BEST PAPER IN INFECTIOUS DISEASE 2022

Infezioni batteriche

Dott. Giacomo Casalini

Dipartimento di Scienze Biomediche e Cliniche Luigi Sacco
Università degli Studi di Milano
U.O. Malattie Infettive III

14 ottobre 2022

Clinical Microbiology and Infection 28 (2022) 550–557

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Seven-versus 14-day course of antibiotics for the treatment of bloodstream infections by Enterobacterales: a randomized, controlled trial

José Molina [1, 2], Enrique Montero-Mateos [3], Julia Praena-Segovia [1, 2], Eva León-Jiménez [4], Clara Natera [5], Luis E. López-Cortés [2, 6], Lucía Valiente [7], Clara M. Rosso-Fernández [2, 8], Marta Herrero [1, 2], Ana I. Aller-García [4], Ángela Cano [5], Belén Gutiérrez-Gutiérrez [2, 6], Ignacio Márquez-Gómez [7], Rocío Álvarez-Marín [1, 2], Carmen Infante [1, 2], Cristina Roca [1, 2], Adoración Valiente-Méndez [2, 6], Jerónimo Pachón [2, 9], José María Reguera [7], Juan Enrique Corzo-Delgado [4], Julián Torre-Cisneros [5, 10], Jesús Rodríguez-Baño [2, 6, 9], José Miguel Cisneros [1, 2, 9, *] on behalf of the SHORTEN trial team[†]

How long do we treat eBSI?

- Guidelines are scarce and, if available, they focus on specific subset of eBSI (i.e., CR-BSI)
- Antibiotic treatment duration has been studied in BSI caused by gram positive bacteria (SAB and Enterococcal bacteremia)
- Two non-inferiority trials comparing 7 vs. 14 days of therapy for gram-negative BSI showed similar outcomes between the two study groups
- More evidence is needed

Yahav D, CID 2019; Von Dach E, JAMA 2020

- **Clinical question.** Is it possible to treat eBSI with a shorter course of antibiotic therapy?

- **Research question.** Will a a 7-day course of antibiotics allow a reduction in patients' *exposure to antibiotics* while achieving clinical *outcomes* similar to those of the traditional 14-day schemes for treating patients with eBSI?

- **Study design.** Open-label, multicenter, randomized, controlled study – SHORTEN trial

