Ore 16.50-17.10 Metallo-β-lattamasi e OXA48: quale terapia

C. Tascini

Prof Carlo Tascini

Direttore Clinica Malattie Infettive

ASUFC Università di Udine

c.tascini@gmal.com

Il sottoscritto Carlo Tascini
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

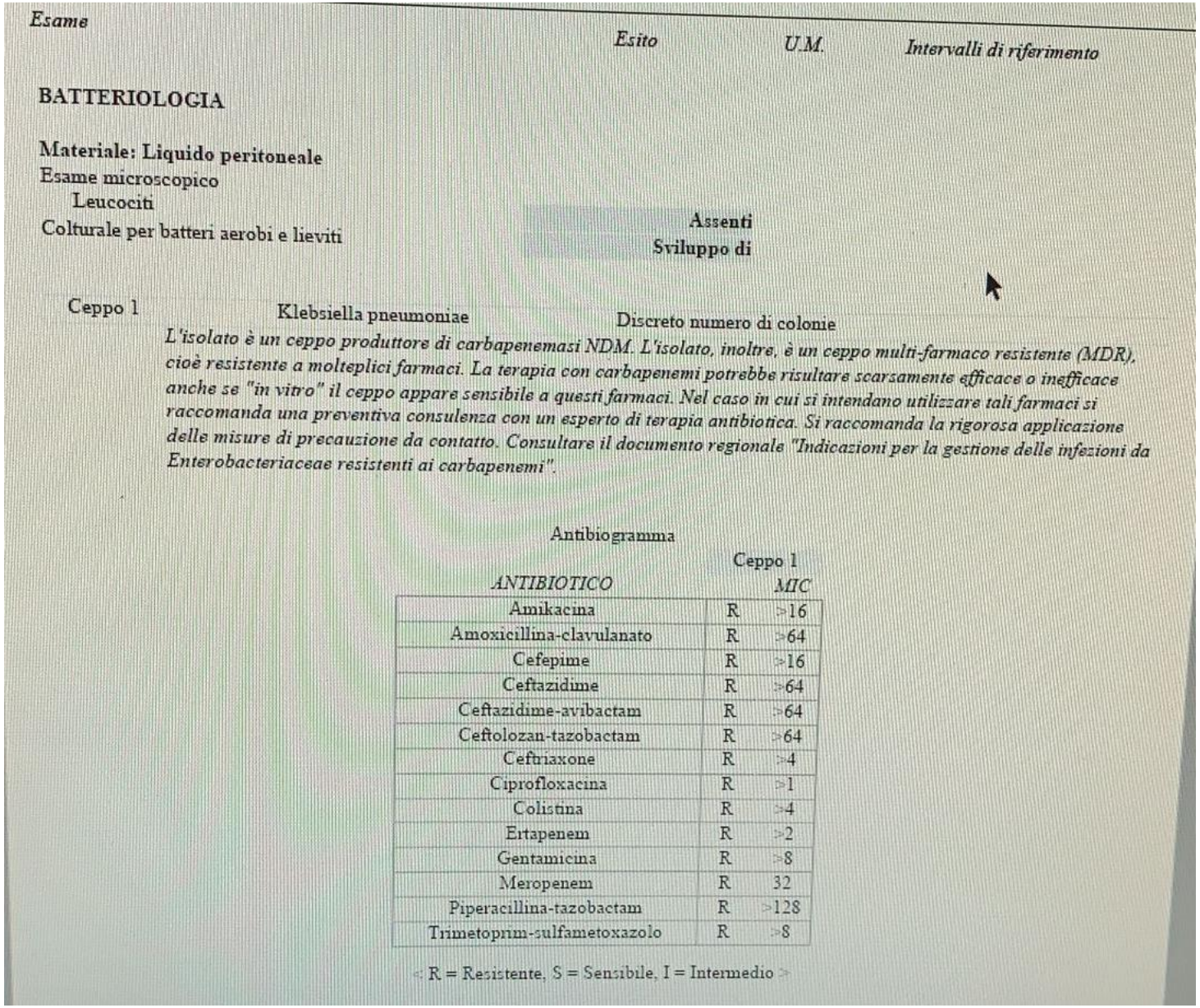
che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- *Astra*
- *Merck*
- *Pfizer*
- *Astellas*
- *Angelini*
- *Gilead*
- *Novartis.*
- *Biomeriex*
- *Thermofischer*
- *Zambon*
- *Avir Pharma*
- *Shionogi*
- *Menarini*

Epatite acuta B sottoposta a OLT

- Paziente migliora emocolture negative
- 10 luglio 2021, relaparotomia, revisione ferita chirurgica, evacuazione ematoma sottocutaneo, biopsie epatiche
- Rigetto acuto trattato con tre boli di steroide
- Replica di CMV trattato con valgancilovir
- Continua terapia antimicrobica fino al 13 luglio 2021
- 14 luglio 2021 isolamento di NDM da liquido di drenaggio cefiderocol >256 mg/L

Liquido di drenaggio addominale del 14 luglio 2021



Esame	*Esito*	*U.M.*	*Intervalli di riferimento*
BATTERIOLOGIA			
Materiale: Liquido peritoneale			
Esame microscopico			
Leucociti	**Assenti**		
Colturale per batteri aerobi e lieviti	**Sviluppo di**		
Ceppo 1	Klebsiella pneumoniae	Discreto numero di colonie	

L'isolato è un ceppo produttore di carbapenemasi NDM. L'isolato, inoltre, è un ceppo multi-farmaco resistente (MDR), cioè resistente a molteplici farmaci. La terapia con carbapenemi potrebbe risultare scarsamente efficace o inefficace anche se "in vitro" il ceppo appare sensibile a questi farmaci. Nel caso in cui si intendano utilizzare tali farmaci si raccomanda una preventiva consulenza con un esperto di terapia antibiotica. Si raccomanda la rigorosa applicazione delle misure di precauzione da contatto. Consultare il documento regionale "Indicazioni per la gestione delle infezioni da Enterobacteriaceae resistenti ai carbapenemi".

Antibiogramma

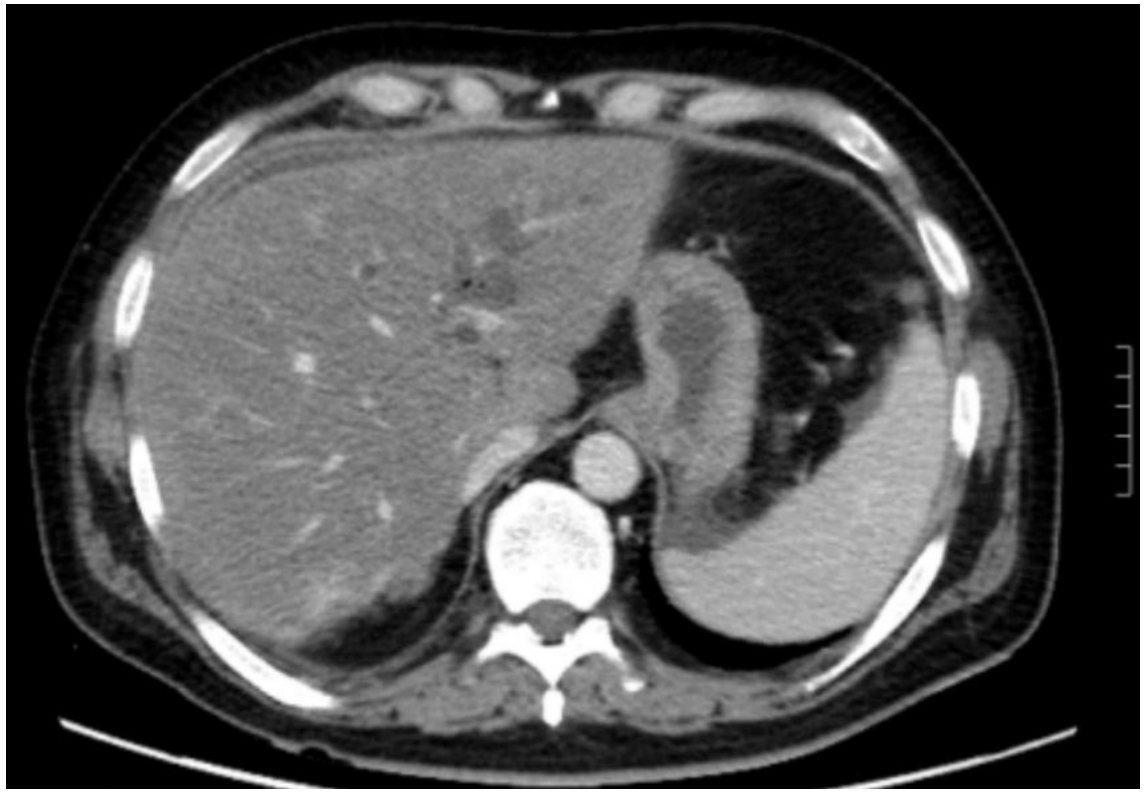
	Ceppo 1	
ANTIBIOTICO		*MIC*
Amikacina	R	>16
Amoxicillina-clavulanato	R	>64
Cefepime	R	>16
Ceftazidime	R	>64
Ceftazidime-avibactam	R	>64
Ceftolozan-tazobactam	R	>64
Ceftriaxone	R	>4
Ciprofloxacina	R	>1
Colistina	R	>4
Ertapenem	R	>2
Gentamicina	R	>8
Meropenem	R	32
Piperacillina-tazobactam	R	>128
Trimetoprim-sulfametoxazolo	R	>8

< R = Resistente, S = Sensibile, I = Intermedio >

Decorso

- Terapia con cefiderocol, tigeciclina dal 16 luglio fino al 16 agosto
- Paziente migliora come indici di flogosi e clinica
- 5 agosto 2021stenosi arteria epatica con angioplastica e stent senza successo , stenosi e ipoperfusione del graft
- Isolamento di NDM da drenaggio addominale del 3 agosto e ferita chirurgica del 16 agosto
- 21 agosto febbre, PCT 20, emocolture positive TAC addome lesione ascessuale del fegato

TAC addome



Decorso

- Terapia ceftazidime avibactam 2,5 g ogni 8 ore in infusione continua
- Aztreonam 2 g ogni 6 ore infusione continua
- Tigeciclina 100 mg x 2 die
- Anidulafungina dose standard
- Paziente inserito in lista per ri-trapianto (discussione sul rischio di futilità)

