Best papers in Infectious Diseases 2024

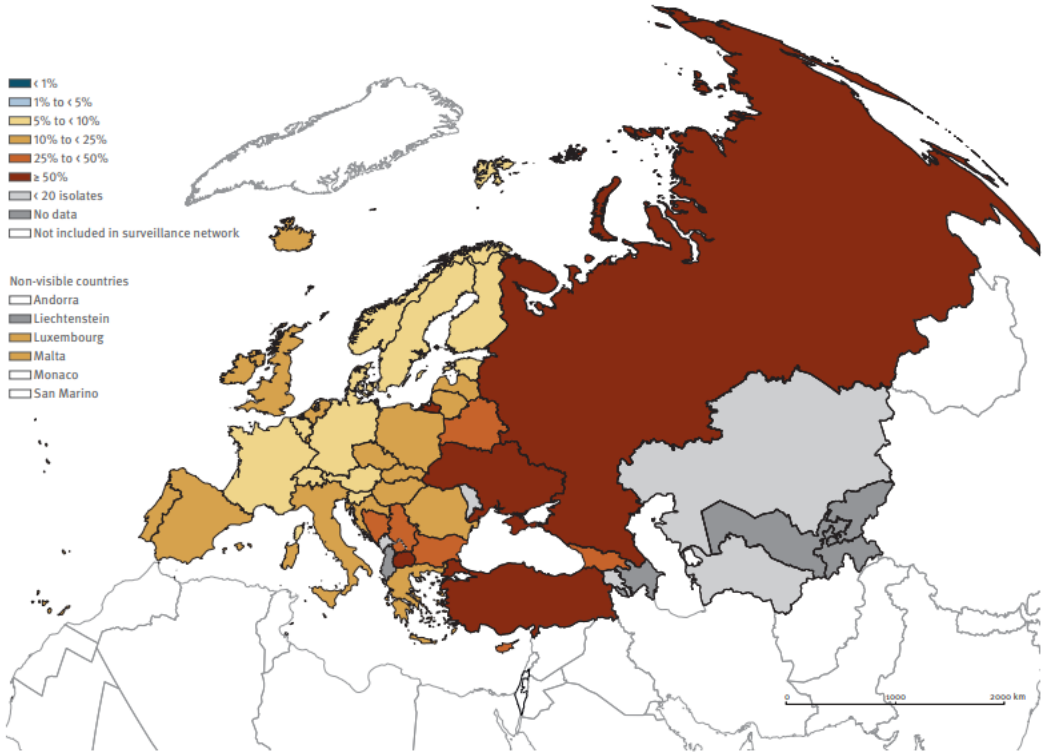
Infezioni da *Enterobacterales* multiresistenti

Mara Tomasello
Resident in Infectious and Tropical Diseases

UNIVERSITÀ DEGLI STUDI DI MILANO
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

Antimicrobial resistance (AMR) is the ability of a microorganism to resist the action of one or more antimicrobial agents. Acquired resistance in bacteria is caused by mutations in chromosomal genes or acquisition of exogenous resistance genes carried by mobile genetic elements that can spread horizontally between bacteria. This is particularly problematic as it may severely limit the treatment alternatives available for the infection.

Fig. 2 ***Escherichia coli.*** **Percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), by country, WHO European Region, 2021**



Note: Data for Serbia and Kosovo (all references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999)) were combined for this map. Data for the United Kingdom for 2021 includes England, Scotland and Northern Ireland.
Data sources: 2021 data from the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2021. All rights reserved) and 2021 data from the European Antimicrobial Resistance Surveillance Network (EARS–Net, ©ECDC 2021).
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Fig. 3 ***Escherichia coli.*** **Percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country, WHO European Region, 2021**

