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Does identification of the causal organism of corneal ulcers influence the outcome?

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PURPOSE. *To investigate whether identification of the causal organism in corneal ulcers influences their outcome.*

METHODS. *We retrospectively studied 114 patients, 72 males and 42 females aged 6-89 years, admitted to this eye clinic during the years 1994-2000 on account of an infectious corneal ulcer. Their examination included a detailed history, visual acuity measurement, and biomicroscopy in everyday follow-up. The ulcers were classified according to their severity and outcome. We assessed the cases where cultures had been done, reviewed the results, and searched for a possible correlation between the outcome and the fact of culturing the ulcer and identifying the causal organism.*

RESULTS. *Of the 114 corneal ulcers studied, 23 were mild, 49 moderate, and 42 severe. Fifty (44%) had not been cultured, but 64 ulcers (56%) had been cultured, with a positive result in 37 cases (58%),* Staphylococcus *and* Pseudomonas *species being the most common organisms found. In moderate and severe ulcers, there was a tendency to a higher proportion of successful outcome for cultured ulcers, but with no significant correlation.*

CONCLUSIONS. *Despite a tendency towards favorable results in culture-positive corneal ulcers, the influence of the detection of the organism on their outcome has not been proved. The role of the initial broad-spectrum antibiotic therapy remains important. (Eur J Ophthalmol 2003; 13: 11-7)*

KEY WORDS. *Infectious keratitis, Corneal ulcer, Culture, Sensitivity, Organism, Empirical therapy*

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INTRODUCTION

The corneal epithelium is an important barrier to the invasion of microbes into the eyeball and is considered more resistant to infectious attack than the conjunctival epithelium (1). A few organisms, like *Pseudomonas aeruginosa*, can pass through the corneal epithelium. Despite this defence, however, infectious keratitis is still common in most parts of the world (30,000 new cases per year in USA (2)) and is potentially vision-threatening if it is not treated properly, in good time.

In comparison with the past, the ophthalmologist has nowadays two important weapons to help treat infectious keratitis. First, better diagnostic tools – smears, cultures, antibiotic sensitivity tests – to identify the causal organism; and second, more efficient antibiotics, despite the continuous development of resistance (3-5).

On the other hand, the ophthalmologist has to face two enemies: time (any delay in starting the medication could worsen the prognosis); and cost of laboratory investigations and latest-generation antibiotics, for both the patient and the health system. Thus, since many ophthalmologists are not willing to follow written guidelines about the need for laboratory tests in treating corneal ulcers (2, 6), culturing specimens in

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order to identify the causal organism needs to be compared to the strategy of empirical antibiotic therapy.

In this study we investigated the utility of detection of the responsible organism in relation to the outcome of infectious corneal ulcers.

MATERIALS AND METHODS

We retrospectively studied 114 consecutive patients, admitted to the Department of Ophthalmology of the University of Patras in Greece during the years 1994-2000 on account of an infectious corneal ulcer. Viral ulcers were not included. The patients were 72 males (63%) and 42 females (37%). Their age was 6-89 years (mean 56); 63 lived in rural areas (55%) and 51 (45%) in urban zones.

Their examination included a detailed history, visual acuity measurement, and biomicroscopy in everyday follow-up. Our assessment of the outcome of the corneal ulcers was based on the appearance of the eye on the first and last day in hospital.

The ulcers were classified according to their severity as mild, moderate and severe. The classification criteria were location, extent, depth and the severity of inflammation of the anterior segment (Tab. I). We then assessed the ulcers for which pretreatment cultures had been done, taking into account the results of the cultures (positive or negative, and which organisms).

When ulcers had been cultured, a Kimura spatula had been used to obtain corneal scrapings for Gram and Giemsa staining and for culture and antibiotic sensitivity testing. Culture specimens had been directly plated onto blood agar, chocolate agar, and Sabouraud agar, and into thioglycolate broth. Antibiotic sensitivities were tested by the Kirby-Bauer method. All microbiological tests were done by the Laboratory of Microbiology of the University of Patras in Greece.

All patients had been initially treated with broad-spectrum antibiotics, including a combination of a fortified tobramycin eye solution (15 mg/ml) with a fortified vancomycin hydrochloride eye solution (25 mg/ml), at an hourly dose of one drop for moderate and severe ulcers, and fewer doses for mild ulcers. Wherever appropriate, judging from the patient's history or the clinical presentation of the ulcer, we also used an antifungal or/and a cycloplegic solution. Any change in the initial treatment was recorded: changes were made when no improvement was obvious after three days of therapy, or when suggested by the antibiotic sensitivity results.

The ulcers were classified according to the outcome. Successful outcome was defined as the healing of the ulcer with disappearance of the epithelial defect within two weeks of beginning treatment.

