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A Review of the Categorizations of Mild, Moderate, and Severe Bacterial Keratitis Ulcers and Day-1 Treatment Regimen When Using the Topical Fluoroquinolones 0.3% Ciprofloxacin and 0.3% Ofloxacin

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ABSTRACT

Background: There are published suggestions that bacterial keratitis (BK) can be classified as mild, moderate, or severe and that the day-1 antibiotic drop regimen may differ for each category using the topical second-generation fluoroquinolones 0.3% ciprofloxacin and 0.3% ofloxacin (2FQ). The classification criteria are not consistently defined and the suggested regimens are often unreferenced and so here, the evidence base for applying such regimens in clinical practice is examined.
Objective: To examine the evidence base regarding the categorization criteria used for BK and determine whether any evidence exists to support suggestions that different day-1 treatment regimen using the 2FQ may be applied based on any assigned categorization.
Methods: The literature on BK treatment was reviewed, as were the clinical studies involving the commercially available 2FQ. All statements pertaining to classification and treatment paradigms involving BK were then collated and reviewed, as were the methodologies employed in the 2FQ clinical studies.
Results: There have been no clinical trials using the 2FQ, or indeed any other topical antibiotics, which have used different day-1 drop regimen depending on the size, depth, and location of the ulcer or for ulcers classified as mild, moderate, or severe. Thus, there is no evidence to support the suggestion that a lower number of drops on day 1 is as effective as a higher number on categorized BK ulcers.
Conclusions: No standardized method of categorizing BK was found, and there is no evidence to support the contention that mild, moderate, or smaller BK ulcers should be treated any differently to larger or severe ulcers on day 1. The manufacturers of 2FQ do not supply different treatment regimens for different ulcer sizes and severity categories. When using the 2FQ, all BK ulcers should be treated equally in line with the manufacturers' recommended day-1 treatment regimen.

Introduction

Bacterial keratitis (BK) is a potentially sight-threatening condition that can often be treated empirically with fluoroquinolone monotherapy using the commercially available second-generation fluoroquinolones (2FQ) ciprofloxacin (0.3%) and ofloxacin (0.3%).[1] Recent reviews have demonstrated the importance of the antibiotic drop regimen employed in the day-1 treatment of BK using these fluoroquinolones.[2,3] The first of those reviews showed that many guidelines for the day-1 treatment of BK were not directly referenced to any clinical trials treatment protocols, and were all lower than the manufacturer's day-1 drop regimen.[2] The second review showed that the manufacturers' regimen provides the required peak corneal antibiotic concentrations required for most bacteria.[3]

All of this begs the question as to whether any BK should be treated with anything other than the manufacturers' recommended levels for the 2FQ. The manufacturers' day-1 regimen for each 2FQ differ greatly and are quite high at 120 drops for 0.3% ciprofloxacin,[4] and 34 to 68 drops for 0.3% ofloxacin.[5] A lack of awareness of these suggested regimens, which were included in

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the product information submitted to, for example, the Australian Register of Therapeutic Goods (ARTG) (0.3% ciprofloxacin ARTG identification No. 42899 and 0.3% ofloxacin ARTG identification No. 47485) to obtain clearance for these drugs to treat BK, seems to have resulted in a number of varying suggested day-1 regimen.

Over the years, a number of treatment guidelines for the 2FQ have been presented for BK on day 1 (see Pearce et al[2]), and this diversity of suggested treatment regimens has further been expanded, in accessible formats, to include different treatment regimens based on the categorization of BK as mild, moderate, or severe. Unfortunately, some references to this categorization do not supply any categorization criteria at all,[6] whereas others provide treatment regimens for central and severe infection[7] but do not refer to mild or moderate infection.

In addition, the term *large* is also used as a criterion for dictating the type and initial level of antibiotic treatment, although this term is not defined either.[7,8] Given the sight-threatening outcomes of poorly managed BK, the validity of these classifications and the lack of agreement between published classifications and the different treatment regimen suggested for different categories requires investigation.

An additional consideration is that many cases of BK are treated empirically without any information on the causative organism and its MIC_{90}. This empirical treatment may be the result of pathology testing being unavailable or, as commonly occurs, corneal scrapes of suspected BK ulcers are often culture negative. A literature review by Ung et al[9] determined that the mean (SD) number of positive swabs in clinically diagnosed microbial keratitis was only 54.2% (12.95%). This percentage is similar to that obtained from the clinical studies that have examined the effectiveness of the 2FQ where the mean (SD) number of culture-positive swabs from eyes suspected of having BK was 52.4% (20.5%).[10–20]

The lack of information on the nature of the causative organism indicates that any empirical treatment should be aligned with the highest nonresistant MIC_{90} for the most common causative organisms of BK. A recent review found that from a pharmacodynamics point of view, with regard to achievable corneal antibiotic concentrations and peak concentration to MIC_{90} ratios, the manufacturers' recommendations for the day-1 treatment of BK using the 2FQ were the most appropriate.[3] From the foregoing, it would appear that treating BK based on categorization ignores the fact that mild, moderate, or small ulcers may have a causative organism (or organisms) with a high MIC_{90}.

