Journal club presentation

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JAMA Network Open™

Original Investigation | Infectious Diseases

Effectiveness of Fosfomycin for the Treatment of Multidrug-Resistant *Escherichia coli* Bacteremic Urinary Tract Infections

A Randomized Clinical Trial

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Table of Contents

Background

The consumption of broad-spectrum drugs has increased as a consequence of the spread of multidrug-resistant (MDR) *Escherichia coli*.

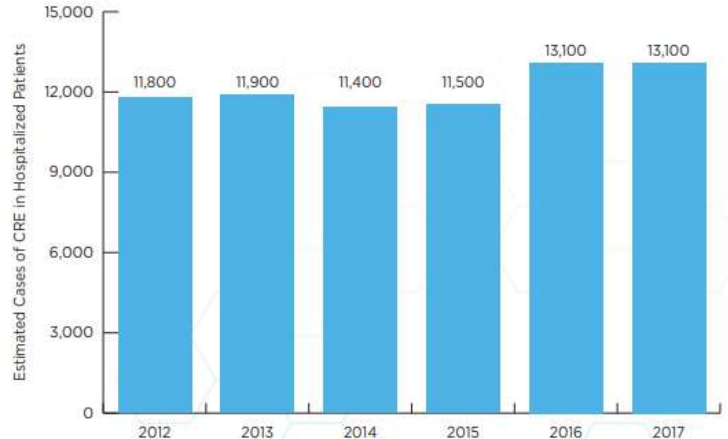
Recent exposure to antimicrobials and carbapenem-resistant Enterobacteriaceae: the role of antimicrobial stewardship

Results: **Recent (less than 3 months) exposure** to antibiotics was the only parameter that was consistently associated with CRE.

2019 Antibiotic Resistance Threats Report

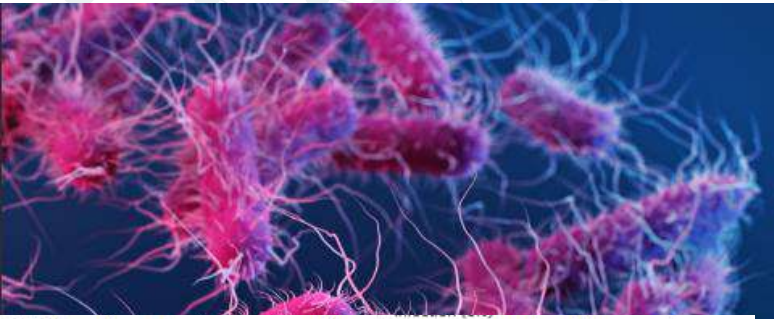
CASES OVER TIME

Containment strategies have prevented further spread of some types of CRE in the United States, but continued action is needed.



Antibiotic Resistance Threats in the United States, 2019 (cdc.gov)

2019 Antibiotic Resistance Threats Report



EXTENDED-SPECTRUM BETA-LACTAMASE (ESBL) PRODUCING

ENTEROBACTERIACEAE

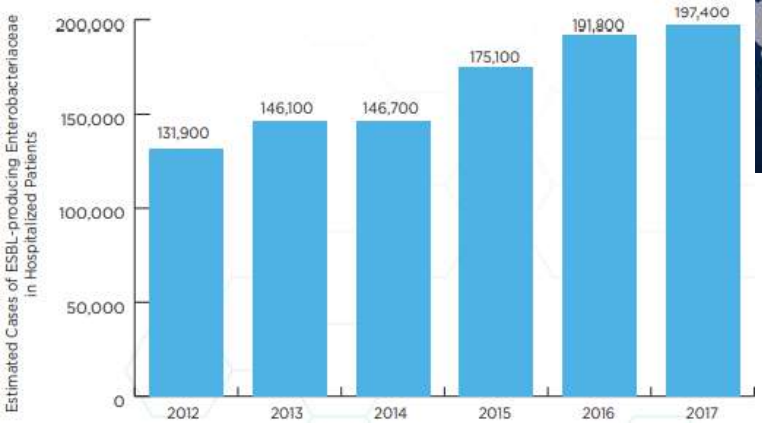
THREAT LEVEL **SERIOUS**

197,400 Estimated cases in hospitalized patients in 2017

9,100 Estimated deaths in 2017

$1.2B Estimated attributable healthcare costs in 2017

CDC and partners are working to assess and address why cases of ESBL-producing Enterobacteriaceae have increased since 2012.



[Antibiotic Resistance Threats in the United States, 2019 (cdc.gov)](#)

Fosfomycin non-susceptibility rate

Trial	Region	Date	Study method	isolates	Fosfomycin non-susceptibility rate (%)
Saeed et al., 2021	Bahrain	2018-2019	retrospectively analyzed urine samples with ESBL-producing E. coli	3044 *E. coli*	2.4%
Mothibi et al., 2020	South Africa	2015/09-2017/08	retrospective analysis of laboratory reports for uropathogens	4142 *E. coli*	1.9%
Tutone et al., 2022	Belgium, UK, Italy, Spain and Russia	2019/04-11	cross-sectional study collected consecutive urinary isolates	2064 *E. coli*	3.6%

