

# Antibiotic management of presumed microbial keratitis

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Key words: Antibiotic, Culture, Infection, Microbial keratitis

## Introduction

It is now 18 years since Dan Jones wrote his fundamental paper 'Decision-making in the Management of Microbial Keratitis'.<sup>1</sup> His advice still applies today - make the clinical diagnosis, perform the correct laboratory procedures, initiate anti-microbial chemotherapy, modify the chemotherapy and (often forgotten) terminate therapy. Unfortunately, it is only the first and third steps that are often followed today - the production of a clinical diagnosis of 'presumed' microbial keratitis and initiation of antibiotic therapy.

Corneal scrape cultures should always be collected when the laboratory has an approximate 50% chance of identifying the organism by microscopy alone. Culture should follow whenever possible with antibiotic sensitivities of the incriminating organism. However, the laboratory may fail to isolate the responsible pathogen. This then gives rise to the clinical diagnosis of 'culture-negative' microbial keratitis,<sup>2</sup> which requires intensive investigation (described in the **Figure 9**) prior to successful chemotherapy.

Good progress has been made in the last 20 years to recognise the different etiologies of microbial keratitis and their geographical distribution according to climate (**Table 1**).<sup>3-10</sup> This needs to be understood before choosing an antibiotic, or a combination of antibiotics, for first-line or second-line chemotherapy (**Table 2**).

## Central versus peripheral microbial keratitis

Central ulceration of the cornea occurs in patients with ocular surface disease or with contact lens wear when virulent organisms may be involved such as *Pseudomonas aeruginosa* presenting with acute suppurative infection

(**Figures 1A and 1B**).<sup>3,11</sup> Such a situation, especially in a young contact lens wearer, should be managed as a medical emergency with use of broad spectrum antibiotics including anti-pseudomonal drugs (**Table 2**). This broad-spectrum cover should also be bactericidal for *Staphylococcus aureus* and virulent streptococci including *S. pneumoniae* and *S. pyogenes* (Lancefield group A). If the infection is chronic and progressive then either mycobacteria or nocardia should be considered (**Figures 2A and 2B**).<sup>12</sup> Second-line broad spectrum antibiotics are required (**Table 2**) together with adjunctive surgery often as a lamellar keratoplasty.

Marginal ulceration, within 2 mm of the limbus, may be due to four different etiologies: (1), inflammatory, as sterile lesions, due to a cell-mediated immune reaction at the limbus due to the presence of *S. aureus* on the lid margin often causing chronic blepharitis;<sup>13</sup> (2), secondary infection of an inflammatory marginal ulcer caused by a low grade pathogen such as *Moraxella* sp. (**Figure 3**); (3), inflammatory from auto-immune disease or representing a Mooren's ulcer; (4), secondary to contact lens wear as a peripheral inflammatory infiltrate which may or may not be ulcerated. This latter group is sterile on approximately 75% of occasions,<sup>3,5,14</sup> representing a possible reaction to contaminating bacterial antigens or toxins. Initial therapy involves withdrawal of the contact lens and observation. Prophylactic antibiotic therapy with non-fortified antibiotics may be considered sensible but care should be taken because virulent bacteria are occasionally present. If these peripheral inflammatory infiltrates are included in the clinical diagnosis of 'presumed' microbial keratitis, then the positive culture rate drops considerably (**Table 1**).

CLAK - contact lens-associated keratitis - is a non-infective inflammatory condition due to tight-fitting soft contact lens wear, probably triggered by hypoxia, that has a differential diagnosis of adenovirus or early acanthamoeba infection (**Figure 4**).<sup>3,12</sup> Antibiotics are not required but the contact lens wear must be withdrawn until the inflammation has subsided which takes about 1 week.



Table 1. Clinical and geographical spectrum of presumed microbial keratitis.

Central ulcer includes axial / paraxial sites. Peripheral is within 2 mm of the limbus. \* not part of study. \*\* includes *Borrelia burgdorferi*

Study	Site of presumed MK	% with cultured organism	<i>S. aureus</i>	CNS	Streptococci	Other Gram + ve bacilli	<i>Ps. aeruginosa</i>	Other Gram - ve bacilli	<i>Nocardia</i> or <i>Mycobacteria</i>	Fungi	<i>Acanthamoeba</i> or other FLAs
Glasgow UK 1998 (3) (all cases)	Central 53% Peripheral 47%	73% (n = 22) 22% (n = 6)	18% 33%	18% 0%	23% 33%	0% 0%	9% 17%	4.5% 0%	4.5% 0%	4.5% 0%	18% 17%
Gothenburg Sweden 1993 (4) Central ulcer MK	Central 100%	63% (n = 30)	30%	23%	17%	0%	10%	20%	0%	0%	0%
Stockholm Sweden 1994 (5) CLW only	Central 12% Peripheral 88%	66% (n = 2) 26% (n = 6)	? ?	? ?	? ?	? ?	12.5% ?	? ?	0% 0%	0% 0%	0% 0%
Taipei 1998 (6) presumed bacterial MK only	Central 94% Peripheral 6%	43% overall (n = 134)	6%	18%	7.5%	4%	33%	33%	0%	*	*
Hong Kong 1998 (7)	Central 70% Peripheral 30%	54% overall (n = 27)	9%	20%	9%	6%	26%	12%	6%	6%	6%
New Orleans 1994 (8)	Central 86% Peripheral 14%	76% overall (n = 22)	4.5%	27%	23%	4.5%	9%	18%**	0%	18%	4.5%
Accra Ghana 1995 (9)	Central 100%	57% (n = 114)	3.5%	12%	11%	3.5%	14%	11%	0%	56%	0%
Perth Australia 1996 (10)	Position not given but all severe	71% (n = 41)	15%	42%	10%	5%	12%	3%	0%	0%	13%

