

Indonesian Journal of Tropical and Infectious Disease

Vol. 6. No. 3 September–December 2016

Literature Review

THE USAGE COMPARISON OF CEFTRIAXONE AND CHLORAMPHENICOL FOR TYPHOID FEVER TREATMENT: AN EVIDENCE BASED CASE REPORT

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ABSTRACT

Typhoid fever is a disease caused by the gram-negative bacterium Salmonella typhi. Since its introduction in 1949, chloramphenicol has become the first-line treatment of typhoid fever for decades. Until now, chloramphenicol is still the first line treatment of typhoid fever in rural areas in Indonesia, due to its low cost. However, in addition to the problem of bacterial resistance, chloramphenicol is known to cause some side effect such as bone marrow suppression. Currently, many other antibiotics are used as the regimens for the treatment of typhoid fever, one of which is ceftriaxone. However, there are evidences on reemergence of chloramphenicol sensitivity in typhoid fever treatment. This report is created to answer the clinical question on whether ceftriaxone is more effective compared to chloramphenicol as the first-line treatment of typhoid fever. A structured search was performed on PubMed, EBSCO, and ScienceDirect and after a screening process and appraisal using the criteria from Center of Evidence Based Medicine at Oxford University, only one article was selected. The article shows higher efficacy of ceftriaxone in term of defervescence rate ($P = 0.0001$). No other study that compares the efficacy of ceftriaxone and chloramphenicol for typhoid fever treatment during the last ten years could be found during article searching. In conclusion, ceftriaxone shows better efficacy in the treatment of typhoid fever compared to chloramphenicol but with the rise of microbial sensitivity to chloramphenicol in recent years, more studies on this topic are needed to support this conclusion.

Keywords: Typhoid fever, enteric fever, Ceftriaxone, Chloramphenicol, Effectiveness

ABSTRAK

Demam tifoid merupakan penyakit disebabkan oleh bakteri gram negatif Salmonella typhi. Sejak diperkenalkan pada tahun 1949, chloramphenicol selama puluhan tahun menjadi lini pertama pengobatan demam tifoid. Hingga saat ini chloramphenicol masih merupakan lini pertama untuk pengobatan demam tifoid di daerah-daerah di Indonesia terutama karena biayanya yang murah. Namun, selain masalah resistensi kuman, chloramphenicol diketahui menimbulkan efek samping berupa supresi sumsum tulang, sehingga saat ini banyak digunakan antibiotik lain sebagai rejimen pengobatan demam tifoid seperti ceftriaxone. Laporan ini dibuat untuk menjawab pertanyaan klinis apakah ceftriaxone lebih efektif dibandingkan chloramphenicol sebagai lini pertama untuk pengobatan demam tifoid. Pencarian artikel terstruktur dilakukan pada PUBMED, EBSCO, dan ScienceDirect. Setelah proses penyaringan dan appraisal menggunakan kriteria Center of Evidence Based Medicine dari Universitas Oxford, didapatkan satu artikel terpilih. Artikel tersebut menunjukkan efektivitas ceftriaxone dalam menurunkan demam yang lebih baik dengan $P = 0,0001$. Tidak ditemukan penelitian lain mengenai perbandingan efektivitas ceftriaxone dengan chloramphenicol dalam menangani demam tifoid pada pencarian artikel. Kesimpulan yang ditarik adalah ceftriaxone menunjukkan efektivitas yang lebih baik dalam tatalaksana demam tifoid dibandingkan dengan chloramphenicol, namun dengan meningkatnya sensitivitas bakteri terhadap chloramphenicol dalam tahun-tahun terakhir, penelitian mengenai topik ini masih sangat diperlukan.

Kata kunci: Demam tifoid, Demam tipus, Ceftriaxone, Chloramphenicol, Efektivitas

INTRODUCTION

Typhoid fever is a disease which is caused by gram negative bacterium *salmonella typhi*. It is categorized as an endemic disease in Indonesia. In 2006, there are 500 cases of typhoid fever reported out of 100,000 people, with 0.65% death rate.¹

Since it was introduced in 1949, chloramphenicol has been used as the first-line treatment for typhoid fever. It is still preferred in many areas in Indonesia due to its relatively affordable price. In many other countries, the use of chloramphenicol has been less and less because many bacteria strains have already resisted it.^{2,3} However, a six years' study conducted by Moehario LH et al showed that 90% of bacteria were still susceptible to this drug.⁴ Other studies in India also showed a reemergence of chloramphenicol sensitivity in typhoid fever treatment.⁵⁻⁹

