

New Developments in Antibacterial Chemotherapy for Bacterial Keratitis

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Core Messages

- The treatment of bacterial keratitis depends on identifying the causative agent and selecting an appropriate antimicrobial.
- The initial antimicrobial that is prescribed should be selected based on
 - (i) The most likely causative bacterium, from contemporaneous clinical and laboratory data (bacterial spectrum and antimicrobial studies)
 - (ii) Knowledge of the pharmacokinetics and pharmacodynamics of the agent
- Treatment is then modified based on
 - (i) Actual bacterial species identified
 - (ii) Antimicrobial susceptibility assays
 - (iii) Clinical response
- Antimicrobial combination therapy should be based on those combinations
 - (i) Which are likely to produce a synergistic response
 - (ii) For which the suspected or isolated bacteria are likely to be susceptible
- Antimicrobial combinations which increase the antimicrobial spectrum but which are likely to be antagonistic or inhibitory should not be used.

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- Host and bacterial factors and their interaction must also be considered as they both play a crucial role in determining clinical outcome and the risk of recurrent disease.
 - (i) Specific host risk factors should be identified such as ocular surface disease.
 - (ii) Bacterial isolates should be kept and investigated for known virulence factors.
- The relevant contribution or interaction of host and bacterial factors to the clinical outcome may be dependent on the individual patient. Future treatment of recurrent disease needs to be tailored according to the relevant contribution of host and bacterial factors in the individual patient. An example might be recurrent *Staphylococcus aureus* corneal ulceration in a patient with chronic meibomian gland disease with nasal colonisation by PVL-producing *Staphylococcus aureus*.
- Novel antimicrobials under evaluation include besifloxacin, meropenem, tigecycline and linezolid

Introduction

The ideal treatment of bacterial keratitis depends on identifying the causative agent and selecting an appropriate antimicrobial. The initial antimicrobial that is prescribed, however, is selected based on the most likely causative bacteria from contemporaneous clinical and laboratory data (bacterial spectrum and antimicrobial studies) and knowledge of the pharmacokinetics and pharmacodynamics of the agent. Treatment is then modified based on the actual bacterium identified and its antimicrobial susceptibility assays, and clinical response. In addition, host and non-antimicrobial virulence factors must also be considered as they both play a crucial role in determining clinical outcome and the risk of recurrent disease.

Epidemiology

The epidemiological patterns of bacterial keratitis vary with patient population, health of the cornea, geographic location and climate. Bacteria are responsible for a larger proportion of corneal ulceration in temperate climates such as the United Kingdom and northern United States than in tropical regions such as south India, where fungal infection predominates [1]. There are approximately 6,000 cases of bacterial keratitis per year in the UK (c.150 per year for a city the size of Liverpool or Manchester).

Visual Morbidity

Bacterial keratitis leads to severe inflammation, thinning, distortion, vascularisation and scarring of the cornea. The severity of the infection correlates positively with increased scarring and corresponding loss of vision. Many cases require hospitalisation with prolonged treatment periods. Bacterial keratitis accounts for approximately 8% of corneal transplants undertaken in the UK [Ocular Tissue Advisory Group to NHS BT UK]. Patients with an abnormal ocular surface from neurotrophic keratopathy, herpes simplex keratitis, Sjogrens syndrome and contact lens wearers, may have different responses to treatment despite having the same bacteria isolated from their corneal ulcer.

Documentation

Attention to clinical detail is helpful in recognising clues to the aetiological agent (characteristics of the corneal ulcer), host factors (presence of ocular surface disease) and for monitoring the clinical response. Precise and accurate documentation and recording of the condition is therefore important, and photography or detailed drawings (Fig. 2.1 [2]) are needed.

