Enterobatteri e Non-fermentanti nel Paziente Critico

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Disclosures

Consultant/advisory board/speaker fees

- Pfizer, MSD, Angelini, Tillots, Menarini
- Thermo Fisher, Shionogi
- BioTest, Nordic Pharma, InfectoPharma
- Gilead Sciences, GSK, Hikma, Advanz, Correvio

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- Pfizer, MSD, Shionogi

New Perspectives In Gram-negative Infections in ICU

Karvouniaris M et al Expert Rev Anti Infect Ther 2021 (7):825-844

- **Multi-drug resistance and difficult-to-treat infections**
- **Review of studies**
  - Older & repurposed antibiotics, i.e., amp-sulbactam, colistin; Fosfomycin
- **Review of newly introduced molecules**
  - Ceftazidime-avibactam, aztreonam-avibactam, ceftolozane-tazobactam, imipenem-relebactam, meropenem-vaborbactam, cefiderocol, plazomicin, and eravacycline
- **Novel & alternative treatments of *P. aeruginosa* and *Klebsiella spp*.**
  - Antibodies, bacteriophages and vaccines
- **Treatment-algorithms**
  - VAP due to *P. aeruginosa* and carbapenemase-resistant *Enterobacterales*

Enterobacterales, *Enterobacter* spp. & Amp-C

- **Number eighth among the top 10 BSI pathogens isolated from 2012 to 2017**
  - Pretty stable ranking that showed little change over time
  - Pretty much low & stable cefepime resistance
  - SENTRY Antimicrobial Surveillance Program
    - Pfaller MA et al *Diagn Microbiol Infect Dis* 2022
- **In BSI in China being the most frequent Enterobacterales 17**
  - *Enterobacter* spp., *Serratia* spp., and *Citrobacter* spp.
    - Hu F et al. *Front Cell Infect Microbiol* 2022
- **In a multicenter european hospital studi of AmpC pathogens from BSIs (2020–22)**
  - *Enterobacter cloacae* complex (44.8%), *Serratia marcescens* (22.7%), and *K. aerogenes* (13.3%)
  - Mainly in patients admitted to medical wards (37.2%) and ICUs (30.9%)
    - Boattini M et al. *Int J Antimicrob Ag* 2024

