LE INFEZIONI NEL NEUROMIELOLESO

SITA
Società Italiana di Terapia Antinfettiva Antibatterica Antivirale Antifungina

12° CONGRESSO NAZIONALE
CATANIA | 17-18 novembre 2022

OSPEDALE CANNIZZARO
CATANIA
AZIENDA OSPEDALIERA PER L'EMERGENZA

CARMELO IACOBELLO

UOC MALATTIE INFETTIVE

AOE CANNIZZARO

CATANIA

Il sottoscritto: IACOBELLO CARMELO

Ai sensi dell'art. 76 sul Conflitto di Interessi dell'Accordo Stato-Regioni del 02 febbraio 2017 in materia di ECM

Dichiara

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

- PFIZER
- ANGELINI
- MSD

Immunol Res. 2015 Dec;63(1-3):3-10. doi: 10.1007/s12026-015-8698-1.

Circulating T cell subsets are altered in individuals with chronic spinal cord injury.

Monahan R[1], Stein A[2], Gibbs K[1,2], Bank M[3], Bloom O[4,5,6,7].

Author information

Abstract

Traumatic spinal cord injury (SCI) induces changes in the immune system, both acutely and chronically. To better understand changes in the chronic phase of SCI, we performed a prospective, observational study in a research institute and Department of Physical Medicine and Rehabilitation of an academic medical center to examine immune system parameters, including peripheral immune cell populations, in individuals with chronic SCI as compared to uninjured individuals. Here, we describe the relative frequencies of T cell populations in individuals with chronic SCI as compared to uninjured individuals. We show that the frequency of CD3+ and CD3+ CD4+ T cells are decreased in individuals with chronic SCI, although activated (HLA-DR+) CD4+ T cells are elevated in chronic SCI. We also examined regulatory T cells (Tregs), defined as CD3+ CD4+ CD25+ CD127lo and CCR4+, HLA-DR+ or CCR4+ HLA-DR+. To our knowledge, we provide the first evidence that CCR4+, HLA-DR+ or CCR4+ HLA-DR+ Tregs are expanded in individuals with SCI. These data support additional functional studies of T cells isolated from individuals with chronic SCI, where alterations in T cell homeostasis may contribute to immune dysfunction, such as immunity against infections or the persistence of chronic inflammation.

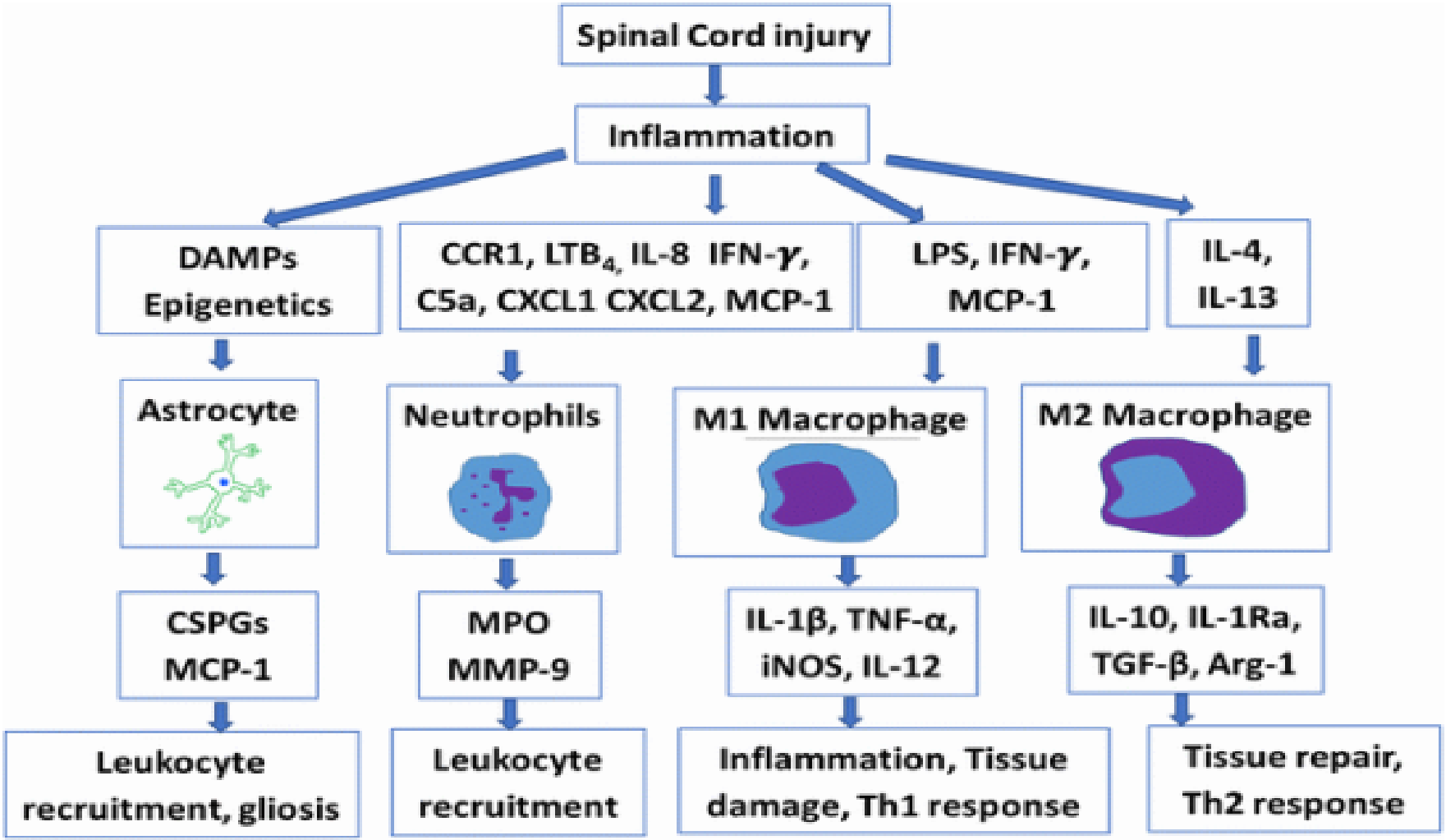


Figure 1.10 Immunological activities in Spinal Cord Patients adopted from [57]

[57]. Ahmed, A., Patil, A. A., & Agrawal, D. K. (2018). Immunobiology of spinal cord injuries and potential therapeutic approaches. *Molecular and cellular biochemistry*, *441*(1-2), 181–189. https://doi.org/10.1007/s11010-017-3184-9

Activation of Neuroprotective Microglia and Astrocytes at the Lesion Site and in the Adjacent Segments Is Crucial for Spontaneous Locomotor Recovery after Spinal Cord Injury

Alexandra Kisucká, Katarína Bimbová, Mária Bačová, Ján Gálik and Nadežda Lukáčová *

cells

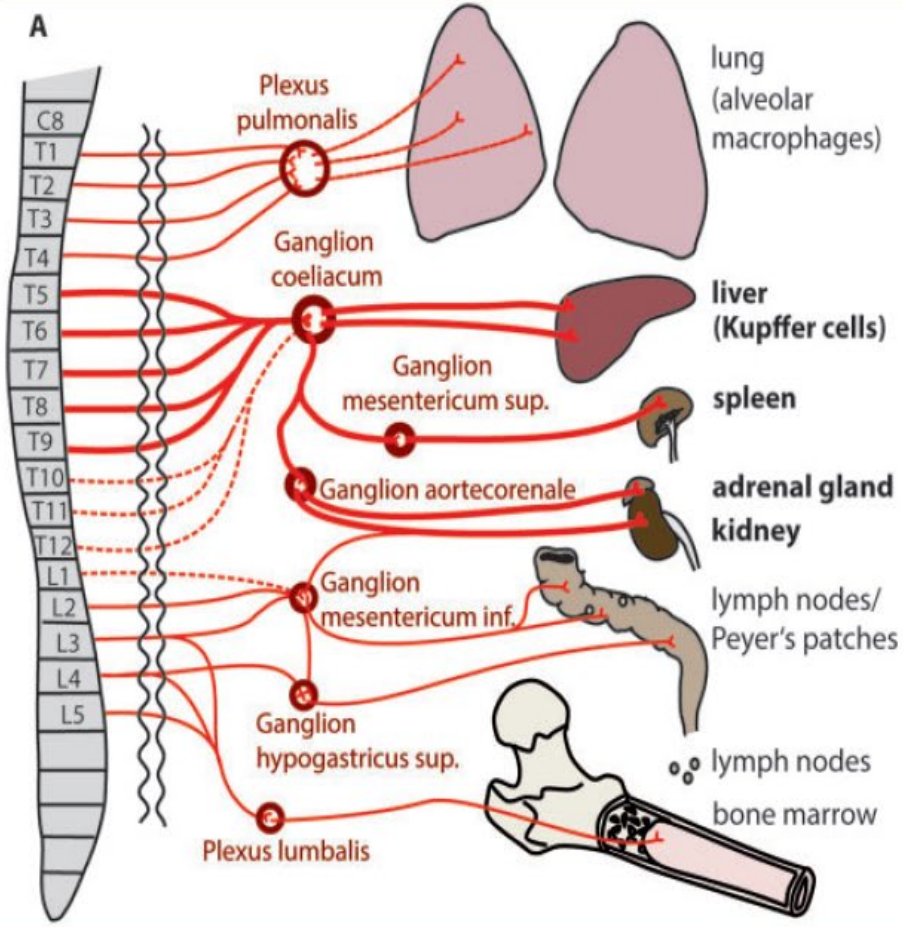
After spinal cord insult, microglia/macrophages polarize into several states: a classically activated pro-inflammatory (M1) phenotype, an alternatively activated anti-inflammatory (M2a and M2b) phenotype and M2c (acquired deactivation) phenotype [36,37]. The neurotoxic M1 sub-group of activated microglia/macrophages is activated soon after SCI, and they express high levels of pro-inflammatory cytokines [38], including IL-1β, Il6 Il-12, the well-studied TNFα (which is attributed to both neurotoxic M1 and A1 subgroups of reactive astrocytes), oxidative metabolites, chemokines and proteases [39]. Conversely, the M2 phenotype releases anti-inflammatory cytokines and down-regulates inflammation and facilitates wound healing. Data reported earlier [19,40] indicated that macrophages/microglia in the injured spinal cord were predominantly polarized to the M1 phenotype, and after their quick activation during the first few days they remained activated for 28 days after injury. Activation of a small number of M2 macrophages/microglia was observed, but this phenotype was short-lived, dissipating within 3–7 days after injury.

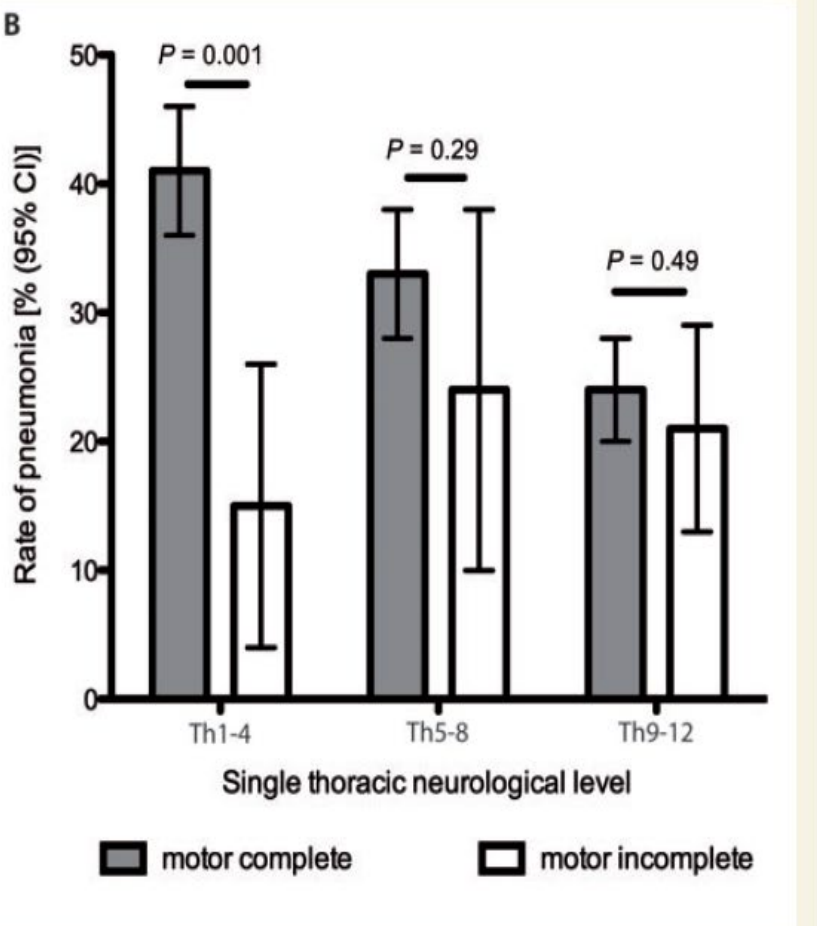
doi:10.1093/brain/aww375 BRAIN 2016: 139; 692–707 | 692