## Geographical variation of microbial keratitis with climate

It is now recognised that there is considerable variation in the types of microbes causing keratitis in different climates as illustrated in Table 1.<sup>3-10</sup> In temperate climates, there is little fungal infection,<sup>3-5</sup> the majority of which is due to *Canidida albicans* or other yeasts but severe keratitis due to the mycelial fungus *Fusarium sp.* occasionally occurs (Figure 5). In contrast, in hot humid tropical climates such as Ghana<sup>9</sup> and South India<sup>15</sup> mycelial fungal pathogens are responsible for up to 56% of all cases of proven central ulcer keratitis either singly or as a cause of polymicrobial infection. In these situations anti-fungal antibiotics (see below) are all important in first-line anti-microbial therapy. Enquiries should also be made about foreign travel as this can result in pathogenic mycelial fungi presenting as a cause of keratitis in temperate zones.<sup>16</sup> In sub-tropical climates, such as South China,<sup>6,7</sup> Louisiana USA,<sup>8</sup> and other similar areas<sup>12</sup> there is an intermediate list of pathogens to consider, which includes all those of temperate and tropical climates for both bacteria

and fungi, when infection by *Nocardia sp.* associated with ocular surface disease and *Acanthamoeba sp.* associated with contact lens wear may be present as well as mycelial fungi. In addition, in the sub-tropics, *Ps. aeruginosa* is the predominant bacterium causing approximately 30% of proven bacterial infections so that first-line antibiotic therapy must be effective for this organism as well.

Hence each major hospital ophthalmological unit should be aware of their own flora causing microbial keratitis, as well as the expected sensitivities of organisms, in order to decide appropriate first- and second-line broad spectrum antibiotic chemotherapy for local use.

## Microbial Keratitis associated with contact lens Wear

As contact lens wear spreads into Asia, and China in particular, more experience will be gained with microbial keratitis associated with it. Acute central ulceration should



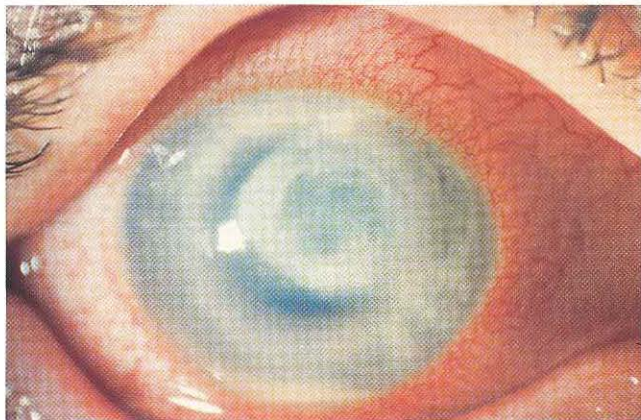


Figure 1A. Acute suppurative central ulcer keratitis due to *Pseudomonas aeruginosa*.

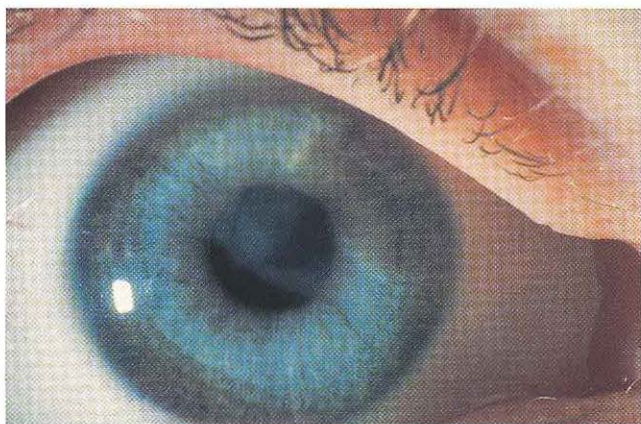


Figure 1B. Successful treatment of *Pseudomonas aeruginosa* with first-line broad spectrum antibiotics leaving a central axial scar.

always be considered to be due to *Ps. aeruginosa* in the first place. It often arises from contaminated disinfecting solutions or storage cases but this type of keratitis may also occur with extended wear of contact lenses without use of storage solutions, when the infection is thought to have arisen by finger contamination of the eye lids and lens.<sup>11</sup> Specific chemotherapy is given below.

Insidious, painful and very photophobic keratitis with few early signs except infiltration of corneal nerves is due to *Acanthamoeba sp.*<sup>12,17</sup> As the infection progresses (Figures 6A and 6B) a ring infiltrate will form with ultimate perforation. Treatment should be commenced with 0.02% chlorhexidine and 1% propamidine (Brolene) as an intensive regime (see below).<sup>12,17,18</sup> Infection with *Acanthamoeba* has been reported from most countries using soft contact lenses including USA, Europe and China.<sup>7,19-21</sup>

### Laboratory assessment prior to choosing an antibiotic for treatment

A corneal scrape should always be performed prior to choosing an antibiotic, with Gram stain as the minimum investigation. A good scrape should be obtained using a sterile needle or surgical blade as the quality of laboratory

investigations demands that a decent sample has been collected. This is processed as described in the Figure 9 and elsewhere.<sup>2,3,12</sup> If the Gram stain does not reveal bacteria, then the smear can be destained with acetone and restained by the modified Ziehl-Neelsen method (using 5% acetic acid without alcohol) to reveal nocardia or mycobacteria organisms; this is particularly useful for investigating chronic progressive keratitis (Figures 2A and 2B).

