

Comparison of the effectiveness of the antibiotics Fosfomycin and levofloxacin in acute cystitis: a systematic review and meta-analysis

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Abstract

Urinary tract infection or UTI is an infection caused by microorganisms that grow in the human urinary tract. Cystitis is a urinary tract infection (UTI) in the bladder (Li & Lesli, 2018). According to the National Kidney and Urological Diseases Information Clearinghouse or NKUDIC, urinary tract infections are the second most common infectious disease after respiratory tract infections, and 8.3 million cases are reported annually. Urinary tract infections can affect patients ranging from new-borns to the elderly. The main treatment for urinary tract infections is treatment using antibiotics according to the 2015 Guidelines on Urological Infections of the European Association of Urology (EAU). Fosfomycin is the main therapy for the treatment of cystitis while levofloxacin is an alternative therapy. Fosfomycin is the main therapy for cystitis, but the drug that is commonly found on the market is levofloxacin. Purpose. This study aims to compare the effectiveness of the antibiotic Fosfomycin with levofloxacin in acute cystitis. method. This meta-analysis research uses various literature sourced from Cochrane, PubMed, Google Scholar, and ScienceDirect. A literature search using the keywords "Fosfomycin" and "levofloxacin" and "cystitis" and "acute". This research uses the Review Manager 5.4 application. Results. Fosfomycin is more effective against *E. coli* bacteria, but levofloxacin is more effective against Fosfomycin on *S. saprophyticus* bacteria. *E. coli* bacteria are more resistant to levofloxacin than Fosfomycin, but Fosfomycin is more resistant to *S. saprophyticus* bacteria than levofloxacin.

Keywords: Cystitis; acute; Fosfomycin; levofloxacin;

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Introduction

Urinary tract infection or UTI is an infection caused by microorganisms that grow in the human urinary tract. Cystitis is a type of urinary tract infection (UTI) in the bladder (Li and Leslie 2021). According to the National Kidney and Urological Diseases Information Clearinghouse (NKUDIC), urinary tract infections are the second most common infectious disease after respiratory tract infections, with 8.3 million cases reported per year (Chafouleas, Blom-Hoffman, and Chafouleas 2006).

The percentage of UTI caused by *Escherichia coli* is 85%, followed by *Klebsiella* sp and *Streptococcus* sp, and several other types of bacteria such as *Staphylococcus epidermidis*, *Pseudomonas aeruginosa* and several other bacteria (Hajiri et al. 2019).

The main treatment for urinary tract infections is treatment using antibiotics (Renaldo and Djojodimedjo 2015). Antibiotics that can be used according to the Guideline on Urological Infections 2015 are Fosfomycin trometamol, nitrofurantoin microcrystal, pivmecillinam, ciprofloxacin, levofloxacin, ofloxacin, cefadroxil, ceftinib, and cefotaxime. TMP-SMX (Trimethoprim and Sulfamethoxazole).

Fosfomycin is the main therapy for acute cystitis, but the drug that is commonly found on the market is levofloxacin (Bientinesi, Murri, and Sacco 2020). So that researchers are interested in conducting research because they want to know the comparison of the effectiveness of the antibiotics Fosfomycin and levofloxacin in acute cystitis based on a systematic review and meta-analysis.

Method

This study uses a systematic review method and meta-analysis with the inclusion criteria:

1. Acute cystitis patient with clinical complaints
2. The patient was given the antibiotic therapy Fosfomycin and levofloxacin
3. The effectiveness of therapy with the administration of the antibiotics Fosfomycin and levofloxacin
4. Comparison of the success of antibiotic therapy and the incidence of antibiotic resistance.

This study also used the exclusion criteria:

1. Journals over the last 10 years
2. Chronic
3. cystitis patients' Acute cystitis patients without clinical complaints

Search and retrieve literature online using Google Scholar, Pubmed, Science Direct, and Cochrane using the keywords "Fosfomycin" and "levofloxacin" and "cystitis" and "acute".

Review the quality of the journals that have been obtained using JBI Critical Appraisal with a maximum score of 10. If the final score of the assessment is below 50% then it has a high risk of bias, if it is between 50-69% then it has a moderate risk of bias, and if it is above 70% the risk of bias is low. The journals that will be used for this research are journals with a low risk of bias.