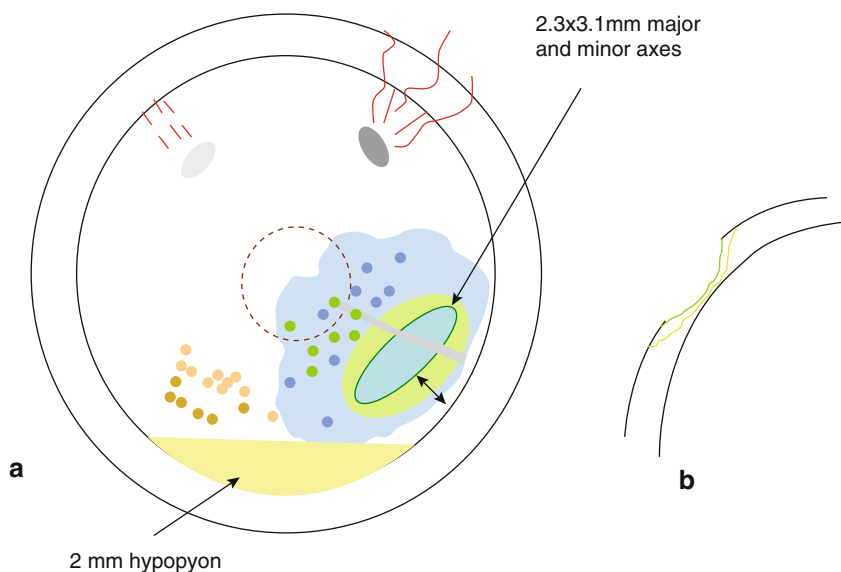


Fig. 2.1 Drawing of corneal ulcer (adapted from Waring et al. [2]) (a) anterior posterior view, (b) cross section through ulcer. *Black continuous circle*, corneal limbus; *outer dashed line*, contact lens. *Blue shade*, stromal oedema; *blue dots*, epithelial oedema. *Green dots*, punctate keratopathy; *green line*, epithelial defect. *Red straight hashed lines*, ghost vessels; *straight lines*, deep stromal vessels; *wavy lines*, superficial vessels. *Grey oval shapes*: light grey, old scar; dark grey recent scar. *Orange and brown dots*: new and old keratitic precipitates. *Yellow shade*: hypopyon, corneal infiltrates and abscess formation. *Brown hashed circle*: pupil

Summary for the Clinician

- Bacterial keratitis almost always results in a corneal scar
- Good accurate documentation is required in follow up of corneal ulcers

Causative Factors

Predisposing factors that facilitate successful bacterial colonisation and invasion of the cornea include trauma, contact lens wear, ocular surface disease [3, 4] and corneal surface abnormalities [5]. These are all significant risk factors and often are associated with recurrent disease [6]. Although the majority of patients have one or more risk factors, contact lens use is seen as the major risk factor in most studies [5, 6]. Lam et al. [7] reported that the incidence of bacterial keratitis was sixfold higher in contact lens wearers than in the general population and an increased incidence of *Pseudomonas aeruginosa* (*P. aeruginosa*) infections coincided with the increased popularity of contact lens wear. Among contact lens users, extended-wear contact lens wearers are at an increased risk of bacterial infection relative to daily disposable lens wearers [3]. Contact lens wear and correspondingly, contact lens-related keratitis is rarer in developing countries [4].

Summary for the Clinician

- In treating bacterial keratitis, host factors must be considered; they may be indicators for recurrent disease.
- Risk factors include contact lens use, ocular surface disease, trauma and Sjogrens Syndrome.

Causative Bacteria

Of the bacteria associated with an ulcerative keratitis, *P. aeruginosa*, a Gram-negative bacillus, and *Staphylococcus aureus*, a Gram-positive coccus, are the most common bacterial pathogens. Although coagulase-negative staphylococci (CNS) account for a significant proportion of bacteria that are isolated from patients with bacterial keratitis, they are found in the conjunctival flora [8, 9] and their primary role in the disease is unclear. For example, a recent study has shown a positive correlation between clinical outcome and in vitro susceptibility for *S. aureus* and *P. aeruginosa*, but not for CNS [10]. Although *Streptococci* spp. are isolated less commonly, *Strep. pneumoniae* is often associated with a poor outcome and accounts for the greatest percentage of cases where eyes are lost [10]. Prompt intervention is crucial if a *Strep. pneumoniae*-related keratitis is suspected.

Table 2.1 Percentage of different bacterial species from patients with bacterial keratitis: comparable studies

Organism	Sueke [11] (UK) n = 772	Tuft [12] (UK) n = 1,312	Bourcier [5] (France) n = 208	Bharati [13] (India) n = 1,109
Gram-positive bacteria				
Coagulase-negative staphylococci	26.9	N/A	48.1	17.4
Methicillin sensitive	21.7	N/A	N/A	N/A
Methicillin resistant	5.2	N/A	N/A	N/A
<i>Staphylococcus aureus</i>	13.6	33.4	7.7	3.9
Methicillin sensitive	12.4	N/A	N/A	N/A
Methicillin resistant	1.2	N/A	N/A	N/A
<i>Streptococcus</i>	12.6	19.0	9.2	42.4
<i>Strep. pneumoniae</i>	3.4	N/A	3.4	37.5
Other alpha-haemolytic	7.8	N/A	5.8	4.4
Beta-haemolytic ^a	1.4	N/A	N/A	0.5
Other Gram-positive ^b	4.4	3.5	17.8	6.3
Gram-positives subtotal	57.4	55.9	82.8	70.1
Gram-negative bacteria				
<i>Pseudomonas aeruginosa</i>	20.9	24.8	10.1	18.0
<i>Enterobacteriaceae</i>	13.4	8.5	6.3	1.1
<i>Serratia</i> spp.	4.4	3.0	5.3	0.2
<i>Klebsiella</i> spp.	2.1	0.4	N/A	0.4
<i>Citrobacter</i> spp.	1.6	0.4	N/A	2.6
<i>Proteus</i> spp.	1.6	0.7	1.0	N/A
<i>E. coli</i>	1.2	0.6	N/A	N/A
<i>Enterobacter</i> spp.	1.0	2.1	N/A	0.8
<i>Morganella morganii</i>	0.1	N/A	N/A	0.5
<i>Pantoea</i> spp.	0.1	N/A	N/A	N/A
Other	1.2	1.3	N/A	29.9
<i>Moraxella</i> spp.	2.6	5.9	0.5	N/A
<i>Haemophilus</i> spp.	1.4	2.2	N/A	N/A
Other Gram-negatives ^c	4.2	2.8	N/A	N/A
Gram-negatives subtotal	42.5	44.2	16.9	20.9

