

Emerging antimicrobial resistance and need for antimicrobial stewardship for ocular infections in India: A narrative review

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Patients with ocular infections are at increased risk of vision impairment and may require immediate medical care to preserve their vision. Management of ocular bacterial infections has evolved in recent years and includes a pragmatic selection of broad-spectrum antibiotics based on the causative bacteria. Nevertheless, the treatment of bacterial ocular infections is increasingly becoming a challenge, as the causative bacterium acquires resistance to antibiotics through intrinsic and acquired methods. From an Indian perspective, along with the challenges of antibiotic resistance, there are other factors such as lack of knowledge on epidemiology, and lack of data on local susceptibility patterns of ocular pathogens that have significant impact on the management of ocular infections. This narrative review summarizes the available knowledge on prescribing antibiotics for five common ocular infections in India. It further highlights the significance of the understanding of antimicrobial susceptibility patterns across India as a cornerstone to promote rational use of ocular antibiotics. This review indicates that large-scale antimicrobial resistance surveillance studies can facilitate the synchronization of ophthalmic antimicrobial prescription policies with local antibiotic resistance patterns. Further, establishment of an antimicrobial stewardship program in ophthalmology can potentially increase the efficacy of diagnostic tools, and implement earlier adoption of effective antibiotics. Overall, this review provides consolidated information and key considerations for treatment decision-making of common ocular infections in India.

Key words: Antimicrobial stewardship, blepharitis, dacryocystitis, India, ocular infections

Common microbial ocular infections include conjunctivitis, keratitis, endophthalmitis, uveitis, blepharitis, orbital cellulitis and dacryocystitis.^[1-5] The diagnosis of these ocular infections is challenging due to diverse presentations; moreover, lack of prompt intervention may result in long-term vision impairment.^[1] Ocular infections are caused by a diverse group of microorganisms such as bacteria, fungi, parasites, and viruses. Bacterial ocular infections are caused by both gram-positive and gram-negative bacteria; however, gram-positive bacteria are predominant.^[6] The most prevalent causative bacterial pathogens include *Staphylococcus aureus* (*S. aureus*), coagulase negative *Staphylococci*, *Streptococcus pneumoniae* (*S. pneumoniae*) and *Pseudomonas aeruginosa* (*P. aeruginosa*).^[6] The management of ocular infections is empiric and usually involves the use of broad-spectrum antibiotics in the form of eye drops, ointments, and intra-ocular formulations.^[7] The widespread and injudicious use of conventional antibiotics in ocular infections, together with improper dosing regimen, polypharmacy, and the absence of global ocular antibiotic prescription guidelines have resulted in antimicrobial resistance (AMR) among gram-positive and gram-negative bacteria.^[8-10]

AMR among ocular pathogens has emerged as a public health concern in the past decade.^[11,12] *S. aureus*, one of the

most prevalent ocular pathogens, has developed resistance to methicillin, producing an ocular methicillin-resistant *S. aureus* (MRSA) strain, which is the principal causative agent in vision-threatening infections.^[13,14] Furthermore, the management of MRSA infections is challenging due to the multidrug resistance accrued by these pathogens.^[15] Similar to MRSA, other ocular pathogens such as *P. aeruginosa* isolates have also developed resistance to broad-spectrum antibiotics.^[9] AMR has a significant impact on the national healthcare system as well as the economy. An economic analysis study conducted by the World Bank in 2017 estimated that by the year 2050, the annual global GDP impact of AMR may range from 1.1% to 3.8%, while the increase in overall global healthcare costs may range from 300 billion USD to more than 1 trillion USD annually.^[16]

Studies estimate that by the year 2050, Asia may experience up to 4.7 million deaths directly attributed to AMR (https://rr-asia.oie.int/wp-content/uploads/2020/03/thailand_thailand-national-strategic-plan-on-amr-2017-2021.pdf). Antimicrobial resistance is attaining significance in India, with up to 12–59% of *E. coli* being extended-spectrum beta-lactamase (ESBL) producers, and up to 30% being carbapenemase producers (CP).