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The data obtained will be entered into the Review Manager 5.4 application (The Cochrane Collaboration, Oxford, UK). Weighted mean difference (WMD) and odds ratio (OR) was used to analyze data for each variable in this study. The Confidence Interval (CI) is set at 95%. A P-value less than 0.05 indicates statistically significant data. Cochran Q test was used to analyze the heterogeneity of the statistical data. The heterogeneity of statistical data is indicated by I², if I² is less than 50%, then the meta-analysis uses a fixed effect, and if I² is more than 50%, this research uses randomized effect.

Result

From 216 literature searched from Google Scholar, PubMed, ScienceDirect, and Cochrane. A total of 211 literatures were excluded based on screening of irrelevant literature titles and abstracts. After being analyzed, it was found that 5 literatures were reviewed in detail, 1 of which was excluded due to duplication. There were 4 relevant literatures that met all the inclusion criteria, the data collected was the number of susceptibility and resistance of the group of bacteria that cause acute cystitis to Fosfomycin and levofloxacin antibiotics.

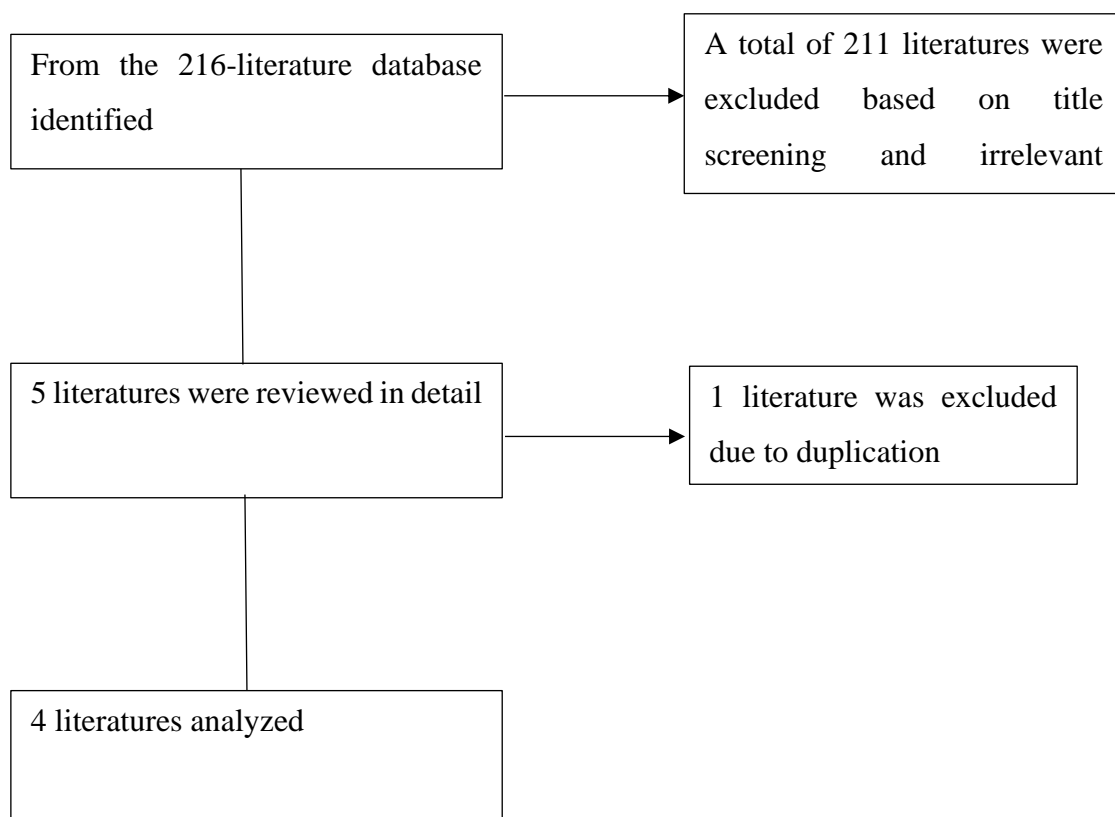


Figure 1. Literature search

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Journal	Year	JBI score	Total number of bacterial samples
Hayami <i>et al.</i>	2013	70%	387 samples
Hayami <i>et al.</i>	2019	70%	324 samples
Wada <i>et al.</i>	2021	90%	711 sample
Owari <i>et al.</i>	2017	70%	219 samples

Table 1. Study Characteristics.

