Fosfomycin Trometamol versus Ciprofloxacin for antibiotic prophylaxis prior transrectal ultrasound guided prostate biopsy: a meta-analysis of clinical studies

KEY WORDS:

Fosfomycin.

Ciprofloxacin.

Urinary tract infection.

ABSTRACT

BACKGROUND: Infectious complications are a major concern after trans-rectal ultrasound-guided prostate needle biopsy (TRUS-PNB). Although Fluoroquinolones are currently the first choice, an increase in resistance has raised the question about its recommendation. Fosfomycin trometamol (FMT) is a wide spectrum oral antibiotic with low bacterial resistance reported. Therefore we performed a systematic review and meta-analysis of clinical studies to assess the comparative prophylactic effectiveness of FMT versus Ciprofloxacin (CIP) in subjects who underwent TRUS-PNB.

METHODS: A systematic review was performed between January 1970 and June 2017 using Web of Science, Scopus and PubMed databases to identify relevant studies. Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria was used for article selection. Outcomes of interest were febrile and afebrile urinary tract infection (UTI) and the presence of Fluoroquinolone-resistant (FQR) or extended spectrum beta-lactamase (ESBL) producing uropathogens in urinary cultures.

RESULTS: Four studies including 2331 subjects were analyzed, 1088 had used FMT and 1243 CIP as antibiotic prophylaxis previous TRSU-PNB. FMT provided a significantly lower afebrile (OR = 0.21, 95%CI = 0.12 − 0.38, P < 0.001) and febrile (OR = 0.15, 95%CI = 0.07 − 0.31, P < 0.001) UTI than CIP. Among all urine cultures, patients in FMT arm also had a significant lower prevalence of FQR and ESBL (*E. coli or K. pneumoniae*) microorganisms when compared to CIP group (OR = 0.25, 95% CI = 0.12 − 0.21, P = 0.001 and OR = 0.24, 95% CI = 0.10-0.58, P = 0.001, respectively).

CONCLUSION: Antibiotic prophylaxis with FMT prior to TRUS-PNB was associated with lower rates of infectious complication when compared to CIP.

INTRODUCTION

Urinary tract infection (UTI) is one of the most common complications following trans-rectal ultrasound-guided prostate needle biopsy (TRUS-PNB), with an incidence varying from 0.1 to 7%.[1,2] Recently, Nan et al reported that infectious complications were responsible for 70% of all hospitalizations in patients who underwent TRUS-PNB, leading to a considerable impact in health costs.[3] Previous studies have found that the incidence of UTI following TRUS-PNB was associated with age, immunosuppression, chronic diseases and previous use of antibiotics.[4,5] Moreover, the bacterial flora of the rectum and the type of antibiotic prophylaxis used have been correlated with infectious complications after TRUS-PNB.[6] Currently, Fluoroquinolones are the most widely used antibiotics prophylaxis for TRUS-PNB.[1] However, several studies reported an increasing incidence of Fluoroquinolone-resistant (FQR) uropathogens.[6,7] These findings urge the reconsideration of Fluoroquinolones as the antibiotic of choice for TRUS-PNB prophylaxis.

Fosfomycin trometamol (FMT) is an antibiotic agent that acts inhibiting the biosynthesis of peptidoglycans and have a wide spectrum against Gram-negative and Gram-positive microorganisms.[8] Its safety and efficacy has been confirmed in previous studies.[10,11] Furthermore, the bacterial resistance rate is extremely low (< 3%) and cross-resistance with Fluoroquinolones is rare.[12] Additionally, it has been shown to be effective against beta-lactamase producing bacteria. For example, Pullukcu *et al* who studied the action of FMT in 54 patients with UTI caused by extended spectrum beta-lactamase (ESBL)-producing *E. coli* demonstrated a treatment success rate of 94.3%.[13] Multiple studies evaluated the safety and efficacy of FMT as a prophylactic agent in patients undergoing TRUS-PNB with mixed results.[14,15] Thus, we sought to perform a systematic review and meta-analysis of the use of FMT in patients undergoing TRUS-PNB compared to ciprofloxacin (CIP) to prevent infectious complications.