Finally, we searched for any correlation between the outcome and the fact of culturing the ulcers and identifying the causal organisms. Statistical analysis was done with the X_2-test with Yates' correction. Differences at the level of $p<0.05$ were considered statistically significant.

RESULTS

Following the criteria set out in Table I, of the 114 corneal ulcers studied, 23 (20.2%) were mild, 49 (43.0%) moderate, and 42 (36.8%) severe. Hospital stays ranged from 3 to 40 days (mean 13 days). In 35 patients (30.7%) there had been a recent injury of the affected eye, 25 (21.9%) were contact lens wearers, 3 (2.6%) presented a history of bullous keratopathy, and 1 (0.9%) had had a corneal transplant. In the remaining 50 patients (43.9%) the history was ambiguous as regards the predisposing factor of their corneal infection (Tab. II).

Of the 114 ulcers, 50 (43.9%) had not been cultured and were treated with the empirical therapy described above. Culture was more frequently not done for the mild cases (15/23, 65.2%) than for the moderate and severe ones (35/91, 38.5%). The remaining 64 ulcers (56.1%) were cultured, and the result was positive in 37 and negative in 27 (Tab. III).

Of the 114 patients studied, 33 (28.9%) were already receiving topical antibiotic therapy but at too low doses (tobramycin in 18 patients and ciprofloxacin in 15 patients). In 14 of these 33 patients (42.4%), the ulcer was cultured after treatment had been stopped for 6 hours. Once the specimens had been taken, these 14 patients were given an empirical topical broad-spectrum antibiotic therapy, as above. Cultures were positive in 8 of these 14 patients (57.1%). In the other 19 patients whose ulcers were not cultured, treatment was interrupted, and they were also given topical broad-spectrum antibiotics thereafter, like the rest of the patients.

At everyday follow-up, the clinical course of each corneal ulcer was evaluated and, when necessary, treatment was modified. Thus, of the 50 ulcers which were not cultured, modification of the treatment was deemed necessary for 12 (24.0%), and 5 of these (41.6%) had a successful outcome. Treatment was also modified in cases with positive cultures, in the light of the Gram and Giemsa staining results, and the identification of the causal organism. Of the 37 corneal ulcers with a positive culture, modification of the treatment was necessary following the results of the cultures in six patients (16.2%), either because of the development of fungi or acantamoeba, or proven resistance of the isolated organism to the initial empirical therapeutic regimen. Four of these six patients (66.7%) had a successful outcome.

The organisms isolated are presented in Table IV. *Staphylococcus* and *Pseudomonas* species were the most common. Table V shows the outcome of the corneal ulcers in each group (mild, moderate, severe) in relation to whether a culture had been done, and whether the results were positive or negative.

Statistical analysis showed no correlation for mild corneal ulcers between the outcome and whether the ulcers had been cultured or not. For the moderate and particularly for the severe ulcers, there was a higher proportion of improvement and successful outcome for those with a positive culture, although the differ-

TABLE I - CLASSIFICATION OF INFECTIOUS CORNEAL ULCERS

	Mild	**Moderate**	**Severe**
Location	Non axial	Central or peripheral	Central or peripheral
Area (size)	< 2 mm	2-6 mm	> 6 mm
Depth in cornea	Outer 1/3	Outer 2/3	Extension to the inner 1/3
Inflammation of anterior segment	Mild	Moderate exudation to fibrosis	Severe. Hypopyon.

TABLE II - OPHTHALMIC HISTORY RELATED TO THE CORNEAL ULCER

Ophthalmic predisposing factors	**No. cases**	**%**
Recent injury	35	30.7
Contact lens wear	25	21.9
Bullous keratopathy	3	2.6
Corneal transplantation	1	0.9
Ambiguous history	50	43.9
Total	114	

TABLE III - SEVERITY OF CORNEAL ULCERS WITH/WITHOUT CULTURES

	Mild	**Moderate**	**Severe**	**Total**
Not cultured	15	21	14	50 (43.9%)
Positive culture	4	16	17	37 (32.4%)
Negative culture	4	12	11	27 (23.7%)
Total	23	49	42	114

ence did not reach statistical significance (p>0.1).

It also appeared that ulcer size influenced its outcome. In ulcers bigger than 6 mm the outcome was successful only for 61.9%, whereas for the rest the proportion was 95.9%. Age did not seem to influence the outcome. The mean age of patients with ulcers >6 mm who had a successful outcome was 67 years, and the mean age of those with an unsuccessful outcome was 65 years.

