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Review Article

Antibiotics Misuse in Conjunctivitis, A Step towards the Post-Antibiotic Era!

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Abstract

Conjunctivitis (inflammation of the conjunctiva) is the most frequent ocular disease worldwide. Acute infective conjunctivitis is a very common disease in primary healthcare. It is usually a mild condition and serious complications are uncommon. Viral conjunctivitis occurs in 80% of all patients of acute conjunctivitis. Topical antibiotics do not prevent repeated attacks, and their use may confuse healthcare providers. Use of Antibiotics in bacterial Conjunctivitis: At least 60% of patients of acute bacterial conjunctivitis are self-limiting within 1 to 2 weeks 'duration. Studies of treatment show that there is a high rate of clinical recovery without any treatment (65% within 2-5 days). Unnecessary usage of antibiotics increases dramatically antibiotic-resistance. Antibiotic resistance among ocular organisms could be a challenge to the ophthalmologists. Antibiotic-resistant infections are a significant socioeconomic burden to the health care system. The problem is Global, reflecting the overuse of these drugs worldwide and the failure of the pharmaceutical companies ' development of new antibiotic agents to resolve the threat. Coordinated efforts are essential in implementing new strategies, establishing research efforts and taking steps to resolve the crisis new medications alone, will not be adequate to overcome the risk of antimicrobial resistance. Thus, WHO works with a lot of Nations to organize Infection control management plans.

Keywords: Conjunctivitis, Acute infective Conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, Antibiotics, Antibiotic resistance, GPs, Healthcare system

Introduction

Red eyes are the major symptom of ocular inflammation. It is usually self-limiting and can be easily managed by primary care physicians. Conjunctivitis is the most common cause of red eye [1]. Conjunctivitis (inflammation of conjunctiva) is the most frequent ocular disease globally [2]. It is one of the most common and curable diseases in children and adults; about 3 million cases of conjunctivitis happen in the US each year [3].

Types

A- Viral Conjunctivitis: viruses occur in 80% of all patients of acute conjunctivitis. Most cases are wrongly diagnosed as bacterial conjunctivitis. Between 65% and 90% of patients of viral conjunctivitis originate from adenoviruses, and they generate 2 of the typical viral conjunctivitis, pharyngoconjunctival fever and endemic keratoconjunctivitis. Pharyjgoconjunctival fever is recognized by rapid onset of high fever, pharyngitis, and bilateral conjunctivitis, and by preauricular lymph node growth, whereas endemic keratoconjunctivitis is more serious and provides with watering discharge, hyperemia, chemosis, and ipsilateral lymphadenopathy. Lymphadenopathy is noticed in up to 50% of viral conjunctivitis situations and is more widespread in viral conjunctivitis in contrast to bacterial conjunctivitis.

Although no efficient therapy prevails, lubricant eye drops, topical antihistamines, or cold compression may be useful in treating most of the symptoms. Available antiviral medications are not useful and topical antibiotics are not indicated. Topical antibiotics are not secure against repeated attacks, and their use may confuse the healthcare professionals by resulting in allergic reaction and toxicity, resulting in prompting delay in identifying other ocular diseases. Use of antibiotic eye drops can boost the threat of spreading the infection to the other eye from infected droplets. Increased level of resistance is also popular with regular use of medicines. unnecessary usage of antibiotics increases dramatically antibiotic-resistance [4].

B-Allergic conjunctivitis: is a group of illnesses impacting the ocular surface and is usually associated with type 1 hypersensitivity. The ocular area inflammation (usually mast cell driven) results in itchiness, ripping, lid and conjunctival edema–redness, and photophobia during the acute stage and can lead to late-phase reaction (with associated eosinophilia and neutrophilia) in some patients. Topical corticosteroids drugs are used in serious situations but are associated with an increased threat for the development of cataracts and glaucoma. Thus, there is a global search for new biotargets for the treatment of these illnesses. There is no role of antibiotics in allergic conjunctivitis [5].

c- Bacterial Conjunctivitis: The occurrence of bacterial conjunctivitis was approximated to be 135 in 10 000 in one study. Contaminated fingertips, oculogenital spread, and contaminated fomites are typical routes of transmitting. In addition, certain conditions such as stress, and immunosuppressed status predispose to bacterial conjunctivitis. The most common infection for bacterial conjunctivitis are staphylococcal species, followed by Streptococcus pneumoniae and Haemophilus influenzae. In children, the disease is often due to H influenzae, S pneumoniae, and Moraxella catarrhalis. The course of the disease usually continues for 7 to 10 days.