BRAIN
A JOURNAL OF NEUROLOGY

Spinal cord injury-induced immune deficiency syndrome enhances infection susceptibility dependent on lesion level

Benedikt Brommer,[1,2,*] Odilo Engel,[3,*] Marcel A. Kopp,[1,*] Ralf Watzlawick,[1] Susanne Müller,[3] Harald Prüss,[1,4] Yuying Chen,[5] Michael J. DeVivo,[5] Felix W. Finkenstaedt,[1] Ulrich Dirnagl,[3,4,6] Thomas Liebscher,[7] Andreas Meisel[3,6] and Jan M. Schwab[1,8,9]





In-hospital mortality in people with complete acute traumatic spinal cord injury at a tertiary care center in India—a retrospective analysis

Spinal Cord (2022) 60:210–215

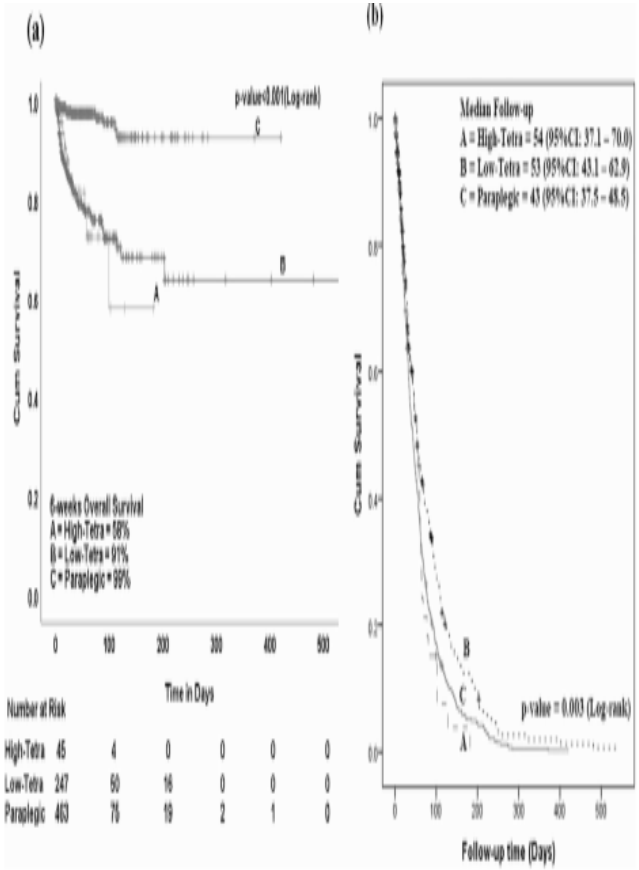


Fig. 1 Person with SCI were divided into three categories high tetraplegia, low tetraplegia, and paraplegia. a, b Kaplan–Meier curve and reverse Kaplan–Meier curve depicting mortality across high tetraplegia, low tetraplegia, and paraplegia. Median follow up and six-week overall survival were significantly different among the three groups.

Table 2. Multivariable logistic regression analysis of risk factors with in-hospital mortality.

Variable	OR (95% CI)	*p* value	C statistics
Age	1.03 (1.01–1.06)	**0.017**	0.955
Neurological level of Injury			
Paraplegia	Ref.		
High tetraplegia	5.09 (2.21–11.72)	**0.019**	
Low tetraplegia	4.84 (1.29–18.09)	**<0.001**	
Associated injuries	2.42 (1.11–5.27)	**0.027**	
Ventilator use	32.99 (15.66–69.51)	**<0.001**	
Management			
Operated	Ref.	0.181	
Conservative	1.66 (0.79–3.51)		
Comorbidities			
Diabetes mellitus	1.06 (0.21–5.47)	0.944	
Anemia	2.73 (0.19–40.22)	0.455	
Complications			
Cardiovascular	39.03 (8.29–183.89)	**<0.001**	
Respiratory	3.46 (1.63–7.33)	**0.001**	
Septicemia	4.60 (1.05–20.07)	**0.042**	

OR odds ratio.
Bold values indicate statistical significance at 5%.

Infections in the spinal cord-injured population: a systematic review

Spinal Cord (2016), 1–9

LY Garcia-Arguello[1,2], JC O'Horo[2,3], A Farrell[4], R Blakney[5,6], MR Sohail[3], CT Evans[5,6] and N Safdar[7,8]

Table 1 Bloodstream infections

Study	*Design*	*Population*	N	*Incidence*	*Microbiology/major pathogens*	*Major conclusions*
Bhatt *et al.*[18]	Retrospective cohort	VA SCI inpatients	3136	1.3%	CONS (36.6%) *S. aureus* (12.2%) *E. coli* (12.2%) *P. mirabilis* (9.8%) *S. marcescens* (9.8%)	17% mortality; not significantly different bacteriology compared with non-SCI reports
Montgomerie *et al.*[9]	Case series	Inpatients with SCI and bacteremia	93	N/A	Varied by primary source; UTI associated were *E. coli* and *enterococci* predominant, skin/soft tissue anaerobe predominant, and no clear predominant species in pneumonia or primary BSIs	No increase in mortality or severity of illness with delayed therapy
Waites *et al.*[8]	Case series	Inpatients with SCI and bacteremia	30	N/A	CONS (38.1) *S. aureus* (16.3%) *Klebsiella* spp. (12.7%)	UTI most frequent site of original BSI, followed by pressure ulcers and respiratory tract. Reinfection and relapse very common.
Wall *et al.*[12]	Case series	VA SCI inpatients	1664	5.8%	Varied by primary source; higher prevalence of MRSA across all sources	Most associated with pressure ulcers or indwelling urinary catheters; malnourishment significant predictor of outcome
Evans *et al.*[5]	Retrospective cohort	VA SCI inpatients	226	16.9%, 6.0/1000 patient days	*S. aureus* (96 isolates (18.9%)) Other *Staphylococcus* species (72 (14.2%)) Untyped Gram-negative bacilli (54 (10.6%))	Majority cases were healthcare associated and had antecedent antimicrobial use
Evans *et al.*[19]	Retrospective cohort	VA SCI inpatients	5699	7.2 BSI/ 100 admissions	*S. aureus* (34.4%) *Enterococcus faceium* (14.0%) *E. coli* (12.6%)	Majority cases were healthcare associated and had antecedent antimicrobial use
Evans *et al.*[15]	Retrospective cohort	VA SCI inpatients	2202	10.7 BSI/ 100 admissions	*S. aureus* (36.6%), *E. faecium* (15.3%), *E. coli* (14.9%), *P. aeruginosa* (12.3%)	Majority cases were healthcare associated and had antecedent antimicrobial use

Abbreviations: BSI, bloodstream infection; CONS, coagulase negative *Staphylococci*; SCI, spinal cord injury, UTI, urinary tract infection; VA, veteran's administration.

Original Article

Spinal Cord **55**, 148–154 (February 2017) | doi:10.1038/sc.2016.176

Outcome of bloodstream infections among spinal cord injury patients and impact of multidrug-resistant organisms

M Saliba, D Saadeh, F Bouchand, B Davido, C Duran, B Clair, C Lawrence, D Annane, P Denys, J Salomon, L Bernard and A Dinh

Overall, 318 BSIs occurring among 256 patients were included in the analysis. Mean age was 50.8 years and gender ratio (M/F) was 2.70, with a mean injury duration of 11.6 years.

Severity and 30-day mortality of BSI episodes were, respectively, 43.4% and 7.9%. BSI severity was significantly more frequent when caused by respiratory tract infections (RTIs) (odds ratio (OR)=1.38; 95% confidence interval (CI): 1.13–1.44) and significantly lower when caused by urinary tract infections (UTIs) (OR=0.47; 95% CI: 0.28–0.76). BSI mortality was significantly higher when caused by RTIs (OR=3.08; 95% CI: 1.05–8.99), catheter-related bloodstream infections (OR=3.54; 95% CI: 1.36–9.18) or Pseudomonas aeruginosa infections (OR=3.79; 95% CI: 1.14–12.55).

Infections in the spinal cord-injured population: a systematic review

Spinal Cord (2016), 1–9

LY Garcia-Arguello[1,2], JC O'Horo[2,3], A Farrell[4], R Blakney[5,6], MR Sohail[3], CT Evans[5,6] and N Safdar[7,8]

Table 3 Urinary tract infections

Study	*Design*	*Population*	N	*UTI incidence*	*Microbiology/major pathogens*	*Major conclusions*
Sugarman *et al.*[43]	Prospective and retrospective cohort	SCI inpatients with fever	33	37%	*E. coli* was identified in the majority (63%) of cases	Most UTI cases were associated with another potential source of co-infection
Maynard and Diokno[42]	Prospective trial	Recent traumatic SCI inpatient	50	26%	NR	Antibacterial prophylaxis decreased significant bacteriuria, but not clinical infection
Menon and Tan[40]	Retrospective cohort	SCI patients in rehabilitation	55	143 episodes of infection	*Klebsiella pneumoniae* (36%) *E. coli* (19%) *P. aeruginosa* (16%) *P. mirabilis* (11%)	All UTIs had $>100\,000$ CFU ml^{-1} of organism
Gribble *et al.*[39]	Prospective randomized control trial	Inpatients with recent SCI	129	N/A	In the placebo group CONS (30%) *K. pneumoniae* (9%), *E. coli* (8%), Gram-positive bacilli (14%) *Enterobacter* spp. (4%)	Low-dose TMP-SMX reduced the risk of UTI, but had increased adverse events
Levi *et al.*[37]	Population-based cohort study	SCI outpatients in the greater Stockholm area	353	68%	NR	UTI was the most common complication of SCI
Noreau *et al.*[44]	Retrospective review and questionnaire-based study	Long-standing SCI outpatients in Quebec	482	54%	NR	UTI was the most common complication of SCI
Dow *et al.*[35]	Prospective randomized control trial	SCI outpatients with symptomatic UTI	60	N/A	*Klebsiella* spp. (30%), *Enterococcus* spp. (22%) *E. coli* (22%), *Pseudomonas* (7%) *Acinetobacter* spp. (10%), *Proteus* spp. (7%), *Staphylococcus* spp. (16%)	Most (62%) were monomicrobial
Girard *et al.*[32]	Nationwide prevalence studies	Rehabilitation unit patients with SCI	78	10%	*E. coli* (22%), *K. pneumoniae* (22%), *S. aureus, Enterobacter aerogenes, candida* spp. *Enterococcus* spp. (11% each)	Indwelling urinary catheters were independently associated with higher risk of SCI
Tantisiriwat *et al.*[30]	Retrospective cohort	Long-standing SCI in rehabilitation patients	76	46 patients (61%) had 68 episodes of UTI	*E. coli* (74%), *K. pneumoniae* (12.8%), *E. faecalis* (5%), *P. mirabilis* (5%), *Citrobacter* spp. (3%)	*E. coli* was the most commonly observed microorganism
Evans *et al.*[5]	Retrospective cohort	VA SCI inpatient population	226	8.9/1000 patient days	*P. aeruginosa* (76 isolates (12.4%)) *E. faecium* (63 (10.3%)) Untyped Gram-negative bacilli (61 (10.0%)) *S. aureus* (57 (9.3%))	UTI was the most common HAI in SCI patients
Singh *et al.*[25]	Prospective cohort	At least C4 level SCI with bladder symptoms	545	0.64 UTI/100 person-days	*E. coli* (16.5%) *Klebsiella* (12%) *Staphylococcus aureus* (8%), *P. aeruginosa* (8%). *(polymicrobial)*	Most of the time the organisms had more than one isolate
Adriaansen *et al.*[24]	Prospective longitudinal study	Wheelchair-dependent adults with SCI, both in and outpatient	139	56.5% at 1 year, 58.3 at 2 years, 58.9% at 5 years	NR	UTI was the most common complication of SCI
Afsar *et al.*[23]	Prospective cohort	New SCI inpatients being followed for bladder management	164	NR	NR	No difference in overall rates of UTIs in indwelling versus clean intermittent catheterization
Ploypetch *et al.*[22]	Retrospective review	SCI patients admitted to rehabilitation ward	100	45 patients had 57 episodes of UTI	*E. coli* (50%) *Pseudomonas* (17.3%) *E. facialis* (7%)	
Togan *et al.*[20]	Prospective cohort	SCI patients followed at rehabilitation	93	23%	*E. coli* (42%), *Klebsiella* spp. (21%), *Enterococcus* spp. (8.3%), *Pseudomonas* spp. (8%)	*E. coli* is the most common cause of UTI, and was associated with urinary catheterization

Original Article

Spinal Cord **54**, 1001–1009 (November 2016) | doi:10.1038/sc.2016.38

Bacterial susceptibility patterns in patients with spinal cord injury and disorder (SCI/D): an opportunity for customized stewardship tools

K J Suda, U C Patel, R Sabzwari, L Cao, S Ramanathan, J N Hill and C T Evans

isolated in SCI/D and non-SCI/D differed. Methicillin-resistant Staphylococcus aureus occurred more frequently in SCI/D (27.8% vs 55.4%; P<0.0001). Gram-negatives had generally lower susceptibilities in SCI/D and a higher frequency of organisms producing extended-spectrum Beta-lactamases (17.6% vs 5.0%; P<0.0001), carbapenem-resistant Enterobacteriaceae (2.4% vs 0.5%; P<0.0001), carbapenem resistance (7.6% vs 2.4%; P<0.0001) and isolates resistant to ≥3 antibiotic classes (60.7% vs 28.0%; P=0.0001).

