

# Antibiotics for the Treatment of Leptospirosis: Systematic Review and Meta-analysis of Controlled Trials

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## ABSTRACT

Leptospirosis is a zoonotic disease prevalent mainly in developing countries and is associated with high case fatality. Antibiotics especially penicillin are the mainstay of treatment for a suspected or confirm case of leptospirosis but role of Penicillin has not been evaluated systematically in the light of current evidence. The present systematic review and meta-analysis is done to evaluate the role of antibiotics in the treatment of leptospirosis. Parallel group clinical trials involving use of penicillin in treatment of leptospirosis were searched from all available sources. Ten clinical trials were found suitable as per laid inclusion criteria eligible for present systematic review and five clinical trials were included in meta-analysis. Clinical trials included for meta-analysis were compared on the basis of mortality, fever days, numbers of patients presenting with oliguria, and number of patients undergoing need-based dialysis. Analysis was done by comprehensive meta-analysis software 2. Qualitative outcomes are summarized as odds ratio and quantitative outcomes are summarized as standard mean difference with 95% confidence interval. Random and fixed models are used for analysis. There was no significant difference between penicillin group and controlled group for mortality (Odds ratio 1.59 (95% CI 0.59-4.29),  $P = 0.35$ ), fever days (std difference in mean =  $-0.223$  (95% CI 0.394-0.995),  $P = 0.358$ ), number of patients presenting with oliguria (Odds ratio 1.795 (95% CI 0.325-9.929),  $P = 0.502$ ), and number of patients who underwent need based dialysis (Odds ratio 1.587 (95% CI 0.919-2.731),  $P = 0.098$ ). This review concluded that role of various antibiotics in treatment of leptospirosis is uncertain, and can be attributed to nonavailability of adequate clinical trials. Role of penicillin in the treatment of leptospirosis can be debated.

**Keywords:** Antibiotics, doxycycline, leptospirosis, penicillin, weils disease

## INTRODUCTION

Leptospirosis is a zoonotic disease prevalent mainly in developing countries, caused by infection with pathogenic spirochetes of genus *Leptospira*. The disease is maintained

in nature by chronic renal infection of carrier mammals, which excrete the organism in their urine. Humans get infection when they come into contact with the contaminated environment and the organism penetrates through the broken skin or mucosa. It may be encountered with increasing interest in adventure travel, or vacation involving water sports, or hiking. Increasing exotic pet trade further enhances the likelihood of transmission. *Leptospira* enters in the blood through abrasions and cuts in the skin and also through oral route.<sup>[1]</sup> Signs and symptoms depend on stage of disease and types of serovar. Incidence of leptospirosis ranges from 0.1 to 10 per 100000 population but it can be much high in endemic areas (up to 50 per 100000 population).<sup>[2]</sup> Case fatality in the case of severe leptospirosis may lie within 5-40%.<sup>[3]</sup>

Antibiotics, particularly of the penicillin group are considered as first line therapy for treatment of leptospirosis. Effects of other antibiotics like cephalosporins, chloramphenicol, doxycycline, and azithromycine have also been also explored in few clinical trials.<sup>[4-13]</sup> Still there is no sufficient evidence to suggest role of antibiotics in treatment of leptospirosis due to nonavailability of enough clinical trials.<sup>[14]</sup> In a review published in 2000 it was concluded that there is insufficient evidence in recommending routine use of antibiotics in leptospirosis. This review was based on only three clinical trials and two of these clinical trials were reportedly having poor methodological qualities.<sup>[15]</sup> Since then no review has been published, suggesting an urgent need of undertaking a systematic review based on current published evidences. This systematic review and meta-analysis was designed to assess current published literature for role of various antibiotics in the treatment of leptospirosis.