^aLancefield Group A (0.3%), Group B (0.1%), Group C (0.3%), Group G (0.8%)

^b*Corynebacterium* spp. (2.6%), *Bacillus* spp. (1.7%), *Enterococcus* spp. (0.9%), *Listeria* spp. (0.1%)

^c*Acinetobacter* spp. (1.2%), *Stenotrophomonas maltophilia* (1.2%), *Neisseria* spp. (0.3%), *Pasturella* spp. (0.3%), *Aeromonas* spp. (0.1%), *Eikenella* spp. (0.1%), *Agrobacterium* spp. (0.1%), *Alcaligines* spp. (0.1%), *Methylbacterium* spp. (0.1%)

Table 2.1 illustrates the wide variability in the proportions of bacteria causing keratitis between four similar studies set in different geographical locations. For example, the proportion of Gram-positive isolates varies between 56% and 83% and the proportion of Gram-negative isolates varies between 17% and 44%. Differences may reflect climate of the country or prevalence of risk factors such as contact lens use, trauma or co-existent ocular disease.

Summary for the Clinician

- Causative bacteria and host factors can vary significantly between geographical locations.
- *Streptococcus pneumoniae* is associated with the worst outcomes and requires prompt treatment.

Investigation of Keratitis

There are various approaches to the microbiological investigation of patients with suspected keratitis. Traditional methods include the use of multiple corneal scrapes with direct inoculation onto different enrichment media. Collecting multiple scrapes, particularly from the eye of an uncooperative patient, is not always easy. Growing a minute sample in culture on an agar plate is technically difficult: the inoculum might be deposited beneath the surface of the agar, a full range of fresh culture media may not be always available and the non-laboratory setting poses an increased risk of extraneous contamination of culture plates. These problems explain the reluctance of some ophthalmologists to perform a corneal scrape to reach a microbiological diagnosis. For example, McDonnell et al. [14] found that 49% of ophthalmologists treated corneal ulcers empirically without attempting to identify the causative organism. Kaye et al. [15] reported that collecting two corneal scrapes, one for a smear and the other placed in an enrichment transport medium (such as brain heart infusion broth), resulted in detection rates similar to those of direct plating with no significant loss of organisms.

The role of polymerase chain reaction (PCR) techniques has recently been evaluated to diagnose bacterial keratitis [16, 17]. PCR has the advantage of being a quicker and more sensitive technique than traditional culture methods; however, its high sensitivity may result in false-positive results. Although further larger studies comparing the two techniques are necessary to evaluate its place in the diagnosis of bacterial keratitis, it would seem reasonable to include PCR as part of the patient's investigation.

Laboratory Diagnosis: Susceptibility Testing

Topical antimicrobials form the mainstay of treatment of bacterial keratitis. Despite their widespread usage, clinical decision making has rested upon susceptibility data derived from and for systemic infections. The relationship between bacterial susceptibility to antimicrobials and clinical outcome has only recently been demonstrated [10]. Although there are significant associations between the

minimum inhibitory concentration of the prescribed antimicrobial and the clinical outcome, the parameters of the association may be dependent on the particular bacterial species and antimicrobial.