EFFETTO DELLA COLONIZZAZIONE DA GERMI MDR/XDR IN AMBIENTE INTENSIVISTICO

ISOLAMENTI UNITA' SPINALE 2022
PAZIENTI N. 78

PATOGENI BRONCOASPIRATO/ESCREATO	NUMERO TOTALE	NUMERO MDR	MORTALITA'
ST. AUREUS	4	MRSA (3)	0
PROTEUS MIRABILIS	1	ESBL	0
PR. STUARTII	1	ESBL	0
KL PNEUMONIAE	9	ESBL (2) KPC (3) OXA-48 (2)	0
AC BAUMANNII	2	2 MDR (2)	0
ST. MALTOPHILIA	1	1 MDR	0
PS AERUGINOSA	16	ESBL (3) MDR (3) VIM (2)	1
TOTALE	34 (43%)	23 (30%)	1 (0,78%)

ISOLAMENTI UNITA' SPINALE 2022
PAZIENTI N. 78

PATOGENI URINE DA CATETERE	NUMERO TOTALE	NUMERO MDR	MORTALITA'
ST. AUREUS	2	1	0
ENTEROCOCCUS FAECALIS	5	5	0
ENTEROCOCCUS FAECIUM	3	3	0
E. COLI	5	2 ESBL 1 CRE	0
P. MIRABILIS	1	1 ESBL	0
CITROBACTER KOSERI	1		0
PR. STUARTII	5	2 ESBL	0
KL PNEUMONIAE	14	5 KPC 2OXA-48	0
AC BAUMANNII	2	2 MDR	0
ST. MALTOPHILIA	1		0
PS AERUGINOSA	9	4ESBL 2 VIM	0
TOTALE	47 (60%)	28 (35%)	0%

ISOLAMENTI UNITA' SPINALE 2022
PAZIENTI N. 78

PATOGENI EMOCOLTURE	NUMERO TOTALE	NUMERO MDR	MORTALITA'
CONS	17	12 MRSE	0
CORYNEBACTERIUM	3	0	0
ENTEROCOCCUS FAECALIS	2	1 VRE	0
KL PNEUMONIAE	5	2 ESBL 2 KPC	1
AC BAUMANNII	1	1 CRE	0
ST. MALTOPHILIA	1	1 MDR	0
PS AERUGINOSA	3	1 ESBL 1 CRE	1
TOTALE	32 (41%)	20 (25%)	2 (1,5%)

Infectious diseases team for the early management of severe sepsis and septic shock in the emergency department.

Viale P et al.: Clin Infect Dis. 2017 Oct 15;65(8):1253-1259

Multivariate Cox Regression Analysis of Risk Factors for All-Cause 14-Day Mortality

Variable	HR	95% CI	P Value
qSOFA score ≥ 2	1.68	1.15-2.45	.007
serum lactate ≥2 mmol/L	2.13	1,39-3.25	<.001
unknown infection source	2.07	1.42-3.02	<.001
being attended by «sepsis team» during post phase	0.64	0.43-0.94	.026

Bacteriology of pressure ulcers in individuals with spinal cord injury: What we know and what we should know

The Journal of Spinal Cord Medicine 2015 VOL. 38 NO. 2

Ali N. Dana[1,2], William A. Bauman[3,4,5]

Table 1 Characteristics of the 11 studies included in our review that examined the bacteriology of pressure ulcers in individuals with SCI

	Galpin *et al.*[23]	Vaziri *et al.*[29]	Sugarman et al.[27]	Sapico *et al.*[26]	Thornhill-Joynes *et al.*[28]	Montgomerie *et al.*[25]	Biering-Sorensen *et al.*[21]	Waites *et al.*[30]	Wall *et al.*[9]	Heym *et al.*[24]	Biglari *et al.*[22]
Study focus	Bacteriology of PU associated with sepsis	Infections in patients undergoing hemodialysis	Osteomyelitis beneath pressure sores	Microbiology of PU in different stages of healing	Evaluation of the frequency of osteomyelitis in patients with SCI and PU	Mortality among patients with bacteremia	Bacterial contamination of bath water	Bacteremia after SCI during hospitalization	Risk factors for mortality from bacteremia in individuals with SCI	Bacteriology of PU and impact on antibiotic therapy	Use of Medihoney as non-surgical therapy for PU
Number of patients	21 (14 M, 7 F)	43 (43 M)	19 (NA)	25 (21 M, 4 F)	40 (35 M, 5 F)	93 (74 M, 19 F)	18 (NA)	59 (48 M, 11 F)	63 (62 M, 1 F)	101 (68 M, 33 F)	20 (13 M, 7 F)
Number of patients with PU	21	27	19	25	40	18	12	NA	36	101	20
Number of PU cultured	47	NA	22	25	35	NA	12	5	21	NA	20
Number of cultures	NA	NA	NA	49	38	20	12	NA	NA	168	20
Sampling method	Needle aspiration, surgical drainage, or cotton swab	Needle aspirate or cotton swab	NA	Cotton swab or tissue biopsy; debridement prior to sampling	Cotton swab	NA	Cotton swab culture	NA	NA	Tissue biopsy, needle aspiration, surgical drainage, or cotton swab; debridement prior to sampling	Cotton swab
Type of cultures	Aerobic and anaerobic	Aerobic and anaerobic	NA	Aerobic and anaerobic	Aerobic and anaerobic	Aerobic and anaerobic	Aerobic	NA	NA	Aerobic and anaerobic	NA
Percentage polymicrobial cultures	NA	55% (≥2 spp.)	16% (1 spp.) 16% (2 spp.) 21% (3 spp.) 31% (4 spp.) 15% (≥5 spp.)	NA	NA	NA	75% (1 spp.) 25% (2 spp.)	NA	NA	69% (≤ 2 spp.) 21% (3 spp.) 8% (≥4 spp.)	70% (1 spp.) 15% (2 spp.) 10% (3 spp.) 5% (4 spp.)
Predominant organism (percentage of bacterial isolates)	*P. mirabilis* (18%)	*P. mirabilis* (17%)	*P. mirabilis* (17%), *P. aeruginosa* (17%)	*S. aureus* (11%) *P. aeruginosa* (11%)	*S. aureus* (16%)	*S. aureus* (20%)	*S. aureus* (30%), *E. faecalis* (30%)	*S. aureus* (50%)	*S. aureus* (57%)	*S. aureus* (23%)	*S. aureus* (30%)

F, female; M, male; NA, not available; PU, pressure ulcer; spp., species.

Pressure ulcers: prevention and management

Clinical guideline
Published: 23 April 2014
nice.org.uk/guidance/cg179

Systemic antibiotics and antiseptics

1.4.18 After a skin assessment, offer systemic antibiotics to adults with a pressure ulcer if there are any of the following:

- clinical evidence of systemic sepsis
- spreading cellulitis
- underlying osteomyelitis.

1.4.19 Discuss with a local hospital microbiology department which antibiotic to offer adults with infection to ensure that the chosen systemic antibiotic is effective against local strains of infection.

1.4.20 Do not offer systemic antibiotics specifically to heal a pressure ulcer in adults.

Concordance between superficial swabs and intraoperative specimen culture was found in only in 25 out of 116 cases (22%). Clin Microbiol Infect. 2017 Dec;23(12):943-94

Hyperbaric oxygen therapy and electrotherapy

1.4.14 Do not offer the following to adults to treat a pressure ulcer:

- electrotherapy
- hyperbaric oxygen therapy.

NICE National Institute for Health and Care Excellence

Table 3 Bacteria species depending on the primary site of infection during bloodstream infection among spinal cord-injured patients

Bacteria species (n,%)	*Urinary tract infection (%)*	*Pressure sore (%)*	*CLA (%)*	*Osteoarticular infection (%)*	*Pulmonary tract infection (%)*	*Other (%)*	*Unknown (%)*	*Total (%)*
MSSA	0	9 (9.0)	5 (12.2)	9 (42.9)	12 (44.4)	3 (15.7)	2 (6.25)	40 (11.4)
MRSA	3 (2.6)	15 (15)	6 (14.6)	5 (23.8)	8 (29.6)	4 (21.0)	4 (12.5)	45 (12.8)
Coagulase negative								
Staphylococcus	0	4 (4)	14 (34.1)	0	1 (3.7)	1 (5.2)	1 (3.1)	21 (6.0)
E. coli	51 (45.5)	8 (8)	2 (4.9)	2 (9.5)	0	3 (15.8)	5 (15.6)	70 (19.9)
Proteus spp.	10 (8.9)	4 (4)	0	0	0	0	2 (6.25)	16 (4.6)
Klebsiella spp.	20 (17.9)	1 (1)	0	0	0	2 (10.5)	1 (3.1)	24 (6.8)
Pseudomonas aeruginosa	11 (10)	4 (4)	4 (9.7)	0	3 (11.1)	0	0	22 (6.3)
Acinetobacter spp.	2 (1.8)	2 (2)	0	0	0	0	1 (3.1)	5 (1.4)
Enterobacter spp.	2 (1.8)	1 (1)	3 (7.3)	1 (4.7)	0	0	2 (6.25)	9 (2.6)
Morganella spp.	1 (0.4)	5 (5)	0	0	0	0	0	6 (1.7)
Providencia spp.	1 (0.4)	0	0	0	0	0	1 (3.1)	2 (0.6)
Stenothrophomonas spp.	0	1 (1)	0	0	0	0	0	1 (0.3)
Streptococcus spp.	3 (2.7)	17 (17)	0	2 (9.5)	2 (7.4)	4 (21.0)	4 (12.5)	32 (28.6)
Enterococcus spp.	4 (3.5)	5 (5)	2 (4.9)	0	0	1 (5.2)	4 (12.5)	16 (4.6)
Anaerobes	0	21 (21)	1 (2.4)	1 (4.7)	0	2 (10.5)	3 (9.3)	28 (8.0)
Other[a]	4 (3.5)	2 (2)	4 (9.7)	1 (4.7)	1 (3.7)	0	2 (6.25)	14 (4.0)
Total	112	99	41	21	27	19	32	351

