Management of acute bacterial keratitis: Fortified antibiotics or fluoroquinolones?

Ana Luisa Höfling-Lima MD, PhD1, Francisco Bandeira e Silva MD2

1. Professor of Ophthalmology and Chair, Federal University of Sao Paulo, Brazil.
2. Post-graduate cornea fellow, Department of Ophthalmology, Federal University of Sao Paulo, Brazil.

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Abstract

Bacterial keratitis (BK) is one of the most frequent causes for emergency hospital admissions. Identifying the causative microorganism promptly and properly is mandatory to achieve acceptable outcomes. Nevertheless, appropriate initial management of these cases requires laboratory-based diagnosis and even a modest laboratory set may not always be available at some clinical settings.

Key words: bacterial keratitis; diagnosis; treatment.

Relevant evidence-based information

Guidelines support an empiric approach for initial treatment of bacterial keratitis but, there is still no consensus over which antibiotics should be a clinician start the treatment. For about four decades, a combination of fortified antibiotics was the preferred therapy, usually with an amynoglicoside (gentamicin or tobramycin) and a cephalosporin (cefazolin) in order to cover both Gram-positive and Gram-negative bacteria, with special concern to Staphylococcus spp., Streptococcus spp. and Pseudomonas aeruginosa. In the 1990’s, quinolones have been made widely accessible for topical use in ophthalmology. Structural changes over the years led to the production of different molecules of fluoroquinolones presenting with distinct pharmacokinetic and pharmacodynamic properties. The characteristics of 4th generation fluoroquinolones, which includes gatifloxacin and moxifloxacin, made them an excellent choice for initial therapy of bacterial keratitis with the perks of a very broad spectrum, higher activity against Gram-positive pathogens, readily accessibility, improved aqueous humor and corneal penetration and no special conditions for conservation. Fourth generation fluoroquinolones have been used worldwide for the last decade; however, there is a lack of consensus regarding which fluoroquinolone generation is most suitable for empirical therapy. For instance, in some countries, such as the UK, the preferred initial therapy is still ciprofloxacin, which is partly justified due to better in vitro activity against Pseudomonas aeruginosa. However, there have been some case reports and retrospective studies showing the development of bacterial resistance to these new fluoroquinolones, probably due to over-the-counter availability in some places and widespread topical and systemic use for both prophylaxis and infection.

Results

Choy et al found that 11% of 65 Pseudomonas aeruginosa isolates in both contact lens- and non-contact lens-related keratitis were non-susceptible in vitro to both ofloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanzos-cabreras et al found a resistance rate of 14.2% to gatifloxacin and moxifloxacin, an increasing trend compared to previous years. Betanza
tobramycin, gentamicin, moxifloxacin and gatifloxacin (Table 1).