The recommended dose of chloramphenicol is 2000 mg per day, divided to 4 dose orally or intravenous for at least 7 days. However, aside from bacteria resistance, chloramphenicol is known to induce bone marrow suppression. With that in mind, other antibiotics are often used as a therapy regiment for typhoid, one of which is a 3rd generation cephalosporin ceftriaxone.² Aside from avoiding the said side effect, the length of treatment using ceftriaxone is shorter than chloramphenicol and can improve a patient's

adherence to the treatment. The recommended dosage for ceftriaxone is 3-4 grams in 100 cc of 40% dextrose solution per day for 3 to 5 days.⁴

CASE

A 18 years old female patient arrived with a chief complaint of fever for 1 week prior to the admission. The fever was accompanied with watery stool up to 3 times a day. Serological widal examination showed a positive result, thus, the patient was treated with intravenous ceftriaxone antibiotic 3 grams per day.

CLINICAL QUESTION

Is ceftriaxone more effective than chloramphenicol as the first-line treatment for typhoid fever?

MATERIAL AND METHOD

The method of this study is a systematic review on some articles relevant to the topic. A structured search was performed on three databases, namely PUBMED Clinical Queries, EBSCO Medline, and ScienceDirect,

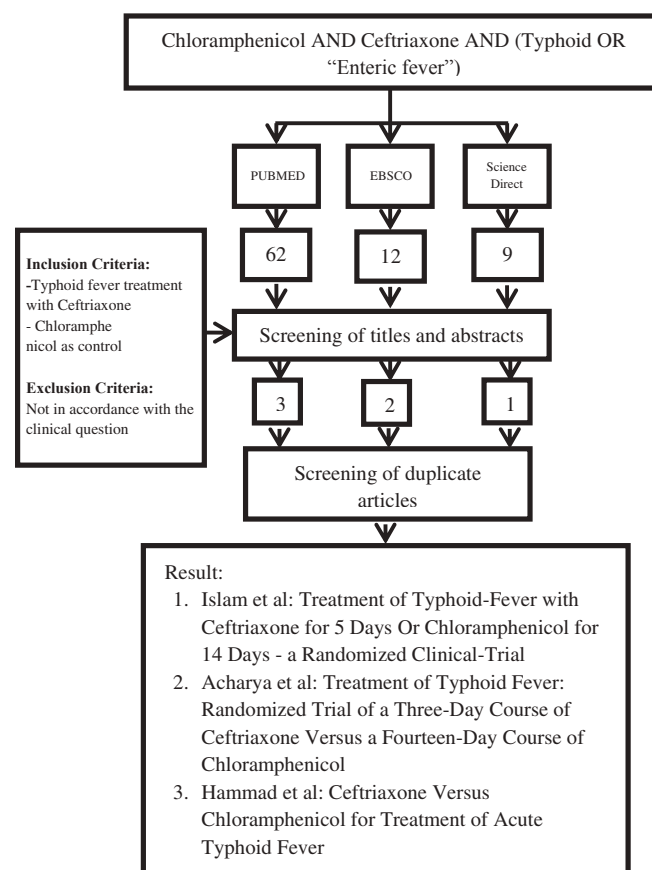


Figure 1. Article searching method and result

Table 1. Keywords and filters for article searching

	Keywords	Filter
PUBMED Clinical Queries	chloramphenicol AND ceftriaxone AND (typhoid OR “enteric fever”)	Therapy; Broad Human species, English language, Full text available
EBSCO Medline	chloramphenicol [AB Abstract] AND ceftriaxone [AB Abstract] AND AND (typhoid OR “enteric fever”) [AB Abstract]	Human, English, Full text available
Science Direct	chloramphenicol AND ceftriaxone AND (typhoid OR “enteric fever”)	Journal

Table 2. The critical appraisal of articles validity

	Islam <i>et al</i> Antimicrobial Agents and Chemotherapy (1993)	Acharya <i>et al</i> American Journal of Tropical Medicine and Hygiene (1995)	Hammad <i>et al</i> Life Science Journal (2011)
Was the assignment of patients to treatments randomized?	Yes	Yes	Yes
Were all patients who entered the trial accounted for at its conclusion?	Yes	Yes	Yes
Were patients and clinicians kept “blind” to which treatment was being received?	Yes	Yes	No
Aside from the experimental treatment, were the groups treated equally?	Yes	Yes	Yes
Were the groups similar at the start of the trial?	Yes	Yes	Yes

using chloramphenicol AND ceftriaxone AND (typhoid OR “enteric fever”) as the keywords (Table 1). From those keywords, we found as many as 62 articles from PUBMED, 12 articles from EBSCO, and 9 articles from Science Direct.