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Klebsiella pneumoniae has emerged as a highly resistant pathogen with up to 50% resistance to carbapenems and rapidly increasing resistance to polymyxins. In addition, methicillin resistance in *S. aureus* is seen in up to 30% of *S. aureus* isolates.^[17]

Ocular microbiome is specially prone to develop AMR due to its unique ability to form biofilms.^[18] Over the last few years, some alarming data have emerged from India, showing antimicrobial resistance in bacterial keratitis and endophthalmitis.^[19]

From an Indian perspective, it is pertinent to highlight that the Indian population is vulnerable to microbial infections including ocular infections, both due to its geographical location and climatic conditions—which promote intrinsic changes in the microbiome—as well as external factors such as antibiotic abuse and overuse.^[20] The daunting challenges of ocular infection management in India are ascribed to the rampant and injudicious use of antibiotics.^[21,22] Drug utilization and antibiotic prescription pattern studies from India have reported a higher average number of drugs per prescription, indicating polypharmacy.^[22] Such prescriptions are particularly rampant in our country due to abundance of quacks and untrained personnel prescribing medicines illegally, as well as due to patient non-compliance. A prospective cross-sectional study analyzing 640 prescriptions from an ophthalmology out-patient department (OPD) setting in India highlighted missing information on the frequency of drug administration and duration of treatment in 96% and 75% prescriptions, respectively.^[22] Recent years have seen an increase in AMR, including MRSA in ocular infections in India.^[20] A ten-year retrospective analysis conducted between 2007 and 2017 on the prevalence of MRSA-associated ocular infections in a tertiary eye care hospital in south India revealed increasing incidence of MRSA from 9% in 2007 to 38% in 2017.^[23] Despite the increasing prevalence, there is a dearth of knowledge on epidemiology, and susceptibility patterns of ocular pathogens and ocular AMR in India.^[9] Thus, updating the current knowledge on the rational use of antibiotics in India is indispensable to reduce the prevalence of AMR.

Furthermore, the variability in generic antibiotic prescriptions is also a potential contributor to increasing AMR.^[24,25] A literature review conducted on 54 different antimicrobial drugs reported that India has the highest variety (39%) of substandard/counterfeit antimicrobials, which includes generic ophthalmology drugs as well.^[26] Counterfeit generic antimicrobial drugs may have substandard quality, formulation inconsistencies, lack of active ingredient, and in some cases, incorrect active ingredients, which may lead to potentially harmful adverse effects and may lead to AMR.^[24,25]

Over the past years, greater emphasis has been laid on establishing antimicrobial stewardship (AMS) programs that encourage prudent use of antibiotics to maintain their clinical effectiveness.^[27] AMS involves optimal selection, dosage, and duration of antibiotics by healthcare practitioners with minimal toxicity to the patient and minimal impact on subsequent resistance.^[28] It further prevents overuse, misuse, and abuse of antibiotics to minimize the development of resistance.^[28] While AMS is a well-established concept for the rational use of antibiotics in systemic infections, it is not prevalent in ophthalmology.^[29] Furthermore, AMS programs

encourage antibiotic prescription based on local resistance patterns.^[27,29] Therefore, an improved understanding of the patterns of antibiotic use and AMR in India is crucial for effective implementation of AMS programs.

The objective of this narrative review is to consolidate current knowledge on the management of common ocular infections, and promote rational use of ocular antibiotics in India. This narrative review is aimed to provide useful insights to the ophthalmologists in treatment decision-making and optimal selection of antibiotics for ocular infections.

Common Bacterial Ocular Infections: Diagnosis and Management

Bacterial infections are the most common ocular infections and can range in severity from self-limiting bacterial conjunctivitis to potentially sight-threatening conditions such as endophthalmitis.^[30] Thorough assessment of distinctive clinical symptoms is essential to determine the ocular involvement and provide accurate diagnosis. The intra-ocular infections may occur subsequent to a corneal ulcer, penetrating eye injury, or a severe bloodstream infection, and presents as iritis, uveitis, chorioretinitis, or endophthalmitis.^[1,20] Common ocular infections in India such as blepharitis, conjunctivitis, dacryocystitis, keratitis and endophthalmitis are discussed in detail below, and treatment recommendation is summarized in Table 1.

