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The Clinical Diagnosis of Microbial Keratitis

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Abstract

Purpose— To evaluate the ability of ophthalmologists to predict the laboratory results of presumed microbial keratitis and to explore which findings might influence diagnostic prognostication.

Design—Prospective cross-sectional study.

Methods— Fifteen ophthalmologists completed study forms at the initial presentation of patients with presumed microbial keratitis. After predicting the category of microbial recovery, clinicians submitted corneal scrapings for masked laboratory processing. The relative effects of ocular inflammatory signs on correct microbial diagnosis were explored with Poisson regression.

Results— Clinical examiners correctly predicted the presence or absence of microbial recovery in 79 (76%) of 104 ulcerative keratitis and successfully distinguished among bacterial, fungal, and amoebic keratitis for 54 (73%) of 74 culture-positive infections, although only 31 (42%) were properly subcategorized. The positive predictive value of clinical diagnosis was 65% (95% confidence interval (CI), 43%–84%) for 20 eyes with *Pseudomonas* keratitis, 48% (95% CI, 32%–63%) for 38 other bacterial keratitis, 45% (95% CI, 17%–77%) for 13 fungal keratitis, and 89% (95% CI, 52%–100%) for nine *Acanthamoeba* keratitis. The recognition of *Pseudomonas* keratitis was significantly improved by the occurrence of a larger infiltrate ($P = .02$), and correctly predicting *Acanthamoeba* keratitis was enhanced by observing a ring infiltrate ($P < .001$). Antimicrobial use before referral significantly attenuated clinical diagnosis ($P = 0.03$) and hampered microbial recovery ($P = 0.004$).

Conclusions— Established *Pseudomonas* keratitis and *Acanthamoeba* keratitis can be suspected before laboratory confirmation, but overlapping inflammatory features and recent empiric antimicrobial treatment limits etiologic recognition of most microbial corneal infections.

The clinical diagnosis of microbial keratitis often relies on a history of infectious exposure and the morphological features of corneal inflammation.[1] Ophthalmologists use clinical clues to recognize ocular surface infection,[2] and some distinctive though not pathognomonic signs may help to differentiate bacterial, fungal, and amoebic pathogens of the cornea.[3–5]

Laboratory demonstration of the infective agent in a corneal sample is recommended[6] but may not be regularly obtained due to time, cost, and availability.[7, 8] Initial antimicrobial therapy is often guided by subjective interpretation of presenting clinical features.[9] We aimed to determine the predictive value of ophthalmologists' opinions about presumed microbial keratitis before microbiological tests were known. We also sought to identify which findings

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of the history or examination might affect provisional judgments about responsible microorganisms.

METHODS

After obtaining institutional review board approval, selected faculty, cornea fellows, and senior ophthalmology residents gave written consent to complete a survey instrument immediately before performing a diagnostic corneal scraping when encountering a patient with presumed microbial keratitis for whom laboratory evaluation was planned. The proforma required an opinion about the most likely infective etiology, selected from a list of microorganisms that consisted of staphylococci, *Streptococcus pneumoniae*, viridans streptococci, *Pseudomonas aeruginosa*, other gram-negative rods, nontuberculous *Mycobacterium*, *Nocardia*, *Candida*, *Fusarium*, other filamentous fungi, and *Acanthamoeba*. Predisposing risk factors, recent antiinfective and corticosteroid use within the preceding four days, and duration of symptoms were recorded. Examination findings were summarized by the size, type, location, and depth of ocular inflammation and corneal ulceration. The reticule of the slit-lamp biomicroscope was used to measure the longest diameter of the inflammatory infiltrate and its perpendicular, and the elliptical area was calculated from these dimensions. Completed surveys were prospectively collated.

Corneal scrapings were obtained under topical anesthesia with a sterile spatula for direct preparation of laboratory materials.[10] Slides for gram and acridine orange stains were prepared. Specimens were directly inoculated to sheep blood and chocolate agar plates, inhibitory mould agar with gentamicin slant, and thioglycollate broth (BBL, Becton Dickinson, Sparks, MD). A buffered charcoal-yeast extract agar plate and Löwenstein-Jensen medium slant were used at the ophthalmologist's discretion. Smeared slides and inoculated media were processed by the hospital microbiology laboratory that was not informed about the clinicians' differential assessment. Isolates were identified by conventional biochemical methods or commercial identification kits. Fungi were corroborated at a reference mycology laboratory. Microbial keratitis was judged to be confirmed if the same microorganism was recovered from two separate culture media or if microbial growth was congruent with the paired smear.