In this review, the evidence base is examined to determine whether any consensus exists on the definitions of mild, moderate, and severe in relation to the categorization of BK. The use of the terms *large* and *small* in relation to BK was also examined to determine whether any criteria exist for this categorization. The literature was then reviewed to determine whether any evidence exists for treating different categories of BK ulcers with different day-1 drop regimen using the 2FQ.

Methods

A literature review was conducted, primarily on PubMed and Google, with the filters of *humans*, *English*, and articles subsequent to 1990 only given that in the United States, Ciloxan (0.3% ciprofloxacin) (Novartis Pharma AG, Basel, Switzerland) was approved under New Drug Application (NDA) 19-992 for the treatment of bacterial conjunctivitis and corneal ulcers in patients aged 1 year and older on December 31, 1990. The search terms *bacterial keratitis treatment guidelines* returned 21 results; reading and review of these articles and reference lists led to other reference sources. From these references, specific authors with an interest in BK were also searched using PubMed. Previous references utilized in BK-related publications by the authors were also re-examined for BK categorization and treatment regimen.[2,3] The search term *categorisation of bacterial keratitis as mild, moderate, and severe* returned 2 results, neither of which was relevant to BK in humans, as did a search substituting classification for categorization.

The search term *review articles on bacterial keratitis treatment* returned 243 results and the search term *topical steroids* and *bacterial keratitis* returned 167 results. These results were examined and titles—and subsequently abstracts—that were relevant were assessed. Where applicable, the full articles were then read and reviewed.

We searched the terms *bacterial keratitis* and *location* (*central*, *paracentral*, or *peripheral*) (2 results); *size* (*small*, *moderate*, or *large*) (no results); *presence of epithelial defect* (10 results); *anterior chamber inflammation* (10 results); *hypopyon* (98 results); and, to determine the severity of BK, the term *stromal depth of ulcer* (4 results).

A reviewer pointed out that our original methodology regarding the review of the literature did not include the Cochrane and Embase databases and that some relevant articles or studies may have been missed. The Embase database was not accessible through our institution (Australian National University). The original search terms were therefore submitted to the Cochrane database with the result that no additional relevant articles or studies were found.

No risk of bias assessment was carried out for any individual studies included in our article. This is due to the fact that no results from any individual study were used in the article, and because there was thus no assessment of any overall intervention effect, no risk of bias assessment was required or included.

Results

Severity classification criteria

A total of 31 publications were found that used either the categorization terms mild, moderate, severe, nonsevere, or mentioned the term *severity* (Table 1). Of these, only 17 provided any definition of at least 1 category and of these, only 2 used the same ulcer criteria for all 3 categories.

The term *severe* was the most often defined (n = 17) (Table 1), and thus engendered the greatest variety of descriptors. In terms of ulcer diameter, the criteria for severe ranged from >2 to >6 mm (n = 15; mean (SD) = 3.95 (1.40), median = 4.00) although even the term *severe* was inconsistently defined, with 3 studies including the term *infiltrate* and 1 using the term *suppuration* in relation to their criterion of ulcer size.

The most consistent criterion for severe was ulcer depth, with 7 articles defining a severe ulcer as being greater than 50% of corneal thickness.[21–27] The specific location of the defect, irrespective of size, was a criterion for severe in 4 studies,[26–29] although another, describing the term *mild*, referred to this category not involving the visual axis.[30] The term *epithelial defect* was explicitly used in only 3 articles.[27,28,30]

According to McDonald et al,[1] only 1 high-quality trial involving the treatment of BK specified a clinical diagnosis of severe BK in their study participants[16] and indeed, for the 2FQ, this is the case. It is also the case that this study did not define severe, as noted by McDonald et al.[1] Perhaps even more interestingly, McDonald et al[1] use "severe BK" in the first 3 words of their abstract, but do not define severe in their article. This omission is compounded in their introduction, where they suggest a treatment protocol of 15 minute-to-hourly drop instillation for fluoroquinolone monotherapy in severe infection, with no definition of severe, no specific fluoroquinolones, and no indication of a treatment protocol for other categorizations of BK.[1]

Individual articles also used undefined terms in their descriptors and are thus difficult to apply in clinical practice. For example, the criteria for severe in Lin et al[7] is "deep stromal involvement

Table 1
Summary of the categories of bacterial keratitis referred to in published articles and guidelines and the criteria for each category for each publication. Where an article does not provide any information on a category, the relevant cell(s) in the table are left blank.