## METHODS

### Search strategy of clinical trials

Present systematic review was done according to the “Cochrane Handbook for Systematic Reviews of Interventions”.<sup>[16]</sup> Clinical trials were searched in PubMed, Cochrane clinical trials register, Google scholar, and Google. Abstracts available on websites of some societies dealing with infectious diseases (American society of tropical medicine and hygiene, International

society of travel medicine, Infectious disease society of America) were also scanned. Various MeSH terms related to leptospirosis and antibiotics were used for searching. [Appendix 1] References mentioned in published articles were also scanned for other published trials. The search was done by first author. Inclusion and exclusion of trials was done by second and third authors by consensus. During any discrepancy between second and third authors related to inclusion or exclusion of trials, decision of first author was considered final. Full texts PDF of all trials were downloaded before deciding inclusion and exclusion. Inclusion and exclusion were decided on the basis of predesigned proforma. Clinical trials published from 1966 were taken in consideration for the PubMed search.

### Inclusion and exclusion criteria for clinical trials

Randomized parallel group controlled trials exploring the effect of various antibiotics on various parameters of leptospirosis were taken into consideration. Clinical trials published only in English language were included in the review. Clinical trials without control and before–after studies were not included in this systematic review. Process of selection of clinical trials is explained in the chart format according to “Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA)” guideline.<sup>[17]</sup>

### Outcome

Predefined outcomes were mortality, hospitalization, days of signs and symptoms, fever days, adverse effects, and various complications like renal failure, hepatic problems, oliguria, number of dialysis, number of patients needing dialysis, etc.

Based on availability of data in included study, outcomes that could be compared were mortality, fever days, number of patients presenting with oliguria and number of patients subjected to need-based dialysis. Mortality, number of patients presenting with oliguria and number of patients subjected to need based dialysis are qualitative variables, whereas ‘fever days’ is a quantitative variable. Data values were entered in the Comprehensive meta-analysis software 2, which can auto-calculate the effect size hence effect size was not calculated manually, however, manual

effect size calculated by the software was validated against manually calculated effect size.

### Statistics

Analysis was done by comprehensive meta-analysis software 2 (CMA 2) (Biostat, 14 North Dean Street, Englewood, NJ 07631, USA). Qualitative values (death, number of patients becoming oliguric, and number of patients needing dialysis) were pooled in the form of odd ratio and 95% confidence interval (CI) around odds ratio. Quantitative variable (fever days) was pooled as standard mean difference and 95% CI around it. Both random and fixed models were used for analysis. Forest plots are showing fixed model. Heterogeneity was measured by Q statistic.

## RESULTS

A total of 10 clinical trials were included in the present systematic review. Out of the included trials, penicillin was compared with placebo or no treatment in five clinical trials. These five clinical trials were included in meta-analysis. Characteristics and biasing in these trials are mentioned in Tables 1 and 2.

In a study by Fairburn and Semple (1956), patients of leptospirosis were divided into three groups. First group was considered as control and was given no antibiotics ( $n = 31$ ), Second group was given intravenous penicillin 600000 unit every 6 hour ( $n = 21$ ), and third group was given chloramphenicol 0.5 g every 6 hourly ( $n = 31$ ). All patients were followed for at least 5 days after starting of treatment. Mean follow up days for penicillin and chloramphenicol group were 6 and 6.2 days. Average time (in days) from start of symptoms to symptom-free day was not significantly different between three groups (Control (C) = 9.4 days, penicillin (P) = 8.2, chloramphenicol (Ch) = 8.9). In the same way, average time (in days) from start of sign to sign free day (C = 9.9 days, P = 9.5 days, Ch = 10 days) and total symptom free and sign free days (C = 10.8, P = 9.7, Ch = 10.5) were not significantly different between three groups [Table 1]. There was no significant difference in renal and hepatic complications in three groups.

In another study (Ross Russel, 1958) role of oxytetracycline was explored in leptospirosis. Patients of leptospirosis were divided into two

groups. In treatment group (T) oral oxytetracycline was given in the dose of initially 1.5 g and then 0.5 g every 6 hourly ( $n = 27$ ) and placebo group (P) was given oral ascorbic acid 50 mg thrice a day. Both groups were followed up for 5 days. It was observed that average duration of pyrexia after treatment (in days) (T = 2.5, P = 6.4), average duration of symptoms after starting of treatment (in days) (T = 4, P = 6.9) and average total duration of pyrexia (before treatment and after treatment) (T = 6.4, P = 9.4 days) were reduced in oxytetracycline group. There was no statistically significant difference between two groups for hepatic and renal complications [Table 1].

