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REVIEW ARTICLE

Antimicrobials and antiseptics: Lowering effect on ocular surface bacterial flora – A systematic review

Mariantonia Ferrara[1] | **Francesca Gatti**[2,3] | **David Lockington**[4] | **Antonio Iaria**[2,3] | **Stephen Kaye**[5,6] | **Gianni Virgili**[7,8] | **Pasquale Aragona**[9] | **Francesco Semeraro**[2,3] | **Vito Romano**[2,3,6]

[1]Manchester Royal Eye Hospital, Manchester, UK

[2]Eye Clinic, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy

[3]ASST Civil Hospital of Brescia, Brescia, Italy

[4]Tennent Institute of Ophthalmology, Gartnavel General Hospital, Glasgow, UK

[5]St. Paul's Eye Unit, Department of Corneal Diseases, Royal Liverpool University Hospital, Liverpool, UK

[6]Department of Eye and Vision Science, University of Liverpool, Liverpool, UK

[7]Eye Clinic, AOU Careggi Teaching Hospital, University of Florence, Florence, Italy

[8]Centre for Public Health, Queen's University Belfast, Belfast, UK

[9]Department of Biomedical Sciences, University of Messina, Messina, Italy

Correspondence
Vito Romano, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, Ophthalmology Clinic, University of Brescia, Viale Europa 15, 25123 Brescia, Italy.
Email: vito.romano@gmail.com

Abstract

Topical antimicrobials and antiseptics are used perioperatively to reduce the ocular surface bacteria flora (OSBF) that are involved in the development of post-operative infectious complications. However, their effectiveness is still a controversial topic. This systematic review, performed according to the PRISMA guidelines and registered in PROSPERO, aims to provide an overview of the efficacy of the agents currently used in peri-cataract surgery and -intravitreal injections (IVI) in lowering the OSBF. Although effective in lowering OSBF, perioperative topical antimicrobials are associated with the risk of resistance development, with no obvious additional benefit compared with topical antisepsis. Conversely, the effectiveness of topical antiseptics before cataract surgery and IVI is strongly supported. Based on the available evidence, perioperative antimicrobials are not recommended, whereas the perioperative use of antiseptics is strongly recommended as prophylactic treatment for lowering the infection due to OSBF. Post-operative antimicrobials may be considered in eyes at higher risk for infection.

KEYWORDS

cataract surgery, intravitreal injections, ocular surface bacterial flora, topical antimicrobials, topical antiseptics

1 | INTRODUCTION

The ocular surface bacteria flora (OSBF) plays a crucial role in the development of post-operative ocular infection including endophthalmitis, rare but potentially sight-threatening complication of ophthalmic invasive procedures (Merani & Hunyor, 2015; Speaker et al., 1991). Indeed, surgical incisions can provide microorganisms with access to the anterior as well as vitreous chamber both intraoperatively and/or during the early post-operative period (Merani & Hunyor, 2015; Speaker et al., 1991). Cataract surgery and intravitreal injections (IVI) are the most commonly performed intra-ocular procedures worldwide, with a reported incidence of post-operative endophthalmitis of 0.023%–0.026% (Peyman et al., 2020) and 0.028%–0.056% (Patel et al., 2020), respectively. Post-operative endophthalmitis is most commonly caused by Gram-positive (G+) organisms, mainly *Staphylococcal* sp. and, among them, coagulase-negative (CoNS) (Aragona et al., 2021; Barry et al., 2013; Patel et al., 2020; Peyman et al., 2020). The causative pathogens, however, vary with geography, with a higher rate of Gram-negative (G−) bacteria and fungi in some Asian countries (Aragona et al., 2021; Barry et al., 2013).

Due to their ability to reduce the bacterial load on ocular surface, topical antimicrobials and antiseptics are commonly used perioperatively for the prophylaxis of ocular infection and endophthalmitis post-cataract surgery and post-IVI (Merani & Hunyor, 2015; Peyman et al., 2020). However, the evidence on the efficacy of

these agents is still limited and controversial. Moreover, a main concern related to the widespread use of antimicrobials is the potential consequent increase of resistance development (Asbell & DeCory, 2018) The ARMOUR (Antibiotic Resistance Monitoring in Ocular Microorganisms) Surveillance Study reported resistance to 3 or more antibiotic classes (multi-drug resistance, MDR) in 30.2% of *S. aureus*, 39% of CoNS and more than 70% of methicillin-resistant *S. aureus* (MRSA) and MR-CoNS isolated from conjunctival swabs of patients with presumed bacterial conjunctivitis (Asbell & DeCory, 2018). This is of particular relevance during the course of multiple intravitreal injections (Grzybowski, Told, et al., 2018; Milder et al., 2012). There is, therefore, growing attention towards different classes of compounds that can reduce bacterial growth without inducing resistance, such as antiseptics. The term "antiseptic" indicates biocides or chemical agents able to inactivate microorganisms on or in living tissues, through killing or growth inhibition (Mcdonnell et al., 1999). Antimicrobials are instead natural or synthetic organic compounds that, usually at low concentrations, inactivate selective microorganisms (Mcdonnell et al., 1999).

This systematic review aims to comprehensively discuss the currently available evidence regarding the efficacy of antimicrobials and other biocides used as antiseptics in reducing the OSBF.

2 | METHOD OF LITERATURE SEARCH

We carried out a systematic review of the literature, in accordance with the PRISMA guidelines (Page et al., 2021) regarding the effectiveness of perioperative topical antimicrobials and antiseptics in reducing OSBF in cataract surgery and intravitreal injections over the last 10 years (from January 2012 to March 2022). The review protocol was registered in PROSPERO (identifier: CRD42022354028, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=354028). We searched the PubMed, Embase and Cochrane databases using the following keywords: cataract surgery; cataract surgery antisepsis; chlorhexidine; conjunctival bacterial flora; intravitreal injections; peri-operative antibiotics; pre-operative ocular surgery prophylaxis; pre-operative intravitreal injection prophylaxis; povidone-iodine; topical antiseptics; disinfectants; and combinations of them. Only publications written in English were included. The bibliographic research was performed by two independent reviewers (MF and FG), and cases of disagreement were resolved through discussion with a third independent reviewer (VR).

2.1 | Selection criteria

We included randomized controlled trials, cohort studies, case–control studies and case series. Reviews, case reports, expert opinions, personal observation, editorials, letters to the editor, non-inherent studies and studies with unclear groups were excluded. The potentially relevant articles were selected assessing title and abstract, and the full texts were then reviewed to select the ones meeting the inclusion criteria. Consensus between all the investigators was used to solve any case of disagreement. The selection process is detailed in the PRISMA flow chart (Figure 1) (Page et al., 2021).