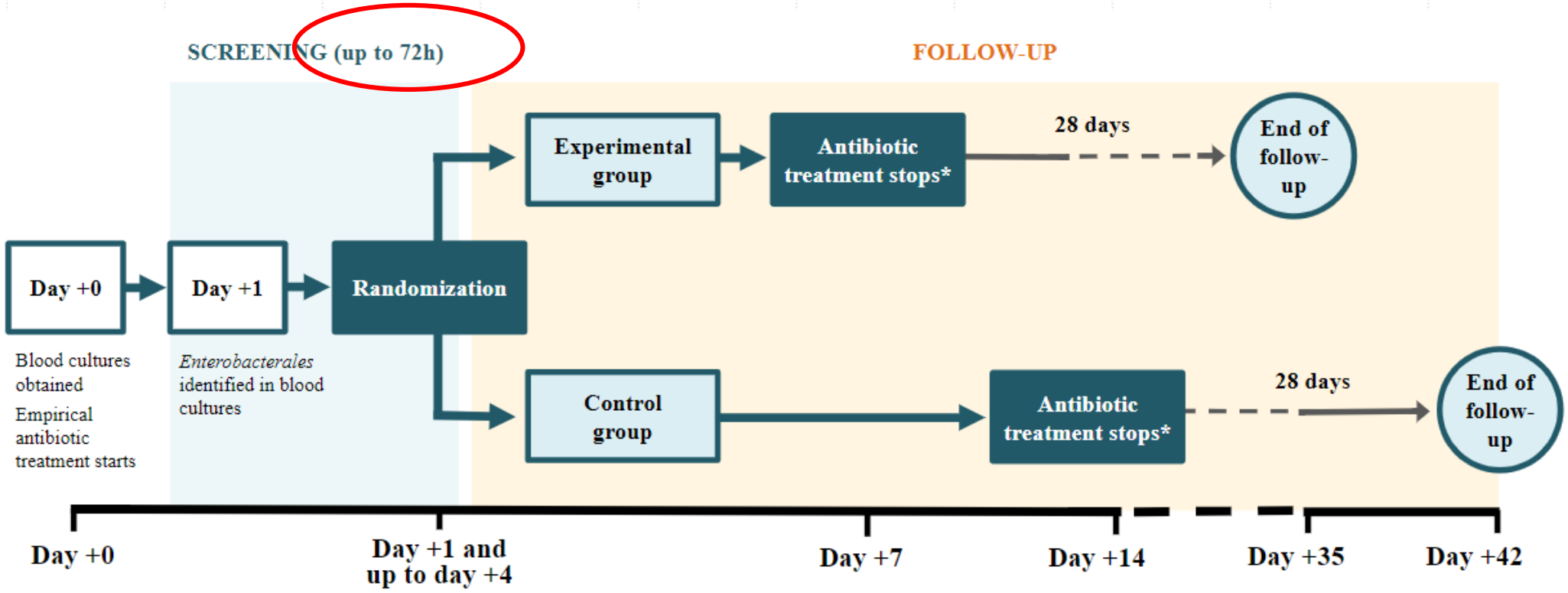
Spain

Population

- Adults with BSI caused by Enterobacterales

- Key exclusion criteria: **uncontrolled and uncontrollable infectious source within 24h**, BSI secondary to infections which require prolonged antibiotic therapy (osteomyelitis, meningitis), carbapenemase-producing Enterobacterales, expected survival < 48h

Intervention - Comparison



* *Antibiotic treatment was stopped at this point if negativization of blood cultures was confirmed and the patient had remained apyretic and without symptoms of infection for at least 72 hours. Antibiotic treatment could be resumed after this point whenever considered necessary by the clinician in charge of the patient if an unfavourable course was observed.*

Outcome

- **Primary outcome** (superiority analysis, 3-days margin): total number of *days of antibiotic treatment* prescribed to the patient for any reason, from the day of the first positive blood sample collection until the end of the follow-up

- **Secondary outcomes** (non-inferiority analysis, 10% margin): clinical/microbiological cure, **mortality**, adverse events

- Desirability of Outcome Ranking (**DOOR**) and Response Adjusted for Duration of Antibiotic Risk (**RADAR**) methods, per protocol, competing clinical outcomes

Table 1
Baseline characteristics of included patients

	Experimental ($n = 119$)	Control ($n = 129$)
Sex female	58/118 (49.2%)	59/129 (45.7%)
Age (median, Q1–Q3)	65 (53–77.5) ($n = 116$)	68 (53–77) ($n = 126$)
Recruiting centre		
HUVR	58/119 (48.7%)	60/129 (46.5)
HUVV	33/119 (27.7%)	35/129 (27.1%)
HURS	13/119 (10.9%)	15/129 (11.6%)
HUVM	13/119 (10.9%)	12/129 (9.3%)
HRM	2/119 (1.7%)	7/129 (5.4%)
Patient care		
Outpatient	25/116 (21.6%)	36/125 (28.8%)
Inpatient	91/116 (78.4%)	90/125 (71.2%)
Charlson index ≥3[a]	54/119 (45.4%)	56/129 (43.4%)
Comorbidities		
Diabetes	45/118 (38.1%)	38/129 (29.5%)
Chronic kidney disease	18/118 (15.3%)	32/129 (24.8%)
Haemodialysis	4/118 (3.4%)	8/129 (6.2%)
Collagenopathies	6/118 (5.1%)	4/129 (3.1%)
Hepatopathy	10/118 (8.5%)	13/129 (10.1%)
Malignancies	32/118 (27.1%)	32/129 (24.8%)
Dementia	3/118 (2.5%)	5/129 (3.9%)
Solid organ transplantation	5/118 (4.2%)	6/129 (4.7%)

Microorganism		
Escherichia coli	76/118 (66.4%)	79/129 (61.2%)
Klebsiella pneumoniae	21/118 (17.6%)	18/129 (14%)
Enterobacter spp.	11/118 (9.2%)	15/129 (11.6%)
Citrobacter spp.	4/118 (3.4%)	3/129 (2.3%)
Serratia marcescens	3/118 (2.5%)	4/129 (3.1%)
Klebsiella oxytoca	2/118 (1.7%)	5/129 (3.9%)
Other	6/118 (5%)	4/129 (3.1%)
Mechanisms of resistance		
ESBL	16/118 (13.6%)	12/129 (9.3%)
AmpC	4/118 (3.4%)	9/129 (7.1%)
BSI acquisition		
Community	49/118 (41.5%)	54/129 (41.9%)
Healthcare-related	33/118 (28.0%)	30/129 (23.3%)
Hospital	36/118 (30.5%)	45/129 (34.9%)
Source of BSI		
Urinary	70/118 (59.3%)	66/129 (51.2%)
Intraabdominal	16/118 (13.6%)	18/129 (14%)
Vascular	14/118 (11.9%)	16/129 (12.4%)
Respiratory	3/118 (2.5%)	12/129 (9.3%)
Unknown	10/118 (8.5%)	11/129 (8.5%)
Other	5/118 (4.2%)	6/129 (4.7%)
Source requiring drainage	30/116 (25.9%)	26/121 (21.5%)
Inadequate empirical treatment	28/117 (23.9%)	25/128 (19.5%)
Presentation sepsis/septic shock	16/108 (13.4%)	17/115 (13.2%)