In a study by McClain *et al.* (1984), effect of doxycycline on various parameters related to leptospirosis was evaluated. Patients of leptospirosis were divided into two groups, doxycycline group ( $n = 14$ ) and placebo group ( $n = 15$ ). Doxycycline was given orally in dose of 100 mg twice a day for 7 days. Patients were followed up for 2-3 weeks. In this study, it was observed that doxycycline reduces the illness days (5.6 vs 7.7), fever (3.7 vs 5.4), fever days (7.2 vs 9.3), and other parameters (fever, myalgia, malaise, GI symptoms, conjunctival suffusion) significantly [Table 1].

Penicillin was compared with ceftriaxone in a trial (Thanachai Panaphut *et al.*, 2003) where one group (P) ( $n = 86$ ) was given intravenous penicillin G 1.5 million unit/6 hour and second group (C) ( $n = 87$ ) was given intravenous ceftriaxone 1 g daily for 7 days. After 7 days there was no significant difference between penicillin and ceftriaxone for median duration of fever in days (P=3, C=3) and death (P=5, C=5). Incidences of renal failure, jaundice, and thrombocytopenia were similar in both groups [Table 1].

In a trial by Suputtamongkol *et al.* (2004) effects of three antibiotics (penicillin, cefotaxime, and doxycycline) on various parameter of leptospirosis was evaluated. Patients of leptospirosis were divided into three groups. In penicillin group (P) ( $n = 87$ ) 1.5 million unit dose was given every 6 hourly through intravenous route. In cefotaxime group (C) ( $n = 88$ ) 1 g dose was given every 6 hourly through intravenous route. In doxycycline group (D) ( $n = 81$ ) initially 200 mg doxycycline is given intravenously in 30 minutes, which was followed by 100 mg intravenous infusion 12 hourly. Parenteral therapy was given

**Table 1:** Characteristics of different clinical trials included in the meta-analysis

Study	Intervention	Follow up	Endpoints
Fairburn and semple (1956)	Group A-Control (No antibiotics) ( <i>n</i> =31)	6 days	Symptom free days (avg.) A=9.4, B=8.2, C=8.9 Sign free days (avg.) A=9.9, B=9.5, C=10
	Group B-Penicillin 600000 unit/6 hour ( <i>n</i> =21)		Total symptom free and sign free days (avg) A=10.8, B=9.7, C=10.5 Jaundice A=2, B=0, C=1
	Group C-Chloramphenicol 0.5 g/6 hour ( <i>n</i> =31)		Oliguria A=2, B=1, C=1
Watt <i>et al.</i> (1988)	Group P-Penicillin G i.v 6 million unit/day	7 day	Fever days (mean and SD) <i>P</i> =4.7 (4.19), C=11.6 (8.34) Afabrile patient after 4 days (No.) <i>P</i> =10, C=1
	Group C-Normal Saline		Ready for discharge (No.) <i>P</i> =16, C=5 Hepatic tenderness <i>P</i> =14, C=9
Daher <i>et al.</i> (2000)	Group T-Crystalline Penicillin i.v 6 million unit/day ( <i>n</i> =16)	8 day	Days of hospitalization (Mean and SD) T=12 (6), Nt=11 (5) Days of fever (Mean and SD) T=3 (4), Nt=2 (3)
	Group nT-Untreated ( <i>n</i> =19)		Days of normalisation of creatinine (Mean and SD) T=10 (6), Nt=9 (6) Days to total bilirubin normalized or reached one third of max value (Mean and SD) T=8 (3), Nt=8 (3) Days of normalization of platelet counts (Mean and SD) T=5 (2), Nt=4 (2) Positive fluid balance (No.) T=13 (81%), Nt=15 (79%) Oliguria (No.) T=3 (19%), Nt=1 (5%) Dialysis needed (No.) T=8 (50%), Nt=10 (52%) No. Of dialysis session (Mean and SD) T=2 (3), Nt=1.4 (1.7) Death (No.) T=1, Nt=0
Costa <i>et al.</i> (2003)	Group P-Penicillin G i.v 6 million unit/day ( <i>n</i> =125)	7 days	Death (No.) <i>P</i> =15/125, NP=8/128 Hospital stay (Mean and SD) <i>P</i> =8.9 (3.9), NP=8.8 (3.6) Peritoneal dialysis (No.) <i>P</i> =35/125, NP=23/128
	Group NP-No penicillin ( <i>n</i> =128)		
Edward <i>et al.</i> (1988)	Group P-Penicillin G i.v 2 million/g hour ( <i>n</i> =38)	5 days	Time for defervescence, Mean (SD) <i>P</i> =6.9 (3.8), F=6.6 (3.2)