Susceptibility and Resistance of Bacterial Isolates

The basic laboratory measurement of the activity of an antimicrobial is the MIC, which is defined as the lowest antimicrobial concentration that will inhibit overnight growth of bacteria. The MIC is used to determine the susceptibility and resistance of an antimicrobial, by comparing it to a set of standard MICs based on the safe achievable concentrations of antimicrobial in the serum. Standards are set by the Clinical and Laboratory Standards Institute in the United States and British Society for Antimicrobial Chemotherapy (BSAC) in the UK. Interpreting resistance and susceptibility needs to be done with caution, as currently there are no standards for topical ocular therapy that relate to the concentrations of antimicrobial in ocular tissue. For example, Sueke et al. [11] found the range of MICs for ciprofloxacin against 140 *P. aeruginosa* isolates to be 0.016 to 6.0 mg/L. Using the breakpoint figure of 1.0 mg/L from BSAC, which was calculated from systemic data, 98% of isolates were susceptible to ciprofloxacin. These figures can be expressed graphically in comparison to the other three fluoroquinolones tested (Fig. 2.2). The MIC₉₀ is a descriptive statistic estimating the antimicrobial concentration which will inhibit the growth of 90% of isolates and the MIC₅₀ is the concentration which inhibits 50% of isolates. Figure 2.3 illustrates the MICs of ciprofloxacin against 126 *S. aureus* isolates. Antimicrobial concentrations that are achieved in the cornea and aqueous are indicated on the graph.

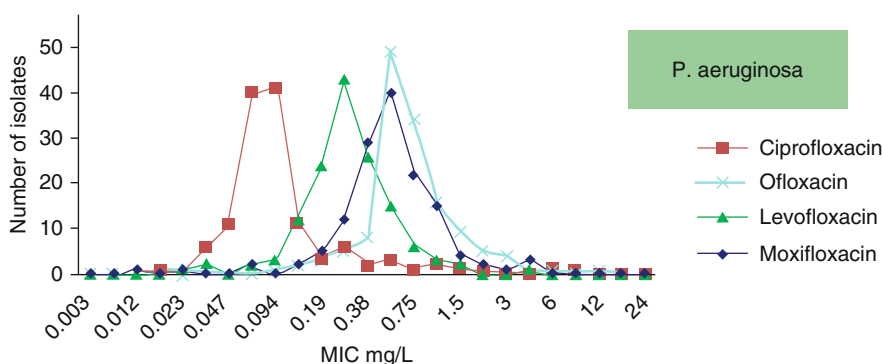


Fig. 2.2 Minimum inhibitory concentrations (mg/L) of four fluoroquinolones against 160 *P. aeruginosa* isolates collected from patients in the United Kingdom with bacterial keratitis [11]

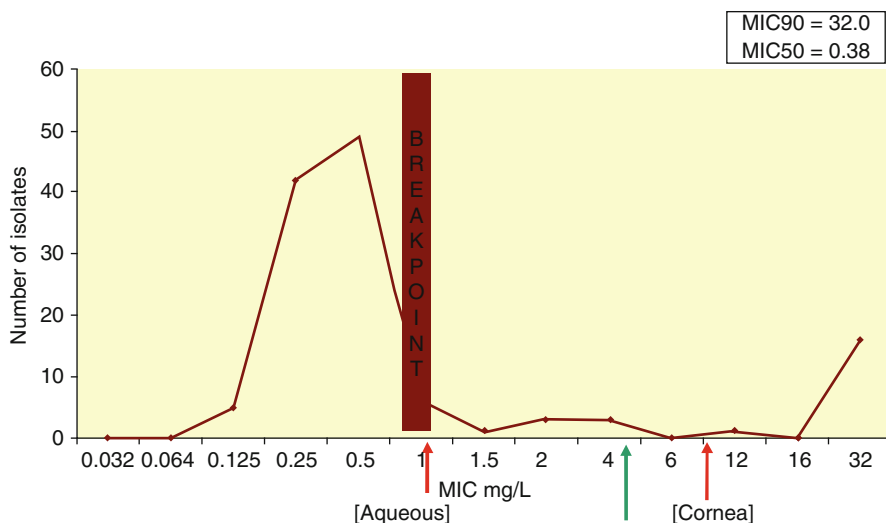


Fig. 2.3 Minimum inhibitory concentrations (mg/L) of ciprofloxacin against 126 *S. aureus* isolates taken from the United Kingdom from patients with bacterial keratitis [11]. Also annotated on the graph are concentrations of ciprofloxacin in the aqueous and cornea (red arrow, chemical concentration; green arrow, bioassay concentration) [18]

Treatment: Antimicrobials

The efficacy of an antimicrobial in the cornea is dependent on the relationship between its pharmacodynamic and pharmacokinetic properties.

