

# Current methods of treating bacterial conjunctivitis



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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, the Scottish physician and bacteriologist Alexander Fleming discovered penicillin – the first antibiotic. However, within only a few years of its use, it became evident that bacteria are capable of developing mechanisms that render them resistant (antimicrobial resistance). The consequence of this phenomenon is a rapid global increase in antimicrobial resistance and the emergence of bacterial strains resistant to all currently available antibiotics.

Antimicrobial resistance is currently estimated to be the third leading cause of mortality worldwide, following cancer and cardiovascular diseases, and was responsible for nearly 5 million deaths in 2019 [1]. It is projected that by 2050, mortality attributable to antimicrobial resistance will rise to 10 million deaths annually [1].

One of the key factors contributing to the development of antimicrobial resistance is the widespread prescribing of antibiotics, combined with suboptimal adherence to recommended treatment regimens. In ophthalmology, a representative example is the management of conjunctivitis. Regardless of its etiology – which may be bacterial but is equally often allergic, viral, or chlamydial – antibiotics are frequently prescribed as first-line therapy, often in combination with a glucocorticosteroid.

In the majority of cases, however, topical antibiotic therapy in the form of eye drops is not required. Given that conjunctivitis is the most common ocular condition, this practice significantly contributes to the development of antimicrobial resistance. It has also been demonstrated that even a single administration of antibiotic eye drops following an ophthalmic procedure may increase the risk of bacterial resistance [2].

## ETIOLOGY OF BACTERIAL CONJUNCTIVITIS

Conjunctival inflammation is most commonly caused by *Staphylococcus* species (*Staphylococcus aureus*, *Staphylococcus epidermidis*) and *Streptococcus* species (*Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Streptococcus viridans*). Less frequently, it is associated with Gram-negative bacilli such as *Haemophilus influenzae*, Gram-negative cocci such as *Moraxella lacunata*, and *Chlamydia trachomatis*. Rarely, pathogens from the genera *Serratia*, *Proteus*, *Enterobacter*, *Klebsiella*, and *Corynebacterium*, as well as *Escherichia coli* and *Pseudomonas aeruginosa*, may be implicated [3–6].

Targeted therapy (i.e., based on microbiological culture) is not routinely employed, primarily due to limited diagnostic reliability (with cultures often yielding commensal flora from the eyelid skin), associated costs, and the typically self-limiting nature of the condition. Consequently, treatment most often involves broad-spectrum antibiotics active against both Gram-positive and Gram-negative organisms.

## EFFICACY OF DIFFERENT ANTIBIOTICS USED IN BACTERIAL CONJUNCTIVITIS

In ophthalmology, three main classes of antibiotics are commonly used: aminoglycosides and fluoroquinolones, while macrolides are used less frequently. However, it remains unclear whether these agents are indeed highly effective in the treatment of bacterial and chlamydial conjunctivitis.

Aminoglycosides are active against *Staphylococcus* species, including *Staphylococcus aureus* (although not all methicillin-resistant strains [MRSA]), whereas their activity against *Streptococcus* species is limited. They are, however, highly effective against Gram-negative bacteria, particularly *Haemophilus*, members of the *Enterobacteriaceae* family, and *Pseudomonas* species [9].

The antibacterial activity of fluoroquinolones depends on the generation of the agent. Fluoroquinolones exhibit strong activity against Gram-negative bacteria (including *Haemophilus*, *Salmonella*, *Neisseria*, members of the *Enterobacteriaceae* family, and *Pseudomonas*), whereas their activity against Gram-positive organisms varies by generation. Second-generation fluoroquinolones (e.g., ofloxacin) demonstrate relatively limited activity against Gram-positive bacteria. Third-generation agents (e.g., levofloxacin) show enhanced activity against Gram-positive microorganisms. Fourth-generation fluoroquinolones (e.g., moxifloxacin) exhibit potent activity against both Gram-negative and Gram-positive bacteria and are additionally effective against anaerobic organisms; moxifloxacin also demonstrates activity against *Chlamydia* species [8].

Among other antibiotics, azithromycin – a macrolide antibiotic – is the only agent used in the treatment of conjunctivitis. It exhibits activity against Gram-positive and Gram-negative bacteria, anaerobes, and *Chlamydia* species, with the highest activity observed against *Haemophilus* and *Moraxella*. Its activity against *Staphylococcus* species (particularly MRSA), *Streptococcus* species (*Streptococcus pneumoniae*, *S. pyogenes*, and *S. viridans*), and *Neisseria gonorrhoeae* is limited due to the rapid development of acquired resistance. Intrinsic resistance is observed in *Enterococcus* species and *Pseudomonas aeruginosa*. Macrolides are generally bacteriostatic; however, at higher concentrations (e.g., azithromycin at 1.0–1.5%), they may exhibit bactericidal activity [9].

The limited efficacy of antibiotics in bacterial conjunctivitis has been confirmed in clinical studies demonstrating similar rates of resolution of inflammation in patients treated with chloramphenicol or moxifloxacin eye drops compared with those receiving placebo [10–12]. In summary, although all three classes represent broad-spectrum antibiotics, their activity is greatest in conjunctival infections caused by Gram-negative bacteria, while it is lower in infections caused by Gram-positive organisms, which

constitute the most common etiological agents of bacterial conjunctivitis. Among these groups, fourth-generation fluoroquinolones exhibit the highest activity against Gram-positive bacteria, followed by third-generation agents with slightly lower activity.

