

Mantova 6 ottobre 2023
Antimicrobico resistenza
Una sfida globale

Le infezioni emergenti in terapia intensiva

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Istituti Ospitalieri di Cremona

Conflitti di interesse

Advisory board

- MSD
- Sobi
- BBraun

Relazioni a congressi

- Gilead

- Introduzione

- I dati epidemiologici

- Gli strumenti

- I germi e le terapie

- Conclusioni

- **Introduzione**

- I dati epidemiologici

- Gli strumenti

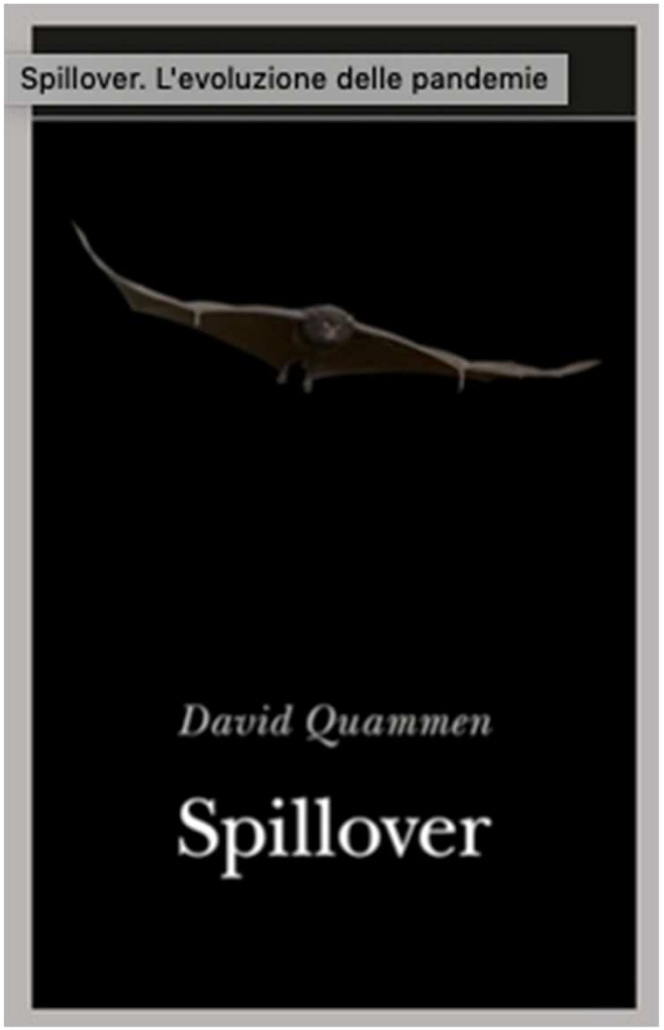
- I germi e le terapie

- Conclusioni

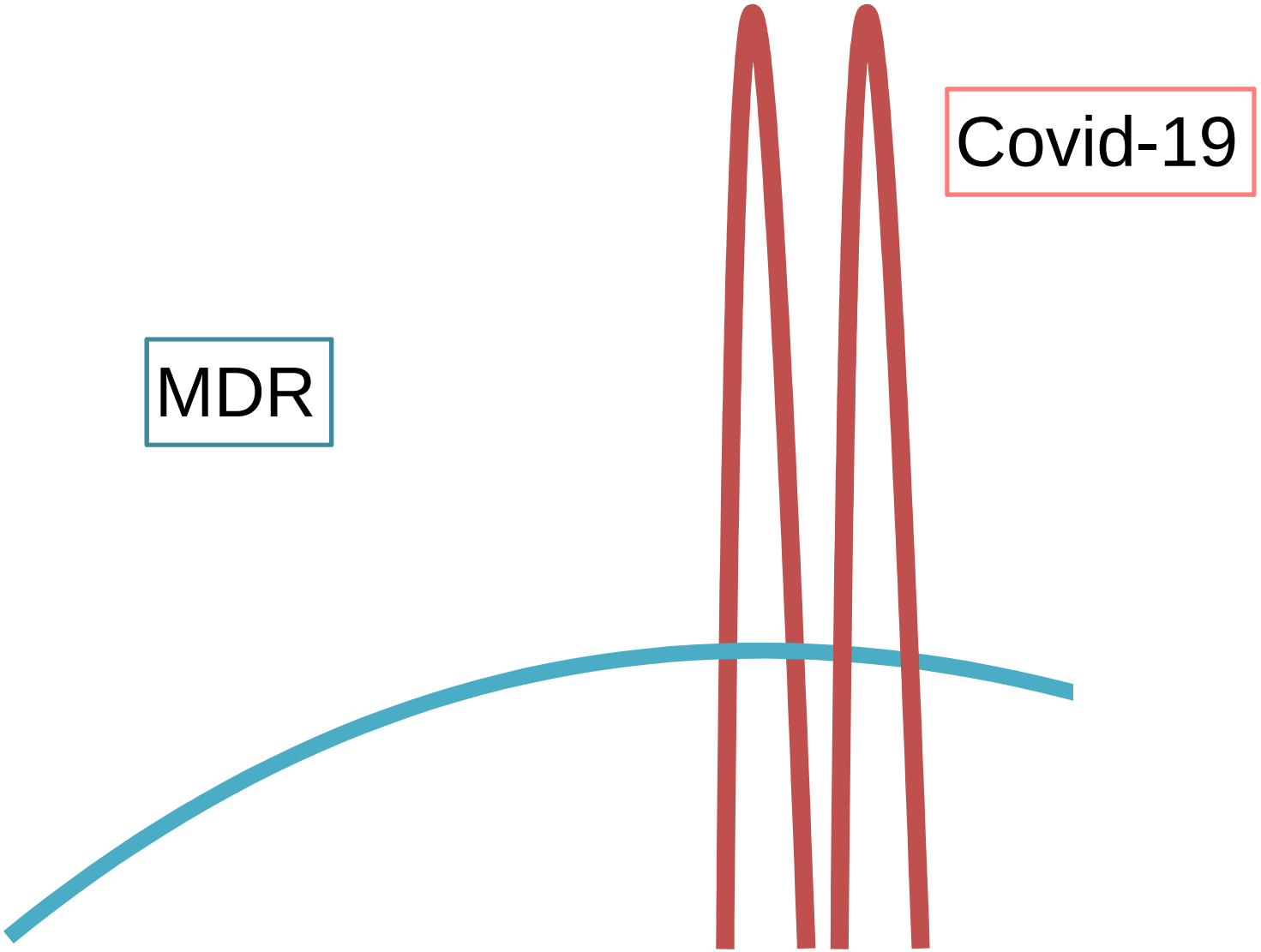
Quanto emergenti?

