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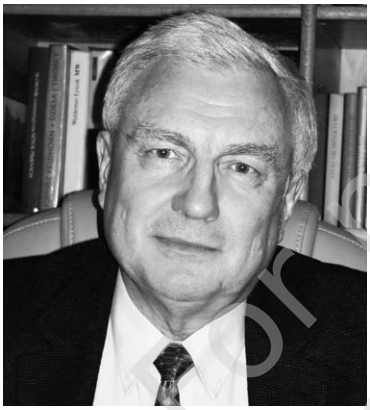
Treatment of conjunctivitis in the 21st century



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HIGHLIGHTS

The growing problem of antibiotic resistance means that antiseptics, not antibiotics, should be the first-line treatment in infectious conjunctivitis.

ABSTRACT

One of the reasons for the development of antibiotic resistance in ophthalmology is the indiscriminate use of antibiotics in the treatment of conjunctivitis, among other things. Therefore, in infectious conjunctivitis, the first-line treatment should be antiseptics rather than antibiotics. This should significantly reduce the development of antibiotic resistance, but also increase the effectiveness of treatment.

Key words: conjunctivitis, treatment, antibiotics, antibiotic resistance, antiseptics

INTRODUCTION

In 1928, Alexander Fleming, a Scottish bacteriologist, discovered penicillin – the first antibiotic – whose industrial-scale production began in 1942. The same year, gramicidin, the first peptide antibiotic, was released. Streptomycin, the first aminoglycoside, was released in 1944, and chlortetracycline, the first antibiotic of the tetracycline group, appeared in 1948. In the following years, new antibiotics were developed almost annually. As a result, some researchers declared the end of infectious diseases, which had devastated human populations since ancient times. However, after just a few years of antibiotic use, it became apparent that bacteria can develop mechanisms to become antibiotic resistant due to antibiotics overuse, their prophylactic use for non-bacterial infections, patient's misuse, use in veterinary, and in mass animal husbandry to increase production efficiency. Currently, animal husbandry utilizes more antibiotics than human therapeutic applications. Only in 2006, the European Union banned the use of antibiotics in animal husbandry, except for therapeutic purposes. In countries where antibiotics are still used in animal husbandry, such as the United States, China, or Russia, approximately 13 million kilograms of antibiotics are used each year, which accounts for roughly 80% of the world's total antibiotic production [1]. The rapid rise of antibiotic use worldwide has led to the emergence of bacterial strains resistant to all antibiotics. Antibiotic resistance is now the third leading cause of death worldwide, after cancer and cardiovascular disease. In 2019, it accounted for nearly 5 million cases globally [2]. The overuse of antibiotics is identified as a contributing factor to the projected increase in mortality due to antibiotic resistance, which is estimated to reach 10 million per year by 2050 [2]. In ophthalmology, antibiotics in combination with glucocorticosteroids are often prescribed as the first-line treatment for conjunctivitis, regardless of the inflammation etiology, which can be bacterial, allergic, viral, or chlamydial. Consequently, in the majority of instances, antibiotic eye drops are not indicated for the treatment of conjunctivitis, which is the most prevalent eye condition in humans. The overuse of antibiotics greatly contributes to the development of antibiotic resistance. Additionally, research has shown that even a single drop of antibiotics after an ophthalmic procedure can worsen bacterial antibiotic resistance [3].

Moreover, registrations of new antibiotics are steadily declining worldwide. New antibiotics introduced in recent years have strict indications for use. For instance, cefiderocol, introduced in 2019, is only approved for treating urinary tract infections and pneumonia if other antibiotics have failed. Another issue is that developing new antibiotics is not profitable for pharmaceutical companies. This is due to their short usage period, typically lasting only about a week. In contrast, chronic diseases such as diabetes and heart disease require long-term treatment. Similarly, producing new cancer drugs is economically viable, as the cost of cancer treatment can reach several hundred thousand dollars per patient.

