

## Off-Label Fortified Antibiotic Therapy as a Standard Regimen for Infective Ophthalmic Pathologies and Real-Time Challenges

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### ABSTRACT

Over time fortified antibiotics have become the therapy of choice for sight-threatening infective ocular pathologies as compared to commercially available low-concentration antibiotics. However, there are multiple challenges to their use. These include preparation under inadequate clinical settings with improperly trained staff, non-availability of designated vehicle systems and storing medicine at extremes of temperatures - facilities for which are not available everywhere. Furthermore, cost of these fortified antibiotics, poor patient compliance and an increased risk of infection question their main stream use. Lastly, an ever-growing problem of the rise of "superbugs" as a result of the injudicious use of these antibiotics along with unnecessary drug waste which contributes to climate change raises question regarding their long-term viability and necessity for treating sight-threatening ocular pathologies.

**Keywords:** Antibiotic resistance, Climate change, Fortified antibiotics, Infective ocular pathologies, , Superbugs, Topical drug waste.

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### INTRODUCTION

Infective ophthalmic pathologies are a major disease burden in developing countries with infectious keratitis being the tip of the iceberg. In the past few decades, there has been a paradigm shift in the Ophthalmology fraternity to prefer fortified topical, intracameral, and intravitreal antibiotics for the treatment of sight-threatening infective ocular pathologies. There has been compelling evidence supported by tons of anecdotal case series and randomized control trials to prefer fortified antibiotics over commercially available low-concentration single or combination antibiotics. Another school of thought believes that fortified antibiotics are being used on the principle of "the more, the better". Even though, in the presence of scarcity of evidence for FDA approval of fortified antibiotic ophthalmic preparations, it is a well-established fact that ocular pathogens are prone to antibiotic resistance just like systemic pathogens.<sup>1</sup> Over recent years, fortified topical antibiotic eye drops are the preferred treatment option for severe sight-threatening microbial keratitis. Fourth-generation Fluoroquinolones (e.g. Ceftazidime) and Aminoglycosides (e.g. Vancomycin) have been supported by clinical evidence to provide broad-spectrum coverage in bacterial keratitis, significantly reducing morbidity.<sup>2</sup> Fortified

Voriconazole eye drops are considered a superior option in the treatment of fungal keratitis. A topical eye drops preparation of antiseptic; Povidone-Iodine 5 and 10% also had a clinically significant role in the treatment of microbial keratitis used alone or in conjunction with other commercially available topical antibiotic eye drops.

Endophthalmitis, another feared intraocular sight-threatening infection is treated empirically by fortified antibiotics (4th generation Cephalosporins and/or Vancomycin) used intravitreally and/ or intracamerally.

Other than these severe sight-threatening disorders, there have been reports of effective treatment of bacterial blepharitis and bacterial conjunctivitis with fortified topical antibiotics and antiseptic eye drops, reducing the duration of disease and infectivity of the patient.<sup>3</sup>

During COVID-19, the frequency of Sino-orbital mucormycosis has exponentially increased, posing a direct threat to the patient's sight and life. A well-in-time administration of retrobulbar injection of fortified Amphotericin B has been reported to combat the disease, reducing the incidence of exenteration and cerebral extension in such patients.<sup>4</sup>

The major challenge faced by Ophthalmologists in the use of these popular treatment regimens is compounding and dispensing fortified antibiotics for ophthalmic use. All such preparations are commer-

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cially unavailable. In our tertiary care Ophthalmology service, fortified antibiotic eye drops are compounded and dispensed by the resident doctors under aseptic conditions. The preparation of fortified antibiotics faces a wide range of real-time challenges.

**Inadequate clinical setting:** Owing to the major clientele in the ophthalmic clinic and a significant daily turnout of patients requiring fortified ophthalmic antibiotics, preparation is subject to an insufficient sterile environment. Furthermore, manual compounding and dispensing are prone to human errors of inadequate preparation (pH, osmolarity, and concentration).

**Non-availability of Vehicle systems:** Neither a designated vehicle system nor a diluting solution is currently available in the market specifically for the preparation of fortified topical eye drops. Makeshift arrangement of using preservative-free lubricant eye drops and their container as a semi-optimal delivery system is another major task.

**Inability to self-preserve:** Antibiotics available for systemic use are titrated according to the desired ophthalmic concentration. The major drawback is the inability of these antibiotics to self-preserve. Thus, all such fortified eye solutions are to be discarded after 3-days of their preparation. Furthermore, there is a need for refrigeration of these manually prepared solutions. Studies have proposed effective preservation of these drops at -70° Celsius (cryo-freeze) for up to 75-days, which is itself a Herculean struggle.

**Cost:** The price of a Vancomycin injection vial (500 mg) available in Pakistan under different brand names ranges from 800 PKR to 3200 PKR. The injection vial once diluted cannot be reused for more than 3-days. Thus, practically speaking a 3-day of fortified eye drops therapy of Vancomycin costs the patient an average of 1500 PKR. Furthermore, the insufficient concentration of leftover drug in the vial renders it unavailable for systemic use, even if an appropriate candidate for systemic therapy is available in the same clinical setting.