1. IV Fosfomycin not available in U.S.
2. Fosfomycin non-susceptibility rate: ~4%

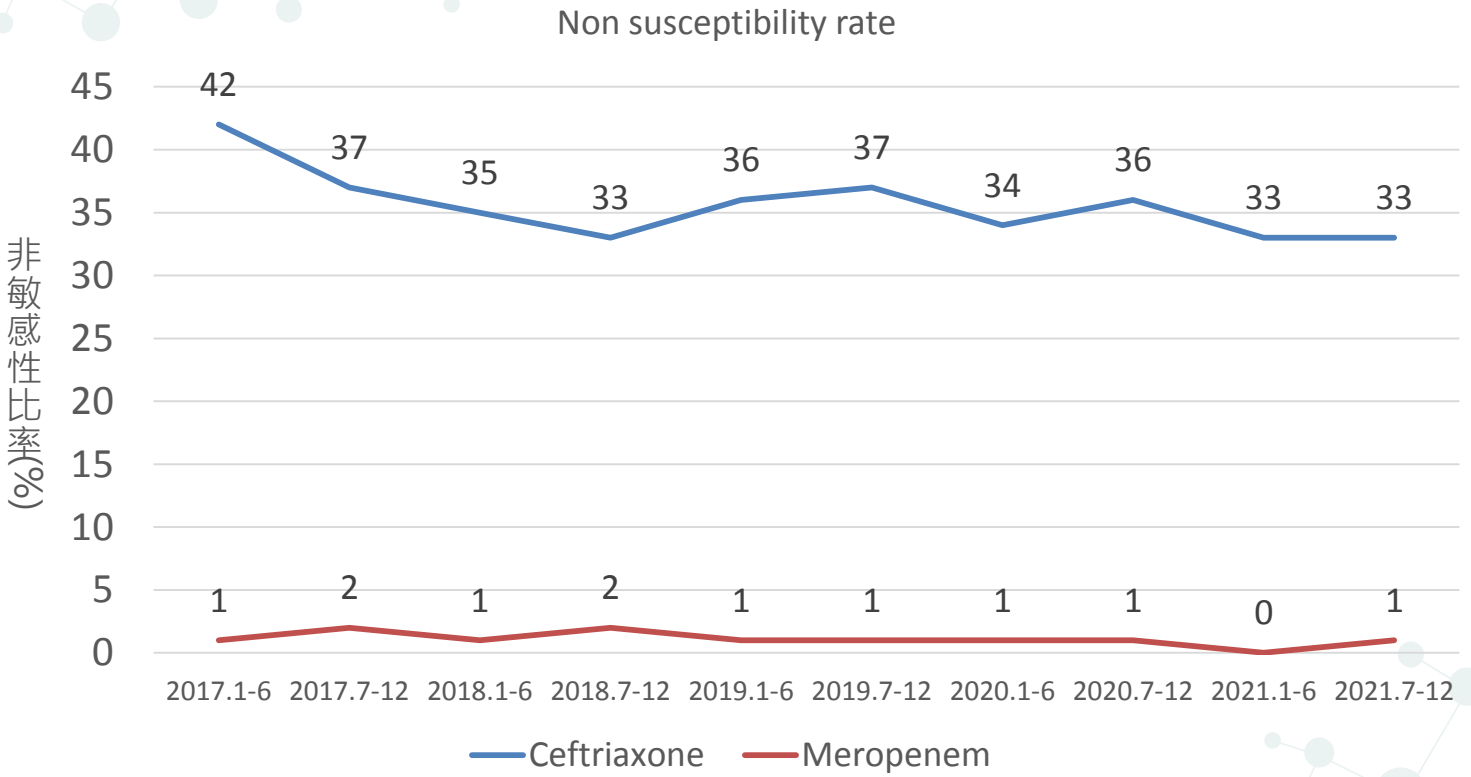
Oman Med J. 2021 Nov 10;36(6):e314.
S Afr J Infect Dis. 2020 Oct 26;35(1):173.
Int J Antimicrob Agents. 2022 Mar 17;106574.

Meropenem and Ceftriaxone non-susceptibility rate

Trial	Region	Date	Study method	*E.coli isolates*	Meropenem Non-susceptibility rate (%)	Ceftriaxone Non-susceptibility rate (%)	MDR
Sader et al., 2022	USA	2018-2020	4,680 isolates from ICU 16,263 isolates from non-ICU in 70 medical centers	8056	0.2	23.1 (ICU) 11.9 (non-ICU)	11.3%(ICU) 5.5%(non-ICU)
Alhumaid et al., 2021	Saudi Arabia	2015-2019	38,624 pathogens from 3 tertiary hospitals	14682	2.5	18.3	
Sadeghi et al., 2021	Iran	2017/04-2018/09	retrospective cross-sectional study conducted on 4029 patients	360	-	47.5	76.1

Ann Clin Microbiol Antimicrob **20,** 43 (2021).
BMC Res Notes . 2021 Mar 9;14(1):88.
Diagn. Microbiol. Infect. Dis. Volume 102, Issue 1, January 2022, 115557

WFH- *E.coli* non-susceptibility rate



UTI treatment- WFH guideline

[4] 複雜性尿路感染 (complicated UTIs)					
建議	Cefotixin	IVD	1-2 g Q8H	5-7 天	±Gentamicin 5 mg/kg once daily *or* Amikacin 15mg/kg once daily
	Cefmetaozne	IVD	2 g Q8H	5-7 天	
	Cefotaxime	IVD	2 g Q8H	7-10 天	
	Ceftriaxone	IVD	1-2 g daily	7-10 天	
	Flomoxef	IVD	1000 mg Q 8-12H	7-10 天	
	Ciprofloxacin[b]	PO	500 mg BID	7-10 天	懷疑感染抗藥性菌株者慎用
	Levofloxacin[b]	PO/ IVD	750 mg daily	5 天	
	TMP-SMX (80/400) [a]	PO	2 tabs PO BID	14 天	
二線	Ceftazidime	IVD	1-2 g Q8H	7-10 天	
	Cefepime	IVD	1-2 g Q12H	7-10 天	
	Piperacillin/tazobactam[c]	IVD	4500 mg Q8H	7-10 天	
	Imipenem[c] (懷疑 ESBL 菌種)	IVD	500 mg Q6H	7-10 天	· 若有癲癇疑慮，建議避免 Imipenem
	Meropenem[c] (懷疑 ESBL 菌種)	IVD	1000 mg Q8H	7-10 天	
	Doripenem[c] (懷疑 ESBL 菌種)	IVD	500 mg Q8H	7-10 天	· 避免併用 valproic acid
	Ertapenem[c] (懷疑 ESBL 菌種)	IVD	1 g once daily	7-10 天	