Table 2
Primary and secondary endpoints, measured at the end of the follow-up (28 days after antibiotic treatment interruption)

	7 days (n = 119)	14 days (n = 129)	Between-group absolute risk difference (1-sided CI 97.5%)
Days of treatment (median, Q1–Q3)			
ITT population[a]	7 (7–14) (n = 110)	14 (14–16) (n = 124)	7 (7–7)
PP population[b]	7 (7–10.5) (n = 93)	14 (14–15) (n = 108)	7 (7–7)
MI analysis	8 (7–16.4)	14 (14–17)	7 (6–7)
Death[a]			
ITT population	3/119 (2.5%)	9/129 (7.0%)	−4.5% (−∞ to 1.2)
PP population	1/93 (1.1%)	6/108 (5.6%)	−4.5% (−∞ to 1.1)
Relapse of the BSI			
ITT population	7/108 (6.5%)	6/121 (5.0%)	1.5% (−∞ to 8.4)
PP population	5/93 (5.4%)	5/107 (4.7%)	0.7% (−∞to 7.8)
MI analysis	9/119 (7.6%)	7/129 (5.4%)	2.1% (−∞ to 8.9)
Relapse of fever[b]			
ITT population	21/110 (19.1%)	23/119 (19.3%)	−0.2% (−∞ to 10.1)
PP population	17/93 (18.3%)	19/106 (17.9%)	0.4% (−∞ to 11.3)
MI analysis	25/119 (21.0%)	26/129 (20.2%)	0.9% (−∞ to 11.0)
Absence of clinical cure			
ITT population	8/110 (7.3%)	12/122 (9.8%)	−2.6% (−∞ to 5.1)
PP population	1/93 (1.1%)	7/108 (6.5%)	−5.4% (−∞ to 0.4)
MI analysis	13/119 (10.9%)	15/129 (11.6%)	−0.7% (−∞ to 7.5)
Superinfections			
ITT population	16/110 (14.5%)	23/121 (19.0%)	−4.5% (−∞ to 5.4)
PP population	11/93 (11.8%)	20/107 (18.7%)	−6.9% (−∞ to 3.4)
MI analysis	19/119 (16.0%)	26/129 (20.2%)	−4.2% (−∞ to 5.5)
Safety			
Adverse events[c]	51/119 (42.9%)	53/129 (41.1%)	1.8% (−∞ to 13.9)
Severe adverse events	15/119 (12.6%)	27/129 (20.9%)	−8.3% (−∞ to 1.1)
Readmissions or prolongation of hospitalization	15/119 (12.6%)	27/129 (20.9%)	−8.3% (−∞ to 1.1)
Drug-related adverse reaction[d]	7/119 (5.9%)	12/129 (9.3%)	−3.4% (−∞ to 3.5)
Acute kidney injury	3/119 (2.5%)	1/129 (0.8%)	1.7% (−∞ to 6.4)
Diarrhoea	2/119 (1.7%)	3/129 (2.3%)	−0.6% (−∞ to 3.9)
Rash	1/119 (0.8%)	4/129 (3.1%)	−2.3% (−∞ to 2.0)