European Multicentre Study on ESCPM, ESBL, CPE & Amp-C

Boattini M et al Int J Antimicrob Ag 2024

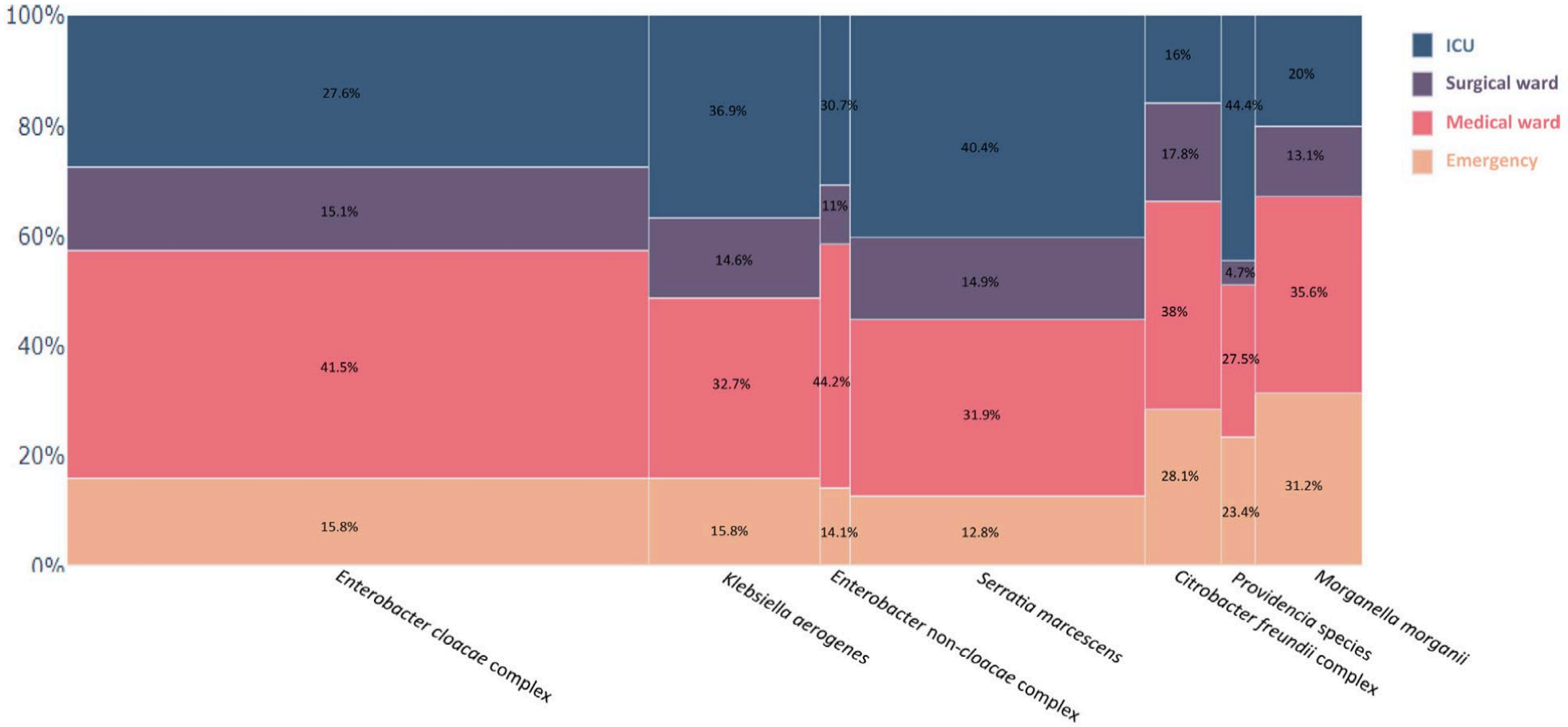


Fig. 2. Distribution of ESCPM species according to hospital ward (Marimekko plot: the width of each column represents the proportion of the ESCPM species within the entire collection. The height of each bar represents the proportion of each ESCPM species within each hospital ward).

ESCPM: *Enterobacter* spp. with *Klebsiella aerogenes* (formerly *E. aerogenes*), Serratia, Citrobacter, Providencia, Morganella

Antibiotic Resistance Phenotypes in ESCPM species (EUCAST V. 13.1)

Boattini M et al Int J Antimicrob Ag 2024

Table 2
Antibiotic resistance phenotypes in ESCPM species isolates according to EUCAST v. 13.1 breakpoints.

Phenotype	Overall % (n)	*Enterobacter cloacae* complex[1] % (n)	*Klebsiella aerogenes* % (n)	*Enterobacter* non-*cloacae* complex[2] % (n)	*Serratia marcescens* % (n)	*Citrobacter freundii* complex[3] % (n)	*Providencia* species % (n)	*Morganella morganii* % (n)
3GC susceptible[4]	70.2 (4740/6754)	64.6 (1955/3028)	55.5 (497/895)	66.9 (109/163)	88.5 (1356/1532)	72.8 (294/404)	46.2 (79/171)	80.2 (450/561)
3GC resistant[4]	15.7 (1059/6754)	15.2 (459/3028)	29.8 (267/895)	15.3 (25/163)	8.1 (124/1532)	20.5 (83/404)	9.9 (17/171)	15 (84/561)
3GC + 4GC resistant[5]	4.6 (312/6754)	7.4 (225/3028)	3.5 (31/895)	5.5 (9/163)	1.8 (28/1532)	2.7 (11/404)	1.2 (2/171)	1.1 (6/561)
Carbapenems resistant	9.5 (643/6754)	12.8 (389/3028)	11.2 (100/895)	12.3 (20/163)	1.6 (24/1532)	4 (16/404)	42.7 (73/171)	3.7 (21/561)
ESBL-producer	6.4 (374/5832)	11.4 (297/2618)	3.1 (24/779)	4.4 (7/159)	1.9 (25/1296)	3.4 (12/349)	2.9 (4/140)	1 (5/491)
AmpC overproducers	15.8 (641/4056)	17.1 (318/1859)	32.1 (176/549)	17.7 (20/113)	4.8 (43/901)	16.5 (38/230)	13.3 (8/60)	11.1 (38/344)
Carbapenemase-producer	3.1 (205/6713)	3.5 (104/3009)	2.3 (21/896)	1.3 (2/154)	1.1 (16/1521)	2.5 (10/402)	29.4 (50/170)	0.4 (2/561)
KPC-producer	1.5 (3/205)	1 (1/104)	–	50 (1/2)	–	10 (1/10)	–	–
VIM-producer	22.9 (47/205)	39.4 (41/104)	–	–	25 (4/16)	10 (1/10)	2 (1/50)	–
NDM-producer	2.5 (5/205)	3.8 (4/104)	4.8 (1/21)	–	–	–	–	–
IMI-producer	0.5 (1/205)	1 (1/104)	–	–	–	–	–	–
OXA-48-producer	16 (33/205)	11.5 (12/104)	33.3 (7/21)	–	18.8 (3/16)	60 (6/10)	6 (3/50)	100 (2/2)
KPC+VIM-producer	0.5 (1/205)	1 (1/104)	–	–	–	–	–	–
KPC+NDM-producer	0.5 (1/205)	–	–	–	–	10 (1/10)	–	–
Not characterised	55.6 (114/205)	42.3 (44/104)	61.9 (13/21)	50 (1/2)	56.2 (9/16)	10 (1/10)	92 (46/50)	–

Abbreviations: 3GC, third-generation cephalosporins; 4GC, fourth-generation cephalosporins.