Author	Severe description	Moderate description	Mild description
Lin et al[7]	Deep (not defined) stromal involvement or an infiltrate larger than 2 mm with extensive suppuration. Also (from Table 1 in that article); large, central, stromal melting, chronic, atypical appearance, sight threatening		
McAllum et al[30]	A 4-mm central, dense, corneal stromal infiltrate with an overlying epithelial defect and a marked anterior chamber reaction with a 2-mm hypopyon		1-mm diameter, anterior stromal infiltrate, not involving the visual axis and associated with a mild (1+) cellular anterior chamber reaction
Cabrera-Aguas et al[21]	size ≥5 mm, depth >50% of corneal thickness and dense infiltrates reaching the deep layers of the corneal stroma	2–5 mm in size with a depth of 20%–50% of corneal thickness with dense infiltrates extending to the mid-stroma	Size <2 mm, depth <20% of corneal thickness, and superficial infiltrates
Acharya et al[22]	Size >5 mm, depth >50%, infiltrate deeper, sclera may be involved	Two to 5 mm, depth 20%–50%, infiltrate midstromal, and no scleral involvement	Less than 2 mm, depth 20%, infiltrate superficial, and no scleral involvement
Al Mujaini et al[25]	Suppuration confined to posterior third of cornea and may present as ring abscess, scleral suppuration, and impending perforation	Suppuration confined to superficial two-thirds of cornea	Focal, superficial suppuration
Ray et al,[39] Srinivasan et al[40]	≥1.7 logMAR	0.3–1.6 logMAR	<0.03 logMAR
Keay et al[29],*	Vision loss requiring surgery, culture positive, any part of lesion within central 4 mm, outside central 4 mm with hypopyon, outside central 4 mm but ≥2 mm diameter		Outside central 4 mm, <2 mm diameter
Allan and Dart[23]	Ulcer >6 mm or >50% max thinning, axial lesions		
Jongkhajornpong et al[28]	Corneal infiltrations larger than 3 mm in the greatest diameter and/or vision-threatening corneal infiltrations that were located within 3-mm zone of corneal center with overlying epithelial defect		
Gicquel et al[26]	Diameter > 5 mm, depth >50% or localized <3 mm from the optic axes with a diameter >2 mm and a moderate-to-severe anterior chamber reaction		
Sheha et al[27]	Epithelial defect >5 mm within 3 mm of visual axis with infiltration >50% of corneal thickness		
Tuft et al[41]	Associated with scleritis		
McDonnell[42]	Large, deep, or central		
Constantinou et al[16]	Mean epithelial defect size 3.21 mm†		
Ho et al[43]	Term used, not defined		Term used, not defined
Wespiser et al[38]	Term used, not defined		Term used, not defined
Carnt et al[6]	Term used, not defined	Term used, not defined	Term used, not defined
McDonald et al,[1] Tena et al,[44] Singh et al,[45] Maier et al,[46] Wong et al,[47] Gebauer et al[48]	Term used, not defined		
Jones[24]	Severe Rapid progression >6 mm area of suppuration Inner one-third of cornea in depth Perforation present or imminent Scleral suppuration present	Nonsevere Slow, moderate progression <6 mm area of suppuration Superficial two-thirds of cornea in depth Perforation unlikely Scleral suppuration absent	
Parmar et al[37],‡	>6 mm area of suppuration Inner 1/3 of cornea in depth Scleral suppuration present	<6 mm area of suppuration Superficial 2/3 of cornea in depth Scleral suppuration absent	
Oliver et al[49]	Cells in the anterior chamber, size > 3 mm and/or involvement of the visual axis		
McLeod et al[50]	More severe 4 mm diameter, central dense overlying infiltrate with overlying epithelial defect and a 2 mm hypopyon	Less severe 2 mm defect outside visual axis, Grade 1+ cells	

(*continued on next page*)

Table 1 (*continued*)