Pharmacodynamics, the effect of the drug on the bacteria, is measured by determining its MIC, as defined above. Pharmacokinetics is the ability of the drug to pass through the body and is therefore also crucial in determining the efficacy of an antimicrobial in treating bacterial keratitis. Topical application of an antimicrobial to the cornea may achieve a very different concentration and bioavailability in the tissue than can be achieved in the serum after systemic administration. Physicochemical properties of the drug such as lipophilicity, molecular weight, pH, and stability in solution may play a critical part. In addition, physiological properties of the cornea and drug formulation may determine drug corneal penetration [19]. For example, the molecular mass of ciprofloxacin is 331 (Fig. 2.4) and that of teicoplanin is 1907 (Fig. 2.5) which may explain why ciprofloxacin has superior corneal penetration than teicoplanin [18]. Studying the relationship between pharmacokinetics and pharmacodynamics (otherwise known as PK/PD analysis) results in a complete overall understanding of how a drug works in practice. This has recently been studied in bacterial keratitis for ciprofloxacin and teicoplanin. Kaye et al. [10] compared the differences between the predicted (tissue concentration based upon chemical measurement) and actual activity of an antimicrobial based upon a bioassay (measurement of antimicrobial activity in the tissue). They found a significant difference

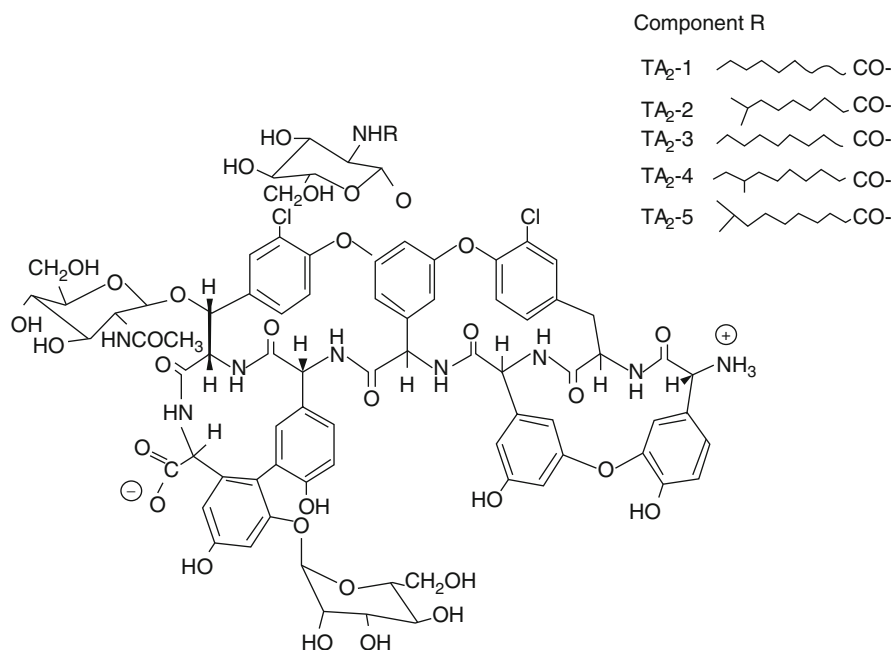
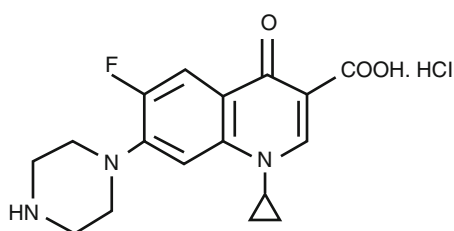


Fig. 2.4 Molecular structure of teicoplanin: molecular mass 1,907

Fig. 2.5 Molecular structure of ciprofloxacin: molecular mass 331



between the chemical concentration and biological activity of ciprofloxacin following topical administration to the cornea.

Current Antimicrobials in Use

The ophthalmologist has a number of potential antimicrobials at their disposal to treat bacterial keratitis. When choosing an antimicrobial prior to the results of bacterial culture and sensitivity, the choice of one drug over another may be determined by a variety of factors, for example local bacterial epidemiology, drug cost, and drug toxicity.

The Fluoroquinolones

The development of an old class of antimicrobials, the fluoroquinolones, in the 1990s, provided for the first time a class of drugs with broad Gram-positive and Gram-negative activity and little corneal toxicity [20]. Fluoroquinolones work by inhibiting DNA gyrase (also known as Topoisomerase II) and topoisomerase IV, enzymes necessary in bacterial DNA synthesis. Second-generation fluoroquinolones, ciprofloxacin (see Fig. 2.4) and ofloxacin, are widely used in treating bacterial keratitis. They offer a great potency against Gram-negative bacilli (including *P. aeruginosa*), moderate activity against *S. aureus* and little activity against streptococci and the pneumococci. Despite the success of the first- and second-generation fluoroquinolones, there has been a trend (based on systemic breakpoints) towards an increase in resistance of both *S. aureus* [21] and *P. aeruginosa* [22].