Emocoltura 22 agosto *Klebsiella* NDM

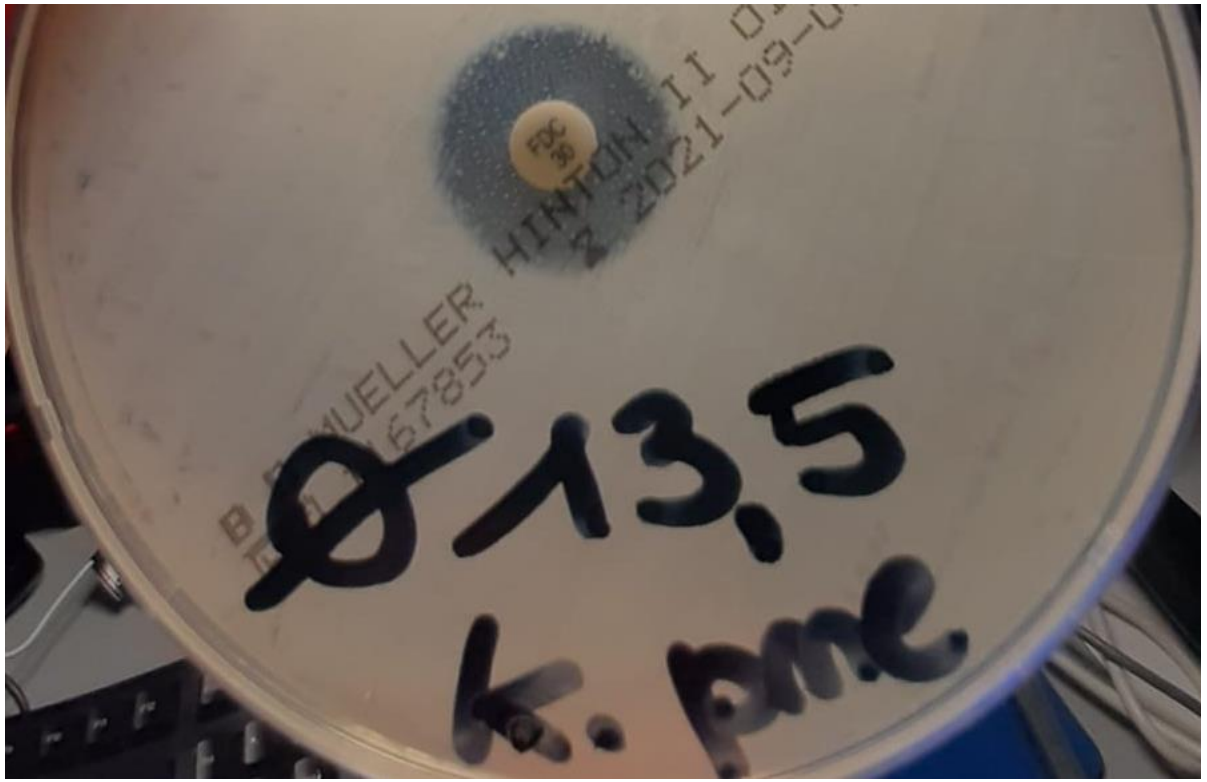
Tigeciclina MIC= 2

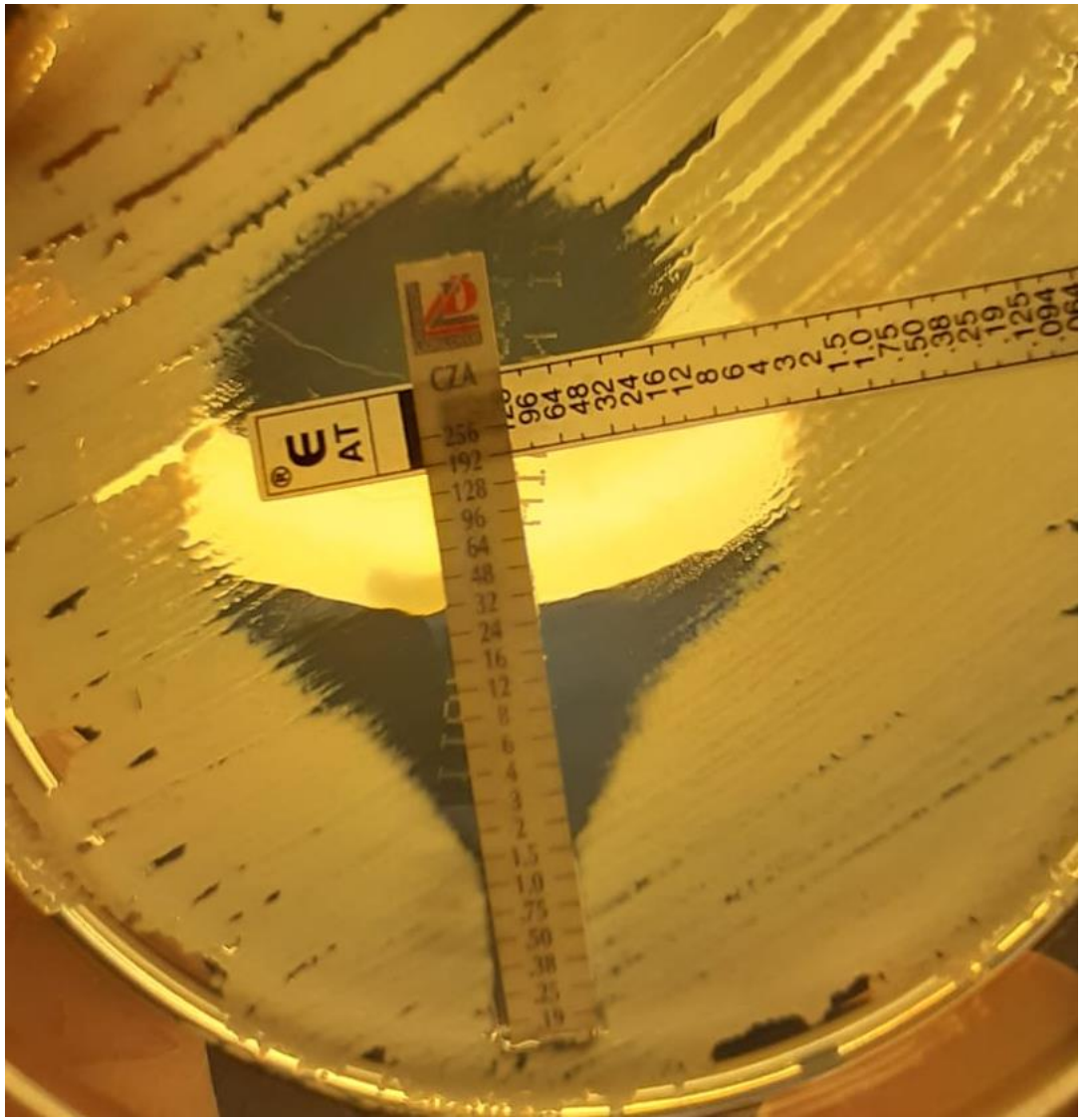
Antibiogramma

	Ceppo 1	
ANTIBIOTICO		*MIC*
Amikacina	R	>16
Amoxicillina-clavulanato	R	>64
Aztreonam	R	>1024
Cefepime	R	>16
Ceftazidime	R	>64
Ceftazidime-avibactam	R	>64
Ceftolozan-tazobactam	R	>64
Ceftriaxone	R	>4
Ciprofloxacina	R	>1
Colistina	S	<=0.5
Ertapenem	R	>2
Fosfomicina c/G6P	R	=64
Gentamicina	R	>8
Meropenem	I	8
Piperacillina-tazobactam	R	>128
Trimetoprim-sulfametoxazolo	R	>8

< R = Resistente, S = Sensibile, I = Intermedio >

Klebsiella NDM, resistente cefiderocol
Sinergismo aztreonam cazavi: MIC in associazione del cazavi 1,5 mg/L

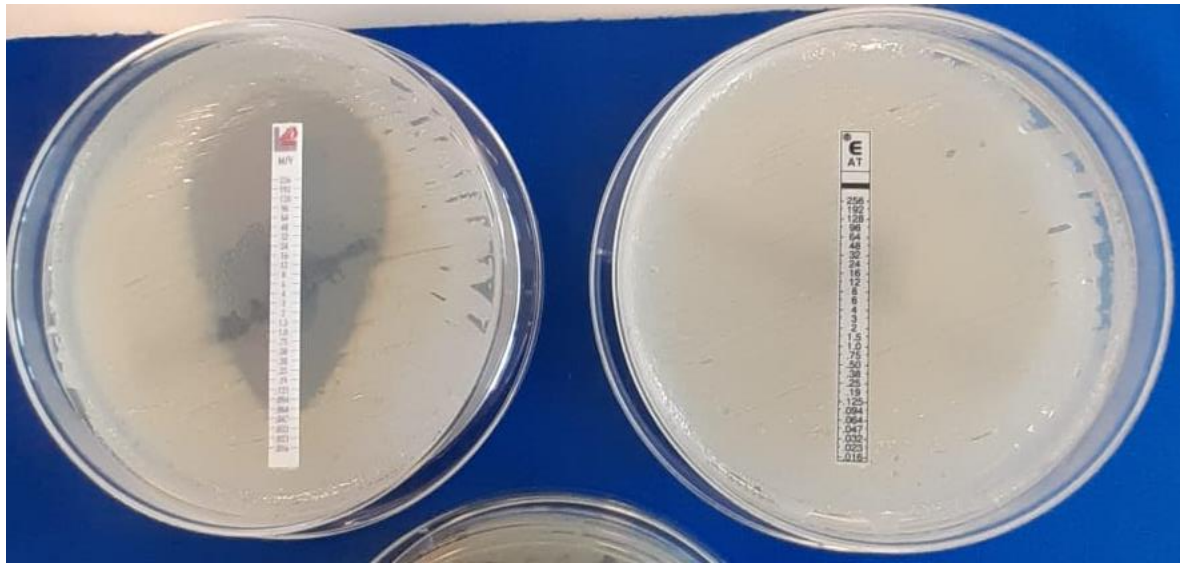


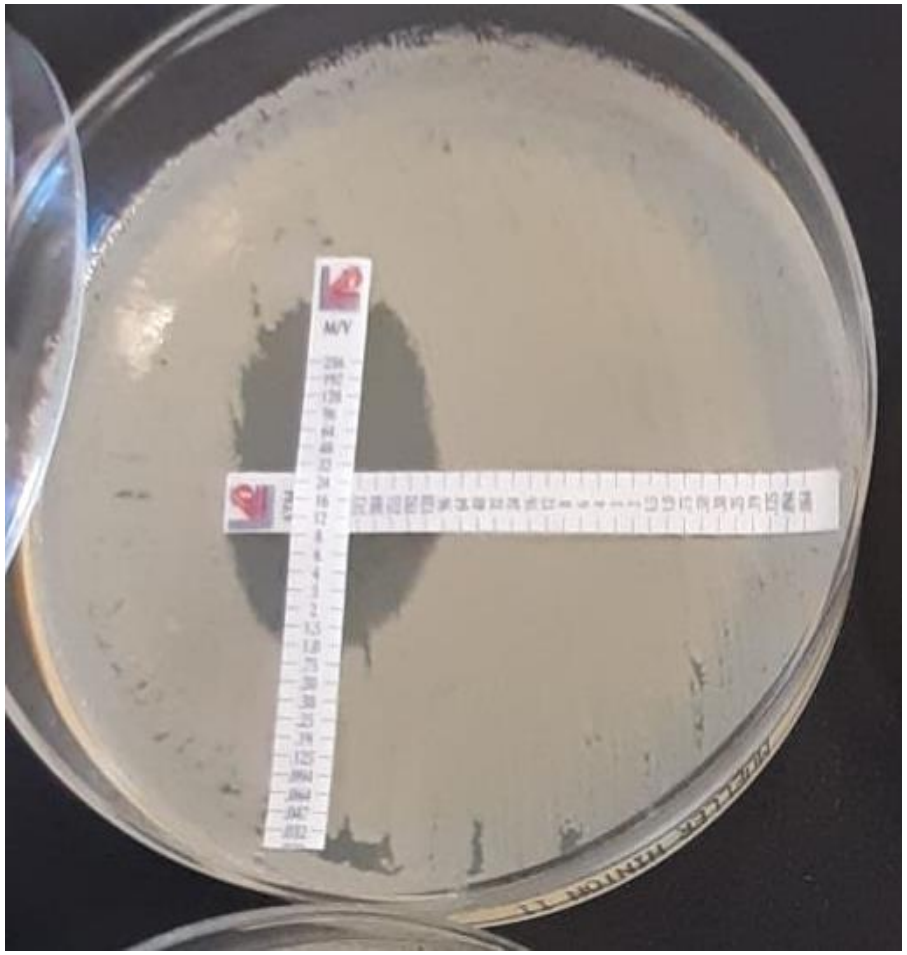


Paziente con NDM

Ceftazidime-Avibactam		
Peso del paziente	**95**	kg
Altezza	**192**	cm
Data-ora del prelievo pre-dose	**25.08.21 7.00**	
Concentrazione Ceftazidime pre-dose	**18.43**	mg/L
Concentrazione Avibactam pre-dose	**3.41**	mg/L
Dose consigliata	**2.5 gr ev ic**	mg
Intervallo di somministrazione	**6**	Ore
Data in cui ripetere il monitoraggio	**lunedì**	
Commento	**Concentrazione al di sotto del range terapeutico**	