Quanto emergenti?

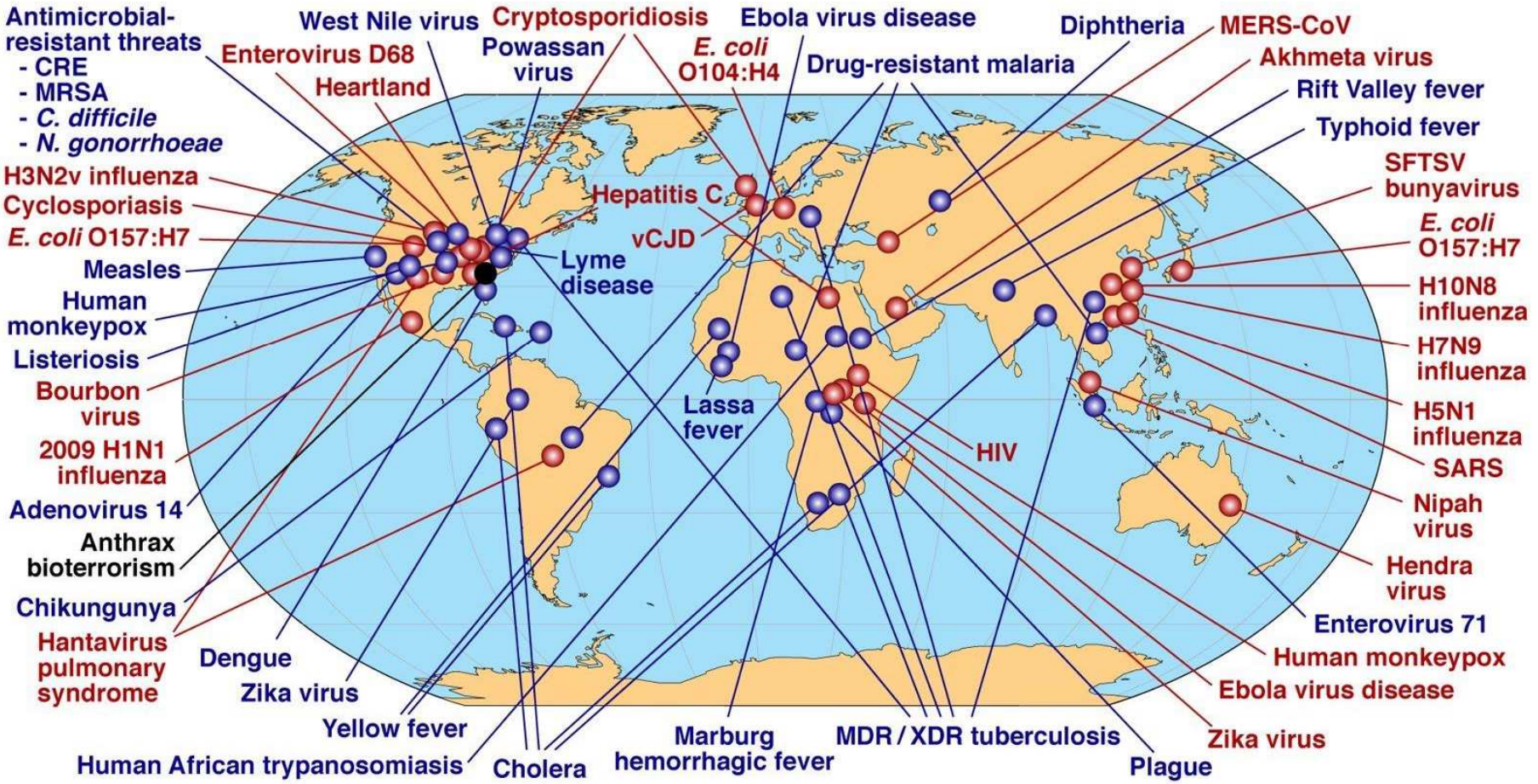




Velocità di emergenza



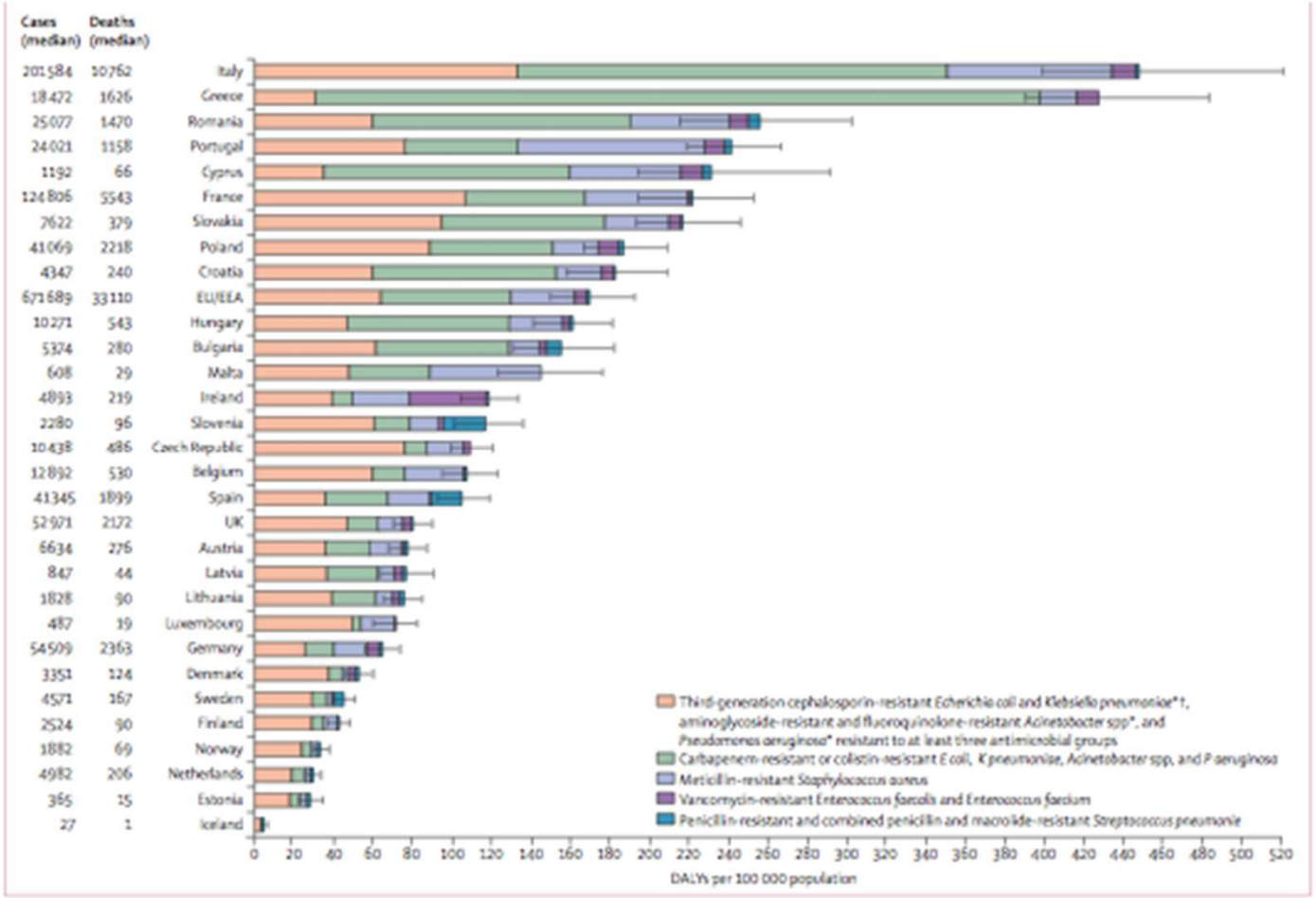
Global Examples of Emerging and Re-Emerging Infectious Diseases



September 2017

Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis

*Alessandro Cassini, Liselotte Diaz Högberg, Diamantis Plachouras, Annalisa Quattrocchi, Ana Hoxha, Gunnar Skov Simonsen, Mélanie Colomb-Cotinat, Mirjam E Kretzschmar, Brecht Devleesschauwer, Michele Cecchini, Driss Ait Ouakrim, Tiago Cravo Oliveira, Marc J Struelens, Carl Suetens, Dominique L Monnet, and the Burden of AMR Collaborative Group**



Cassini A, Lancet Infect Dis 2018



Antibiotic resistance

Recent developments

While there are some new antibiotics in development, none of them are expected to be ef