All the management guidelines mentioned in this paper have been quoted from the National Treatment Guideline for Antimicrobial Use in Infectious Diseases published in the year 2016 by the National Centre for Disease Control, DGHS, MoH&FW, GoI.^[37] Unfortunately, since then there have been no comprehensive guidelines published to guide ophthalmologists regarding updated judicious use of antimicrobials in eye infections. The Treatment Guidelines for Antimicrobial Use in Common Syndromes published by the ICMR in 2019 which provided updated guidelines for judicious antimicrobials omitted eye infections altogether.^[17]

Blepharitis

Blepharitis is a chronic ophthalmic disease characterized by inflammation of the eyelids.^[38] Although the exact pathogenesis of blepharitis is unknown, the etiology of blepharitis is attributed to staphylococcal bacteria (*S. aureus*, *S. epidermidis*, methicillin-susceptible *S. aureus* (MSSA) or MRSA), eye inflammation, or tarsal gland abnormalities.^[38] Common symptoms associated with bacterial blepharitis include irritation of the eyelids, tearing, eyelash loss, eyelid ulceration, eyelid scarring, itching, tear film instability, and red eyes.^[37]

Primary clinical management of blepharitis involves maintaining ocular and hand hygiene.^[32,39,40] Warm wet compresses to the eye are suggested to soften eyelid debris and dilate meibomian glands followed by gentle wash.^[38] The National Centre for Disease Control guidelines (NCDC) in India recommends the use of oral cloxacillin and oral cephalexin for blepharitis caused due to MSSA/*S. epidermidis*, and oral trimethoprim when the causative pathogen is MRSA.^[32] Topical antibiotics like bacitracin or erythromycin that are applied to the lid margins are used for the management of acute blepharitis.^[38,37] Topical agents like fusidic acid, metronidazole, and fluoroquinolones have also proven their efficacy in

Table 1: Recommendations for the management of common ocular infections in India

Ocular infection	Causative pathogen	Pharmacological treatment	Surgical treatment	Supportive care	Source
Blepharitis	MSSA/ <i>S. epidermis</i> MRSA	Oral Cloxacillin 250-500 mg qid or Oral Cephalexin 500 mg qid Oral Trimethoprim sulphamethoxazole 960 mg BD or Linezolid 600 mg BD		Lid margin care with baby shampoo and warm compresses 24 hourly. Artificial tears, if associated with dry eye. Thermal pulsation and intense pulsed light therapy for posterior blepharitis. ^[31]	NCDC Guidelines ^[32]
Conjunctivitis (Bacterial)	<i>S. aureus</i> , <i>S. pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Neisseria gonorrhoeae</i> or, <i>Chlamydia trachomatis</i>	Ophthalmologic solution: Moxifloxacin 0.5% 1-2 drops q2h while awake during first 2 days, then q4-8h upto 7 days, Gatifloxacin 0.3%, levofloxacin 0.5%		Maintaining ocular and hand hygiene. Antibiotics to be avoided for self-limiting viral conjunctivitis.	NCDC Guidelines ^[32]
Dacryocystitis	<i>Staphylococcus</i> and <i>Streptococcus</i> , <i>Haemophilus influenzae</i> , <i>P. aeruginosa</i> and <i>Fusobacterium</i>	Topical antibiotics: Broad-spectrum antibiotics - fluoroquinolones, aminoglycoside antibiotic (gentamicin). ^[33] Oral antibiotics: Fluoroquinolones, amoxicillin-clavulanic acid , and third generation cephalosporins. ^[33,34] Intravenous antibiotics: Combination of penicillin antibiotic and beta-lactam antibiotic, ^[33] cephalosporin (ceftriaxone), and fluoroquinolones.	Dacryocystorhinostomy ^[35]	Warm compresses, Crigler massages over lacrimal sac.	National Institute of Health and Family, Dacryocystitis. ^[35]
Keratitis (Bacterial)	<i>S. aureus</i> , <i>S. pneumoniae</i> , <i>S. pyogenes</i> , <i>Haemophilus</i> and <i>Pseudomonas species</i>	First-line agent: Moxifloxacin topical (0.5%): 1 drop, hourly for first 48 h, then reduce first 48 h, then reduce as per response. Alternate regimen: Gatifloxacin 0.3% ophthalmic solution, 1 drop, hourly for 1 st 48 h then reduce as per response	Severe infectious keratitis: Surgical intervention in the form of amniotic membrane transplant and keratoplasty. ^[36]		NCDC Guidelines ^[32]
Endophthalmitis (bacterial)	Post-ocular surgery: <i>S. epidermidis</i> , <i>S. aureus</i> , <i>Streptococci</i> , <i>enterococci</i> , Gram- negative bacilli Hematogenous: <i>S. pneumoniae</i> , <i>N. meningitidis</i> , <i>S. aureus</i> , <i>Streptococcus</i> , <i>K. pneumoniae</i>	Intravitreal antibiotics (Injection vancomycin Injection vancomycin + Injection ceftazidime) Intravitreal antibiotics: Injection vancomycin + Injection, Cefazidime + +Systemic antibiotics: Injection meropenem 1 gm IV q8h/Inj Ceftriaxone 2 gm Ceftriaxone 2 gm IV q24h+Injection Vancomycin 1 g IV q12h	Vitrectomy		NCDC Guidelines ^[32]