Meropenem vaborbactm ed aztreonam





Ceppi inviati a Firenze

- Sequenza: NDM 1, ST type 147
- MIC con metodo di riferimento
- Ceppo Urine 28 giugno Cefiderocol MIC 8 mg/L
- Ceppo liquido peritoneale 3 luglio Cefiderocol MIC 32 mg/L
- Ceppo drenaggio 3 luglio Cefiderocol MIC 0,125 mg/L
- Ceppo Ferita 16 agosto Cefiderocol MIC 64 mg/L
- Ceppo emocoltura 22 agosto Cefidrocol MIC 128 mg/L

Paziente con NDM

- Risoluzione della sepsi
- Ritrapianto in due tempi 9 e 10 settembre 2021, con grave coagulopatia
- Esce dalla sala con 13 di PCT
- Sostituzione (11 settembre 2021) della terapia antibiotica con meropenem/vaborbactam ed aztreonam più tigeciclina
- PCT in calo ad 1
- TDM meropenem

Peso del paziente	**110**	kg
Altezza	**185**	cm
Data-ora del prelievo pre-dose	**15.09.21 6.30**	
MEROPENEM: Concentrazione pre-dose	**14.69**	mg/L
Commento	**Concentrazione in range terapeutico**	

Meropenem I.C.:
Css, 8-16 mg/L IN EMPIRICO
Css, > 16 MIC guidata Css 4-6 volte la MIC

colonizzazione

- Colonizzazione da K. Pneumoniae Oxa-48

Open Forum Infectious Diseases

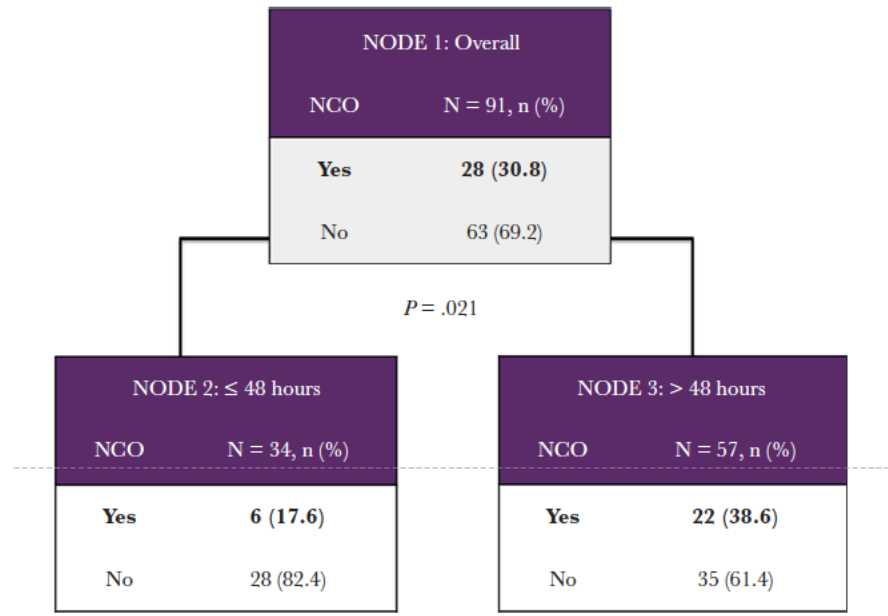
MAJOR ARTICLE

Real-world, Multicenter Experience With Meropenem-Vaborbactam for Gram-Negative Bacterial Infections Including Carbapenem-Resistant *Enterobacterales* and *Pseudomonas aeruginosa*

Sara Alosaimy,[1] Abdalhamid M. Lagnf,[1] Taylor Morrisette,[1] Marco R. Scipione,[2] Jing J. Zhao,[2] Sarah C. J. Jorgensen,[1,3] Ryan Mynatt,[1,4] Travis J. Carlson,[5,6] Jinhee Jo,[5] Kevin W. Garey,[5] David Allen,[7] Kailynn DeRonde,[8] Ana D. Vega,[8] Lilian M. Abbo,[8] Veena Venugopalan,[9] Vasilios Athans,[10] Stephen Saw,[10] Kimberly C. Claeys,[11] Mathew Miller,[12] Kyle C. Molina,[12] Michael Veve,[1,13,14] Wesley D. Kufel,[15,16] Lee Amaya,[17,18] Christine Yost,[17] Jessica Ortwine,[19] Susan L. Davis,[1,20] and Michael J. Rybak[1,2,21]

Table 2. Treatment-Related Outcomes

Variable[a]	Total Study (n = 126)	PsA Spp. (n = 8)[b]	Non PsA Spp. (n = 118)	CRE Spp. (n = 99)
Active antibiotics before MEV[c]	31 (24.6)	4 (50.0)	27 (22.9)	24 (24.2)
Time to active antibiotics, h	14.3 (0.0–75.5)	41.7 (0.05–83.2)	14.3 (0.0–74.3)	36.5 (0.75–75.2)
ID consult	125 (99.2)	7 (87.5)	118 (100)	99 (100.0)
ID consult within 48 h	93 (73.8)	6 (75.0)	87 (73.7)	71 (71.7)
Time to ID consult, h	6.7 (0.0–48.9)	0.0 (0.0–8.3)	8.6 (0.0–52.5)	11.1 (0.0–56.8)
Surgical consult	39 (30.9)	3 (37.5)	36 (30.5)	35 (35.4)
Source control[d]	40 (31.7)	3 (37.5)	37 (31.4)	35 (35.4)
Time to MEV, h	78.6 (29.8–124.3)	81.9 (56.2–116.7)	78.6 (28.5–126.57)	85.1 (48.6–133.1)
MEV duration, d	11.7 (5.9–15.2)	14.4 (5.3–15.2)	11.7 (6.0–14.9)	11.8 (6.7–16.0)



*The time breakpoint illustrated was the only time breakpoint identified by Classification and Regression Tree analysis
NCO: negative clinical outcome defined as 30-day mortality and/or 30-day recurrence

Figure 1. Classification and regression tree analysis–derived meropenem-vaborbactam initiation time breakpoint for negative clinical outcomes. [a]The time breakpoint illustrated was the only time breakpoint identified by classification and regression tree analysis Abbreviation: NCO, negative clinical outcome, defined as 30-day mortality and/or 30-day recurrence.

Meropenem vaborbactam

- Come impatta sul microbioma?

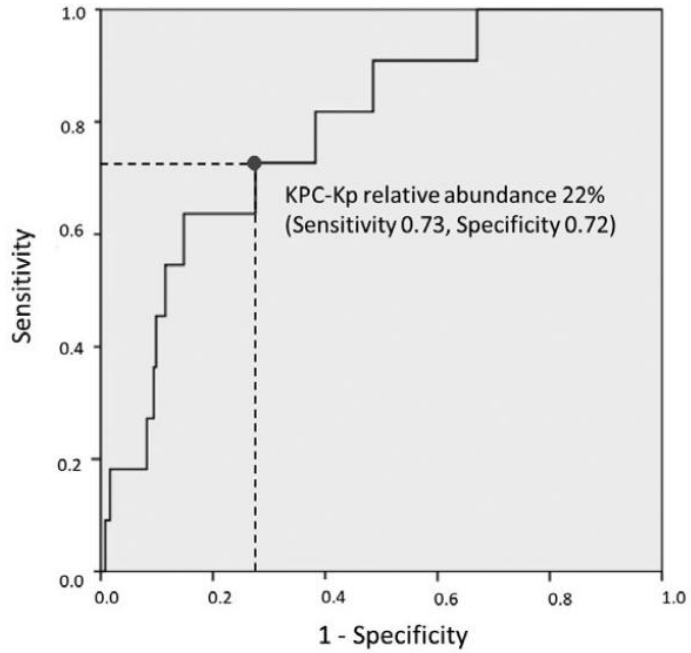
Table 3. Risk Factors Associated With ≥22% Relative Abundance of *Klebsiella pneumoniae* Carbapenemase-producing *Klebsiella pneumoniae* in the Gut Microbiota

Clinical Predictor	Hazard Ratio (95% Confidence Interval)	*P* Value
Age, years	0.99 (0.97–1.02)	.549
Charlson comorbidity index	0.90 (0.74–1.09)	.277
Any medical device use	1.05 (0.25–4.48)	.943
Mechanical ventilation	0.82 (0.39–1.71)	.588
Gastrostomy tube	0.62 (0.30–1.29)	.204
Central line	1.17 (0.55–25)	.689
Hemodialysis	0.77 (0.23–2.54)	.666
Urinary catheter	0.73 (0.34–1.55)	.409
Any antibiotic exposure	0.70 (0.24–2.07)	.519
Carbapenem	2.19 (1.06–4.55)	.036
Beta-lactam/beta-lactamase inhibitor	0.66 (0.23–1.90)	.436
Vancomycin (intravenous)	0.79 (0.38–1.66)	.537
Metronidazole	0.50 (0.12–2.12)	.351

Clinical Infectious Diseases
MAJOR ARTICLE

Increased Relative Abundance of *Klebsiella pneumoniae* Carbapenemase-producing *Klebsiella pneumoniae* Within the Gut Microbiota Is Associated With Risk of Bloodstream Infection in Long-term Acute Care Hospital Patients

Teppei Shimasaki,[1,©] Anna Seekatz,[2] Christine Bassis,[2] Yoona Rhee,[1] Rachel D. Yelin,[1] Louis Fogg,[3] Thelma Dangana,[1] Enrique Cornejo Cisneros,[1,4] Robert A. Weinstein[1], Koh Okamoto,[1,5] Kar
for the Centers for Disease Control and Pr



Results. We collected 2319 samples from 562 admissions (506 patients); KPC-Kp colonization was detected in 255 (45.4%) admissions and KPC-Kp bacteremia in 11 (4.3%). A relative abundance cutoff of 22% predicted KPC-Kp bacteremia with sensitivity 73%, specificity 72%, and relative risk 4.2 ($P = .01$). In a multivariable Cox regression model adjusted for age, Charlson comorbidity index, and medical devices, carbapenem receipt was associated with achieving the 22% relative abundance threshold ($P = .044$).

