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# Rational therapy of ocular surface bacterial infections with fluoroquinolones

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**HIGHLIGHTS**

Fluoroquinolones are chemotherapeutic agents characterized by broad antibacterial spectrum. New generations of fluoroquinolones, for example moxifloxacin, with greater antibacterial activity, should be reserved for resistant infections, that could not be treated with using older generations of fluoroquinolones.

## ABSTRACT

There are many mechanisms, that protect healthy ocular surface from invasion of pathogenic bacteria. Infection and inflammation develop on the ocular surface in case of damaging natural defensive barrier. One of the most common ocular surface infections are bacterial conjunctivitis and keratitis. Rational therapy of these diseases should be based on antibiotics that have broad antimicrobial spectrum, good efficacy and safety. All these qualities have fluoroquinolones: ofloxacin, levofloxacin and moxifloxacin.

**Key words:** bacterial conjunctivitis, bacterial keratitis, ophthalmic fluoroquinolones, moxifloxacin

## INTRODUCTION

Due to its location, the ocular surface is constantly exposed to pathogens. However, thanks to the barrier formed by the protective apparatus of the eye, tear film, non-specific immune mechanisms, and the microbial flora, it is protected against infections.

Tears not only dilute toxins and reduce the concentration of potential inoculum, but thanks to the content of lactoferrin, defensin, immunoglobulin class A, components of complement cascade and cytokines, they provide an environment for non-specific immune response mechanisms. In addition, by providing oxygen and nutrients, they keep the cornea in good health.

The normal conjunctiva, due to the presence of neutrophils, lymphocytes, macrophages, plasma cells, antigen-presenting cells and a rich vascular network, ensures development and regulation of a specific immune response directed against antigens on the ocular surface. Langerhans dendritic cells, which are antigen presenting cells capable of stimulating T-lymphocytes, are also present in the cornea.

The physiological flora, which consists predominantly of Gram-positive bacteria: *Staphylococcus epidermidis* and *Corynebacterium xerosis*, is also responsible for maintaining well-being of the surface of the eye. Violation of the natural defense mechanisms of the eye surface facilitates invasion of pathogenic microorganisms, which through their exotoxins and proteolytic enzymes lead to the development of infection and damage to eye tissues.

The most common factors predisposing to damage of the ocular surface barrier are trauma, contact lens wear, chronic topical steroid therapy, abnormalities of the ocular protective apparatus and tear film dysfunction, and immunosuppressed states.

## OCULAR SURFACE INFECTIONS

Ocular surface disorders are a significant clinical problem worldwide. Most patients present to the ophthalmology emergency room with the so-called "red eye", most commonly caused by conjunctivitis and keratitis. In a study by Caiado et al. published in 2018, 38.56% of patients (of total 783) sought emergency care for conjunctivitis. Of these, 74.8% (226) were diagnosed with bacterial conjunctivitis [1].

The etiology of bacterial conjunctivitis varies according to the patient's age. In children, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* predominate among isolated pathogens, whereas *Staphylococcus spp.* prevail in adults. Moreover, infections with Gram-negative bacilli are more frequently found in contact lens wearers [2]. A much more serious clinical problem is infectious keratitis considered the leading cause of corneal visual impairment in both developed and developing regions of the world. They have an estimated incidence of 2.5–799/100,000/year [3].

Bacteria are the most common etiologic agents of keratitis. Ting et al. reported that the percentage of bacterial keratitis, which varies by geographic region, is 91–93% in Great Britain, 86–92% in North America, 79–88% in South America, 91.8% in the Middle East, and 93–100% in Australia and Asia [3].

## CLINICAL PICTURE

The clinical picture of typical ocular surface inflammation is redness, discomfort or pain, as well as varying degrees of visual impairment. Corneal inflammations are caused mainly by Gram-positive cocci, with the predominance of coagulase-negative staphylococci (24–46%), *Staphylococcus aureus* (5–36%), and streptococci (7–16%). *Pseudomonas aeruginosa* infections are found in 5–24% of cases, more commonly in contact lens wearers [3]. Bacterial infections of the superficial tissues of the eye are usually established based on the clinical picture. One of the most characteristic symptoms suggestive of bacterial etiology is the presence of purulent discharge. In such a situation, empirical treatment is recommended.

Only when the implemented empirical treatment is unsuccessful or the course of the infection is severe and threatening to vision, chronic or recurrent, should material be collected for microbiological examination. According to available data, bacterial conjunctivitis is self-limiting and generally resolves within 1–2 weeks. The implementation of topical antibiotic therapy shortens the duration of symptoms, brings a 10% clinical improvement, and reduces the transmission of infection [4]. If the infection involves the cornea, it is recommended to collect material for microbiological examination prior to the treatment. Only in cases of small infiltrations without epithelial loss, there is no need to collect the material.

## PRINCIPLES OF ANTIBIOTIC THERAPY

Empirical antibiotic therapy should include in its spectrum microorganisms that are the most common etiologic agents of a given inflammation type. Empirical antibiotic therapy with the use of broad-spectrum antimicrobial chemotherapeutics is the first-line treatment in bacterial ocular surface infections. Ophthalmic pharmacotherapy is characterized by certain variations that influence treatment efficacy. A drug administered into the conjunctival sac reaches different concentrations that are changing over time depending on the form, the tear exchange rate, and the severity of inflammation on the ocular surface.