2.2 | Quality assessment

The quality assessment was conducting by three reviewers independently applying the Cochrane Collaboration's tool (for RCTs) and the Newcastle-Ottawa Scale (for non-randomized studies) (Stang, 2010). For each study, two main parameters were assessed: comparability of the study groups and outcome assessment. A 9-point scale grading system was used to grade the studies' quality with a minimum of 1 point and a maximum of 9 points. Study quality was considered high for scores between 7 and 9, moderate for scores between 4 and 6 or low for scores less than or equal to 3. Discrepancies and disagreement were resolved through discussion.

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (Sterne et al., 2019) and risk of bias in non-randomized studies of interventions (ROBINS-I) tools (Sterne et al., 2016) were used to assess randomized and non-randomized studies, respectively (Figures 2 and 3).

2.3 | Data extraction

The eligible studies were reviewed independently by two authors (MF and FG) and, for each of them, the following data extracted: author's name, country, year of publication, study design, level of evidence, number of index and control eyes included, type of topical antimicrobial(s)/antiseptic(s) analysed, administration regimen, surgical procedure type, use of intracameral antimicrobial at the end of the surgery (in case of cataract surgery), timing of conjunctival swab and corresponding timing. The studies were divided on the basis of the procedure performed (cataract surgery or intravitreal injections) and, then, according to the topical agent investigated (antimicrobials or antiseptic). Descriptive data were extracted for the outcomes. The primary outcome was the reduction of OSBF. Senior investigators (VR, SK, PA, GV and FS) resolved discrepancies and disagreements between reviewers.

3 | TOPICAL ANTIMICROBIALS AND ANTISEPTICS USED AS PROPHYLAXIS

3.1 | Antimicrobials

Topical antimicrobials are widely used by ophthalmologists before or after intra-ocular procedures (Barry et al., 2013). The classes of antimicrobials commonly used as topical ophthalmic solutions are quinolones, aminoglycosides and chloramphenicol.

The quinolones are synthetic broad-spectrum antimicrobials, active on both G+ and G− bacteria (Pham

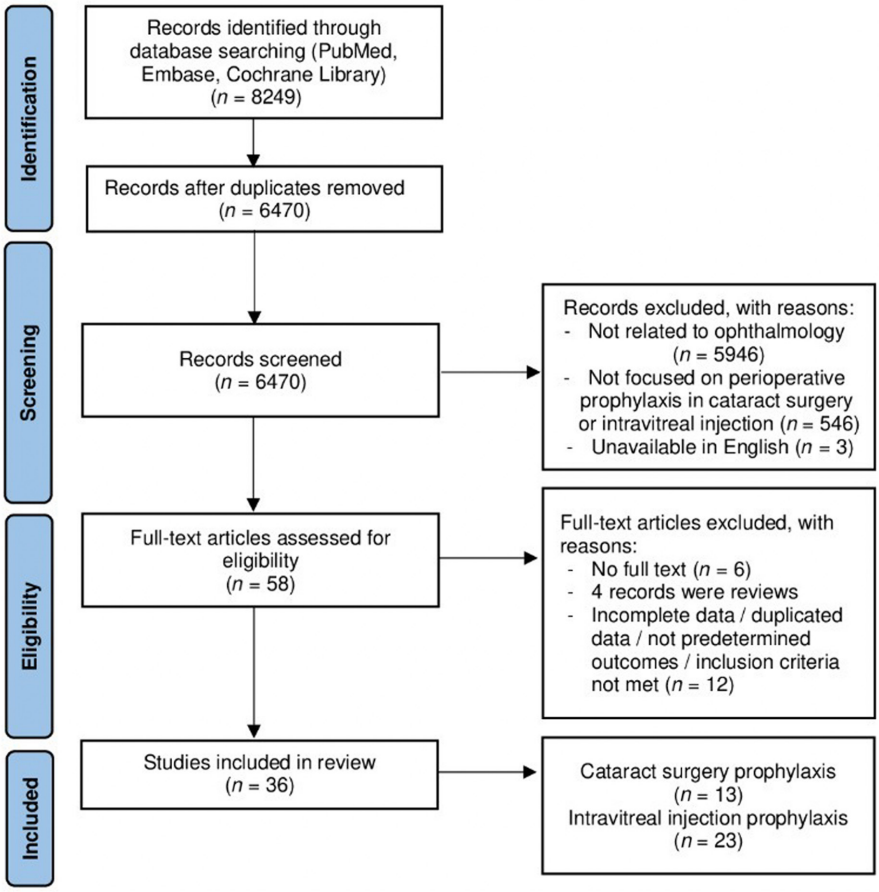

FIGURE 1 Flow chart showing the selection process according to PRISMA guidelines.

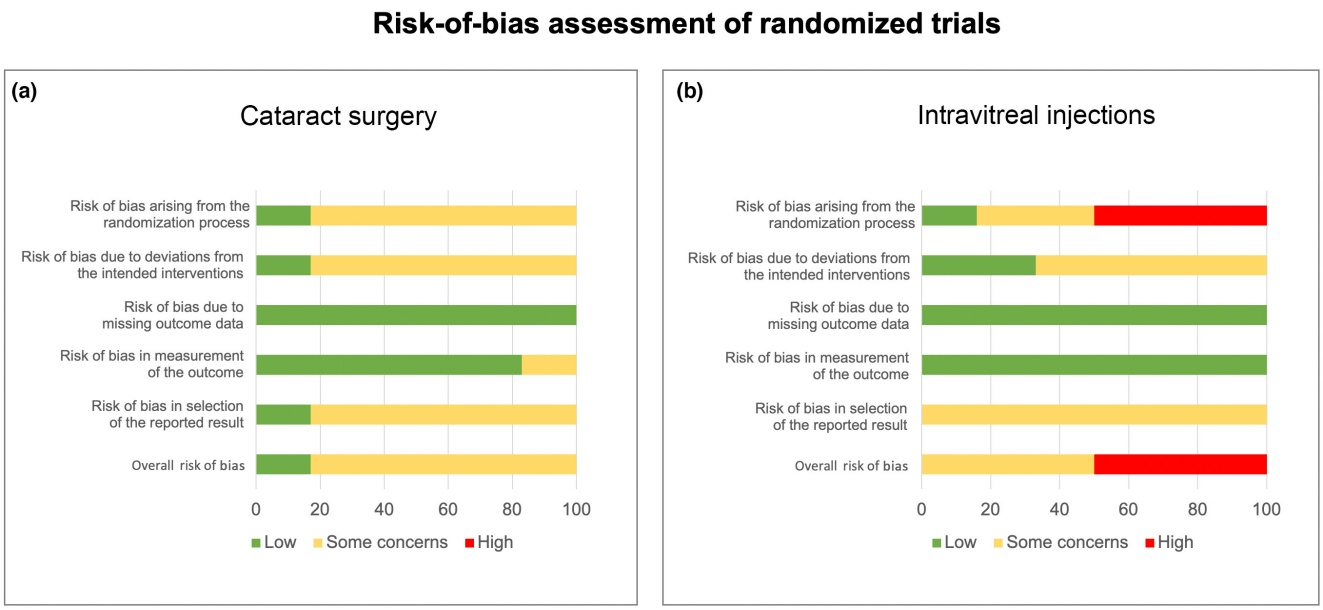

FIGURE 2 Diagram of the risk of bias assessment of randomized clinical/controlled studies included.