Hagan *et al* have shown the benefit of choosing an appropriate antibiotic based solely on the Gram stain of a corneal scrape in 87 out of 199 patients investigated.<sup>9</sup> It was important because fungi constituted 56% of all cases of microbial keratitis either alone or in combination. Their results showed that microscopy is particularly useful in tropical microbial keratitis for the identification of fungi and Gram negative rods (sensitivity 80% and 76%, specificity 93% and 92% respectively).

Culture of the corneal scrape should be performed on a chocolate agar plate which should be incubated in 4% carbon dioxide for at least 48 hours at 37°C; if there is no growth, the plate should be incubated for a further 7 days. In addition, a Sabouraud agar plate should be inoculated and incubated for fungi for 2 weeks at 32°C and a broth culture medium, such as thioglycolate, should be inoculated and incubated for 3 weeks for microaerophiles, anaerobes and fungi.

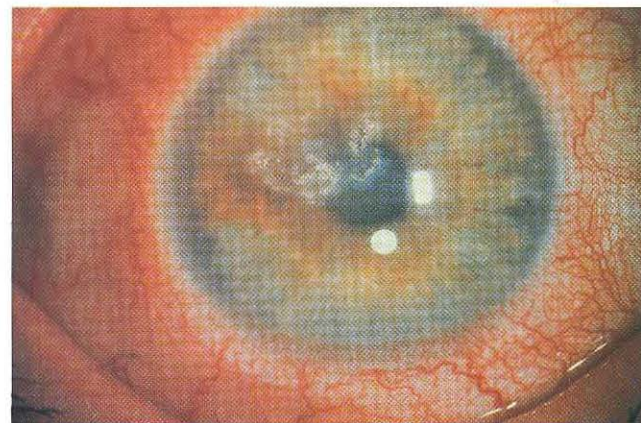


Figure 2A. Chronic progressive central ulcer keratitis due to *Nocardia sp.* that was controlled with a second-line antibiotic combination and lamellar keratoplasty.



Figure 2B. Modified Ziehl-Neelsen stain of corneal scrape showing nocardia bacilli.





Figure 3. Marginal ulcer secondarily infected with *Moraxella* sp.

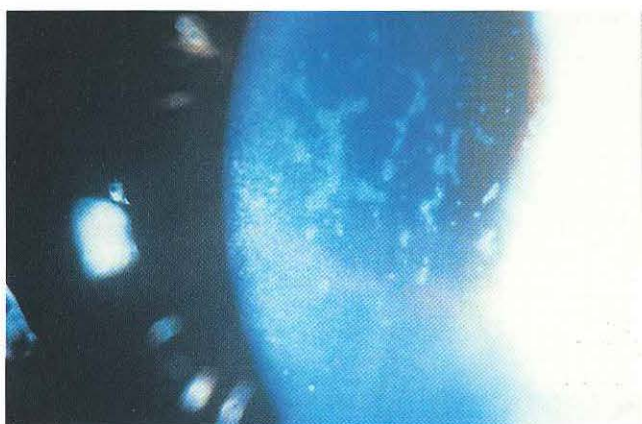


Figure 4. CLAK - contact lens-associated keratitis from a tight fitting contact lens due to non-infective inflammation (differential diagnoses - adenovirus, *Acanthamoeba*).

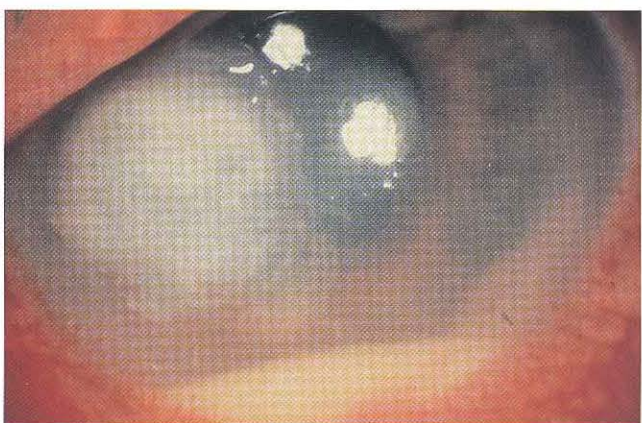


Figure 5. Severe keratitis with hypopyon due to *Fusarium* sp. (resistant to imidazoles, sensitive to polyenes [amphotericin/natamycin]).

A non-nutrient agar plate, seeded with a killed coliform bacterium, should be inoculated and incubated for 4 weeks at 32°C whenever there is a possible *Acanthamoeba* infection. The recent Hong Kong study<sup>7</sup> has shown that use of antibiotics at the time of the corneal scrape reduces the chances of recovering micro-organisms (bacteria, fungi and amoebae) from 65% to 42% - thus, it is best whenever

possible, and particularly after failure of first-line antibiotic treatment, to stop the use of antibiotics for 24 hours prior to performing the corneal scrape (Figure 9).

Some bacteria causing microbial keratitis do not stain with Gram's stain. The most important of these is *Mycobacterium chelonae* which requires a full Ziehl-Neelsen stain as it is acid and alcohol fast. The other organism to consider is *Nocardia* sp. which requires the modified Ziehl-Neelsen stain decolourising only with weak acetic acid (5%). Both organisms will grow weakly on chocolate or nutrient agar if incubated for 1 week at 37°C but mycobacteria will grow better on Lowenstein-Jensen medium.