DISCUSSION

This study investigated the significance of the detection of the causal organism in relation to the outcome of corneal ulcers in our eye clinic during the last seven years. The need for this study had arisen from the high prevalence of infectious keratitis in the general population (2), and from the potential risks of late or wrong treatment (2, 7). The devastating con-

TABLE IV - ORGANISMS ISOLATED

Organism	No. single cases	No. mixed cases	Total	%
Staphylococcus	10	2	12	29.3
- *aureus*	6	1	7	
- coagulase (-)	4	1	5	
Pseudomonas aeruginosa	10	2	12	29.3
Streptococcus	5	-	5	12.2
- group D	2	-	2	
- pneumoniae	2	-	2	
- viridans	1	-	1	
Candida albicans	3	1	4	9.8
Serratia spp	2	1	3	7.3
Proteus spp	2	-	2	4.9
Nocardia	1	-	1	2.4
Enterobacter aglomerans	-	1	1	2.4
Acantamoeba	-	1	1	2.4
Total	33	8	41	

TABLE V - OUTCOME OF MILD, MODERATE, AND SEVERE ULCERS, WITH/WITHOUT CULTURES

	Successful	Unsuccessful	Total cases
Mild ulcers *	23 (100.0%)	-	23
Not cultured	15 (100.0%)	-	15
Positive culture	4 (100.0%)	-	4
Negative culture	4 (100.0%)	-	4
Moderate ulcers †	45 (91.8%)	4 (8.2%)	49
Not cultured	18 (85.7%)	3 (14.3%)	21
Positive culture	16 (100.0%)	-	16
Negative culture	11 (91.7%)	1 (8.3%)	12
Severe ulcers ‡	26 (61.9%)	16 (38.1%)	42
Not cultured	7 (50.0%)	7 (50.0%)	14
Positive culture	13 (76.5%)	4 (23.5%)	17
Negative culture	6 (54.5%)	5 (45.5%)	11
Total	94 (82.5%)	20 (17.5%)	114

*=p>0.1, X_2 with Yates' correction; †=p>0.1, X_2 with Yates' correction; ‡=p>0.1, X_2 with Yates' correction

sequences for vision of late or inappropriate treatment, particularly in severe corneal ulcers created by fast-invading microbes (e.g. *Pseudomonas*) is not unknown to most ophthalmologists.

The fundamental treatment of infectious corneal ulcers is certainly antibiotics, either as a cause-directed therapy after identifying the organism and testing its sensitivity, or as an empirical therapy without searching for the responsible organism (1). In the latter case, medicines are selected on the basis of the patient's history, the morphological details of the ulcer, and the rapidity of the progression of the lesions, aiming at the treatment of a broad spectrum of microbes as fast as possible. In our series, the patient's history was revealing about how the ulcer had developed in 56.1% of the cases (Tab. II).

Today the ophthalmologist is in a better position to treat a corneal ulcer than in the past. There are more reliable and sophisticated methods of detecting the microbes, making the possibility of their discovery higher. There are also newer antibiotics with a broader spectrum, covering far more cases, especially if used in combination (6, 8).

In our series, slightly more than half the ulcers had been cultured (64 out of 114, 56.1%). Mild ulcers had more frequently not been cultured (65.2%) than moderate and severe ones (38.5%). The ulcers had been cared for by different ophthalmologists, whose belief about the utility of cultures tended to vary, and whose opinions about the possible organisms involved often differed too. Thus, the initial management of the ulcers had not been uniform. This has been routinely mentioned in the medical literature.

In a study conducted in California in 1992 (9), McDonnell et al reported that in the series of patients studied only 50% of the corneal ulcers were cultured, and in only 60% of them was the culture done in accordance with official guidelines.

Three years later, in 1995 (10), McLeod and DeBacker sent a questionnaire to 300 ophthalmologists in USA to assess current practice in the treatment of infectious keratitis. The main questions were: first, whether they had access to the necessary equipment for culturing a corneal ulcer; and second, what would be their diagnostic and therapeutic procedure for a presumed mild and a presumed severe corneal ulcer. Of the 124 ophthalmologists who answered, only half had access to facilities for culturing a corneal ulcer. In response to the second question, 56% of the ophthalmologists said they would treat the mild ulcer without a culture, and 13% would treat even the severe ulcer without a culture.

Therefore, as McDonnell says in 1996 (6), in everyday clinical practice a large proportion do not follow the guidelines published in books and articles recommending the detection of the responsible organism in all corneal ulcers. McDonnell therefore wonders whether the ophthalmologist should always do microbiological tests on corneal ulcers, with the related cost and delay, or whether the cautious selection of the appropriate antibiotics with a high possibility of success according to the literature would be enough.

Kowal et al in 1997 (11), in a preliminary study, assessed the clinical importance of antibiotic sensitivity testing in the management of corneal ulcers, concluding that antibiotic sensitivity testing does not provide clinically useful information. In agreement with that, McLeod (4) explains that frequently an antibiotic proves to be clinically effective in eliminating a corneal infection even though the organism is reportedly resistant, and that ulcers may worsen even when testing says the organism is sensitive.