Conclusion. Carbapenem receipt was associated with increased hazard for high relative abundance of KPC-Kp in the gut microbiota. Increased relative abundance of KPC-Kp was associated with KPC-Kp bacteremia. Whether bacteremia arose directly from bacterial translocation or indirectly from skin contamination followed by bloodstream invasion remains to be determined.

J Antimicrob Chemother
doi:10.1093/jac/dkab306

Journal of Antimicrobial Chemotherapy

Increasing frequency of OXA-48-producing Enterobacterales worldwide and activity of ceftazidime/avibactam, meropenem/vaborbactam and comparators against these isolates

Mariana Castanheira[1]*, Timothy B. Doyle[1], Timothy D. Collingsworth[1], Helio S. Sader[1] and Rodrigo E. Mendes[1]

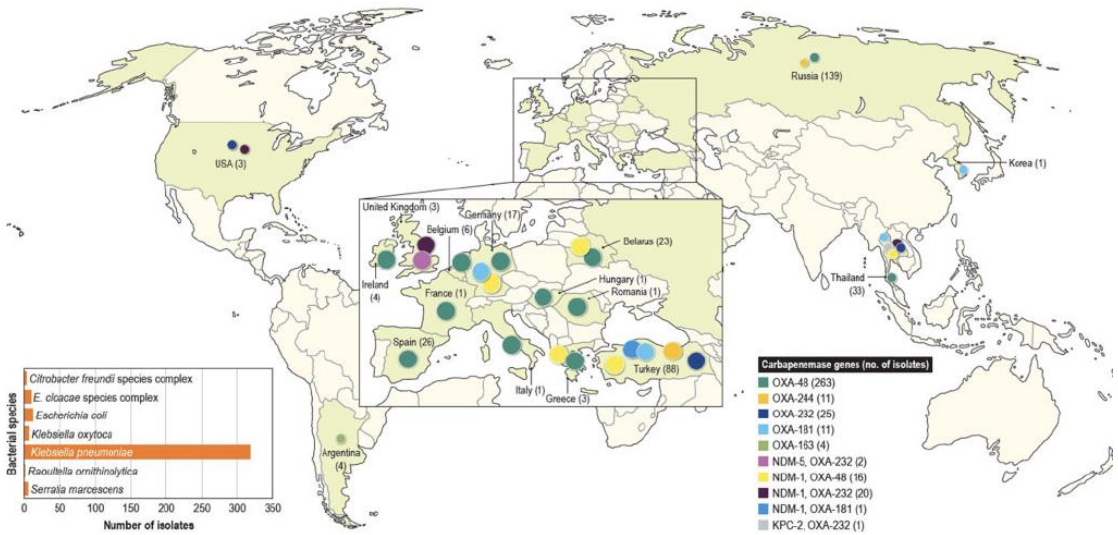
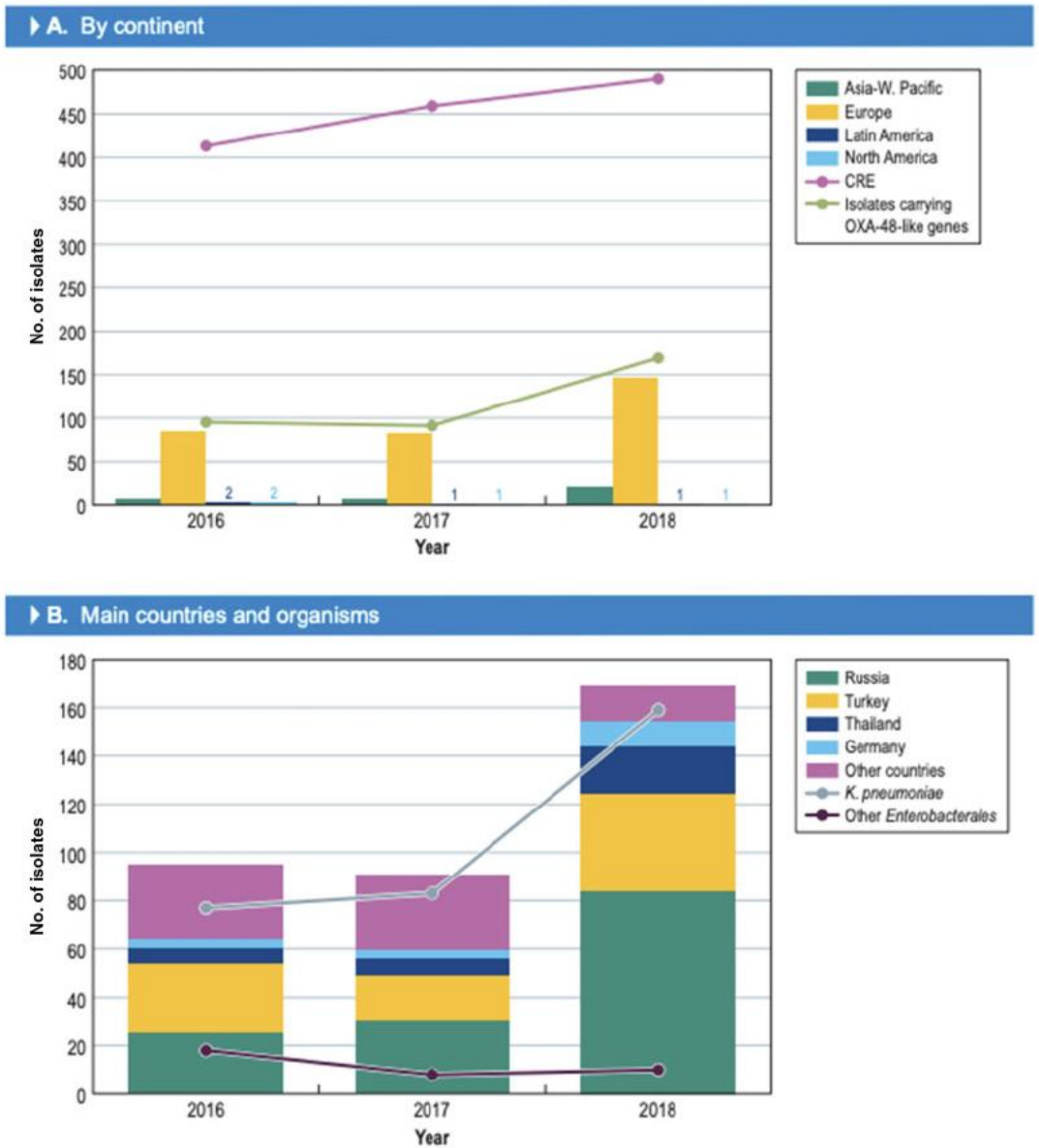


Figure 2. Distribution of OXA-48-like-encoding genes worldwide.



1. Increase in CRE and/or isolates carrying OXA-48-like genes in 2018 compared with 2016 and 2017.

J Antimicrob Chemother
doi:10.1093/jac/dkab306

Journal of Antimicrobial Chemotherapy

Increasing frequency of OXA-48-producing Enterobacterales worldwide and activity of ceftazidime/avibactam, meropenem/vaborbactam and comparators against these isolates

Mariana Castanheira[1]*, Timothy B. Doyle[1], Timothy D. Collingsworth[1], Helio S. Sader[1] and Rodrigo E. Mendes[1]

Table 2. Susceptibility profiles of 315 OXA-48-producing Enterobacterales without MBL genes

				CLSI[a]			EUCAST[a]		
Antimicrobial agent	MIC_{50}	MIC_{90}	Range	%S	%I	%R	%S	%I	%R
Ceftazidime/avibactam	2	4	0.06 to >8	99.0		1.0	99.0		1.0
Meropenem/vaborbactam	16	>16	0.06 to >16	46.7	3.2	50.2	49.8		50.2
Ceftazidime	>32	>32	0.06 to >32	20.6	1.3	78.1	15.9	4.8	79.4
Ceftriaxone	>8	>8	0.25 to >8	7.6	5.7	86.7	7.6	5.7	86.7
Cefepime	>16	>16	≤0.12 to >16	15.2	6.0	78.7[b]	10.8	8.6	80.6
Aztreonam	>16	>16	≤0.03 to >16	18.1	0.3	81.6	16.8	1.3	81.9
Imipenem	4	>8	≤0.12 to >8	7.3	18.4	74.3	25.7	29.5	44.8
Meropenem	>8	>8	0.06 to >8	24.8	11.1	64.1	35.9	11.7	52.4
Ampicillin/sulbactam	>32	>32	>32 to >32	0.0	0.0	100.0	0.0		100.0[c]
Piperacillin/tazobactam	>128	>128	2 to >128	0.6	0.3	99.0	0.6	0.0	99.4
Ceftolozane/tazobactam	>8	>8	0.25 to >8	10.2	9.8	80.0	10.2		89.8
Ciprofloxacin	>4	>4	≤0.03 to >4	7.0	1.6	91.4	7.0	1.6	91.4
Levofloxacin	>4	>4	≤0.03 to >4	11.2	1.6	87.2	11.2	1.6	87.2
Tetracycline	>16	>16	1 to >16	21.7	10.5	67.8			
Minocycline	8	>32	0.5 to >32	46.7	23.2	30.2			
Doxycycline	>8	>8	0.5 to >8	29.8	7.6	62.5			
Tigecycline	1	2	0.12 to 8	95.6	3.8	0.6[c]			
Amikacin	8	>32	0.5 to >32	56.8	1.9	41.3	51.1		48.9
Gentamicin	>8	>8	≤0.12 to >8	35.9	1.0	63.2	35.9		64.1
Tobramycin	>8	>8	≤0.12 to >8	17.1	9.5	73.3	14.9		85.1
Colistin	0.25	>8	≤0.06 to >8		81.5	18.5	81.5		18.5
Trimethoprim/sulfamethoxazole	>4	>4	≤0.5 to >4	21.0		79.0	21.0	6.7	72.3

J Antimicrob Chemother
doi:10.1093/jac/dkab306

Journal of Antimicrobial Chemotherapy

Increasing frequency of OXA-48-producing Enterobacterales worldwide and activity of ceftazidime/avibactam, meropenem/vaborbactam and comparators against these isolates

Mariana Castanheira[1]*, Timothy B. Doyle[1], Timothy D. Collingsworth[1], Helio S. Sader[1] and Rodrigo E. Mendes[1]