Fungal hyphae may or may not stain with Gram stain. It is better to perform a separate wet preparation of a corneal scrape using Lactophenol Cotton Blue stain.<sup>12</sup>

Other microbes to consider include *Acanthamoeba*, which requires wet preparation microscopy from corneal scrapings and culture on non-nutrient agar<sup>12</sup> and microsporidia which require a corneal biopsy and electron microscopy.<sup>22</sup>



Figure 6A. Corneal nerve infiltrate and 'snow storm' appearance of epithelium due to *Acanthamoeba griffini*, successfully treated with 0.02% chlorhexidine and 1% propamidine (Brolene).<sup>12,17</sup>

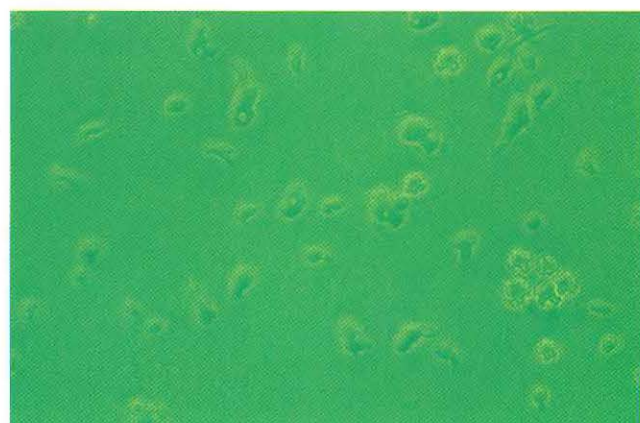


Figure 6B. Trophozoites and cysts of *Acanthamoeba* cultured on non-nutrient agar.



Underlying viral infection, particularly with *Herpes simplex*, should not be forgotten. Further differential diagnoses include topical anaesthetic or other chemical abuses, such as the topical application of perfume, which can present as 'presumed' microbial keratitis including possible *Acanthamoeba* infection.<sup>2</sup> These latter conditions will all result (falsely) in antibiotic failure and a clinical diagnosis of 'culture-negative' keratitis.

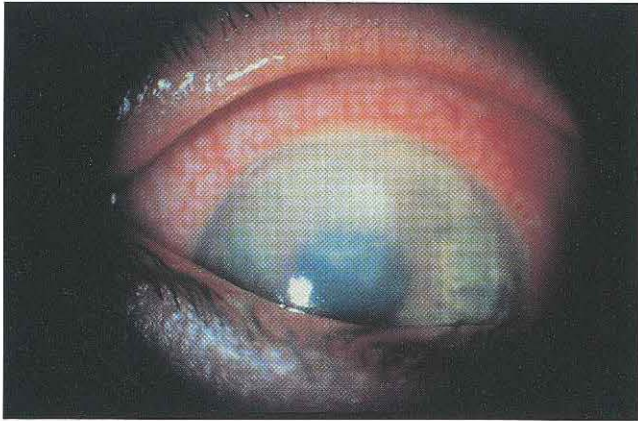


Figure 7. Acute progressive keratitis with hypopyon following trauma due to microaerophilic streptococcus that failed to respond to first-line broad spectrum chemotherapy but did respond well to second-line broad spectrum antibiotics.



Figure 8A. Keratitis due to a lichen infection following a concrete dust injury from sawing building blocks, before tetracycline treatment.



Figure 8B. Patient from (8A) following four weeks treatment with tetracycline 1% ointment giving a partial response before grafting (PK).



Figure 8C. H & E stain of cornea at time of grafting showing unique appearance of constituents of lichen in the stroma.

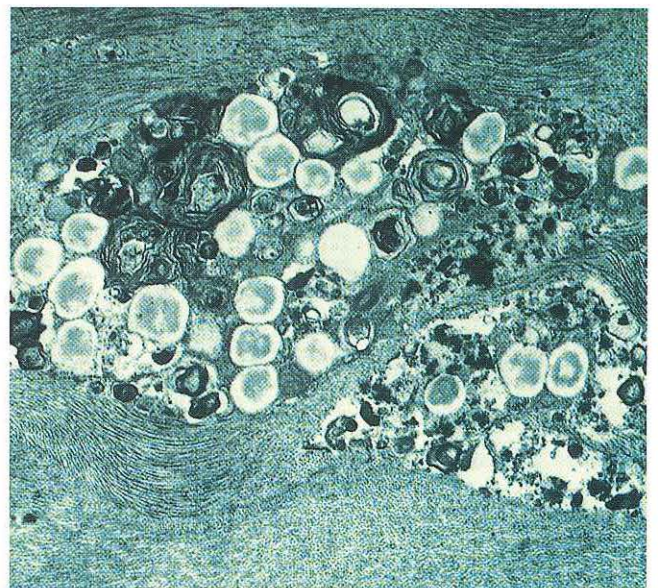


Figure 8D. Transmission electron microscopy showing constituents of the lichen in the stroma - the whorled spores represent the fungal spores.



Figure 8E. Transmission electron microscopy showing an algal cell containing a chloroplast in the stroma.



## Choice of route for antibiotic application

The original route used for antibiotic treatment of microbial keratitis was by subconjunctival injection. This route allowed antibiotics to leak back slowly from the injection site to penetrate, and be absorbed into, the cornea including the aqueous.<sup>12</sup> This treatment worked well but was abandoned largely due to pain at the injection site particularly when gentamicin was given. This route is still applicable however for treating microbial keratitis with antibiotics in an unreliable patient or if the patient is seen on a single visit with no follow-up.