EFFICACY OF ANTIBIOTIC TREATMENT FOR CONJUNCTIVITIS

Three groups of antibiotics are typically used in ophthalmology: aminoglycosides, fluoroquinolones and, less commonly, macrolides. The efficacy of these antibiotics in treating conjunctivitis is a matter of inquiry. Conjunctival inflammation is primarily caused by Staphylococci (*Staphylococcus aureus*, *Staphylococcus epidermidis*), Streptococci (*Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Streptococcus viridans*), Gram-negative bacilli (*Haemophilus influenzae*), Gram-negative granulomas such as *Moraxella lacunata*, *Chlamydia trachomatis*, *Serratia*, *Proteus*, *Enterobacter*, *Klebsiella*, and *Corynebacterium*, as well as *Escherichia coli* and *Pseudomonas aeruginosa* are a rarer cause [4–7]. Conjunctivitis is typically not treated with targeted therapy. Bacterial cultures are not reliable as they often detect random bacteria from the eyelid skin. Moreover, the test is costly and impractical due to the short duration of inflammation. Therefore, broad-spectrum antibiotics are used to treat both Gram-positive and Gram-negative bacteria. In Poland, chlamydia-induced inflammation is rarely diagnosed. Therefore, it is desirable for the medications used to be effective against these bacteria. The antibiotics used should penetrate the conjunctiva and cornea effectively. Ideally, they should be bactericidal rather than bacteriostatic to reduce the risk of developing antibiotic resistance. To ensure reliable use, they should be administered as infrequently as possible, optimally twice daily. While preservative-free antibiotics are preferred, it is not as crucial as it is for anti-glaucoma drugs, which are used for an extended period of time. In cases of conjunctivitis, aminoglycosides and fluoroquinolones are the most commonly used antibiotics. Both groups of drugs are effective against Gram-positive and Gram-negative bacteria. Aminoglycosides are effective against Staphylococci, including *Staphylococcus aureus*, except for some methicillin-resistant (MRSA) strains. However, their efficacy against Streptococci is limited. Aminoglycosides are highly effective against Gram-negative bacteria, particularly *Haemophilus*, *Enterobacteriaceae*, and *Pseudomonas genera*. They bind to the bacterial ribosome and disrupt the function of ribosomal RNA, leading to the disruption of genetic information reading and inhibition of bacterial protein synthesis. The effectiveness of fluoroquinolones as antibacterial agents depends on their generation. These antibiotics are highly effective against Gram-negative bacteria such as *Haemophilus*, *Salmonella*, *Neisseria*, *Enterobacteriaceae*, and *Pseudomonas*. However, their efficacy against Gram-positive bacteria varies depending on the drug generation. The fluoroquinolones of the second generation, such as ciprofloxacin, ofloxacin,

and lomefloxacin, have limited activity against Gram-positive bacteria. In contrast, third-generation drugs, such as levofloxacin, exhibit greater activity against Gram-positive microorganisms. The fourth-generation fluoroquinolones, including gatifloxacin, moxifloxacin, and besifloxacin, are effective against Gram-negative, Gram-positive, and anaerobic bacteria. Moxifloxacin is also effective against chlamydia. Fluoroquinolones inhibit bacterial enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which prevent DNA replication and synthesis, ultimately leading to bacterial death [8, 10]. Topoisomerase II inhibition is primarily responsible for activity against Gram-negative bacteria, while topoisomerase IV inhibition is responsible for activity against Gram-positive bacteria. Third- and fourth-generation antibiotics are more effective as they act on both enzymes, whereas second-generation drugs only inhibit topoisomerase II activity [10]. Among the available antibiotics, azithromycin, a macrolide antibiotic, is the only one used for treating conjunctivitis. It is effective against Gram-positive and Gram-negative bacteria, anaerobes, and *Chlamydia*. Its efficacy is highest against *Haemophilus* and *Moraxella* strains. However, their effect on Staphylococci (particularly MRSA), Streptococci (*Streptococcus pneumoniae*, *pyogenes* and *viridans*) and *Neisseria gonorrhoeae* is limited due to the rapid development of acquired resistance. *Enterococcus* and *Pseudomonas aeruginosa* are resistant to macrolides. Macrolides are bacteriostatic antibiotics, but they can have bactericidal properties at higher concentrations (e.g., azithromycin at 1.0–1.5%) [8, 11]. Polymyxin B and oxytetracycline are still occasionally used among other antibiotics. However, clinical studies confirm the low efficacy of antibiotics in treating bacterial conjunctivitis. In fact, the rate of inflammation healing was found to be similar in the group using chloramphenicol and moxifloxacin eye drops compared to the group receiving a placebo [12–14]. In conclusion, it can be stated that while all three groups contain broad-spectrum antibiotics, they are most effective in treating conjunctival infections caused by Gram-negative bacteria. However, their efficacy is weaker against infections caused by Gram-positive microorganisms, which are the most common cause of bacterial conjunctivitis. Among these groups, IV fluoroquinolones have the highest efficacy against Gram-positive bacteria, while the third-generation fluoroquinolones are slightly less effective. To ensure the effectiveness of conjunctivitis treatment, it is essential to use IV fluoroquinolones as a first-line therapy.