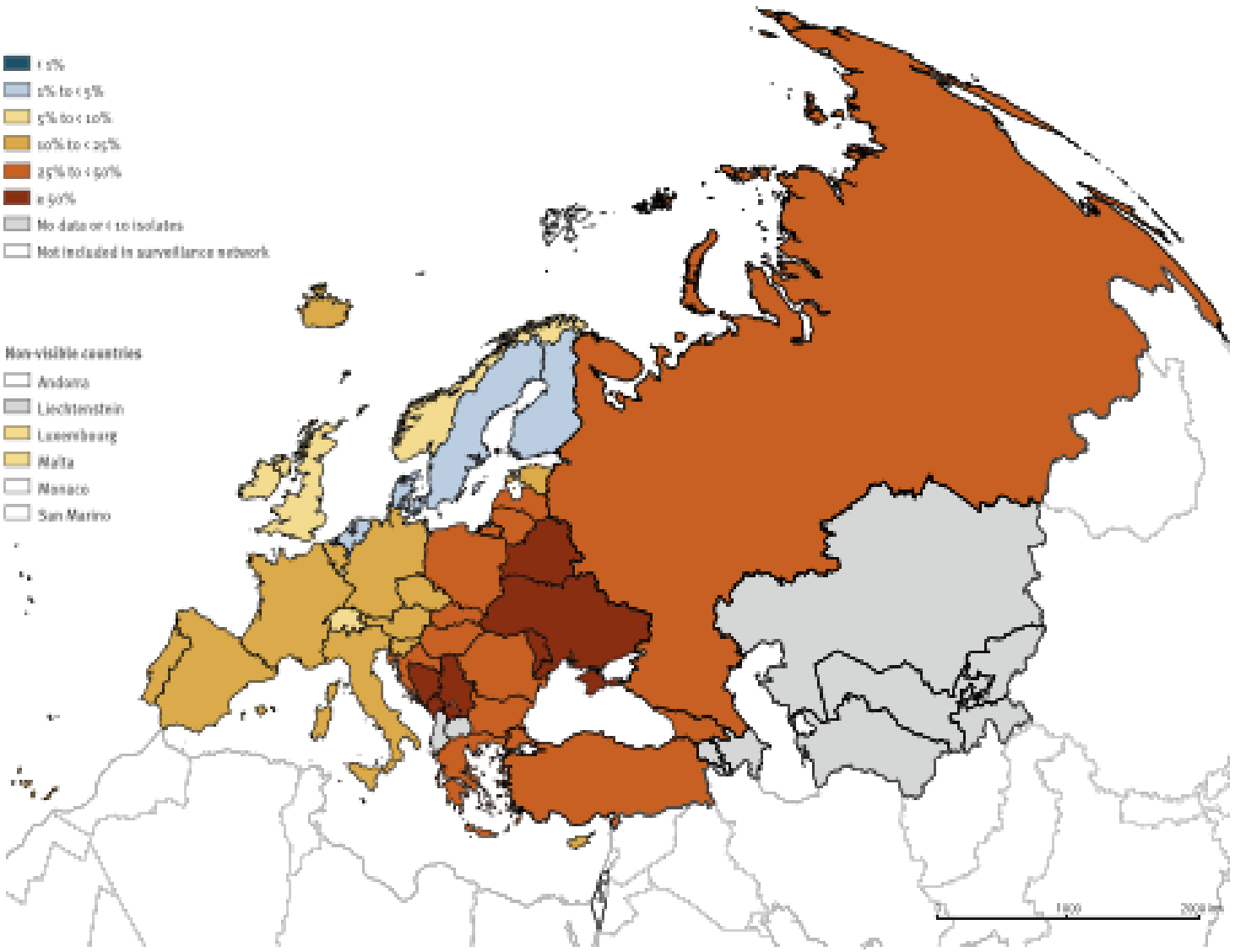
Abbreviations: CLA, catheter line-associated; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.
One episode had both MRSA and MSSA.
[a]*Haemophilus spp.*, *Serratia spp.*, *Citrobacter spp.*, unidentified micro-organisms.

Table 4 Severity and mortality depending on bacteria species during bloodstream infection among spinal cord-injured patients

Bacteria species	*Severity (n;%)*	*Mortality (n;%)*
MSSA (n = 40)	19 (47.5)	4 (10)
MRSA (n = 45)	23 (51.1)	4 (8.8)
Coagulase-negative *Staphylococcus* (n = 21)	6 (28.6)	0
E. coli (n = 70)	28 (40)	6 (8.6)
Pseudomonas aeruginosa (n = 22)	12 (54.5)	4 (18.1)
Proteus spp. (n = 16)	7 (43.7)	2 (12.5)
Klebsiella spp. (n = 24)	8 (33.3)	1 (4.1)
Acinetobacter spp. (n = 5)	1 (20)	1 (20)
Enterobacter spp. (n = 9)	5 (55.6)	2 (22.2)
Morganella spp. (n = 6)	2 (33)	0
Providencia spp. (n = 2)	2 (100)	0
Stenothrophomonas spp. (n = 1)	0	0
Anaerobes (n = 28)	12 (42.9)	1 (3.6)
Streptococcus spp. (n = 32)	11 (34.3)	4 (12.5)
Enterococcus spp. (n = 16)	7 (43.7)	1 (6.25)
Other (n = 14)[a]	5 (35.7)	2 (14.2)
Total	148	32

Abbreviations: MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.
[a]Other: *Haemophilus spp. Serratia spp.*, *Citrobacter spp.*, unidentified micro-organisms.

Fig. 6 *P. aeruginosa*: percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country/area, WHO European Region, 2020



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 2020 do not include Scotland and Wales.

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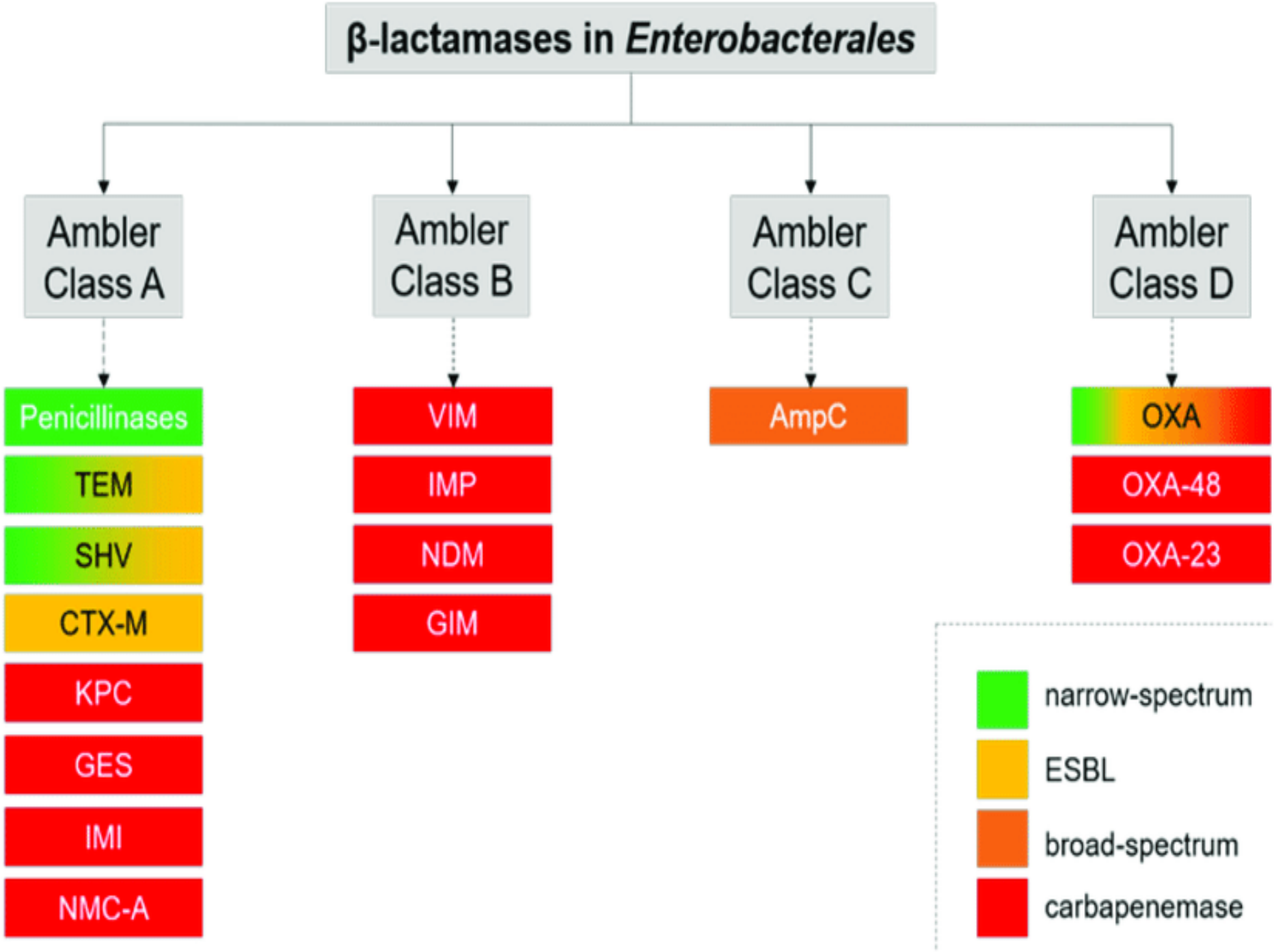

β-lactamases in *Enterobacterales*
Ambler Class A
Ambler Class B
Ambler Class C
Ambler Class D
Penicillinases
TEM
SHV
CTX-M
KPC
GES
IMI
NMC-A
VIM
IMP
NDM
GIM
AmpC
OXA
OXA-48
OXA-23
narrow-spectrum
ESBL
broad-spectrum
carbapenemase

NUOVI ANTIBIOTICI ATTIVI CONTRO LE CARBAPENEMASI

Antimicrobial agents	Approved for	KPC	NDM	IMP	VIM	OXA-48
Ceftazidime/ avibactam	UTI, cIAI, HAP/VAP, Gram-negative with limited treatment options	Yes	No	No	No	Yes
Meropenem/ vaborbactam	HAP/VAP, cUTI, cIAI	Yes	No	No	No	No
Ceftolozane/ tazobactam	HAP/VAP, cUTI, cIAI	No	No	No	No	No
Imipenem/ cilastatin/ relebactam	HAP/VAP, HAP/VAP associated bacteraemia, Gram-negative with limited treatment options	Yes	No	No	No	No
Cefiderocol	Gram-negative with limited treatment options	Yes	Yes	Yes	Yes	Yes
Aztreonam/ avibactam	Phase III	Yes	Yes	Yes	Yes	Yes

Table 1. Main resistance mechanisms of new antibiotics.

Anti-Pseudomonals in Clinical Use	Main Resistance Mechanisms
Ceftolozane-tazobactam	AmpC structural mutations, β-lactam target modification (PBP) [21,22,47], OprD mutation and efflux pumps upregulation [28], MBL productions [27], OXA-2 and OXA-10 mutations [23–25]
Ceftazidime-avibactam	OprD mutation and efflux pumps upregulation [28,47,62–64], AmpC structural mutations, β-lactam target modification (PBP) [22,28,47], OXA-2 and OXA-10 mutations [24,25,65], MBL production [61]
Cefiderocol	Mutations in major iron transport pathways, possible AmpC mutations [79] mutations in β-lactamases [78]
Meropenem-vaborbactam	Porin mutations, efflux pump upregulation, MBL and OXA production [108]
Imipenem-cilastatin-relebactam	MBL and GES carbapenemases [85], mutations in MexB or in ParS [98]
Plazomicin	16S rRNA methyltransferases (i.e. Rmt or Arm) [145]

Spettro di attività inibitori delle Beta-lattamasi

		Clavulanic acid	Tazobactam	Avibactam
Class A	TEM, SHV	✓	✓	✓
	CTX-M	✗	✓	✓
	PER, VEB, GES	✗	✓	✓
	KPC	✗	✗	✓
Class B	e. g. IMP, VIM, NDM1	✗	✗	✗
Class C	Enterics chromos. AmpC	✗	✗	✓
	Pseudomonas chromos. AmpC	✗	✗	✓
	Plasmid-encoded ACC, DHA, CMY, FOX, LAT, MOX, MIR, ACT	✗	✗	✓
Class D	Non carbapenemase e. g. OXA-1, -31, -10, -13	Variable	Variable	Variable
	Carbapenemase e. g. OXA-23, -40, -48, -58	Variable	Variable	Variable OXA-48

Lagacé-Wiens P et al. *Core Evid.* 2014;9:13.

What Makes Ceftolozane/Tazobactam Different? Activity vs. *Pseudomonas aeruginosa*

Ceftolozane

- Stable against common *P. aeruginosa* resistance mechanisms, including loss of outer membrane porin (OprD), chromosomal AmpC, and up-regulation of efflux pumps (MexXY, MexAB)[1]
- Isolates resistant to other cephalosporins may be susceptible, although cross-resistance may occur[2]

Resistance Mechanisms	Outer Membrane Porin Loss	β-lactamase Enzyme	Efflux Pump	Efflux Pump
	OprD	AmpC	MexXY	MexAB
Ceftolozane	●	●	●	●
Ceftazidime	◐	○	●	○
Cefepime	●	○	○	○
Piperacillin/tazobactam	●	○	●	○
Imipenem	○	●	●	●
Meropenem	◐	●	○	◐

○ Activity greatly decreased >> ● Retains activity

Table adapted from Castanheira M, et al. 2014

1. Castanheira M, et al. *Antimicrob Agents Chemother.* 2014;58:6844-6850. 2. ZERBAXA [prescribing information]. Cubist Pharmaceuticals; Lexington, MA; 2014.