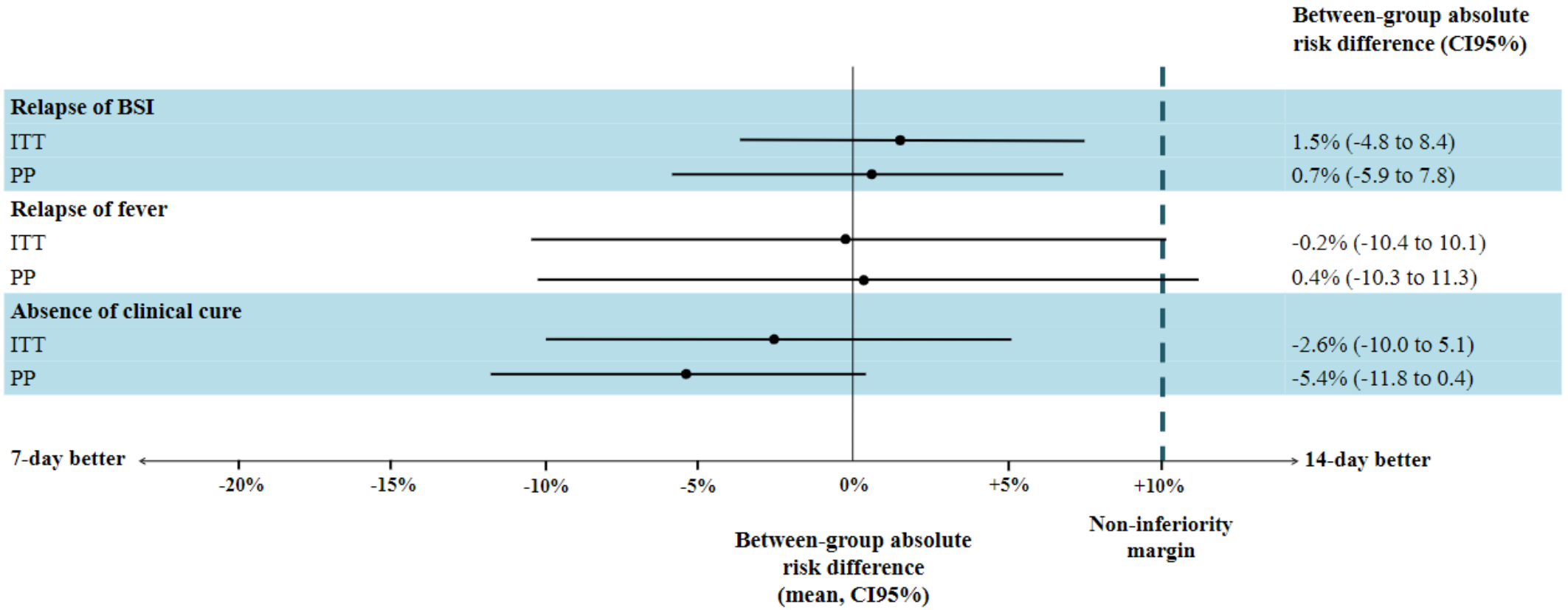
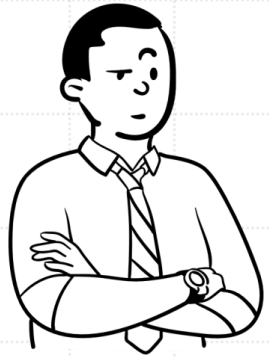


Fig. 3. Non-inferiority analysis for clinical outcome measures.

Patients receiving 7-day courses had 77.7% higher probabilities of achieving better results compared to those receiving 14-day courses, considering altogether clinical cure, adverse events, mortality and antibiotic exposure (DOOR/RADAR)

Primary outcome and intervention

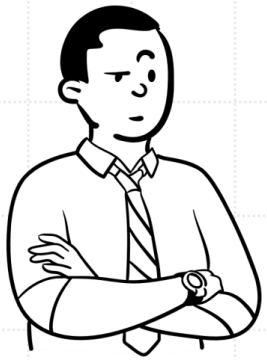


- Primary outcome results are driven *by the intervention*
- Sample size calculation
- **10% non-inferiority margin and mortality**
- Previously published trial use different composite primary outcomes with clinical variables

Sadana D, CMI 2022.

Strenghts and pittfalls

- This trial demonstrate a good *adherence* to the intervention
- A shorter course of therapy in eBSI is however feasible (provided that source control is adequate) and desirable in terms of AMR/antibiotic exposure
- Early randomization
- However, this trial cannot provide definite evidence for clinical efficacy and safety of a 7-day course of antibiotic therapy in eBSI
- More evidence is needed (BALANCE)



In conclusion, this trial points to a 7-day course of antibiotics as the preferential treatment for eBSI, as long as the source is properly controlled. The potential impact of implementing this recommendation in clinical practice would be significant in the fight against bacterial resistance. A possible need for retreating a limited number of patients after short courses without clinical impact on the final outcomes cannot be discarded by this trial, but seemed to be overcome by the benefits of shortening antibiotic treatments.