The predicted etiology was compared with the principal laboratory isolate as the reference standard. Sensitivity, specificity, and predictive values were estimated with exact binomial confidence intervals (CIs) for any confirmed microbial recovery and for bacterial, fungal, and protozoal strata. Categorical signs were compared using Fisher's exact test, and continuous variables were compared using a *t*-test or an equality-of-medians test. The effect of categorized risk factors and clinical signs on making a correct clinical diagnosis was explored with robust Poisson regression using Intercooled Stata version 9.[11] Statistical significance was set at $P < .05$.

RESULTS

Survey forms were completed for 104 unilateral cases of ulcerative keratitis from July 2004 through April 2006 at three eye clinics in one medical center. Fifty-two (50%) corneal scrapings yielded bacteria, 13 (12.5%) grew fungi, 9 (9%) yielded *Acanthamoeba*, and 30 (29%) had no growth (Table 1). Sixty-eight (92%) of 74 culture-positive cases were correctly predicted to have any microbial recovery, and 15 (75%) of *P. aeruginosa* infections and 8 (89%) of *Acanthamoeba* infections had these isolates correctly predicted.

The sensitivity of smear evaluation was 34% (95% CI, 23%–46%) among 71 culture-positive eyes that had corneal scrapings processed for light microscopy, and the positive predictive value of stained smears was 100% (95% CI, 74%–100%). The median duration of symptoms

was four days (25% and 75% quartiles, 3 and 10 days). Contact lenses were worn in 23 bacterial keratitis, 6 fungal infections that were each associated with ReNu products (Bausch & Lomb, Rochester, NY), and 9 *Acanthamoeba* infections. Among 61 patients using an antimicrobial medication at presentation, 46 (75%) used a fluoroquinolone, 13 another antibacterial, one an antifungal, and one an antiamebic agent. Recent antimicrobial therapy occurred in 37 (50%) of 74 culture-positive eyes and 24 (80%) of 30 culture-negative eyes ($P = .004$).

Eighty-nine (86%) survey forms were completed by corneal specialists, and 15 (14%) by senior ophthalmology residents. Faculty did not differ from residents in correctly predicting culture positivity ($P = 0.81$). Clinicians correctly classified culture-positive and culture-negative keratitis in 79 (76%; 95% CI, 67%–84%) eyes. The sensitivity, specificity, positive predictive value, and negative predictive value for the clinical diagnosis of any culture-confirmed corneal infection were 92% (95% CI, 83%–97%), 37% (95% CI, 20%–56%), 78% (95% CI, 68%–86%), and 65% (95% CI, 38%–86%), respectively.

Clinicians correctly distinguished the microbial kingdom for 54 (73%) of 74 culture-positive infections, including 41 (79%) of 52 bacterial keratitis, 5 (38%) of 13 fungal keratitis, and 8 (89%) of 9 amoebic keratitis and correctly categorized 11 (37%) of 30 sterile infiltrates that had corneal scrapings (Figure). Duration of symptoms of 4 days or less, the lack of recent antimicrobial treatment, and the presence of a ring infiltrate significantly improved clinical prediction of bacterial, fungal, amoebic, or sterile keratitis (Table 2).

Correct clinical prediction of microbial etiology varied among microbial categories. The probability of a particular category of infection following a positive clinical diagnosis was greater for *Pseudomonas* keratitis and for *Acanthamoeba* keratitis than for other bacterial or fungal infections (Table 3). The correct clinical diagnosis of *Pseudomonas* keratitis occurred 2.96 (95% CI, 1.14–7.68) times more often when the infiltrate area exceeded 8 mm^2 ($P = .026$). The correct prediction of *Acanthamoeba* keratitis occurred 23.1 (95% CI, 6.86–77.8) times more often when a ring infiltrate was present ($P < .001$).

Thirty-one (42%) of 74 culture-positive infections had the bacterial genus, fungal category, or *Acanthamoeba* correctly predicted. Misdiagnoses included one candidal keratitis that was clinically suspected to be staphylococcal, one *Staphylococcus aureus* keratitis clinically diagnosed as candidal, two filamentous fungal infections thought to be pseudomonal, four *Serratia marcescens* keratitis diagnosed as staphylococcal, one *Nocardia* keratitis predicted to be fungal, one *Eikenella* keratitis diagnosed as *Pseudomonas* keratitis, and 3 cases of coagulase-negative staphylococcal keratitis suspected to be sterile.

