (%)*
21–30	18	20.7
31–40	19	21.8
41–50	22	25.3
51–60	28	32.2
Total	87	100.0
Age statistics (Mean ± SD)	42.5 ± 10.4	

Table 2: Characteristics of the patient population with corneal ulcer status

Parameter			*Total patients*	*Non-healing*		*Healing*		*p-value*
				N	*%*	*n*	*%*	
		Smoker	9	7	77.8	2	22.2	0.087NS
		Alcohol	9	8	88.9	1	11.1	0.017
Risk factors		Steroid use	33	25	75.8	8	24.2	0.001
		Diabetes mellitus	62	49	79.0	13	21.0	<0.001
		Trauma	59	36	61.0	23	39.0	0.037
H/O previous corneal surgery Absent		Present	22	17	77.3	5	22.7	0.006
		152	70	46.1	82	53.9		
Use of contact lens absent		Present	20	12	60.0	7	40.0	0.224NS
		154	75	48.7	80	51.3		
Bacterial growth absent		Present	62	38	43.7	24	27.6	0.027
		112	49	56.3	63	72.4		
Fungal growth absent		Present	78	48	55.2	30	34.5	0.006
		96	39	44.8	57	65.5		
Intraocular pressure	Elevated	46	32	36.8	14	16.1		<0.001
	Normal	83	25	28.7	58	66.7		
	Reduced	45	30	34.5	15	17.2		
Corneal sensation	Absent	76	46	52.9	30	34.5	<0.001	
	Normal	63	16	18.4	47	54.0		
	Reduced	35	25	28.7	10	11.5		

p-value by Chi-Square test. *p-value* <0.05 is statistically significant. NS – Statistically non-significant.

non-healing ulcers (34.5 *vs.* 17.2%), with all differences statistically significant ($p < 0.001$).

The Table also shows a significant association between corneal sensation and ulcer type ($p < 0.001$). Absent (52.9%) and reduced (28.7%) sensation were more common in non-healing ulcers, whereas normal sensation predominated in healing ulcers (54.0%).

DISCUSSION

This study presents a comprehensive analysis of patients with non-healing corneal ulcers, offering insight into demographic, clinical, microbiological, and morphological factors that may contribute to delayed healing.

The mean age of participants (42.5 ± 10.4 years) reflects a younger cohort compared to previous studies, which often focus on elderly populations with refractory ulcers.[6,7] This age distribution may reflect regional or referral biases and highlights the importance of age-specific preventive strategies. Gender distribution in our study was nearly equal, with a slight female predominance (51.7%), consistent with previous findings showing no strong gender predisposition for infectious keratitis.[8]

A significant rural predominance (66.7%) was observed, aligning with reports indicating higher corneal disease burden in underserved populations. Occupation played a vital role: farmers (33.3%) and laborers (16.1%) were most frequently affected, reinforcing occupational exposure as a major risk factor. Similar trends were reported by Srinivasan *et al.*, underlining the need for targeted education and eye protection in these groups.[9]

Diabetes mellitus was present in 56.3% of patients, underscoring its well-documented role in impairing corneal healing through delayed epithelial regeneration and compromised immune response. The mean HbA1c (6.5 ± 0.92%) indicates generally moderate glycemic control. However, recent evidence suggests that extremely tight control may not necessarily improve healing outcomes in ulcer-related complications, suggesting the need for individualized metabolic management.[10]

Steroid use was reported in 28.7% of cases. This is clinically significant given the immunosuppressive effects of corticosteroids, which may exacerbate infections and delay epithelialization.[8] Trauma was identified in 41.4% of participants, particularly vegetative (11.5%) and dust-related injuries (10.3%), with a notable portion (58.6%) reporting no history of trauma, indicating alternative etiologies such as neurotrophic or infectious causes.

Prior corneal surgery was documented in 19.5% of cases. Literature suggests that procedures like keratoplasty and refractive surgery can predispose to persistent ulcers, particularly when epithelial healing is compromised.[11] Although most patients in our cohort had no surgical history, this remains a critical consideration for post-operative monitoring.

Fungal pathogens were isolated in 44.8% of cases and bacterial agents in 43.7%, with co-infections observed in 82.8%—a striking finding that reflects the complexity and chronicity of these ulcers. This mirrors the results of Khanal *et al*. and Mselle *et al*., emphasizing the importance of dual-pathogen screening, especially in immunocompromised hosts.[12,13] Potassium hydroxide (KOH) mounts confirmed fungal elements in 49.4% of cases, underscoring its utility as a primary diagnostic tool, though sensitivity can be enhanced with adjunctive stains like calcofluor white.

Antibiotic susceptibility testing revealed variable resistance patterns: 21.8% of isolates were resistant to ciprofloxacin, 16.1% to moxifloxacin, and 12.6% to tobramycin. Nonetheless, over 60% of isolates remained sensitive to these agents, highlighting the importance of culture-guided therapy. Notably, tobramycin retained the highest sensitivity (70.1%).

Contact lens use was infrequent (14%), but remains a recognized risk factor for microbial keratitis, particularly with extended-wear lenses. Although the prevalence was low, the clinical vigilance for lens-related ulcers must remain high, especially in urban and younger populations.[14]

Corneal sensation was diminished in the majority of patients—52.9% had absent and 28.7% had reduced sensation—supporting a diagnosis of neurotrophic keratopathy in a large proportion. The role of corneal nerve integrity in wound healing is well documented, and therapies targeting nerve regeneration, such as recombinant human nerve growth factor (rhNGF), offer emerging promise.[15,16]

Elevated erythrocyte sedimentation rate (ESR) was found in 54% of patients, suggesting systemic inflammation. Intraocular pressure abnormalities were also frequent, with 36.8% exhibiting elevated and 34.5% reduced IOP, pointing to altered ocular physiology secondary to ulcerative processes or secondary glaucoma.

Lastly, the presence of slough (37.9%) in the ulcer bed is consistent with impaired wound healing and may signal the need for mechanical debridement. The mean fasting blood sugar level (134.3 ± 32.6 mg/dL) indicates borderline hyperglycemia, which, in combination with HbA1c levels, warrants close metabolic monitoring during treatment.

CONCLUSION

Non-healing corneal ulcers result from a complex interplay of demographic, systemic, and microbiological factors, with diabetes, trauma, microbial infections, and impaired corneal sensation playing central roles. Effective management requires a multidisciplinary approach focusing on glycemic control, targeted antimicrobial therapy, and regular monitoring, while further research into advanced therapeutic strategies is needed to improve patient outcomes.

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