

# Microbial keratitis and the selection of topical antimicrobials

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Microbial keratitis is a major cause of corneal opacity and loss of vision worldwide, and topical antimicrobial therapy is a critical component in its management. The study by Austin *et al*<sup>1</sup> found that there are regional variations in practice patterns influenced by concern over availability and toxicity versus broad-spectrum coverage and resistance. Respondents in the USA were more likely to treat with fortified antibiotics than their international peers.<sup>1</sup>

This raises some important points and questions in the treatment of suspected bacterial keratitis.

Why do some clinicians opt for monotherapy and others fortified antimicrobials? What is understood by combination therapy? What are the treatment considerations when the microbiological report says susceptible or resistant?

The clinical outcome in microbial keratitis is dependent on host factors, the virulence of the infecting bacteria and the minimum inhibitory concentration (MIC) of the antimicrobial against the respective bacteria.<sup>2–4</sup> The MIC is used to determine susceptibility criteria in order to choose an appropriate antimicrobial for treatment.<sup>5–7</sup> Although there is a relationship between clinical outcome and the MIC of antimicrobials in microbial keratitis, the actual MICs of the available antimicrobials against the respective isolate are seldom provided to the clinician. In addition, resistance and susceptibility are usually based on systemic breakpoint criteria rather than ophthalmic breakpoints.<sup>4</sup> That is, the breakpoints that are used to determine resistance and susceptibility are based on the anticipated response of the bacteria against concentrations of the antimicrobial that can be achieved in serum. Clearly, the antimicrobial concentrations achieved in the cornea and aqueous humour following topical administration differ from that achieved in the serum following systemic administration. The corneal penetration and effectiveness of a topical antimicrobial agent

is dependent on the physicochemical properties of the antimicrobial and structure of the cornea.<sup>8–11</sup> In addition, the pH and protein binding of the local environment and interaction with other agents not only differ from systemic conditions but also differ in the non-inflamed to the inflamed eye added to mixing with the tear film.<sup>12–14</sup> Furthermore, the concentration of an antimicrobial does not necessarily equate to the activity and bioavailability of the drug.<sup>15</sup> The biological activity of an antimicrobial in the cornea is usually much lower than the chemical concentration and may be less than 10% of the instilled amount.<sup>12–15</sup> For these reasons, the setting and use of ophthalmic breakpoints is very limited.

The comparative antimicrobial activity of antimicrobials against a particular bacterial species, however, is an important guide to selecting treatment. The fluoroquinolones are effective agents used to treat microbial keratitis.<sup>16</sup> It is, however, important to be selective in choosing a particular fluoroquinolone for a particular bacteria. For example, for the equivalent concentration, ciprofloxacin has a better inhibitory effect against *Pseudomonas aeruginosa* than moxifloxacin or levofloxacin.<sup>7</sup> The effectiveness of the fluoroquinolones against bacteria such as streptococcus and strains of staphylococcus may be limited. Although the newer generation fluoroquinolones have enhanced activity against Gram-positive bacteria, these agents are not a panacea for the treatment of microbial keratitis, particularly with the emergence of resistant strains of staphylococci, streptococci and Enterobacteriaceae.<sup>17–21</sup> As such, there is a need to consider other antimicrobials for topical administration, such as meropenem, or combination therapy.<sup>22–24</sup>

As opposed to single therapy, an antimicrobial combination offers a broader spectrum of activity and may reduce selective pressures. Either knowingly or unknowingly, ophthalmologists use combination therapy either simultaneously or



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sequentially, for example, a fluoroquinolone followed by chloramphenicol. This leads to an effect of indifference, addition, synergism or antagonism. Although the use of combination therapy may increase the spectrum, the potential benefit is to increase the antimicrobial effect of the respective combination, that is, an additive or preferably a synergistic effect. For example, the combination of penicillin and gentamicin in the treatment of enterococcal endocarditis produces a synergistic effect,<sup>25</sup> whereas conversely, the combination of chloramphenicol and penicillin in the treatment of pneumococcal meningitis is antagonistic.<sup>26</sup> It is important, therefore, to select a combination which is either additive or synergistic and to avoid a combination which is antagonistic. For keratitis isolates, it has been shown in vitro that the combination of meropenem and ciprofloxacin was synergistic in 20%–25% and either additive or synergistic in 55%–60% of both *Staphylococcus aureus* and *P. aeruginosa* keratitis isolates.<sup>22</sup> Against *S. aureus*, the combinations of teicoplanin with meropenem, ciprofloxacin or moxifloxacin had an additive or synergistic effect in more than 50% of *S. aureus* keratitis isolates.<sup>22</sup>

Although there has been debate, an overriding issue in improving the treatment of suspected microbial keratitis is the need to sample a corneal ulcer and to try and isolate the microorganism.<sup>27–28</sup> Larger corneal ulcers usually start off as smaller ulcers and the need for a simple and readily available method for use in all cases to identify and isolate the causative microorganism(s) would be a significant advantage.<sup>29–30</sup> This together with adjunctive antibacterial therapy against the bacterial toxins and virulence factors would be significant forward steps in improving outcomes in microbial keratitis.

There is a clear need to establish ophthalmic breakpoints to aid the ophthalmologist in deciding on the appropriate antimicrobial treatment. These would then form the basis for author's suggestion of a 'well-designed clinical trial on the treatment of bacterial ulcers to help clinicians initiate the best treatment and ultimately reduce morbidity.'<sup>1</sup>

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