Other authors suggest that cultures should be done for more severe ulcers or centrally located ones (2, 12, 13). Yet others stress the need to culture all ulcers, like Levey et al (14), who showed the significant utility of cultures in the treatment of 119 consecutive ulcers in a retrospective study, in contrast with cultures from the conjunctiva or the eyelids. Rodman et al (8) advise cornea specialists to culture most corneal ulcers. McLeod and DeBacker (10) also point to the increase in the cost of treating corneal ulcers in cases where empirical therapy fails.

In our study, as shown in Table V, the outcome of the mild ulcers was 100% successful, regardless of whether a culture was done or not. In moderate and, particularly, in severe ulcers, successful outcomes were more frequent when cultures were done, but the difference was not statistically significant.

Among the microbes isolated, the most common were *Staphylococcus* and *Pseudomonas* species in equal proportions. In many studies (2, 7, 15), the most commonly isolated microbe is *Staphylococcus* (43-57%), and *Pseudomonas* follows (15-22%). However, Wang et al in 1998 (16) found *Pseudomonas* was

the most common in their series (34%) and *Staphylococcus* followed (24%). In Forster's study in Miami (12), *Pseudomonas aeruginosa* accounted for 20% of the bacterial isolates. In 1996 (17), van Bijsterveld and Jager reported that *Pseudomonas* was isolated in 25% of the cultures of corneal ulcers caused by improper use of contact lenses and only 11% of cultures were due to other causes. In our series, eight of the 12 ulcers with *Pseudomonas* were in contact lens wearers, and the other four were due to other causes.

Fungi were isolated in only four ulcers. In fact, even in areas with a warm climate and rural population, which are favorable to the development of fungi, bacteria prevail in cultures of corneal ulcers (69.1% according to McLeod) (2).

Prior-to-referral antibiotic therapy, if it is stopped for 6 hours before culturing the ulcer, does not seem to alter the percentage of positive cultures. In our series, cultures were positive in 37 of the 64 ulcers (57.8%). Of these 64, 14 had already received antibiotics at inadequate doses before the patients were initially referred to our eye clinic, and the remaining 50 had had no therapy. Cultures were positive in eight of the 14 inadequately treated ulcers (57.1%) and in 29 of the 50 non-treated ones (58.0%). Thus the before culture antibiotic therapy, having been interrupted for 6 hours, did not influence the results of the cultures.

The role of the initial empirical therapy of the corneal ulcers remains important. An inappropriate initial therapy may not manage to eliminate the microbe that caused the lesion, as shown by the high percentage of positive cultures (73.86%) in a hospital-based study of patients who had already received empirical therapy before admission to hospital, in India (7). None of those patients had been given a fortified broad-spectrum antibiotic, and those patients who had been given fluoroquinolones had received too low a dose.

The most commonly suggested initial empirical therapies aiming at a high rate of control of the infection include fluoroquinolones (2, 6) and combinations of a fortified aminoglycoside + cephalosporin (2) or a fortified aminoglycoside + vancomycin. Donnenfeld reports an equivalent efficacy for ciprofloxacin ophthalmic solution 0.3% and fortified tobramycin + cefazolin in treating bacterial corneal ulcers (18). The initial empirical therapy in our protocol was fortified tobramycin + vancomycin in frequent instillation, occasionally associated with antifungal solutions in cases of suspected fungi.

The lack of adoption of uniformly acceptable and applicable antibiotic therapies has led to the emergence of many resistant species . Examples are the resistance of *Streptococcus pneumoniae* to fluoroquinolones, *Pseudomonas* to gentamicin (3, 5), but also the predominance of vancomycin upon Gram+ species, such as the methicillin-resistant *Staphylococcus aureus* (1). Also important is the tendency of many ophthalmologists to treat the milder and the more severe ulcers with different empirical therapies (10).

A larger ulcer and previous ophthalmic disease appeared to have a negative influence on the outcome of the corneal ulcers (in ulcers >6 mm improvement appeared only in 61.9%, compared to 95.9% in the rest). The size of the ulcer has been reported as a risk factor (19, 20), and so has advanced age in large ulcers (21), which, however, did not seem to influence the outcome in our study.

In conclusion, although there appeared to be a tendency to better results in culture-positive corneal ulcers, the influence of identification of the responsible organism on their outcome was not proved. As this question still arouses much debate, a prospective study of infectious corneal ulcers is needed. Standard initial empirical antibiotic therapy, clarification of when to modify the initial therapy, and how its results correlate with cultures, would be of great value. *Staphylococcus* and *Pseudomonas* species prevailed in cultures. Large ulcers and previous eye disease were adverse prognostic factors. Last but not least, the role of the initial empirical antibiotic therapy is clearly important.

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