METHODS

Evidence Acquisition

After a systematic literature search including articles published between January 1970 and June 2017 using Web of Science, Scopus and PubMed databases with the following relevant search terms: "Fosfomycin", "prostate", "prostate biopsy", we retrieved 8506 abstracts. After exclusion of 134 duplicates this resulted in 8372 abstracts. We retrieved a total of 262 abstracts selected for review based on the following criteria: study comparing FMT to other antibiotics for TRUS-PNB prophylaxis, English language, original research, and adult human subjects. Only published studies comparing FMT versus another antibiotic used as antibiotic prophylaxis previous TRUS-PNB were included. Following the same criteria we carefully selected a total of 12 for full text review. Of these, 8 additional studies were excluded, 7 due to absence of CIP in control group and one due to absence of data about UTI, for a final study sample of 4 studies. The final study sample was 1088 subjects in FMT group and 1243 in CIP group. Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria (www.prismastatement.org) was used (**Figure 1**). Search of literature is described in **Table 1** and studies characteristics were described on **Table 2**.

Outcomes measured

Infectious complications were divided in two groups: afebrile and febrile UTI. Afebrile UTI was defined as the presence of irritative urinary symptoms like, dysuria, urgency or frequency and pyuria (> 10 leucocytes/high-power field; > 5 leucocytes/high-power in Fahmy et al study) within one month after the biopsy. Febrile UTI was defined as the association among, irritative urinary symptoms, pyuria and fever $> 38^0C$ within four weeks after the procedure. Significant bacteriuria was defined as the presence of $>10^5$ colony forming units per ml of urine. Data were collected within one month after the procedure.

Types of intervention

Patients received of FMT or CIP as preoperative antibiotic prophylaxis before TRUS-PNB.

Statistical analysis

The main objective of the meta-analysis is to evaluate the infectious outcomes among patients who underwent TRUS-PNB comparing FMT to CIP as antibiotic prophylaxis. Outcomes considered included afebrile, febrile and FQR or ESBL UTI. The presence of heterogeneity across studies was evaluated using the I^2 statistic. Summary of effects for the outcomes evaluated were calculated as odds ratio (OR) and 95% confidence intervals (CI) comparing FMT to CIP using random effects model given the methodological variability across studies, e.g. different antibiotic dose and schedule. Risk of bias was assessed using the Cochrane Risk of Bias Tool for clinical trials and the Newcastle-Ottawa Scale for observational studies.[16] All statistical analyses were performed using Review Manager software (RevMan v5.1, Cochrane Collaboration, Oxford, UK). $P < 0.05$ was considered statistically significant.

RESULTS

A total of 2331 subjects were included in the final analysis. Among these, 1088 had used FMT and 1243 CIP as antibiotic prophylaxis. Of the 4 studies included in the meta-analysis, Cai and Ongun were retrospective and Sen and Fahmy were prospective randomized studies. All studies included subjects who were submitted to TRUS-PNB due to elevated PSA levels and/or had abnormal DRE (digital rectum evaluation). Sen and Ongun studies reported PSA cutoff levels of > 2.5 ng/dl as an indication for the procedure while Cai and Fahmy did not reported PSA cutoff levels data. Transrectal ultrasound was performed in lithotomy or lateral decubitus under local anesthesia. Prostate specimens (10 to 14 cores) were taken using an automated biopsy gun with a 16- or 18-gauge needle. Subjects with positive urinary culture and use of indwelling urethral catheter were excluded. Ongun also excluded subjects with previous history of urinary tract surgery in the last month or who had undergone

saturation biopsy (24 cores). Fahmy and Sen excluded patients with previous history of UTI while Cai excluded only those with previous CIP or FMT-resistant UTIs. Moreover, in the Cai study men diagnosed with urinary tract structural abnormalities and with Charlson comorbidity index higher than 3 were also excluded. Patients with previous use of any kind of antibiotics one month before TRUS-PNB were also excluded in the Sen study. All four studies reported UTI complications as described previously except for Fahmy where the diagnosis of UTI was based on a positive urine culture. All studies used the same 3 grams of oral FMT dosage before the procedure.[18,19] However, Cai used another FMT dose 24 hours after the biopsy. The CIP dose and schedule varied across studies. In the Sen study, patients received a single of 500 mg oral CIP 60 minutes before the procedure, while in Fahmy 500 mg of oral metronidazole and 500 mg of CIP were given 1 hour prior to TRUS-PNB followed by CIP and metronidazole twice a day for three days.[19] The other two studies reported the use of 500 mg oral CIP twice daily for 5 days starting one day before the procedure.