Author	Severe description	Moderate description	Mild description
Park et al[51]	Large, central or deep	Not defined	
Vital et al[52,§]	Potentially sight threatening Any one of 1. Cells ≥1+ in the anterior chamber (10 cells or greater in 1-mm beam) 2. Dense infiltrate ≥2 mm in size in greatest linear dimension (by slit-lamp light measurement) 3. Edge of infiltrate ≤3 mm from the center of cornea (by slitlamp light measurement)	Rarely sight threatening All of the following must be present 1. Cells <1+ in the anterior chamber (<10 cells in 1-mm beam) 2. Dense infiltrate <2 mm in size in greatest linear dimension (by slit-lamp light measurement) 3. Edge of infiltrate >3 mm from the center of cornea (by slitlamp light measurement)	
Herretes et al[32]	The term *severity* was used, but no categorization information supplied		
Chidambaram et al[53]	Defined moderate to severe as having an epithelial defect and a stromal infiltrate >3 mm in longest diameter		

* Although this study included the caveat that a culture positive result automatically upgraded an ulcer to severe irrespective of the ulcer size or location criteria, the size and location criteria are included here for analysis and completeness.

† Mean defect size calculated from Table 1 in that article and used in ulcer size calculations. However, article not included in sample size as defining severe.

‡ The criteria used in the Parmar et al[37] study references Jones.[24] Because it represents duplication, it is not included in any calculations but is included here for completeness.

§ Criteria for sight threatening was included in the analysis as severe.

or an infiltrate larger than 2 mm with extensive suppuration," although deep and extensive suppuration are not defined.

Ulcer location

The use of the term *central* in relation to defining an ulcer as severe was inconsistent. In a survey-based study,[30] the term *mild* refers to a 1-mm diameter ulcer not involving the visual axis, and the criteria for severe are a 4-mm ulcer and a central location. In Cabrera-Aguas et al,[21] although the term *central* does not appear in their categorization criteria (Table 1), the authors equate central with severe BK by stating that, "For central or severe keratitis, an initial frequent dosage every 5 to15 minutes is recommended followed by hourly applications."

Acharya et al[22] present a categorization algorithm for BK (Table 1) that did not include any location criteria. However, in their article they later state that fluoroquinolone monotherapy is usually reserved for keratitis that is not severe or does not involve the visual axis, implying that visual axis involvement equates to a categorization of severe. No reference is supplied for this statement.

The American Academy of Ophthalmology Eye Wiki website states that "Small, non-staining peripheral ulcers may be started on fluoroquinolone eye drops every 2 to 6 hours."[8] Note that this introduces the term *peripheral*, but does not define it and it further introduces the term *small*, but does not define that either. In addition, the treatment protocol is not referenced, the fluoroquinolone is not defined, and no clinical study involving the 2FQ[10–20] has used a day-1 drop regimen of <1 drop per hour on BK ulcers of any size.

EyeWiki goes on to state that, "For ulcers with epithelial defects and an anterior chamber reaction, a fluoroquinolone drop every hour around the clock is recommended."[8] Note that there is no reference to ulcer location or size, no fluoroquinolone is specified, and no reference is cited to the statement regarding an evidence base for the treatment protocol.

Keay et al[29] defined severe as an ulcer with any part of the lesion within the central 4 mm. However, in this study, an ulcer with a culture-positive result was automatically upgraded to severe irrespective of size and/or location. Whilst this caveat seems to render irrelevant their criteria regarding ulcer size and location, we have included their size and location criteria in our analysis because it remains applicable in clinical practice where either no culture is available or a culture-negative result is returned.

To add to the lack of clarity, animal models for grading BK have used scoring systems that have not used centrality as a criterion at all.[31]

Ulcer size

The terms *large* and *small* in relation to ulcer size were used in 6 publications (Table 2) but only the term *large* was defined in 1 study.[15] However, that definition arose from the distribution of ulcer sizes in their study, whereby the median corneal ulcer size was 2.75 mm^2 and the authors, for the purposes of the study, therefore considered large to be >2.75 mm^2.[15] This criterion is thus an artefact of the study population rather than an evidence-based definition and results in an ulcer diameter of >1.87 mm (clinically, 2 mm) being classified as large.

Lin et al[7] state that, "Fortified antibiotics should be considered for large and/or visually significant corneal infiltrates, especially if a hypopyon is present," although the authors do not define large. The guideline for BK in EyeWiki further suggests that "large or vision threatening ulcers (with moderate to severe anterior chamber reaction and/or involving the visual axis) should be cultured then treated with fortified tobramycin or gentamicin (15 mg/mL) every hour around the clock alternating with fortified vancomycin (25–50 mg/mL) every hour around the clock."[8] Again, the term *large* is not defined.[8]

Herretes et al[32] stated that, "Dosing of the antibiotic is often dependent on the size of the ulcer and severity of keratitis," but provided no information on severity categorization, dosing regimen, or ulcer size and make no reference to location. The authors provided no reference for this statement.[32] There is thus no evidence-based definition of large and small in relation to ulcer size.