UTI treatment- WFH guideline

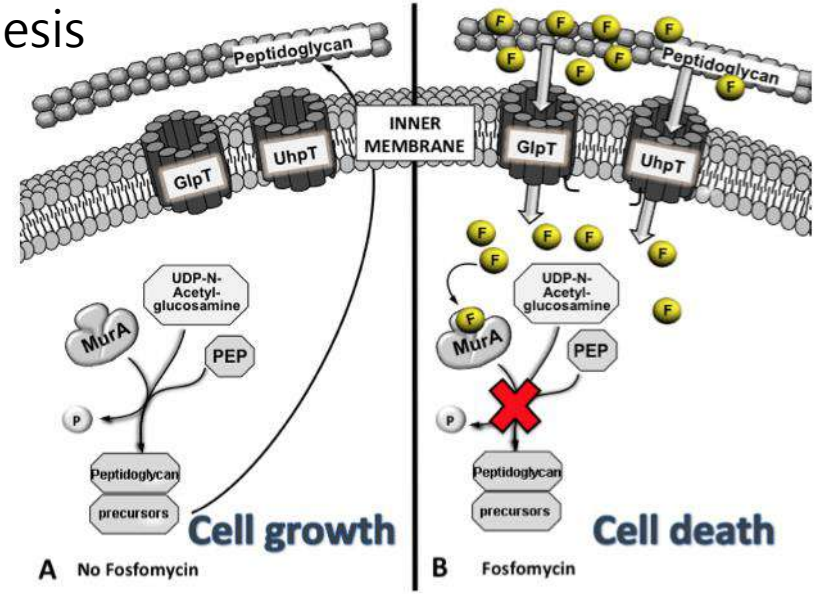
[5] 非複雜性腎盂腎炎 (uncomplicated pyelonephritis) *初始靜脈注射，症狀緩解且無藥品吸收疑慮者，建議盡早換口服* *若個案於一般建議療程時間狀況仍不適合停止抗生素，建議抗生素使用至退燒或消除治病複雜因素後 3-5 天*				
建議	Cefotaxime	IVD	2 g Q8H	7-10 天	±Gentamicin 5 mg/kg once daily ***or*** Amikacin 15mg/kg once daily
	Ceftriaxone	IVD	1-2 g daily	7-10 天	
	Ciprofloxacin[b]	PO	500 mg BID	7-10 天	懷疑感染抗藥性菌株者慎用
	Levofloxacin[b]	PO/ IVD	750 mg daily	5 天	
	TMP-SMX (80/400) [a]	PO	2 tabs PO BID	14 天	
二線	Ceftazidime	IVD	1-2 g Q8H	7-10 天	
	Cefepime	IVD	1-2 g Q12H	7-10 天	
	Piperacillin/tazobactam[c]	IVD	4500 mg Q8H	7-10 天	
	Imipenem[c] (懷疑 ESBL 菌種)	IVD	500 mg Q6H	7-10 天	· 若有癲癇疑慮，建議避免 Imipenem · 避免併用 valproic acid
	Meropenem[c] (懷疑 ESBL 菌種)	IVD	1000 mg Q8H	7-10 天	
	Doripenem[c] (懷疑 ESBL 菌種)	IVD	500 mg Q8H	7-10 天	
	Ertapenem[c] (懷疑 ESBL 菌種)	IVD	1 g once daily	7-10 天	

1. 台灣泌尿科醫學會(TUA): 泌尿科治療指引, 2020
2. European Association of Urology(EAU): Guidelines on urological infections, 2021

Fosfomycin sodium

Bactericidal

- 院內品項：Folsmycin 2g/vial 復司黴素注射劑(急採)
- Mechanism: Inhibitor of the MurA enzyme, that catalyzes the first committed step in peptidoglycan synthesis
- 適應症：綠膿菌、變形菌、沙雷氏菌、葡萄球菌、大腸菌等具有感受性細菌所引起之下列感染症(敗血症、支氣管炎、細支氣管炎、支氣管擴張症、肺炎、肺化膿症、膿胸、腹膜炎、**腎盂腎炎、膀胱炎**)



Fosfomycin sodium

- Acute **uncomplicated** cystitis:
  1. 3 g PO single dose
  2. Multidose regimens: 3 g QOD-Q3D for 3 doses

口服：
Fosfomycin trometamol
"贊邦" 梅樂黴素顆粒劑

- Urinary tract infection, **complicated** (including pyelonephritis):
  1. 12 to 16 g/day IV in 2 to 3 divided doses (maximum: 8 g/dose).
- Elimination:
  1. IV [Canadian product]: 80% to 90% (urine as unchanged drug)
- Sodium content: 14.4mEq/ g (331.2 mg Na/ g)

Methods

Study Design

- Phase 3
- Multicenter
- Open-label
- Randomized control trial

Fosfomycin vs **ceftriaxone** or **meropenem**

in the targeted treatment of bUTI caused by MDR *E coli.*

bUTI: bacteremic urinary tract infection

Patients

- **June 2014 to December 2018** at 22 **Spanish** hospitals.
- The original protocol included only **ESBL**–producing *E coli*, **meropenem** as comparator
- In January 2015, include any **MDR *E. coli***, **ceftriaxone** as comparator for susceptible isolates due to low recruitement

ESBL: extended-spectrum β-lactamase

Inclusion and exclusion criteria

- **Inclusion** criteria
  1. Hospitalized UTI adult
  2. *E. coli* with resistance to ≥ 1 drug from 3 different families
  3. Susceptible to Fosfomycin
  4. Susceptible to ceftriaxone or meropenem
  5. Need at least 4 days of intravenous therapy.

- **Exclusion** criteria
  1. Septic shock, prostatitis, kidney transplantation, polycystic kidney disease, palliative care, NYHA class III or IV, liver cirrhosis, hemodialysis
  2. Allergy to study drugs
  3. Active empirical treatment for ≥ 72 hrs

Randomization and Masking

- Randomly assigned **1:1**
  1. **Fosfomycin** disodium (4 g Q6H IV)
  2. **Ceftriaxone** (1 g QD IV) or if resistant, **meropenem** (1 g Q8H IV)
- After **4 days** IV, switch to oral drug was allowed
  1. Fosfomycin group: fosfomycin trometamol 3 g PO QOD
  2. Comparator group: cefuroxime, ciprofloxacin, amoxicillin/clavulanate, or trimethoprim-sulfamethoxazole

Randomization and Masking

- Centrally previously prepared list integrated in the electronic case report form.
- Stratified for **empirical therapy** and **ceftriaxone susceptibility**.
- **Not** blinded for drug allocation.
- 2 investigators **blinded for endpoints**.