Original Investigation

October 4, 2022

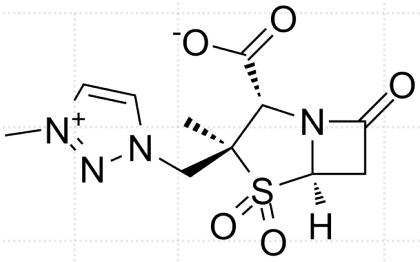
Research

JAMA | Original Investigation

Effect of Cefepime/Enmetazobactam vs Piperacillin/Tazobactam on Clinical Cure and Microbiological Eradication in Patients With Complicated Urinary Tract Infection or Acute Pyelonephritis

A Randomized Clinical Trial

Keith S. Kaye, MD; Adam Belley, PhD; Philip Barth, PhD; Omar Lahlou, PharmD; Philipp Knechtle, PhD; Paola Motta, PhD; Patrick Velicitat, MD



ESBL	KPC	OXA-48	MBL

Cefepime/enmetazobactam

- Enmetazobactam is a novel β-lactamase inhibitor closely related to tazobactam
- It restores the activity of cefepime againt β-lactamase-producing gram negative pathogens

Antibacterial agent	Cumulative % of isolates at MIC (µg/mL) of: [a]																MIC range (µg/mL)
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	>256	
Ceftazidime			2.9	14.7	45.9	68.3	76.8	79.9	81.4	**82.9**	84.6	87.7	91.2	94.7	100.0			≤0.03 to >64
Ceftriaxone		16.7	41.5	60.9	70.6	76.3	78.7	**79.8**	80.6	81.3	81.9	83.0	84.5	86.3	100.0			≤0.015 to >64
Cefepime [b]	0.5	6.1	43.3	67.0	75.2	80.2	82.8	85.0	**87.0**	88.6	**89.9**	91.0	92.2	93.6	100.0			≤0.008 to >64
Aztreonam			24.5	51.4	69.4	76.8	79.2	80.5	81.6	**82.8**	84.5	86.7	90.5	100.0				≤0.03 to >32
Meropenem		25.1	79.7	93.4	96.5	97.0	97.3	**97.6**	97.9	98.3	98.5	98.8	99.1	100.0				≤0.015 to >32
Ampicillin/sulbactam								2.9	12.3	31.7	**46.4**	62.7	77.9	100.0				≤1 to >32
Amoxicillin/clavulanate								2.7	14.4	36.8	**49.2**	61.8	72.9	100.0				≤1 to >32
Piperacillin/tazobactam						3.4	7.5	32.8	67.7	78.5	83.6	**87.4**	90.4	92.7	94.7	96.0	100.0	≤0.25 to >256
Ceftolozane/tazobactam			0.2	3.6	43.2	73.2	85.5	90.5	**92.7**	94.8	96.1	97.3	97.9	98.5	100.0			≤0.03 to >64
Ceftazidime/avibactam			12.6	44.3	76.1	92.0	97.0	98.5	99.2	99.5	**99.6**	99.6	99.6	99.6	100.0			≤0.03 to >64
Meropenem/vaborbactam[c]	0.7	35.1	89.0	96.4	97.7	98.0	98.5	99.0	99.3	**99.5**	99.6	99.7	100.0					≤0.004 to >16
Cefepime/enmetazobactam[d]	0.5	8.0	53.5	79.8	89.0	94.1	96.5	97.7	***98.3***	98.6	***98.8***	98.9	99.1	99.3	100.0			≤0.008 to >64

Belley A, J Glob Antimicrob Resist 2021; Vázquez-Ucha JC, Antimicrob Agents Chemother 2022.

- **Clinical question.** Can we use cefepime/enmetazobactam for treating patients with cUTI or acute pyelonephritis?

- **Research question.** Is cefepime/enmetazobactam noninferior to piperacillin/tazobactam with respect to **efficacy** in adult patients with cUTI or acute pyelonephritis? What about the **safety** profile?

- **Study design.** Phase 3, Randomized, Double-Blind, Active-controlled, Multi-Center Study – ALLIUM Trial

East-Europe, Spain, US, South-America and South-Africa

Population

Adults with:

- Urine culture collection
- **pyuria** (urine WBC > 10/mm3 or positive leukocyte esterase) AND
- clinical signs of **cUTI or AP**

Among the numerous exclusion criteria, we must mention:

- **In the opinion of the Investigator, the patient is considered unlikely to survive the approximately 6-week study period**
- **eGFR < 30 mL/min/1.73 m2**
- **Sepsis**

cUTI

- Dysuria, increased urinary frequency or urinary urgency
- Lower abdominal or pelvic pain
- Nausea or vomiting
- Suprapubic tenderness
- Fever