et al., 2019). The basic molecular structure consists of the fusion of a 3-carboxy-4-pyridone ring to an aromatic ring with substituents. These antimicrobials exert their bactericidal activity by inhibiting two bacterial enzymes, namely topoisomerase IV and DNA gyrase, and, consequently, nucleic acid synthesis (Pham et al., 2019). The quinolones more commonly used as ophthalmic solutions are 0.5% levofloxacin, 0.3% ciprofloxacin, 0.5% moxifloxacin and 0.3% gatifloxacin.

The aminoglycosides are broad-spectrum antimicrobials, active against G−, several G+ bacteria, including methicillin-resistant and vancomycin-resistant *S. aureus* and *Pseudomonas aeruginosa* (Krause et al., 2016). Structurally, these molecules have a core of amino sugars linked to a dibasic aminocyclitol and act by inhibiting the bacterial protein synthesis binding of the 16S ribosomal RNA of the 30S ribosome (Krause et al., 2016). The commonly used aminoglycosides licensed for topical use are

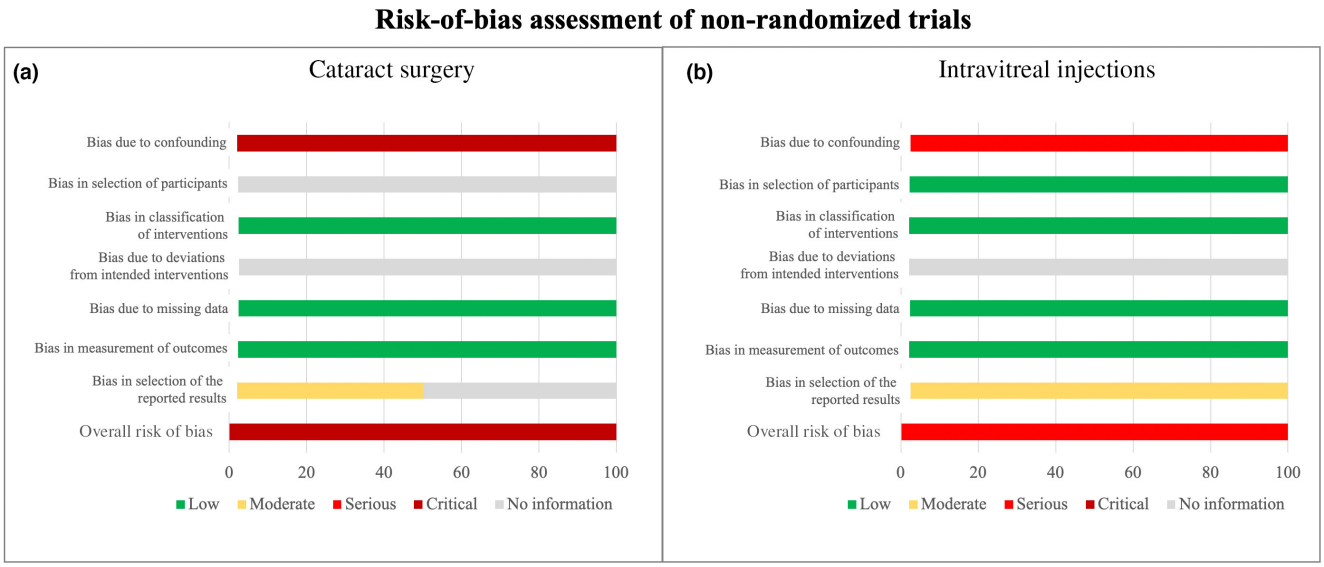

FIGURE 3 Diagram of the risk of bias assessment of non-randomized studies included.

0.35% neomycin, 0.3% netilmicin, 0.3% gentamicin and 0.3% tobramycin.

Chloramphenicol belongs to the nitrobenzenes, organic compounds containing a benzene ring with a carbon linked to a nitro-group. This broad-spectrum antimicrobial is active on G+ and G− bacteria, both aerobic and anaerobic, through inhibition of protein synthesis acting on the 50S ribosomal fraction (Pilly, 2018). Depending on its concentration and the type of microorganism, this antimicrobial can behave as bacteriostatic or bactericidal (Pilly, 2018). Specifically, chloramphenicol has a bacteriostatic activity on Streptococci and *S. aureus* (Pilly, 2018). It is used at a concentration of 0.5% and 1%.

3.1.1 | WHO AWaRe Classification Database

Due to increasing antibiotic resistance, the World Health Organization developed the WHO AWaRe Classification Database (https://www.who.int/publications/i/item/2021-aware-classification) aiming to optimize the use and monitoring of antimicrobials. The database divides the antimicrobials into three different categories, namely "Access, Watch or Reserve", based on their activity and resistance potential. Specifically, the "Access group" includes antimicrobials with broad-spectrum activity and low resistance potential, thus recommended as first/second-choice empiric treatments for infectious pathologies; the "Watch group" includes compounds with higher resistance potential and/or relative high risk of bacterial resistance selection; the antimicrobials included in the "Reserve group" should be the last choice to treat confirmed or suspected infectious diseases attributed to MDR organisms.

In line with the WHO recommendation to increase the use of antimicrobials in the "Access group", these might be preferred for post-operative infection prophylaxis. Among the antimicrobials more commonly used as topical ophthalmic preparation, chloramphenicol and gentamicin are classified as "Access" in the latest WHO AWaRe Classification Database.

It is worth noting that the term "resistance" with respect to the eye needs to be used with caution as there are no ophthalmic breakpoints, and resistance and susceptibility are based on systemic concentrations and breakpoints, not on ophthalmic or ocular surface concentrations (Tuft et al., 2022). However, as not specific database for ophthalmic antimicrobials is available, the WHO AWaRe Classification Database can be used as a reference to adapt daily ophthalmic practice to general clinical recommendations.