Contd...

**Table 1:** Contd...

Study	Intervention	Follow up	Endpoints
	Group F-i.v fluids only ( <i>n</i> =41)		Return of biochemical parameters to normal <i>P</i> =5.70 (3.3), <i>F</i> =5.65 (3.7) Normal LFT (Weeks (SD)) <i>P</i> =5.70 (3.3), <i>F</i> =5.65 (3.7) Urine culture positive (No.) <i>P</i> =0, <i>F</i> =6 Incidence of iritis (No.) <i>P</i> =1, <i>F</i> =2 Death (No.) <i>P</i> =1, <i>F</i> =3

**Table 2:** Assessment of the bias in the trials included in systematic review

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data?	Selective reporting?	Free of other bias?
Fairburn and Semple (1956)	No	No	Yes	No	No	Yes
Suputtamongkol <i>et al.</i> (2004)	Yes	Yes	No	Yes	No	Unclear
Thanachai Panaphut <i>et al.</i> (2003)	Yes	Yes	Yes	No	No	Unclear
Watt <i>et al.</i> (1988)	No	No	No	No	No	Yes
Elizabeth De Francesco Daher <i>et al.</i> (2000)	No	No	No	Yes	No	No
Costa <i>et al.</i> (2003)	No	No	No	No	No	Yes
Edward CN <i>et al.</i> (1988)	Yes	No	No	No	No	Unclear
McClain JB <i>et al.</i> (1984)	Yes	Yes	Yes	No	No	Yes
Kriangsak Phimda <i>et al.</i> (2007)	Yes	Yes	No	No	No	Unclear
Ross Russel (1958)	No	No	No	No	Yes	Yes

till patients condition improved (afebrile) and then oral therapy was started. In penicillin and cefotaxime group amoxicillin (2 g/day) was given and in doxycycline group doxycycline 200 mg per day given orally. Patients were monitored for 7 days. After 7 days, there was no significant difference between three groups for death ( $P = 2$ ,  $C = 0$ ,  $D = 2$ ), median time to defervescence in hours ( $P = 72$ ,  $C = 60$ ,  $D = 72$ ) and median duration of hospitalization ( $P = 6$ ,  $C = 5.5$ ,  $D = 5$ ) [Table 1].

Doxycycline was compared with azithromycin in a trial done by Kriangsak Phimda *et al.* (2007). In doxycycline group (D) ( $n = 34$ ) doxycycline was

given in the dose of 100 mg twice a day by oral route for 7 days while in azithromycin group (A) ( $n = 35$ ) azithromycin was given 1 g initially followed by 500 mg once daily for 2 days by oral route. Patients were followed up for 7 days. After the study period there was no significant difference between both groups for endpoints (No. of patient showing defervescence within 5 days ( $D = 5$ ,  $A = 4$ ) and median time to defervescence in hours ( $D = 45$ ,  $A = 40$ ) [Table 1].