Baseline patient characteristics (age, prostate volume and PSA level) are presented in **Table 3**. Subjects in the FMT groups were more likely to have a prior biopsy but this did not reach statistical significance (**Table 4**). Two articles evaluated history of diabetes and cancer and found no association with treatment arm (P < 0.05). (Supplemental Material)

Among all participants in the 4 studies, afebrile UTI was diagnosed in 103 subjects (4.4%). The was no significant heterogeneity across the studies ($I^2 = 0\%$, P = 0.61). The presence of afebrile UTI was significantly lower in the FMT group compared to CIP (OR = 0.21, 95%CI = 0.12 − 0.38, P < 0.001, **Figure 2**).

A total of 65 patients (2.8%) were diagnosed with febrile UTI, 8 (12.3%) in the FMT and 57 (87.7%) in the CIP group (**Figure 3**). This represents 0.7% of all FMT and 4.6% CIP subjects. There was no significant heterogeneity across studies ($I^2 = 0\%$, P=0.46). The odd of febrile UTI was significantly less frequent in subjects who were in the FMT group (OR= 0.15, 95%CI=0.07 − 0.31, P<0.001). Figure 4 demonstrate a forest plot with significantly decreased number of all UTI events in FMT group. Among all urine culture obtained, FQR and ESBL (*E. coli* or *K. pneumoniae*) microorganisms were found more frequently in the CIP group (OR=0.25, 95% CI=0.12 − 0.21, P=0.001 and OR=0.24, 95% CI=0.10-0.58, P=0.001, respectively). (**Supplementary Figures 1** and **2**)

DISCUSSION

Currently, Fluoroquinolones are the first choice of antibiotic prophylaxis for TRUS-PNB since its safety and efficacy have been tested through several clinical trials.[21,22] However, the increasing prevalence of ciprofloxacin-resistant bacteria in several countries is a matter of concern.[23] Recent studies have shown that the incidence of bacteria resistant to CIP is, on average, 25% but, in some cases, it can be as high as 70%.[24,25] This led to research investigating alternative antibiotics for TRUS-PNB prophylaxis including FMT, an oral broad-spectrum antibiotic with a very low microbial resistance and cross-resistance to ciprofloxacin.[8,9] Unfortunately, previous studies evaluating the role of FMT in TRUS-PNB prophylaxis were underpowered and showed mixed results. Therefore, we performed a systematic review and meta-analysis comparing FMT to CIP in patients undergoing TRUS-PNB. We found that FMT was associated to a lower incidence of febrile and afebrile UTI in these patients.

Previously, two randomized clinical trials have compared FMT versus CIP.[18,19] Sen et al studied 300 patients allocated to receive either 3g of oral FMT the night before the procedure or 500 mg of CIP 60 minutes before the TRUS-PNB. Infectious complications were more common in CIP group when compared to FMT group (P = 0.03). However, while afebrile UTI was significantly more frequent in the CIP arm (1.3% vs 6.0%), the incidence of febrile UTI was not different between the groups. In that study, 45.5% of patients with urinary infection who receive CIP had *E. coli* or *K. pneumoniae* resistant to Fluoroquinolones while in the FMT group the incidence of CIP-resistant infection was much lower.[18] More recently, Fahmy et al randomized 412 patients undergoing TRUS-PNB to receive either 3 grams of oral FMT or oral CIP 500 mg associated to metronidazole 500 mg 1 hour before the intervention and then twice daily for 3 days. In that study, the incidence of febrile and afebrile UTIs was higher in the CIP group (8.57%) compared to FMT group (1.98%, P = 0.001). Interestingly, the rate of FQR infection was four times more frequent in the CIP group compared to FMT (1.48% vs 6.19%). Moreover, all strains that were resistance to CIP were also EBSL producing *E. coli* and *K. pneumoniae*.[19]