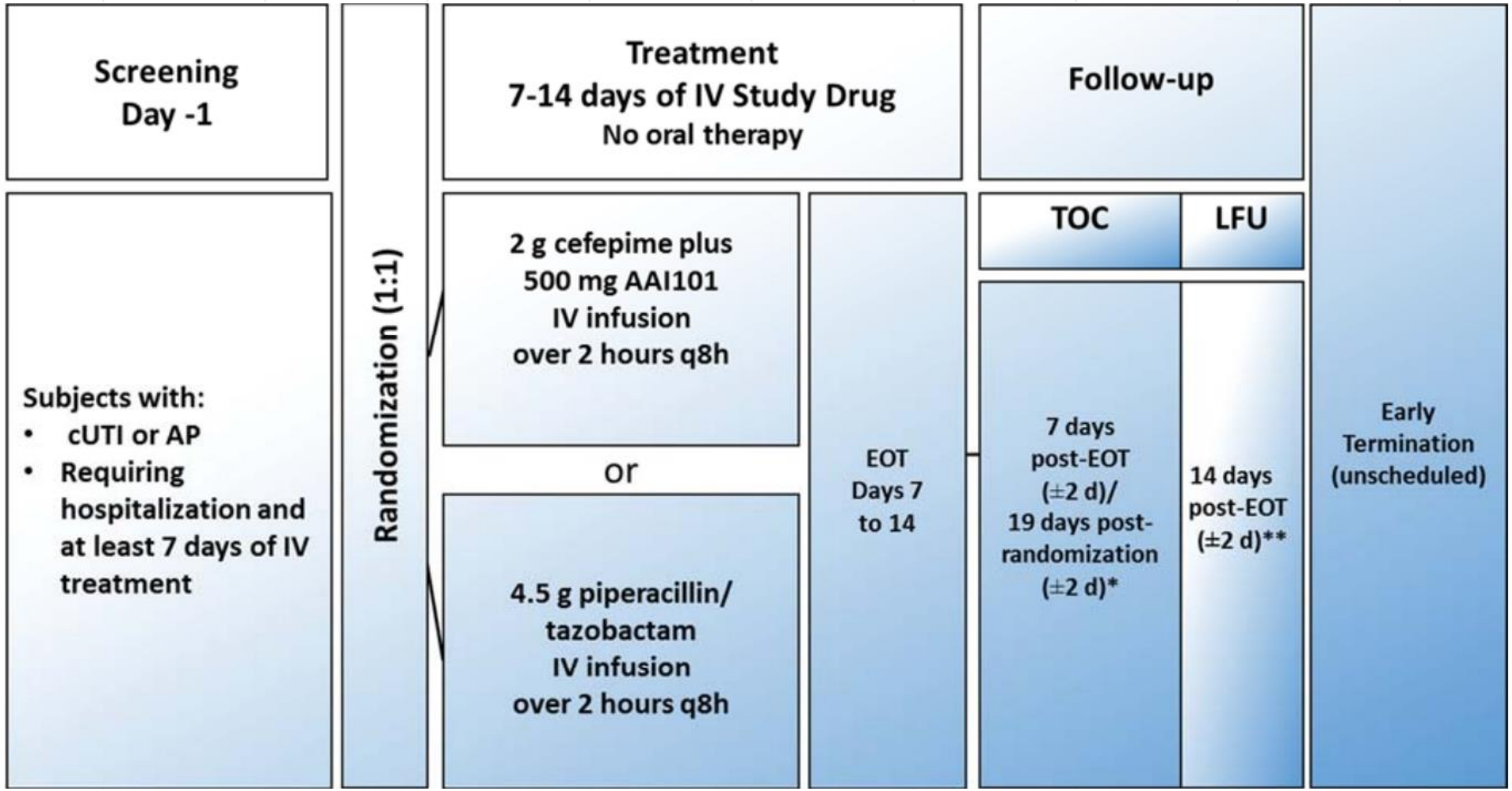
AP

- Dysuria, increased urinary frequency or urinary urgency
- Fever
- Flank pain
- Nausea or vomiting
- Costo-vertebral angle tenderness

Complicating factors

- Male with urinary retention
- Obstructive uropathy
- Creatinine > 1.4 mg/dL, BUN > 20 mg/dL or urea > 42.8 mg/dL
- Urinary catheter
- Functional/anatomical abnormalities with voiding disturbances

Intervention - Comparison



Outcomes

- **Primary outcome.** *Composite*: clinical cure + microbiological eradication at day 14