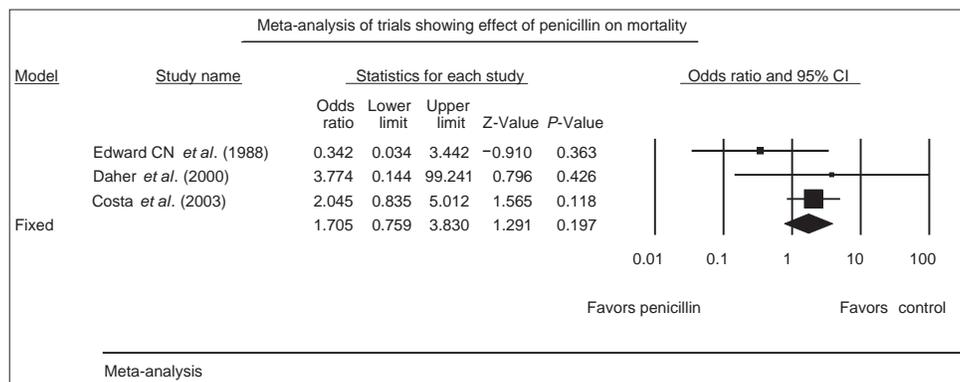
Five clinical trials were dealing with comparison of penicillin with placebo or no treatment (Fairburn and semple (1956), Watt G *et al.* (1988), Daher *et al.* (2000), Costa *et al.* (2003),

and Edward CN *et al.* (1998)). [Table 1] These clinical trials were included in the meta-analysis. Out of various predefined endpoints we could compare these clinical trials on the basis of only four endpoints (death, fever days, oliguria, and number of patients needing dialysis) on the basis of available data.

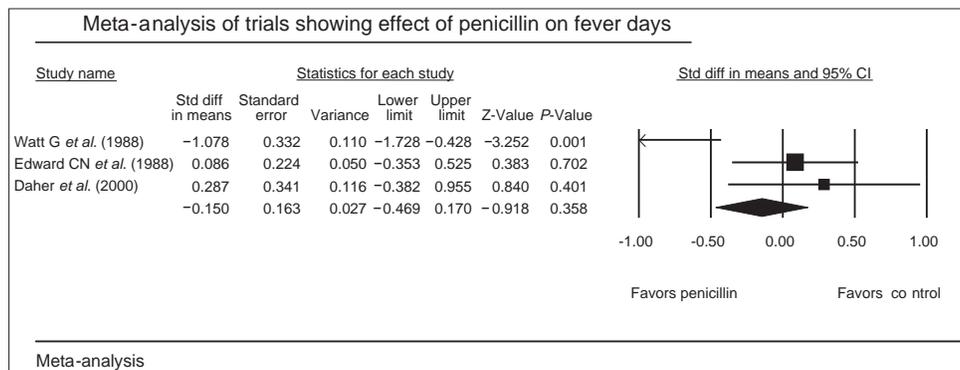
Three trials were dealing with death in each group as endpoints (Edward CN *et al.* (1998), Daher *et al.* (2000), and Costa *et al.* (2003)). A total of 179 patients were enrolled in penicillin group and 188 in control group. Death events were 17 (7.8%) in penicillin group and 11 (5.8%) in control group. After pooling data from these trials it was observed that penicillin shows no protection as compared with control [Random model = Odds ratio 1.59 (95% CI 0.59-4.29)  $Z = 0.93$ ,  $P = 0.35$ ]. Similar results were obtained by fixed model [odds ratio 1.70 (95% CI 0.75-3.82)  $Z = 1.29$ ,  $P = 0.19$ . [Figure 1].

Fever days as endpoint was measured in three trials [Watt G *et al.* (1988), Edward CN *et al.* (1998), Daher *et al.* (2000)]. There were a total of 77 patients in penicillin group and 79 in control group. On analyzing data from these trials it was observed that there was no significant difference between penicillin and control [Random model – std difference in mean =  $-0.223$  (95% CI 0.394-0.995),  $Z = -0.918$ ,  $P = 0.358$ ]. Similar results were obtained by fixed model [std difference in mean =  $-0.150$  (95% CI 0.469-0.170),  $Z = -0.918$ ,  $P = 0.358$ ] [Figure 2].