[1] *Enterobacter* cloacae complex corresponds to *E. cloacae, E. asburiae, E. hormaechei, E. kobei, E. ludwigii, E. mori*, and *E. Nimipressuralis*.

[2] *Enterobacter* non-cloacae complex corresponds to *Enterobacter* species not included in the *Enterobacter* cloacae complex.

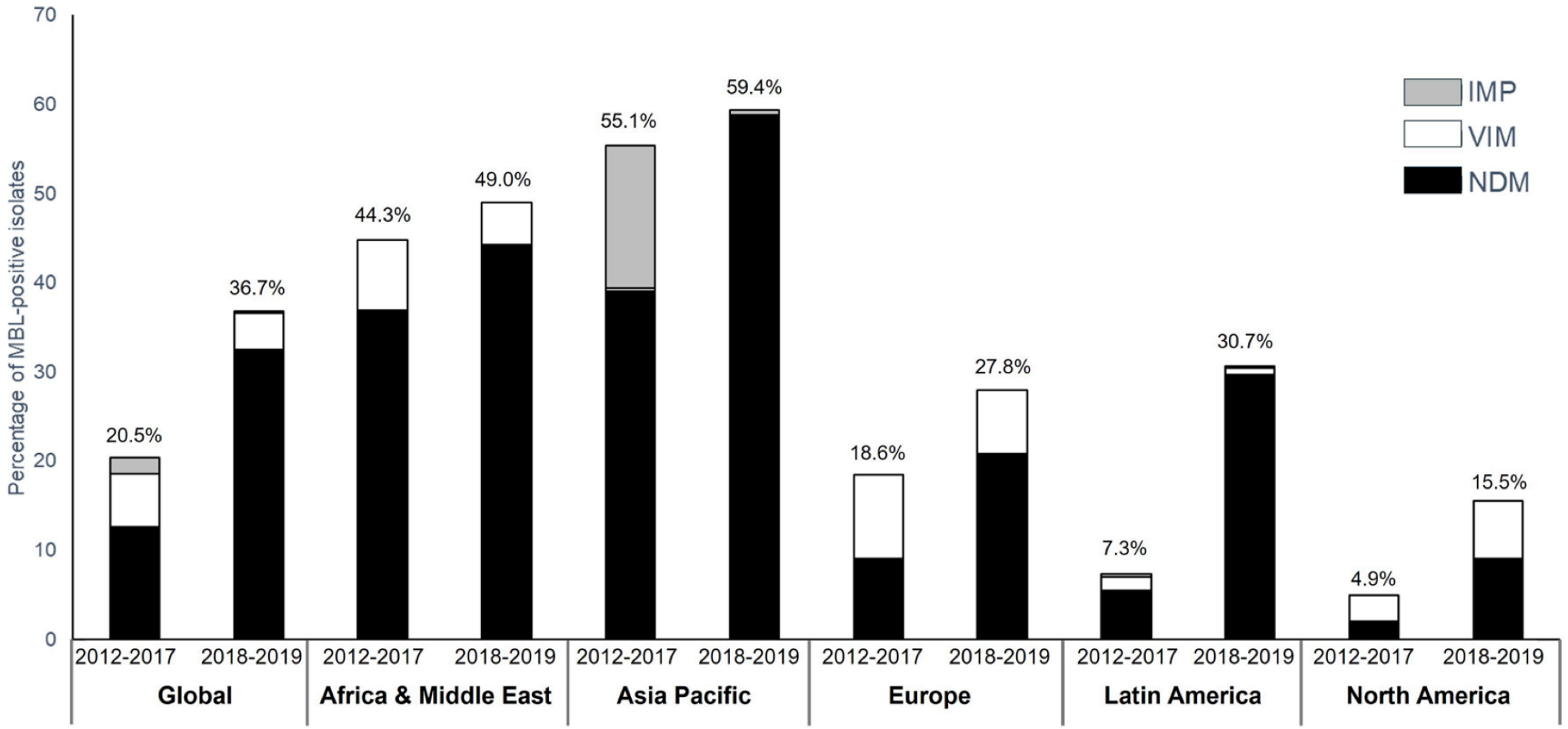
[3] *Citrobacter freundii* complex corresponds to *C. freundii, C. braakii, C. youngae, C. portucalentis, C.gillenii, C. murliniae, C. sedlakii*, and *C. wekmenii*.