Primary endpoints

Clinical **and** microbiological cure (CMC) at 5-7 days after final treatment (test of cure, TOC) in the modified intention-to-treat (MITT) population.

- **Clinical cure**: resolution of signs and symptoms of infection at TOC
- **Microbiological cure**: no causative *E. coli* strain in blood cultures from day 5 or in urine culture at TOC.

- Clinical failure: not reaching clinical cure, worsening signs or symptoms after 48 hours of treatment, death.
- Microbiological failure: not reaching microbiological cure.

Secondary endpoints

- Clinical cure in the clinically evaluable population (CEP) at TOC
- Microbiological cure in the microbiologically evaluable population (MEP) at TOC
- Length of hospital stay
- **Relapses**
- **Reinfections**
- 30-day mortality
- Adverse events (AEs)

Exploratory endpoints

- Rate of
  1. Resistant bacteria from follow-up cultures
  2. Ceftriaxone-resistant and carbapenem-resistant gram-negative bacteria acquisition in rectal swabs among a subset of patients.

Study Populations, and Follow-up

- MITT population: received at least 1 dose
- The CEP: patients evaluated at TOC or had a previous failure.
- The MEP: patients with urine cultures at TOC.
- Subgroup analyses: age, sex, empirical treatment, Charlson Comorbidity Index score, severe sepsis status.
- The patients were followed up for **60 days**.

Microbiology and Rectal Carriage Substudy

- Rectal carriage by ceftriaxone or carbapenem-resistant Enterobacterales or *Acinetobacter baumannii*,.
- Rectal swabs: at days 0, 3, or 4 and at end of treatment.
- Identification and antimicrobial susceptibility.
- European Committee on Antimicrobial Susceptibility Testing

Statistical Analysis

- Estimated a clinical cure rate of 85% with meropenem or ceftriaxone and 90% with fosfomycin based on observations.
- To reject the inferiority of fosfomycin with a **margin of −7%** for CMC, 80% power and 1-sided α of 5%, **188 patients** would need to be recruited.
- Exploratory study on rectal colonization: 40 patients was targeted.

Statistical Analysis

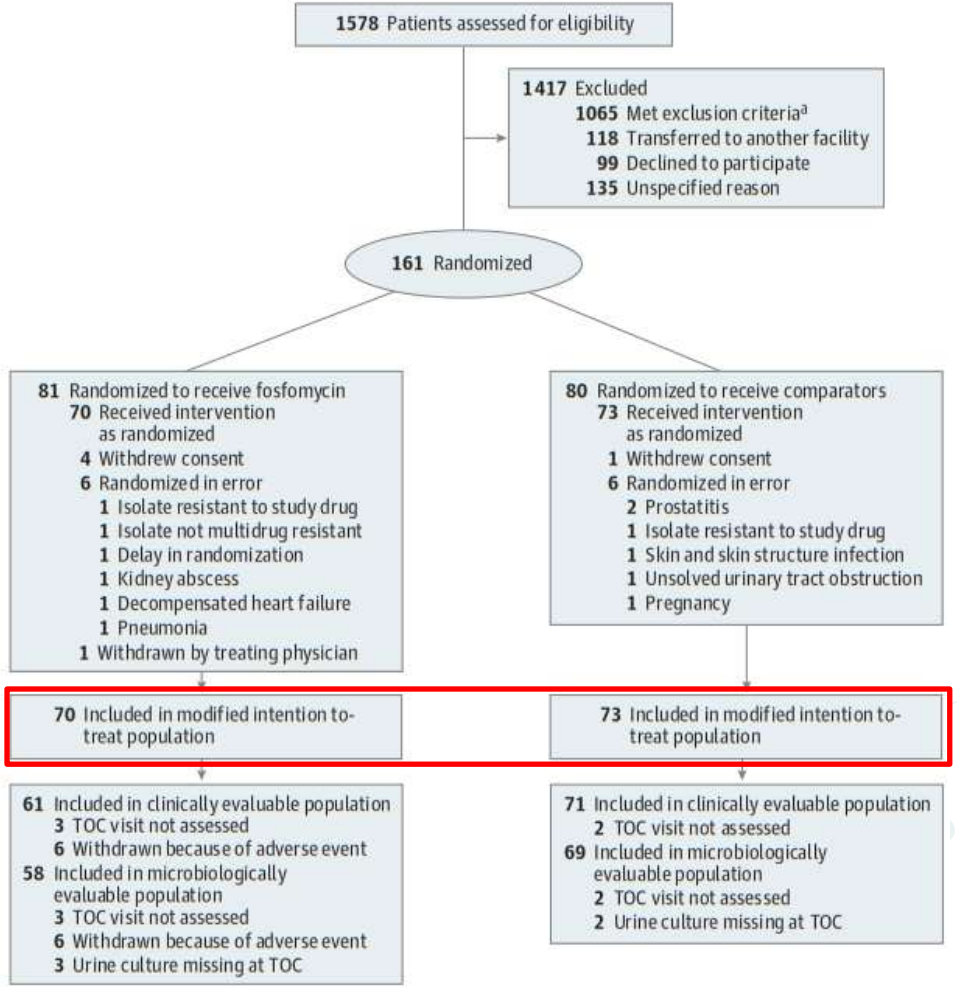
- 1-sided 95% CI
  1. Differences in proportions with categorical endpoints
  2. Direct comparisons between study groups
- $P < 0.05$ for comparisons not evaluating noninferiority
- SPSS Statistics and R

Results

Recruitment

- 70 patients to fosfomycin
- 73 patients to the comparator (31 to ceftriaxone and 42 to meropenem)

Figure. Patient Recruitment and Flow Through Study



Baseline characteristics

- 73 patients (51.0%) were women
- Median (IQR) age was 72 (62-81)
- **Similar** baseline characteristics.
- Fosfomycin group had more frequently invasive procedure of the urinary tract (12 patients [17.1%] vs 4 patients [5.5%]).