the treatment of blepharitis.^[39] Macrolides (erythromycin and azithromycin) have the advantage of exhibiting anti-inflammatory and antibacterial properties, and are therefore ideal in blepharitis cases with co-existent bacterial infection and inflammation.^[39-41] In cases with significant ocular inflammation, topical anti-inflammatory agents (e.g., corticosteroids, cyclosporine) provide symptomatic relief.^[37] Thermal pulsation and intense pulsed light therapy are also used to treat posterior blepharitis due to meibomian gland dysfunction.^[31] Blepharitis has good prognosis; however it is sporadically associated with recurrent episodes due to the pathogenic susceptibility of the patient.^[38,39]

Conjunctivitis

Conjunctivitis or inflammation of the conjunctiva is the most common cause of acute red eye.^[5] Symptoms of conjunctivitis include intense redness of eyes, swelling of conjunctiva, watering of eyes, ropy discharge (pus or mucus), pain in the eyes, and sensitivity to light or blurred vision.^[5,42] Conjunctivitis can be infectious or non-infectious; viruses and bacteria are the most common infectious causes of conjunctivitis while non-infectious conjunctivitis is attributed to allergy, toxicity, and inflammation secondary to immune-mediated diseases.^[43] Common bacterial pathogens causing infectious conjunctivitis include *S. aureus*, *S. pneumoniae*, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis*.^[42] An observational study conducted in the ophthalmology OPD in a tertiary hospital in India reported infective conjunctivitis as the most commonly diagnosed ocular infection in 21.5% of patients.^[21] The primary cause of viral conjunctivitis is adenoviruses, herpes simplex virus, or varicella (herpes) zoster virus. Viral and bacterial conjunctivitis are highly contagious; therefore, patients are instructed to exercise proper eye and hand hygiene.^[43] It can be distinguished through symptomatic variability and slit lamp examination.^[43] Mild bacterial conjunctivitis is usually self-limiting; however, antibiotic treatment is necessary in severe cases characterized by purulent discharge, pain, and marked inflammation of the eyes.^[5] Fluoroquinolones (moxifloxacin, gatifloxacin and levofloxacin) are recommended for bacterial conjunctivitis as per the NCDC guidelines.^[32] Fluoroquinolones are recommended for wearers of contact lens, diagnosed with conjunctivitis to provide empiric coverage for *Pseudomonas*.^[43] Topical corticosteroids are not recommended for bacterial or viral conjunctivitis.^[5,42] Chlamydial infections, which include trachoma, neonatal inclusion conjunctivitis, and adult inclusion conjunctivitis are also common eye infections seen in India. Mass azithromycin treatment has been used for control of the disease, along with promotion of hygiene and environmental changes. Antimicrobial resistance in *Chlamydia* has thankfully remained low.^[44]