HOW DO ANTIBIOTICS PENETRATE THE CONJUNCTIVA?

Moxifloxacin, gatifloxacin, and azithromycin are the most effective in terms of penetration into the conjunctiva [8, 11]. Azithromycin is particularly well absorbed into the conjunctiva and somewhat less well into the cornea. Its elimination time from these tissues is quite long, which means that its therapeutic concentration (above MIC90) can persist for up 7 days. Azithromycin is captured, transported and released by neutrophil granulocytes and phagocytes and is therefore actively transported to sites of infection [11].

DOES THE OVERUSE ANTIBIOTICS IN TREATING CONJUNCTIVITIS CONTRIBUTE TO THE DEVELOPMENT OF ANTIBIOTIC RESISTANCE?

Antibiotic resistance develops when bacteria are repeatably exposed to a drug at sublethal doses [8–11]. Periods of antibiotic ineffectiveness can occur due to several reasons, including the antibiotic's inability to effectively target the specific bacterial strain, poor penetration into inflammatory areas, and non-compliance with recommended dosage or usage instructions. It is important to follow the doctor's recommendations and use antibiotics as directed to avoid periods of ineffectiveness when bacteria can develop various mechanisms leading to antibiotic resistance.

Aminoglycosides are a group of antibiotics that exhibit lower rate of resistance compared to other antibiotics. This is especially true considering their long history of use in medicine, with streptomycin being used since 1944, gentamicin since 1963, tobramycin since 1967, and amikacin since 1972. Antibiotic resistance can develop due to a variety of factors, including decreased permeability of the bacterial wall to the drug, formation of bacterial enzymes that alter the structure of the antibiotic and prevent it from binding to ribosomes, and mutations in bacterial ribosomes that prevent aminoglycoside binding. In the case of aminoglycosides, cross-resistance to other drugs in this group of antibiotics is less frequent compared to others [11]. Fluoroquinolone resistance occurs due to spontaneous mutations in genes that encode enzymes topoisomerase II (DNA gyrase) and topoisomerase IV which are the most common mechanism in their antibacterial activity [10].

Moreover, antibiotic resistance can develop due to the inhibition of drug penetration into bacteria, which can be caused by the overactivity of efflux pumps that transport drugs outside of bacterial cells [9–11]. Second-generation fluoroquinolones typically develop antibiotic resistance with just one mutation, while third- and fourth-generation drugs require two mutations. Unfortunately, the first mutation often leads to the development of the second one [10, 11], resulting in a common buildup of antibiotic resistance among fluoroquinolones, which is a significant problem associated with their use. Resistance to fluoroquinolones develops particularly with Gram-positive bacteria, making second-generation drugs less effective against these microorganisms. Additionally, the use of second- and third-generation fluoroquinolones can lead to cross-resistance, making it easier for bacteria to develop resistance to fourth-gen-