[4] Cefepime-and-carbapenem-susceptible.

[5] Carbapenem-susceptible.

Navigating the Current Treatment Landscape of Metallo-β-Lactamase-Producing Gram-Negative Infections: Which Limitations?

Grabein B et al. Infect Dis Ther 2024;13(11):2423-2447



Wards Relative Percentages: A Comparison

	Enzyme	Period	BSI N	Med Int N & %		ICU N & %	
Corcione Biomed 2022	KPC	2010-2019	435	146	33,5%	127	29,2%
Falcone CID 2024	MBL	2019-2022	199/343 (58%)	NA	NA	144	42%

Most patients were previously colonized: 75% in Corcione & 94% in Falcone

New Delhi metallo-betalactamase-producing carbapenem-resistant Enterobacterales (NDM-CRE), Tuscany, Italy, 2018 to 2019

Tavoschi L et al. Eurosurveillance 2020

Table

NDM-CRE inpatient cases per health facility of detection, Tuscany, Italy, November 2018–October 2019 (n = 1,496)

Area	Hospital type (n)	Confirmed NDM-CRE cases														Rate per 100,000 hospital days[a]
		Total	Per case definition						Per ward							
			Intestinal carriage		BSI		Other		ICU		Other than ICU		LTCU		NA		BSI
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	
North-West	TH (n = 1)	290	231	79.7	45	15.5	14	4.8	52	17.9	219	75.5	4	14	15	5.2	15.46
	DH (n = 4)	727	594	81.7	45	6.2	88	12.1	92	12.7	567	78.0	56	7.7	12	1.7	9.97
	Other[b] (n = 11)	247	178	72.1	24	9.7	45	18.2	17	6.9	108	43.7	108	43.7	14	5.7	12.84
	All facilities	1,264	1,003	79.4	114	9.0	147	11.6	161	12.7	894	70.7	168	13.3	41	3.2	11.84
Central	TH (n = 1)	26	25	96.2	1	3.8	0	0	3	11.5	23	88.5	0	0	0	0.	0.32
	DH (n = 5)	64	58	90.6	1	1.6	5	7.8	12	18.8	47	73.4	0	0	5	7.8	0.19
	Other[b] (n = 8)	27	25	92.6	1	3.7	1	3.7	2	7.4	19	70.4	4	14.8	2	7.4	0.64
	All facilities	117	108	92.3	3	2.6	6	5.1	17	14.5	89	76.1	4	3.4	7	6.0	0.3
South-East	TH (n = 1)	52	37	71.2	4	7.7	11	21.2	11	21.2	41	78.8	0	0	0	0.0	2.35
	DH (n = 2)	12	7	58.3	0	0	5	41.7	2	16.7	9	75.0	1	8.3	0	0.0	0
	Other[b] (n = 13)	51	35	68.6	7	13.7	9	17.6	4	7.8	30	58.8	17	33.3	0	0.0	3.32
	All facilities	115	79	68.7	11	9.6	25	21.7	17	14.8	80	69.6	18	15.7	0	0.0	1.9
Total (whole region)	All facilities	1,496	1,190	79.5	128	8.6	178	11.9	195	13.0	1,063	71.1	190	12.7	48	3.2	5.02

BSI: bloodstream infection; DH: district hospital; ICU: intensive care unit; LTCU: long-term care unit; NA: ward data not available; NDM-CRE: New Delhi metallo-beta-lactamase-producing carbapenem-resistant Enterobacterales; TH: teaching hospital.

[a] Hospitalisation days were calculated based on data for the corresponding months in the previous calendar year.

[b] Other facilities include all hospitals not included in the former categories, e.g. primary hospitals, excluding long-term care facilities.