Characteristic	Patients, No. (%) Receiving fosfomycin (n = 70)	Receiving comparator (n = 73)
Age, median (IQR), y	69 (62-81)	73 (62-84)
Sex		
Women	34 (48.6)	39 (53.4)
Men	36 (51.4)	34 (46.6)
Charlson Comorbidity Index score[b]		
Median (IQR)	1 (0-3)	2 (1-3)
≥3	22 (31.4)	22 (30.1)
Congestive heart failure[c]	8 (11.4)	11 (15.1)
Chronic pulmonary disease[c]	12 (17.1)	11 (15.1)
Diabetes[c]	19 (27.1)	19 (26.0)
Chronic kidney disease[c]	9 (12.9)	14 (19.2)
Cancer[c]	14 (20.0)	16 (21.9)
Full dependence for basic activities	4 (5.7)	6 (8.2)
Urinary catheter at enrollment	21 (30.0)	22 (30.1)
Invasive procedure in the urinary tract in previous month[d]	12 (17.1)	4 (5.5)
Immunosuppressive drugs	7 (10.0)	9 (12.3)
Present infection		
Community-acquired infection[e]	33 (47.1)	39 (53.4)
Health care-associated infection[e]	25 (35.7)	23 (31.5)
Nosocomial infection[e]	12 (17.1)	11 (15.1)
Low urinary tract symptoms[f]	39 (55.7)	45 (61.6)
Flank pain or tenderness	27 (38.6)	26 (35.6)
Severe sepsis at presentation[g]	15 (21.4)	22 (30.1)
Pitt score, median (IQR)[h]	1 (0-1.25)	1 (0-2)
eGFR<60 mL/min/1.73 m^2 at enrollment	21 (30.0)	22 (30.1)
Hydronephrosis in echography at enrollment	9 (12.9)	6 (8.2)
Active treatment ≤24 h after blood culture	48 (68.6)	50 (68.5)

Baseline characteristics

- Similar length of IV and antibiotic therapy days.
- Switch to oral therapy
  1. Fosfomycin: 60 patients (85.7%)
  2. Comparator: 48 patients (65.7%)

Characteristic	Patients, No. (%) Receiving fosfomycin (n = 70)	Receiving comparator (n = 73)
Susceptibility of baseline *Escherichia coli* (local laboratory)		
Amoxicillin	7 (10)	5 (6.8)
Amoxicillin-clavulanic acid	38 (54.3)	29 (39.7)
Piperacillin-tazobactam	55 (78.6)	54 (74.0)
Cefotaxime	32 (45.7)	33 (45.2)
Cefepime	34 (48.6)	32 (48.6)
Meropenem	70 (100)	73 (100)
Ciprofloxacin	14 (20.0)	11 (15.1)
Trimethoprim-sulfamethoxazole	33 (47.1)	21 (28.8)
Amikacin	59 (84.3)	66 (90.4)
Fosfomycin	70 (100)	73 (100)
Length of intravenous therapy with study drug, mean (SD), d	5.4 (0.9)	5.5 (1.8)
Length of antibiotic therapy with study drug, mean (SD), d	11.5 (3.9)	11.9 (2.0)
Oral antibiotic therapy after intravenous therapy with study drug	60 (85.7)	48 (65.7)
Oral drug used		
Fosfomycin trometamol	60 (85.7)	1 (1.4)[j]
Cefuroxime axetil	0	28 (38.3)
Amoxicillin-clavulanic acid	0	7 (9.6)
Trimethoprim-sulfamethoxazole	0	7 (9.6)
Ciprofloxacin	0	5 (6.8)
Parenteral ertapenem after study drug	0	13 (17.8)

Primary endpoints

- 6 adverse events treated with fosfomycin
  - ✓ 4 heart failure (5.7%)
  - ✓ 1 alithiasic cholecystitis
  - ✓ 1 persistent fever

Table 2. Patients Reaching CMC and Reasons for Not Reaching It

	Patients, No./total No. (%)			
	Receiving fosfomycin	Receiving comparator	Risk difference (1-sided 95% CI)[a]	*P* value, 1-sided
CMC at TOC among MITT (measures of success)				
All patients	48/70 (68.6)	57/73 (78.0)	−9.4 (−21.5 to ∞)	.10
Patients with ceftriaxone-susceptible isolates[b]	25/31 (80.6)	27/31 (87.0)	−6.4 (−21.7 to ∞)	.24
Patients with ceftriaxone-resistant isolates[b]	23/39 (59.0)	30/42 (71.4)	−12.4 (−29.8 to ∞)	.12
Reasons for not reaching CMC at TOC among MITT (measures of failure)				
Clinical or microbiological failure				
All patients	10/70 (14.3)	14/73 (19.7)	−5.4 (−∞ to 4.9)	.19
Patients with ceftriaxone-susceptible isolates[b]	3/31 (9.7)	4/31 (12.9)	−3.2 (−∞ to 10.0)	.34
Patients with ceftriaxone-resistant isolates[b]	7/39 (17.9)	10/42 (23.8)	−8.9 (−∞ to 6.9)	.25
Other reasons				
Withdrawn because of adverse events	6/70 (8.5)[c]	0/73 (0)	8.5 (−∞ to 13.9)	.006
Missed assessment at TOC	3/70 (4.2)	2/73 (2.7)	1.5 (−∞ to 6.5)	.31
TOC assessed but urine culture at TOC not available	3/70 (4.2)	0/73 (0)[d]	4.2 (−∞ to 8.1)	.03

Secondary endpoints

Table 3. Analysis of Secondary End Points

	Patients, No./total No. (%)[a]			
	Receiving fosfomycin	Receiving comparators	Risk difference (1-sided 95% CI)[b]	*P* value, 1-sided
Measure of success				
Clinical cure at TOC (CEP)				
All patients	59/61 (96.7)	64/71 (90.1)	6.6 (−0.2 to ∞)	.05
Patients with ceftriaxone-susceptible isolates	29/29 (100)	29/31 (93.5)	6.5 (−1.1 to ∞)	.08
Patients with ceftriaxone-resistant isolates	30/32 (93.8)	35/40 (87.5)	6.3 (−5.2 to ∞)	.18
Microbiological cure at TOC (MEP)				
All patients[c]	48/58 (82.8)	59/69 (85.5)	−2.7 (−13.3 to ∞)	.33
Patients with ceftriaxone-susceptible isolates	25/28 (89.3)	29/31 (93.5)	−4.2 (−18.4 to ∞)	.28
Patients with ceftriaxone-resistant isolates	23/30 (76.6)	30/38 (78.9)	−2.3 (−18.9 to ∞)	.41