Dacryocystitis

Dacryocystitis is an infection of the nasolacrimal sac leading to inflammation and blockage of the nasolacrimal duct.^[45] Dacryocystitis manifests as epiphora, erythema, edema, induration, and pain over the nasolacrimal sac.^[35,45] Pathogenesis of dacryocystitis is the bacterial overgrowth in the lacrimal sac; common causative pathogens for dacryocystitis include strains of *Staphylococcus* and *Streptococcus*, *Haemophilus influenzae*, *P. aeruginosa* and *Fusobacterium*.^[35,46] A prospective study from eastern India

indicated that aerobic gram-positive isolates (74.2%) were the more frequently observed causative pathogens among 95 patients with unilateral chronic dacryocystitis, including a high prevalence of MRSA (>90%) in the *S. aureus* isolates.^[47] Acute dacryocystitis can be treated with topical antibiotic eye drops, oral antibiotics, and anti-inflammatory drugs.^[35] Broad-spectrum antibiotics and subsequent empiric treatments with fluoroquinolones (moxifloxacin, gatifloxacin, and ofloxacin), amoxicillin-clavulanic acid, and third generation cephalosporins represent the standard treatment pattern for infectious dacryocystitis.^[34] Intravenous antibiotics are recommended if dacryocystitis progresses to cellulitis despite oral antibiotic treatment.^[34] Warm compresses and crigler massages over the lacrimal sac are conservative treatments suggested along with antibiotics.^[34,35] Surgical interventions including syringing, probing, and external dacryocystorhinostomy (DCR) offer a definitive management for dacryocystitis.^[34,35] In a retrospective cohort study conducted over a period of 22 years among 320 patients with acute dacryocystitis presented in a tertiary eyecare center in India, oral amoxicillin and dicloxacillin constituted 61% of the antibiotics chosen as initial medical management, while DCR was performed in 82.5% patients.^[48] In Mitra *et al.*^[47] study, highest sensitivity to linezolid (100%) and higher generation fluoroquinolones were observed among the gram-positive isolates.

Keratitis

Keratitis is an inflammation of the cornea characterized by the presence of white or yellowish infiltrates in the corneal stroma.^[49] Complications of keratitis include scarring in the cornea, and if left untreated, can lead to corneal opacity and blindness.^[49] A majority of keratitis cases in India are infectious due to bacterial, fungal, or viral pathogens.^[50-52] The most common bacterial pathogens of infectious keratitis are *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *Haemophilus* and *Pseudomonas* species.^[50-52] Keratitis diagnosis is conducted through slit lamp examination while the corneal scraping for laboratory analysis helps to determine the causative organism.^[19,53,54] A specific diagnosis of the causative organism can assist in prompt and accurate therapy, and avoid redundant use of antibiotics.^[54] Topical broad-spectrum antibiotics, primarily fluoroquinolone monotherapy, have been the mainstay for the treatment of bacterial keratitis.^[54] According to the NCDC guidelines, topical moxifloxacin (0.5%) is recommended as the first line of treatment, and gatifloxacin (0.3%) as the alternative treatment for acute bacterial keratitis.^[32] Fortified antibiotics, cephalosporins (cefazolin 5% or cefuroxime 5%), and aminoglycosides (tobramycin 1.3%, gentamicin 1.4%) have been used topically in the treatment of bacterial keratitis. However, studies have shown similar efficacy with commercially available topical fluoroquinolone eye drops.^[55] They are useful in fluoroquinolone-resistant cases.^[56] Corticosteroids may be considered after 24 to 48 hours, as the causative pathogen is identified and primary therapy is effective. However, they should be avoided in viral and fungal keratitis.^[53] Surgical intervention may be required for severe infectious keratitis in the form of keratoplasty or amniotic membrane transplant.^[36] Recommending appropriate antimicrobial therapy also necessitates the knowledge of evolving local susceptibility patterns. A retrospective cross-sectional study spanning 12 years analyzing AMR trends

in 3,685 bacterial keratitis isolates from a large tertiary eyecare hospital in south India established that the two most common organisms presenting resistance were *S. pneumoniae* (33%) and *P. aeruginosa* (24%).^[57] A significant increase in MRSA isolates was observed during the 12-year study period together with increased fluoroquinolone resistance in *S. aureus* and MSSA isolates (e.g. ofloxacin resistance in MSSA increased from 11.1% in 2002 to 66.7% in 2013).^[57]