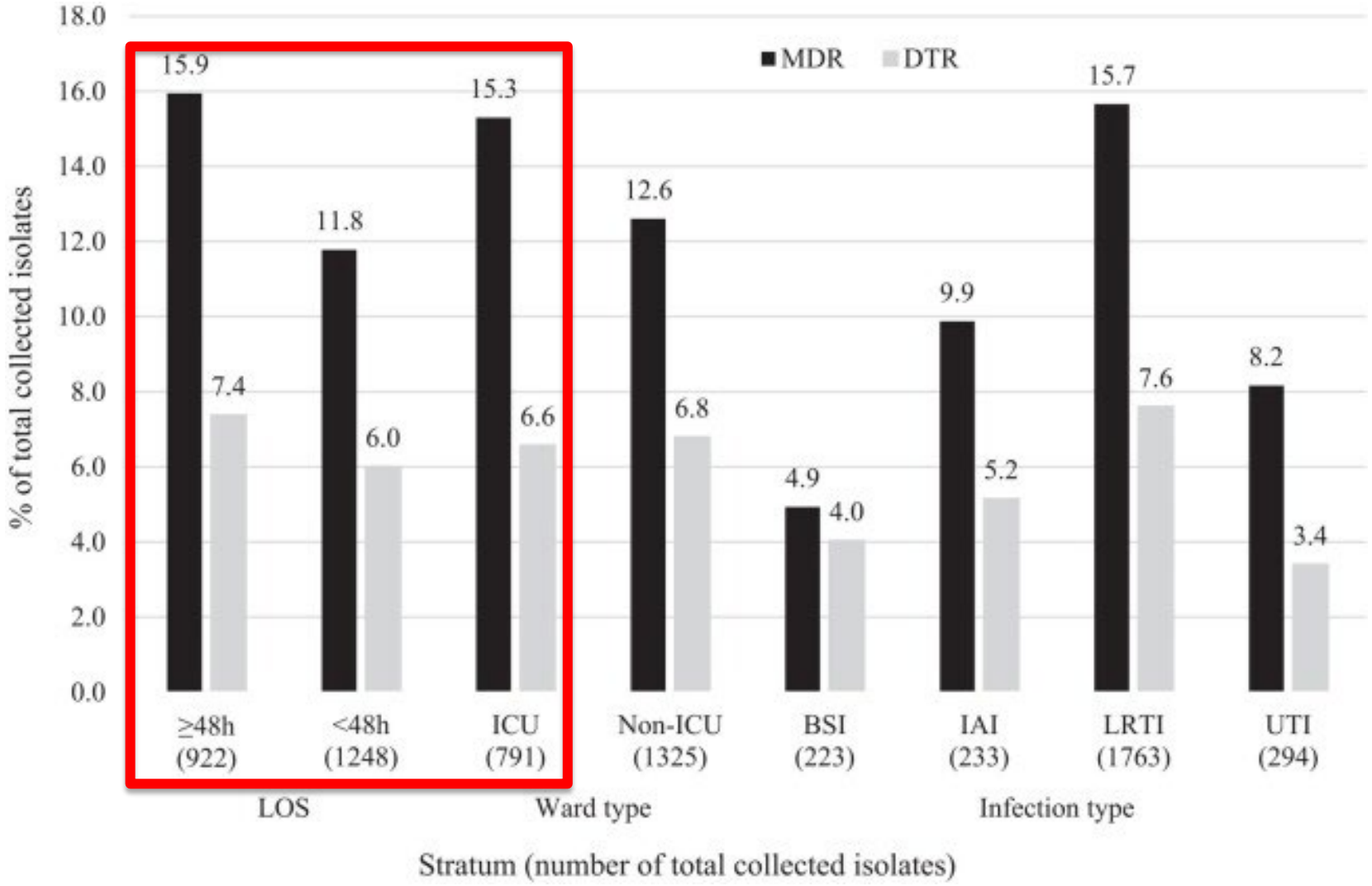
Ceftolozane & Imipenem-REL Activity Vs. *Enterobacterales* & *P. aeruginosa* in Greece & Italy 2024

Karlowsky JA et al Eur J Clin Microbiol Infect Dis 2024;43(7):1343-1348

- **Up to 250 consecutive gram-negatives/year**
  - Lower respiratory tract, intraabdominal, urinary tract, and bloodstream infections
  - CLSI broth microdilution method & 2022 EUCAST breakpoints
- **C/T growth inhibition of**
  - 85-87% of Enterobacterales
  - 94-96% of ESBL-positive non-CRE NME (non-Morganellaceae Enterobacterales)
- **IMI/REL growth inhibition of**
  - 95-98% of NME
  - 100% of ESBL-positive non-CRE NME
  - 98-99% of KPC-positive NME isolates
- **Country-specific differences more pro**
- **C/T and IMI/REL inhibition of *P. aerug***
  - 84% from Greece & 91-92% from Italy

- KPC rates in Enterobacterales similar 7-8%
- OXA-48-like in Enterobacterales only in Italy 1%
- MBL rates amongst Enterobacterales & *P. aeruginosa*
  - 4% & 10% from Greece
  - 1% & 3% from Italy
- GES identified in *P. aeruginosa* only in Italy 2%