Hyperacute bacterial conjunctivitis provides a serious massive purulent discharge and reduced visual acuity. It is often associated with eyelid swelling, tenderness, and preauricular adenopathy. It is often due to Neisseria gonorrhoeae and provides probability for corneal involvement and following corneal perforation. Treatment for hyperacute conjunctivitis due to N. gonorrhoeae includes intramuscular ceftriaxone, and chlamydial infection should be treated accordingly.

Chronic bacterial conjunctivitis is used to explain any conjunctivitis for long-term more than a month, with Staphylococcus aureus, Moraxella lacunata, and enteric viruses being the most typical causes in this setting; ophthalmologic assessment should be encouraged for management. Signs and symptoms include red eye, purulent or mucopurulent discharge, and chemosis. The period of incubation and communicability is approximately 1 day to one week. Bilateral involvement of the eyelids and sticking of the eyelids, lack of itchiness, and no history of viral conjunctivitis are strong beneficial predictors of bacterial conjunctivitis. Severe purulent discharge should always be cultured and gonococcal conjunctivitis should be considered. Conjunctivitis which is not responding to standard antibiotic therapy in sexually active patients should be suspected as chlamydial infection. Possibly bacterial keratitis is common in contact lens users, who should be treated with topical antibiotics and must be referred by ophthalmologist and contact lens must be discouraged.

Use of Antibiotics in Bacterial Conjunctivitis: At least 60% of patients of acute bacterial conjunctivitis are self-limiting within 1 to two weeks duration. Although topical antibiotics reduce the duration of the disease, no variations have been noticed in results between therapy and placebo categories.

Choices of Antibiotics: All broad-spectrum antibiotic eye drops seem in general to be effective for bacterial conjunctivitis. There are no important variations in accomplishing medical treatment between any of the broad-spectrum topical antibiotics. Factors that impact antibiotic choice are local accessibility, allergic reactions, level of resistance, and cost. There is no research that has been performed to evaluate the effectiveness of ocular decongestant, topical saline, or warm compresses for the treatment of bacterial conjunctivitis. Topical steroid drugs should be ignored because of the probability of possibly increasing the course of the disease and potentiating the disease. Finally, advantages of antibiotic treatment consist of quicker recovery, decrease in transmissibility, and acceleration return to school for children. Therefore, no treatment, a wait-and-see policy, and immediate treatment all appear to be reasonable approaches in instances of mild conjunctivitis. Antibiotic treatment should be regarded in instances of purulent or mucopurulent conjunctivitis and for patients who have distinct pain, who wear contact lens, who are immunocompromised, and who have suspected chlamydial and gonococcal conjunctivitis. [4].

D- Chemical burns: are possibly blinding ocular injuries which are requiring immediate evaluation and initiation of treatment. Many victims are younger. Alkali injuries occur more often than acid injuries. Chemical injuries of the eye start general harm to the ocular surface epithelium, cornea, anterior segment and limbal stem cells producing long lasting unilateral or bilateral visual impairment. Emergency management if appropriate may be the best factor in establishing a good visual outcome. Mild burns will lead to conjunctivitis, while more serious burns may cause the cornea to turn white (opaque).

Initial evaluation and immediate treatment. Acute stage treatment: Once the immediate treatment and evaluation are completed, the treatment of the chemical injured eye begins. The significant treatment goals that are essential throughout the treatment phases are: (a) reestablishment and maintenance of an intact healthy corneal epithelium (b) management of the stability between collagen production and collagenolysis and (c) minimizing the adverse sequelae that often follow a substance harm. Acute stage treatment contains a wide variety of external antibiotics, cycloplegic and antiglaucoma treatment. Apart from above mentioned medications various therapies to promote reepithelialization and repair, and control of inflammation [6].

