

2019

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Recommended Citation

ROLAIN MM. Empiric antibiotic use for infectious conjunctivitis provides little clinical benefit. Clin. Res. Prac. 2019 Mar 14;5(1):eP1876. doi: 10.22237/crp/1552521720

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Empiric antibiotic use for infectious conjunctivitis provides little clinical benefit

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ABSTRACT A critical appraisal and clinical application of Rose PW, Harnden A, Brueggemann AB, et al. Chloramphenicol treatment for acute infective conjunctivitis in children in primary care: a randomised double-blind placebo-controlled trial. *Lancet*. 2005;366(9479):37-43. doi: [10.1016/S0140-6736\(05\)66709-8](https://doi.org/10.1016/S0140-6736(05)66709-8).

Keywords: *viral, conjunctivitis, antibiotics, treatment*

Clinical Context

A 47-year-old African American male presented with a chief complaint of eye redness and irritation for two days. On exam, the patient had unilateral conjunctival injection, watery/mucoid discharge with no pus, and follicular conjunctival reaction indicating infectious conjunctivitis, likely of viral etiology. The patient stated his wife was recently diagnosed with conjunctivitis of unknown etiology, and she was given an antibiotic eye drop for treatment. He was wondering whether he should also use an antibiotic drop for his conjunctivitis.

Clinical Question

Does empiric antibiotic use for infectious conjunctivitis of likely viral etiology provide any treatment benefit?

Research Article

Rose PW, Harnden A, Brueggemann AB, et al. Chloramphenicol treatment for acute infective conjunctivitis in children in primary care: a randomised double-blind placebo-controlled trial. *Lancet*. 2005;366(9479):37-43. doi: [10.1016/S0140-6736\(05\)66709-8](https://doi.org/10.1016/S0140-6736(05)66709-8)

Related Literature

A search on UpToDate for “conjunctivitis” and on Dynamed for “infectious conjunctivitis” provided a background for current recommendations in the treatment of infectious conjunctivitis. Historically, physicians tended to treat conjunctivitis empirically with topical antibiotics due to difficulty distinguishing between viral and bacterial etiologies, prevention of secondary bacterial infection, and requirements from many institutions of treatment before return to work or school. Current recommendations are to avoid use of topical antibiotics in infectious conjunctivitis, since most cases are viral in etiology and self-limiting.¹

A PubMed search of “viral conjunctivitis treatment” (126 results), “viral conjunctivitis” (1,562 results), and “viral conjunctivitis antibiotics” (582 results) pulled up several reviews on the topic. One review provided recommendations aligned with those on UpToDate and Dynamed, citing another review from a panel of ophthalmologists.² Recommendations from this review included avoidance of antibiotics in viral conjunctivitis to limit antibiotic resistance, allergic or toxic reactions, and contamination of

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ISSN: 2379-4550

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medication bottles leading to spread to the contralateral eye.¹ This article referenced two studies which demonstrated that secondary bacterial infections in viral conjunctivitis are uncommon.^{3,4} It also made reference to a Cochrane analysis which found that even bacterial conjunctivitis infections are mostly self-limiting and resolve spontaneously in immunocompetent hosts.⁵ A more recent Cochrane analysis by Sheikh et. al. labeled two primary research articles as good quality, Rietveld et. al and Rose et al.⁶ A meta-analysis by Jefferis et. al., which used the same two studies, was acknowledged in Sheikh et. al., and agreed with the findings. However, in the Jefferis analysis a third study was used which was excluded from Sheikh et. al. because it was not placebo controlled.^{6,7}

The Rietveld study was a double-blind, randomized, placebo-controlled trial of adults presenting with red eye and either (muco)purulent discharge or glued eyelid(s). Patients treated with topical fusidic acid had similar cure rates as placebo at 7 days.⁸ The Rose study was a double-blind, randomized, placebo-controlled trial of children aged 6 months to 12 years with a clinical diagnosis of conjunctivitis. Patients treated with topical chloramphenicol had similar cure rates at 7 days compared to placebo.⁹

The Rose study was chosen for this appraisal. There were almost twice as many subjects in the Rose study compared to the Rietveld study. The Rose study performed eye swabs to determine the etiology of the infections, allowing for the determination of treatment benefit based on etiology. In addition, the Rose study followed up with the patients after 6 weeks in order to look for relapse, which can address the physician concern of secondary bacterial infection. Although trimethoprim-polymyxin B and erythromycin are the standard antibiotics of conjunctivitis treatment in the U.S., the strengths of this study as mentioned above outweigh the potential effect on generalizability.