3.2 | Antiseptics

The most commonly used antiseptic in ophthalmology is povidone-iodine (PVI), also known as povidone, a water-soluble polymer consisting of iodine and the hydrophilic carrier polyvinylpyrrolidone (Grzybowski, Kanclerz, & Myers, 2018). The rapid bactericidal effect is due to the free iodine, which has a strong oxidizing power against bacterial molecules, while povidone acts as iodine hydrophilic carrier (Grzybowski, Kanclerz, & Myers, 2018). PVI has broad-spectrum activity against bacteria, viruses, fungi and protozoa (Grzybowski, Kanclerz, & Myers, 2018). Two additional advantages of PVI are the absence of reported cases of resistance, even when used repetitively, and the low cost (Grzybowski, Kanclerz, & Myers, 2018). As mentioned above, use of the term resistance in this context needs, however, to be interpreted with caution (Tuft et al., 2022). As such studies need to report the minimum inhibitory concentrations (MIC) before, during and following the use of an antimicrobial or antiseptic (Tuft et al., 2022).

While PVI 10% is widely used for skin disinfection, including the periocular area, formulations of PVI based on lower concentrations, such as 5%, 1%, 0.66% and 0.25%, have been tested for the ocular surface disinfection aiming to limit the potential damage to the corneal epithelium (Gower et al., 2017). A dose-dependent endothelial and epithelial toxicity of PVI has been detected in rabbit corneas (Grzybowski, Kanclerz, & Myers, 2018;

Jiang et al., 2009). Although anaphylaxis has never been reported, PVI can lead to allergic reactions due to its carrier excipients (Grzybowski, Kanclerz, & Myers, 2018).

Biguanides, oxidizing compounds containing the group $C_2H_7N_5$, have been proposed as alternatives to PVI due to their activity against both G+ and G− microorganisms, anaerobic bacteria, fungi and several enveloped viruses (Kanclerz & Myers, 2022). Biguanides act by binding to bacterial cell wall and inducing alteration in the osmotic equilibrium with subsequent cytoplasmic damage and cell death (Kanclerz & Myers, 2022). Among them, the most commonly used is chlorhexidine (CLX), cationic biguanide insoluble in water, supplied as salts. For ophthalmic use, CLX is prepared in the form of aqueous solution since alcohol-based CLX is highly toxic on corneal epithelium (Kanclerz & Myers, 2022; Merani et al., 2016) Chlorhexidine is recognized as a well-tolerated alternative to PI, in particular in patients with PVI-sensitivity (Kanclerz & Myers, 2022). In terms of adverse effects, CLX has been associated with allergy and more severe reactions, such as anaphylaxis (Merani et al., 2016). Finally, some cases of resistance have been reported (Merani et al., 2016). Again, however, this is based on systemic breakpoints, with no presented MICs (Merani et al., 2016).

Among the biguanides, polyhexamethylene biguanide (PHMB) and picloxydine dihydrochloride can be also used as topical ophthalmic antiseptics, but the evidence of their use in prophylaxis of infectious complication in cataract surgery and intravitreal injections is limited (Budzinskaya et al., 2020).

Finally, over the last few years, several different antimicrobial compounds have been introduced as topical ocular antiseptics, such as liposomal ozonized oil eyedrops (Spadea et al., 2021), citrus extract in liposomal form combined with hypromellose (Vagge et al., 2021), and some agents used as preservatives for ophthalmic formulations with broad antimicrobial activity, including benzalkonium chloride (BAK), hypochlorous acid, polyquaternium-1 (PQ1), PQ133, PQ160 and PQ165 (Rolando et al., 2011). However, the evidence supporting the efficacy of these new antiseptics in preventing postoperative infections is very limited; thus, these compounds will not further discussed in this review.

4 | OCULAR SURFACE BACTERIAL FLORA

The ocular surface is colonized by multiple commensal bacteria (ocular surface bacterial flora, OSBF) (Aragona et al., 2021). The OSBF plays a crucial role in the ocular surface homeostasis thanks to its effect of competition towards pathogenic bacteria and consequent growth inhibition of microorganisms potentially leading to ocular infections (Aragona et al., 2021). The composition of the normal OSBF is not completely known and can be altered by several factors, including infections, cosmetics, contact lenses use, topical antibiotics or preservatives, ocular surgery and ocular/systemic disorders (Aragona et al., 2021). In the OSBF of healthy noninflamed eyes, G+ bacteria (eg. *Staphylococcus, Streptococcus* and *Propionibacterium* spp.) are more commonly detected, whereas G− microorganisms, viruses and fungi are rarely identified (Aragona et al., 2021). However, the overgrowth of G+ bacteria, such as CoNS, can lead to severe ocular infection (Aragona et al., 2021).

OSBF is frequently used as a surrogate marker for post-operative infection risk; however, the translational clinical relevance of a certain reduction of conjunctival bacterial load (CBL) in terms of decreased endophthalmitis rate is not established.

5 | CATARACT SURGERY

In terms of post-operative infection prophylaxis for cataract surgery, two measures are so far supported by strong evidence: the use of povidone-iodine for preoperative skin antisepsis (Ciulla et al., 2002) and the intracameral injection of antimicrobials at the end of the surgery (Barry et al., 2007). Conversely, the use of prophylactic topical antimicrobials for cataract surgery is still controversial and associated with the concern of a potential increase in antibiotic resistance (Nejima et al., 2017). Consistently, pre-operative topical antibiotics was graded with the lowest level of clinical recommendation in the review by Ciulla et al. (2002) assessing different prophylactic techniques for the prevention of cataract surgery-related endophthalmitis. Table 1 summarizes the studies analysing the effect of topical antimicrobials and antiseptics on CBL.

5.1 | Antimicrobials

Few studies supported the effectiveness of various regimens of pre-operative topical antimicrobials in significantly reducing CBL (Eslami et al., 2021; Li et al., 2015; Matsuura et al., 2020). However, there is no evidence of superiority of topical antimicrobials vs. topical antiseptics (Matsuura et al., 2020).

Nejima et al. (2017) compared conjunctival swabs obtained in patients treated with topical levofloxacin after cataract surgery and reported that the eyes treated for 1 month showed persistently higher MICs and lower susceptibility of *S. epidermidis* (collected from conjunctival sac) when compared to those treated with a 1-week regimen.

5.2 | Antiseptics

5.2.1 | Povidone-iodine

Povidone-iodine 5% is widely used in current surgical practice for the antisepsis of the ocular surface just before cataract surgery (Edington et al., 2020). However, there are still some unresolved questions regarding the optimal topical PVI regimen. For instance, PVI irrigation of the ocular surface may result in a better eradication rate than instilling drops (Merani & Hunyor, 2015).

Regarding concentration and exposure time, PVI 5% for a minimum of 3 min appears to be a regimen widely

TABLE 1 Studies analysing the effect of topical antimicrobials and antiseptics on conjunctival bacterial flora.