E- Ophthalmia Neonatorum: All infants should obtain ocular prophylaxis at birth to avoid gonococcal ophthalmia. Neonates introduced with symptoms and symptoms of conjunctivitis should have a conjunctival swab sent for Gram stain and culture. If Gram-negative diplococci are existing on the Gram stain results, the infants and their parents should be managed immediately for

assumed gonorrhea. Infants with chlamydial infection should be treated with oral antibiotics. Most of all other types of microbial conjunctivitis may be treatable with oral antibiotics, with the exception of Pseudomonas infection. Infants should be followed during their treatment and upon completion of treatment to ensure determination of symptoms. For patients which sexually transmitted bacteria are suggested as a factor, the mothers and their sexual partners should be managed [7].

F- Zika Virus: A lot of individuals who have been contaminated with Zika virus could not recognize they have the infection because they do not have symptoms. The most typical symptoms and symptoms of Zika are high temperature, rash, pain, or conjunctivitis (red eyes). Other typical symptoms consist of joint pain and headache. The incubation period for Zika virus is unknown, but is likely to be short from a few days to a week. There is no available medication or vaccine to treat or prevent Zika virus. Thus, start by treating the symptoms: Get plenty of rest. Drink fluids to avoid dehydration. Take medication such as acetaminophen (Tylenol®) or paracetamol to lessen high temperature and pain. If the patient takes medication for another healthcare problem, it is advised to talk to physician before taking additional medication [8].

G- SARS-CoV-2 (Coronavirus): Conjunctivitis is reported and it is associated with fever and respiratory symptoms such as sneezing,cough and shortness of breath besides a history of international travel. There is no available treatment or vaccine against it. Therefore, prophylaxis by protecting the mouth, nose and eyes with goggles is highly recommended [9].

Differential Diagnosis

A-blepharitis

A usually chronic inflammation of the eyelids with scaling, mostly self-limiting [10].

B-subconjunctival hemorrhage

Sometimes dramatic, but usually harmless bleeding underneath the conjunctiva most often from spontaneous rupture of the small, fragile blood vessels, could be from a cough or sneezing [1].

C-dry eye syndrome

Triggered by either decreased tear production or increased tear film evaporation which often leads to irritation and redness [11].

D-acute Glaucoma

Implies damage to the optic nerve with the potential for irreversible vision damage which might be permanent unless treated rapidly, because of increased intraocular pressure inside the eyeball. Not all types of glaucoma are acute and not all are related with increased pressure [12].

E-keratitis

A possibly inflammation or damage to the cornea, often associated with significant pain, light intolerance, and deterioration in visual acuity. Numerous causes consist of virus infection. Injury from contact lenses can cause to keratitis [12].

F-iritis

Together with the ciliary body and choroid, the iris makes up the uvea, some portion of the center, pigmented, structures of the eye. Irritation of this layer (uveitis) requires rapid control and is assessed to be in charge of 10% of visual impairment in the United States [1].

G-scleritis

A serious inflammation, often agonizing, that can lead to loss of vision, more than half patients have no identifiable cause. About 30-40% have an underlying auto-immune disease [13].

H-episcleritis

Most often a mild inflammation related disorder of the 'white' of the eye unassociated with eye complications on the other side to scleritis, it is usually self-limiting and symptomatic patients are usually initially treated with artificial eye drops with or without NSAID eye drops [14]. Acute infective conjunctivitis is a common presentation in primary healthcare. It is usually a mild condition and serious complications are rare. Clinical signs are a poor discriminator of bacterial and viral infections. Studies of treatment show that there is a high rate of clinical cure without any treatment (65% within 2-5 days). Treatment with topical antibiotics improves the rate of clinical recovery and this is more marked in the first 2-5 days after presentation, but less by 6-10 days. Studies comparing treatment with different antibiotics do not demonstrate that any one antibiotic is superior; the choice of antibiotic should be based on consideration of cost and bacterial resistance. The present practice of prescribing antibiotics to most cases is not necessary [15].