- **Secondary outcomes.** Clinical cure and microbiological eradication at day 3-EOT-21 etc…

Table 1. Demographic and Baseline Characteristics of Patients Who Received at Least 1 Dose of Study Drug

	No. (%)	
	Cefepime/ enmetazobactam (n = 516)	Piperacillin/ tazobactam (n = 518)
Age, mean (SD), y	55.0 (19.0)	54.3 (19.1)
Age group, y		
<65	312 (60.5)	324 (62.5)
65 to <75	126 (24.4)	118 (22.8)
≥75	78 (15.1)	76 (14.7)
Presence of concurrent bacteremia at baseline	41 (7.9)	30 (5.8)
Diabetes at baseline	79 (15.3)	78 (15.1)
Enterobacterales baseline pathogen, extended-spectrum β-lactamase producing	98 (19.0)	89 (17.2)

Microbiology: *E. coli* 76.4%, *K. pneumoniae* 9.7%, *P. mirabilis* 5.6%, *P. aeruginosa* 3.5%

Source control: ≈ 20% of patients with removable source of infection, 67.5% vs. 72% rate of source control

Microbiological-Modified ITT Population: at least one dose of study drug + gram negative pathogen in urine and/or blood NON resistant to study drugs

Table 2. Primary Outcome, Clinical Cure, and Microbial Eradication in the Primary Analysis Set

Response at visit	No. (%) Cefepime/ enmetazobactam (n = 345)	No. (%) Piperacillin/ tazobactam (n = 333)	Treatment difference, % (95% CI)[a]
Day 14[b]			
Overall success[c]	273 (79.1)	196 (58.9)	21.2 (14.3 to 27.9)
Clinical cure	319 (92.5)	296 (88.9)	3.5 (−1.0 to 8.0)
Microbiological eradication	286 (82.9)	216 (64.9)	19.0 (12.3 to 25.4)
Day 3 of treatment			
Overall success	318 (92.2)	293 (88.0)	4.1 (−0.6 to 8.9)
Clinical cure	18 (5.2)	16 (4.8)	0.5 (−3.1 to 4.0)
Improvement[d]	317 (91.9)	302 (90.7)	Not determined
Microbiological eradication	323 (93.6)	299 (89.8)	3.8 (−0.6 to 8.3)
End of treatment			
Overall success	318 (92.2)	311 (93.4)	−1.3 (−5.3 to 2.9)
Clinical cure	323 (93.6)	315 (94.6)	−1.1 (−4.8 to 2.7)
Microbiological eradication	332 (96.2)	322 (96.7)	−0.7 (−3.7 to 2.5)
Day 21[e]			
Overall success	236 (68.4)	196 (58.9)	10.7 (3.4 to 17.8)
Clinical cure	299 (86.7)	279 (83.8)	2.8 (−2.7 to 8.3)
Microbiological eradication	258 (74.8)	221 (66.4)	9.5 (2.6 to 16.3)

Microbiological-Modified ITT Population: at least one dose of study drug + gram negative pathogen in urine and/or blood NON resistant to study drugs

Table 2. Primary Outcome, Clinical Cure, and Microbial Eradication in the Primary Analysis Set

Response at visit	No. (%) Cefepime/enmetazobactam (n = 345)	No. (%) Piperacillin/tazobactam (n = 333)	Treatment difference, % (95% CI)[a]
Day 14[b]			
Overall success[c]	273 (79.1)	196 (58.9)	21.2 (14.3 to 27.9)
Clinical cure	319 (92.5)	296 (88.9)	3.5 (−1.0 to 8.0)
Microbiological eradication	286 (82.9)	216 (64.9)	19.0 (12.3 to 25.4)
Day 3 of treatment			
Overall success			.6 to 8.9)
Clinical cure			.1 to 4.0)
Improvement[d]			termined
Microbiological eradication			.6 to 8.3)
End of treatment			
Overall success	318 (92.2)	311 (93.4)	−1.3 (−5.3 to 2.9)
Clinical cure	323 (93.6)	315 (94.6)	−1.1 (−4.8 to 2.7)
Microbiological eradication	332 (96.2)	322 (96.7)	−0.7 (−3.7 to 2.5)
Day 21[e]			
Overall success	236 (68.4)	196 (58.9)	10.7 (3.4 to 17.8)
Clinical cure	299 (86.7)	279 (83.8)	2.8 (−2.7 to 8.3)
Microbiological eradication	258 (74.8)	221 (66.4)	9.5 (2.6 to 16.3)