### DOES WIDESPREAD USE OF ANTIBIOTICS IN CONJUNCTIVITIS CONTRIBUTE TO ANTIMICROBIAL RESISTANCE?

Antimicrobial resistance may develop when bacteria are exposed to antibiotics, particularly during repeated periods of sublethal drug concentrations in tissues or on their surfaces [8, 9]. Such conditions arise when the administered antibiotic is ineffective against a given bacterial strain, exhibits limited penetration into the site of infection, or is used inappropriately (e.g., poor adherence or incorrect dosing regimens).

Under these circumstances, bacteria may develop adaptive mechanisms that promote antimicrobial resistance [8, 9]. Therefore, the widespread use of antibiotics with limited activity against the causative pathogens contributes to the development and spread of antimicrobial resistance.

Antimicrobial resistance most commonly develops following systemic antibiotic administration; however, topical use of ophthalmic drops and ointments may also promote the emergence of resistant bacterial strains. Notably, even a single instillation of an antibiotic into the eye may be sufficient to promote resistance to fluoroquinolones [2].

Based on the above findings, the following conclusions can be drawn:

1. Due to the antimicrobial spectrum of currently available agents, topical antibiotics have limited activity against Gram-positive bacteria, which represent the most common cause of bacterial conjunctivitis.
2. The widespread prescription of antibiotics for conjunctivitis significantly contributes to the development of antimicrobial resistance and may adversely affect the management of systemic bacterial infections. This problem is further exacerbated by poor patient adherence to prescribed regimens (approximately 50%) [13].
3. In the vast majority of cases, antibiotics are prescribed for conjunctivitis without confirmation of a bacterial etiology and therefore without clear therapeutic justification. Most cases are attributable to non-bacterial causes, yet antibiotics are prescribed based on the assumption that some form of treatment should be offered. Such practice contributes to antimicrobial resistance without improving treatment outcomes.
4. Controlled clinical trials demonstrate comparable rates of resolution of inflammation in patients treated with antibiotic eye drops and those receiving placebo.

5. Given the current scale of antimicrobial resistance, a shift from traditional approaches to the management of conjunctivitis is urgently required.

### NEW THERAPEUTIC OPTIONS FOR CONJUNCTIVITIS

Until recently, antibiotics constituted the only practical option for the treatment of bacterial conjunctivitis. However, antiseptics had been introduced much earlier – in the mid-19<sup>th</sup> century – for the prevention and treatment of infections. Despite this, commercially available ophthalmic antiseptic preparations for the treatment of conjunctivitis and prophylaxis of ocular infections were not widely available until recently, which significantly limited their clinical use.

For some time, instillation of 5% povidone-iodine solution before and after surgery has been the standard of care in perioperative infection prophylaxis [14–16]. Nevertheless, no commercially available povidone-iodine eye drops are currently available, and such preparations are typically compounded *ex tempore* in the operating room.

In recent years, however, ophthalmic solutions containing antiseptic agents have been introduced, creating new therapeutic opportunities for the management of conjunctivitis.

### ADVANTAGES AND LIMITATIONS OF ANTISEPTICS IN THE TREATMENT OF CONJUNCTIVAL DISEASES

Antiseptics exhibit a very broad spectrum of antimicrobial activity. Laboratory studies and meta-analyses of clinical trials have demonstrated their efficacy against Gram-positive and Gram-negative bacteria, *Acanthamoeba*, certain viruses, and fungi [17–27]. These studies have evaluated agents such as povidone-iodine, chlorhexidine, ozonated oil in liposomes, polyhexanide, octenidine, picloxydine, and hexamidine [17–27]. Antiseptics are particularly effective against Gram-positive bacteria, which are often less susceptible to commonly used topical antibiotics. An additional advantage of antiseptics is their rapid onset of action – often within minutes – as well as the near absence of resistance development [17, 20–22, 26, 27].

A limitation of antiseptics is the potential risk of damage to the corneal and conjunctival epithelium when these agents are used at excessively high concentrations [19, 20]. Another limitation is that their use is restricted to the treatment of skin and mucosal conditions and they are not suitable for systemic therapy.

In recent years, commercially available antiseptic formulations in the form of ophthalmic drops and gels have been introduced, expanding therapeutic options for ocular surface diseases. One of the most commonly used preparations is Ocusept – an ophthalmic solution containing 0.02% chlorhexidine – which combines a broad antimicrobial spectrum with a favorable safety profile (tab. 1).

TABLE 1

Characteristics of chlorhexidine-containing ophthalmic solution (Ocusept).

Active substance	Trade name	Indications	Notes
<b>Chlorhexidine 0.02%</b>	Ocusept	<ul style="list-style-type: none"> <li>• Treatment of corneal infections</li> <li>• Treatment of infections of ocular adnexa (eyelid margins, lacrimal ducts, eyelashes)</li> <li>• Treatment of conjunctivitis</li> <li>• Treatment of keratitis</li> <li>• Preoperative prophylaxis</li> <li>• Treatment of dacryocystitis</li> <li>• Treatment of conjunctival infections</li> </ul>	Can be used with reusable contact lenses

## USE OF ANTISEPTICS IN CONJUNCTIVITIS

At present, relatively few studies have evaluated the use of antiseptics in the treatment of conjunctivitis. However, available evidence suggests that these agents (e.g., chlorhexidine) may serve as effective first-line therapy in such conditions [28].

Controlled clinical studies have also demonstrated that povidone-iodine is an effective treatment option for conjunctivitis in pediatric patients [29].

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