Cai *et* al, in an observational cohort study, included data from 1109 patients who had received 3 grams oral FMT before and 3 grams 24h after the biopsy versus 500 mg of CIP starting 1 day before the procedure and continued twice a day for 5

days. The rate of UTI was significantly higher in the CIP group compared to FMT (P < 0.001).[20] In that study, the presence of FQR uropathogens was not different between groups. Ongun *et al* analyzed 640 patients who had undergone TRUS-PNB and received 3 grams of oral FMT the night before the procedure or 500 mg of CIP twice daily for 5 days. The incidence of urinary infection was not different between the groups. However, in that article the prevalence of FQR bacteria in febrile UTI cases was more than 60% and was present only in the CIP group.[17]

Our results show that FMT was associated to lower incidence of infectious complications (both afebrile and febrile UTI). The most plausible biological explanation for such a finding is the lower bacterial resistance associated with FMT. This is corroborated by studies showing that bacteria in rectum flora is typically sensitive to FMT and the worldwide increase in bacterial resistance to Fluoroquinolones.[9,24,25] Moreover, Liss *et al* showed that the main cause for UTI following transrectal procedures is the presence of FQR bacteria, usually *E. coli*.[26] Thus, given the high prevalence of CIP resistance and the lower efficacy of CIP to prevent TRUS-PNB related UTIs, a safer alternative to CIP in TRUS-PNB prophylaxis should be highly consider. Given some studies have demonstrated that infectious complications are the most common cause of hospitalization after TRUS-PNB, any efforts to reduce UTI in this setting can lead to a substantial reduction in morbidity and suffering. As such, FMT seems to be a safe and efficacious antibiotic prophylaxis alternative to CIP with and excellent tolerability which can minimize complications and costs associated with TRUS-PNB.

Our meta-analysis has several limitations. First, the dosage of antibiotics among the studies was heterogenous. Moreover. Sen *et al* and Fahmy *et al* excluded patients who received antibiotics within a month prior to the biopsy. Second, the studies included in the meta-analysis were performed in multiple countries with likely diverse microbiologic colonic flora. Although this increases the heterogeneity of our sample, it increases the external validity and applicability of four results. Third, patients with certain comorbidities, diabetes for example, were excluded in some studies Furthermore, given the reduced number of studies about this subject we included observational and randomized clinical trials to increase our sample. that could lead to a potential selection bias. Fourth, the number of biopsy cores, bowel preparation, cleansing enema and needle disinfection were not controlled or standardized in the studies.

CONCLUSION

In conclusion, in a meta-analysis of 4 studies evaluating FMT versus CIP to prevent infections complications among men undergoing TRUS-PNB, FMT was associated with lower febrile, afebrile and all UTI rates. The increased incidence of FQR bacteria in urinary cultures strongly suggests that alternatives to CIP should be studied to mitigate infectious complications. Although our results should be carefully analyzed since we included observational and randomized clinical trials, FMT seems a good option for TRUS-PNB prophylaxis, potentially reducing the incidence of infections complications.

REFERENCES

1. Loeb S, Carter HB, Berndt SI, Ricker W, Schaeffer EM. Complications After Prostate Biopsy: Data From SEER-Medicare. The Journal of Urology. 2011;186(5):1830-4. doi: 10.1016/j.juro.2011.06.057.

2. Mosharafa AA, Torky MH, El Said WM, Meshref A. Rising Incidence of Acute Prostatitis Following Prostate Biopsy: Fluoroquinolone Resistance and Exposure Is a Significant Risk Factor. Urology. 2011;78(3):511-4. doi: 10.1016/j.urology.2011.04.064.

3. Nam RK, Saskin R, Lee Y, Liu Y, Law C, Klotz LH, et al. Increasing Hospital Admission Rates for Urological Complications After Transrectal Ultrasound Guided Prostate Biopsy. The Journal of Urology. 2013;189(1):S12-S8. doi: 10.1016/j.juro.2012.11.015.

4. Loeb S, van Den Heuvel S, Zhu X, Bangma CH, Schröder FH, Roobol MJ. Infectious Complications and Hospital Admissions After Prostate Biopsy in a European Randomized Trial. European Urology. 2012;61(6):1110-4.

5. Carignan A, Roussy J-F, Lapointe V, Valiquette L, Sabbagh R, Pépin J. Increasing Risk of Infectious Complications After Transrectal Ultrasound–Guided Prostate Biopsies: Time to Reassess Antimicrobial Prophylaxis? European Urology. 2012;62(3):453-9.