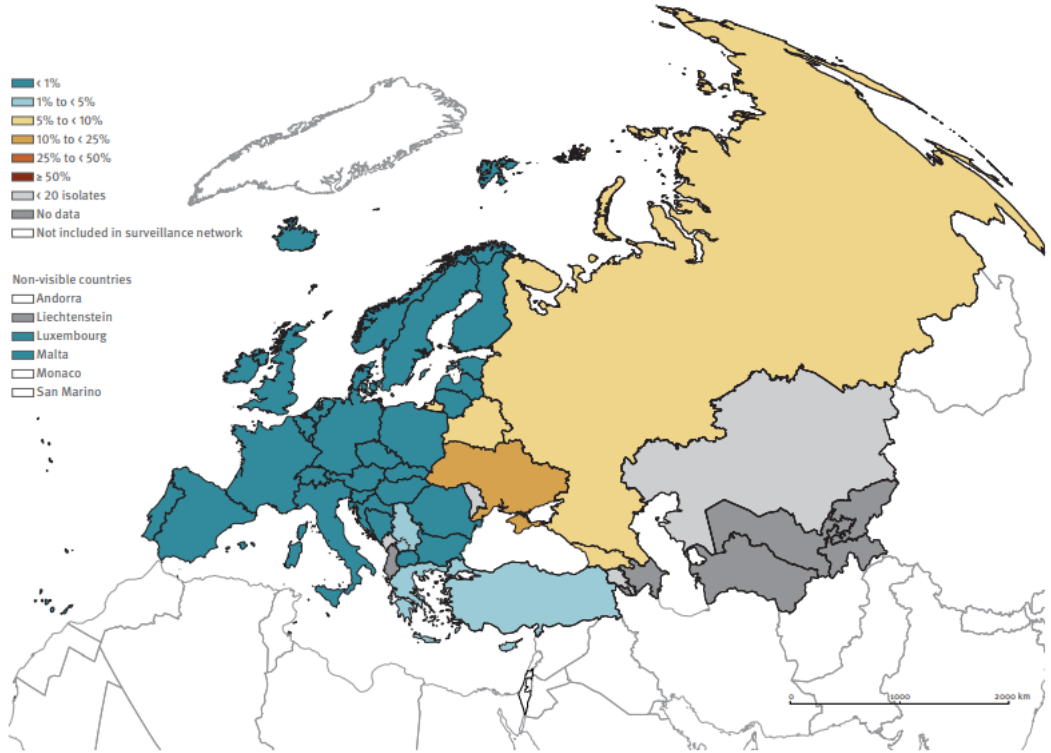

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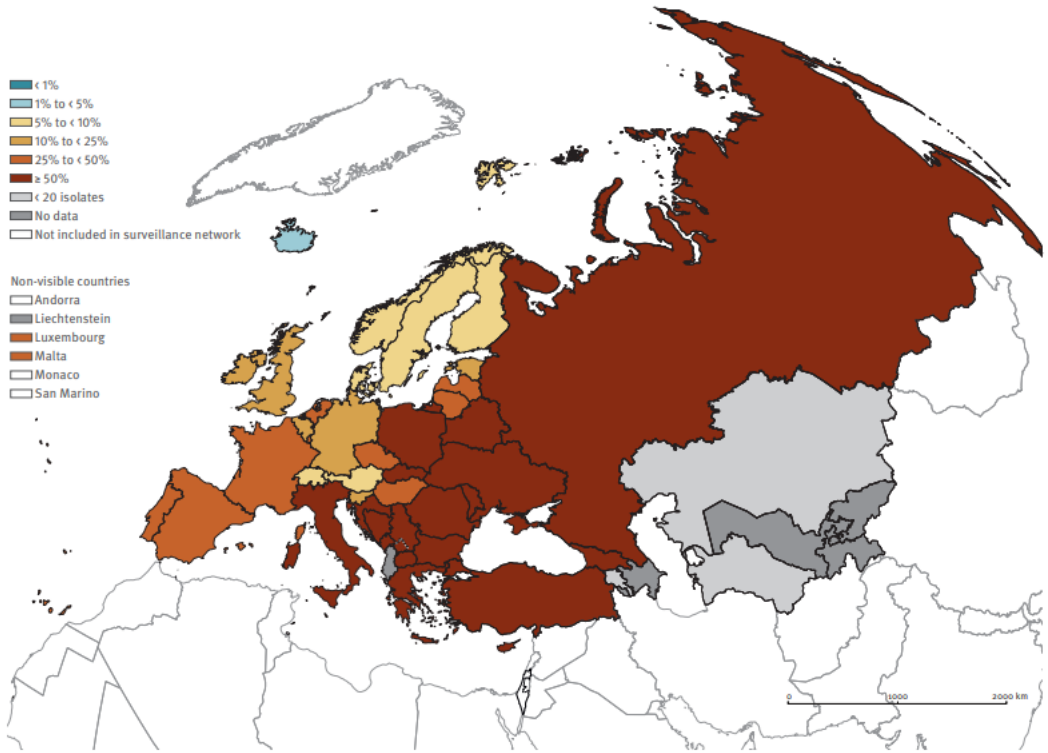
Fig. 4 ***Klebsiella pneumoniae.*** **Percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), by country, WHO European Region, 2021**



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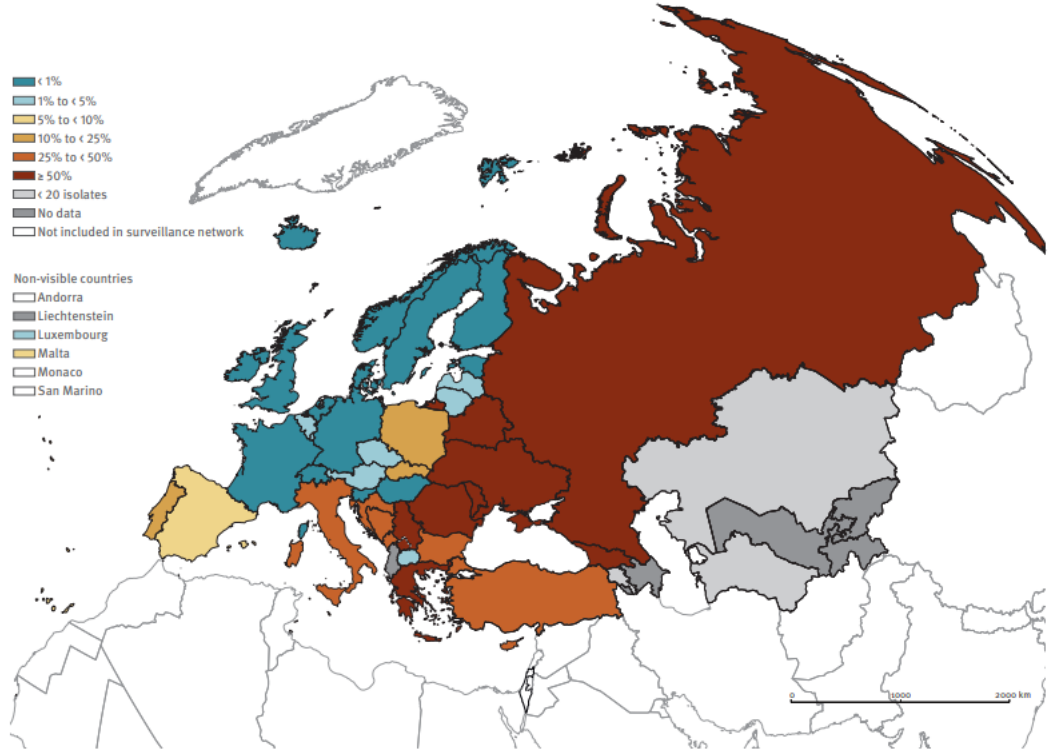
Map production: ©WHO.

Fig. 5 ***Klebsiella pneumoniae.*** **Percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country, WHO European Region, 2021**



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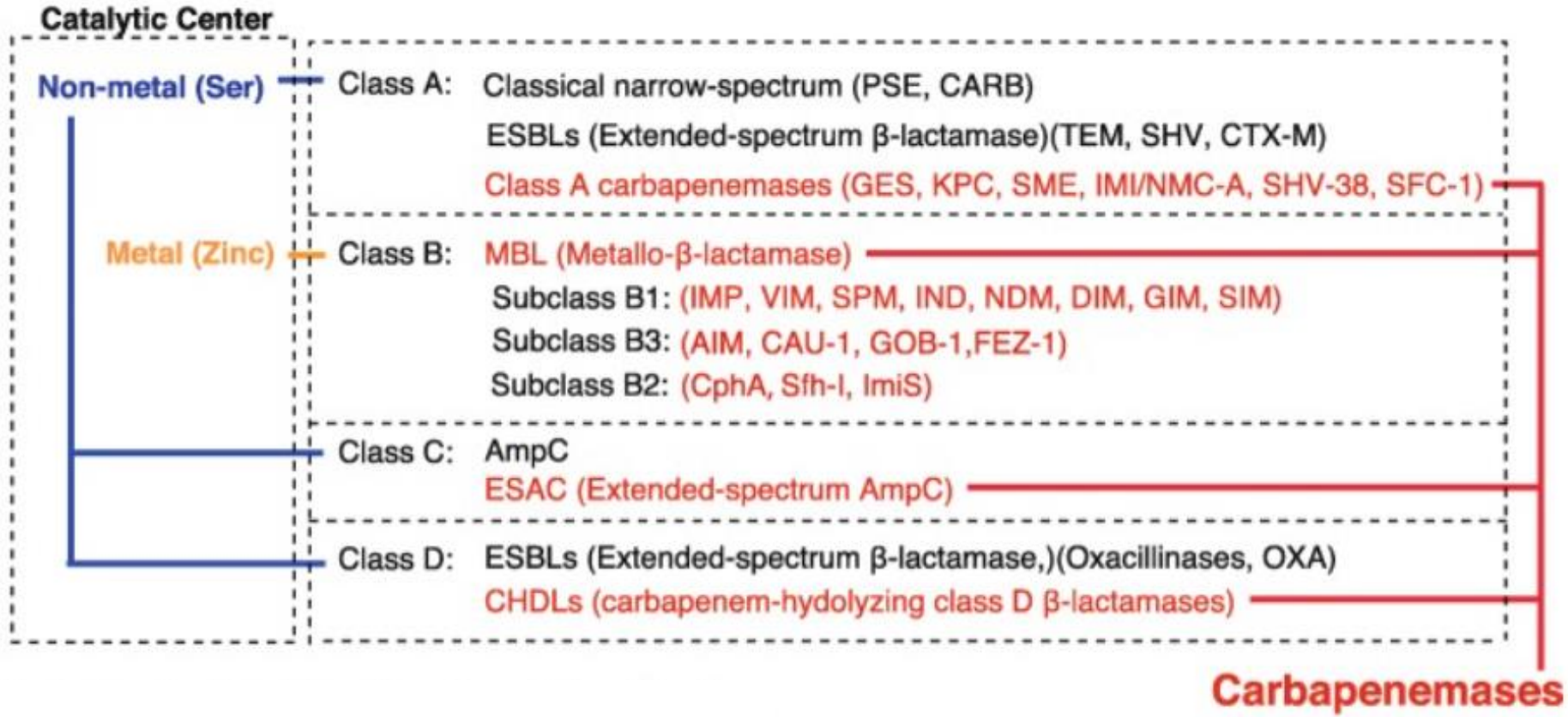
Map production: ©WHO.