In two trials number of patients having oliguria after the completion of study period were compared [Fairburn and Semple (1956) and Daher *et al.* (2000)]. There were 37 patients in penicillin group and 50 in control group. No. of patients becoming oliguric in penicillin group were 4 (10.8%) and in control group 3 (6%). There was no significant difference in both groups



**Figure 1:** Effect of penicillin therapy on mortality in the patients of leptospirosis [Random model = Odds ratio 1.59 (95% CI 0.59-4.29)  $Z = 0.93$ ,  $P = 0.35$ ]. Fixed model [odds ratio 1.70 (95% CI 0.75-3.82)  $Z = 1.29$ ,  $P = 0.19$ ]



**Figure 2:** Effect of penicillin therapy on fever days in the patients of leptospirosis. [Random model-std difference in mean =  $-0.223$  (95% CI 0.394-0.995),  $Z = -0.918$ ,  $P = 0.358$ ]. Fixed model [std difference in mean =  $-0.150$  (95% CI 0.469-0.170),  $Z = -0.918$ ,  $P = 0.358$ ]

for this parameter by Random model [Odds ratio 1.795 (95% CI 0.325-9.929),  $Z = 0.675$ ,  $P = 0.502$ ] as well as fixed model [Odds ratio 1.795 (95% CI 0.325-9.929),  $Z = 0.675$ ,  $P = 0.502$ ] [Figure 3].

Number of patients who needed dialysis was measured in two clinical trials [Daher *et al.* (2000) and Costa *et al.* (2003)]. There were 141 patients in penicillin group and out of these 141, dialysis was needed in 43 (30.4%) patients. A total of 147 patients were enrolled in control group and out of 147, dialysis was needed in 33 (22.4%) patients. There was no significant difference between both groups for number of patients who needed dialysis by both random [Odds ratio 1.587 (95% CI 0.919-2.731),  $Z = 1.657$ ,  $P = 0.098$ ] as well as fixed model [Odds ratio 1.587 (95% CI 0.919-2.731),  $Z = 1.657$ ,  $P = 0.098$ ] [Figure 4].

Parameters of heterogeneity in the studies are shown in Table 3. Funnel plot to assess literature

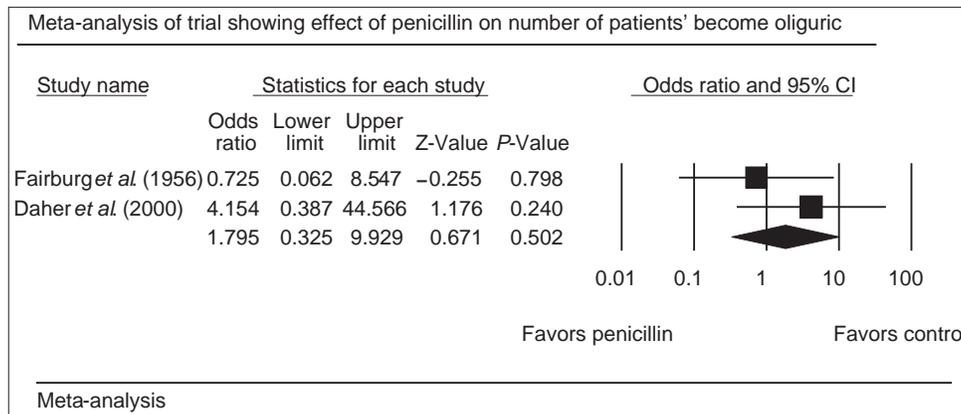
was not plotted because of less number of clinical trials.