DISCUSSION

We studied the predictive value of clinical decision-making in the evaluation of ulcerative keratitis. At presentation, clinicians could often distinguish infected eyes from sterile infiltrates, but the use of topical antibiotics before corneal specimen collection made this judgment more difficult. Because the majority of patients with ulcerative keratitis referred for diagnosis and management were already using antibiotics, provisional determination and rapid laboratory confirmation of the etiology of microbial keratitis were problematic.[12]

Ophthalmologists were reasonably good at identifying *Pseudomonas* keratitis, apparently by recognizing the association of a large suppurative infiltrate with gram-negative bacterial infection.[13] Several amoebic infections presented with a stromal ring infiltrate resulting in a high sensitivity and specificity for diagnosing advanced *Acanthamoeba* keratitis.[5] In contrast, the predictive values for clinically classifying other bacterial or fungal keratitis were modest. The proportion of correctly predicted fungal infections was less than expected,[1] and we doubt that clinical features could dependably replace laboratory investigation of keratomycosis.[13]

While the occurrence and type of corneal infection could often be discerned, less than half had bacterial genus, fungal category, or *Acanthamoeba* correctly predicted.

Several limitations could affect the validity of our findings. Our study took place at a subtropical referral center that treated a range of corneal infections including unusual bacterial isolates such as *Pseudomonas oryzihabitans* and *Kingella denitrificans* and uncommon fungal pathogens such as *Verticillium*.[14] Enrollment also occurred during an apparent national resurgence of *Acanthamoeba* keratitis[15] and in the course of an international epidemic of *Fusarium* keratitis associated with contact lens wear.[16] As we included both primary care and referral clinics, the results may have been affected if atypical or nonresponsive infections were more difficult to recognize and to classify. The findings could have been biased in the opposite direction if progressive infections were not referred until distinctive features materialized. For example, the majority of cases of *Acanthamoeba* keratitis had a ring infiltrate, but this finding is often not seen in the early stage of infection when laboratory investigations may be a better indication for starting treatment. Since this study blends several levels of referral patterns the results should be generalized with caution. Expanding this study to other locations could perhaps reveal other attributes that affect ophthalmologists' clinical decision-making.

Despite these shortcomings, we believe that our experience shows the complementary roles of clinical and laboratory evaluation. The good specificity for recognizing several corneal infections should encourage ophthalmologists to communicate their preliminary diagnostic suspicions to microbiologists. However, clinical examination cannot be the only basis for deciding how to treat suspected microbial keratitis. Beginning empiric antimicrobial therapy without laboratory evaluation may delay correct diagnosis and proper care if improvement does not promptly take place. The microbiological identification of specific microbial isolates is a more reliable guide for the individualized treatment of microbial keratitis.

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Biography

Matthew A. Dahlgren, MD is in private practice at Milwaukee Eye Care Associates in Milwaukee, Wisconsin. He received his medical degree from the Medical College of Wisconsin in 2001, and was elected to Alpha Omega Alpha. His residency training in ophthalmology was at the Cullen Eye Institute at Baylor College of Medicine, where he also served as chief resident. Afterwards, he completed a fellowship in cornea and anterior segment surgery at the University of Minnesota.

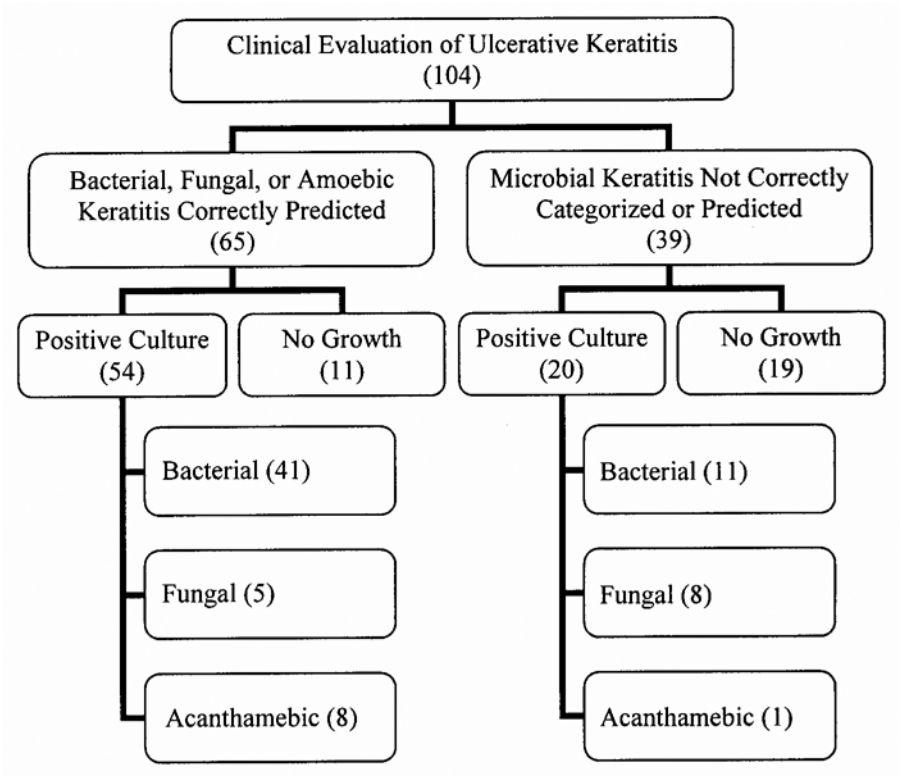

FIGURE.
Ophthalmologists' ability to predict the presence and type of microbial recovery from presumed microbial keratitis.