In patients with baseline ESBL pathogens, cefepime/enmetazobactam was noninferior to piperacillin/tazobactam
(treatment difference 30.2% [95% CI, 13.4% to 45.1%])

Safety

Table 3. Treatment-Emergent Adverse Events in Patients Who Received at Least 1 Dose of Study Drug

System organ class preferred term[a]	No. (%)	
	Cefepime/ enmetazobactam (n = 516)	Piperacillin/ tazobactam (n = 518)
Patients with any treatment-emergent adverse event[b]	258 (50.0)	228 (44.0)
Investigations	140 (27.1)	135 (26.1)
Alanine aminotransferase increased	59 (11.4)	60 (11.6)
Aspartate aminotransferase increased	47 (9.1)	46 (8.9)
Blood bilirubin increased	30 (5.8)	20 (3.9)
Transaminases increased	13 (2.5)	19 (3.7)
Gastrointestinal disorders	46 (8.9)	49 (9.5)
Diarrhea	21 (4.1)	26 (5.0)
Infections and infestations	44 (8.5)	57 (11.0)
Urinary tract infection	7 (1.4)	11 (2.1)
Vascular disorders	30 (5.8)	12 (2.3)
Phlebitis	14 (2.7)	1 (0.2)
Nervous system disorders	29 (5.6)	16 (3.1)
Headache	25 (4.8)	12 (2.3)
Kidney and urinary disorders	22 (4.3)	19 (3.7)

Now we can answer our questions

- **Research question.** Is cefepime/enmetazobactam noninferior to piperacillin/tazobactam with respect to **efficacy** in adult patients with cUTI or acute pyelonephritis? YES. What about the **safety** profile? IT'S SAFE

- **Clinical question.** Can we use cefepime/enmetazobactam for treating patients with cUTI or acute pyelonephritis? IT CAN BE AN OPTION

Now we can answer our questions

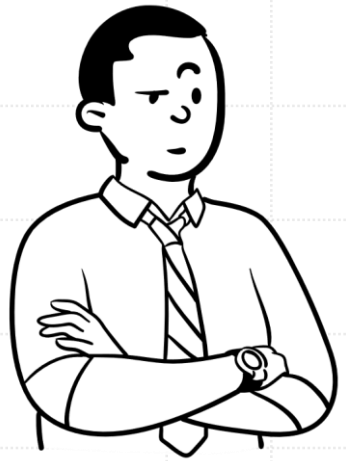
- **Research question.** Is cefepime/enmetazobactam noninferior to piperacillin/tazobactam with respect to **efficacy** in adult patients with cUTI or acute pyelonephritis? YES. What about the **safety** profile? IT'S SAFE

- **Clinical question.** Can we use cefepime/enmetazobactam for treating patients with cUTI or acute pyelonephritis? IT CAN BE AN OPTION

But, do you think that's enough?

- **Study design.** cUTI definition
- **Population.** ≈ 60% of patients were less than 65 years old and had CCI < 3.
- **Microbiology**. Almost 80% of patients did not have an ESBL-Eb. Over treatment? Appropriate empiric therapy in this setting?
- **Intervention**. TZP dosing q8h, 2h infusion
- **Outcome**. Superiority is mainly driven by microbiological eradication. But, it is usually advisable to obtain follow-up urine cultures in cUTI or AP?

logical cure. Additionally, cefepime/enmetazobactam was superior to piperacillin/tazobactam for the primary outcome. These findings suggest that cefepime/enmetazobactam may be an appropriate empirical therapy for suspected gram-negative complicated UTI.

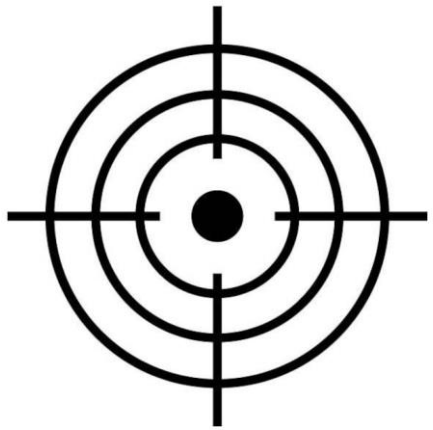


Results from a noninferiority trial can be extrapolated to demonstrate superiority?

Future directions

- Performance in bloodstream infections
- Head to head with carbapenems in ESBL infections
- Empirical treatment in setting with high prevalence of MDR bugs

Position in the clinical setting



Grazie per l’attenzione