Group of *K. pneumoniae* isolates (no. of isolates)	% Susceptibility applying CLSI breakpoints								
	ceftazidime/avibactam	meropenem/vaborbactam	imipenem	meropenem	ceftazidime	ceftriaxone	cefepime	aztreonam	piperacillin/tazobactam
All *K. pneumoniae* (282)	99.6	42.6	6.4	19.9	15.6	5.7	13.1	15.6	0.7
OMPs									
OmpK35 stop codon (12)	100.0	75.0	8.3	50.0	0.0	0.0	0.0	0.0	0.0
OmpK36 alterations (67)	100.0	52.2	6.0	25.4	9.0	6.0	9.0	10.4	0.0
OmpK35 stop codon/OmpK36 alteration (175)	99.4	29.7	4.0	9.1	18.3	5.1	14.9	18.9	0.6
OmpK35 stop codon/OmpK36 G134 alteration (110)	99.1	0.9	0.9	0.9	18.2	5.5	13.6	18.2	0.9
OmpK35 stop codon/OmpK36 A183 alteration (63)	100.0	81.0	9.5	23.8	19.0	4.8	17.5	20.6	0.0
OmpK35 WT/OmpK36 WT (28)	100.0	85.7	21.4	60.7	21.4	10.7	17.9	14.3	3.6
ESBLs/transferable AmpC									
ESBL/transferable AmpC (245)	99.6	42.9	7.3	21.2	4.1	1.2	2.9	4.1	0.8
CTX-M-15 plus OXA-1 (155)	99.4	51.0	6.5	20.6	0.6	0.6	0.6	0.6	1.3
CTX-M-15 alone (58)	100.0	22.4	6.9	19.0	1.7	0.0	0.0	1.7	0.0
other CTX-M enzymes (15)	100.0	13.3	0.0	0.0	13.3	0.0	0.0	0.0	0.0
other ESBLs/transferable AmpC (12)	100.0	66.7	25.0	58.3	33.3	16.7	16.7	33.3	0.0
absent of ESBL/transferable AmpC (37)	100.0	40.5	0.0	10.8	91.9	35.1	81.1	91.9	0.0
ESBL plus OmpK35 stop codon/OmpK36 G134 alteration (91)	98.9	1.1	1.1	1.1	2.2	0.0	0.0	2.2	1.1
Both resistance mechanisms									
ESBL plus OmpK35 stop codon (64)	100.0	78.1	10.9	32.8	1.6	1.6	1.6	3.1	0.0
ESBL plus OmpK36 G134 alteration (25)	100.0	8.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
OmpK35 stop codon/OmpK36 G134 alteration without ESBL (21)	100.0	0.0	0.0	0.0	85.7	28.6	71.4	85.7	0.0
ESBL plus OmpK35 WT/OmpK36 WT (65)	100.0	80.0	15.4	46.2	10.8	3.1	9.2	9.2	1.5
OmpK35 stop codon without ESBL (11)	100.0	90.9	100.0	18.2	90.9	100.0	0.0	0.0	0.0
absent of ESBL plus OmpK35 WT/OmpK36 WT (5)	100.0	100.0	100.0	100.0	100.0	100.0	0.0	80.0	0.0

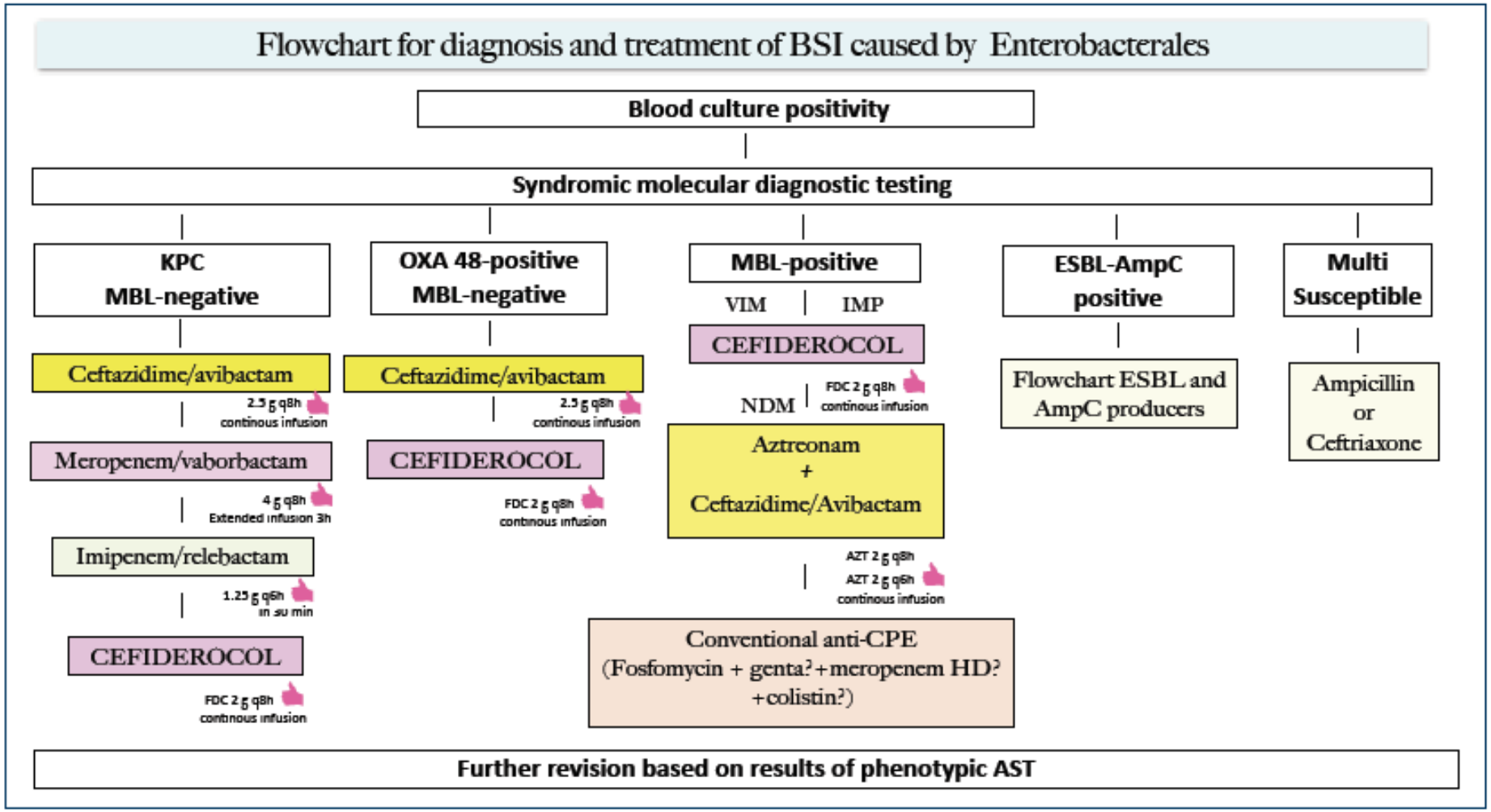


Figura 20. *Algoritmo decisionale diagnostico/terapeutico per il trattamento delle infezioni del torrente circolatorio da Enterobacterales KPC, OXA-48 e MβL-produttrici.*

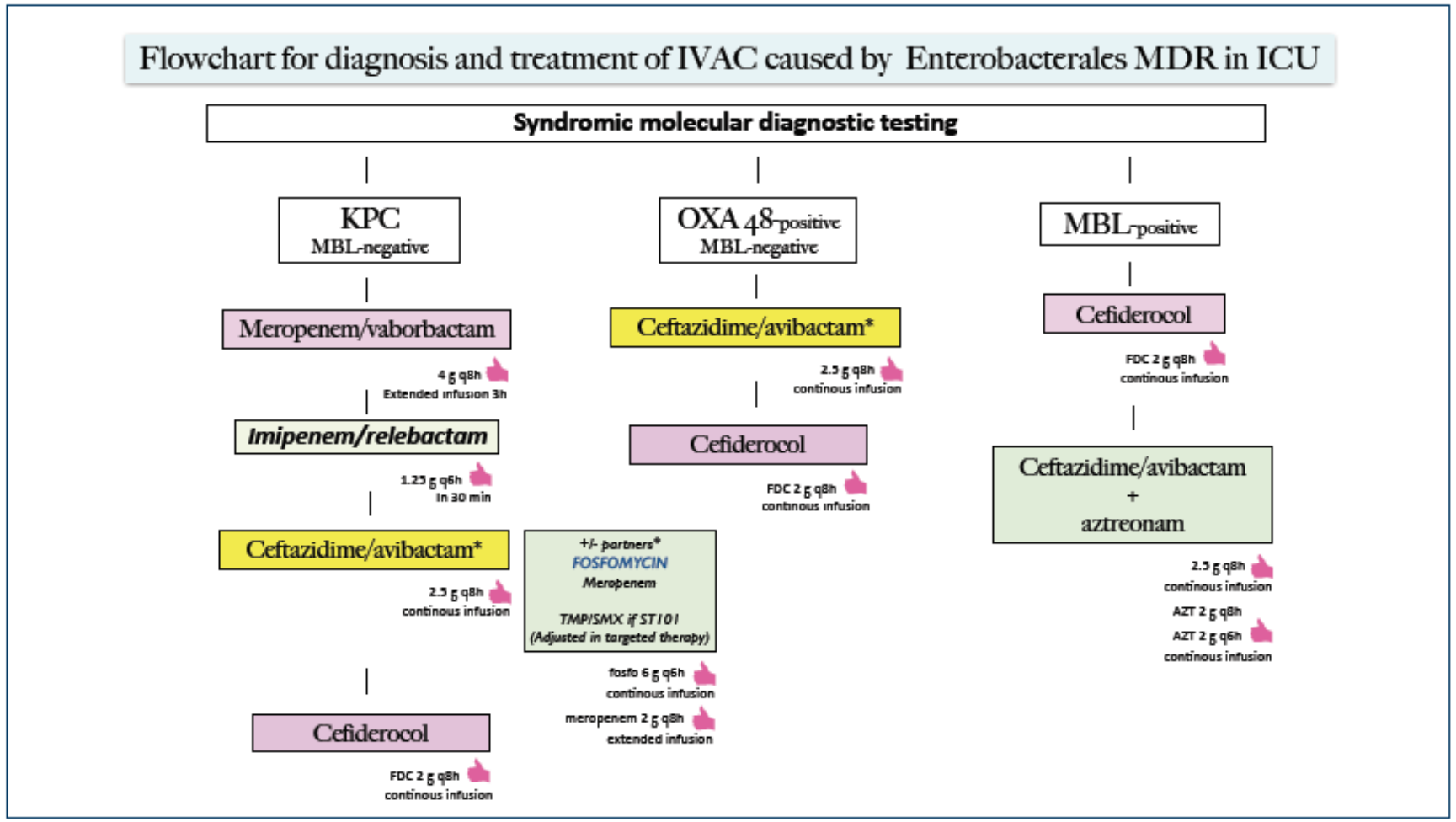
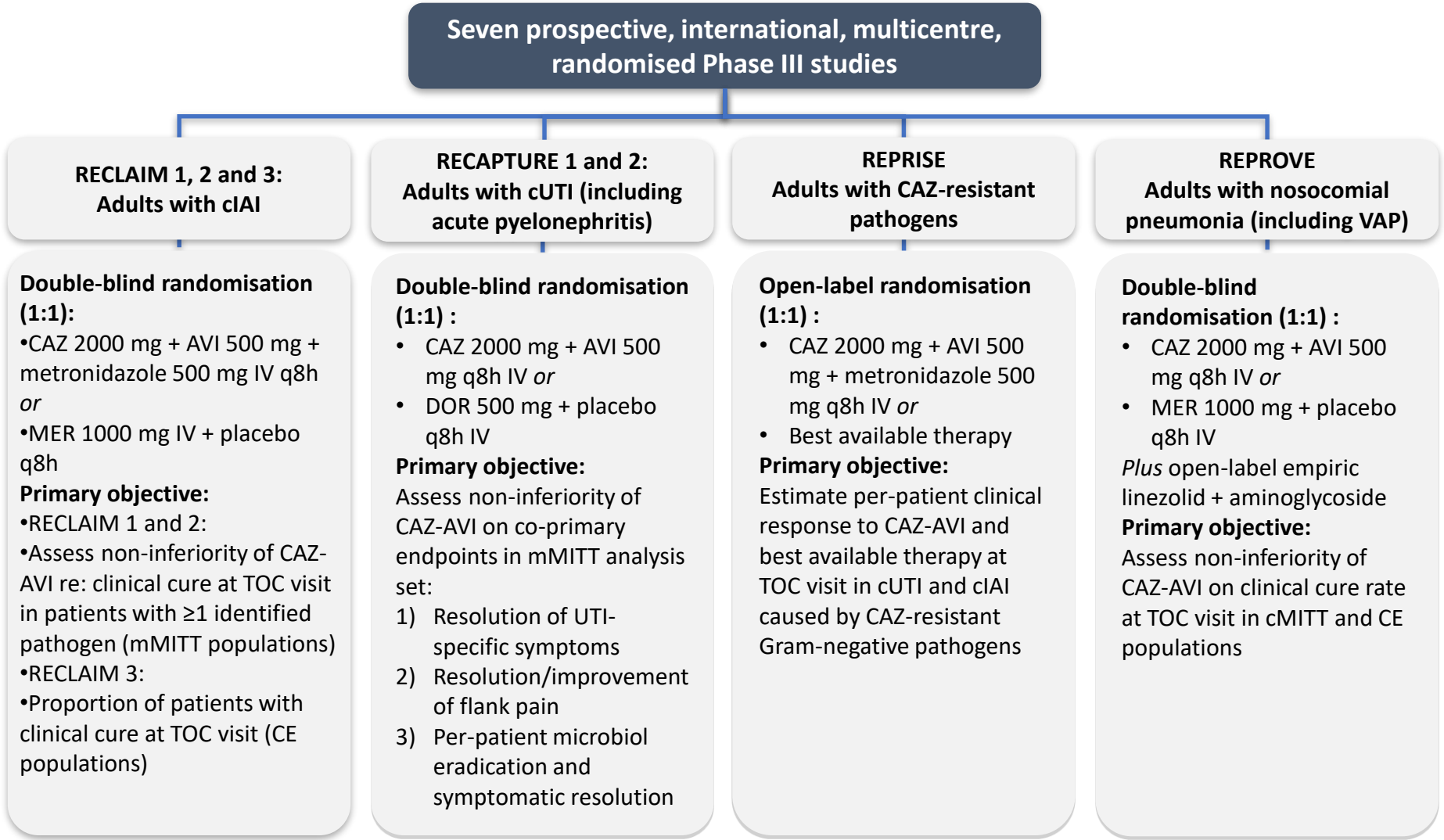