Authors, year, country	Study design	Eyes, *n*.	Subgroups (*n*)	Preop topical antimicrobials	Preop topical antiseptics (in all eyes)	Conjunctival bacterial load evaluation timing (conj swab)	Positive culture rate	Conclusions
Antimicrobials								
Li et al. (2015), Germany	RCliT	133	Group 1 (64): neo/polyB 1 h pre-sx Group 1C (64): control (fellow eye) Group 2 (69): neo/polyB 1 d pre-sx Group 2C (69): control (fellow eye)	Group 1: neo/polyB q15m x4 Group 2: neo/polyB QDS	PVI 1% conj irrigation	T0: after AM, before PI T0c: baseline control eye T1: after PVI T2: at the end of sx	T0: 65.6% in Group 1 vs. 78.1% in Group 1C, $p=0.028$ 66.7% in Group 2 vs. 88.4% in Group 2C, $p=0.000$ T1: 25% in Group 1 vs. 78.1% in Group 1C, $p=0.000$ 13% in Group 2 vs. 88.4% in Group 2C, $p=0.000$ T2: 7.8% in Group 1 vs. 8.7% in Group 2, $p=0.739$	Preop topical neo/polyB and PVI 1% significantly reduced CBL PVI had the greatest effect on CBL reduction.
Nejima et al. (2017), Japan	RCliT	103	Group 1 (53): levo1.5% 1 week after sx Group 2 (50): levo1.5% 1 month after sx	Levo 1.5% tds for 3 d	NA	T0: baseline T1: 1 w after sx T2: at the end of tx T3: 1 m after postop tp T4: 3 m after postop tp T5: 6 m after postop tp	At T1-T2: higher MIC and lower susceptibility to levo in both groups T4: MIC of levo was significantly higher in Group 2 From T2 to T4 more resistant strains were found in Group 2	Perioperative levo significantly reduced CBL Perioperative levo administration influences MIC and susceptibility of conjunctival S epidermidis.
Antiseptics								
Nentwich et al. (2012), Germany	RCT	263	Group 1 (132): 3 drops of PVI 10% pre-sx Group 2 (131): control (no PVI drops pre-sx)	Outpatients (OP, 112): neo 1 h pre-sx Inpatients (IP, 151): neo QDS 1 d pre-sx+1 drop 1 h pre-sx	PVI 1% conj irrigation	T1: pre-PVI, after AM T2: after PVI, pre-sx T3: at the end of sx	T0: 86% in Group 1 OP vs. 92.7% in Group 2 OP ($p=0.2474$) 85.5% in Group 1 IP vs. 69% in Group 2 IP ($p=0.0128$) T1: 16.4% in Group 1 OP vs. 28.8% in Group 2 OP ($p=0.1134$) 11.7% in Group 1 IP vs. 28% in Group 2 IP ($p=0.0116$) T3: 3.7% in Group 1 OP vs. 15.8% in Group 2 OP ($p=0.0332$) 1.3% in Group 1 IP vs. 9.6% in Group 2 IP ($p=0.0251$)	Additional drops of 10% PVI pre-sx further reduce CBL compared with PVI 1% irrigation alone.
Li et al. (2013), Germany	RCliT	271	Group 1: PVI 1% Group 2: PVI 5% Group 3: PVI 10%	Levo 0.3% QDS 1 d pre-sx	PVI conj irrigation	T0: before PVI T1: after PVI T2: at the end of sx.	T1 (TB): 17% in Group 1, 16.1 in Group 2, 8.3 in Group 3 Group 3 vs. Group 1, $p=0.024$; Group 3 vs. Group 2, $p=0.029$ T1 (BA): 11% in Group 1, 10.3 in Group 2, 2.4 in Group 3 Group 3 vs. Group 1, $p=0.000$; Group 3 vs. Group 2, $p=0.010$ T2: no significant difference ($p>0.05$) between groups	PVI 10% showed the greatest effect in CBL reduction

TABLE 1 (Continued)

Authors, year, country	Study design	Eyes, *n*.	Subgroups (*n*)	Preop topical antimicrobials	Preop topical antiseptics (in all eyes)	Conjunctival bacterial load evaluation timing (conj swab)	Positive culture rate	Conclusions
Inagaki et al. (2013), USA	RCliT	75	Group 1: PVI 5% Group 2: CLX 0.02% +eyelid eversion Group 3: CLX 0.02% −eyelid eversion	Levo 0.5% qds for 3 d	Irrigation after skin disinfection (see groups)	T1: pre- AS irrigation T2: post- AS irrigation T3: at the end of sx AC tap at the end of the sx	T1: 50% in Group 1, 41.6% in Group 2, 37% in Group 3 T2: 16.7% in Group 1, 25% in Group 2, 11.1% in Group 3 T3: 16.7% in Group 1, 4.2% in Group 2, 7.4% in Group 3	No significant differences between PVI 5% and CLX 0.02%
Musumeci et al. (2021), Italy	Ps	212	Group 1 (106): PVI 0.66% tds for 3 d pre-sx Group 2 (106): control (fellow eye)	NA	NA	T0: before PVI 0.66% T1: after PVI 0.66% pre-sx	T1: 38.7% in Group 1 vs. 90.6% in Group 2, $p<0.0001$	PVI 0.66% reduced significantly CBL
Antimicrobials vs. antiseptics								
Matsuura et al. (2020), Japan	Ps	204	Group 1: intraop PVI 0.25% irrigation Group 2: levo 1.5%	Levo 1.5%: tds for 3 d pre-sx+1 drop on the day of sx	PVI 5% x2	T0: 1–2 weeks pre-sx T1: before corneal incision T2: 2 h after sx	T0: 95.1% in Group 1 vs. 98.0% in Group 2, $p>0.05$ At T1 7.8% in Group 1 vs. 5.9% in Group 2, $p>0.05$ At T2 60.8% in Group 1 vs. 62.7% in Group 2, $p>0.05$	Intraoperative PVI 0.25% and pre-operative levo 1.5% were equally effective in reducing CBL
Antimicrobials+antiseptics								
Eslami et al. (2021), Iran	RCT	142	Group 1: PVI 10%+levo 0.5% Group 2: control (fellow eye)	Levo 0.5% 1 h pre-sx	PVI 10% just before sx	T1: before tx T2: before the second application of PVI T3: 3 min after the second PVI T4: just post-operatively	T1: 70.4% in Group 1 vs. 73.2% in Group 2, $p=0.709$ T2: 15.5% in Group 1 vs. 71.8% in Group 2, $p<0.001$ T3: 7% in Group 1 vs. 19.7% in Group 2, $p=0.027$ T4: 5.6% in Group 1 vs. 4.2% in Group 2, $p=0.698$	Additional administration of PVI 10%+levo 0.5% before surgery further reduced the CBL