### **Patient Compliance**

Fortified topical antibiotics are often prescribed initially 1 or 2 hourly in a patient with a heavily diseased eye. This often leads to poor patient compliance. The lack of clinical recommendations for appropriate frequency is one of the contributing factors. Non-availability of fortified antibiotic ointments or ocular inserts/implants to improve bioavailability and patient compliance is another drawback of this regimen.

### **Risk of Infection with Intravitreal/ Intracameral Preparation**

Although, in our practice, intravitreal and intracameral preparations of fortified antibiotics are usually administered under aseptic conditions in operation rooms, still, an inadvertent risk of asepsis breach during preparations always exists. Thus, an infected intraocular antibiotic injection for endophthalmitis would ironically be augmenting the intraocular infection.

**Antibiotic resistance:** Antibiotic resistance is a huge and well-established problem in Pakistan today as a result of over-the-counter availability and liberal prescribing by doctors. A recent study published by Tariq *et al.* described a case of Ligneous conjunctivitis which had been exacerbated by a Multi-drug resistant (MDR) *Pseudomonas Aeruginosa* which was resistant to 8 different antibiotics except for Colistin.<sup>5</sup> Liberal use of fortified antibiotics will only augment this problem and hasten the development of "superbugs".<sup>6</sup>

**Unnecessary Topical Drug Waste:** Climate change is a huge problem in the world today, Pakistan being the largest victim in the recent calamity of country wide flash floods affecting 2/3rd of country's population. The healthcare sector is thought to produce around 9% of the total greenhouse emissions out of which 30% is thought to originate from operating theaters. It is also thought to be the second-largest source of landfill trash. Similarly, prescription drugs are thought to account for around 10% of healthcare costs. According to a study published in the United States, two-thirds of topical drugs were discarded after a single use and amounted to approximately \$195000 (PKR 39 million) of wasted medication.<sup>7</sup> This amounted to approximately \$150 (PKR 300000) per case. This drug waste alone is thought to contribute an estimated 105,000 metric tons of unnecessary CO<sup>2</sup> emissions in the United States annually. Although no study has been done in Pakistan to evaluate the drug wastage cost, we believe the numbers may be the same as Pakistan has a nearly similar population size to the United States. This number may very well be much greater as judicious use, improper preparation and poor compliance may result in extra medication being wasted.

### **Way Forward**

Apropos in view, a holistic approach towards the use of fortified ophthalmic antibiotic solutions is the need of the hour. Multicenter randomized clinical trials to determine the safety and efficacy of fortified antibiotics in the treatment of infective ocular pathologies are warranted to compare it with

commercially available antibiotic preparations. The development of commercially available self-preserving vehicle delivery systems by pharmaceutical industries is crucial in the safe and cost-effective dispensing of these fortified antibiotic eye solutions. Artificial intelligence promises to greatly accelerate new drug discovery to combat the rise of "superbugs" and hence solve the problem of drug resistance. But until then, ophthalmologists must question the judicious use of fortified antibiotics. Finally, we suspect that these drugs are a huge burden on the environment and the healthcare sector in terms of greenhouse gas emissions and cost respectively. An exact number is still to be measured.

**Conflict of Interest:** None.

**Author's Contribution**

Following authors have made substantial contributions to the manuscript as under:

TAK & AR: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

SHB & TAJ: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

MS & MAM: Conception, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

conceptualized the study, collected the data, analysed it, written the manuscript and proof read the final document.

**REFERENCES**

1. Fintelman RE, Hoskins EN, Lietman TM. Topical Fluoroquinolone use as a risk factor for in vitro fluoroquinolone resistance in ocular cultures. *Arch Ophthalmol* 2011; 129(4): 399-402.
2. Al-Badriyeh D, Neoh CF, Stewart K, Kong DC. Clinical utility of voriconazole eye drops in ophthalmic fungal keratitis. *Clin Ophthalmol* 2010; 4(1): 391-405
3. Bremond-Gignac D, Chiambaretta F, Milazzo S. A European perspective on topical ophthalmic antibiotics: Current and evolving options. *Ophthalmol Eye Dis* 2011; 3(1): 29-43.
4. Hirabayashi KE, Kalin-Hajdu E, Brodie FL, Kersten RC, Russell MS, Vagefi MR, et al. Retrobulbar injection of amphotericin b for orbital mucormycosis. *Ophthalmic Plast Reconstr Surg* 2017; 33(4): e94-e97.
5. Tariq M, Zahid MA, Khan TA, Shah HG. Ligneous conjunctivitis exacerbated by pseudomonas aeruginosa - diagnostic and therapeutic approach. *Oman J Ophthalmol* 2021; 14(3): 184-186.
6. Kowalski RP, Nayyar SV, Romanowski EG, Jhanji V. Anti-Infective Treatment and Resistance is Rarely Problematic with Eye Infections. *Antibiotics (Basel)* 2022; 11(2): 204.
7. Tauber J, Chinwuba I, Kleyn D, Rothschild M, Kahn J, Thiel CL, et al. Quantification of the cost and potential environmental effects of unused pharmaceutical products in cataract surgery. *JAMA Ophthalmol* 2019; 137(10): 1156-1163.

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