6. Eruz ED. Risk factors for infection development after transrectal prostate biopsy and the role of resistant bacteria in colonic flora. Journal of Infection in Developing Countries. 2017;11(2):188-92.

7. Dumford 3rd D. Outbreak of Fluoroquinolone- Resistant Escherichia coli Infections after Transrectal Ultrasound- Guided Biopsy of the Prostate. Infection Control & Hospital Epidemiology. 2013;34(3):269-74.

8. Michalopoulos AS, Livaditis IG, Gougoutas V. The revival of fosfomycin. International Journal of Infectious Diseases. 2011;15(11):e732-e9.

9. Gardiner BJ, Mahony AA, Ellis AG, Lawrentschuk N, Bolton DM, Zeglinski PT, et al. Is fosfomycin a potential treatment alternative for multidrug-resistant gram-negative prostatitis? Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014;58(4):e101.

10. Grayson ML, Macesic N, Trevillyan J, Ellis AG, Zeglinski PT, Hewitt NH, et al. Fosfomycin for Treatment of Prostatitis: New Tricks for Old Dogs. 2015. p. 1141-3.

11. Keating GM. Fosfomycin Trometamol: A Review of Its Use as a Single-Dose Oral Treatment for Patients with Acute Lower Urinary Tract Infections and Pregnant Women with Asymptomatic Bacteriuria. Drugs. 2013;73(17):1951-67.

12. Kahlmeter G, Poulsen HO. Antimicrobial susceptibility of Escherichia coli from community-acquired urinary tract infections in Europe: the ECO·SENS study revisited. International journal of antimicrobial agents. 2012;39(1):45-51.

13. Pullukcu H, Tasbakan M, Sipahi OR, Yamazhan T, Aydemir S, Ulusoy S. Fosfomycin in the treatment of extended spectrum beta-lactamase-producing Escherichia coli-related lower urinary tract infections. International Journal of Antimicrobial Agents. 2007;29(1):62-5.

14. Lista F, Redondo C, Meilán E, García-Tello A, Ramón de Fata F, Angulo JC. Efficacy and safety of fosfomycin-trometamol in the prophylaxis for transrectal prostate biopsy. Prospective randomized comparison with ciprofloxacin. Actas Urológicas Españolas (English Edition). 2014;38(6):391-6.

15. Matthews PC, Barrett LK, Warren S, Stoesser N, Snelling M, Scarborough M, et al. Oral fosfomycin for treatment of urinary tract infection: a retrospective cohort study.(Report). BMC Infectious Diseases. 2016;16(1).

16. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. Cochrane Bias. Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343:d5928.

17. Ongün Ş. The Effectiveness of Single- Dose Fosfomycin as Antimicrobial Prophylaxis for Patients Undergoing Transrectal Ultrasound-Guided Biopsy of the Prostate. Urologia Internationalis. 2012;89(4):439-45.

18. Sen V, Aydogdu O, Bozkurt IH, Yonguc T, Sen P, Polat S, et al. The use of prophylactic single-dose fosfomycin in patients who undergo transrectal ultrasound-guided prostate biopsy: A prospective, randomized, and controlled clinical study. Canadian Urological Association journal = Journal de l'Association des urologues du Canada. 2015;9(11-12):E863.

19. Fahmy AM, Kotb A, Youssif TA, Abdeldiam H, Algebaly O, Elabbady A. Fosfomycin antimicrobial prophylaxis for transrectal ultrasound-guided biopsy of the prostate: A prospective randomised study. Arab Journal of Urology. 2016;14(3):228-33.

20. Cai T, Gallelli L, Cocci A, Tiscione D, Verze P, Lanciotti M, et al. Antimicrobial prophylaxis for transrectal ultrasound-guided prostate biopsy: fosfomycin trometamol, an attractive alternative. World Journal of Urology. 2017;35(2):221-8.

21. Kapoor DA, Klimberg IW, Malek GH, Wegenke JD, Cox CE, Patterson AL et al: Single- dose ciprofloxacin versus placebo for prophylaxis during transrectal prostate biopsy. Urology 1998;52:552.