Further molecular modifications of the fluoroquinolones in 2000s lead to the development of the third-generation levofloxacin, and the fourth-generation moxifloxacin and gatifloxacin. These agents have greater potency against Gram-positive bacteria, in particular the Streptococci. The later-generation fluoroquinolones unfortunately have not been a treatment panacea because of the emergence of resistance (albeit based on systemic breakpoint data) [23, 24]. Park et al. [25] showed a rate of 2% resistance (based again on systemic breakpoint data) to moxifloxacin and 5% to gatifloxacin in isolates of normal bacterial ocular flora. Sueke et al. [11] showed a rate of 2% resistance using systemic breakpoint data to moxifloxacin and 16% to ciprofloxacin in *S. aureus* isolates from patients with bacterial keratitis. A number of pharmacokinetic studies have shown moxifloxacin to have superior corneal penetration compared to the other fluoroquinolones [26–28]. For example, in a rabbit endophthalmitis model [28], aqueous levels of levofloxacin were 9.4 mg/L, and moxifloxacin was 43.3 mg/L after topical administration. The greater lipophilicity of moxifloxacin compared to the other fluoroquinolones may explain this phenomenon.

Aminoglycosides

Aminoglycosides such as gentamicin and tobramycin are often used in treating bacterial keratitis. They have a broad range of bactericidal activity against many bacterial species, particularly Gram-negative rods. They have an affinity to bacterial 30 S and 50 S ribosomal subunits producing a non-functional 70 S initiation complex resulting in an inhibition of protein synthesis. They are sometimes given in combination with predominantly Gram-positive antimicrobials. Their use is limited by their associated corneal toxicity [29].

Sueke et al. [11] showed gentamicin to have 4% resistance using systemic breakpoints against *S. aureus* and *P. aeruginosa*, whereas amikacin had no resistance to *S. aureus* and 4% to *P. aeruginosa*. Gentamicin has, however, been shown to have poor corneal penetration which may be due to the hydrophobic nature of the compound. Baum et al. [30] showed that the concentration of gentamicin in the aqueous at 1 hour is only 1 mg/L, which is lower than the suggested MIC using systemic breakpoints.

Cephalosporins

Cephalosporins have a broad spectrum of activity, including effective action against *Haemophilus* species. They contain a β -lactam ring similar to penicillin but have the advantage of being resistant to the penicillinases. They inhibit bacterial cell wall synthesis and are well tolerated topically. The first-generation cephalosporins include cephalazolin, second-generation cefuroxime and third-generation ceftazidime. Cefuroxime has often been used in combination with an aminoglycoside for the empirical treatment of suspected bacterial keratitis. Cefuroxime and ceftazidime had high MICs against *S. aureus* and *P. aeruginosa* suggesting a significant degree of antimicrobial resistance; however, systemic breakpoints were not available to formally assess this. Jenkins et al. [31] found that following topical administration to cataract surgery patients, aqueous concentrations of cefuroxime were only significant when applied once the corneal wound had been fashioned. This suggests poor corneal penetration of cefuroxime which may be explained as the cephalosporins are hydrophobic [31].

Other Antimicrobials Used

Glycopeptides such as teicoplanin and vancomycin have activity against Gram-positive bacteria, including methicillin and penicillin-resistant staphylococci. They inhibit the biosynthesis of peptidoglycan polymers during the second stage of bacterial cell wall formation, at a different site of action from that of the β -lactam antimicrobials. They also have an excellent activity against a variety of Gram-positive bacilli, but not Gram-negative bacteria which are inherently resistant. The glycopeptides are, however, large molecules and in the intact corneal epithelium show a reduced corneal penetration, as mentioned previously [18].

Summary for the Clinician

- The fluoroquinolones provide good activity against Gram-negative and most Gram-positive bacteria causing an ulcerative keratitis, although resistance of the latter is emerging.
- Additional specific Gram-positive coverage is offered by teicoplanin or vancomycin.

Development of Existing and New Classes of Drugs

Besifloxacin

Besifloxacin is a novel fluoroquinolone for topical ophthalmic use, recently approved by the US Food and Drug Administration (USFDA) for the treatment of bacterial conjunctivitis [32]. Besifloxacin appears to have a broad spectrum of activity against

aerobic and anaerobic bacteria, possibly due to its cyclopropyl group and chloride substituent at C-8 improving its activity against DNA gyrase and topoisomerase IV enzymes. Besifloxacin has been shown to be active against both Gram-positive (*S. aureus*, *Strep. pneumoniae*, *Corynebacterium* and *Propionibacterium acnes*) and Gram-negative organisms (*H. influenzae*, *Moraxella*, *Escherichia coli*, *Neisseria gonorrhoeae* and *P. aeruginosa*). Recent studies have found besifloxacin to have good pharmacokinetic parameters in vitro [33] as well as excellent efficacy in animal models of keratitis, compared to fourth-generation fluoroquinolones [34, 35].