Total number of invasive isolates tested (n) and percentage of isolates with resistance phenotype (%)[a], by bacterial species and antimicrobial group/agent, 2021 EU/EEA range, population-weighted mean and trend, Italy, 2017–2021

Bacterial species	Antimicrobial group/agent	2017		2018		2019		2020		2021		2021 EU/EEA range and population-weighted mean[b]	Trend 2017–2021[c]
		n	%	n	%	n	%	n	%	n	%		
E. coli	Aminopenicillin (amoxicillin/ampicillin) resistance	4078	67.1	7533	64.5	4457	68.1	4214	64.5	5518	58.9	53.1 (31.7–70.2)	↓
	Third-generation cephalosporin (cefotaxime/ceftriaxone/ceftazidime) resistance	7077	29.5	16253	28.7	18409	30.9	18750	26.4	21153	23.8	13.8 (5.5–37.3)	↓*
	Carbapenem (imipenem/meropenem) resistance	7280	0.3	15452	0.4	17086	0.4	18001	0.5	19905	0.4	0.2 (0.0–1.1)	–
	Fluoroquinolone (ciprofloxacin/levofloxacin/ofloxacin) resistance	6945	44.9	16043	41.7	18417	40.6	18840	37.6	20989	32.5	21.9 (9.6–51.6)	↓*
	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance[d]	7134	18.4	15901	16.0	18382	15.9	17994	14.9	20614	13.2	9.6 (4.1–27.0)	↓*
	Combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides[d]	6454	13.7	15622	11.4	17961	11.6	17593	9.8	20392	8.3	5.1 (1.2–14.8)	↓*
K. pneumoniae	Third-generation cephalosporin (cefotaxime/ceftriaxone/ceftazidime) resistance	2546	54.6	5832	53.6	7699	57.6	8400	54.3	9094	53.3	34.3 (3.4–81.4)	–
	Carbapenem (imipenem/meropenem) resistance	2633	29.5	5660	26.8	7325	28.5	8293	29.5	8760	26.7	11.7 (0.0–73.7)	–
	Fluoroquinolone (ciprofloxacin/levofloxacin/ofloxacin) resistance	2562	55.7	5752	52.7	7692	54.7	8486	52.4	9028	50.0	33.6 (0.0–80.0)	↓*
	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance[d]	2571	34.5	5693	27.0	7682	32.6	8084	31.6	8821	30.1	23.7 (0.0–69.1)	–
	Combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides[d]	2352	31.6	5587	24.8	7560	30.3	7842	29.5	8712	27.5	21.2 (0.0–67.4)	–
P. aeruginosa	Piperacillin-tazobactam resistance	1309	23.2	2938	23.9	3768	24.1	4537	24.2	4530	23.4	18.7 (0.0–47.2)	–
	Ceftazidime resistance	1332	20.0	2974	19.9	3798	19.0	4473	19.3	4560	19.1	15.8 (2.3–46.0)	–
	Carbapenem (imipenem/meropenem) resistance	1433	19.6	3014	15.8	3794	13.7	4615	15.9	4708	16.4	18.1 (3.5–45.9)	–
	Fluoroquinolone (ciprofloxacin/levofloxacin) resistance	1390	25.1	2994	22.9	3875	21.7	4599	19.6	4665	18.6	18.7 (3.3–48.0)	↓*
	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance[e]	1428	18.0	2983	12.8	3859	11.4	ND	ND	ND	ND	8.9 (0.0–41.7)	NA
	Combined resistance to ≥ 3 antimicrobial groups (among piperacillin-tazobactam, ceftazidime, carbapenems, fluoroquinolones and aminoglycosides)[e]	1182	15.9	2849	14.5	3581	13.0	ND	ND	ND	ND	12.6 (0.0–42.1)	NA
Acinetobacter spp.	Carbapenem (imipenem/meropenem) resistance	868	78.7	1383	79.2	1588	79.3	2552	80.8	2734	86.9	39.9 (0.0–99.5)	↑*
	Fluoroquinolone (ciprofloxacin/levofloxacin) resistance	804	79.2	1368	81.1	1636	82.5	2522	83.4	2729	88.1	43.0 (1.5–99.8)	↑*
	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance[d]	836	76.1	1369	77.0	1637	78.8	2496	80.2	2697	85.1	39.6 (2.1–98.8)	↑*
	Combined resistance to carbapenems, fluoroquinolones and aminoglycosides[d]	763	72.6	1351	75.7	1569	76.6	2451	78.7	2649	84.7	36.8 (0.0–98.5)	↑*
S. aureus	MRSA[f]	3591	33.9	8263	34.0	9681	34.3	10923	33.5	11344	30.0	15.8 (0.9–42.9)	↓*
S. pneumoniae	Penicillin non-wild-type[g]	522	10.5	928	9.2	1017	11.9	516	13.4	481	10.0	16.3 (3.6–35.7)	–
	Macrolide (azithromycin/clarithromycin/erythromycin) resistance	599	22.7	1095	20.3	1298	22.3	639	24.1	630	24.0	18.3 (0.0–36.0)	–
	Combined penicillin non-wild-type and resistance to macrolides[g]	474	5.3	879	4.7	989	6.7	491	7.7	463	6.5	9.9 (0.0–28.0)	–
E. faecalis	High-level gentamicin resistance	1630	45.9	2927	39.9	2395	34.9	3028	37.4	3018	36.3	29.0 (6.7–55.2)	↓*
E. faecium	Vancomycin resistance	1049	14.6	2273	18.9	2839	21.3	4166	23.6	4736	28.2	17.2 (0.0–66.4)	↑*

Ambler molecular classification



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cefepime–Taniborbactam in Complicated Urinary Tract Infection

Florian M. Wagenlehner, M.D., Leanne B. Gasink, M.D., Paul C. McGovern, M.D., Greg Moeck, Ph.D., Patrick McLeroth, M.D., MaryBeth Dorr, Ph.D., Aaron Dane, M.Sc., and Tim Henkel, M.D., Ph.D., for the CERTAIN-1 Study Team*

Contents lists available at ScienceDirect

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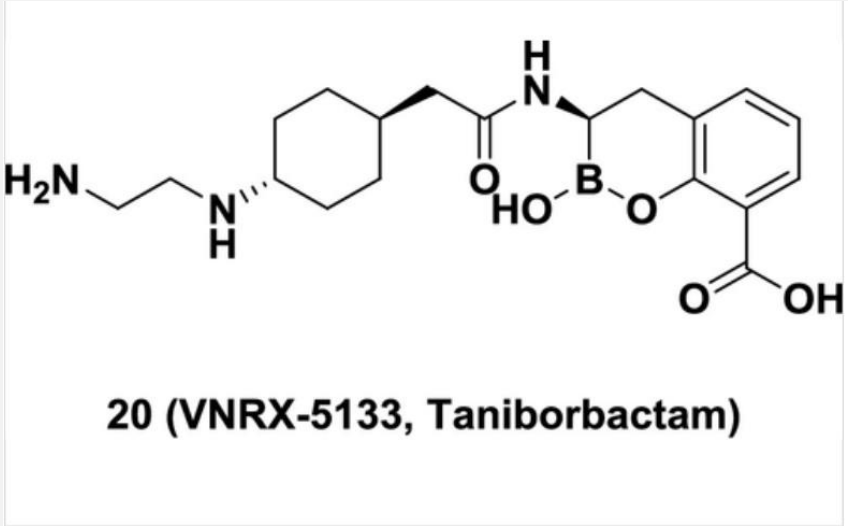
journal homepage: www.elsevier.com/locate/ijantimicag