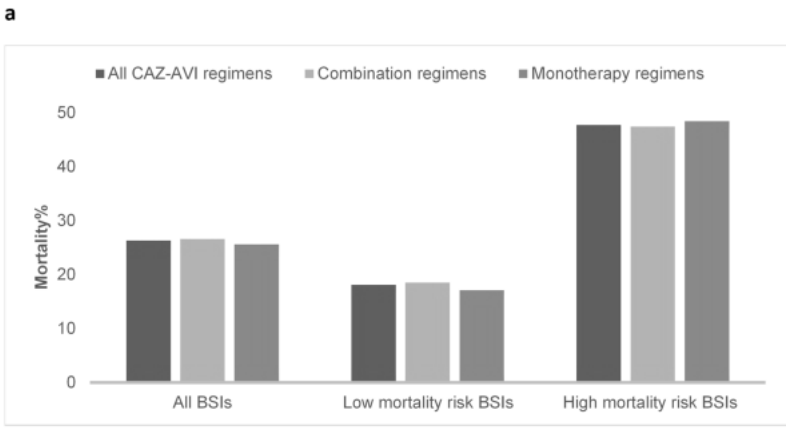
Figura 21. *Algoritmo decisionale diagnostico/terapeutico per il trattamento delle polmoniti associate al ventilatore da Enterobacterales KPC, OXA-48 e MβL-produttrici.*

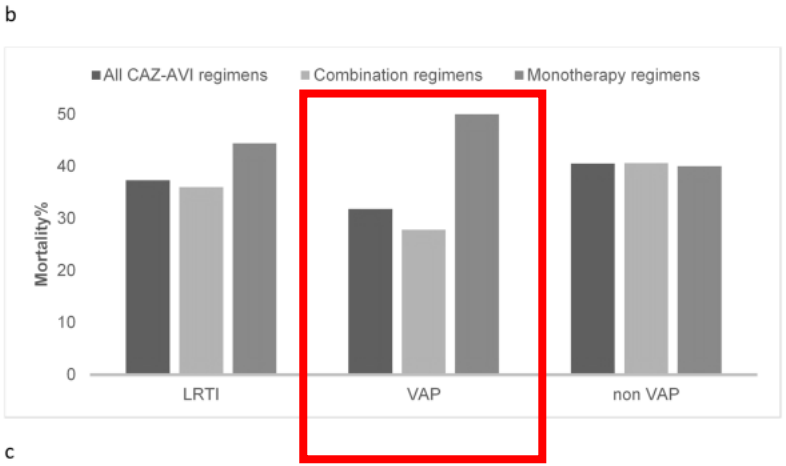


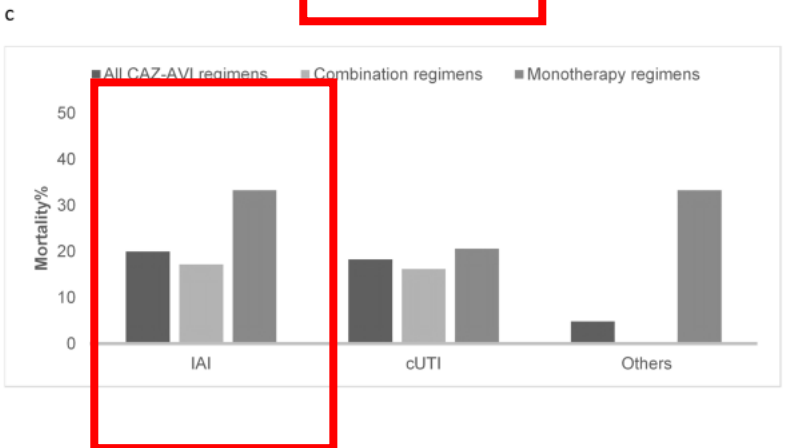
AVI, avibactam; CAZ, ceftazidime; CE, clinically evaluable; cIAI, complicated intra-abdominal infection; cMMIT, clinically modified intent-to-treat; cUTI, complicated urinary tract infection; DOR, doripenem; IV, intravenous; MER, meropenem; mMITT, microbiological modified intent-to-treat; q8h, every 8 h; TOC, test of cure; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

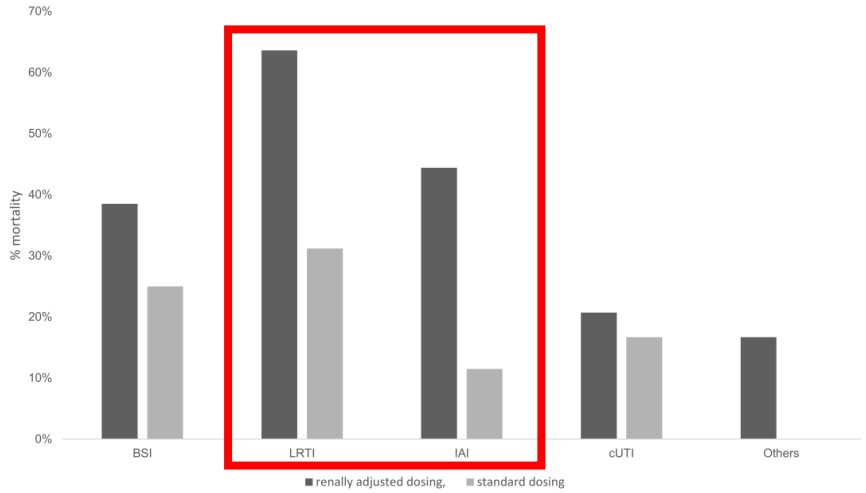
Zavicefta EMA EPAR. April 2016. Accessed Nov 2017 (www.ema.europa.eu, ceftazidime-avibactam PI)

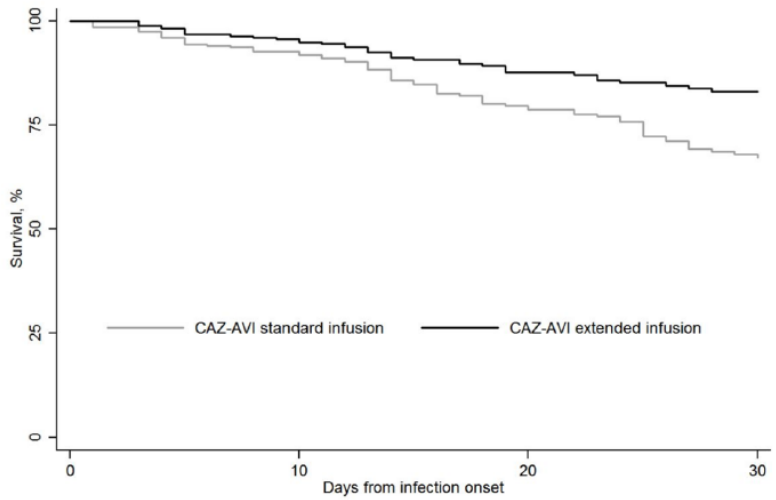
Tumbarello et al CID 2021







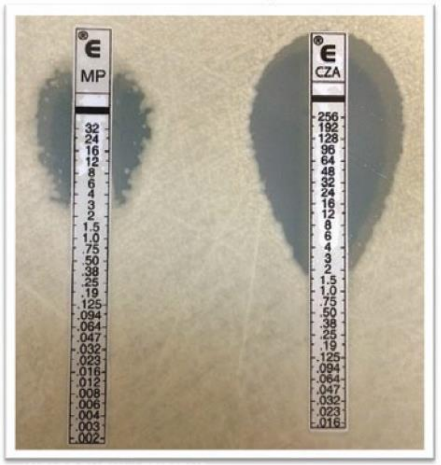




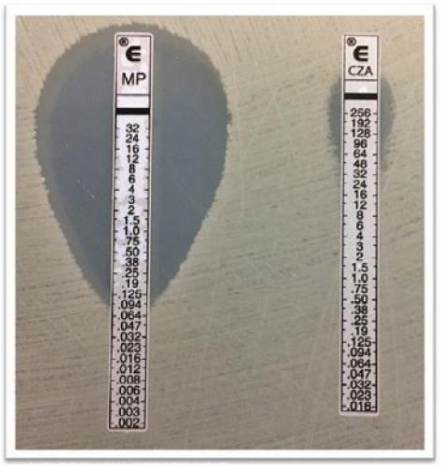
Emergence of Ceftazidime-Avibactam Resistance and Restoration of Carbapenem Susceptibility in *Klebsiella pneumoniae* Carbapenemase-Producing *K pneumoniae*: A Case Report and Review of Literature

Ryan K. Shields,[1,2] M. Hong Nguyen,[1,2] Ellen G. Press,[1] Liang Chen,[3] Barry N. Kreiswirth,[3] and Cornelius J. Clancy[1,2,4]

Isolate 4-A:
Meropenem-resistant
Ceftazidime-avibactam susceptible



Isolate 4-C:
Meropenem-susceptible
Ceftazidime-avibactam resistant



- Meropenem at clinically achievable concentrations was bactericidal against ceftazidime-avibactam-resistant *K pneumoniae* in vitro, and it eradicated isolate 4-C from our patient's bloodstream.
- However, meropenem resistance has emerged in ceftazidime-avibactam-resistant isolates from our patients during in vitro passage at subinhibitory meropenem concentrations.