Tigecycline

Tigecycline [36] is a glycylcycline with activity against most aerobic and anaerobic Gram-positive and -negative bacteria but with limited activity against *P. aeruginosa*. Glycylcyclines are bacteriostatic agents that inhibit protein synthesis in bacteria by reversibly binding to the 30 S ribosomal subunit. Sueke et al. [27] showed tigecycline to have no resistance to any Gram-positive isolates using systemic breakpoints, but complete resistance to *P. aeruginosa*. Corneal pharmacokinetics of tigecycline, however, have not yet been determined.

Linezolid

Linezolid [37], the first of a new class, the oxazolidinones, is a synthetic compound with activity against all the major Gram-positive groups of bacteria, but no activity against Gram-negative bacteria. Linezolid works by inhibiting bacterial ribosomal protein synthesis by binding to a site on the 50 S ribosomal subunit, thus preventing the formation of a 70 S initiation complex. Pharmacokinetic studies using animal models of keratitis have showed good corneal penetration and no recorded toxicity with linezolid [38, 39]. Sueke et al. [11] showed linezolid to have no resistance against Gram-positive isolates including methicillin-resistant *S. aureus*.

Meropenem

Meropenem [40] is a broad-spectrum carbapenem that is currently FDA approved to treat skin infections, intraabdominal infections and bacterial meningitis. Like other carbapenems, it is a β -lactam antimicrobial, working through bacterial cell wall inhibition. It has activity against Gram-positive and -negative pathogens, including extended-spectrum lactamases (ESBL) and AmpC-producing Enterobacteriaceae. Sueke et al. [11] showed meropenem to have wide coverage against both Gram-positive and Gram-negative microorganisms, where only one of the 772 isolates tested (*P. aeruginosa*) was resistant using systemic breakpoints. Corneal pharmacokinetics of meropenem are not yet known; however, intravitreal meropenem in a rabbit model of endophthalmitis [41] did not show any evidence of toxicity.

Similarly, intravenous meropenem prior to cataract surgery showed penetration of the drug into the anterior chamber with no notable side effects [42].

Developing Ophthalmic Breakpoints: Relation Between MIC and Clinical Outcome

There is good evidence demonstrating the relationship between the MIC of topically applied antimicrobials and clinical outcome in bacterial keratitis [10]. This relationship is particularly well established for pathogenic bacteria such as *P. aeruginosa* and *S. aureus*. Figure 2.6 summarises the relationship for the patients in a study by Kaye et al. [10] between a measure of clinical outcome (healing time to ulcer size: HT/UA) and the lowest MIC of the particular antimicrobial agent used. The general linear multivariate model revealed a weak but significant association between the MIC of the antimicrobial prescribed and clinical outcome defined by the ratio of healing time to ulcer size. The importance of the bacterial type and antimicrobial used for treatment is indicated by the significant associations between the fluoroquinolone MIC and clinical outcome for *Pseudomonas* spp., *S. aureus* and *Enterobacteriaceae* but not for *Streptococcus* spp. or CNS. The MIC is therefore an important measure for evaluating the potential effectiveness of topically applied antimicrobials in the treatment of bacterial keratitis.

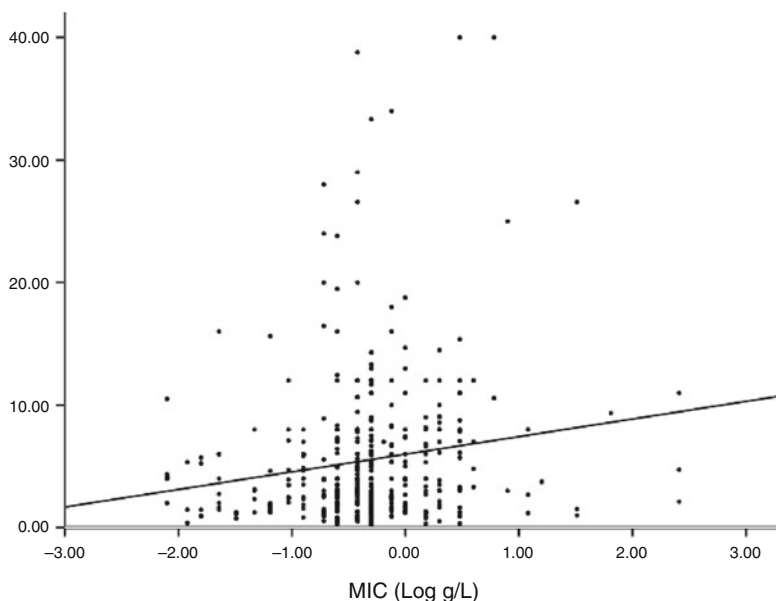


Fig. 2.6 Clinical outcome and MIC: antimicrobial used and all bacterial isolates. Healing time to ulcer area (HT/UA) (days per mm²), logarithm (Log) of Minimum inhibitory concentration (MIC mg/L). Hypothetical susceptible and resistant outcomes (HT/UA of 3.5 and 7 days/mm²) corresponds to an MIC of 0.1 and 10 mg/L [10]

Summary for the Clinician

- The minimum inhibitory concentration (MIC) is defined as the lowest antimicrobial concentration that will inhibit overnight growth of bacteria.
- A relationship has now been determined between MIC and clinical outcome for *S. aureus* and *P. aeruginosa*.