Given the ease and frequency with which people now travel, antibiotic resistance is a glob

https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance

- Introduzione

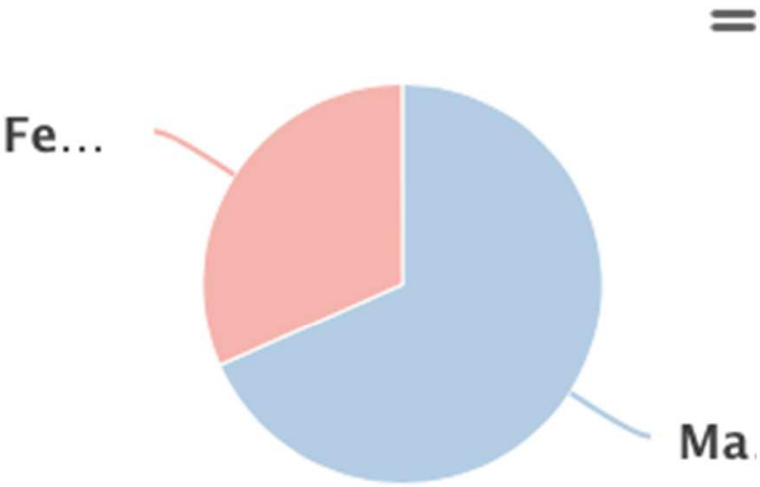
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La popolazione da curare

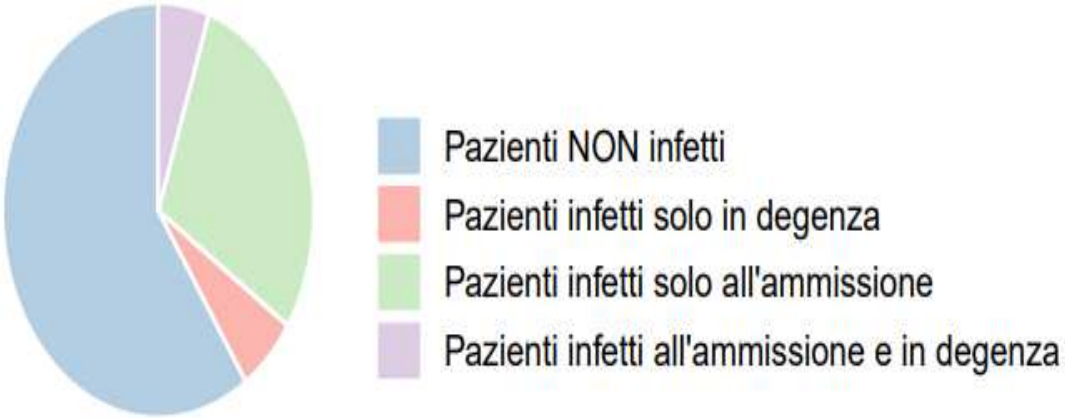


Sesso	N	%
Maschio	2378	68.3
Femmina	1102	31.7
Missing	0	0

Range età	N	%
<17	12	0.3
17-45	430	12.4
46-65	1163	33.4
66-75	1103	31.7
>75	772	22.2
Missing	0	0

Le dimensioni del problema

Infetti
40,5%



Pazienti	N	%
Pazienti NON infetti	15682	59.5
Pazienti infetti solo in degenza	1612	6.1
Pazienti infetti solo all'ammissione	7658	29.1
Pazienti infetti all'ammissione e in degenza	1391	5.3

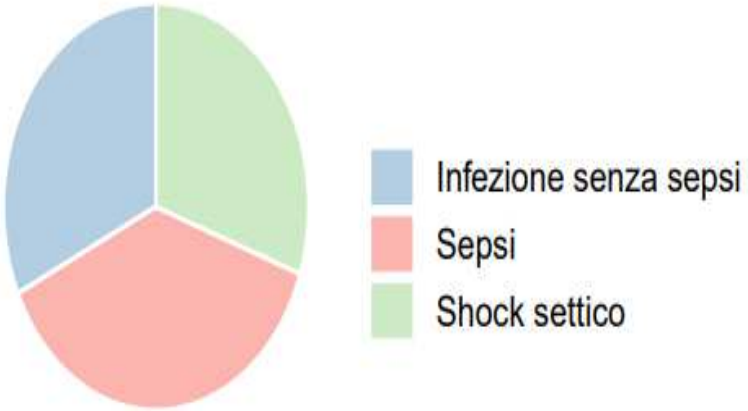
GiViTI Report infection full 2022

Le infezioni da curare

Infezione	N	%
Polmonite	1391	40.0
Inf. basse vie respiratorie NON polmonite	831	23.9
IVU catetere correlata	488	14.0
Batteriemia primaria sconosciuta	383	11.0
Batteriemia da catetere (CR-BSI)	379	10.9
Peritonite post-chirurgica	105	3.0
Infezione cute/tessuti molli post-chir.	97	2.8
Sepsi clinica	91	2.6
Infezione delle alte vie respiratorie	90	2.6
COVID-19	88	2.5
Missing	0	NA