Activity of Ceftolozane-Tazobactam and Ceftazidime-Avibactam against Beta-Lactam-Resistant *P. aeruginosa* Isolates

Humphries RM et al. AAC 2017

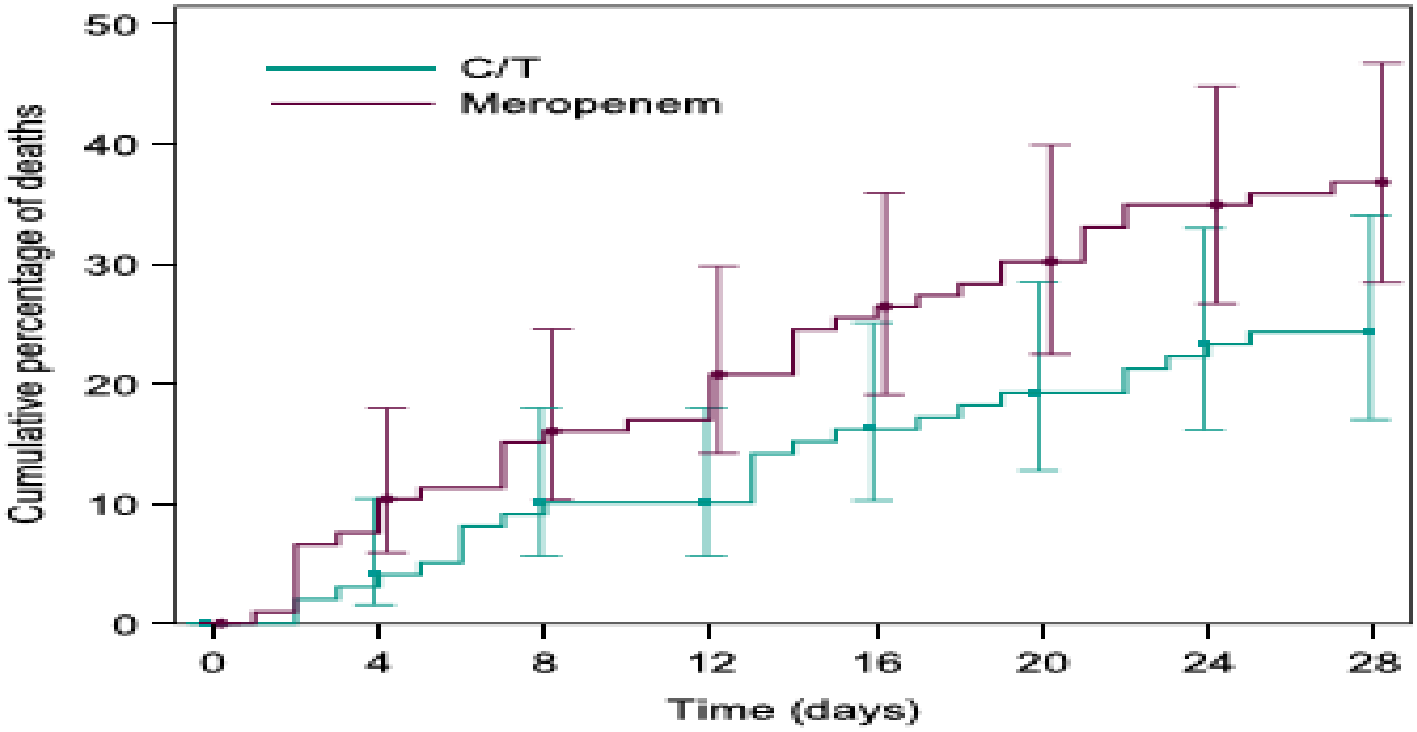
- Ceftolozane-tazobactam (C/T) and ceftazidime-avibactam (CZA)
- MICs study of 309 beta-lactam-resistant isolates of *P. aeruginosa*
  - *T*hree institutions in the area of Los Angeles, CA
- Overall susceptibilities:

IMIPENEM	MEROPENEM	PIP/TAZO	CEFEPIME	CAZ/AVI	C/T
12%	16%	20.7%	26%	61.8%	72.5%

- C/T-resistant isolates → 9% were CZA susceptible
- CZA-resistant isolates → 36% were C/T susceptible

Lo sviluppo clinico nelle Polmoniti

	C/T	Meropenem
Number of participants	99	108
Number of deaths (%)	31 (31.3)	43 (39.8)



Patients at risk

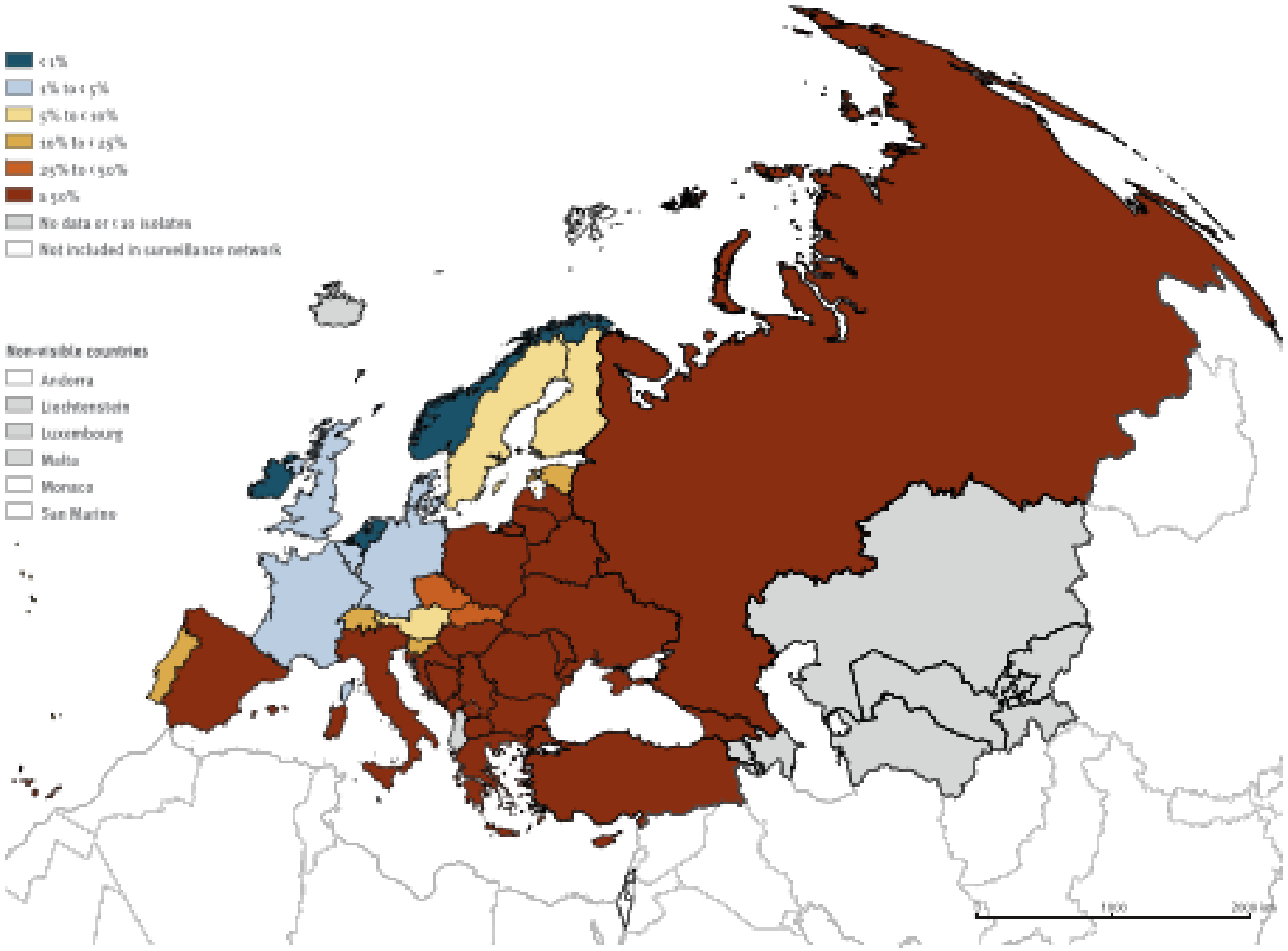
C/T	99	95	89	89	83	79	75	74
Meropenem	108	95	89	84	78	74	69	67

Fig. 2 Time to death in participants with vHABP (ITT population). C/T, ceftolozane/tazobactam. ITT, intention to treat population (all randomized patients). vHABP, ventilated hospital-acquired bacterial pneumonia

- Higher dose used in this study than in cUTI/cIAI based on ELF PK data in HVs

Timsit *et al. Crit Care* (2021) 25:290

Fig. 7 *Acinetobacter* spp.: percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country/area, WHO European Region, 2020



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 2020 do not include Scotland and Wales.

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Map production: ©WHO.

Cefiderocol

- Cefiderocol è una cefalosporina legata ad un sideroforo con una porzione catcol in posizione 3 della catena.

- **La porzione catecol permette agli ioni ferro di legarsi consentendo alla molecola dell'antibiotico di penetrare all'interno della cellula batterica sfruttando i canali di trasporto del ferro.**

- **Cefiderocol ha dimostrato di avere una potente azione battericida in vitro contro CRE e MDR P. aeruginosa e A. baumannii.**

Two Important Mode of Action of Cefiderocol

- High stability to carbapenemases
  - Stable to both serine-type (KPC, OXA etc) and metallo-type carbapenemases (VIM, IMP, NDM, L1 etc)
- Efficient penetration through the outer membrane via active iron transporters
  - Strong chelating ability to Fe^{3+} as well as siderophores
  - Utilization of multiple iron transporters of multiple bacterial species of Gram-negative bacteria

Cefiderocol- Compared to Colistin-Based Regimens for the Treatment of Severe Infections Caused by Carbapenem-Resistant *Acinetobacter baumannii*

Marco Falcone,[a] Giusy Tiseo,[a] Alessandro Leonildi,[b] Leonardo Della Sala,[a] Alessandra Vecchione,[b] Simona Barnini,[b] Alessio Farcomeni,[c] Francesco Menichetti[a]

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May 2022 Volume 66 Issue 5

TABLE 1 Type of infection and relative treatment regimens in 47 patients with CRAB infections treated with cefiderocol-containing regimens[a]

Type of infection	Treatment regimen	
BSI N = 27 (57.4%)	Cefiderocol monotherapy	*n* = 12
	Cefiderocol + tigecycline	*n* = 10
	Cefiderocol + fosfomycin	*n* = 3
	Cefiderocol + ertapenem	*n* = 1
	Cefiderocol + ampicillin/sulbactam	*n* = 1
VAP N = 12 (25.5%)	Cefiderocol monotherapy	*n* = 2
	Cefiderocol + tigecycline	*n* = 6
	Cefiderocol + fosfomycin	*n* = 3
	Cefiderocol + meropenem-vaborbactam	*n* = 1
Other infections N = 8 (17%)	Cefiderocol monotherapy	*n* = 1
	Cefiderocol + tigecycline	*n* = 5
	Cefiderocol + fosfomycin	*n* = 2

[a]BSI, bloodstream infection; CRAB, carbapenem-resistant *A. baumannii*; VAP, ventilator-associated pneumonia; other infections were: 5 surgical site infections; 1 intra-abdominal infection; 1 perianal abscess and 1 central nervous system infection.

TABLE 2 Type of infection and relative treatment regimens in 77 patients with CRAB infections treated with colistin-containing regimens[a]

Type of infection	Treatment regimen	
BSI *N* = 52 (67.5%)	Colistin-containing regimens	*N* = 52
	Colistin alone	*n* = 11
	Colistin + tigecycline	*n* = 30
	Colistin + tigecycline + meropenem	*n* = 5
	Colistin + tigecycline + rifampin	*n* = 2
	Colistin + tigecycline + fosfomycin	*n* = 1
	Colistin + meropenem + fosfomycin	*n* = 1
	Colistin + rifampin	*n* = 1
	Colistin + aminoglycosides	*n* = 1
VAP *N* = 23 (29.9%)	Colistin-containing regimens	*N* = 23
	Colistin alone	*n* = 1
	Colistin + tigecycline	*n* = 9
	Colistin + tigecycline + rifampin	*n* = 1
	Colistin + tigecycline + meropenem	*n* = 2
	Colistin + tigecycline + fosfomycin	*n* = 2
	Colistin + meropenem + fosfomycin	*n* = 1
	Colistin + tigecycline + ampicillin/sulbactam	*n* = 6
	Colistin + ampicillin/sulbactam	*n* = 1
Other infections	Colistin-containing regimens	*N* = 2
N = 2 (2.6%)	Colistin alone	*n* = 1
	Colistin + tigecycline	*n* = 1

[a]BSI, bloodstream infection; CRAB, carbapenem-resistant *A. baumannii*; VAP, ventilator-associated pneumonia; other infections were 1 urinary tract infection and 1 surgical site infection.