Frequent application of topical drop therapy to the cornea has now become standard practice and has been used successfully for 15 years. For serious central ulcers, antibiotics drops are applied every 15 minutes for the first one hour, then every hour by day and night for 48 hours, reducing the frequency thereafter. Previously, the disadvantage of this route was the requirement to make up 'forte' preparations of antibiotics (aminoglycosides and cephalosporins) in the hospital pharmacy, that were not stable, as commercial preparations were not available. The advent of successful chemotherapy with topical quinolones, which are stable in solution and commercially available, has made this type of treatment much easier to use on a clinic or out-patient basis.

The most popular combination that has been used, and a highly effective one, has been a cephalosporin (cefuroxime or ceftazidime) at 5% concentration (50 mg/ml) and an aminoglycoside (gentamicin or tobramycin) at 1.5% (15 mg/ml). The cefuroxime preparation is only stable for 1 week and has to be kept at +4°C; this does not apply to the gentamicin or tobramycin preparation. This situation has now been superseded by the introduction of the quinolone group of antibiotics (ciprofloxacin and ofloxacin) which are commercially available for topical drop therapy at 0.3% (3 mg/ml) (Ciloxan, Alcon; Exocin, Allergan). They have been shown in large controlled trials of bacterial keratitis to be equally effective to the cephalosporin/aminoglycoside combination.<sup>23,24</sup>

## Choice of antibiotics to use in microbial keratitis

### First-line Broad Spectrum Anti-microbial Therapy

#### Bacterial keratitis:

The decision for antibiotic choice is made after reviewing the history, clinical and laboratory examination. If a specific organism is seen viz. *Streptococcus pneumoniae* (as Gram positive diplococci) then a narrow spectrum antibiotic such as penicillin G (0.3% = 3 mg/ml [5000 units/ml]) should be used.<sup>12</sup> If a bacterial infection is suspected, or Gram positive or negative cocci or bacilli are seen in the corneal scrape, then first-line broad spectrum antibiotic therapy should be initiated (Table 2). The choice is either a commercially

Table 2. Choice of antibiotic or antimicrobial drug for chemotherapy of presumed or confirmed (culture-proven) microbial keratitis.

1% drugs = 10 mg/ml		
First-line Drugs	Narrow Spectrum	Broad Spectrum
Bacterial:	<i>S. pneumoniae</i> : Penicillin 0.3% (5000 units / ml)  <i>Ps. aeruginosa</i> : Ofloxacin or ciprofloxacin 0.3% + ceftazidime 5% or ticarcillin 5% or gentamicin 1.5% or tobramycin 1.5%  Marginal ulcer secondary to <i>S. aureus</i> blepharitis: Ofloxacin 0.3% drops to ulcer + Fucithalmic (fucidin) gel to lid margin	Gram positive & negative bacteria: Monotherapy with Ofloxacin or ciprofloxacin 0.3%  or  Combination therapy with Gentamicin or tobramycin 1.5% + cephalosporin (cephazolin, cefuroxime, ceftazidime) 5%
Fungal:	<i>Candida albicans</i> or yeasts: 5-FC 1% or a topical imidazole (miconazole, fluconazole) 1%  Mycelial fungus (hyphae seen on microscopy): Amphotericin 0.1% or natamycin 5% <i>Pseudallescheria boydii</i> Imidazoles 1% (resistant to polyenes)	Less severe cases: Imidazole (miconazole, fluconazole) 1% topically or itraconazole 200 mg orally once daily  More severe cases: Polyene (amphotericin 0.1% or natamycin 5%) (can also add an imidazole topically or itraconazole orally)
Mixed bacterial & fungal:	---	Choose combination of anti-bacterial and anti-fungal drug according to microscopy
Protozoal:	<i>Acanthamoeba</i> : Chlorhexidine 0.02% (or, if unavailable, PHMB) + propamidine (Brolene) 1% (or, if unavailable, hexamidine [Desmodine]) Microsporidium: topical 0.01% fumagillin 3 hrly	Do NOT use chlorhexidine and PHMB together (use only one biguanide as monotherapy)
Second-line Drugs	Narrow Spectrum	Broad Spectrum
Bacterial:	<i>Mycobacterium chelonae</i> : Amikacin 1.5% + / - or ciprofloxacin 0.3%  <i>Nocardia sp.</i> : Vancomycin 5% + / - amikacin 1.5% + / - trimethoprim given as 'Polytrim' drops or as neat Bactrim IV given topically  <i>Fastidious / anaerobic streptococci</i> (or Gram positive anaerobes): Vancomycin 5% + / - or clindamycin 2%  <i>Capnocytophaga sp.</i> : Penicillin, cephalothin, clindamycin, tetracycline erythromycin	Vancomycin 5% + amikacin 1.5% + / - ciprofloxacin 0.3% or trimethoprim ("Polytrim" or topical use of IV Septrin [Bactrim]) or rifampicin 2.5% ointment (for other possibilities, refer to [12])
Fungal:	Specific sensitivities for an isolated fungus:  For a 'lichen' infection, attempt therapy with tetracycline (1% ointment)	Polyene drug instead of an imidazole or vice versa or Combination of polyene drug and an imidazole - this should not be used prior to monotherapy of each Consider use of oral itraconazole for adjunctive therapy of keratitis by the systemic route
Protozoal:	Propamidine (Brolene) 1% + neomycin 0.5%. Only use this combination if chlorhexidine (or PHMB) is unavailable. Most cysts are resistant to neomycin.	