Treatment of infections caused by multidrug-resistant Gram-negative bacilli: A practical approach by the Italian (SIMIT) and French (SPILF) Societies of Infectious Diseases

Marianna Meschiari[a], Antoine Asquier-Khati[b], Giusy Tiseo[c], David Luque-Paz[d], Rita Murri[e], David Boutoille[b], Marco Falcone[c], Cristina Mussini[a], Pierre Tattevin[d,*], on behalf of the Italian Society of Infectious and Tropical Diseases (SIMIT), and the French Society of Infectious Diseases (SPILF)

CEFEPIME-TANIBORBACTAM

- Cefepime is a broad spectrum fourth generation cephalosporin. Resistance to cefepime has increased with the spread of extended spectrum beta-lactamase and carbapenemase enzymes
- Taniborbactam is a bicyclic boronate beta-lactamase inhibitor with potent selective direct inhibitory activity against Ambler class A, B, C and D enzymes, including prevalent serine and metallo-beta-lactamase
- The cefepime– taniborbactam combination is active *in vitro* against most isolates of carbapenem-resistant Enterobacterales species, multidrug-resistant Pseudomonas aeruginosa, and Enterobacterales species and P. aeruginosa organisms that are resistant to both ceftolozane–tazobactam and ceftazidime– avibactam
- Cefepime–taniborbactam has shown *in vivo* efficacy against cefepime- and carbapenemresistant Enterobacterales species and against P. aeruginosa



20 (VNRX-5133, Taniborbactam)

CERTAIN-1 TRIAL – METHODS

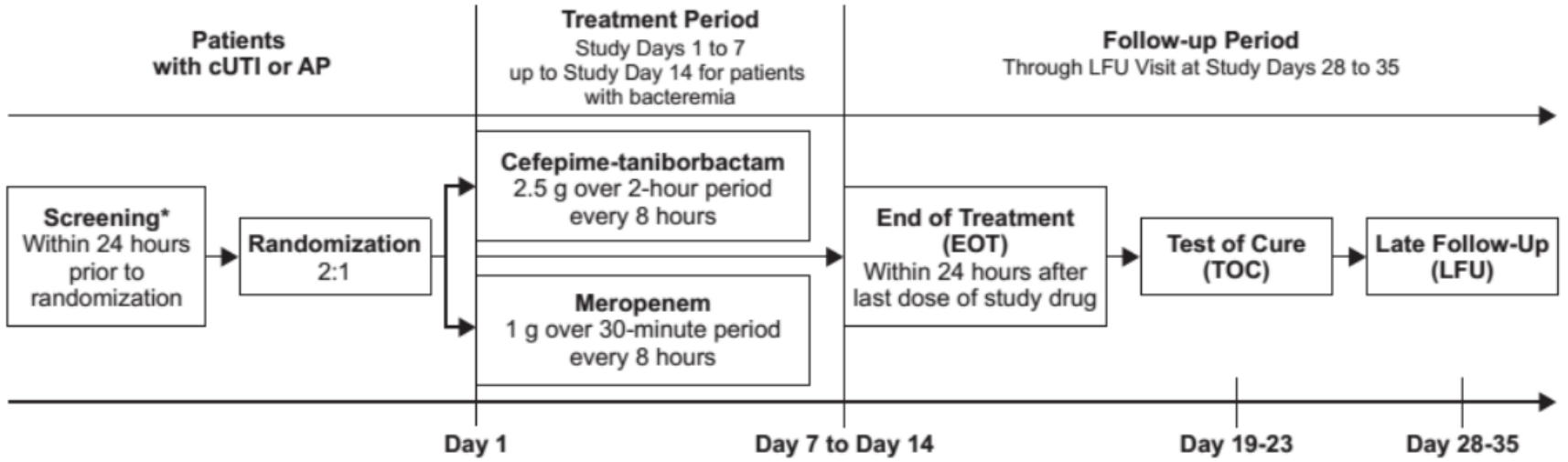
- Double-blind, double-dummy, randomized, active-controlled trial at 68 sites in 15 countries.

INCLUSION CRITERIA	EXCLUSION CRITERIA
Signed informed consent	Received effective antibacterial drug therapy for cUTI for a continuous duration of more than 24 hours during the previous 72 hours prior to randomization
≥ 18 years	Infection with a meropenem resistant pathogen
Diagnosis of cUTI (pyuria, at least one systemic sign and at least one local sign or symptom; at least one complicating factor eg urinary tract functional or anatomic abnormality)	Warranted nontrial systemic antibiotic
Diagnosis of acute pyelonephritis (pyuria, at least one systemic sign or symptom, and flank pain or costovertebral angle tenderness)	eGFR <30 mL per minute per 1.73 m^2 of body surface area
	Prostatitis, perinephric or renal abscess
	Renal transplantation, hemodilaysis or peritoneal dialysis
	Severe hepatic impairment
	Hypersensivity to any beta-lactam antibiotic

CERTAIN-1 TRIAL – METHODS

Primary objective: to evaluate the efficacy of cefepime–taniborbactam as compared with meropenem in patients with complicated UTI, including acute pyelonephritis