Our findings display an overall high rate of resistance to 4th generation fluoroquinolones comparable to the resistance rates found for cephalothin and aminoglycosides. MRSA and MRCNS seem to be the most concerning bacterial agents, since resistance levels for both fortified combinations and 4th generation fluoroquinolones are the highest found among our isolates. Newer reviews show that main aspects one has to take into account when choosing an empirical antibiotic therapy are the following: treatment success, time to treat, serious complications of infection and adverse effects of the medication.7 Studies had compared and reviewed thoroughly the sensitivity profile, advantages and drawbacks related to commercial accessibility, bioavailability presentation, toxicity, preservation, and effectiveness of each drug.10,17 Treatment outcomes with either group vary greatly according to geographical differences, patient profile (severe or non-severe keratitis), clinical setting (hospital and outpatient clinics). Absolute data seems solid at first in most of these papers; however, when their design is unraveled, results often lose power. The main reason for that is related to the criteria used to recruit patients and protocol used to determine which antibiotics and posology would be applied, which often, do not match with other studies. A metanalysis evaluation of this data is not very feasible. Besides, when it comes to bacterial resistance to antibiotics, analysis becomes even more difficult since culture and antimicrobial susceptibility methods vary widely among the studies and in several publications the amount of positive samples for each identified microorganism is small for a reliable statistical evaluation. Another hiccup for microbiology studies in BK is that methods for antimicrobial susceptibility testing for ophthalmology purposes are bound to major groups, such as Clinical and Laboratory Standards Institute and EUCAST, and all of their data is based on the levels of antibiotics achieved in tissues after systemic use, which may not work the same way for topical application of drugs, since the relationship between drug bioavailability and ocular penetration depends on other factors related to the specific anatomy of ocular structures. Furthermore, some of the drugs used in ophthalmology are not available for systemic use, hence, they are not listed in these guidelines. For instance, 2014 EUCAST provided a guidance document on breakpoints for topical use of antimicrobial agents. However, topical breakpoints for 4th generation fluoroquinolones or other aminoglycosides other than gentamicin are not listed in this document. Alternatively to the status-quo dilemma, new treatments are under evaluation such as the effect of crosslinking on antimicrobial activity18 and effectiveness of besifloxacin. Besifloxacin, for topical use, is a new fluoroquinolone that has an adhesive component in its composition, allowing it to remain for longer periods in the ocular surface, thus providing a greater concentration over time when compared to antibiotics that are quickly removed by blinking and/or tear drainage. Nevertheless, there are no clinical trials evaluating the role of besifloxacin in BK. In one of the few papers available on the matter, Chung et al compared the penetration of four fluoroquinolones and demonstrated that besifloxacin does not reach high levels within corneal tissues.19 Furthermore, when there is already epithelial disruption, such as in BK, it would probably penetrate better20 and, since its retention time is the longest of all topical antibiotics, it may be taken into account as a therapeutic option. McDonald and colleagues conducted a thorough systematic review and metanalysis that resulted in 16 high quality clinical trials concerning topical antibiotics for management of BK and concluded that none of the trials took into consideration cost analysis and time without antibiotics until treatment. They support that there are significant differences between fluoroquinolones and fortified antibiotics when it comes to ready accessibility, and suggest that whereas fluoroquinolones are easily dispensed from hospitals or community pharmacies and can be kept in room temperature, fortified aminoglycoside-cephalosporin combination must be prepared in compound pharmacies and must remain refrigerated for approximately 4 days. In their review, they also denote that the time requirement for fortified antibiotics formulation might be hazardous for patients with severe corneal infections and melting that require immediate treatment, such as in P. aeruginosa keratitis. Although we are in agreement with both statements, we believe that the rise in fluoroquinolone resistance is a major factor
to take into account when choosing an initial therapy. Antibiotic resistance due to genetic mutation is the most dreaded phenomena to infections disease experts, while there have been some published papers on the subject but we also agree that lack of fluoroquinolones susceptibility for some bacteria may be due to intrinsic antibiotic, rather than acquired resistance through mutation. Nevertheless, some bacteria that show resistance to ciprofloxacin have a high probability to be resistant to treatment with 4th generation fluoroquinolones, disregarding the mechanism of resistance. This hypothesis is supported based on several essays demonstrating that ciprofloxacin is the most active fluoroquinolone against P. aeruginosa. However, further research has not been able to show strains that are resistant to ciprofloxacin and susceptible to other generation of fluoroquinolones, such as 4th generation.

On that account, in a community setting with a high prevalence of P. aeruginosa, ciprofloxacin could be preferred initial treatment over fourth generation fluoroquinolones for BK. In most South American ophthalmology hospitals and outpatient wards, the preferred initial treatment for BK starts with 4th generation fluoroquinolones. We suggest that for both severe and non-severe BK, treatment should be initiated with 4th generation fluoroquinolones and adjusted according to clinical course and culture/antimicrobial susceptibility results. In the setting of severe and/or fast evolving infections, the time taken in order to get results from cultures and antimicrobial infections is golden; because a delay in the decision taking of exchanging 4th generation fluoroquinolones for fortified antibiotics might result in poorer outcomes. Sometimes, the sole identification of pathologic bacteria may help in choosing whether and when to start fortified antibiotics, specially if there is previous epidemiologic data available for BK.

Conclusion and recommendation

In conclusion, gold standard initial therapy for BK is far from a clinical and academic consensus. Bacterial resistance to the antimicrobials used in ophthalmology varies greatly according to geographic location, and initial treatment choice should be guided by local antimicrobial resistance profile data, clinical course and laboratory evidence of antibiotic susceptibility. In severe cases that need prompt treatment, 4th generation fluoroquinolones seem to be a more suitable option, once they are readily available virtually anywhere and they do not need special conditions for storage. Clinical course will dictate further change in therapy to fortified antibiotics, when there is no objective or subjective evidence of clinical improvement, and laboratory results are unavailable.

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REFERENCES