produced quinolone at 0.3% (ciprofloxacin or ofloxacin) or a 'forte' preparation of aminoglycoside and cephalosporin.<sup>23,24</sup> Although streptococci can be recorded as resistant to ciprofloxacin or ofloxacin in the laboratory, the high concentration obtained in the cornea with frequent drop therapy has provided successful chemotherapy - at least equivalent to the cephalosporin / aminoglycoside combination - in controlled trials.<sup>23,24</sup> Unfortunately, most hospital microbiology laboratories perform quinolone sensitivity tests at too low a concentration to reflect those obtained in the cornea with frequent drop therapy. Therapy should be continued until there is satisfactory resolution or, if therapy fails, stopped for reassessment (Figure 9).

An advantage gained by quinolone therapy, compared to cephalosporin / aminoglycoside (gentamicin or tobramycin) therapy, is the much broader range of pathogens against which it is effective. This includes *Mycobacterium chelonae* and *Nocardia sp.* both of which are resistant to the previously used combination therapy. Quinolones are highly effective against Gram negative rods and are the treatment of choice for *Pseudomonas aeruginosa* infections, combined with a second anti-pseudomonal drug.<sup>25</sup> The disadvantage of ciprofloxacin, which does not occur with ofloxacin, is that it precipitates in the cornea as crystals. This eventually reabsorbs after 9 months but meanwhile interferes with vision if there had been a central ulcer, causing haze and difficulty with night driving. In laboratory studies, ciprofloxacin has slightly more bactericidal activity against *Pseudomonas aeruginosa* than ofloxacin, but both have been effective in clinical trials for treating this infection; ofloxacin has more *in vitro* activity against *Chlamydia*.<sup>12</sup>

### Fungal keratitis:

First-line therapy for fungal infection depends on the genera involved. Hence, a corneal scrape should always be collected to distinguish as a minimum criteria whether there is a yeast or filamentous mycelial infection. Most yeasts are sensitive to all three groups of anti-fungal drugs - 5-FC (5-fluorocytosine), polyenes (amphotericin or natamycin) and the imidazoles (miconazole, clotrimazole, fluconazole - all given topically - and itraconazole given orally).<sup>26</sup> Mycelial fungi are all resistant to 5-FC, while those causing keratitis in the tropics in particular are variable in their sensitivities. However, serious fungal keratitis should always be treated with a polyene drug since they are fungicidal as opposed to the imidazoles which are fungistatic.<sup>12</sup> Dosages are given in Table 2. Full details of all preparations and how to produce them are given elsewhere.<sup>12</sup>

Infection with *Aspergillus sp.* will often respond to imidazoles, at least when treated with it in the UK, but *Fusarium sp.* are usually resistant and should always be treated with a polyene drug. The one exception is infection by *Pseudallescheria boydii*, which is resistant to the polyenes and should be treated with an imidazole. All anti-fungal therapy is by the topical route except for itraconazole, which is only available as tablets by the oral route. It has been shown to work effectively for keratitis due to *Aspergillus sp.*<sup>26</sup> In some countries, such as the UK, all therapy requires the drug to be produced by the hospital pharmacy as there are no commercial anti-fungal ocular preparations available. In

other countries, such as the USA and India, topical natamycin 5% is available commercially for topical ocular use. Therapy can also be successful for yeasts and *Aspergillus sp.* with commercially available itraconazole tablets (dose 200 mg, once daily) - this imidazole is concentrated into the cornea from the systemic route.<sup>12,26</sup>

### Presumed fungal and polymicrobial keratitis:

The prevalence of fungal keratitis needs to be known for the area in which the patient has developed keratitis. If the patient lives in a tropical country, such as Paraguay,<sup>27</sup> Ghana,<sup>9</sup> or South India,<sup>15</sup> then the chance of the keratitis being due to a fungus is at least 50% of which approximately half (up to 25% of all cases) will be polymicrobial with a mixed bacterial and fungal infection. In New Orleans, Louisiana (Southern USA) a rate of fungal keratitis was found of 18%.<sup>8</sup> In Singapore a retrospective survey has shown that fungi were a proven cause of keratitis on 17% of occasions compared to bacteria, while a rate of 6% was found in the recent study from Hong Kong.<sup>7</sup> In that study,<sup>7</sup> polymicrobial keratitis was seen particularly in patients who had used corticosteroid eye drops prior to presentation. Interestingly, fungal keratitis could not be detected in the intense dry heat of the Western Australian desert,<sup>10</sup> despite specific cultures for them. A corneal scrape should always be performed for Gram stain, and in the tropics, a second scrape should be obtained for a wet preparation stained with lactophenol cotton blue.<sup>12</sup>

First-line chemotherapy should include an anti-bacterial and an anti-fungal drug (Table 2) as it is not always easy to distinguish between a bacterial and fungal infection,<sup>12</sup> as well as the possibility of polymicrobial infection. In India, where there is more experience than elsewhere but also more polymicrobial disease, it has been suggested that the 'best guess' is wrong on 1 occasion out of every 4. Classically, a fungal keratitis has a dry lesion with a feathery edge, and there may be satellite lesions. However, acute purulent keratitis with hypopyon, similar to acute bacterial infection, can also occur with fungi especially with *Fusarium sp.*<sup>12</sup> For less severe cases of probable polymicrobial disease, a combination of topical ofloxacin 0.3% and miconazole (or another imidazole) 1% in arachis oil should be used. Treatment should be given by an intensive regime as outlined above. For more severe cases, topical amphotericin 0.1% or natamycin 5% should be used instead of the imidazole.<sup>29</sup> Adjunctive surgery may be needed to remove tissue made necrotic by the fungal infection - if this is not done, the anti-fungal drug will not penetrate to be fungicidal.<sup>12</sup>