Combination Therapy

As opposed to single therapy, an antimicrobial combination offers a broader spectrum of activity and may reduce selective pressures. This may be of particular importance for the fluoroquinolones, as increasing resistance has been reported in *S. aureus* and *P. aeruginosa* isolates from cases of bacterial keratitis [9, 21–24]. An often overlooked reason for combination therapy, however, is not for providing a broader spectrum but for an increased antimicrobial effect. In particular, combination therapy may result in synergy as occurs, for example, with the combination of penicillin and gentamicin when used in the treatment of enterococcal endocarditis [43, 44]. This synergistic effect can be explained by the increased ease of gentamicin passage into the bacterial cell, due to cell wall disruption caused by the action of penicillin. Conversely, combinations of antimicrobials may be antagonistic, as occurs with the combination of chloramphenicol and penicillin in the treatment of pneumococcal meningitis [45]. The presumed reason for this antagonism is that chloramphenicol, a bacteriostatic agent, by reducing growth prevents penicillin, which requires a dividing and growing organism from having its full effect on the cell wall synthesis. It is important therefore not to use combination therapy which may have inhibitory or antagonistic effects. A recent in vitro combination study [46] using isolates from patients with bacterial keratitis demonstrated that the combination of meropenem and ciprofloxacin was predominantly additive or synergistic for both *S. aureus* and *P. aeruginosa*. Furthermore, teicoplanin combined with meropenem, ciprofloxacin or moxifloxacin was also additive or synergistic against *S. aureus*.

Drug Delivery to the Cornea

The most commonly used route of antimicrobial delivery into the cornea is topically, in the form of drops, solutions, emulsions or suspensions. However topical administration and its resultant pharmacokinetics and pharmacodynamics remain an inefficient method of delivery and may in part account for the poor outcome from bacterial keratitis. Furthermore, in the acute inflamed eye, there is increase in tearing which, together with the associated pain, makes instillation of a topical antimicrobial difficult. Hospitalisation is often needed to deliver the antimicrobials at frequent intervals (15 min) through consecutive nights. It is clear therefore that drug delivery systems need to be rethought.

Novel Methods of Drug Delivery to the Cornea

Alternative methods of delivery of antimicrobials to treat keratitis are currently being studied [47, 48]. Various drug delivery devices have been evaluated for the treatment of keratitis. They broadly fall into two categories: matrix and reservoir based. Matrix-based implants distribute the drug throughout a degradable polymer matrix, for example, Lacrisert® [49]. In a reservoir implant, the drug is stored within a reservoir made of a non-degradable substance such as collagen shields. Drug penetration into the cornea can be also enhanced by altering its physico-chemical properties with the addition of particulates such as nano-particles and other penetration enhancers, as well as using the prodrug and mucoadhesive dosage forms.

Summary for the Clinician

- Resistance to commonly used antimicrobials in keratitis has prompted the development of novel strategies in treating bacterial keratitis.
- Novel antimicrobials such as besifloxacin, tigecycline, meropenem and linezolid are currently under consideration.
- Additional improvements to clinical outcome may arise through utilising synergistic combinations of antimicrobials, as well as using novel corneal drug delivery systems.

Conclusion

It is clear that although there is a significant relationship between the MIC of the prescribed topical antimicrobial and clinical outcome, this relationship is relatively small; c.14%. Other bacterial and host factors play a role in the progression of infection. This is underlined by the finding that although the majority of bacterial isolates from keratitis based upon systemic breakpoint data were reported to be susceptible to prescribed antimicrobials, the actual outcome was far worse than expected. It is clear therefore that although ophthalmic susceptibility data to topical antimicrobials gives a better indication of outcome, the main determinants of outcome relate to factors such as the host–bacterial interaction. This is particularly evident for infections caused by *S. aureus* which accounts for up to 31% of cases of keratitis with the majority of ocular surface infections occurring in patients living in the community in the United Kingdom. This nevertheless presents an opportunity to develop treatments aimed at interfering with the action of the bacteria on its host target. These treatments could also be delivered in novel ways, reducing the dependency of instilling intensive topical antimicrobials.

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