MDR and DTR Phenotypes of *P. aeruginosa*
SMART United States 2019-21
Karlowsky JA et al. AC Antimicrob Resist. 2024



Cefto/Taz, Imi/Rel & Caz/Avi Vs. *P. aeruginosa* SMART United States 2019-21

Karlowsky JA et al. AC Antimicrob Resist. 2024

Cefto more active than both Caz/Avi & Imi/Rel Vs. *P. aeruginosa*

- **Susceptibility**
  - Ceftolozane/tazobactam **97%**
  - Ceftazidime/avibactam **95%**
  - Imipenem/relebactam **91%**
- **MDR & difficult-to-treat resistance (DTR) phenotypes**
  - 13% and 7% of *P. aeruginosa* isolates, respectively
- **Phenotypes activity of Cefto Vs. Caz/Avi & Imi/Rel**
  - **MDR** **78%**
    - 13% and 23% higher, respectively
  - **DTR** **74%**
    - 24% and 37% higher, respectively

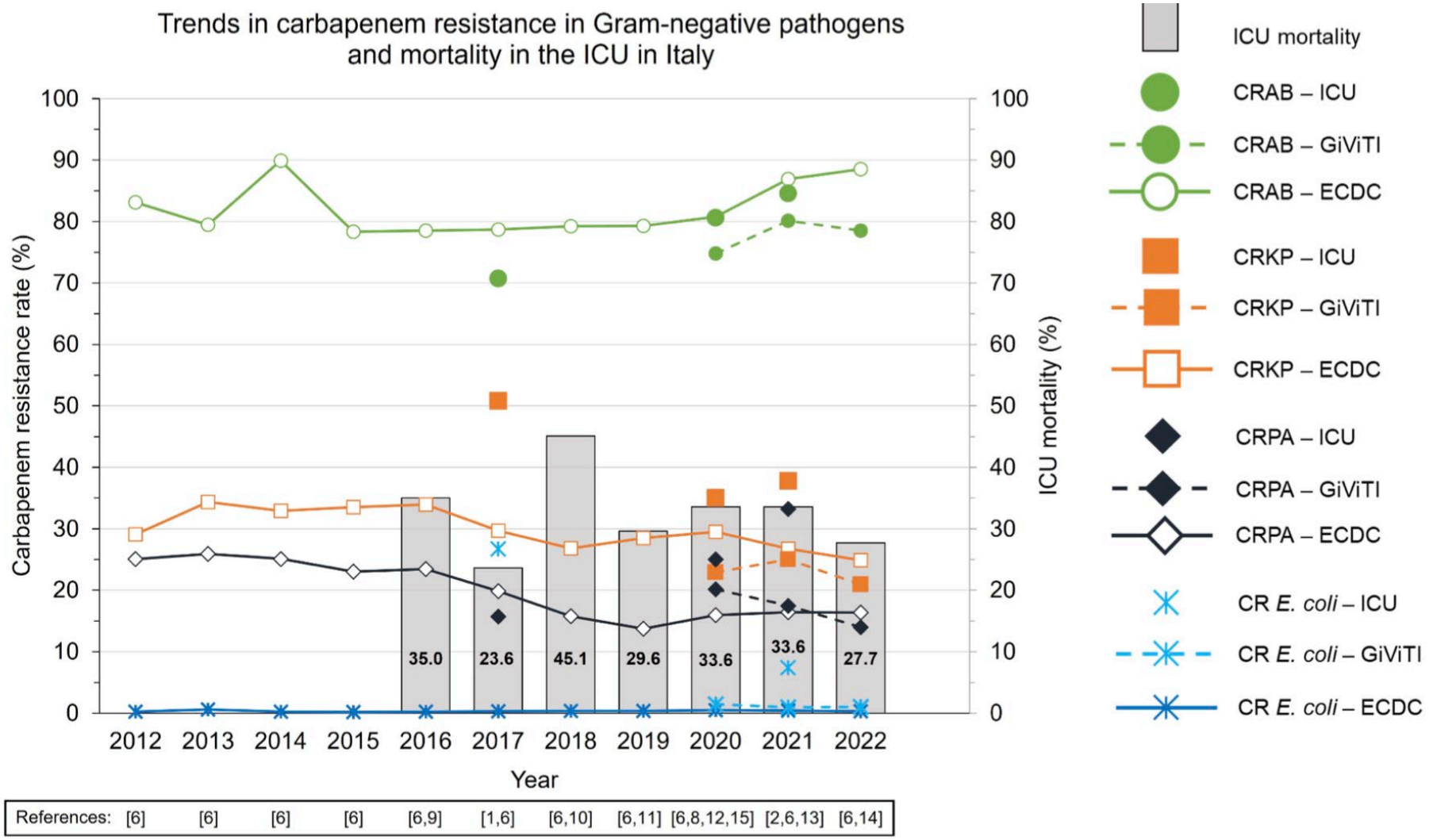
A. baumannii & Carbapenem Resistance (CR)