Secondary endpoints

Measure of failure				
30-day mortality (CEP)				
All patients	2/61 (3.2)	2/71 (2.8)	0.4 (−∞ to 5.2)	.44
Patients with ceftriaxone-susceptible isolates	1/29 (3.4)	0/31 (0)	3.3 (−∞ to 8.8)	.15
Patients with ceftriaxone-resistant isolates	1/32 (3.1)	2/40 (5.0)	−1.9 (−∞ to 5.8)	.34
Relapse (CEP)				
All patients	8/61 (13.1)	6/71 (8.4)	4.7 (−∞ to 13.5)	.19
Patients with ceftriaxone-susceptible isolates	3/29 (10.3)	1/31 (3.2)	7.1 (−∞ to 17.6)	.13
Patients with ceftriaxone-resistant isolates	5/32 (15.6)	5/40 (12.5)	3.1 (−∞ to 16.5)	.35
Reinfection (CEP)				
All patients	4/61 (6.5)	4/71 (5.6)	0.9 (−∞ to 7.7)	.41
Patients with ceftriaxone-susceptible isolates	1/29 (3.4)	1/31 (3.2)	0.2 (−∞ to 7.7)	.48
Patients with ceftriaxone-resistant isolates	3/32 (9.3)	3/40 (7.5)	1.8 (−∞ to 12.5)	.39

Secondary endpoints

Other measure				
Hospitalization after randomization, mean (SD), d				
All patients	7.8 (8.0)	6.4 (4.7)	1.4 (−∞ to 3.1)	.10
Patients with ceftriaxone-susceptible isolates	6.0 (1.9)	4.4 (1.3)	1.6 (−∞ to 2.2)	<.001
Patients with ceftriaxone-resistant isolates	9.5 (10.8)	7.9 (5.8)	2.9 (−∞ to 6.1)	.07

Subgroup Analyses and Multivariate Analysis

- Fosfomycin had decreased CMC rates in all subgroups except **severe sepsis**.

- CMC receiving Fosfomycin versus comparators,
  1. Nonadjusted OR:

     0.61 (95% CI, 0.28-1.29; P = .20)
  2. Adjusted OR:

     0.55 (95% CI, 0.24-1.21; P = .14)

Table 4. Analyses of Clinical and Microbiological Cure Rates at the Test of Cure in Subgroups of Modified Intention-to-Treat Population

Subgroup	Patients, No./total No. (%)		Risk difference (1-sided 95% CI)[a]	*P* value, 1-sided
	Receiving fosfomycin	Receiving comparator		
Age, y				
≤80	34/50 (68.0)	40/53 (75.5)	−7.5 (−22.0 to ∞)	.19
>80	14/20 (70.0)	17/20 (85.0)	−15.0 (−36.7 to ∞)	.12
Women	24/34 (70.6)	29/39 (74.4)	−3.8 (−21.0 to ∞)	.35
Men	24/36 (66.7)	28/34 (82.4)	−15.7 (−32.8 to ∞)	.06
Empirical treatment				
Active	32/48 (66.7)	37/50 (74.0)	−7.3 (−22.5 to ∞)	.21
Inactive	16/22 (72.7)	20/23 (87.0)	−14.3 (−34.2 to ∞)	.11
Charlson Comorbidity Index score[b]				
≤2	33/48 (68.8)	41/51 (80.4)	−11.6 (−25.9 to ∞)	.09
>2	15/22 (68.2)	16/22 (72.7)	−4.5 (−27.1 to ∞)	.37
Severe sepsis[b]				
No	35/55 (63.6)	41/51 (80.4)	−16.8 (−31.2 to ∞)	.02
Yes	13/15 (86.7)	16/22 (72.7)	14.0 (−8.6 to ∞)	.15
Community-acquired infection[b]				
Yes	22/33 (66.7)	29/39 (74.4)	−7.7 (−25.3 to ∞)	.23
No	26/37 (70.3)	28/34 (82.4)	−12.1 (−28.7 to ∞)	.11
Fosfomycin MIC, mg/L[c]				
≤1	19/27 (70.4)	17/20 (85.0)	−14.6 (−35.1 to ∞)	.12
>1	22/33 (66.7)	28/37 (75.7)	−9.0 (−26.7 to ∞)	.20

Safety

	Fosfomycin	Comparators	p-value
AEs	44 (62.9%)	41 (56.2%)	0.41
Serious AEs	13 (18.6%)	10 (13.7%)	0.42

In the fosfomycin group, 6 patients (8.6%) developed heart failure

1. All aged ≥ 81 years
2. 2 had chronic heart failure, and 3 had chronic kidney insufficiency.
3. 5 was considered serious, drug was discontinued among 4.

Microbiological Studies

	Fosfomycin (n=70)	Comparators (n=73)	
ALL CEFTRIAXONE-RESISTANT BACTERIA	20 (29.5%)	27 (36.9%)	(P=0.29)
ALL MEROPENEM-RESISTANT BACTERIA	2 (2.8%)	3 (4.1%)	(P> 0.99)
ALL FOSFOMYCIN-RESISTANT BACTERIA	8 (11.4%)	6 (8.2%)	(P= 0.58)

Rectal colonization substudy, 38 patients were included;

Acquired a new ceftriaxone or meropenem-resistant gram-negative bacterial infection

- Fosfomycin: 0 of 21 patients
- Comparator: 4 of 17 patients (23.5%)

(1-sided $P = .01$)

Discussion and Conclusions

Efficacy

- Fosfomycin **did not reach noninferiority** criteria but not due to lack of efficacy
- Clinical or microbiological failure rate was numerically lower with fosfomycin in the MITT
- The high success rate with fosfomycin among patients with severe sepsis reinforces the idea that fosfomycin is efficacious in this infection.

Comparison with previous trials

- Previous randomized clinical trials on intravenous fosfomycin mostly included nonbacteremic cUTI.