Visual acuity

In Table 1, 3 studies used visual acuity criteria to categorize ulcers as severe, moderate, or mild. Whilst presenting and final visual acuities can be used as treatment outcome measures, presenting acuity can be confounded by preexisting patient factors such as amblyopia and previous history of retinal pathology. Indeed, Keay et al[29] refer to a vision loss of 2 or more lines of best corrected visual acuity as a criterion for an ulcer to be designated as severe. This implies a previous knowledge of the patients' acuity, which may not be known, and visual acuity has therefore been excluded from any consideration in the categorization criteria in Table 3

Table 2
Summary of published articles and guidelines that have referred to the categorization of bacterial keratitis ulcers as large or small.

Author	Large	Definition	Small	Definition
Lin et al[7]	Yes	No		
Feldman et al (EyeWiki)[8]	Yes	No	Yes	No
McDonnell[42]	Yes	No		
Park et al[51]	Yes	No		
Isenberg et al[15]	Yes	>2.75 mm^2		
Herretes et al[32]	Refers to antibiotic dosing being dependent on the size of the ulcer, but does not specifically mention large or small			

Table 3
Proposed severity grading system based on the review and analysis of the published grading criteria presented in Table 1. A single severe criterion automatically designates the ulcer as severe.

Ulcer parameter	Severe	Consensus base from Table 1
Size*	>4.0 mm	The mean of published severe ulcer size criterion was 3.95 mm; 4.00 mm was the median severe ulcer size criterion
Depth	>50% of corneal thickness	Seven out of 11 articles that referred to depth indicated that severe was 50% or more of corneal thickness
Location	≤ 3 mm of visual axis	Four out of 5 articles that defined central location indicated that ≤3 mm of the visual axis denoted severe
Scleral involvement	Yes	Four out of 13 articles that defined severe used scleral involvement as a criterion
Anterior chamber reaction†	Marked (3+) and/or hypopyon	Five out of 14 articles mentioned anterior chamber reaction as a severe criterion. Two indicated a 2-mm hypopyon was severe, 1 said 2+ to 3+, 1 said >1+, and 1 did not specify a grade

* Epithelial defect or infiltrate, whichever is the greater.
† Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol*. 2005;140:509–516. doi:10.1016/j.ajo.2005.03.057

because it is not an objective measurement that relates specifically to the clinical BK presentation.

Antibiotic selection

Mean ulcer diameters of up to 6.8 mm (0.3% ofloxacin[33]) and 6 mm (0.3% ciprofloxacin[13]) have been treated in clinical trials. A recent review reported that a "cornea with limbus" diameter would be approximately 14.1 mm, which is larger than the results obtained using the horizontal visible iris diameter.[34] Using this upper value (14.1 mm) gives a corneal radius of 7.05 mm, with the result that ulcers >4.05 mm may encroach within 3 mm of the central cornea/visual axis. This value ties in nicely with the calculated (Table 3) mean severe ulcer criterion of 4.0 mm and shows that the 2FQ have been used in clinical trials to treat BK ulcers that would meet a definition of severe with regard to centrality defined as being within 3 mm of the visual axis (Table 3).[13,33]

Several clinical trials have reported no differences in efficacy between the 2FQ and fortified antibiotics in the treatment of BK. The cure rate for patients with severe BK (no definition supplied) using 0.3% ofloxacin was reported to be no different to that of patients using a combination of fortified tobramycin (1.33%) and cephazolin (5%).[16] Panda et al[33] reported that the average time for symptomatic relief was significantly lower ($P = 0.05$) for 0.3% ofloxacin versus 1.5% tobramycin and 10% cefazolin, although this was clinically insignificant at 0.53 days and there was no significant difference ($P = 0.46$) in the duration of healing between the 2 treatment protocols. In this study, all ulcers were grade III (ulcers extended from >5 to 7 mm in any 1 meridian[35]) and 11 of the 15 ofloxacin patients and 9 out of 15 of the control group had a hypopyon present. O'Brien et al[17] also reported no significant differences for treatment outcomes using 0.3% ofloxacin versus 1.5% tobramycin and 10% cefazolin. Hyndiuk et al[14] reported no clinical or statistical difference between 0.3% ciprofloxacin and fortified tobramycin (1.3%) and cephazolin (5.0%).