Endophthalmitis

Endophthalmitis is a severe ocular inflammation triggered by infection of the intra-ocular tissues that can have potentially devastating vision consequences without prompt and effective treatment.^[58] A systematic review from India which included data from 1992 to 2012 reported that the incidence of clinical endophthalmitis ranged from 0.04% to 0.16%.^[59] Endophthalmitis manifests itself as reduced or blurred vision, red eye, pain, and eyelid swelling.^[60] Progressive vitritis is a vital observation during diagnosis and ophthalmological examination in endophthalmitis.^[3] Bacterial infections, mostly gram-positive Staphylococcus species (*S. epidermis*, *S. aureus*), Streptococci, enterococci and gram-negative bacilli Pseudomonas species are the most common cause of postoperative endophthalmitis.^[59,61] Treatment for endophthalmitis must be prompt, even prior to a definitive diagnosis. Intravitreal antibiotic therapy is the main stay of treatment for endophthalmitis. First-line intravitreal antimicrobial agents for the management of endophthalmitis include glycopeptide (vancomycin), cephalosporin (ceftazidime), and aminoglycoside (amikacin).^[62] Alternative intravitreal antibiotics for potential use in management of endophthalmitis due to antimicrobial susceptibility to standard antimicrobials include oxazolidinone (linezolid), cyclic lipoglycopeptide (daptomycin), glycylicycline (tigecycline), carbapenem (imipenem), and fluoroquinolones (moxifloxacin, ciprofloxacin, and levofloxacin).^[60,62] Recommended systemic antibiotics for the treatment of endophthalmitis include meropenem (1 gm, IV, every 8 hours), ceftriaxone (2 gm, IV, every 2 hours) + vancomycin (1g, I, every 12 hours).^[32] Vitrectomy with vitreous biopsy is recommended in severe endophthalmitis with vitritis and retinal infiltration. However, considerable antibiotic susceptibilities have also been observed globally in the spectrum of etiological agents of endophthalmitis.^[61,63] In a study to determine the clinico-microbiological and antibiotic susceptibility profile in 1,110 patients diagnosed with endophthalmitis from a single center in India, gram-positive bacteria showed susceptibility to glycopeptides like vancomycin (80–100%) and fluoroquinolones (87–91%), whereas gram-negative bacteria (*Pseudomonas* and *Klebsiella*) showed susceptibility toward fluoroquinolones (61–82%).^[61] A recently published study estimated an increasing trend of antibiotic resistance of *Pseudomonas* to fluoroquinolones, amikacin, and ceftazidime in endophthalmitis, including alarming increase in multidrug resistance, particularly in post-surgical patients.^[63] Despite aggressive treatment, prognosis in *Pseudomonas* endophthalmitis cases remains poor with a high number of cases requiring enucleation.^[64]

Antimicrobial Resistance Trends in Ocular Infection

AMR has gained attention as a major global health threat of the 21st century owing to its current and potential consequences