### Acanthamoeba keratitis:

First-line therapy for *Acanthamoeba* keratitis should include use of the topical bis-biguanide 'chlorhexidine' 0.02% in normal saline which has to be individually prepared.<sup>12,17,18</sup> It should be used together with the diamidine 'propamidine' 1% drops (as Brolene - commercially available). If chlorhexidine cannot be obtained locally, it should be ordered from Zeneca Pharma, Macclesfield, Cheshire, UK. In its absence, use can be made of the polymeric molecule - polyhexamethylene biguanide (PHMB) - but it is not



licensed as a drug being produced as a hard surface chemical sterilant in various grades of impurity. If propamidine is not available, another diamidine 'hexamidine' (Desmodine) has been used successfully in several cases.<sup>30</sup>

### Second-line broad spectrum Anti-microbial therapy

Second-line therapy is initiated when first-line therapy has failed. The cornea should be scraped again and new stained preparations made (Figure 9). Additional stains will be needed for those organisms which do not stain with Gram stain.<sup>2</sup> A diagnostic corneal biopsy may be required which has the advantage of allowing histology or electron microscopy to be performed on the tissue sample. An assumption is made that there is infection - microbial keratitis - with a fastidious organism that has not been seen or isolated. These include:

1. microaerophiles (such as some strains of streptococci which may be resistant to penicillin [Figure 7]), capnophiles (such as *Capnocytophaga* or some strains of *S. aureus*)<sup>31</sup> or anaerobic bacteria (such as anaerobic streptococci or *Clostridium perfringens*)<sup>12</sup>
2. *Nocardia* sp.
3. *Mycobacterium chelonae*, *fortuitum* or *gordonae*
4. Fungi (normally plant or vegetable species) that will not grow on Sabouraud's agar
5. Free-living amoebae or microsporidia

These microbes will be sensitive to the various combinations of antibiotics recommended in Table 2. This includes penicillin-resistant streptococci which are sensitive to vancomycin given alone or in combination as part of second-line broad spectrum chemotherapy (Figure 7). The bacteria above are mostly resistant to the aminoglycosides and cephalosporins but are expected to be sensitive to vancomycin, tetracycline, clindamycin and clarithromycin / azithromycin except for *M. chelonae* which is only sensitive to amikacin and quinolones; some microaerophiles and anaerobic bacteria will also be sensitive to penicillin. In addition, in particular for *Nocardia* sp., therapy can be given with Bactrim or Septrin (sulphonamide / trimethoprim mixture) using the intravenous preparation for topical ocular drop therapy without any dilution - this has been reported as treating nocardial infection very satisfactorily after 10 days as monotherapy.

If therapy fails again after using a second-line antibiotic combination, corneal biopsy is indicated (Figure 9). It is a very useful technique to identify the incriminating organism deep inside the stroma when it has not been seen on microscopy of a corneal scraping or cultured in the laboratory. Additional histological stains include Periodic Acid Schiff and methenamine silver to stain hyphal fragments and protozoal cysts or other unsuspected organisms. In addition, transmission electron microscopy can be particularly useful here as micro-organisms (bacteria, fungi, protozoa and others) can be recognised without the need for any special stain. Such a situation can follow trauma to the eye when, for example, concrete chips contaminated with a lichen (algal / fungal mixture) cause a stromal injury. This may occur in

building workers who cut concrete blocks without wearing protective eye goggles. A progressive keratitis can develop that is refractory to first-line antibiotics (Figures 8A-E). In this case a 'glacier' keratitis developed due to the lichen. Treatment with tetracycline alone was only partially successful and a corneal graft was required but this did not become reinfected afterwards. The components of the lichen can be seen on the histopathological and EM sections from the corneal biopsy; with difficulty there was growth of a cyanobacterium and *Azotobacterium* sp.

### Adjunctive use of corticosteroids

When a corneal infection with a fungus or *Acanthamoeba* is treated with corticosteroids, the keratitis becomes considerably worse because of the suppression of macrophages.<sup>12</sup> Corticosteroids should never be used in the treatment of fungal keratitis and should be withheld for as long as possible in the treatment of *Acanthamoeba* keratitis.<sup>32,33</sup> In the recent Hong Kong study,<sup>7</sup> not only was polymicrobial keratitis seen more frequently when patients presented using corticosteroid eye drops but both cases of nocardial infection occurred whilst corticosteroids were being administered. Gebauer *et al*<sup>10</sup> found that 26% of 39 patients in their study of severe microbial keratitis in Western Australia were being treated with corticosteroids on presentation. Although 37 out of 39 patients were also receiving topical antibiotics, 25 were being treated with chloramphenicol which is only bacteriostatic; all patients failed to respond and had continuing severe infection.