Figure S1. Overview of Study Design

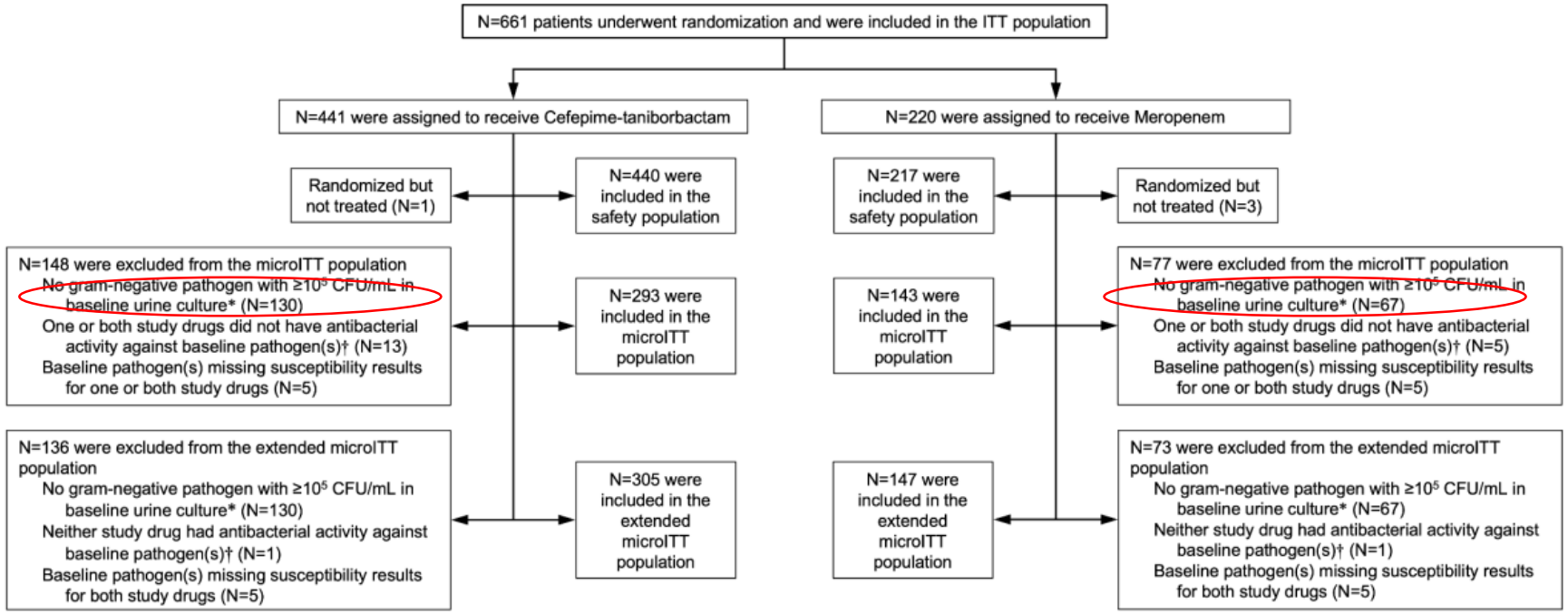


AP = acute pyelonephritis; cUTI = complicated urinary tract infection; EOT = end of treatment; TOC = test of cure; LFU = late follow-up.
*Samples taken for determination of eligibility in primary analysis population (microbiologic intent-to-treat [microITT]).

!!! ORAL STEP DOWN WAS NOT PERMITTED

CERTAIN-1 TRIAL – METHODS

Figure S2. Patient Disposition – CONSORT Diagram



CFU = colony forming unit; ITT = intent-to-treat population; microITT = microbiologic intent-to-treat population; N = number of patients.
A patient may have more than one reason for exclusion from a given population.
* A baseline urine pathogen is defined as the presence of causative bacteria present at $\geq 10^5$ CFU/mL in baseline urine culture with no more than 2 organisms isolated from the sample collected.
† Antibacterial activity is defined as susceptible or intermediate according to Clinical and Laboratory Standards Institute (CLSI) criteria[1] for meropenem and provisionally susceptible (minimal inhibitory concentration [MIC] ≤ 16 µg/mL) for cefepime-taniborbactam.

CERTAIN-1 TRIAL – METHODS

Primary efficacy outcome: both microbiologic and clinical success in the microITT population at test of cure on trial days 19 to 23

Key secondary outcome: composite success in the extended microITT population and composite success, microbiologic success and clinical success in the microITT population at the end of treatment (≤ 24 hours after the last dose of a trial drug) and at late follow up (trial days 28 to 35)

CERTAIN-1 TRIAL – RESULTS

Table 1. Characteristics of the Patients at Baseline (Microbiologic Intention-to-Treat Population).*

Characteristic	Cefepime–Taniborbactam (N=293)	Meropenem (N=143)
Age		
Mean	56.5±17.6	55.8±17.9
Distribution — no. (%)		
<65 yr	180 (61.4)	90 (62.9)
65 to 75 yr	72 (24.6)	35 (24.5)
>75 yr	41 (14.0)	18 (12.6)
Female sex — no. (%)	161 (54.9)	69 (48.3)
Race or ethnic group — no. (%)†		
American Indian or Alaska Native	3 (1.0)	0
Asian	26 (8.9)	6 (4.2)
Black	1 (0.3)	0
White	257 (87.7)	131 (91.6)
Other	6 (2.0)	6 (4.2)
Hispanic or Latino ethnic group — no. (%)†		
Yes	29 (9.9)	12 (8.4)
No	263 (89.8)	130 (90.9)
Missing data	1 (0.3)	1 (0.7)
Geographic region — no. (%)		
North America or western Europe	14 (4.8)	8 (5.6)
Eastern Europe	236 (80.5)	121 (84.6)
Rest of world	43 (14.7)	14 (9.8)
Body-mass index — no. (%)‡		
<18.5	10 (3.4)	3 (2.1)
18.5 to 24.9	89 (30.4)	45 (31.5)
25 to 29.9	113 (38.6)	54 (37.8)
≥30	81 (27.6)	39 (27.3)
Missing data	0	2 (1.4)
Status for eGFR — no. (%)§		
Normal: ≥90 ml/min/1.73 m²	66 (22.5)	29 (20.3)
Mild impairment: 60 to <90 ml/min/1.73 m²	138 (47.1)	75 (52.4)
Moderate impairment: 30 to <60 ml/min/1.73 m²	84 (28.7)	38 (26.6)
Severe impairment: <30 ml/min/1.73 m²	5 (1.7)	1 (0.7)
Infection type — no. (%)		
Complicated UTI	167 (57.0)	85 (59.4)
Acute pyelonephritis	126 (43.0)	58 (40.6)
Bacteremia — no. (%)	38 (13.0)	19 (13.3)
SIRS criteria — no. (%)¶	70 (23.9)	36 (25.2)
Diabetes — no. (%)	49 (16.7)	24 (16.8)

Table 1. (Continued.)

Characteristic	Cefepime–Taniborbactam (N=293)	Meropenem (N=143)
Gram-negative pathogen — no. (%)	293 (100)	143 (100)
Enterobacterales species		
Any	281 (95.9)	137 (95.8)
Cefepime-resistant	66 (22.5)	30 (21.0)
ESBL-producing‖	76 (25.9)	40 (28.0)
Multidrug-resistant**	100 (34.1)	55 (38.5)

Baseline pathogens resistant to cefepime, phenotypic ESBL producing pathogens and MDR pathogens were detected in 22.0%, 26.6% and 35.6% respectively

CERTAIN-1 TRIAL – RESULTS

Table 2. Primary and Secondary Efficacy Outcomes.*

Outcome, Population, and Time of Assessment	Cefepime–Taniborbactam	Meropenem	Treatment Difference (95% CI)
	no./total no. of patients (%)		*percentage points*
Microbiologic intention-to-treat population			
Primary outcome†			
Composite success at test of cure	207/293 (70.6)	83/143 (58.0)	12.6 (3.1 to 22.2)‡
Microbiologic§	229/293 (78.2)	95/143 (66.4)	11.7 (2.9 to 21.0)
Clinical¶	251/293 (85.7)	116/143 (81.1)	4.5 (–2.6 to 12.6)
Secondary outcome‖			
Composite success at end of treatment	261/293 (89.1)	123/143 (86.0)	3.1 (–3.2 to 10.4)
Microbiologic§	284/293 (96.9)	139/143 (97.2)	–0.3 (–3.5 to 4.1)
Clinical¶	265/293 (90.4)	127/143 (88.8)	1.6 (–4.1 to 8.5)
Composite success at late follow-up	187/293 (63.8)	74/143 (51.7)	12.1 (2.2 to 21.9)
Microbiologic§	207/293 (70.6)	90/143 (62.9)	7.7 (–1.6 to 17.3)
Clinical¶	238/293 (81.2)	102/143 (71.3)	9.9 (1.5 to 18.8)
Extended microbiologic intention-to-treat population			
Secondary outcome			
Composite success at test of cure	216/305 (70.8)	86/147 (58.5)	12.3 (3.0 to 21.8)
Microbiologic§	238/305 (78.0)	98/147 (66.7)	11.4 (2.7 to 20.5)
Clinical¶	262/305 (85.9)	119/147 (81.0)	4.9 (–2.1 to 12.9)