The title and abstract of those articles were then screened (as seen on Figure 1) with inclusion criteria being: (1) a trial on typhoid fever treatment with Ceftriaxone and (2) chloramphenicol as control.

The articles found were as follows: (1) Treatment of Typhoid-Fever with Ceftriaxone for 5 Days Or Chloramphenicol for 14 Days - a Randomized Clinical-Trial, by Islam *et al*; (2) Treatment of Typhoid Fever: Randomized Trial of a Three-Day Course of Ceftriaxone Versus a Fourteen-Day Course of Chloramphenicol, by Acharya *et al*; and (3) Ceftriaxone Versus Chloramphenicol for Treatment of Acute Typhoid Fever, by Hammad *et al*.¹⁰

These articles were appraised using the criteria from Center of Evidence Based Medicine Oxford University (Table 2). Articles by Islam *et al* and Acharya *et al* were published more than 20 years ago and therefore are not included in this review.

RESULT AND DISCUSSION

Hammad *et al* did a study on 2007 to re-asses the effectiveness of chloramphenicol as typhoid treatment in

response to the increase of multidrug resistance to the first-line antimicrobials in Egypt for the last 30 years.¹⁰

Fifty-two patients of acute typhoid fever with positive blood culture for *Salmonella typhi* were divided into 2 groups. Twenty-seven patients were randomly allocated to be treated with chloramphenicol (50 mg/kg bw/day orally or intravenously) which is given 6 times hourly until defervescence for further 5 days.¹⁰

Twenty five patients were randomly allocated to be treated with ceftriaxone parenterally (80 mg/kg/day for children and 2 gm/day for adults) the treatment is given once a day for 7 days.¹⁰

Clinical cure occurred on all patients. The mean time (mean±SD) of defervescence for ceftriaxone and chloramphenicol was 3.3±1.2 and 5.8±1.2 days respectively (P = 0.0001, 95% CI = 1.8-3.2). Ceftriaxone treatment showed a shorter time of defervescence compared to chloramphenicol.¹⁰

We found only one article on PUBMED Clinical Queries, EBSCO Medline, and ScienceDirect using Center of Evidence Based Medicine Oxford University criteria.

A study by Hammad *et al* showed that ceftriaxone has more efficacy than chloramphenicol in treating typhoid fever. Ceftriaxone treatment had a shorter time of defervescence (3.3±1.2 days) compared to chloramphenicol (5.8±1.2 days).

This study also showed an increased risk of bone marrow suppression in using chloramphenicol as a

treatment. It was showed by the decreased of hematocrit mean value compared to the ceftriaxone group.

Unfortunately, no other clinical trial that compares the efficacy of ceftriaxone treatment and chloramphenicol treatment in the last 10 years was found during article searching.

Although ceftriaxone showed better efficacy and less side effect, chloramphenicol treatment can still be considered effective in treating typhoid. All patients experienced clinical cure after being treated with either ceftriaxone or chloramphenicol. This can be considered an improvement from years ago when chloramphenicol was rendered ineffective as a treatment because of widespread microbial resistance.⁷

CONCLUSION

In conclusion, the use of chloramphenicol is still effective for the treatment of typhoid fever. However, ceftriaxone showed greater effectiveness in typhoid fever treatment as shown by shorter time of defervescence compared to chloramphenicol. The use of ceftriaxone also poses less risk on bone marrow suppression compared to cephalosporin. Another advantage of using ceftriaxone as a treatment is the shorter length of treatment which can improve a patient's adherence to the treatment.

Only one clinical trial was found from article searching and with the rise of microbial sensitivity to chloramphenicol

in recent years⁵⁻⁹, more studies on this topic are needed to support this conclusion.

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