Open Forum Infectious Diseases
ID CASE

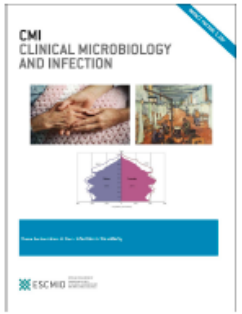
EUCAST clinical breakpoint: *Enterobacterales*

Enterobacterales *

Expert Rules and Intrinsic Resistance Tables

Cephalosporins[1]	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			N
	S ≤	R >	ATU		S ≥	R <	ATU	N
								Le
Cefaclor	-	-			-	-		1.
Cefadroxil (uncomplicated UTI only)	16	16		30	12	12		(in
Cefalexin (uncomplicated UTI only)	16	16		30	14	14		ge
Cefazolin (infections originating from the urinary tract), *E. coli*, and *Klebsiella spp.* (except *K. aerogenes*)	0.001[2]	4[2]		30	50[A]	20[A]		ES rec 2/
Cefepime	1	4		30	27	24		3. ins
Cefiderocol	2[3]	2[3]		30	22	22	18-22	htt
Cefixime (uncomplicated UTI only)	1	1		5	17	17		4.
Cefotaxime (indications other than meningitis)	1	2		5	20	17		*En* An typ
Cefotaxime (meningitis)	1	1		5	20	20		5.
Cefoxitin (screen only)[4]	Note[4]	Note[4]		30	19	19		6.
Cefpodoxime (uncomplicated UTI only)	1	1		10	21	21		7.
Ceftaroline	0.5	0.5		5	23	23	22-23	
Ceftazidime	1	4		10	22	19		
Ceftazidime-avibactam	8[5]	8[5]		10-4	13	13		

Journal Pre-proof



Molecular analysis of clinical isolates of ceftazidime-avibactam-resistant *Klebsiella pneumoniae*

Carolina Venditti, Ornella Butera, Marcello Meledandri, Maria Pia Balice, Giulio Cesare Cocciolillo, Carla Fontana, Silvia D'Arezzo, Chiara De Giuli, Mario Antonini, Alessandro Capone, Francesco Messina, Carla Nisii, Antonino Di Caro

Results: Molecular analyses highlighted the circulation of the ST512, 101 and 307 high-risk clones; 26/31 carried a mutated KPC variant, 5/31 a *wild-type* KPC-3. Among the KPC variants detected, 11 were different mutations within the bla_{KPC-3} gene, 4 of which were novel mutational changes.

Conclusions: Different mutations including single amino-acid substitutions, insertions or deletions within the bla_{KPC} gene were found in 26/31 CZA -resistant KPC-Kp strains belonging to high-risk clones circulating in Italy. Of note, in 14/31 cases the isolates displayed resistance to both CZA and carbapenems, raising the alarm for the possible selection of a multi-drug-resistant phenotype.

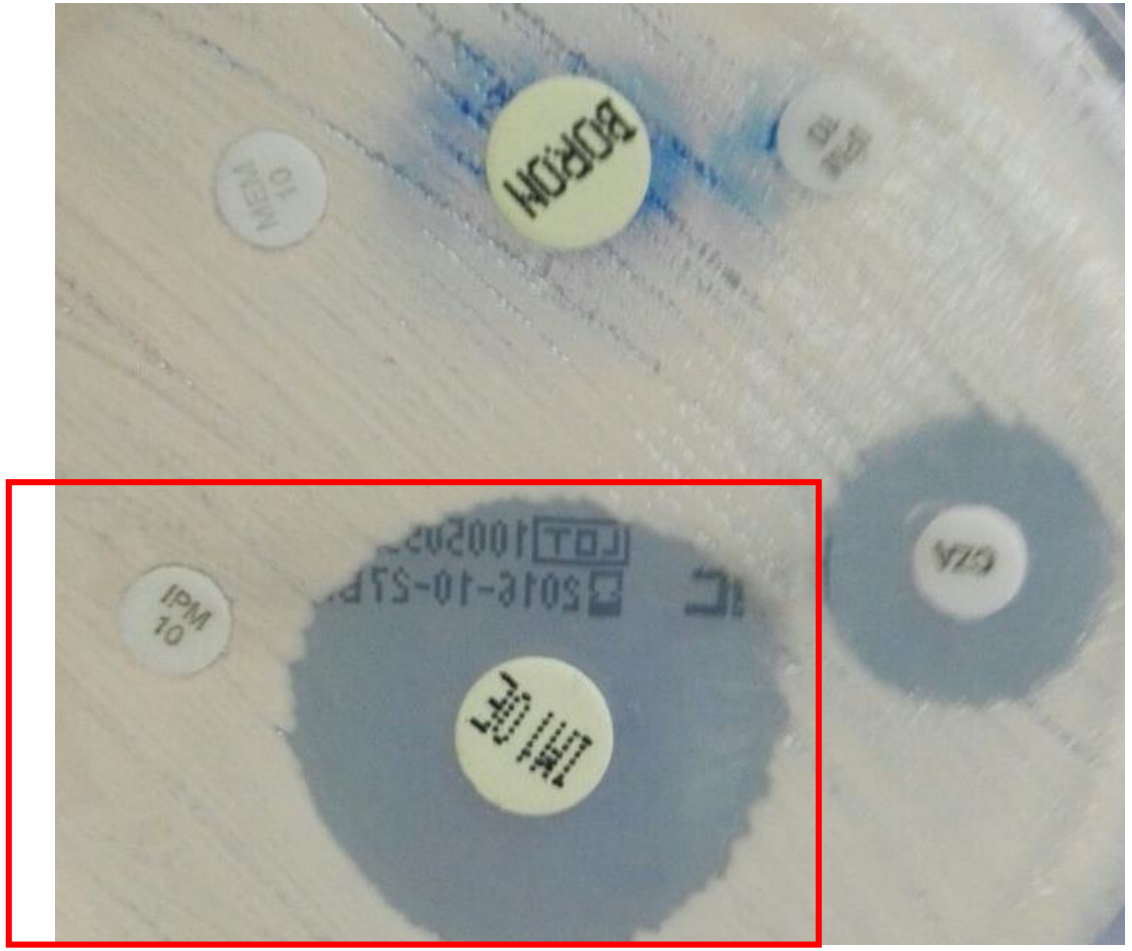
Journal Pre-proof

Molecular analysis of clinical isolates of ceftazidime-avibactam-resistant *Klebsiella pneumoniae*

Carolina Venditti, Ornella Butera, Marcello Meledandri, Maria Pia Balice, Giulio Cesare Cocciolillo, Carla Fontana, Silvia D'Arezzo, Chiara De Giuli, Mario Antonini, Alessandro Capone, Francesco Messina, Carla Nisii, Antonino Di Caro

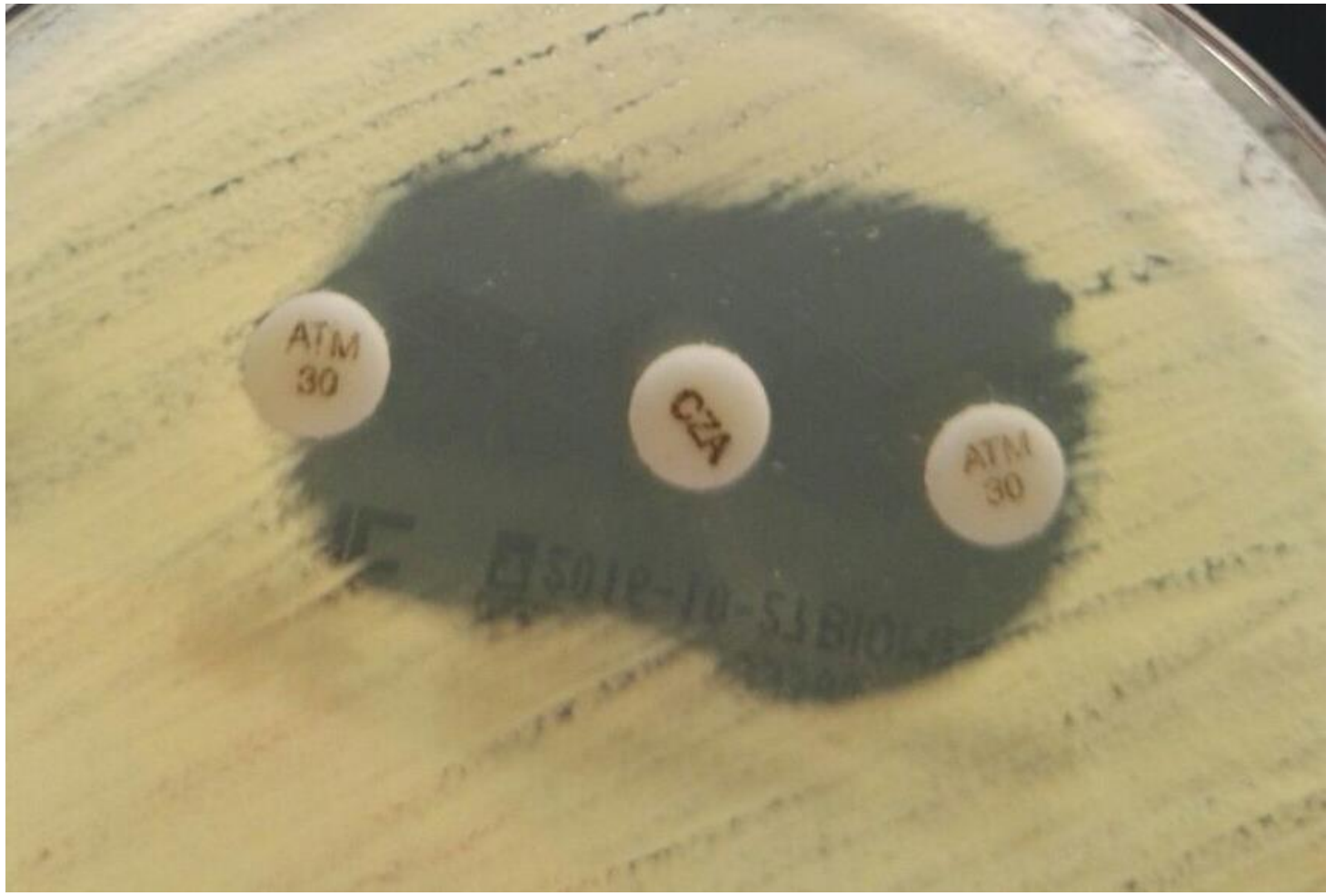
Patient[1]	Strain	Sample	KPC variant	Antibiotic MIC values (mg/L)[2]						
				CZA	ETP	IPM	MEM	GEN	COL	TGC
P-1	KP-1S	Blood	KPC-3	2, S	>8, R	≥32, R	>32, R	4, I	0.5, S	0.25, S
	KP-2R	Blood	KPC-46	32, R	>8, R	0.5, S	2, S	4, I	0.5, S	0.25, S
P-2	KP-3S	Brain abscess	KPC-3	1, S	2, R	4, I	3, I	4, I	0.5, S	0.25, S
	KP-4R	Blood	KPC-31	64, R	0.25, S	0.19, S	0.094, S	>4, R	0.5, S	0.25, S
P-9	KP-11S	Bile	KPC-3	1, S	>8, R	≥32, R	>32, R	4, I	0.25, S	1, S
	KP-12R	Blood	KPC-62	64, R	8, R	0.5, S	1.5, S	2, S	0.25, S	0.5, S
P-11	KP-14S	Rectal swab	KPC-3	2, S	4, R	3, I	3, I	4, I	0.25, S	1, S
	KP-15R	Rectal swab	KPC-53	12, R	1, R	2, S	0.5, S	2, S	0.25, S	0.5, S
P-13	KP-17S	Blood	KPC-3	3, S	≥32, R	16, R	32, R	0.5, S	0.5, S	0.38, S
	KP-18R	Blood	KPC-62	16, R	4, R	1, S	1, S	0.5, S	0.5, S	0.38, S
P-15	KP-20S	Blood	KPC-3	2, S	≥32, R	16, R	32, R	2, S	8, R	0.38, S
	KP-21R	Rectal swab	KPC-39	32, R	1.5, R	4, I	6, I	2, S	8, R	0.38, S
P-25	KP-31S	Sputum	KPC-3	2, S	≥32, R	12, R	4, I	2, S	0.5, S	1, S
	KP-32R	Rectal swab	KPC-64	>256, R	8, R	2, S	0.19, S	1, S	0.5, S	1, S
P-26	KP-33S	Blood	KPC-3	4, S	≥32, R	8, R	4, I	2, S	0.5, S	1, S
	KP-34R	Rectal swab	KPC-31	≥256, R	8, R	0.5, S	1.5, S	2, S	0.25, S	1, S