Acute conjunctivitis is managed by ophthalmologists and other health care providers. Practice Pattern guidelines which is preferred by the American Academy of Ophthalmology declared that viral conjunctivitis does not react to antibiotics and mild bacterial conjunctivitis is usually self-limited. According to Shekhawat 's study of US Health care claimed that the information from Health care authorities reported an increase in the prevalence of prescribing topical antibiotics. Six million cases annually of acute conjunctivitis spend millions of dollars every year. The Aim of the study was to spot an increased number of patients who have had acute conjunctivitis treated with topical antibiotics and furthermore to decide the factors related to antibiotic utilization. To conclude, patients who have an ICD-9 diagnosis of unspecified conjunctivitis, unspecified acute conjunctivitis or adenoviral conjunctivitis should be monitored in the Health care facilities for at least 14 days after the initial diagnosis.

Conclusion measures and guidelines for the usage of antibiotics were discussed and advised that additional prescriptions for all

significant major antibiotic classes such as fluoroquinolones, macrolides, aminoglycosides, sulfonamides, polymyxins and antibiotic-steroid combinations should be filled within 14 days from the initial diagnosis. Surprisingly, around 98% of patients filled their prescriptions within 3 days of the diagnosis, not 14 days as expected. Sociodemographic factors affect the usage which is more with younger, white, richer, more educated patients who have higher chances of filling prescriptions of topical antibiotics; nevertheless, health conditions, for example, diabetes or HIV infection did not seem to impact the utilization. Few patients of the study were only suitable candidates for antibiotics. Although an epidemiological information regarding relative incidence of bacterial vs. Viral conjunctivitis is limited, it may be exceptionally hard to accept that 58% of patients with red eyes examined at the primary outpatient offices across the U.S. have a severe, unremitting bacterial infection that warrants prompt antibiotic treatment [16].

To decide GPs' determination of acute infective conjunctivitis (AIC)- one of the most common but least searched and investigated diseases of acute infections in primary health Care. Regarding Everitt et al, 236 (78%) GPs responded well to the survey. 92% of them who responded were certain about the finding of AIC. 95% normally prescribed topical antibiotics for AIC. Regardless of 58% expressed that they thought during the management that half of the cases they examined would be viral in origin. 36% claimed that they might misdiagnosis the viral conjunctivitis with the bacterial infection. GPs depend on variable findings to determine the type of AIC (99% using eye discharge, 31% using conjunctival edema). Also the Characteristics used to differentiate between viral and bacterial infections were not confirmed. GPs rarely performed eye swabs or cultures.

Most GPs still prescribe topical antibiotics for most cases of AIC-a condition which is self-limiting. New guidelines are required to investigate the potential benefits and impediments of topical antibiotics, and to create clinical or microbiological strategies to assist GPs during the prescription of the antibiotics [17].

A review by Sheikh et al which consists of five trials which randomized a complete of 1034 participants. Three of the trials have been performed on specialist care centers and the two trials have been carried out in community care hospitals. The trials were heterogeneous in terms of their inclusion and exclusion criteria. The character of the intervention and the final results were assessed. Meta-analyses of the study on clinical and microbiological findings revealed that topical antibiotics were only an advantage in the early improvement for acute bacterial conjunctivitis from day 2 to day 5 and microbiological remission phases. From days 6-10 they noticed that those early improvements in medical and microbiological remissions phases were decreased but persisted. Antibiotics versus placebo for acute bacterial conjunctivitis; most cases resolved spontaneously with clinical remission accomplished in 65% from day 2 to day 5 for the patients who tried placebo. No serious side effects have been stated in both the active or placebo trials, indicating that critical sight-threatening complications are infrequent.

Acute bacterial conjunctivitis is a self-limiting disease, but the use of antibiotics is associated with substantially improved rates of medical and microbiological remission. Acute bacterial conjunctivitis is an infective condition in which the eyes are red and inflamed. The disease isn't always critical and commonly recedes spontaneously within one week. Patients with acute conjunctivitis are often commenced on antibiotics, commonly eye drops or ointment to speed the recovery. The advantages of antibiotics for the patients of conjunctivitis were questioned. The evaluation of trials determined that the signs and symptoms of conjunctivitis improved rapidly in the patients taken antibiotics, but the benefits are marginal because the infection is mostly self-limiting [18].