GiViTI Report infection full 2022

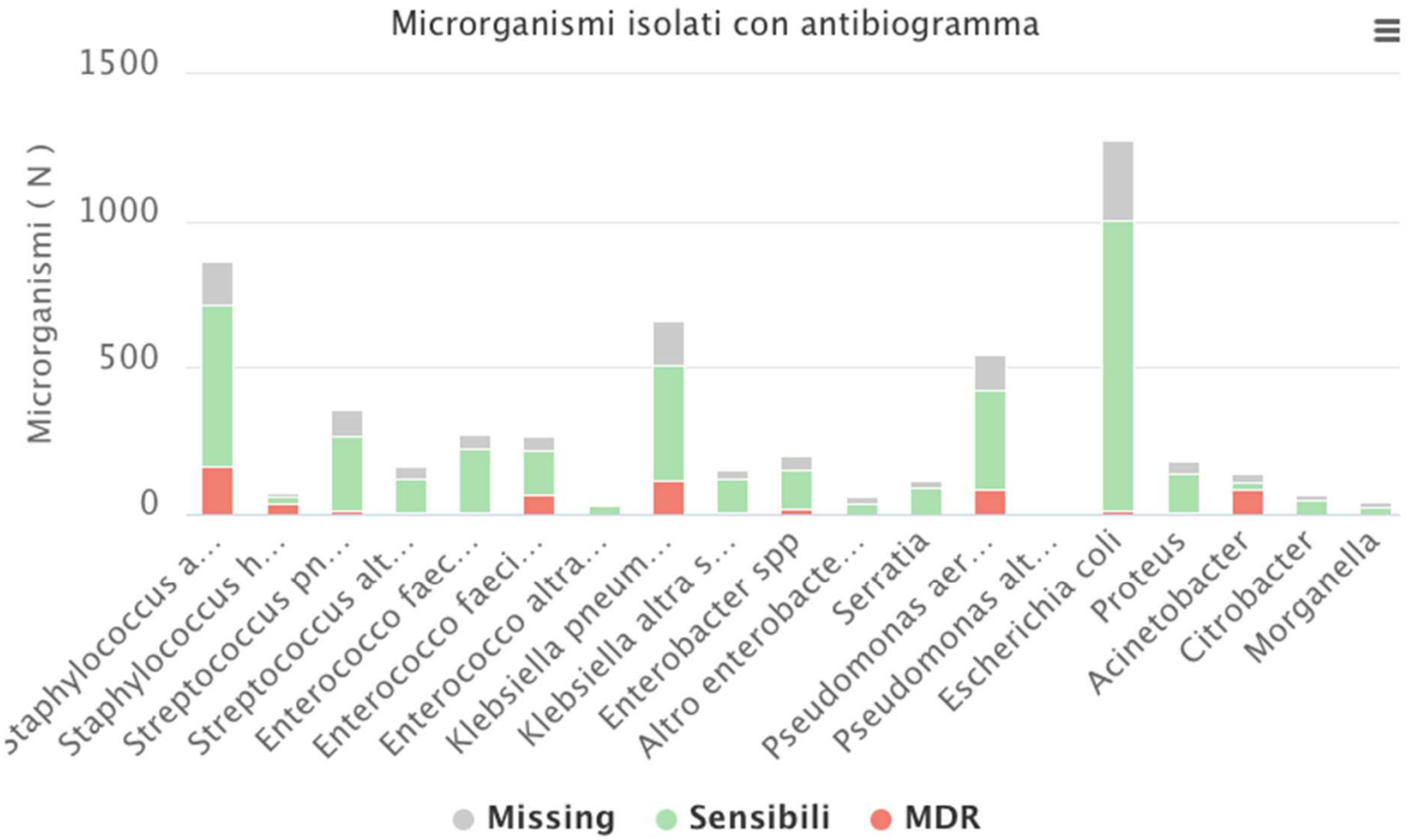
Massima gravità



Gravità massima dell'infezione	N	%
Infezione senza sepsi	3412	32.0
Sepsi	4011	37.6
Shock settico	3235	30.4
Missing	3	0