Abbreviations: AC, anterior chamber; AM, antimicrobials; AS, antiseptics; BA, blood agar; CBL, conjunctival bacterial load; CC, case–control; cef, cefuroxime; CI, confidence interval; CLX, chlorhexidine; conj, conjunctival; d, day; h, hour; HM, Hypromellose; IOL, intraocular lens; levo, levofloxacin; m, month; NA, not applicable; neo, neomycin; NS, not specified; OR, odds ratio; polB, polymyxin B; Ps, prospective; qds, four times a day; RCliT, randomized clinical trial; RCT, randomized controlled trial; sx, surgery; TB, thioglycolate broth; tds, three times a day; tx, therapy; van, vancomycin; w, week.

reported as effective (Barry et al., 2013; Cao et al., 2013; Huang et al., 2016). This protocol, however, is not sufficient to completely eradicate MDR organisms in vitro (O'Rourke et al., 2021). In general, more diluted PVI formulations, namely from 0.1% to 1%, are characterized by a rapid (within 15 s) but short bactericidal effect requiring repeated applications, whereas PVI from 2.5% to 10% showed a delayed onset of bactericidal activity (from 30 to 120 s) with longer duration of bactericidal effect (Berkelman et al., 1982). Few clinical studies have claimed the superiority of PVI 10% over PVI 5% and PVI 1% (Li et al., 2013; Nentwich et al., 2012) in terms of OSBF reduction; however, there is no evidence that this results in a different efficacy in endophthalmitis rate reduction. In addition, the use of PVI 10% can frequently result in superficial punctuate epitheliopathy and corneal damage (Li et al., 2013), whereas PVI 5% may provide a prolonged bactericidal effect and reduce the risk of corneal epithelial toxicity (Grzybowski, Kanclerz, & Myers, 2018; Grzybowski, Told, et al., 2018; Jiang et al., 2009). However, corneal epitheliopathy has been described after the use of PVI 5% (Ali et al., 2021).

Recently, more dilute PVI formulations, such as 0.66% and 0.25%, have been investigated. PVI 0.6% showed in vitro antimicrobial activity against *S. aureus*, *S. epidermidis*, *P. aeruginosa* and *Candida* spp (Pinna et al., 2020). In addition, PVI 0.6% demonstrated a more rapid bactericidal effect in vitro when compared to PVI 5% (Musumeci et al., 2019). Clinically, Musumeci and co-workers, reported the efficacy of topical PVI 0.66%, administered three times a day for 3 days before cataract surgery, in significantly reducing CBL (Musumeci et al., 2021).

5.2.2 | Povidone-iodine vs. antimicrobials

Matsuura et al (Matsuura et al., 2020) found that the intraoperative administration of PVI 0.25% was equally effective as pre-operative levofloxacin 1.5% in reducing the CBL.

5.2.3 | Povidone-iodine vs. chlorhexidine

According to ESCRS Guidelines, when povidone-iodine is contraindicated (as in the case of hypersensitivity or allergy to iodine), CLX, most commonly used at 0.05%–0.1%, may be a valid alternative (Barry et al., 2013). Yokoyama and co-workers reported that PVI 10% was superior to CLX 0.05% in terms of an antimicrobial effect (Yokoyama et al., 2008). Conversely, Inagaki et al. (2013) documented no difference in the reduction of CBL achieved with PVI 5% vs. CLX 0.02%. Finally, PVI 5% for 3 min may be more effective in the eradication of MRSA and MR S. epidermidis compared with CLX 0.05% for the same contact time (O'Rourke et al., 2021).

6 | INTRAVITREAL INJECTIONS

With the advent of anti-vascular endothelial growth factor (VEGF) agents, the number of IVI has increased exponentially over the last decade (Lau et al., 2018). So far, there are no worldwide accepted protocols or guidelines regarding the endophthalmitis prophylaxis pre- and post-IVI (Patel et al., 2020; Teberik et al., 2019). As for cataract surgery, PVI or, less commonly, CLX are used for periocular skin and ocular surface antisepsis due to their recognized safety and efficacy in reducing IVI-related endophthalmitis rate (Bhavsar et al., 2016; Mulcahy et al., 2021). In addition, topical antimicrobials are often prescribed, either pre-IVI or post-IVI, to reduce OSBF (Benoist D'Azy et al., 2016; Grzybowski, Told, et al., 2018; Merani & Hunyor, 2015). Table 2 resumes the currently available studies analysing the efficacy of topical antimicrobials and antiseptics before and/or after IVI.

6.1 | Antimicrobials

Topical fluoroquinolones and macrolides can be effective in reducing OSBF in patients receiving IVI (Plotas et al., 2017; Teberik et al., 2019). Moreover, topical antimicrobials may have a synergistic or additive effect with PVI resulting in a higher eradication rate when compared with PVI alone (Teberik et al., 2019). In general, topical antimicrobials may need more time than PVI to achieve their antimicrobial effect (Wykoff et al., 2011). Moreover, several studies raised concerns regarding the potential of prolonged and repetitive use of antimicrobials to result in a significant increase of bacterial MDR (Milder et al., 2012; Storey et al., 2016; Yin et al., 2013).

6.2 | Antiseptics

Although PVI and CLX are extensively used for endophthalmitis prophylaxis before IVI, several important aspects of the therapeutic regimen are still under debate, such as the optimal concentration, exposure time and duration of administration.

6.2.1 | Povidone-iodine

The Euretina Expert Consensus on IVI recommended the administration of PVI 5% into the conjunctival sac for a minimum of 30 s (Grzybowski, Told, et al., 2018). However, conjunctival disinfection with PVI at concentrations varying from 0.25% to 10% led to promising results. For instance, Ikuno et al. (2012), found that PVI 1.25% was not less effective than PVI 5% in reducing OSBF when administered before IVI. Furthermore, PVI 0.66% was demonstrated to reduce significantly the OSBF in eyes undergoing IVI (Reibaldi et al., 2019; Tognetto et al., 2021). Finally, PVI 0.6% may be well tolerated and improve the ocular surface in patients with dry eye after 28 days of treatment, suggesting that its use could be useful when para-surgical procedures, like IVI, require repeated instillation of antiseptics (Oliverio et al., 2021).

With regard to the minimum contact time of 30 s, a prospective randomized trial comparing the effect of

TABLE 2 Studies analysing the efficacy of topical antimicrobials and antiseptics before intravitreal injections.