Critical Appraisal

Participants were deemed eligible for the trial if they presented during office hours with a diagnosis of acute infectious conjunctivitis, were not allergic to chloramphenicol, were not treated with antibiotics within the past 48 hours, were immunocompetent, and had no evidence of severe infection. Patients ranged in age from ages 6 months to 12 years. Clinical severity was assessed at baseline by a nurse, and two conjunctival swabs were obtained for culture. Participants were randomly assigned to receive either preservative-free chloramphenicol 0.5% drops (n=163) or placebo (n=163), which contained distilled water, boric acid 1.5%, and borax 0.3%. The patients were followed up at 7 days with a nurse, who made a clinical assessment of the disease and obtained 2 more conjunctival cultures. A phone call at 6 weeks was made to inquire about any additional eye problems. Aside from the eye drops administered, the groups were treated equally. The primary outcome measured was clinical cure rate by 7 days, which was determined from parent diaries during the trial. The subjective nature of this outcome can potentially decrease validity of the study, but the addition of the nurse evaluation allowed for an additional means of evaluation to mitigate this weakness. Secondary outcomes measured were microbiological cure rate at 7 days, time to cure, clinical cure at 3 days, and relapse rate. Data were analyzed with intention to treat.

The study results showed that there was no statistical difference in any of the outcomes measured, except microbiological cure at day 7 (Difference 16.8% with 95% CI 5.5-28.1%), which was higher in the treatment group. There was no significant difference between the treatment groups in the types and prevalence of bacteria and viruses detected. About 80% of children tested positive for a pathogen, of which 67% grew a bacterial pathogen, 3% grew a virus, and 10% grew both a bacterium and a virus. The relapse rates within 6 weeks of treatment were low in both groups, suggesting that secondary infection is not a major concern and antibiotics do not alter the chances of this occurring. The treatment group did show a statistically-significant reduction in the number of bacteria on culture, however this was not clinically relevant and did not correlate with resolution of the disease. About 95% of the recruited children were followed up with at 6 weeks; six were lost to follow up in the chloramphenicol group and 13 were lost to follow up in the placebo group. The level of evidence of this study is 1 based on the SORT algorithm.

The enrollment process allowed for the selection of patients that fit the study goal: children with mild conjunctivitis treated initially in the primary care setting. Participants were asked to enroll by their family doctors. Randomization was successful with no statistical difference in baseline characteristics of the treatment and placebo groups. A group of children were not randomized due to parent request of antibiotics (n=30), but these children were not included in the main analysis. Blinding was extensive, with no obvious compromise. The study patients differed from my patient in that mine was an adult from the U.S. and the study participants were children from the UK.



The NNT for one more clinical cure by day 7 was 14. Considering the insignificant difference in clinical cure between placebo and treatment groups, as well as the potentially high economic, allergic, and resistance burden that antibiotic prescription can have, this effect size is not large enough to recommend empiric treatment of conjunctivitis patients with antibiotics, although this would be feasible in practice. The typical clinical course of conjunctivitis lasts from 2-3 weeks. One of the reported benefits of antibiotic use is to shorten the clinical course, so an evaluation at 7 days was appropriate to determine if this effect was present. However, an additional evaluation at 2 or 3 weeks could have helped to further elucidate the time course of each treatment group.

Based on this study, it is not possible to rule out the potential effects of eye lubrication from the drops on clinical course of conjunctivitis. In addition, borax and boric acid are not benign compounds, with both having an application as antiseptics. It is possible that these compounds may contribute to resolution of the infection. The study could have been stronger if a third group, no intervention, was included in the design. The fact that clinical cure was determined from the subjective documentation of the parents allowed for some potential error, however this was addressed in the study by including an evaluation from a nurse at 7 days. The study was funded by the Medical Research Council as part of a program grant in childhood infection in primary care. The authors stated in the paper that the sponsor of the study had no role in design, data collection, analysis, interpretation, or writing of the report.

Clinical Application

The conclusion drawn from the study is that healthy children with acute conjunctivitis do not need antibiotics at first presentation to primary care, which makes sense in the context of the study. The conclusion is limited to the patient population studied in the paper and does not try to overgeneralize the results.

The generalizability of the study to our patient may be limited. However, other than age and location of presentation, our patient fit the inclusion criteria of the study. Based on the other studies done on infectious conjunctivitis, there is not much evidence indicating that our patient's clinical course should vary from what was seen in this study. Therefore, the results of the study were applied to our patient, and we did not prescribe him topical antibiotics.

As a practicing physician, it is always important to consider cost of treatment as a major determinant in care. Since many studies have found little, if any, benefit to antibiotic use in infectious conjunctivitis, the price of a prescription for antibiotics may not be worth the benefit.¹⁰ In addition, there is the potential for allergic reactions and increased antibiotic resistance with the prescription of antibiotics.^{1,11} There is also no apparent benefit in the prevention of secondary bacterial infections.³⁻⁵

Learning points:

1. It is very difficult to distinguish between viral and bacterial conjunctivitis, so physicians often rely on their clinical judgement in making a treatment decision.¹²⁻¹⁴
2. Antibiotics have shown little benefit compared to placebo even in mild bacterial conjunctivitis, so it is often safe to start with supportive care.^{1,6}
3. Secondary bacterial infections in viral conjunctivitis are rare and not significantly affected by prophylactic antibiotic use, so this concern should not influence the treatment decision of the physician.³⁻⁵

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