on public health, and economic burden.^[65] AMR occurs when microorganisms develop cellular mechanism to adapt and transform on exposure to antibiotics, rendering the medication ineffective.^[66] Being the world's largest consumer of antibiotics for human health (10.7 units per person), India carries a major burden of AMR.^[67] High rates of MRSA (ranging from 32–80%) have been reported in diverse studies.^[67] An increase in MRSA from 29% of *S. aureus* isolates in 2009 to 39% in 2015 was observed in a large private laboratory network study.^[68] The past decades have witnessed an alarming increase in AMR in general bacterial pathogens, and ocular pathogens are no exception.^[9,12,13,62,69] The identification of causal pathogen for the ocular infection is crucial for treatment decision-making. However, to avoid treatment delays, preliminary selection of antibiotics for the treatment of ocular infections in clinical practice is empiric, and is based on the most frequently encountered pathogens, pharmacokinetics of the antibiotic, dosage, and costs.^[43] Empirical treatment increases the probability of antibiotic prescription to a resistant pathogen that may subsequently lead to treatment failure. Variability and under-potency in generic ocular antibiotics could be potential contributors to emerging AMR.^[70] A study on the unstable outcome of generic ciprofloxacin antibiotic eye drops in India, highlighted that about 20% of samples showed under-potency to the standard advisory ranges.^[24] Antibiotic prescription pattern studies across ophthalmic OPDs in India identified antibiotic overuse, polypharmacy, and common prescription writing errors such as undefined duration of therapy, frequency of administration, or dosage form.^[21,71] A recent study to analyze antibiotic prescription patterns in an ophthalmology OPD in a tertiary care hospital in India reported only 1.6% of the prescriptions from the National Essential Medicines List (2015).^[72,73] Prescribing peri-operative antibiotic regimen is a common practice among ophthalmologists;^[74] however, judicious and optimal use of antibiotics should be considered to control the threat of AMR.^[75] Widespread antibiotic susceptibilities have been observed among common ocular antibiotics in multi-center AMR surveillance studies conducted in the past decade. The Surveillance Network (TSN) data on ocular isolates of *S. aureus* (2000–2005) conducted in the US estimated that the proportion of ocular infections caused by MRSA increased from 29.5% in 2000 to 41.6% in 2005.^[76] Another surveillance study was ocular tracking resistance in the U.S. Today (Ocular TRUST) conducted in 2005–2006.^[12] Ocular TRUST evaluated the in-vitro antimicrobial susceptibility of *S. aureus*, *S. pneumoniae*, and *H. influenzae* to a variety of commonly used ophthalmic antibiotics including fluoroquinolones, aminoglycosides, penicillin, macrolides, polymyxin B, and trimethoprim.^[12] Ocular TRUST study reported virtually identical MSSA (79.9% to 81.1%) or MRSA (15.2%) susceptibility patterns for fluoroquinolone.^[12] Most recent ophthalmic surveillance study from the US setting is the AMR monitoring in ocular microorganisms (ARMOR) conducted in 2009. The study prospectively evaluated antimicrobial susceptibility of *S. aureus*, *S. pneumoniae*, *H. influenzae*, and *P. aeruginosa* isolated from cases of ocular infections. Thirty-four institutions across the US participated in the ARMOR study, which demonstrated a reduction of MRSA as compared to TSN study data (39% vs 41.6%, respectively).^[11]

Although there is a dearth of largescale surveillance studies determining antibiotic susceptibility patterns

across India, few local epidemiological studies have added evidence for ocular antibiotic susceptibilities.^[56,77,78] A 5-year retrospective analysis of microbiological samples from patients diagnosed with ocular infections demonstrated susceptibility to moxifloxacin (98.7%) and vancomycin (97.9%) among gram-positive isolates, and to amikacin (93.5%) and gatifloxacin (92.7%) among gram-negative isolates.^[77] Recent years have witnessed an increasing trend in AMR across India. A cross-sectional study from south India in patients with bacterial keratitis, underlined increased ofloxacin resistance in MSSA from 11.1% in 2002 to 66.7% in 2013.^[57] Another retrospective review conducted in a tertiary care center in India to analyze the evolving trends of MRSA ocular infections revealed an increase in MRSA-associated ocular infections from 26% in 2006 to 38% in 2008.^[78] Further long-term antibiotic resistance surveillance studies are justified to formulate rationale-based decisions in antibiotic treatment of bacterial ocular infections in India.

Antimicrobial Stewardship Programs

Antimicrobial stewardship (AMS) refers to a coherent set of actions at the individual, national, or global level to promote appropriate use of antibiotics through implementation of evidence-based interventions.^[79] A global action plan was adopted by the World Health Organization (WHO) in 2015 to combat AMR. Strategic objectives of this action plan include enhancing awareness and understanding of AMR, strengthening knowledge through surveillance and research, and optimizing the use of antibiotics.^[80] With AMR emerging as a global health threat, the perspective of AMS has broadened, mirroring its application in diverse range of contexts from hospitals, One Health AMS programs,^[81] and the WHO global stewardship framework.^[82] AMS programs have effectively reduced the emergence of AMR and healthcare-associated infections, use of targeted antimicrobials, and duration of antibiotic therapy.^[83] It has also contributed to a reduction in healthcare-related costs.^[84] A systematic review to determine the effect of AMS programs involving 77 studies showed reduced antibiotic use, and associated costs in 90% and 100% studies respectively.^[85]