Corticosteroids may be used adjunctively to suppress inflammation in a bacterial infection once sufficient antibiotics have been given, but only with great caution, particularly with *Pseudomonas aeruginosa* infection when frequent use of anti-pseudomonal drugs is also required in maximum dosage or there will be a severe recurrence.<sup>34</sup>

### Conclusions

1. Before initiating antimicrobial chemotherapy for keratitis, collect a corneal scraping for Gram stain and other stains as necessary. If indicated, collect a second scrape for fungi making a wet preparation using lactophenol cotton blue. If the patient wears soft contact lenses and has excessive pain and photophobia with infiltration of corneal nerves seen on slit-lamp microscopy, also collect a wet preparation for *Acanthamoeba*, using normal saline. Carry out an appropriate culture of the corneal scrape whenever possible.
2. Consider the site of the ulcer, the type of infiltrate, the history of eye disease or trauma and whether contact lenses are worn; in the latter case, examine the storage case for bacteria and amoebae.
3. Begin empirical treatment with first-line broad spectrum antibiotics (quinolones or a cephalosporin / aminoglycoside combination). Include an anti-fungal drug if hyphae are seen on the corneal scrape smear or if the patient lives in a tropical area where fungal keratitis is prevalent.
4. Modify antibiotic therapy according to cultures and antibiotic sensitivities when available.



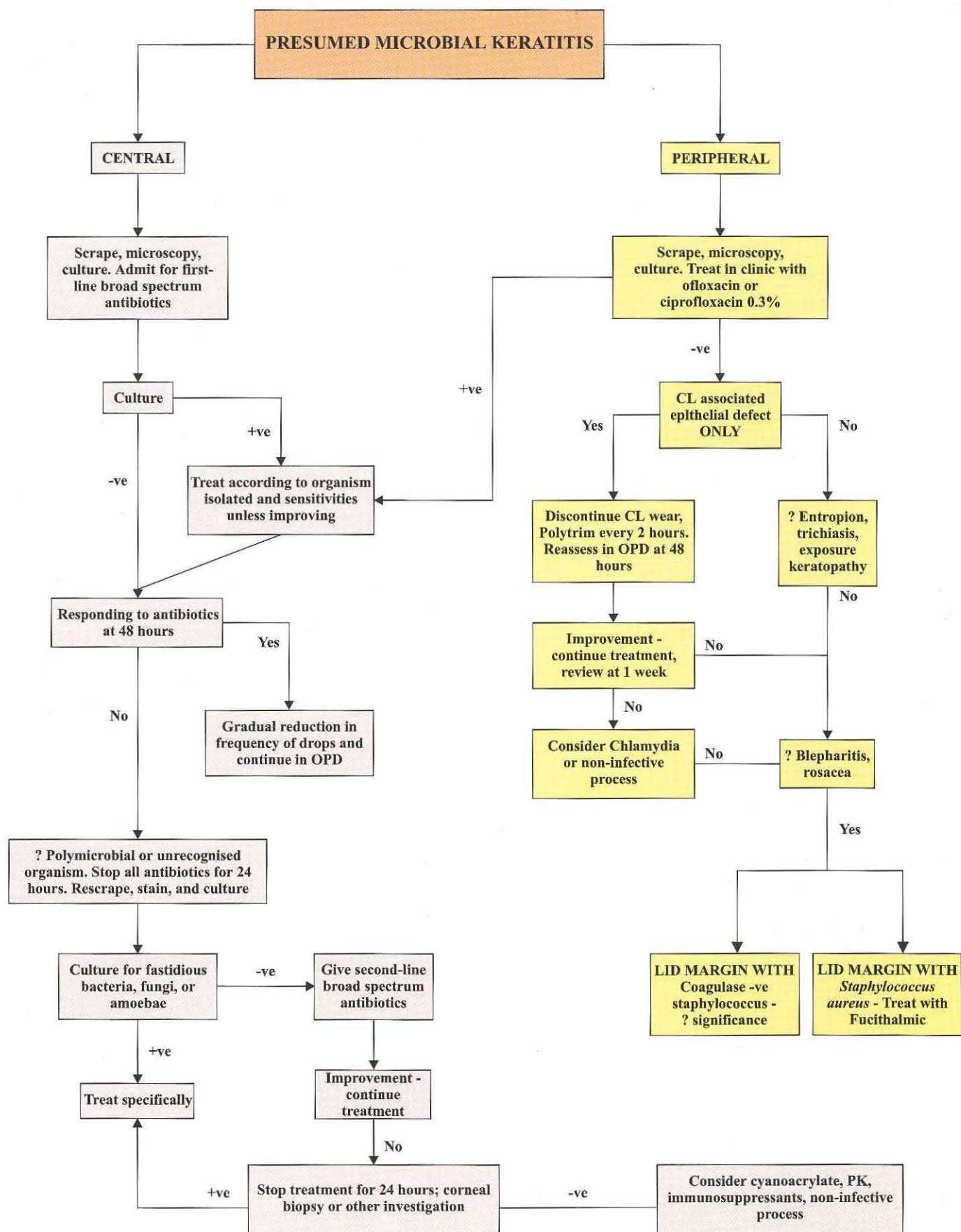


Figure 9.

Adapted from Figure 3 Chemotherapeutic algorithm for the management of presumed microbial keratitis, BJO 1998;82:137-45.



5. For non-responsive 'culture-negative' microbial keratitis, stop first-line antibiotics and liaise with the laboratory. Stop antibiotics for 24 hours and rescrabe the cornea to culture for fastidious organisms - microaerophilic and anaerobic streptococci especially with trauma, mycobacteria or nocardia or capnophilic organisms especially with pre-existing ocular surface disease and *Acanthamoeba* or other free-living amoebae for soft

contact lens wearers.

6. Begin a second-line combination of antibiotics and/or anti-fungal and/or broad spectrum anti-protozoal drugs for possible microbes as considered relevant.

7. If failure occurs, perform an investigative corneal biopsy.

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