The utilization of antibiotics eye drops for conjunctivitis increased by nearly 50% in UK since they were accessible over the counter (OTC) in the pharmacy in 2005 in spite of the truth from the clinical trials at the same year that antibiotics eye drops had a negligible benefit. According to the results of many studies in the United Kingdom, there was an urgent need to decrease the usage of antimicrobial agents considerably to restrain microscopic organisms procuring resistance to the drugs. It's exceptionally imperative that antibiotics are utilized where they're not needed. Eye drops over the counter for conjunctivitis have been extensively used however it has proved that they have a small benefit.

In June 2005, the Medicines and Healthcare Products Regulatory Agency (MHRA) reported that chloramphenicol eye drops were used for the treatment of bacterial conjunctivitis. Patients were able to obtain it from the Pharmacy as OTC instead of requiring a receipt from a specialist. At the same time in summer 2005, three clinical trials (one of them in the University of Oxford) were done to compare the usage of antibiotics eye drops versus Placebo for the treatment of conjunctivitis. The conclusion of these studies confirmed that antibiotics for both children and adults were used only to speed recovery of conjunctivitis. Around 80% of cases of conjunctivitis were self-limiting.

After these trials, the number of prescriptions for eye drops prescribed by GPs continuously dropped, however; the number of OTC eye drops were significantly increased by pharmacists. There were figures on chloramphenicol eye drops were received in the United kingdom between 2004 and 2007 from a National database that logs all NHS Medications. The number of chloramphenicol Eye drops which prescribed by GPs fell from 2.30 million in 2004 to 1.94 million in 2007, whereas over-the-counter medicines by drug specialists have expanded since they started in June 2005 to 1.46 million in 2007. Meaning adds up to chloramphenicol utilization has expanded from 2.30 million in 2004 to 3.40 million in 2007, a 47.8% increasement [19]. Whereas chloramphenicol has been

around for 50 years and there have been exceptionally few issues with microbes obtaining resistance. Another antimicrobial for treatment of chlamydia was made accessible over the counter in 2008 and the MHRA has counseled around making an antimicrobial for urinary tract infections additionally accessible. There are no advanced antibiotics that could be accessible at the chemist. The move to supply greater convenience and include patients more in their treatment choices could be a worthy objective. But within the case of antimicrobials, policymakers have to adjust this point on how such moves influence in the general utilization

Antibiotic- Resistance

There is antibiotic resistance between ocular pathogens during the era of increasing the resistance of systemic pathogens. The components contributing to the development of the resistance among ocular diseases due to the abuse of antibiotics for systemic infections as well as abuse of topical antibiotics within the eye [20]. Other contributing factors may promote such as improper dosing, abuse of antimicrobial for the treatment of viral and other non-bacterial infections, and repeated and extended use of antibiotics.

There is no available method to measure antimicrobial concentration in ocular tissues during the topical treatment. Eye tissue-specific breakpoints are not accessible to determine the liability of ocular tissues to antibiotics. The concentration of external antibiotics in ocular tissue with topical treatment may surpass the minimum inhibitory concentration for common ocular infections [21,22];however, the high concentration of the topical antimicrobial in ocular tissue may be quickly weakened through tearing. Hence, considerations are required to resolve the elements of breakpoint versus antimicrobial resistance of ocular tissues and its relationship to the clinical reaction. Scientists declared that within the current guidelines the utilization of systemic breakpoints to decide the liability of ocular isolated remains valuable to track patterns of isolates and compare all available information [23].

Different classes of topical antibiotics that have been utilized for the treatment of bacterial conjunctivitis, including aminoglycosides, polymyxin B combinations, macrolides and fluoroquinolones. Chloramphenicol is prohibited in the USA for its rare serious side effect of bone marrow depression. Resistance to gentamicin, tobramycin and polymyxin B was confirmed in a huge number of Streptococcus pneumoniae organisms for children with acute conjunctivitis [24]. Although there was no resistance reported in S. pneumoniae between 1989 and 1992 to gentamicin and tobramycin, it increased to 42.3 and 56% within the year 1997 and 2000 and 43.6 and 46% within a particular long duration [25]. No resistance has been found out within Haemophilus influenzae, a common cause of bacterial conjunctivitis, against aminoglycosides and polymyxin B. A large study was done between 1994-2003 of bacterial conjunctivitis conducted in South Florida, USA, 5.4% of Staphylococcus aureus organisms were ensured to be resistant to gentamicin. High resistance to azithromycin was found to H. influenzae, S. pneumoniae, S. aureus and S. epidermidis organisms from bacterial conjunctivitis.