Test EDTA positivo, boronico negativo: metallo enzima, no KPC



Laboratorio Microbiologia Azienda Ospedaliera dei Colli

Sinergismo ceftazidime/avibactam ed aztreonam contro *Klebsiella* matallo-enzima (meropenem/vaborbactam?)



Laboratorio Microbiologia Azenda Ospedaliera dei Colli

Ceftazidime ed aztreonam da soli

Laboratorio Microbiologia Azienda Ospedaliera dei Colli

NDM

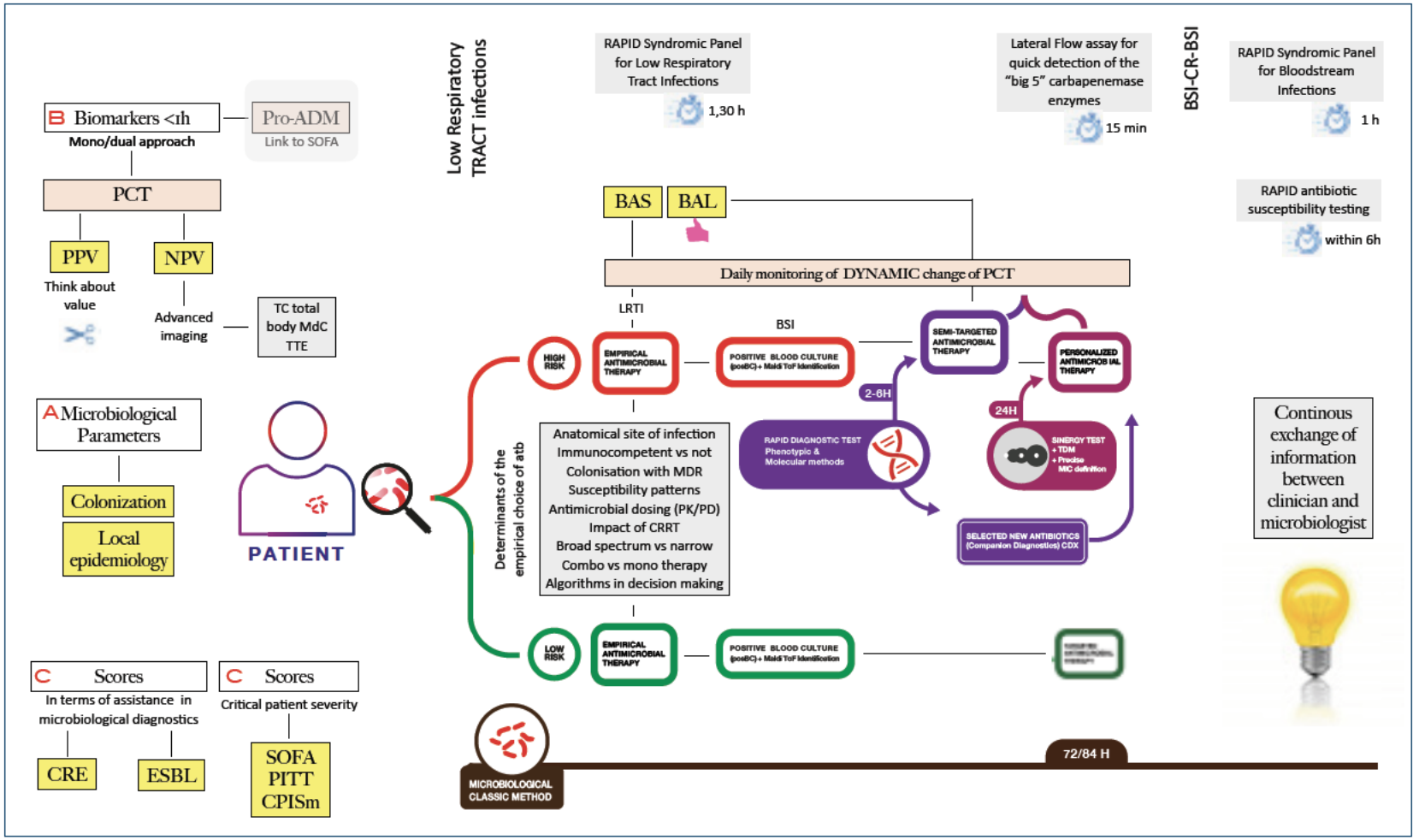
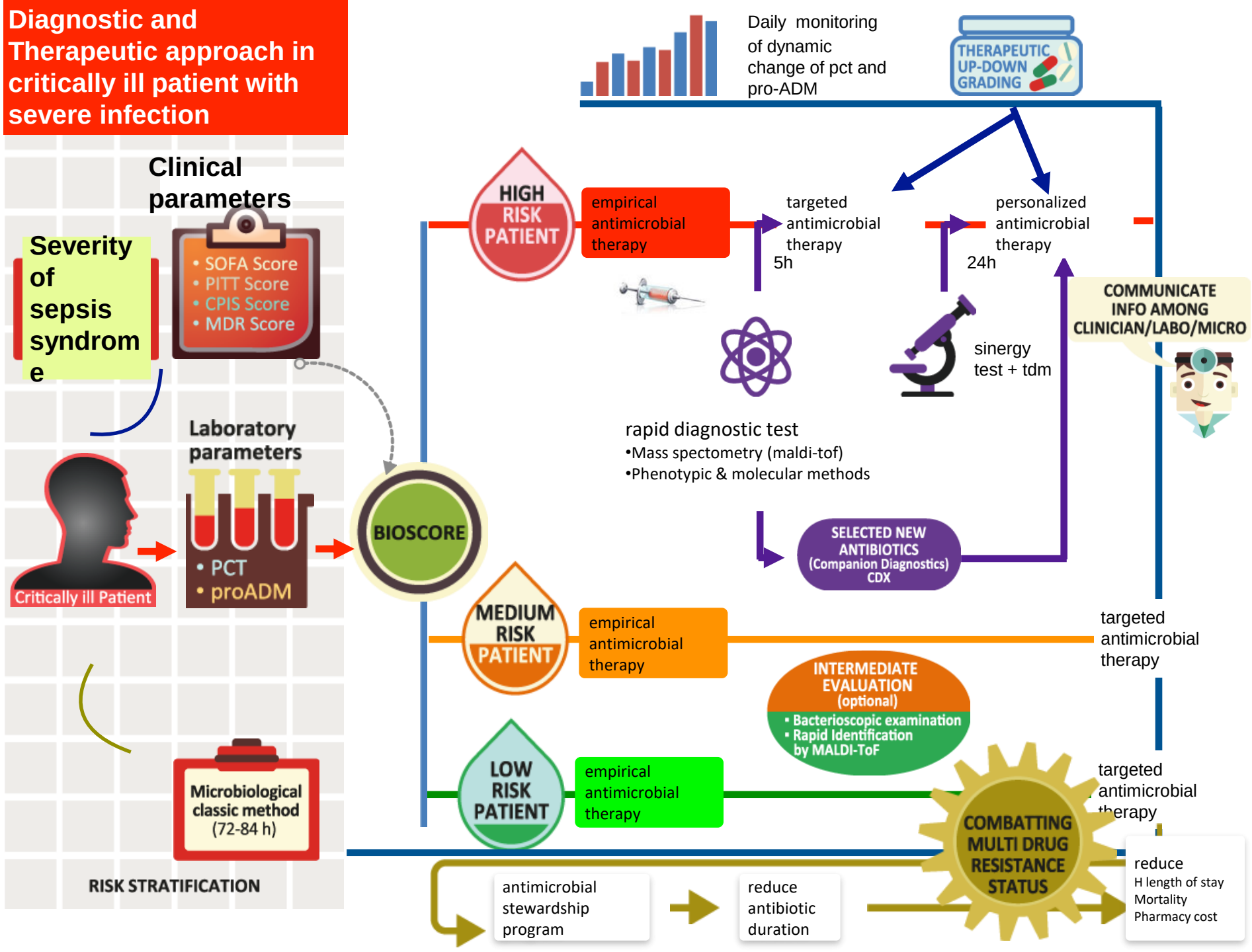


Figura 3. *Modello di Bioscore: strumento a supporto del miglior percorso di cura diagnostico-terapeutico del paziente critico affetto da grave infezione da MDR capace di rispondere alla domanda "chi va in diagnostica rapida?"*

Diagnostic and Therapeutic approach in critically ill patient with severe infection



Conclusioni

- Il laboratorio di microbiologia e farmacologia deve essere portato al letto del malato