TABLE 1

Microbial Recovery from Corneal Scrapings and Clinical Prediction of Corneal Isolates

Principal Corneal Isolate	No.	No. isolates in category (n = 104)	No. category correctly predicted (n = 46)	No. kingdom correctly predicted (n = 65)	No. growth correctly predicted (n = 79)
Pseudomonas aeruginosa	20	20	15		
Other gram-negative rods					
Achromobacter sp.	1				
Eikenella corrodens	1				
Enterobacter cloacae	1				
Kingella denitrificans	1	10	2		
Pseudomonas oryzihabitans	1				
Serratia marcescens	4				
Stenotrophomonas maltophilia	1			41*	
Gram-positive cocci					
Staphylococcus aureus	7				
Coagulase-negative staphylococci	7	16	5		
Streptococcus pneumoniae	1				
Streptococcus sp.	1				
Other gram-positive or acid-fast bacteria					
Corynebacterium sp.	1				
Mycobacterium abscessus	1	6	0		
Nocardia sp.	1				
Propionibacterium acnes	3				68†
Filamentous fungi					
Acremonium sp.	1				
Aspergillus flavus	1				
Bipolaris sp.	1				
Curvularia sp.	2	12	5		
Exophiala spinifera	1				
Fusarium sp.	5			5	
Verticillium sp.	1				
Yeast					
Candida albicans	1	1	0		
Acanthamoeba	9	9	8	8	
No growth	30	30	11	11	11

* Total exceeds sum of preceding column because all bacterial species were considered equivalent, as noted in the Figure.

† Total of positive growth exceeds sum of preceding column because any suspected infection, regardless of predicted etiology, was included in overall growth prediction.

TABLE 2

Relative Effect of Risk Factors and Clinical Signs on Correctly Predicting Bacterial, Fungal, Amoebic, or Sterile Keratitis

Characteristic	No. (%) (n = 104)	Risk Ratio (95% Confidence Interval)	*P* Value
Symptomatic duration ≤ 4 days	53 (51%)	1.64 (1.19–2.28)	.003
Contact lens wear	55 (53%)	1.18 (0.87–1.60)	.30
Prior corneal disorder or injury	38 (51%)	0.87 (0.64–1.18)	.37
No recent antimicrobial use	43 (41%)	1.38 (1.03–1.84)	.032
Recent corticosteroid use	36 (35%)	0.84 (0.60–1.18)	.31
Epithelial defect	91 (87%)	1.02 (0.64–1.61)	.94
Central corneal infiltrate	60 (58%)	0.97 (0.72–1.31)	.84
Area of corneal infiltrate > 4 mm^2	50 (48%)	1.11 (0.83–1.50)	.48
Stromal infiltrate of deeper third	23 (22%)	0.88 (0.59–1.31)	.53
Stromal ulceration > one third depth	22 (21%)	0.76 (0.49–1.19)	.23
Multifocal stromal infiltrates	23 (22%)	0.80 (0.52–1.22)	.29
Ring stromal infiltrate	7 (7%)	1.41 (1.00–1.99)	.050
Inflammatory endothelial plaque	13 (12%)	0.71 (0.39–1.31)	.27
Hypopyon	26 (25%)	1.06 (0.76–1.48)	.72

TABLE 3

Diagnostic Performance of Clinical Prediction for Categories of Microbial Keratitis

Diagnosis	Sensitivity (95% CI)	Specificity (95% CI	Positive predictive value (95% CI	Negative predictive value (95% CI
Pseudomonal keratitis	75% (51%–91%)	90% (82%–96%)	65% (43%–84%)	94% (86%–98%)
Other bacterial keratitis	66% (47%–81%)	68% (56%–79%)	48% (32%–63%)	82% (70%–90%)
Fungal keratitis	38% (14%–68%)	93% (86%–97%)	45% (17%–77%)	91% (84%–96%)
Acanthamoeba keratitis	89% (52%–100%)	99% (94%–100%)	89% (52%–100%)	99% (94%–100%)

CI, confidence interval.