- Sweden RCT: 38 adults with pyelonephritis (79% with *E. coli*),
  1. Fosfomycin (2 g Q8H) 44% clinical cure rates
  2. Ampicillin (2 g Q8H) 27% clinical cure rates

- A phase 2/3 double-blind RCT cUTI; 73% *E. coli*, 9% bacteremic. 465 patients. Younger and more women
  1. Fosfomycin (6 g Q8H) CMC: 64.7%
  2. Piperacillin-tazobactam (4.5 g Q8H) CMC : 54.5%

Chemioterapia . 1988 Apr;7(2):96-100.
Clinical Infectious Diseases, Volume 69, Issue 12, 15 December 2019, Pages 2045–2056

Safety

- Fosfomycin was discontinued among 6 patients because of AEs.
  1. Not mentioned in previous double-blind trial using similar total daily dose
  2. Suggesting a negative impact of the open design
- Heart failure in 6 patients with fosfomycin
  1. 5 had chronic heart failure (NYHA class I or II) or kidney insufficiency, all age ≥ 80
  2. Not described in the cUTI trial, might be due to difference in age
  3. Described 2 of 2672 patients in a meta-analysis
  4. May be caused by the sodium content (14.4 mEq/g)
- Suggest avoiding IV fosfomycin among patients
  1. Aged ≥ 80
  2. Chronic heart or kidney insufficiency.

Limitations

- Sample size not reached. (143 included, but 188 is needed)
- Highly exigent noninferiority margin
- Lack of blinding
- The options for switching were diverse in the comparator group
- Small subset of rectal colonization study

Strengths

- Randomization
- Pragmatic design
- Recruitment of older patients with comorbidities
- Exclude patients stable enough to allow an early discharge with oral drugs.
- Provide exploratory data on the ecological impact of the study drugs.

Conclusion

- Fosfomycin **did not demonstrate noninferiority** in bUTI caused by MDR *E coli*.
- Fosfomycin is effective and may be considered among selected patients
  1. Without previous heart disease
  2. low risk of sodium overload–related problems.
- Some safety concerns with fosfomycin were raised.
- The potential decreased ecological impact of fosfomycin deserves further study.

Appraisal

Did the study address a clearly focused research question?

YES

O

nvestigation | Infectious Diseases

I

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Effectiveness of Fosfomycin for the Treatment of Multidrug-Resistant *Escherichia coli* Bacteremic Urinary Tract Infections

A Randomized Clinical Trial

C

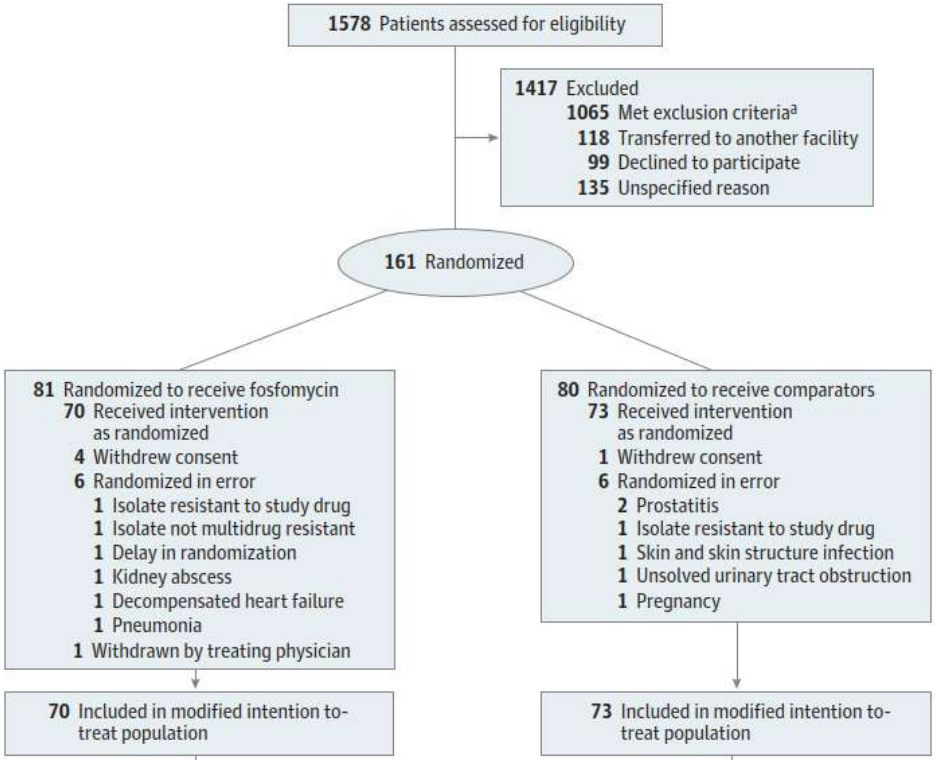
OBJECTIVE To determine whether fosfomycin is noninferior to ceftriaxone or meropenem in the targeted treatment of bacteremic urinary tract infections (bUTIs) due to MDR *E coli*.

Was the assignment of participants to interventions randomised?

Assignment to the treatment group was done centrally using a previously prepared list integrated in the electronic case report form. Randomization was stratified for empirical therapy (ie, active or not) and ceftriaxone susceptibility.

Were all participants who entered the study accounted for at its conclusion?

YES



- Flowchart shows progress of patients through the trial
- MITT was performed
- Exclusion reasons are given

Blinding

Were the **participants** 'blind' to intervention they were given? ☒ NO

Were the **investigators** 'blind' to the intervention they were giving to participants? ☒ NO

Were the **people assessing/analysing outcome**/s 'blinded' ? ☑ YES

> Assignment to the treatment group was done centrally using a previously prepared list integrated in the electronic case report form. Randomization was stratified for empirical therapy (ie, active or not) and ceftriaxone susceptibility. No blocks were used. Investigators were not blinded for drug allocation, with the exception of 2 investigators (J.S.-D. and J.R.-B.) who were blinded for checking end points.