22. Savoca G, Raber M, Lissiani A, Plaino F, Ciampalini S, Buttazzi L et al: Comparison of single preoperative oral rufloxacin versus perioperative ciprofloxacin as prophylactic agents in transurethral surgery. Arch Ital Urol Androl 2000; 72:15.

23. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2014. Stockholm, Sweden: ECDC; 2014. http://ecdc.europa.eu/en/publications/publications/ antimicrobial-resistance-europe-2014.

24. Dalhoff A. Global fluoroquinolone resistance epidemiology and implications for clinical use. Interdiscip Perspect Infect Dis 2012;2012:976273.

25. Williamson DA, Masters J, Freeman J, Roberts S. Travel-associated extended-spectrum beta-lactamase-producing Escherichia coli bloodstream infection following transrectal ultrasound-guided prostate biopsy. BJU Int 2012;109:E21–2.

26. Liss MA, Ehdaie B, Loeb S, Meng MV, Raman JD, Spears V, Stroup SP. An Update of the American Urological Association White Paper on the Prevention and Treatment of the More Common Complications Related to Prostate Biopsy. J Urol. 2017 Mar 29. pii: S0022-5347(17)42253-1. 3. [Epub ahead of print]

Figure 1. PRISMA flow-chart

Figure 2. Febrile

Figure 3. Afebrile UTI.

Figure 4. All UTI.

Supplementary Figure 1. Fluoroquinolone-resistant strains

Supplementary Figure 2. EBSL *E. coli* or *K. pneumoniae* strains

Table 1. Search of the literature in medical databases. The search was conducted on May 02, 2017.*

Database	Search strategies	Papers found	Related papers
MEDLINE (via PubMed, Embase	"Fosfomycin";"Fosfomycin" AND"prostate";"Fosfomycin" AND"prostate biopsy"	8506	8372

			and Web of Science)			

*selection of articles is described in PRISMA-flow figure.

Table 2. Studies characteristics

	Year of publication	Study Design	Number of cases (FMT/CIP)	Type of intervention
Ongun et al.	2012	Observational	104/406	CIP 500 mg VO twice/day 5 days Vs. FMT 3000 mg VO single dose
Cai et al.	2017	Observational	632/477	CIP 500 mg VO twice/day 5 days Vs. FMT 3000 mg VO with another dose 24 after

Fahmy et al.	2016	Randomized clinical trial	202/210	CIP 500 mg + MTZ 500 mg VO twice/day 3 days Vs. FMT 3000 mg VO single dose
Sen et al.	2015	**Randomized clinical trial**	150/150	CIP 500 mg VO Vs. FMT 3000 mg VO both single dose

FMT= Fosfomycin trometamol, CIP = Ciprofloxacin MTZ = metronidazole

Table 3. Demographic and clinical data

	Studies	Number of cases (FMT/CIP)	Mean (± SD)
Age (years)	Cai et al	632/477	65.9 (± 8.3)
	Fahmy et al	202/210	68.8 (± 4.2)
	Ongun et al	104/406	61.5 (± 6.3)
	Sen et al	150/150	63.5 (± 7.5)
Prostate volume (cm^3)	Fahmy et al	202/210	67.3 (± 31.2)
	Ongun et al	104/406	46.1 (± 22.6)
	Sen et al	150/150	53.1 (± 22.5)

PSA (ng/ml)	Cai et al	632/477	7.14 (± 4.31)
	Fahmy et al	202/210	23.9 (± 5.8)
	Sen et al	150/150	12.9 (± 1.8)

FMT= Fosfomycin trometamol, CIP= Ciprofloxacin

Table 4. History of prior prostate biopsy in patients who received FMT or CIP

	Studies	**N (FMT/CIP)**	**Mean (± SD)**	**OR [95% IC]**	**OR [95% IC]**
Prior prostate-biopsy	Cai et al	632/477	14.2%/13.2%	1.09 [0.77-1.54]	1.58 [0.92-2.73]
	Fahmy et al	202/210	6.4%/2.4%	2.82 [0.99- 8.06]	
	Ongun et al	104/406	16.3%/9.1%	1.95 [1.05-3.62]	

FMT= Fosfomycin trometamol, CIP= Ciprofloxacin, N= number of cases