eration drugs with only one mutation required instead of two [9]. Activation of the drug efflux pump, which removes antibiotics from the bacterial cell, not only impedes the penetration of fluoroquinolones but also other classes of antibiotics, leading to increased cross-resistance [10]. Antibiotic resistance to macrolides can develop quickly and easily due to the induction of enzymes that alter the structure of bacterial ribosomes. This mechanism is usually cross-reactive and occurs with both macrolides and lincosamides [11]. Antibiotic-resistance mechanisms result from the widespread use of antibiotics, including their topical application in the form of eye drops and ointments. It is important to note that even a single dose of an antibiotic into the eye can lead to the development of fluoroquinolones resistance [3]. Based on the information presented above, it can be concluded that:

1. IV gen. fluoroquinolones are the most effective antibiotics for treating conjunctivitis due to their broad spectrum of activity against bacteria. Third-generation fluoroquinolones are slightly less effective. Other antibiotics have limited efficacy against the most common cause of conjunctivitis, which is Gram-positive bacteria.
2. The mass prescription of antibiotics to treat conjunctivitis has had a significant impact on the development of antibiotic resistance and treatment options for bacterial infections in general. This problem is compounded by the low patients' adherence (only 50%) [15].
3. In most cases, antibiotics are prescribed to treat conjunctivitis without confirming the bacterial cause, which is not therapeutically justified. Often, these inflammations have a different cause, and ophthalmologists prescribe antibiotics based on the assumption that the patient should receive some form of treatment. However, this approach only exacerbates antibiotic resistance with no treatment efficacy.
4. The controlled clinical trials indicate that the rate of inflammation healing was similar in the group using antibiotic eye drops and in the group receiving placebo.
5. Due to the significant problem of antibiotic resistance, it is necessary to modify the traditional treatment regimen for conjunctivitis.

NEW TREATMENT OPTIONS FOR CONJUNCTIVITIS

In the past, antibiotics were the only practical treatment option for bacterial conjunctivitis until the introduction of antiseptics in the mid-19th century. However, their use is problematic because they can only be applied to the surface of the body, rather than being administered systemically. Additionally, many antiseptics can be toxic to mucous membranes, including the conjunctiva. Until recently, there were no commercial ocular preparations available for treating conjunctivitis or preventing ocular infections. For some time, the standard of care for preventing perioperative infections has been preoperative and postoperative infusion with 5% povidone iodine solution [16–18]. Currently, there are no commercially available povidone iodine eye drops. Instead, they are prepared ex tempore in the operating room. However, in recent years, eye drops containing antiseptics have been more commonly used, providing new treatment options for conjunctivitis.

ADVANTAGES AND DISADVANTAGES OF ANTISEPTICS IN THE TREATMENT OF CONJUNCTIVAL DISEASES

Antiseptics have a wide range of therapeutic properties. Laboratory studies and meta-analyses of clinical papers have shown that antiseptics are effective against Gram-positive and Gram-negative bacteria, acanthamoeba, certain viruses, and fungi (tab. 1) [19–29].

The use of various antiseptics, including povidone iodine [19, 22–25, 27, 28], chlorhexidine [19, 22–25, 27, 28], ozonated oil in liposomes [20, 25–27], polyhexanide [20, 24, 25], octenidine [24], picloxidine [20, 24], and hexamidine [19–29] have been thoroughly investigated. Bacteriological studies have demonstrated that chlorhexidine has a wider range of antibacterial activity than povidone iodine [28]. Furthermore, antiseptics demonstrate antiviral activity within a few minutes, and the development of resistance to antiseptics in healthcare facilities is not a significant concern [19, 22–24, 28, 29].

FIGURE 1

The spectrum of antibacterial activity of various antiseptics [19, 22, 29].