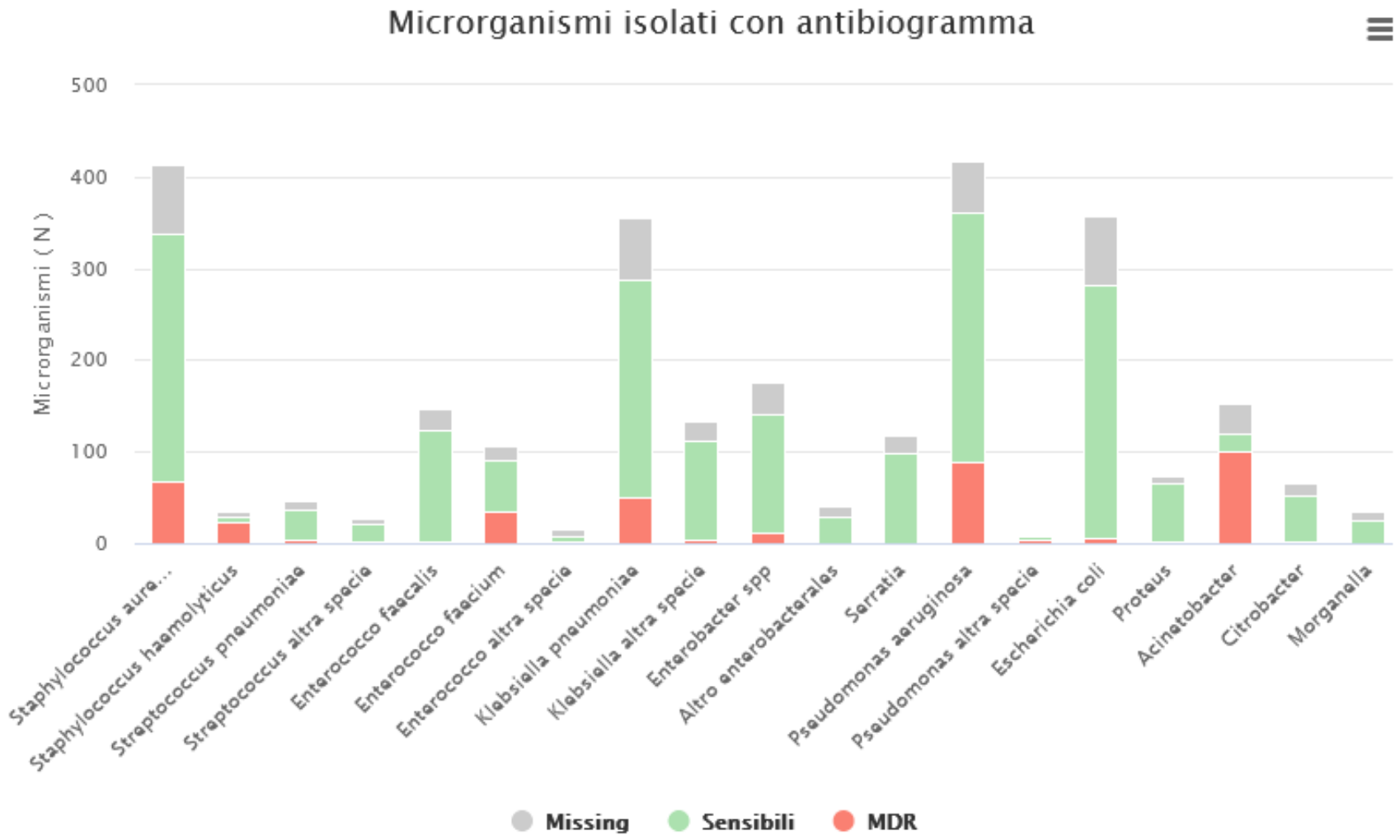
GiViTI Report infection full 2022

Microrganismi isolati al ricovero



GiViTI Report infection full 2022

Microrganismi isolati in degenza



GiViTI Report infection full 2022

Gli isolamenti

Batterio	Al ricovero	In degenza	Totale
MRSA	165 (23,1%)	87 (19,6%)	252
Pseudomonas aeruginosa CR	85 (20%)	131 (26%)	216
Acinetobacter baumannii CR	84 (78,5%)	131 (80,4%)	215
Klebsiella pneumoniae CR	113 (22,3%)	89 (22,9%)	202
VRE	69 (31,4%)	45 (36,3%)	114

GiViTI Report infection full 2022

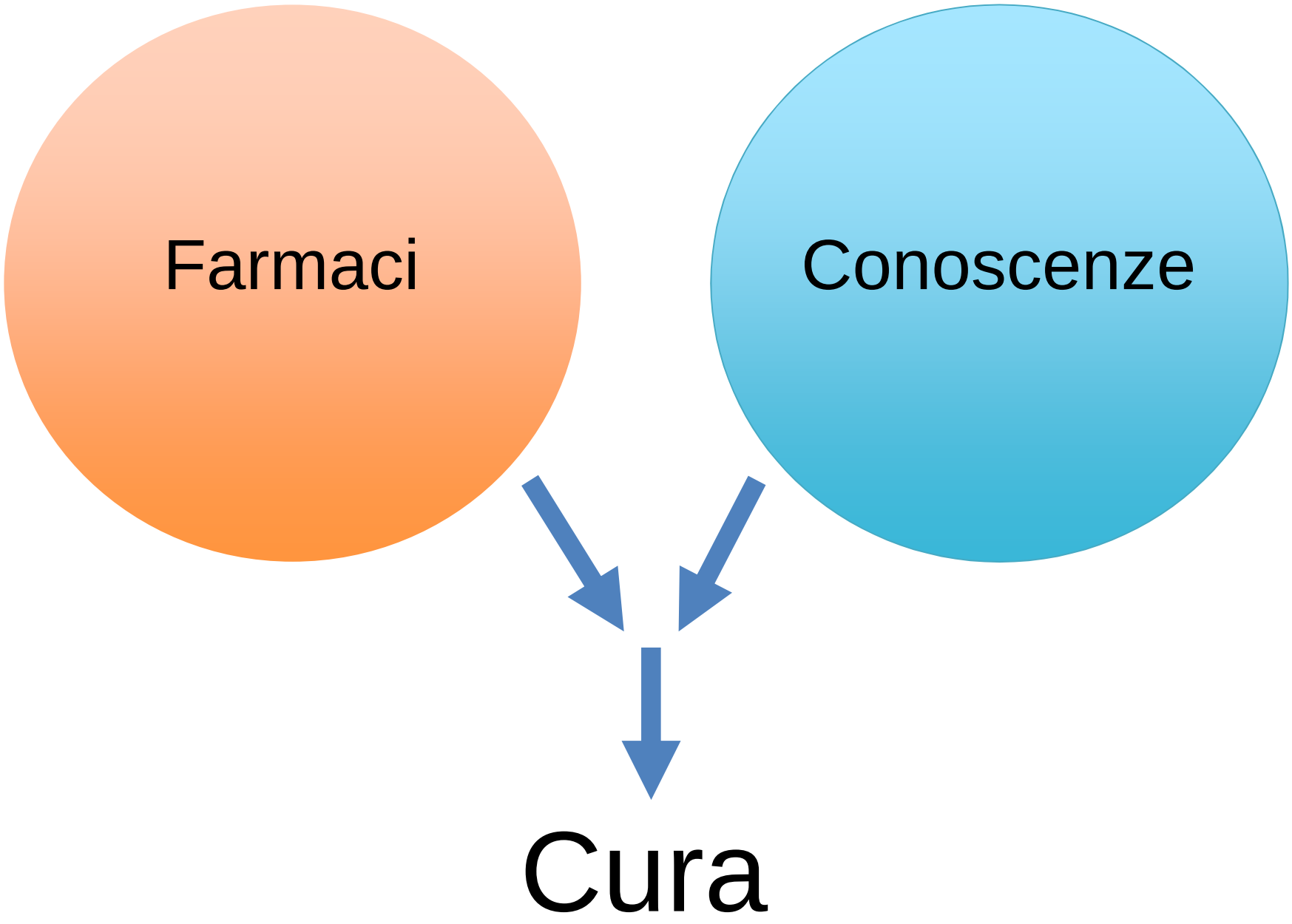
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Farmaci
Conoscenze
Cura