Viasus D et al. Curr Op Crit Care 2024

- ***A. baumannii***
  - Intrinsically resistant & easily acquiring resistance
  - Once carbapenem-resistant → it typically exhibits multiple resistances compared to its wild-type form
- **Resistance mechanisms**
  - OXA carbapenemases, metallo-blactamases
  - Other serine carbapenemases (e.g., *A. baumannii*-derived cephalosporinases)
  - Sulbactam resistance by mutations affecting penicillin-binding proteins (PBPs) and b-lactamase production
- **Resistance rates to IMI & MERO** **62% and 64% respectively**
  - Highest resistance rate in Asia & lowest in Europe **70% & 57% for MER**
  - Systematic review: *Tavasol A et al. Infect Dis Clin Practice 2023*
- **EUROBACT-2 study Vs. EUROBACT → CR (>AB) higher in adults with hospital-acquired BSI**
  - 11 years difference **68.7% to 84.6%**
  - *Tabah A et al. Intens Care Med 2012; Tabah A et al. Intens Care Med 2023*

Predicting Early Appropriate Therapy for ICU Patients with Carbapenem-resistant Pathogens

Bassetti M et al. Antimicrobial Resistance & Infection Control 2024;13:91



Predicting Early Appropriate Therapy for Patients Infected by Carbapenem-resistant Pathogens in ICU