A study has detected an increase in MRSA (Methicillin-Resistant Staphylococcus aureus) in bacterial conjunctivitis from 4.4% (1994-1995) to 42.9% (2002-2003). There was a high resistance in MRSA to a lot of antibiotics including fluoroquinolones [26]. Because of coagulase-negative Staphylococcus (CoNS), there were dangerous devastating conditions such as keratitis and endophthalmitis. 19% of CoNS were reported to be resistant to gentamicin till 2003 and 2% were resistant to gatifloxacin [27]. In 2006, about 11% of CoNS from normal ocular surfaces and 53% of CoNS from endophthalmitis were thought to be resistant to gatifloxacin [28]. All ciprofloxacin considered to be resistant MRSA and MRSE (Methicillin-Resistant Staphylococcus epidermidis) to 4th generation fluoroquinolones such as gatifloxacin and moxifloxacin but not to besifloxacin, the most recent among the fluoroquinolones [29]. Besifloxacin is the primary fluoroquinolone that has been created for ophthalmic utilization and it is anticipated to escape the resistance among organisms because of lack of systemic utilization

The reduction of susceptibility of S. aureus to vancomycin was first reported in Japan in 1997 within systemic infections [30]. Using disc diffusion susceptibility testing method, there are some reports of vancomycin resistant S. aureus (VRSA) ocular infections [31]; however, till today there are no confirmed VRSA ocular isolates. U.S Healthcare systems in addition to patients and their relatives are suffering from antibiotic-resistant infections which are considered a significant socioeconomic burden in the U.S.. They are common in the hospitals because of high rates of invasive procedures, and antibiotic usage. Statistically around two million Americans per year have experienced healthcare–associated infections (HAIs) which results in 99,000 deaths, because of antibacterial-resistant organisms. It was reported that two HAIs (sepsis and pneumonia) were the main reason for the deaths of nearly 50,000 Americans which cost more than $8 billion to the US health system [32].

The exceptional health benefits gained with antibiotics are threatened by the rapidly evolving resistant bacteria.This problem is global, representing the overuse of these drugs worldwide and the lack of the pharmaceutical companies ' development of new antibiotic agents to tackle the challenge. Antibiotic-resistant infections put a significant burden on the U.S. health and economy. Most of the drugs right now are modifications of existing classes of antibiotics and they are short-term arrangements. The report found exceptionally few potential treatment alternatives for those antibiotic-resistant diseases distinguished by WHO as the most prominent danger to health.

Antibiotic resistance may be a worldwide health crisis that will genuinely jeopardize advances in cutting-edge medication. There's a critical requirement for more venture in research

and advancement for antibiotic-resistant diseases, unless we'll be constrained back to a time when patients are dreaded from common infections and risked their lives from minor surgery. There are moreover exceptionally few oral antibiotics, however, these are basic definitions for treating infections outside medical centers or in resource-limited settings. Pharmaceutical companies and scientists must critically search for new antibiotics against certain sorts of diseases which could kill patients in a matter of days since we have no line of protection [33]

.New medications alone, will not be adequate to combat the risk of antimicrobial resistance. WHO works with nations and accomplices to avoid infections and to cultivate utilization of existing and future antimicrobials. WHO is additionally creating guidance for the responsible use of antimicrobials within the human, creature and agrarian divisions. In conclusion, antibiotic resistance among ocular organisms could be a challenge to the ophthalmologists and a global crisis to healthcare systems including patients and their families. Resistance to most groups of antibiotics is expanding within a decrease of the effectiveness of numerous commonly used topical antibiotics. New scientific guidelines should be arranged to help both doctors and patients to avoid misuse of antibiotics. In addition to new generations of antibiotics, proper use of antibiotics could be a life saving factor and help to decrease billions of unnecessary costs.

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