Journal	Bacterial	Strains	Fosfomisin		Levofloxacin	
			Susceptible	Resistant	Susceptible	Resistant
Hayami <i>et al.</i> , 2013	E. coli	301	301	0	277	18
	ESBL-producing	14	14	0	4	9
	E. coli					
	S.Saprophyticus	20	13	4	20	0
Hayami <i>et al.</i> , 2019	E. coli	20	20	0	207	9
	ESBL-producing	9	9	0	6	3
	E. coli					
	S.Saprophyticus	36	2	6	36	0
Wada <i>et al.</i> , 2021	E. coli	514/552	504	1	466	79
	ESBL-producing	46/53	44	0	21	31
	E. coli					
Owari <i>et al.</i> , 2017	E. coli	179	169	5	145	32

Table 2. Data included

To assess the effectiveness and incidence of resistance to these antibiotics, inoculated

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Data were analyzed using the Review Manager 5.4 application and obtained the results:

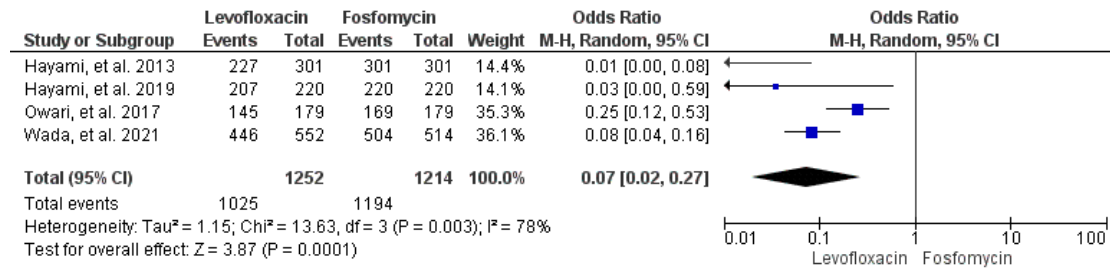


Figure 2. The results of the meta-analysis of the comparison of the effectiveness of levofloxacin against Fosfomycin in *E. coli* bacteria.

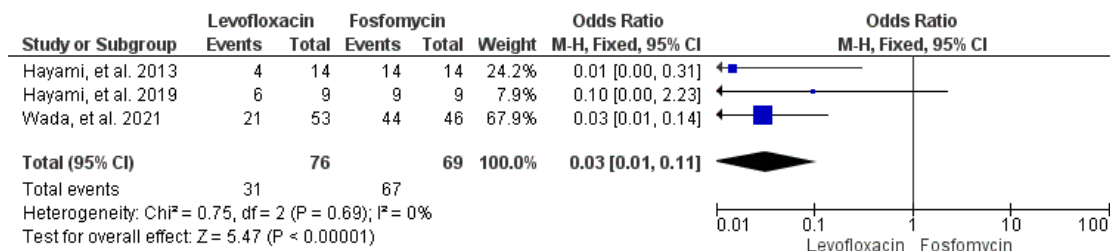


Figure 3. Results of the meta-analysis of the comparison of the effectiveness of levofloxacin against Fosfomycin in ESBL-producing *E. coli* bacteria.