Bassetti M et al. Antimicrobial Resistance & Infection Control 2024;13:91

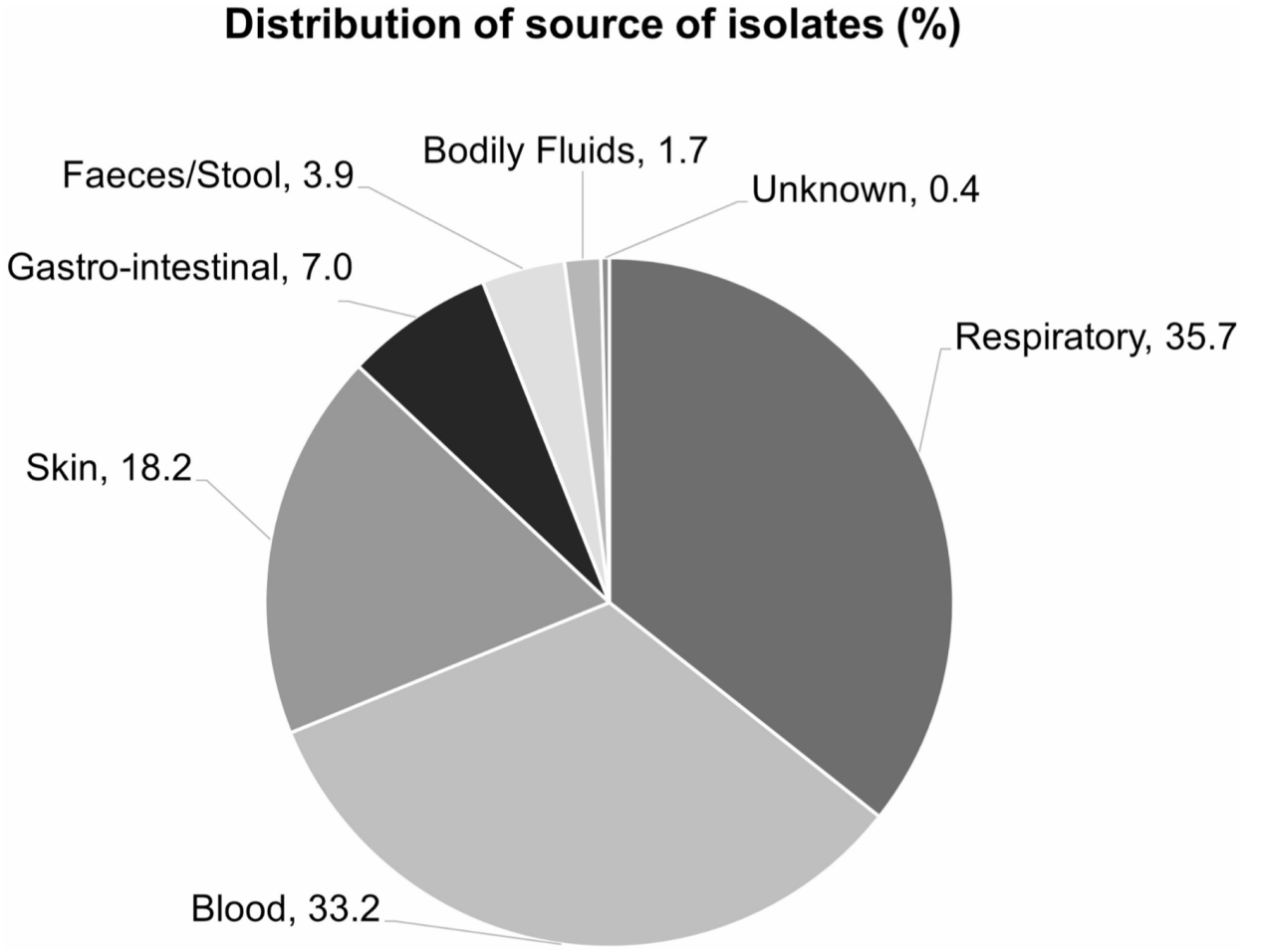


Fig. 2 Infection sources for 771 Italian isolates[a, b] collected in the ARTEMIS surveillance study
[a]Gram-negative isolates included in the current surveillance: *A. baumannii* 138; *P. aeruginosa* 206; *K. pneumoniae* 187; *E. coli* 93
[b]Additional Gram-negative isolates collected in Italy: *Klebsiella oxytoca* 15; *Klebsiella aerogenes* 11; *Klebsiella variicola* 5; *Klebsiella unspeciated* 3; *Enterobacter* spp. 57; *Serratia* spp. 12; *Citrobacter* spp. 7; *Proteus* spp. 12; *Morganella morganii* 11; *Providencia stuartii* 2; *Acinetobacter* spp. 1

Stenotrophomonas maltophilia: *in vitro* Activity of Ceftazidime/avibactam Alone & with Aztreonam

Ranieri EM et al. J Chemother 2023;24:1-4

- **Evaluation of the *in vitro* activity vs. *S. maltophilia***
  - E-test method
  - Ceftazidime/avibactam (CZA) alone
  - CZA in combination with aztreonam (ATM)
  - SXT and Levofloxacin (LEV) also investigated
- **Resistance:**
  - 22% to CZA, 2% to SXT and 26% to LEV
- **CZA-ATM combination:**
  - Synergistic activity against 86% of the strains
  - Including all those resistant to CZA
- **CZA / ATM → New therapeutic option**
- **Severe respiratory infections in critically ill patients**

PBP-3 Modifications on Susceptibility to New Beta-Lactams
Le Terrier C et al AAC 2024

- **AZA is a new option for MBL producers**
- **Enterobacterales & Broad spectrum cephalosporins resistance:**
  - β-lactamase production is the most common mechanism
  - PBP modifications may play a significant role with novel BL/BLI, such as AZA
- **AZA activity in *E. coli* is reduced with:**
  - Alterations of the PBP3 sequence
  - Particularly insertions of four amino acids YRIN or YRIK
- **AZA reduction of sensitivity of *E. coli***
  - Particularly with co-expression of acquired broad-spectrum β-lactamases
    - Class C β-lactamase CMY-42
    - Class B β-lactamase NDM-5
  - Co-expression of CTX-M-15 → high affinity for aztreonam
- **FEP, FDC & FEP-TAN activities may also be affected by PBP3 modifications**

AZA: Aztreonam-avibactam; MBL: metallo-beta lactamases; FEP: cefepime; FEP-TAN: cefepime-taniborbactam

Treatment Recommendations for MBL-producing Pathogens: IDSA Guidances & ESCMID guidelines

Grabein T et al. Infect Dis Ther 2024

	IDSA Guidances	ESCMID Guidelines
CRE	ATM + CAZ-AVI or Cefiderocol	ATM+CAZ-AVI or Cefiderocol
	ATM + MEM-VAB or IMI-REL	
	Tigecycline or Eravacycline	Combo Therapy with two of: Polymixins, aminoglycosides or fosfomycin
DTR-PA	Cefiderocol	Combo Therapy with two of: Polymixins, aminoglycosides or fosfomycin
CRAB	Combo Therapy with high dose ampicillin-sulbactam with either tetracyline derivatives (mino or tige) or polymyxin B or Cefiderocol	Ampicillin-sulbactam
		Polymyxin or high dose Tigecycline
		Combo Therapy with two of: polymyxins, aminoglycosides, tigecycline, sulbactam
S. maltophilia	Combo Therapy with two of: TMP-SMX, mino ot tige, cefiderocol, ATM + CAZ-AVI	