Fluoroquinolone specification and drop regimen

Specifying the fluoroquinolone to be used is critical, given that the manufacturer's recommendation for 0.3% ciprofloxacin[4] is almost 2 to 4 times that of the manufacturer's recommendation for 0.3% ofloxacin.[36] The risk of not specifying the fluoroquinolone may lead to increased failure rates given that a recent review found that higher treatment failure rates were significantly associated with lower drop numbers on day 1 for 0.3% ciprofloxacin.[2] On that basis, prescribing a day-1 regimen for 0.3% ciprofloxacin at the same manufacturer's recommended minimum for 0.3% ofloxacin[36] may lead to increased treatment failure rates with 0.3% ciprofloxacin as opposed to using higher rates up to the manufacturer's recommended regimen.[4]

In addition, a later literature review and analysis[3] suggested that the manufacturer's regimen for 0.3% ciprofloxacin was pharmacodynamically appropriate, as was the manufacturer's recommendation for 0.3% ofloxacin. Prescribing outside the manufacturer's recommendations for either 2FQ may therefore not be appropriate, and any suggested treatment regimen for a topical fluoroquinolone, whether that be a 2FQ or a subsequent-generation fluoroquinolone, must specify the fluoroquinolone.

Carnt et al[6] suggest a fluoroquinolone (not specified) drop regimen of every 1 to 2 hours for the first 24 hours for mild to moderate cases of microbial keratitis. Presumably they mean BK, because antibiotics are inappropriate for fungal and acanthamoeba causes of microbial keratitis. There is no definition supplied as to what constitutes mild or moderate, no reference supplied for their drop regimen, and furthermore no clinical trial involving the 2FQ has used <1 drop per hour on day 1.[10–20]

In Cabrera-Aguas et al,[21] a different categorization algorithm was used. Although the term *central* does not appear in their categorization criteria (Table 1), in their article, the authors equate central with severe BK by stating that "For central or severe keratitis, an initial frequent dosage every 5 to 15 minutes is recommended followed by hourly applications," although the duration of this frequent application period is not defined and neither is the term *central* or the specific medication. No mention is made of a drop regimen for moderate or mild BK.

Later, they state that empiric therapy with the 2FQ involves 1 drop every hour, including overnight, with no mention of an initial drop regimen of every 5 to 15 minutes.[21] There is no severity categorization associated with this statement, and it is therefore not

clear which BK category they are referring to with this treatment paradigm.

Sundry information

Jones[24] categorized microbial keratitis as severe and nonsevere (Table 1). The categorization is included here as the term *microbial keratitis* does include BK and this classification was the basis for the categorization used in 1 clinical study of 0.3% ciprofloxacin in the treatment of BK.[37]

A survey-based review of antibiotic prescribing for BK on 5 continents presented 2 pictures of what the authors categorized as a mild and a severe case of BK, although no definition was supplied.[38]

A summary of the published BK categorization criteria is presented in Table 1, but it should be noted here that the majority of the articles that defined severe (11 out of 17) are not referenced to any source or studies and as such, although published, do not represent a true evidence base definitively applicable to clinical decision making.

Discussion

None of the clinical studies involving the 2FQ treated BK ulcers any differently based on either their size or location.[10–20] Further, review and analysis of these studies[2] revealed that there was no association between ulcer diameter or ulcer area and failure rates for either of the 2FQ over the duration of the studies. There is thus no evidence to support the contention that lower drop numbers on smaller ulcers on day 1 using the 2FQ would result in similar treatment outcomes to higher drop numbers.

No published consensus definition of how to categorize BK into mild, moderate, and severe was found, and as a result, a wide variety of definitions were found (Table 1). The published criteria were therefore analyzed to determine their validity based on their own criteria. Lin et al[7] defined severe keratitis as having "e.g. deep stromal involvement or an infiltrate larger than 2 mm with extensive suppuration." They also used the term *central* separately to *severe*, but suggested the same treatment regimen for both. This seems to suggest that a centrally located ulcer that does not meet their supplied criterion of severe (ie, an ulcer <2 mm in size with moderate suppuration) is treated, and by default is classified as severe or sight-threatening. Ipso facto, that same ulcer located noncentrally would not be treated with the severe ulcer regimen.

The question arises: Why not? Presumably, the answer is that any scarring because of a central ulcer would have a greater effect on visual acuity and thus centrally located ulcers are classified differently and treated differently. Implicit in this logic though is that even for small central ulcers, fortified antibiotics are recommended ("Fortified antibiotics should be considered for large and/or visually significant"[7]) presumably because they are more likely to result in less corneal scarring. If a fortified antibiotic regimen is used to minimize central scarring, why is the same regimen not used for noncentral ulcers to minimize scarring? The treatment goal in BK must surely be the limitation of tissue damage and promotion of wound healing[54] to provide the most rapid resolution with the minimum amount of scarring, and yet the application of a different antibiotic regimen for noncentral ulcers seems to contradict this goal. Indeed, this approach seems to accept the risk of greater scarring in noncentral ulcers that is neither evidence-based nor acceptable, and the location of an ulcer should not necessarily dictate a treatment regimen.