Authors, country, year	Study design	Eyes, *n*.	Subgroups (*n*)	Pre-IVI topical antimicrobials	Post-IVI topical antimicrobials	Pre-IVI topical antiseptics	Conjunctival bacterial load evaluation timing (conj swab)	Positive culture rate	Conclusions
Antimicrobials									
Plotas et al. (2017), Greece	RCliT	92	Group 1 (32): 1 d pre-IVI Group 2 (29): 1 h pre-IVI Group 3 (31): 1 d + 1 h pre-IVI	Oflo 0.3% qds Oflo q15m x4 Oflo 0.3% qds+q15m x4	NS	PVI 5%	T0: pre-AM T1: after AM, pre-PVI	At T0 vs. T1 Group 1 (BB): 84.4% vs. 50%, $p=0.007$ (BA): 65.63% vs. 34.38%, $p=0.02$ Group 2 (BB): 79.3% vs. 48.28%, $p=0.027$ (BA): 68.97% vs. 37.13%, $p=0.034$ Group 3 (BB): 77.42% vs. 32.26%, $p=0.0008$ (BA): 58.06% vs. 22.58%, $p=0.009$	Pre-IVI Oflo 0.3% significantly reduce CBL
Teberik et al. (2019), Turkey	RCT	132	Group 1 (41): azi pre-+post-IVI Group 2 (41): mox pre+post-IVI Group 3 (50): No AM	Azi qds for 3 d Mox qds for 3 d	Azi qds for 3 d Mox qds for 3 d	PVI 5%	T0: pre-AM T1: pre-IVI pre-PVI T2: pre-IVI, post-PVI T3: 3 d post-IVI, post-AM	Group 1 vs. Group 2 vs. Group 3 T0: 29.3% vs. 31.7% vs. 36%, $p=0.27$ T1: 22% vs. 9.8% vs. 30%, $p=0.042$ T2: 9.8% vs. 0% vs. 22%, $p=0.002$ T3: 9.8% vs. 7.3% vs. 26%, $p=0.217$	AB pre- and post-IVI increased eradication rate. Mox was more effective than PVI 5% in reducing CBL
Antiseptics									
Ikuno et al. (2012), Japan	RCliT	100	Group 1 (52): Levo+PVI 1.25% Group 2 (48): Levo+PVI 5%	Levo 0.5%: q5m x3	None	PVI 1.25% or PVI 5%: q3m x3	T0: baseline T1: after AM+PVI	T0: 86.5% in Group 1 vs. 77.1% in Group 2 T1: 48.1% in Group 1 vs. 56.3% in Group 2, $p=0.43$ CBL reduction rate: 46.7% in Group 1 vs. 33.4% in Group 2, $p=0.48$	PVI 1.25% was not inferior to PVI 5% in reducing CBL
Friedman et al. (2013), USA	RCliT	131	Group 1 (26): PVI 5% for 15 s Group 2 (26): PVI 5% for 30 s Group 3 (70): PVI 5% for 60 s	None	None	PVI 5%	T0: baseline T1: after lid speculum T2: after PVI 5%	T0 vs. T1 vs. T2 (p for T1 vs. T2) Group 1: 69% vs. 84% vs. 65%, $p=0.08$ Group 2: 69% vs. 65% vs. 42%, $p=0.0003$ Group 3: 59% vs. 60% vs 30%, $p=0.0003$	PVI 5% for 30 or 60 s significantly reduced CBL

(Continues)

TABLE 2 (Continued)

Authors, country, year	Study design	Eyes, *n*.	Subgroups (*n*)	Pre-IVI topical antimicrobials	Post-IVI topical antimicrobials	Pre-IVI topical antiseptics	Conjunctival bacterial load evaluation timing (conj swab)	Positive culture rate	Conclusions
Reibaldi et al. (2019), Italy	RCliT	507	Group 1 (254): PVI 0.6 Group 2 (253): placebo	NS	NS	Tds for 3 d + 1 drop 3 h before IVI +PVI 5% pre-IVI	T0: pre-tx T1: post-tx	Group 1: CBL significantly decreased from T0 to T1, $p < 0.001$ in both BA and CA Group 2: CBL did not significantly decreased from T0 to T1, $p = 0.806$ in BA, $p = 0.390$ in CA	PVI 0.6% significantly reduced CBL
Ali et al. (2021), USA	RCT	100	Group 1 (50): PVI 5% Group 2 (50): CLX 0.1% (contralateral eye)	None	NS	PVI 5% CLX 0.1%	T0: before AS T1: after IVI	T0: 66% in Group 1 vs. 52% in Group 2, $p = 0.16$ T1: 34% in Group 1 vs. 28% in Group 2, $p = 0.52$	No significant difference between PVI 5% and CLX 0.1% in reducing CBL
Tognetto et al. (2021), Italy	Ps	416	Group 1 (208): PVI 0.6% Group 2 (208): no PVI (fellow eye) G2 (30): control. G2 (20): Tob (1st IVI) G3 (20): NBD (>20 IVI) G4 (20): picloxydine 0.05% (1st IVI)	None Tob 3 d pre-IVI Tob or NBD 3 d pre-IVI	None Tob 5 d post-IVI Tob or NBD 5 d post-IVI	PVI 0.6% tds for 3 d PVI 5% + picloxydine 3 d pre-IVI to 5 d post-IVI	T0: before AS T1: after AS	CBL decreased significantly only in Group 1 from T0 to T1 ($p < 0.001$).	PVI 0.6% significantly reduced CBL.

Abbreviations: AM, antimicrobials; AS, antiseptics; ASB, spray antiseptic containing Biosecur citrus extract; Azi, azithromycin; BA, blood agar; BB, BACTEC broth; BSS, balanced salt solution; CA, chocolate agar; CBL, conjunctival bacterial load; CLX, chlorhexidine; IVI, intravitreal injection; levo, levofloxacin; mox, moxifloxacin; NA, not applicable; NBD, neomycin, polymyxin B and dexamethasone; NS, not specified; oflo, ofloxacin; Ps, prospective; PVI, povidone-iodine; qds, four times a day; RCliT, randomized clinical trial; RCT, randomized controlled trial; tds, three times a day; tob, tobramycin; tx, therapy.

PVI 5% after 15-, 30- and 60-s exposure identified "30 s" as the minimum contact time to achieve a significant reduction of OSBF (Friedman et al., 2013).

6.2.2 | Chlorhexidine

The last Euretina Expert Consensus on IVI recommended the use of CLX in patients with PVI-induced local irritation (Grzybowski, Told, et al., 2018). No significant differences have been reported between CLX 0.1% and PVI 5% in terms of OSBF reduction (Ali et al., 2021; Lau et al., 2018; Oakley et al., 2018). Moreover, with regard to the optimal concentration, different CLX dilutions, from 0.05% to 0.2%, have been described as safe, but have not been compared in terms of bactericidal effects (Merani et al., 2016).