## DISCUSSION

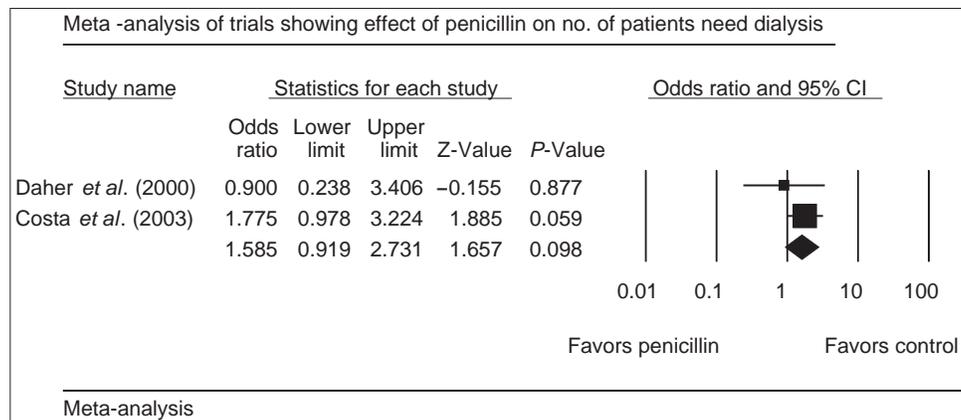
The present systematic review and meta-analysis observes no conclusive evidence to show superiority of one single antibiotic over others in the treatment of leptospirosis due to availability of very few clinical trials that may assist to reach a conclusion with certainty. In meta-analysis of five clinical trials comparing penicillin with placebo

**Table 3:** Heterogeneity in the trials included in the analysis for various parameters (Q statistic)

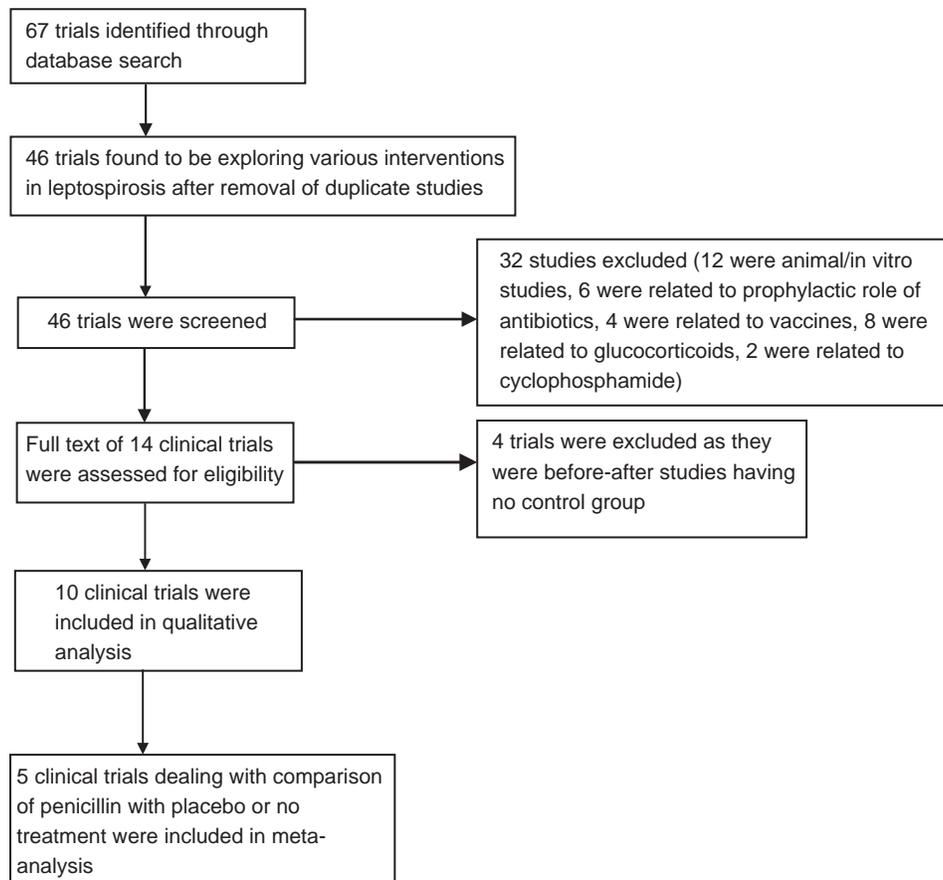
Outcomes	Q value	df	P value	I <sup>2</sup>
Death	2.24	2	0.32	10.88
Fever days	10.58	2	0.005	81.10
No. of patients become oliguric	0.999	1	0.318	0.00
No. of patients needed dialysis	0.833	1	0.361	0.00