(95% confidence interval [CI], 3.1 to 22.2; P=0.009)

Table 3. Composite, Microbiologic, and Clinical Success at Test of Cure, According to Pathogen (Microbiologic Intention-to-Treat Population).*

Baseline Pathogen and Outcome	Cefepime–Taniborbactam	Meropenem
	no./total no. of patients (%)	
Composite success		
Enterobacterales species or category	202/281 (72)	80/137 (58)
Enterobacter cloacae complex	11/14 (79)	1/3 (33)
Escherichia coli	147/202 (73)	58/99 (59)
Klebsiella pneumoniae	24/40 (60)	12/20 (60)
Proteus mirabilis	8/10 (80)	4/10 (40)
Cefepime-resistant	47/66 (71)	16/30 (53)
ESBL-producing	54/76 (71)	22/40 (55)
Multidrug-resistant	68/100 (68)	33/55 (60)
Pseudomonas aeruginosa	5/12 (42)†	3/6 (50)
Microbiologic success		
Enterobacterales species or category	224/281 (80)	91/137 (66)
E. cloacae complex	11/14 (79)	1/3 (33)
E. coli	163/202 (81)	67/99 (68)
K. pneumoniae	27/40 (68)	14/20 (70)
P. mirabilis	9/10 (90)	4/10 (40)
Cefepime-resistant	50/66 (76)	18/30 (60)
ESBL-producing	57/76 (75)	25/40 (62)
Multidrug-resistant	71/100 (71)	38/55 (69)
P. aeruginosa	5/12 (42)†	4/6 (67)
Clinical success		
Enterobacterales species or category	241/281 (86)	111/137 (81)
E. cloacae complex	14/14 (100)	3/3 (100)
E. coli	177/202 (88)	80/99 (81)
K. pneumoniae	29/40 (72)	14/20 (70)
P. mirabilis	9/10 (90)	9/10 (90)
Cefepime-resistant	54/66 (82)	25/30 (83)
ESBL-producing	64/76 (84)	32/40 (80)
Multidrug-resistant	87/100 (87)	46/55 (84)
P. aeruginosa	10/12 (83)	5/6 (83)

During the trial, resistance to cefepime–taniborbactam or meropenem did not develop in any of the pathogens identified at baseline.

CERTAIN-1 TRIAL – RESULTS

Table 4. Summary of Adverse Events (Safety Population).*

Event	Cefepime–Taniborbactam (N=440)	Meropenem (N=217)
Any adverse event — no. of patients (%)	156 (35.5)	63 (29.0)
No. of adverse events	341	114
Mild — no./total no. (%)	226/341 (66.3)	82/114 (71.9)
Moderate — no./total no. (%)	100/341 (29.3)	25/114 (21.9)
Severe — no./total no. (%)	15/341 (4.4)	7/114 (6.1)
Adverse event related to a trial drug — no. of patients (%)†	59 (13.4)	19 (8.8)
Adverse event reported in ≥1% of patients in either treatment group — no. of patients (%)‡		
Headache	27 (6.1)	8 (3.7)
Diarrhea	18 (4.1)	5 (2.3)
Constipation	14 (3.2)	3 (1.4)
Hypertension	10 (2.3)	2 (0.9)
Nausea	9 (2.0)	2 (0.9)
Abdominal distention	7 (1.6)	3 (1.4)
Anemia	7 (1.6)	3 (1.4)
Dizziness	7 (1.6)	1 (0.5)
Hypokalemia	7 (1.6)	1 (0.5)
Phlebitis	6 (1.4)	1 (0.5)
Vomiting	6 (1.4)	1 (0.5)
Cough	5 (1.1)	2 (0.9)
Pyrexia	5 (1.1)	3 (1.4)
Increased alanine aminotransferase	4 (0.9)	5 (2.3)
Vulvovaginal candidiasis	3 (0.7)	3 (1.4)
Discontinuation of trial drug — no. (%)§	13 (3.0)	2 (0.9)
Serious adverse event — no. of patients (%)¶		
Any	9 (2.0)	4 (1.8)
Related to a trial drug†	2 (0.5)	0

Table S10. Treatment-emergent Adverse Events Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term (Safety Analysis Population)

System Organ Class Preferred Term	Cefepime-taniborbactam (N=440) n (%)	Meropenem (N=217) n (%)
Patients with any TEAE leading to discontinuation of study drug	13 (3.0%)	2 (0.9%)
Gastrointestinal disorders	2 (0.5%)	0
Abdominal pain	1 (0.2%)	0
Glossitis	1 (0.2%)	0
General disorders and administration site conditions	1 (0.2%)	0
Generalized oedema	1 (0.2%)	0
Infections and infestations	4 (0.9%)	1 (0.5%)
COVID-19	1 (0.2%)	0
Endocarditis	1 (0.2%)	0
Gastrointestinal candidiasis	1 (0.2%)	0
Renal abscess	1 (0.2%)	0
Tubo-ovarian abscess	0	1 (0.5%)
Injury, poisoning and procedural complications	1 (0.2%)	0
Procedural dizziness	1 (0.2%)	0
Procedural nausea	1 (0.2%)	0
Musculoskeletal and connective tissue disorders	1 (0.2%)	0
Muscle spasms	1 (0.2%)	0
Skin and subcutaneous tissue disorders	3 (0.7%)	1 (0.5%)
Urticaria	1 (0.2%)	1 (0.5%)
Angioedema	1 (0.2%)	0
Rash	1 (0.2%)	0
Vascular disorders	1 (0.2%)	0
Thrombophlebitis	1 (0.2%)	0

CERTAIN-1 TRIAL – CONCLUSIONS

- Cefepime–taniborbactam was superior to meropenem therapy regarding composite (both microbiologic and clinical) success at test of cure among hospitalized adults with complicated urinary tract infection.
- The between-group differences in treatment response were sustained at late follow-up, at which time the cefepime–taniborbactam group had higher frequencies of composite and clinical success than the meropenem group.
- Cefepime–taniborbactam had a similar risk of adverse events and serious adverse events as meropenem. Although gastrointestinal events were the most common adverse events in the two groups, the incidence of any specific event was less than 5%.
- The number of patients who discontinued cefepime–taniborbactam because of adverse events was higher than that observed for meropenem (3.0% vs. 0.9%); events leading to discontinuation were heterogeneous. Overall, the safety profile of cefepime–taniborbactam was similar to that of meropenem and to the historical profile of cefepime.