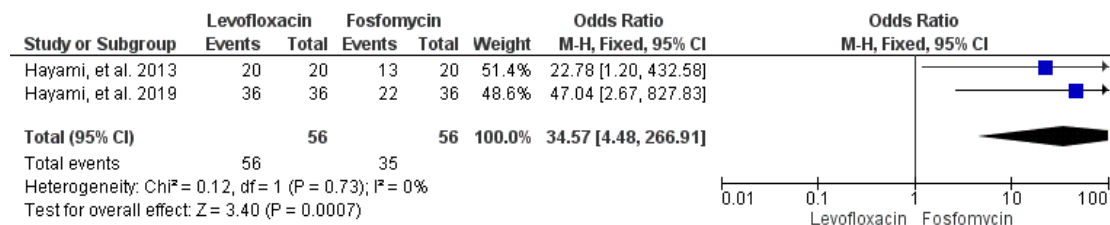


Figure 4. The results of the meta-analysis of the comparison of the effectiveness of levofloxacin against Fosfomycin in *S. saprophyticus*

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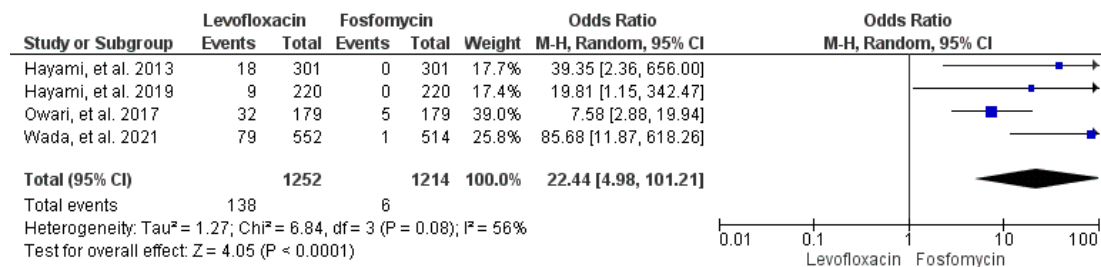


Figure 5. The results of the meta-analysis of the comparison of the resistance of levofloxacin to Fosfomycin in *E. coli* bacteria

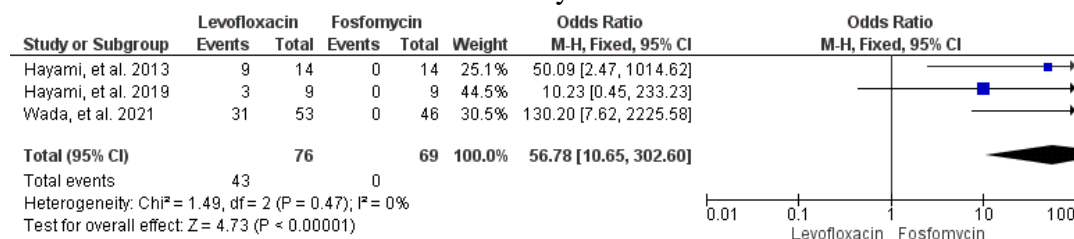


Figure 6. Results of the meta-analysis of the comparison of levofloxacin resistance to Fosfomycin in ESBL-producing *E. coli* bacteria

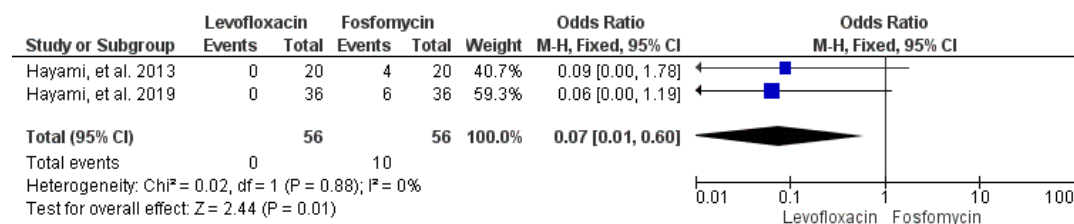


Figure 7. The results of the meta-analysis of the comparison of levofloxacin resistance to Fosfomycin in *S. saprophyticus*.

Discussion

From these data, it was found that the effectiveness test of levofloxacin against Fosfomycin in *E. coli* was not significant (OR 0.07, 95% CI 0.02; 0.27, $P = 0.0001$). It can also be seen from the diamond (Total Odds Ratio combined) in the levofloxacin group and the P value = 0.0001 which indicates that susceptible bacteria are seen less in the levofloxacin group than in the Fosfomycin group, the diamond shape does not touch the line without an effect indicating that the difference found between the two groups was statistically significant.