6.2.3 | Povidone-iodine vs. chlorhexidine

In the absence of significant differences in terms of OSBF reduction, CLX 0.1% may be associated with a lower pain score and less corneal damage when compared with PVI 5% (Ali et al., 2021). However, CLX may have a delayed onset of action compared with PVI (Anderson et al., 2010; Koburger et al., 2010; Zargham-Boroujeni et al., 2014).

7 | DISCUSSION

7.1 | Cataract surgery

Multiple clinical studies suggested that topical antimicrobials in addition to intracameral injection do not provide any further benefit compared with intracameral injection alone and topical antisepsis, whether given pre-operatively or post-operatively (Barry et al., 2007; Gower et al., 2017; Herrinton et al., 2016). Consistently, both ESCRS and AAO guidelines recommend the use of intracameral antimicrobials. The use of the recommended dose of intracameral cefuroxime (1 mg in 0.1 mL) was effective in decreasing significantly the rate of post-operative endophthalmitis in a multicenter randomized controlled trial conducted on 16 603 patients (Barry et al., 2007). Moreover, the European Medicines Agency approved Aprokam (cefuroxime) in 2012 as commercial single-use preparation of powdered solution of cefuroxime intended for intracameral use only (https://www.ema.europa.eu/en/documents/psusa/cefuroxime-sodium-intracameral-use-list-nationally-authorised-medicinal-products-psusa/00010206/201505_en.pdf). Alternatively to cefuroxime, vancomycin and moxifloxacin have shown to be effective in the form of intracameral injection at the end of cataract surgery (Bowen et al., 2018).

In addition, ESCRS Guidelines suggest that topical antimicrobials should be prescribed when surgical complications occur, or when wound healing may be poor, to prevent infection (Barry et al., 2013). Indeed, in the post-operative period, a topical antimicrobial may reduce viable microorganisms from the ocular surface entering the anterior chamber if the surgical wound is not completely closed (Bandello et al., 2020). Conversely, once wound closure is complete (usually in <1 week) and the corneal epithelium is intact, it is crucial to take into account that the concentration of topical antimicrobial into the anterior chamber is low (much lower than conjunctival concentration) and may be less than the minimum inhibitory concentration (MICs) needed for the invading bacteria, potentially reducing their effectiveness (Barry et al., 2013). Several factors contribute to this aspect, such as poor transepithelial penetration, aqueous humour and interpatient variability (Barry et al., 2013). It follows that, if needed, it might appear reasonable to prescribe post-operative antimicrobials for not more than 1 week. In general, antimicrobials should be given wisely to avoid the development of MDR bacteria.

With regard to the efficacy of topical antiseptics after cataract surgery, the evidence is still limited due to the paucity and weak methodological design of the studies available. No ESCRS and AAO recommendations are currently available regarding the use of antiseptics before and/or after cataract surgery.

7.2 | Intravitreal injections

7.2.1 | Antimicrobials

Despite their ability to reduce the OSBF, the last Euretina Expert Consensus Recommendations on IVI discouraged the peri-IVI use of topical antimicrobials (Grzybowski, Told, et al., 2018). Indeed, clinical studies assessing the potential beneficial effect of perioperative topical antimicrobials in terms of reduction of endophthalmitis rate as well as a recent meta-analysis, concluded that their administration, either before or after IVI, was not associated with any significant difference compared with topical PVI alone (Benoist D'Azy et al., 2016; Bhavsar et al., 2016; Chaikitmongkol et al., 2018; Li et al., 2016; Morioka et al., 2020). Paradoxically, Cheung et al. (2012) and Storey et al. (2016) reported a trend towards an increased incidence of clinically suspected IVI-related endophthalmitis when post-operative antimicrobials were used. However, these studies had significant limitations, including, primarily, the retrospective nature, the lack of assessment of patients' compliance to the post-operative drop regimen and the inclusion of culture-negative cases that could have represented acute intraocular inflammation instead of infectious endophthalmitis (Chaikitmongkol et al., 2018). On the other hand, several studies highlighted that prolonged and repetitive use of antimicrobials in eyes treated with IVI may lead to a statistically significant increase of bacterial MDR (Milder et al., 2012; Storey et al., 2016; Yin et al., 2013).

7.2.2 | Antiseptics

There is strong evidence supporting the use of topical PVI, as well as growing studies supporting the safety and

efficacy of CLX as an alternative to PVI, in particular in patients with reported sensitivity or allergy to PVI. In this regard, Merani et al. (2016) found an endophthalmitis rate lower than that reported in the literature (0.0074% vs. 0.028%–0.056%) (Patel et al., 2020) associated with the pre-IVI use of CLX 0.05% or 0.1%. The optimal therapeutic regime, including concentration and exposure time, however, is still under debate. In general, a repeated application of PVI immediately before IVI may be beneficial in terms of endophthalmitis rate (Mulcahy et al., 2021).

New antiseptic formulations have proven to be effective in reducing OSBF; however, further studies would be necessary to investigate whether their administration would be effective in preventing post-operative endophthalmitis.

8 | CONCLUSIONS

Topical antiseptics appears to have a crucial role in reducing the OSBF for the prophylaxis of post-operative endophthalmitis after both cataract surgery and intravitreal injections. Conversely, the pre- and post-operative use of topical antimicrobials appears to be not supported.

Analysing the overall evidence present in the literature, some recommendations may be made. For cataract surgery, the use of intracameral antimicrobials and pre-operative antiseptics (four times a day for 3 days) is strongly recommended. Antimicrobials during the first post-operative week may be administered in case of risk factors for endophthalmitis, such as ocular surface disease, complicated and/or prolonged surgery, local or systemic immunosuppression. Based on their efficacy to significantly reduce the OSBF, antiseptics might be used as alternative to antimicrobials with the additional advantage of not inducing the development of resistant microorganisms. However, further prospective comparative studies will be needed to evaluate the appropriate therapeutic regimen, as the limited evidence currently available does not allow to make specific recommendations.

Regarding IVI, the use of pre-operative antisepsis (four times a day for 3 days) is strongly recommended, whereas despite their ability to reduce the OSBF, the routine use of pre-operative and post-operative antimicrobials is not recommended as not supported by significant evidence.

In the light of the high risk of bias in the studies available, more accurate recommendations on the ideal therapeutic regimen cannot be drawn; future randomized trials may clarify the best administration regimen of topical antiseptics, including concentration and exposure time.

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ORCID

Mariantonia Ferrara https://orcid.org/0000-0002-1191-4989
Pasquale Aragona https://orcid.org/0000-0002-9582-9799
Vito Romano https://orcid.org/0000-0002-5148-7643

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