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Treatment of infections caused by multidrug-resistant Gram-negative bacilli: A practical approach by the Italian (SIMIT) and French (SPILF) Societies of Infectious Diseases

Marianna Meschiari[a], Antoine Asquier-Khati[b], Giusy Tiseo[c], David Luque-Paz[d], Rita Murri[e], David Boutoille[b], Marco Falcone[c], Cristina Mussini[a], Pierre Tattevin[d,*], on behalf of the Italian Society of Infectious and Tropical Diseases (SIMIT), and the French Society of Infectious Diseases (SPILF)

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Guidelines

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine)

Mical Paul [1, 2, §], Elena Carrara [3, §], Pilar Retamar [4, 5], Thomas Tängdén [6], Roni Bitterman [1, 2], Robert A. Bonomo [7, 8, 9], Jan de Waele [10], George L. Daikos [11], Murat Akova [12], Stephan Harbarth [13], Celine Pulcini [14, 15], José Garnacho-Montero [16], Katja Seme [17], Mario Tumbarello [18], Paul Christoffer Lindemann [19], Sumanth Gandra [20], Yunsong Yu [21, 22, 23], Matteo Bassetti [24, 25], Johan W. Mouton [26, †], Evelina Tacconelli [3, 27, 28, *, §], Jesús Rodríguez-Baño [4, 5, §]

Clinical Infectious Diseases

IDSA GUIDELINE

Infectious Diseases Society of America Guidance on the Treatment of AmpC β-Lactamase–Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

[1]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [2]Department of Pharmacy, University of Michigan Health, Ann Arbor, Michigan, USA; [3]Medical Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, University Hospitals Cleveland Medical Center and Departments of Medicine, Pharmacology, Molecular Biology, and Microbiology, Case Western Reserve University, Cleveland, Ohio, USA; [4]Departments of Medicine and Pathology, University of Virginia, Charlottesville, Virginia, USA; [5]Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA; and [6]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

RESPIRATORY TRACT INFECTIONS

Table 1
Pneumonia.

Pathogens	ESCMID recommendations	Comments and practical approach
Ventilator-associated pneumonia caused by AmpC-producing Enterobacterales	No specific recommendations for AmpC-producing Enterobacterales pneumonia For 3GCephRE infections: piperacillin-tazobactam or quinolones for non-severe infections; carbapenems for severe infections	**Cefepime as first-line treatment** Cefepime as monotherapy when MIC ≤2 mg/L Higher mortality was only found in ESBL-producing Enterobacterales infections with high cefepime MIC For AmpC-producing Enterobacterales infections, cefepime performed at least as well as comparators in observational studies, including in ICUs
Severe pneumonia caused by difficult-to-treat resistant *Pseudomonas aeruginosa* with resistance to ceftolozane-tazobactam	No recommendation in case of ceftolozane-tazobactam resistance Lack of evidence for imipenem-relebactam, cefiderocol and ceftazidime-avibactam use No clear recommendation for combination therapy	**Combination therapy: at least one in-vitro active agent + aerosolized antibiotics** If susceptible: imipenem-relebactam or ceftazidime-avibactam For MBL: cefiderocol in combination regimen with in-vitro active partner, such as fosfomycin Systematic use of aerosolized colistin or tobramycin therapy: favourable PK/PD profile, improved microbiological outcomes, good tolerability

ESCMID, European Society of Clinical Microbiology and Infectious Diseases; 3GCephRE, third-generation cephalosporin-resistant Enterobacterales; MBL, metallo-β-lactamases; ESBL, extended-spectrum beta-lactamase; ICU, intensive care unit; PK/PD, pharmacokinetic/pharmacodynamic; MIC, minimum inhibitory concentration.

Cefepime 2 g every 8 hours

Combination therapy: BL/BLI most active in vitro, FDC+FOF; aerosolized colistin or aminoglycosides per MBL-producing PA

IDSA Guidelines: cefepime is recomended for AmpC Enterobacterales with MIC $\leq$ 2 mg/L

URINARY TRACT INFECTIONS

Table 2
Severe complicated urinary tract infections.

Pathogens	ESCMID recommendations	Comments and practical approach
ESBL-producing Enterobacterales	Carbapenems (meropenem or imipenem; ertapenem if no septic shock) Under AMS consideration, piperacillin-tazobactam can be used as the first-line therapy in low-inoculum, non-severe 3GCephRE infections, and as a step-down therapy for severe infections Conditional recommendation/ good practice statement against the use of new BLBLIs for 3GCephRE	**For AMS purposes, consider carbapenem-sparing strategies** cUTIs due to ESBL-producing Enterobacterales with piperacillin-tazobactam MIC <8 mg/L: high-dose piperacillin-tazobactam, with loading dose and continuous infusion cUTIs due to ESBL-Enterobacterales with piperacillin-tazobactam MIC >8 mg/L, aminoglycosides or intravenous fosfomycin are alternatives alone or in combination strategies due to high urinary concentrations and low prevalence of resistance Cefoxitin may be an option for ESBL-producing *Escherichia coli*, as well as temocillin, based on drug-susceptibility testing studies New BLBLIs should be reserved for settings with concomitant high rates of resistance to piperacillin-tazobactam and carbapenems
AmpC-producing Enterobacterales	Carbapenems (meropenem or imipenem; ertapenem if no septic shock) No recommendations for organisms with moderate to high likelihood of AmpC production due to inducible AmpC gene (e.g. *Enterobacter cloacae, Citrobacter freundii)* Conditional recommendation against the use of cefepime for 3GCephRE	**For AMS purposes, consider carbapenem-sparing strategies** cUTIs due to AmpC-producing Enterobacterales with cefepime MIC ≤2 mg/L: high-dose cefepime (2 g t.i.d.) cUTIs due to AmpC-producing Enterobacterales with cefepime MIC >2 mg/L: new BLBLIs may be considered, instead of carbapenems, based on local resistance rates

ESCMID, European Society of Clinical Microbiology and Infectious Diseases; cUTIs, complicated urinary tract infections; AMS, antimicrobial stewardship; BLBLI, β-lactam/β-lactamase inhibitor combination; ESBL, extended-spectrum beta-lactamase; 3GCephRE, third-generation cephalosporin-resistant Enterobacterales; MIC, minimum inhibitory concentration.

Piperacillin/tazobactam (MIC ≤8): loading dose (9 g over 30 min) followed by continuous infusion (4.5 g every 6-8h)

Piperacillin/tazobactam (MIC >8): aminoglycosides* or IV fosfomycin alone or in combination**

Meropenem

C/T for settings with concomitant high rates of resistance to TZP and carbapenems

* Aminoglycosid monotherapy failed to reach non-inferiority for BSI of urinary source due to ESBL-Enterobacterales other than *E. coli*

* *Trial ZEUS and FOREST

URINARY TRACT INFECTIONS

Table 2
Severe complicated urinary tract infections.

Pathogens	ESCMID recommendations	Comments and practical approach
ESBL-producing Enterobacterales	Carbapenems (meropenem or imipenem; ertapenem if no septic shock) Under AMS consideration, piperacillin-tazobactam can be used as the first-line therapy in low-inoculum, non-severe 3GCephRE infections, and as a step-down therapy for severe infections Conditional recommendation/ good practice statement against the use of new BLBLIs for 3GCephRE	**For AMS purposes, consider carbapenem-sparing strategies** cUTIs due to ESBL-producing Enterobacterales with piperacillin-tazobactam MIC <8 mg/L: high-dose piperacillin-tazobactam, with loading dose and continuous infusion cUTIs due to ESBL-Enterobacterales with piperacillin-tazobactam MIC >8 mg/L, aminoglycosides or intravenous fosfomycin are alternatives alone or in combination strategies due to high urinary concentrations and low prevalence of resistance Cefoxitin may be an option for ESBL-producing *Escherichia coli*, as well as temocillin, based on drug-susceptibility testing studies New BLBLIs should be reserved for settings with concomitant high rates of resistance to piperacillin-tazobactam and carbapenems
AmpC-producing Enterobacterales	Carbapenems (meropenem or imipenem; ertapenem if no septic shock) No recommendations for organisms with moderate to high likelihood of AmpC production due to inducible AmpC gene (e.g. *Enterobacter cloacae, Citrobacter freundii)* Conditional recommendation against the use of cefepime for 3GCephRE	**For AMS purposes, consider carbapenem-sparing strategies** cUTIs due to AmpC-producing Enterobacterales with cefepime MIC ≤2 mg/L: high-dose cefepime (2 g t.i.d.) cUTIs due to AmpC-producing Enterobacterales with cefepime MIC >2 mg/L: new BLBLIs may be considered, instead of carbapenems, based on local resistance rates

ESCMID, European Society of Clinical Microbiology and Infectious Diseases; cUTIs, complicated urinary tract infections; AMS, antimicrobial stewardship; BLBLI, β-lactam/β-lactamase inhibitor combination; ESBL, extended-spectrum beta-lactamase; 3GCephRE, third-generation cephalosporin-resistant Enterobacterales; MIC, minimum inhibitory concentration.