Cefiderocol- Compared to Colistin-Based Regimens for the Treatment of Severe Infections Caused by Carbapenem-Resistant *Acinetobacter baumannii*

Marco Falcone,[a] Giusy Tiseo,[a] Alessandro Leonildi,[b] Leonardo Della Sala,[a] Alessandra Vecchione,[b] Simona Barnini,[b] Alessio Farcomeni,[c] Francesco Menichetti[a]

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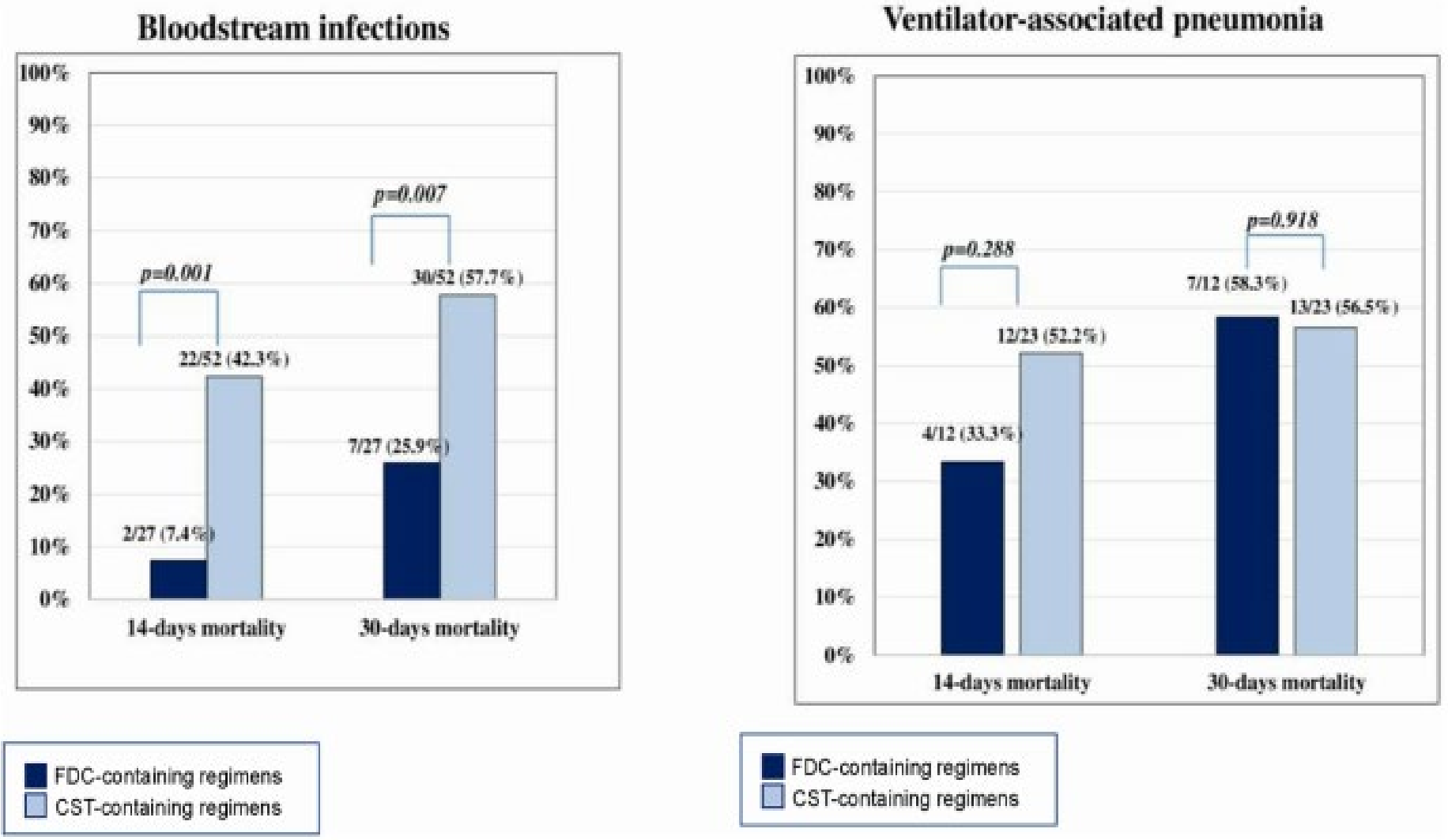

FIG 2 Fourteen- and 30-days mortality in patients with bloodstream infection (BSI) and ventilator-associated pneumonia (VAP). FDC cefiderocol.

Cefiderocol- Compared to Colistin-Based Regimens for the Treatment of Severe Infections Caused by Carbapenem-Resistant *Acinetobacter baumannii*

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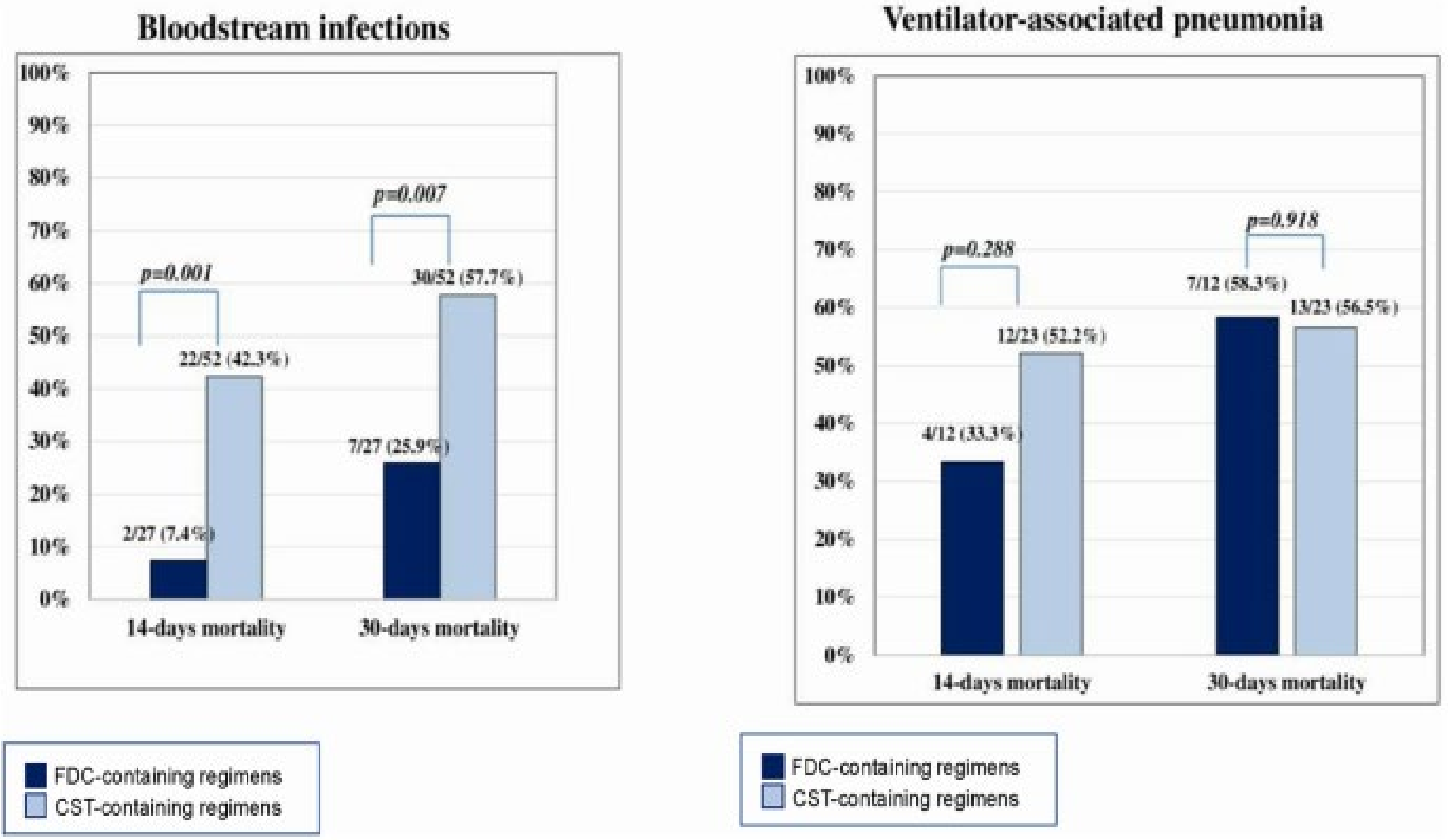


FIG 2 Fourteen- and 30-days mortality in patients with bloodstream infection (BSI) and ventilator-associated pneumonia (VAP). FDC cefiderocol.

CURRENT OPINION

Clinical evidence supporting cefiderol for serious *Acinetobacter baumannii* infections

Curr Opin Infect Dis 2022, 35:545–551

Matteo Bassetti[a,b], Antonio Vena[a,b], Nadia Castaldo[c], Daniele Roberto Giacobbe[a,b], Maddalena Peghin[d] and Paolo Antonio Grossi[d]

KEY POINTS

- Management of patients with infections by carbapenem-resistant -*A. baumanii* is challenging and there is limited high quality evidence in this field.
- Cefiderocol is a siderophore cephalosporin with excellent in-vitro activity against *A. baumannii* isolates.
- Despite low-quality of evidence, cefiderocol represents a promising and safe treatment option for patients with carbapenem-resistant *A. baumanii* infections.
- The use of cefiderocol as monotherapy or in combination with other drugs remains an unresolved issue.
- Due to conflicting mortality data from available experience, further well-designed randomized controlled trials and real-life studies are needed to consolidate the use of cefiderocol.