The effect of antibiotic resistance must be reduced through largescale implementation of surveillance activities and training of health professionals. Ophthalmologists must invariably comply with the antibiotic prescription guidelines.^[32,75,86] Antibiotics must be adequately administered at an optimal dose and duration.^[32] The concentration of antibiotics must be more than or equal to the minimum inhibitory concentration, and preferably the minimum bactericidal concentration at the site of infection.^[87] Combination therapy can be considered in empiric treatment to enhance therapeutic efficacy or by broadening the spectrum of activity.^[32] Irrational use of antibiotics such as overuse, polypharmacy or undefined duration of therapy, frequency of administration or dosage form must not be exercised.

Phase IV studies, or post-marketing surveillance of antibiotic drugs hold the key to analyzing real-world usage patterns of the drugs as well as its abuse and overuse.^[88] These studies need to be conducted from time to time, analysed, and prescription guidelines issued in order to ensure homogeneity of prescriptions throughout the country.

The Indian Ministry of Health & Family Welfare also formulated the National Action Plan for AMR (NAP-AMR) containment in April 2017.^[89] The strategic priorities of NAP-AMR are to a) strengthen awareness and understanding of AMR through effective communication, education, and training; b) enhance knowledge and evidence in AMR through surveillance; c) reduce the incidence of infection through effective infection prevention and control; d) optimize the use of antimicrobial agents in all sectors; e) promote investments for AMR activities, research and innovations; and f) strengthen India's leadership on AMR by establishing collaborations on AMR at the international, national and sub-national levels. Though AMR in ocular pathogens have evolved with the widespread use of antimicrobials, AMS strategies in ophthalmology have not been explored at the global or national level. There is sparse literature globally that highlights this pressing issue in ophthalmology. This is an elementary article in India that underlines the prominence of AMR in ocular infections, and emphasizes the establishment of national ocular AMS programs that will aid in the rational use of antimicrobials in this field. General measures from the NAP-AMR program can also be adopted in ophthalmology practice. Limiting indiscriminate use of antibiotics for ophthalmic use and choosing wisely can reduce AMR.^[90] Furthermore, largescale microbiological surveillance and antibiotic susceptibility studies for ocular infections in India are indispensable.

Summary and Recommendations

With the increase in AMR of ocular infections in India, there is a compelling need to establish antimicrobial prescription guidelines and policies for ophthalmic infections. Largescale AMR surveillance studies across India are a requisite to reassess the ophthalmic antimicrobial prescription policies in India in accordance with local resistance patterns. Evidence from these surveillance studies will assist in tailoring antibiotic prescription policies by patient demographics and clinical settings. Emergence of antibiotics embarked a golden era in healthcare, and enabled humanity to overcome its worst nemesis—the microbes. It is ethically imperative that rational and judicious use of antibiotics is exercised, to preserve the efficacy of these magic drugs for continued use.

Based on experiences with antimicrobial stewardship in other therapy areas, it is recommended that a similar programme be initiated in the field of ophthalmology with a focus on the following:

1. Research to identify the current use of antimicrobials in ophthalmology. Regular reporting of information on antibiotic use and resistance to prescribers, pharmacists, nurses, and hospital leadership.
2. Collaboration with microbiologists/laboratories to understand current sensitivity and resistance patterns in India.
3. Nodal society/organization in the field of ophthalmology can lead the creation of guidelines/protocols for antimicrobial usage for the management of ocular infections.
4. Educate prescribers, pharmacists, nurses, and patients about adverse reactions to antibiotics, antibiotic resistance, and optimal prescription for ocular infections.
5. Regular monitoring and assesment to evaluate the

implementation of the guidelines and the impact of interventions in preventing antimicrobial resistance.

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Ethics approval

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Conflicts of interest

Dr Neha Gurha and Dr Nitin Maksane are employees of Novartis Healthcare Private Limited. The other authors have no conflicts of interest to declare.

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