This variation in treatment protocols is also promoted in relation to ulcer size. Herretes et al[32] state that "dosing of the antibiotic is often dependent on the size of the ulcer" but provide no reference for this statement. Feldman et al[8] refer to treating small (not defined) nonstaining peripheral ulcers with a fluoroquinolone (not specified) every 2 to 6 hours but provide no reference for this treatment. At this point in time, no clinical study involving the 2FQ has ever used <1 drop per hour on day 1.[10–20]

A retrospective review of patients with microbial keratitis (64% of whom had BK) by Khoo et al[55] reported that poor patient outcomes were associated with larger epithelial defect size, although no treatment regimen was supplied. Chidambaram et al[53] also reported that poorer outcomes were associated with larger ulcers in what they defined as moderate to severe microbial keratitis (Table 1). Although the vast majority of these patients (84%) had a fungal keratitis, the posterior one-third of the cornea was involved at presentation in 74% of BK cases and 64% of fungal cases. The BK patients in that study received moxifloxacin 0.5% eye drops, and although the frequency was not reported, no difference in drop regimen was given based on ulcer size.

It should be noted here that moxifloxacin, a fourth-generation fluoroquinolone, is often used in clinical practice to treat BK. At present, it does not have Food and Drug Administration clearance for the treatment of BK, although 2 clinical trials have reported no difference in treatment failure rates between moxifloxacin and fortified antibiotics.[16,56] It should be noted that in 1 of those trials,[16] 1.0% moxifloxacin was used, whereas commercially available moxifloxacin (Vigamox; Novartis Pharma AG, Basel, Switzerland) is 0.5%.[57] Even so, no difference in cure rate was found between moxifloxacin (1.0%) and 0.3% ofloxacin in that trial. In the absence of Food and Drug Administration clearance and the lack of commercial availability of topical moxifloxacin in many countries, we have not included moxifloxacin in our considerations regarding categorization and day-1 treatment regimen.

Whilst this recent research indicates that presenting ulcer size may be a predictor of patient outcomes, it also supports the contention that ulcers of all sizes should be treated equally. If smaller ulcers that receive the same treatment as larger ulcers have better patient outcomes,[53,55] this seems to indicate that they should be treated with the same stringent manufacturer's recommended regimen as larger ulcers.

In a retrospective review, Vital et al[52] treated ulcers differently based on size and location (Table 1), but did not have a control population for comparative purposes to determine whether the different treatments made any difference to their results. In their article, they also noted the lack of consistency in grading BK ulcers based on severity and the lack of any definition for large ulcers.[52]

None of the recommendations that allude to categorization make any mention of the relevance of the MIC_{90} of the causative organism. Pharmacodynamics would dictate that the peak corneal antibiotic concentration requirement for the same causative MIC_{90} present in a large or small, central, or noncentral ulcer would be the same. This issue is particularly pertinent in the empirical treatment of BK, where frequently no culture result is available.[9–20] The empirical treatment must therefore be aimed at the highest MIC_{90} that would be encountered by the fluoroquinolone, and that MIC_{90} is neither dependent on ulcer location or ulcer size. This neglect of the importance of MIC_{90} is further compounded by the risk of therapeutic failures if inappropriate drop regimens are used to treat BK.[58]

This statement is supported by Bennett et al[59] who reported virulent bacteria were found in the corneal scrapes of peripheral ulcers, although despite this finding, they also propose considering central and peripheral infiltration separately. O'Brien et al[17] reported that an epithelial defect of 2.8 mm diameter with a superficial infiltrate of 1.6 mm diameter contained 3 organisms and Mah-Sadorra et al[60] reported no significant association between ulcer size and culture positivity or negativity for ulcers <2 mm^2 versus those >2 mm^2 ($P = 0.24$) and no association between organism type and ulcer size ($P = 0.23$) or between ulcer location and organ-

ism type ($P = 0.25$). These findings reinforce the proposition that smaller ulcer size or location should not be a criterion for prescribing a less intensive treatment regimen.