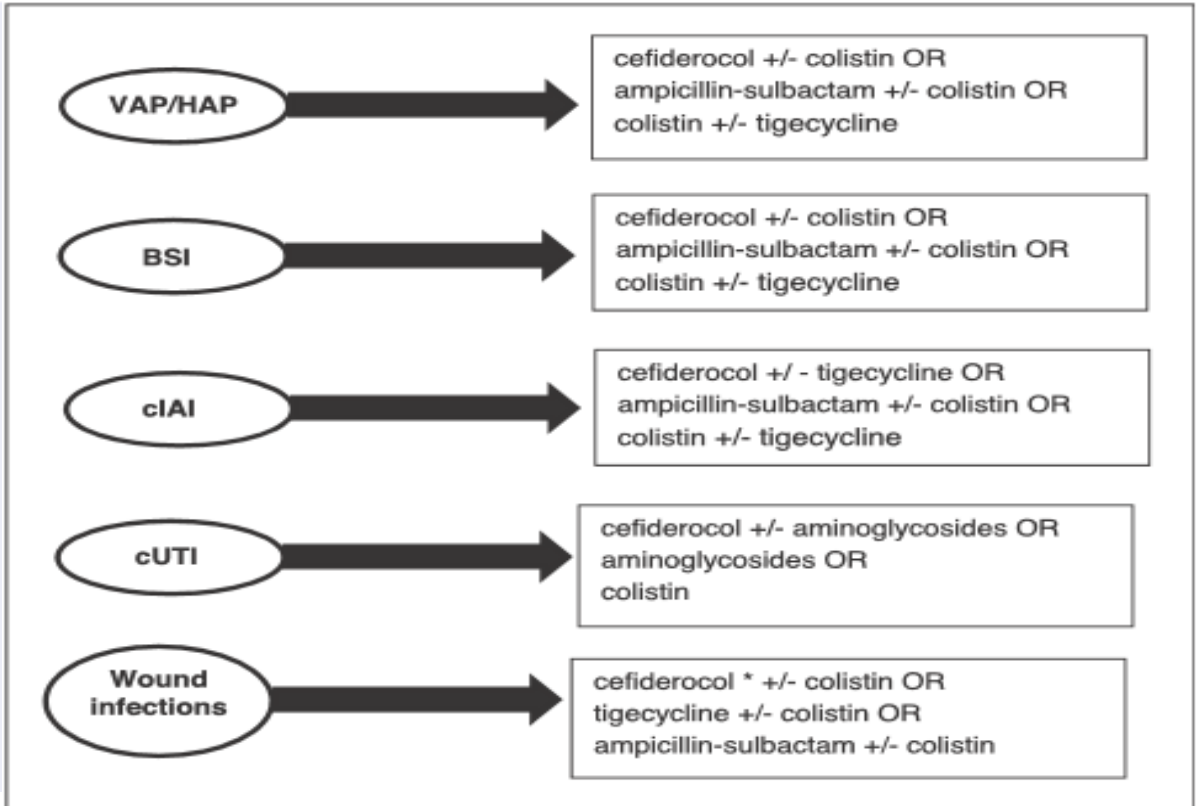
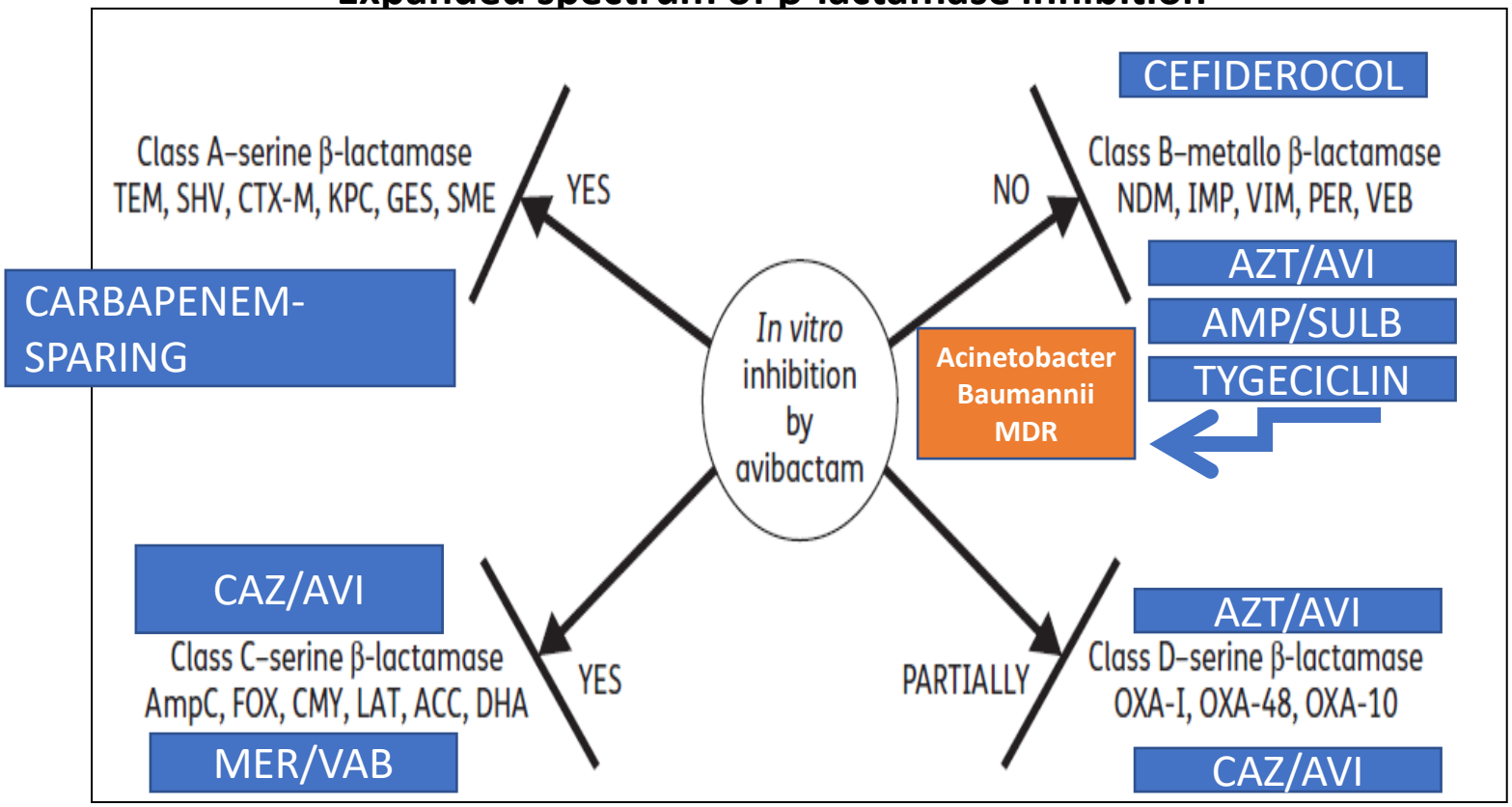


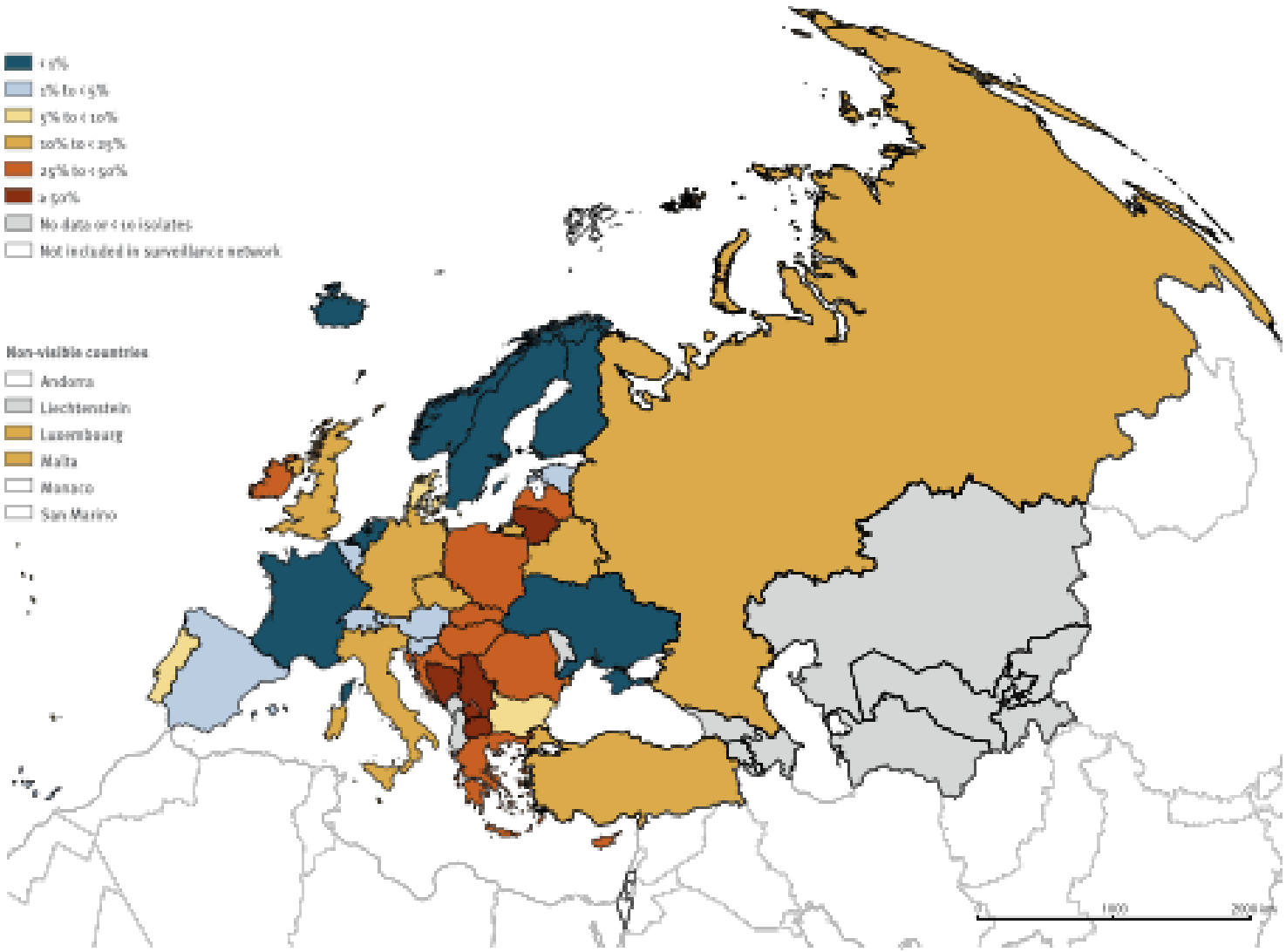
FIGURE 1. Suggested targeted treatment of carbapenem-resistant- *A. baumannii* infections. Recommended dosages and infusion for patients without renal adjustment. Ampicillin-sulbactam: 9 g of sulbactam: 6 g ampicillin/3 g sulbactam q8 h IV over 4 h. Aminoglicosides: gentamicin 3–5 mg/kg q24 h IV or amikacin 15–20 mg/kg q24 h IV. Cefiderocol: 2 g q8 h IV over 3 h. Colistin: loading dose 9 MU followed by maintenance doses with 4.5 MU q12 h. Tigecycline: loading dose 200 mg in 1 h followed by maintenance dose 100 mg q12 h. BSI, bloodstream infections; cIAI complicated intra-abdominal infections; cUTI complicated urinary tract infections HAP Hospital acquired pneumonia; VAP ventilator associated pneumonia; ^ poor activity of cefiderocol against anaerobes: consider anaerobes coverage in association * poor activity of cefiderocol against aerobic Gram-positive organisms: consider Gram-positives coverage in association.

Expanded spectrum of β-lactamase inhibition



Modified from Falcone & Paterson

Fig. 10 ***E. faecium*: percentage of invasive isolates resistant to vancomycin, by country/area, WHO European Region, 2020**



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Map production: ©WHO.

Associazioni contro *E. faecalis*

- Beta-lattamici e glicopeptidi rompono il cell-wall battico
- Gli aminoglicosidi sono sempre inefficaci contro E. faecalis
- IN caso di associaizone, la perdita del Cell-wall permette il passaggio degli aminoglicosi: associazione battericida
- Meccanismi di resistenza: mancato legame ai ribosomi: alta resistenza alla gentamicina; MIC > 500 mg/L

Ampicillin Plus Ceftriaxone Is as Effective as Ampicillin Plus Gentamicin for Treating *Enterococcus faecalis* Infective Endocarditis

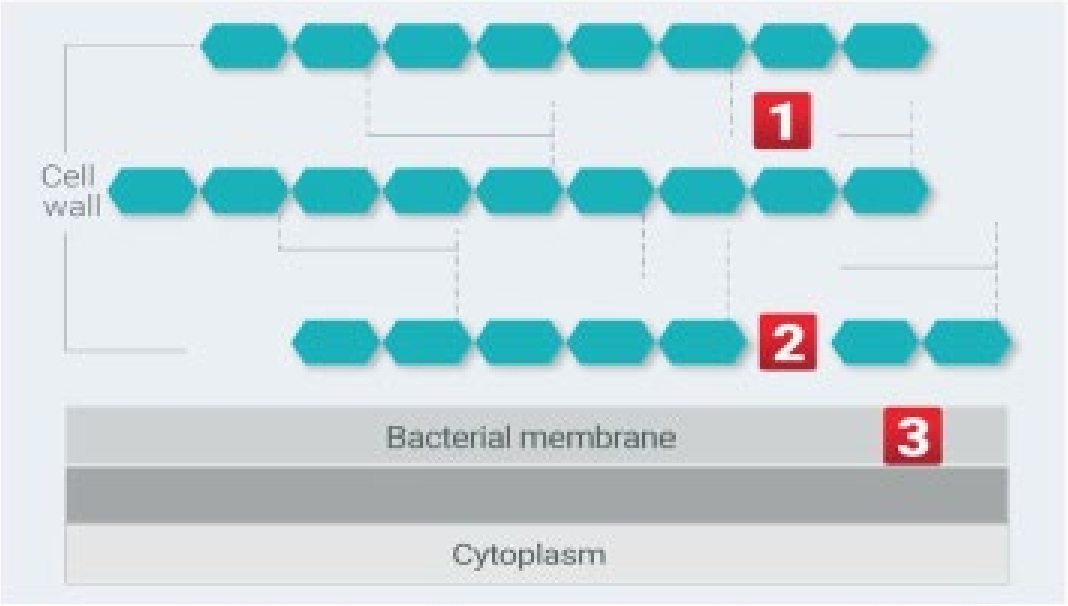
Nuria Fernández-Hidalgo,[1] Benito Almirante,[1] Joan Gavaldà,[1] Mercè Gurgui,[2] Carmen Peña,[3] Aristides de Alarcón,[4] Josefa Ruiz,[5] Isidre Vilacosta,[6] Miguel Montejo,[7] Nuria Vallejo,[8] Francisco López-Medrano,[9] Antonio Plata,[10] Javier López,[11] Carmen Hidalgo-Tenorio,[12] Juan Gálvez,[13] Carmen Sáez,[14] José Manuel Lomas,[15] Marco Falcone,[16] Javier de la Torre,[16] Xavier Martínez-Lacasa,[17] and Albert Pahissa[1]

Clinical Infectious Diseases 2013;56(9):1261–8

Table 18 Antibiotic treatment of infective endocarditis due to *Enterococcus* spp.