Group of antiseptics	Active substance	Efficacy against bacteria	
		Gram-positive	Gram-negative
Biguanides	chlorhexidine	+++	++
	picloxidine	+++	++
	polyhexamethylene biguanide polyhexanide (PHMB)	+++	++
	octenidine	+++	++
Halogen	chlorates (sodium hypochlorite)	+++	++
	iodophors (povidone iodine)	+++	+++
Hexamidine		+++	++
Alcohols	ethanol	++	++
Phenolic compounds	triclosan	++	++
Other	hydrogen peroxide	++	+

+++ very strong effect; ++ strong effect; + weak effect.

However, antiseptics pose a risk of damaging corneal and conjunctival surfaces if used in high concentrations [21, 22]. Comparative clinical studies have shown that patients tolerate chlorhexidine better than povidone-iodine [22, 28]. Antiseptics are limited to treating skin and mucous membrane diseases, and cannot be used for general treatment.

Table 1 displays the antibacterial activity spectrum of commonly used antiseptics. The table indicates that antiseptics are most effective against Gram-positive bacteria, which are typically resistant to antibiotics used in eye drops (as previously mentioned).

Recently, antiseptics in the form of eye drops and gels have been commercially available, which has changed our options for treating ocular surface disorders (tab. 2).

THE USE OF ANTISEPTICS IN CONJUNCTIVITIS

Currently, there are few reports on the use of antiseptics for treating conjunctivitis. However, initial indications suggest that chlorhexidine is an effective first-line therapy for this inflammatory condition [30]. Controlled clinical trials have shown that povidone-iodine effectively treats conjunctivitis in children [31]. Recent randomized, placebo-controlled trials have also demonstrated the efficacy and safety of treating acute viral inflammation with povidone-iodine and dexamethasone [32, 33].

Tables 2 and 3 display the available antiseptic eye drop formulations and the resulting changes in conjunctivitis treatment regimens. The aim of these changes is to enhance the therapy efficacy and significantly reduce the development of antibiotic resistance.

FIGURE 2

Antiseptic eye drops preparations available in Poland.

Active substance	Trade name	Indications for use	Comments
Chlorhexidine 0.02%	Ocusept	• in pre-operative prophylaxis • in the treatment of conjunctival infections • in the treatment of corneal infections • for the treatment of infections of the eye appendages (eyelid margins, tear ducts, eyelashes) • in the treatment of conjunctivitis • in the treatment of keratitis • in the treatment of lacrimal sac inflammation	Can be used with reusable contact lenses
Ozonated vegetable oil 0.5% in liposomes	Ozodrop Ozodrop Gel K®	• "red eye" • conjunctivitis regardless of etiology • keratitis regardless of etiology • eye injuries • after foreign body removal • after thermal and chemical burns • dry eye syndrome • prophylactically in the prevention of infection in contact lens wearers	Can be used with reusable contact lenses
Hexamidine diisethionate 0.05%, Polyhexanide hydrochloride 0.0001%, Methylsulfonylmethane, Disodium edetate (EDTA)	Keratosept	• infections caused by staphylococci, streptococci and *Candida*	Can be used by hard and soft contact lens wearers

FIGURE 3

How to treat conjunctivitis in the 21st century - therapeutic indications.

1. A very large proportion of conjunctival inflammation does not require treatment.
2. Do not use antibiotics (or antibiotic + corticosteroid combination therapy) as first-line treatment.
3. If, for various reasons, you want to start treating conjunctivitis with clear symptoms of bacterial inflammation (profuse purulent discharge, sticky eyelids after a night's sleep), start treatment with antiseptics due to their high efficacy and lack of impact on the development of antibiotic resistance.
4. If this treatment is not effective, after 7 days, use an antibiotic, preferably from the group of IV-generation fluoroquinolones due to the widest range of antibacterial action and very good penetration into the conjunctiva.
5. If the cause of the inflammation is known (allergy, dry eye syndrome), use causal treatment.
6. In all other cases of undetermined etiology (including suspected chlamydial, viral, fungal, Acanthamoeba keratitis), start treatment with antiseptics.

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