It was also found that the effectiveness of levofloxacin against Fosfomycin on ESBL-producing *E. coli* was not significant (OR 0.03, 95% CI 0.01; 0.11, $P < 0.00001$). It can also be seen from the diamond (Total Odds Ratio combined) in the Fosfomycin group and the P value < 0.00001 which indicates that susceptible bacteria are seen less in the levofloxacin group than in the Fosfomycin group, the diamond shape does not touch the line without an effect indicating that the difference found between the two groups was statistically significant.

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However, the effectiveness of levofloxacin against Fosfomycin in *S. saprophyticus* was significant (OR 34.57, 95% CI 4.48;266.91, $P = 0.0007$). It can also be seen from the diamond (Total Odds Ratio combined) in the Fosfomycin group and the P value = 0.0007 which indicates that susceptible bacteria are seen more in the levofloxacin group than in the Fosfomycin group, the diamond shape does not touch the line without an effect indicating that the difference found between the two groups was statistically significant.

For comparative data on the level of resistance, the resistance level of levofloxacin to Fosfomycin in *E. coli* bacteria was significant (OR 2.44, 95% CI 4.98; 101.21, $P < 0.0001$). It can also be seen from the diamond (Total Odds Ratio combined) in the Fosfomycin group and the P -value < 0.0001 which indicates that resistant bacteria are seen more in the levofloxacin group than in the Fosfomycin group, the diamond shape does not touch the line without an effect indicating that the difference found between the two groups was statistically significant.

It was also found that levofloxacin resistance to Fosfomycin in ESBL-producing *E. coli* bacteria was significant (OR 56.78, 95% CI 10.65; 302.60, $P < 0.00001$). It can also be seen from the diamond (Total Odds Ratio combined) in the Fosfomycin group and the P -value < 0.00001 which indicates that resistant bacteria are seen more in the levofloxacin group than in the Fosfomycin group, the diamond shape does not touch the line without an effect indicating that the difference found between the two groups was statistically significant.

However, the resistance of levofloxacin to Fosfomycin in *S. saprophyticus* was not significant (OR 0.07, 95% CI 0.01; 0.60, $P = 0.01$). It can also be seen from the diamond (Total Odds Ratio combined) in the levofloxacin group and the P -value = 0.01 which indicates that resistant bacteria are seen more in the Fosfomycin group than in the levofloxacin group, the diamond shape does not touch the line without an effect indicating that the difference is significant. was found between the two groups to be statistically significant.

Conclusion

The effectiveness of levofloxacin against Fosfomycin on *E. coli* was significant (OR 2.44, 95% CI 4.98;101.21, $P = 0.0001$). It was concluded that Fosfomycin was more effective against *E. coli* bacteria, but the effectiveness of levofloxacin against Fosfomycin on *S. saprophyticus* was significant (OR 34.57, 95% CI 4.48; 266.91, $P = 0.0007$). So, it was concluded that levofloxacin was more effective for *S. saprophyticus* bacteria.

The level of resistance of levofloxacin to Fosfomycin in *E. coli* was significant (OR 2.44, 95% CI 4.98; 101.21, $P = 0.0001$). So, it was concluded that *E. coli* bacteria were more resistant to levofloxacin than Fosfomycin, but the level of levofloxacin resistance to Fosfomycin in *S. saprophyticus* bacteria was not significant (OR 0.07, 95% CI 0.01; 0.60, $P = 0.01$). so, it was concluded that *S. saprophyticus* bacteria were more resistant to Fosfomycin than levofloxacin

Fosfomycin is recommended to be the main therapy for acute cystitis because Fosfomycin is more effective and not more resistant than levofloxacin for the main

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bacteria causing cystitis, namely *E. coli* bacteria, but for *S. saprophyticus* bacteria it is more advisable to use levofloxacin so that levofloxacin is suitable as therapy. alternative.

It is necessary to monitor the administration of levofloxacin therapy in cystitis due to an increase in levofloxacin resistance to *E. coli* bacteria showing excessive drug use for therapy, so that the use of levofloxacin drug in cystitis for *S. saprophyticus* bacteria must be monitored so that it is not excessive and does not cause resistance.

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