Cefepime (MIC ≤2): high dose cefepime (2 g tid)

Cefepime (MIC >2): new BLBLIs (carbapenems sparing)

INTRA-ABDOMINAL INFECTIONS

Table 3
Intra-abdominal infections.

Pathogens	ESCMID recommendations	Comments and practical approach
Third-generation cephalosporin-resistant Enterobacterales	Severe infections: Carbapebems as first choice	For AMS purposes, consider early de-escalation to ceftolozane-tazobactam (if active *in vitro*) plus metronidazole as soon as clinical stability is achieved
	Non-severe infections: Piperacillin-tazobactam or amoxicillin-clavulanate or Quinolones	High prevalence of resistance to piperacillin-tazobactam, amoxicillin-clavulanate or quinolones among ESBL-producing *E. coli* isolates from IAIs in Europe
Carbapenem-resistant Enterobacterales	Severe infections: Meropenem-vaborbactam or ceftazidime-avibactam as first choice Cefiderocol if MBL or resistant to meropenem-vaborbactam or ceftazidime-avibactam (conditional) No evidence for or against imipenem-relebactam or fosfomycin monotherapy	First-line antibiotic regimens should be based on carbapenemase type, local epidemiology (prevalence of ceftazidime-avibactam resistance) and concomitant isolates: KPC: Imipenem-relebactam (also active against enterococci) or meropenem-vaborbactam or ceftazidime-avibactam plus metronidazole as first choice MBL: Ceftazidime-avibactam plus aztreonam plus metronidazole as first choice Cefiderocol combination regimens (plus tygecicline or plus fosfomycin and metronidazole as alternative regimen) OXA-48: Ceftazidime/avibactam plus metronidazole or cefiderocol-containing regimens (plus tigecycline or plus fosfomycin and metronidazole)

ESCMID, European Society of Clinical Microbiology and Infectious Diseases; AMS, antimicrobial stewardship; IAI, intra-abdominal infection; ESBL, extended-spectrum beta-lactamase; MBL, metallo-beta-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase.

Septic-shock: empirical treatment with carbapenems followed by early de-escalation to C/T + metronidazole

NO sepsis: C/T + metronidazole

INTRA-ABDOMINAL INFECTIONS

Table 3
Intra-abdominal infections.

Pathogens	ESCMID recommendations	Comments and practical approach
Third-generation cephalosporin-resistant Enterobacterales	Severe infections: Carbapebems as first choice	For AMS purposes, consider early de-escalation to ceftolozane-tazobactam (if active *in vitro*) plus metronidazole as soon as clinical stability is achieved
	Non-severe infections: Piperacillin-tazobactam or amoxicillin-clavulanate or Quinolones	High prevalence of resistance to piperacillin-tazobactam, amoxicillin-clavulanate or quinolones among ESBL-producing *E. coli* isolates from IAIs in Europe
Carbapenem-resistant Enterobacterales	Severe infections: Meropenem-vaborbactam or ceftazidime-avibactam as first choice Cefiderocol if MBL or resistant to meropenem-vaborbactam or ceftazidime-avibactam (conditional) No evidence for or against imipenem-relebactam or fosfomycin monotherapy	First-line antibiotic regimens should be based on carbapenemase type, local epidemiology (prevalence of ceftazidime-avibactam KPC: Imipenem-relebactam (also active against enterococci) or meropenem-vaborbactam or ceftazidime-avibactam plus metronidazole as first choice MBL: Ceftazidime-avibactam plus aztreonam plus metronidazole as first choice Cefiderocol combination regimens (plus tygecicline or plus fosfomycin and metronidazole as alternative regimen) OXA-48: Ceftazidime/avibactam plus metronidazole or cefiderocol-containing regimens (plus tigecycline or plus fosfomycin and metronidazole)

ESCMID, European Society of Clinical Microbiology and Infectious Diseases; AMS, antimicrobial ewardship; IAI, intra-abdominal infection; ESBL, extended-spectrum be a-lactamase; MBL, metallo-beta-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase.

PRIMARY BLOODSTREAM INFECTIONS

Table 4
Primary bloodstream infections.

Pathogens	ESCMID recommendations	Comments and practical approach
CRAB	Ampicillin-sulbactam for HAP/VAP with CRAB susceptible to sulbactam Combination therapy for patients with severe and high-risk CRAB infections, including two in-vitro active agents (e.g. polymyxin, aminoglycoside, tigecycline, sulbactam)	**Ampicillin sulbactam in association with colistin as first choice** Combination therapy associated with better survival for CRAB, particularly for primary BSIs (high-risk infections), particularly with sepsis or septic shock New data support the use of ampicillin-sulbactam as part of combination therapy Combination with colistin is recommended because of its in-vitro activity, its widespread use, and its efficacy with ampicillin-sulbactam documented in a randomized study [40] Results from CREDIBLE-CR study advocate against the use of cefiderocol as a single agent in this situation
KPC-producing *K. pneumoniae*	Meropenem-vaborbactam or ceftazidime-avibactam if active *in vitro* for patients with severe infections due to CRE Cefiderocol for severe infections due to CRE carrying MBL or resistant to meropenem-vaborbactam or ceftazidime-avibactam Monotherapy for patients with CRE infections susceptible to ceftazidime-avibactam or meropenem-vaborbactam	**Meropenem-vaborbactam** For AMS purposes, consider the following: Among CPE, meropenem-vaborbactam is only active against KPC, while the spectrum is wider for ceftazidime-avibactam (OXA-48, DTR-PA), imipenem-relebactam (DTR-PA) and cefiderocol (OXA-48, MBL and DTR-PA). Hence, meropenem-vaborbactam may be prioritized as the new BLBLI with the narrowest spectrum Ceftazidime-avibactam and imipenem-relebactam as alternative options

ESCMID, European Society of Clinical Microbiology and Infectious Diseases; BSI, bloodstream infection; AMS, antimicrobial stewardship; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacterales; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamases; VAP, ventilator-associated pneumonia; HAP, hospital-acquired pneumonia; DTR-PA, difficult-to-treat resistant *Pseudomonas aeruginosa*; BLBLI, β-lactam/β-lactamase inhibitor combinations.

High dose ampicillin-sulbactam (24/12g daily) and colistin (9 M IU after loading dose 4.5 M IU)
Cefiderocol for strains resistant to sulbactam

Meropenem-vaborbactam
Ceftazidime-avibactam
Imipenem-relebactam

Nosocomial *K. pneumoniae* is the main cause of CRE infections in Europe!

THANK YOU FOR THE ATTENTION!