Were the study groups similar at the start of the randomised controlled trial?

catheter. The characteristics of the patients by study group are shown in **Table 1**.[19-22] Overall, patients in the fosfomycin and comparator groups had similar baseline characteristics (median [IQR] age, 69 [62-81] years vs 73 [62-84] years; 34 [48.6%] women vs 39 [53.4%] women), but patients in the fosfomycin group had more frequently undergone a recent invasive procedure of the urinary tract (12 patients [17.1%] vs 4 patients [5.5%]). Active empirical therapy was received by 98 patients

Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?

YES

6.4 Schedule of visits

Visit	1	2	3	4	5	6	7
Day	1	3	5-7	12±2 (end of therapy)	5-7 after end of treatment (test of cure)	60±10	Unscheduled visit(s)
Informed consent	x						
Inclusion/exclusión criteria	x						
Pregancy test	x						
Randomization	x						
Clinical history, anamnesis	x	x	x	x	x	X	x
Physical examination	x	x	x	x	x	(x)	x
Blood count/chemistry[1]	x	x	x	x			x
Urine (elementary)	x		x		x		x
Urine culture	x		x		x		x
Blood culture	x	x	x[2]				x
Urinary tract ultrasound	X						x
Electrocardiogram	x						x
PK/PD samples[3]		x					x
Rectal swab[4]	x		x	x			
Urinary catheter change of present	x						
Medication dispensing	x	x	x	x			
Adverse events reporting		x	x	x	x	x	x
Concomitant medication checking		x	x	x	x	x	x

- Clearly defined study protocol for schedule of visits
- Same follow-up intervals the for each study group

Were the effects of intervention reported comprehensively?

- 80% power and 1-sided α of 5%
- Clinical and microbiological cure clearly specified.
- Few missing or incomplete data
- p values reported
- Fosfomycin was discontinued among 6 patients because of AEs in the study which could affect the results

Was the precision of the estimate of the intervention or treatment effect reported?

YES

Table 2. Patients Reaching CMC and Reasons for Not Reaching It

	Patients, No./total No. (%)			
	Receiving fosfomycin	Receiving comparator	Risk difference (1-sided 95% CI)[a]	*P* value, 1-sided
CMC at TOC among MITT (measures of success)				
All patients	48/70 (68.6)	57/73 (78.0)	−9.4 (−21.5 to ∞)	.10
Patients with ceftriaxone-susceptible isolates[b]	25/31 (80.6)	27/31 (87.0)	−6.4 (−21.7 to ∞)	.24
Patients with ceftriaxone-resistant isolates[b]	23/39 (59.0)	30/42 (71.4)	−12.4 (−29.8 to ∞)	.12

Table 3. Analysis of Secondary End Points

	Patients, No./total No. (%)[a]			
	Receiving fosfomycin	Receiving comparators	Risk difference (1-sided 95% CI)[b]	*P* value, 1-sided
Measure of success				
Clinical cure at TOC (CEP)				
All patients	59/61 (96.7)	64/71 (90.1)	6.6 (−0.2 to ∞)	.05
Patients with ceftriaxone-susceptible isolates	29/29 (100)	29/31 (93.5)	6.5 (−1.1 to ∞)	.08
Patients with ceftriaxone-resistant isolates	30/32 (93.8)	35/40 (87.5)	6.3 (−5.2 to ∞)	.18

Table 4. Analyses of Clinical and Microbiological Cure Rates at the Test of Cure in Subgroups of Modified Intention-to-Treat Population

	Patients, No./total No. (%)			
Subgroup	Receiving fosfomycin	Receiving comparator	Risk difference (1-sided 95% CI)[a]	*P* value, 1-sided
Age, y				
≤80	34/50 (68.0)	40/53 (75.5)	−7.5 (−22.0 to ∞)	.19
>80	14/20 (70.0)	17/20 (85.0)	−15.0 (−36.7 to ∞)	.12

- 1-sided 95% **CI** were all reported in primary endpoints, secondary endpoints and subgroup analysis.

Do the benefits of the experimental intervention outweigh the harms and costs?

can’ t tell

- The calculated sample size was not reached.
- Fosfomycin did not demonstrate noninferiority
- The potential decreased ecological impact of fosfomycin deserves further study.

Can the results be applied to your local population/in your context?

Characteristic	Patients, No. (%)	
	Receiving fosfomycin (n = 70)	Receiving comparator (n = 73)
Age, median (IQR), y	69 (62-81)	73 (62-84)
Sex		
Women	34 (48.6)	39 (53.4)
Men	36 (51.4)	34 (46.6)
Charlson Comorbidity Index score[b]		
Median (IQR)	1 (0-3)	2 (1-3)
≥3	22 (31.4)	22 (30.1)
Congestive heart failure[c]	8 (11.4)	11 (15.1)
Chronic pulmonary disease[c]	12 (17.1)	11 (15.1)
Diabetes[c]	19 (27.1)	19 (26.0)
Chronic kidney disease[c]	9 (12.9)	14 (19.2)
Cancer[c]	14 (20.0)	16 (21.9)
Full dependence for basic activities	4 (5.7)	6 (8.2)
Urinary catheter at enrollment	21 (30.0)	22 (30.1)
Invasive procedure in the urinary tract in previous month[d]	12 (17.1)	4 (5.5)
Immunosuppressive drugs	7 (10.0)	9 (12.3)

YES

- Similar population, except for races unknown
- Outcomes important to our population

Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?

can’ t tell

- Susceptibility test of fosfomycin isn’ t performed from urine culture in WFH practice; therefore, use of fosfomycin might be a concern.
- Oral fosfomycin is not available in WFH.

Considerations for non-inferiority trials

Was the choice of the NI margin appropriate?

YES

The selection of −7% was decided considering the −10% suggested by the European Medicines Agency for cUTI and given that this study included only bacteremic episodes.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 October 2013
EMA/CHMP/351889/2013
Committee for Human Medicinal Products (CHMP)

Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections.

What type of analysis strategy was employed? ITT or PP?

- MITT was employed, ITT and PP are not
- Only if both the ITT and the PP analyses support noninferiority can it be adequately determined that noninferiority was achieved.

Risk difference or risk ratio

- Risk ratio may be less affected by variability in the event rates in a placebo group that would occur in a future study.

Thanks!

DO YOU HAVE ANY QUESTIONS