Antibiotic	Dosage and route	Duration, weeks	Class[g]	Level[h]	Ref.[i]	Comments
Beta-lactam and gentamicin-susceptible strains (for resistant isolates see [a,b,c])						
Amoxicillin* with Gentamicin[d]	200 mg/kg/day i.v. in 4–6 doses	4–6	I	B	6,8, 129, 135, 136, 186	6-week therapy recommended for patients with >3 months symptoms or PVE
	3 mg/kg/day i.v. or i.m. in 1 dose	2–6**	I	B		
	Paediatric doses:[e] Ampicillin 300 mg/kg/day i.v. in 4–6 equally divided doses Gentamicin 3 mg/kg/day i.v. or i.m. in 3 equally divided doses					
Ampicillin with Ceftriaxone	200 mg/kg/day i.v. in 4–6 doses	6	I	B	183–185	This combination is active against *Enterococcus faecalis* strains with and without HLAR, being the combination of choice in patients with HLAR *E. faecalis* endocarditis. This combination is not active against *E. faecium*
	4 g/day i.v. or i.m. in 2 doses	6	I	B		
	Paediatric doses:[e] Amoxicillin as above Ceftriaxone 100 mg/kg/12 h i.v. or i.m.					
Vancomycin[f] with Gentamicin[d]	30 mg/kg/day i.v. in 2 doses	6	I	C		
	3 mg/kg/day i.v. or i.m. in 1 dose	6	I	C		
	Paediatric doses:[e] Vancomycin 40 mg/kg/day i.v. in 2–3 equally divided doses. Gentamicin as above					

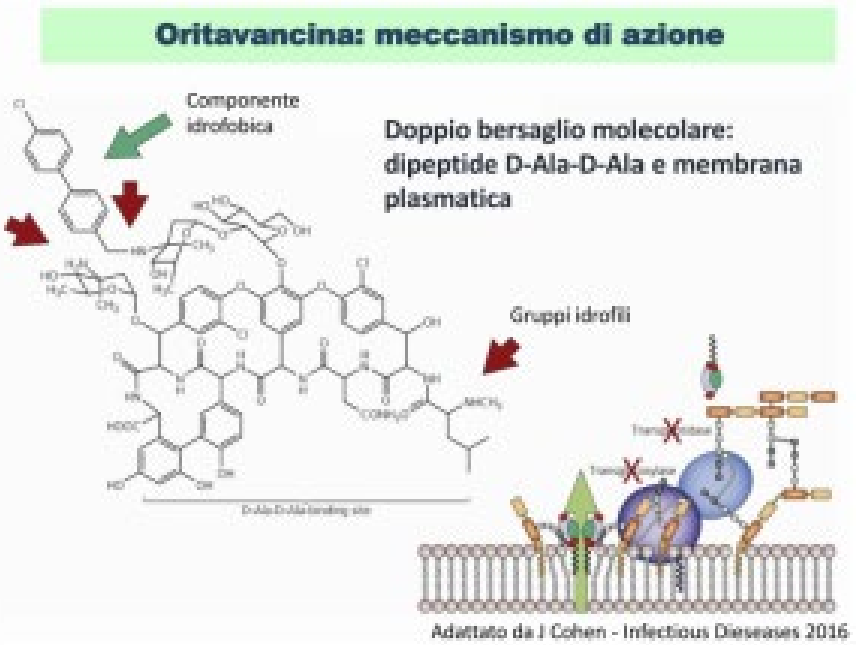
ORITAVANCINA

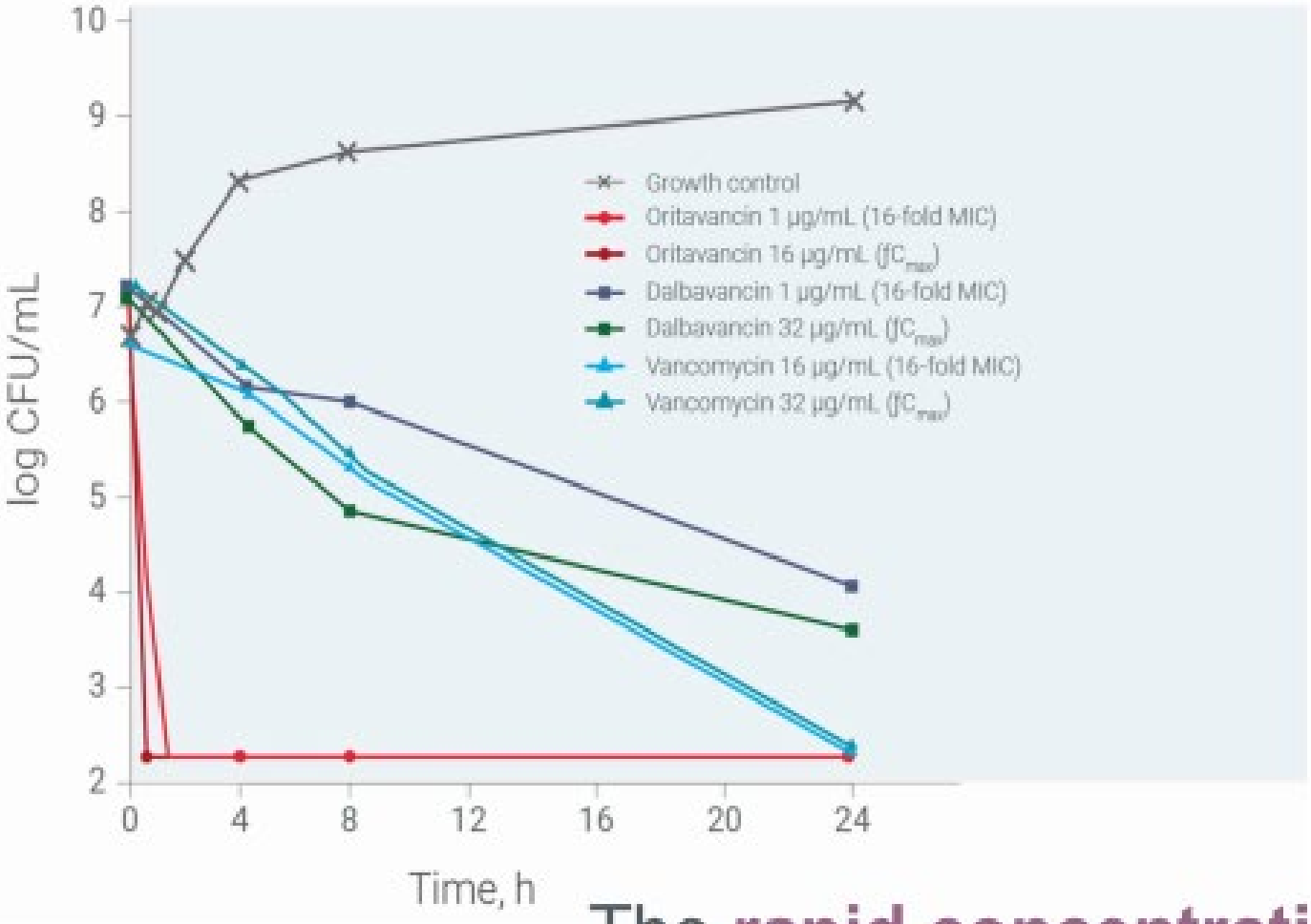


1 **Inhibition of the transpeptidation** (cross-linking) step of cell wall biosynthesis by binding to the peptide bridging segments of the cell wall[1]

2 **Inhibition of the transglycosylation** (polymerization) step of cell wall biosynthesis by binding to the stem peptide of peptidoglycan precursors[1]

3 **Disruption of bacterial membrane integrity**, leading to depolarization, permeabilization, and cell death[1]





- Killing of MRSA isolate by oritavancin was rapid, with bactericidal activity **within 1 hour**[11]
- Dalbavancin and vancomycin occurred more slowly over the 24-hour period[11]

The **rapid concentration-dependent bactericidal activity** of oritavancin results from **multiple mechanisms of action**.

SOLO 1
SOLO 2

ORITAVANCIN is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused or suspected to be caused by susceptible isolates of the following gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible [MSSA] and methicillin-resistant [MRSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), and ***Enterococcus faecalis.***

Fenotipi di resistenza *Enterococcus faecium/faecalis*.

Enterococcus spp.

Antibiotics	Ampicillin-R *Enterococcus*	VRE (VanA)	VRE (VanB)
Oxacillin	🔴	🔴	🔴
Ampicillin	🔴	🔴	🔴
Vancomycin	🟢	🔴	🔴
Teicoplanin	🟢	🔴	🟢
Dalbavancin	🟢	🔴	🟢
Telavancin	🟢	🔴	🟢
Oritavancin	🟢	🟢	🟢

Rationalizing antimicrobial therapy in the ICU: a narrative review

Intensive Care Med (2019) 45:172–189

Jean-François Timsit[1,2*], Matteo Bassetti[3], Olaf Cremer[4], George Daikos[5], Jan de Waele[6], Andre Kallil[7], Eric Kipnis[8], Marin Kollef[9], Kevin Laupland[10], Jose-Artur Paiva[11], Jesús Rodríguez-Baño[12], Étienne Ruppé[2,13], Jorge Salluh[14], Fabio Silvio Taccone[15], Emmanuel Weiss[16,17] and François Barbier[18]

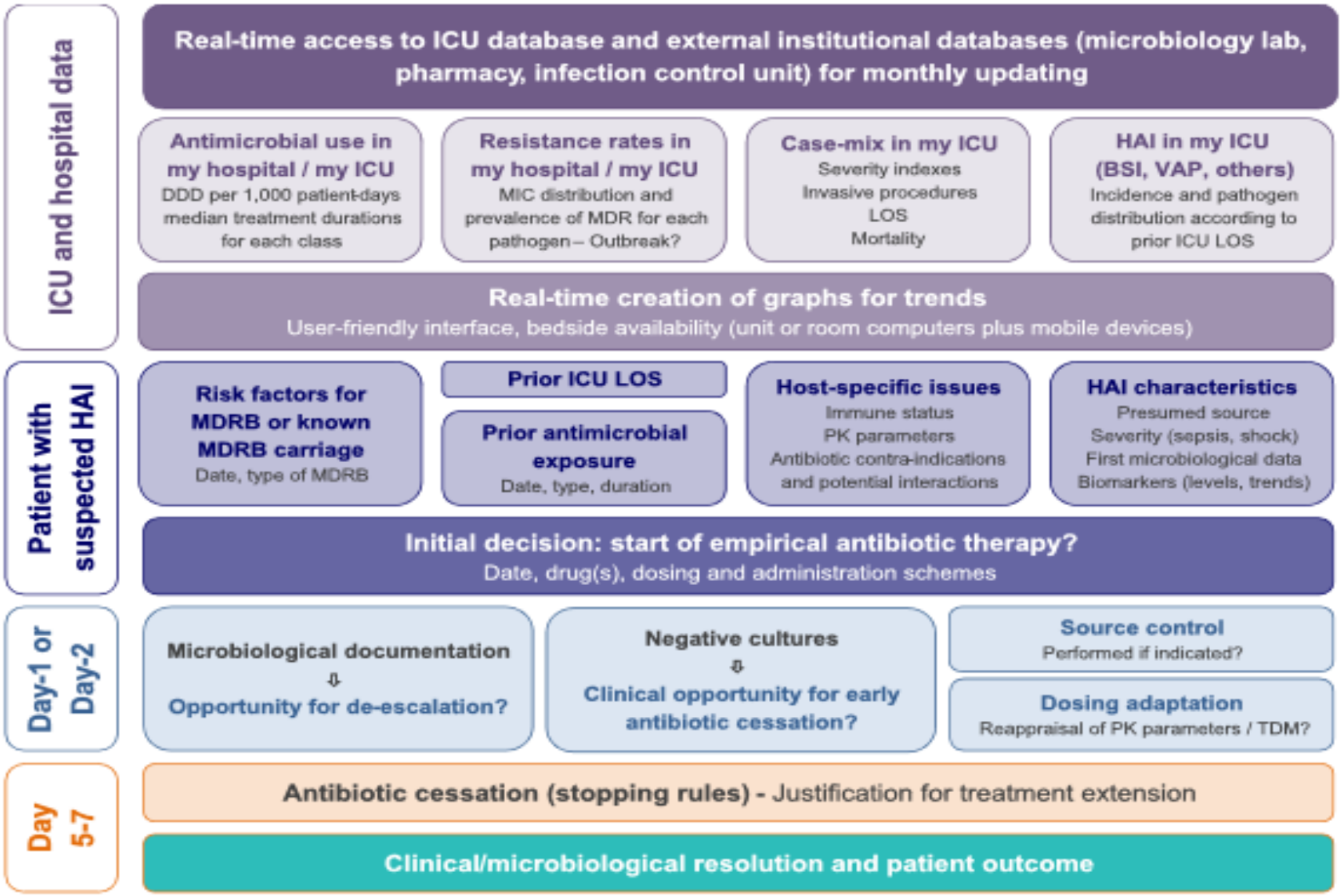


Fig. 4 A dashboard of dynamic and near real-time assessment of multi-resistance patterns in the ICU. *HAI* hospital-acquired infection, *LOS* length of stay, *ICU* intensive care unit


GRAZIE PER L’ATTENZIONE