It seems likely that cornea specialist ophthalmologists and ophthalmologists working in hospitals are aware of the importance of the MIC_{90} of the causative organism. In a survey-based study of management practices in BK, 35% of respondents stated that they would carry out a microbiological examination of a mild case of BK (based on a photo of what was defined as mild BK in the survey) and that study reported that cornea specialist ophthalmologists and ophthalmologists working in hospitals were more likely to carry out a microbiological examination.[38] This finding would seem to support the contention that the MIC_{90} of the causative organism, rather than any categorization, should dictate the treatment and antibiotic concentrations required. This in turn suggests that if, as is often the case, the MIC_{90} of the causative organism is not known, then all cases of BK treated using the 2FQ should be treated equally using the appropriate day-1 drop regimen.[4,5]

A literature-based review of the pharmacodynamics of the 2FQ reported that the manufacturer's day-1 drop regimen generated corneal antibiotic concentrations that met the peak concentration to MIC_{90} requirements for the majority of nonresistant causative organisms in BK.[3] A review of the clinical trials involving the 2FQ found that with the exception of 1 trial involving ofloxacin,[17] they all used a lower number of drops on day 1 than suggested by the manufacturers.[2] It may be that the presence of these lower drop numbers in the clinical trials literature has led to the use of lower drop numbers on day 1 for the 2FQ in cases of BK perceived to be nonsevere. Not only does this practice not take into account the possible MIC_{90} of the causative organism, but also an analysis of the clinical trials results for 0.3% ciprofloxacin showed that higher failure rates were associated with lower drop numbers on day 1 ($P < 0.002$).[2]

The choice of antibiotic (ie, fortified or 2FQ) may be influenced by additional patient factors such as age and immune status, history of contact lens use, interval between onset and presentation, presenting best corrected visual acuity level, and associated ocular surface problems such as dry eyes. It should be noted here that in 1 retrospective review, the 2FQ were used on a similar percentage of contact lens wearers, significantly older patients, and a higher percentage of patients with systemic diseases and those taking systemic immunosuppressive drugs than those prescribed fortified antibiotics.[61] This study also reported an 8.9-fold increased risk of serious complications with the 2FQ, and on that basis suggested caution should be exercised using the 2FQ on large, deep ulcers in elderly patients. However, the day-1 drop regimen of 1 drop every hour for the 2FQ in that review is below the manufacturers' recommendation for both 2FQ[4,5] and higher drop numbers may have produced a different outcome in this regard.[2,3]

Whilst additional patient factors may influence the initial choice of antibiotic, the drop regimen for the chosen antibiotic should not differ between patients. If a 2FQ is chosen for a young patient with a healthy immune system who is not a contact lens wearer and an older immunocompromised contact lens wearer, the same day-1 drop regimen should be used for both patients.

To assist clinicians in their treatment protocol decisions, a consensus-based grading system was derived from Table 1 and is presented in Table 3. For simplicity, providing only 1 category (severe) removes potential ambiguities from ulcer grading between clinicians. It is either severe or it isn't, and a patient's clinical record can then be annotated under the heading of "severe" as either "yes" or "no," and Table 3 provides the definition of severe for clinicians.

The descriptors large and small should no longer be used under any circumstances and neither should the descriptors mild and moderate. Recording the size of the ulcer and relating that to the descriptor >4.0 mm diameter for severe automatically incorporates size as a severity grading rather using large or small as ambiguous, ill-defined standalone categories.

It is important to reiterate that if a 2FQ is the antibiotic chosen, based on any assessment of a presenting BK case, it should be prescribed in line with the manufacturer's recommendations.

A further consideration is the risk of bacteria developing tolerance or resistance due to antibiotic undertreatment. In 1 study, it was reported that enhancement of the development of resistance was facilitated by increased tolerance via cyclic antibiotic exposures.[62] The undertreatment of small ulcers that possess causative organisms with inherently high MIC_{90} could only be expected to exacerbate resistance development in bacterial corneal isolates.

Finally, it should be noted that neither of the manufacturers of 0.3% ciprofloxacin[4] or 0.3% ofloxacin[5] make any reference to ulcer size, severity, or location in their recommended day-1 treatment regimen guidelines.

Conclusions

There are no formal guidelines or consistent published criteria for the categorization of BK presentations into mild, moderate, severe, large or small. No clinical trials involving the 2FQ[10–20] or fortified antibiotics[14,16,33,56,63] have treated different sizes or categories of ulcers with different day-1 treatment regimen. When using the 2FQ, clinicians should treat all ulcers equally using the manufacturers' recommended day-1 regimen. In Table 3, we propose a consensus based grading system to assist clinicians in their initial clinical decision making and standardise future clinical trial definitions.

Declaration of Competing Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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