**Figure 3:** Effect of penicillin therapy on number of patient becoming oliguric. Random model (Odds ratio 1.795 (95% CI 0.325-9.929),  $Z = 0.675$ ,  $P = 0.502$ ), Fixed model (Odds ratio 1.795 (95% CI 0.325-9.929),  $Z = 0.675$ ,  $P = 0.502$ )



**Figure 4:** Effect of penicillin therapy on number of patient needed dialysis. Random model (Odds ratio 1.587 (95% CI 0.919-2.731),  $Z = 1.657$ ,  $P = 0.098$ ) and fixed model (Odds ratio 1.587 (95% CI 0.919-2.731),  $Z = 1.657$ ,  $P = 0.098$ )



### PRISMA chart

or no treatment it was observed that penicillin does not have significant favorable response in the patients of leptospirosis in comparison to placebo or no treatment. Out of all four endpoint measured in this meta-analysis only in one endpoint (fever day) summary statistics were moving toward penicillin group though it was not significant in all other endpoints (mortality, number of patients becoming oliguric, number of patient needing dialysis) summary statistics (odds ratio) were favoring control as compared with penicillin though it was also not significant. In icteric phase of leptospirosis, it is difficult to isolate organism through blood culture or through spinal fluids but symptoms and signs are clearly observed. The symptoms and signs in this phase of leptospirosis may be because of the release of some virulent factors like lipopolysaccharides, hemolysins, outer member protein, etc.<sup>[18]</sup> These virulent factors may progress the disease toward complications like renal failure.<sup>[18]</sup> There is a hypothetical possibility that fever may be because of direct involvement

of leptospira hence, it was significantly decreased in penicillin group compared with effect on other endpoints, which were not affected by penicillin. Findings of this review debates the role of penicillin in the treatment of leptospirosis. Many guidelines cites penicillin as more effective in early disease as compared with when it is used in late disease, however, no convincing evidence supporting this view can be generated in present systematic review. Except in one clinical trial in which fever days were compared when treatment was started within 4 days or after 4 days and it was found that there was no significant difference between both the groups for this endpoint (fever days).<sup>[4]</sup>

We could not see publication bias through funnel plot as numbers of clinical trials were small. We could not compare adverse effects as there were under reporting of these events in clinical trials. Except penicillin, data could not be pooled for other antibiotics like doxycyclines. Etc., as very few clinical trials were available; moreover clinical trials having same case and control in

more than one trial were not available. Majority of clinical trials were of low and moderate quality and hence conclusion based on these trials should be assessed cautiously. Present review emphasizes an urgent need of properly designed clinical trials to explore use of various antibiotics in treatment of leptospirosis to reach a certain conclusion and assist in area specific policy formulation for treatment of leptospirosis.

## CONCLUSION

On the basis of this systematic review, the role of antibiotics particularly penicillin is debatable in the treatment of leptospirosis. More clinical trials with better methodologies are needed to explore the role of antibiotics in leptospirosis.

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## APPENDIX 1: MESH WORD USED FOR SEARCHING OF LITERATURE (SINGLE AS WELL AS IN COMBINATION)

Leptospirosis (Mesh, Text Word)  
 Weil Disease (Mesh, Text)  
 (“Leptospirosis”[Mesh]) AND “therapy”  
 [Subheading]  
 Anti-Bacterial Agents (MeSH, Text Word)  
 Antibiotics (MeSH, Text Word)  
 Penicillins (MeSH, Text Word)  
 Doxycycline (MeSH, Text Word)  
 Chloramphenicol (MeSH, Text Word)  
 Cephalosporins (MeSH, Text Word)  
 Ceftriaxone (MeSH, Text Word)  
 Cefotaxime (MeSH, Text Word)  
 Azithromycine (MeSH, Text Word)  
 Tetracyclines (MeSH, Text Word)  
 Oxytetracyclines (MeSH, Text Word)  
 Clinical Trials (Publication Type)  
 Randomized Controlled Trials (Publication Type)  
 Controlled Trails (Publication Type)

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