Higher lipophilicity compounds are characterized by better bioavailability, thus providing higher concentrations in ocular tissues. The drug concentration in vivo should equal or exceed the minimum inhibitory concentration (MIC) and achieve mutant prevention concentration (MPC) values. The latter represents the concentration of a drug above which bacteria do not develop drug-resistance mutations. It has been estimated that MPC is 10 times the MIC [5]. Moreover, the drug applied to the ocular surface should be safe and have the least toxic effect on the ocular surface epithelial cells so as not to interfere with healing and regeneration processes. Fluoroquinolones have all the above characteristic and can be considered a good antibiotic.

## FLUOROQUINOLONES

Fluoroquinolones, nalidixic acid derivatives, are a group of synthetic chemotherapeutic agents introduced to ophthalmic pharmacotherapy in 1991. Due to increasing bacterial resistance, subsequent generations of fluoroquinolones have had an extended spectrum of antimicrobial activity and better pharmacokinetic properties.

Fluoroquinolones are antibacterial compounds which can bind gyrase and topoisomerase IV (essential enzymes in DNA replication) to block the synthesis of bacterial genetic material leading to cell death. Currently, there are four generations of fluoroquinolones used in ophthalmic pharmacotherapy: second-generation ofloxacin, third-generation levofloxacin and fourth-generation moxifloxacin.

Ofloxacin is a second-generation fluoroquinolone with antibacterial activity against Gram-negative aerobic bacteria and limited efficacy against Gram-positive infections.

The drug is safe and well-tolerated. Among all fluoroquinolones used in ophthalmology, it has the lowest bioavailability and reaches the lowest aqueous concentrations after instillation to conjunctival sac [6].

Levofloxacin is a third-generation fluoroquinolone with an extended spectrum of antimicrobial activity against aerobic Gram-positive and Gram-negative bacteria. Compared to ofloxacin, it has better intraocular penetrability. After conjunctival administration, it achieves an aqueous concentration of 2.89 μm/ml [6, 7]. Moreover, it shows the least toxicity compared to other fluoroquinolones [8–10].

Moxifloxacin is the newest, fourth-generation fluoroquinolone with the broadest spectrum of antimicrobial activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria.

Due to its high solubility and lipophilicity, it is dosed less frequently than the older generation fluoroquinolones – only 3 times daily, but it still achieves even 2–4 times higher tissue concentration than levofloxacin or ofloxacin [6, 7]. Owing to its highest bioavailability, moxifloxacin tissue concentration in vivo reaches the MPC level, which protects against the development of bacterial resistance mechanisms against it [11].

However, moxifloxacin is known as the most toxic fluoroquinolone used in ophthalmology. Toxic effects on corneal epithelial cells were found during prolonged exposure to high concentrations of the substance [8–10]. At standard dosage, moxifloxacin is safe and well-tolerated. Adverse effects such as pinching, lacrimation, dryness, and irritation, as well as subconjunctival hemorrhage or punctate corneal epitheliopathy are mostly caused by preservatives. Thus, preservative-free formulation significantly improves the tolerability of the drug.

Moxifloxacin is the only fluoroquinolone registered for use by pregnant and lactating women. Unlike older generation fluoroquinolones, moxifloxacin can be safely used in all age groups, including neonates. The efficacy of the above-mentioned three fluoroquinolones against microorganisms which most frequently cause ocular surface infections is mostly similar [12].

Moxifloxacin shows better activity than ofloxacin or levofloxacin against Gram-positive bacteria, particularly *Staphylococcus aureus* and *Streptococcus pneumoniae*. Due to better pharmacokinetic parameters and higher bioavailability, the use of moxifloxacin gives good results in treating serious vision-threatening ocular infections. Better penetration into ocular structures also makes moxifloxacin an effective antibiotic for perioperative prophylaxis.

Fluoroquinolone monotherapy is currently gaining popularity in the treatment of bacterial keratitis, as it has demonstrated to be as effective as combination therapy with vancomycin and fluoroquinolone or with fortified antibiotics such as vancomycin and gentamicin [13].

Considering additional benefits of fluoroquinolone monotherapy such as good availability of ready-to-use preparations, reduced toxicity, better patient compliance, and the possibility of outpatient treatment, fortified antibiotics should be used only in case of severe, vision-threatening ulcers unresponsive to the first-line treatment [14].

Due to the problem of increasing antibiotic resistance, a lot of attention is paid to the rationalization of treatment. An unnecessary use or inappropriate selection of antibiotics is not only ineffective, but it also destroys the microbial flora of the ocular surface and promotes the selection of resistant strains. Therefore, judicious use of available drugs is necessary to maintain their effectiveness [15].

## CONCLUSIONS

Fluoroquinolones are broad-spectrum antimicrobial drugs that remain effective against bacteria causing the most

common ocular infections. They represent a safe form of treatment in all age groups and are well-tolerated by patients. Subsequent generations are characterized by a broader antimicrobial activity, but at the same time (due to the increasing concentration of the preparations) also by potential cytotoxicity to the corneal epithelium. Therefore, it seems that higher-generation fluoroquinolones, such as moxifloxacin, should be reserved for treating infections that threaten vision loss and the ones that do not respond to treatment with lower-generation fluoroquinolones.

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