Ricambio dei medici nel SSN

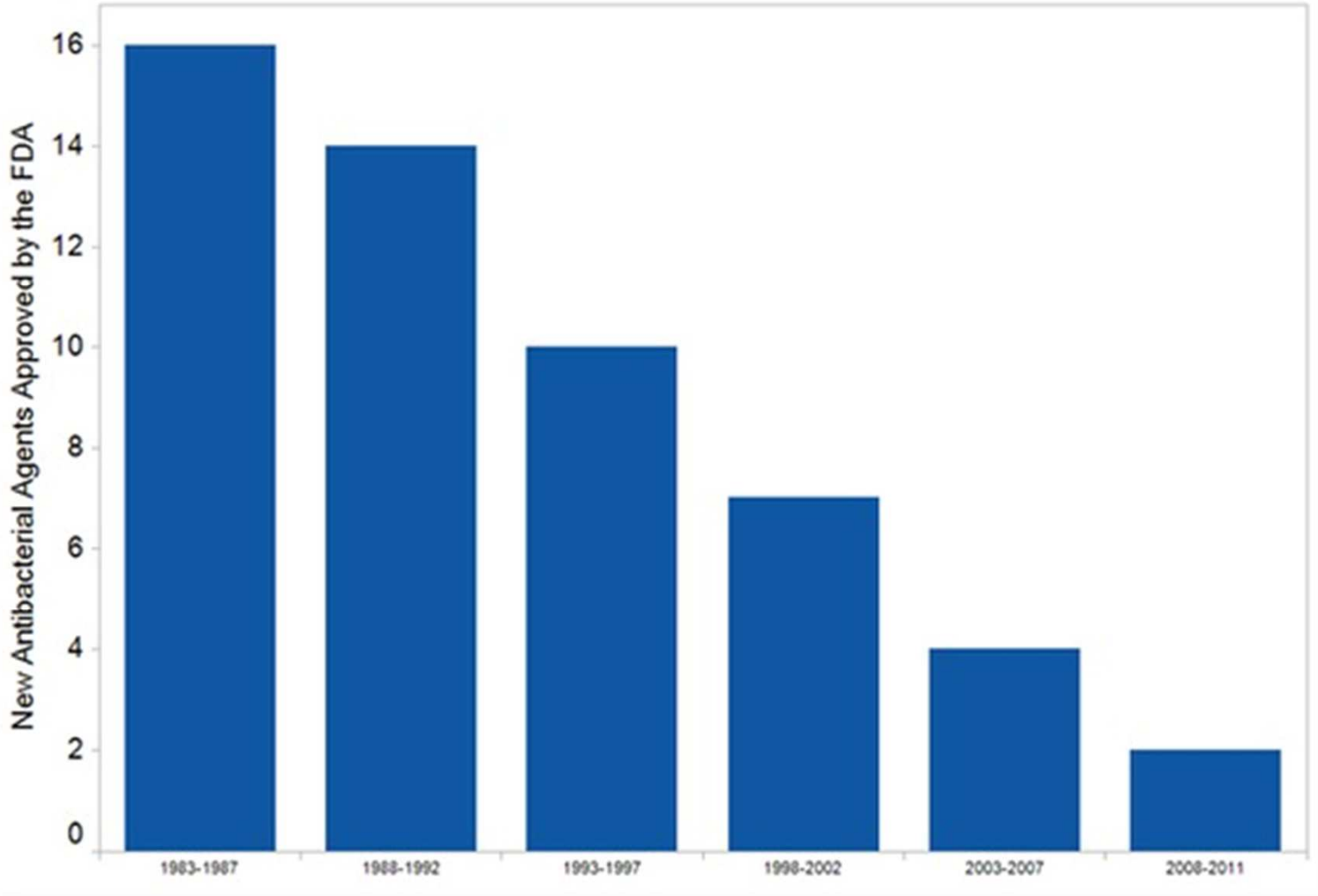
Molti medici in uscita

Meno medici in entrata

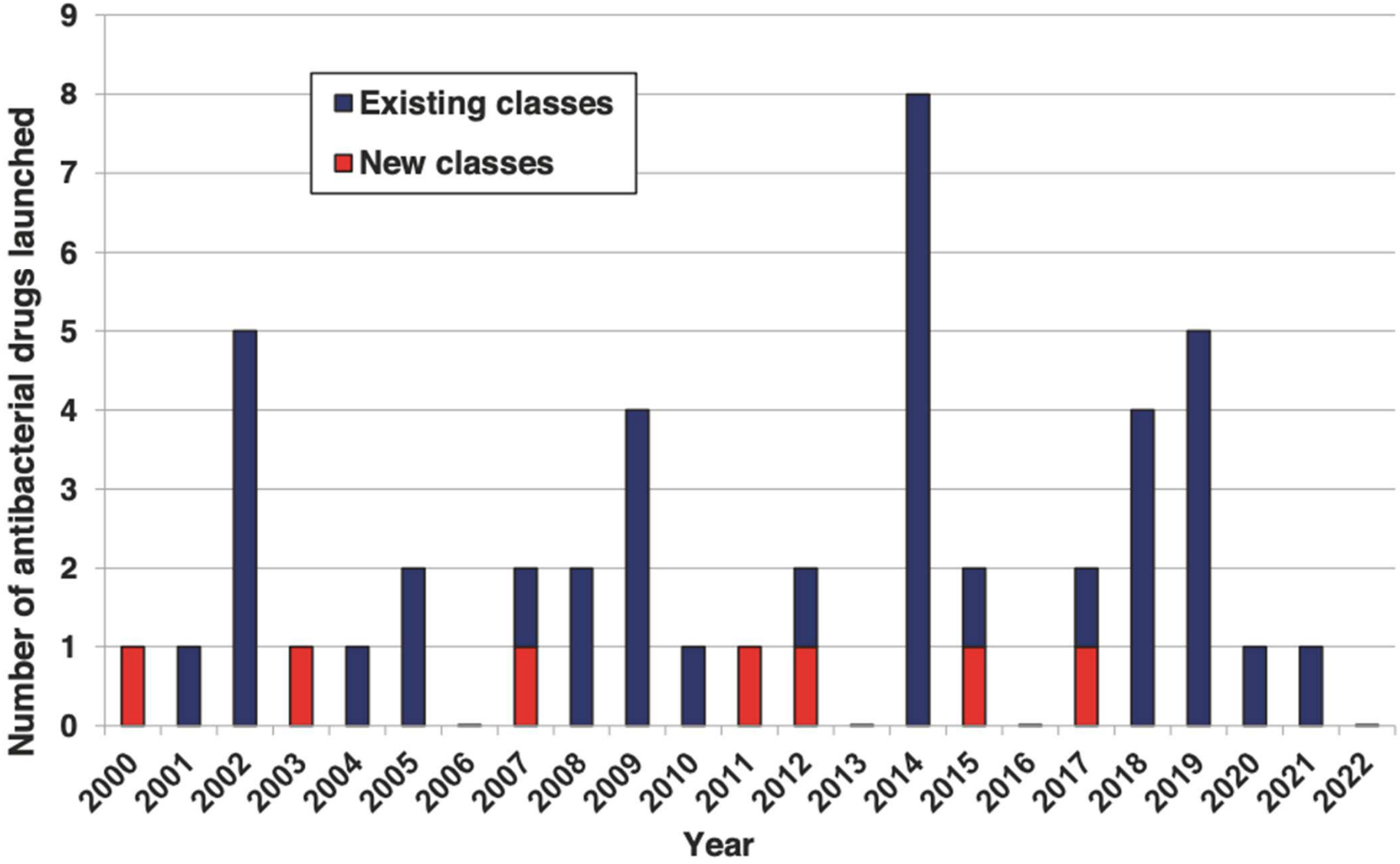
Come conservare le competenze?



Nuovi antibiotici 1983-2011



Nuovi antibiotici 2000-2022



Butler M, J Antibiot 2023

Antibiotici registrati 2013 - 2022
Farmaci a piccola molecola

Anno	Molecola	Classe	Indicazione
2014	desafinad	nitroimidazolo	TB
2014	dalbavancina	glicopeptide	G+ve SSSI
2014	oritavancina	glicopeptide	G+ve SSSI
2014	tedizolid	oxazolidinone	G+ve SSSI
2014	nemonoxacina	chinolone	G+ve / G-ve SSSI
2014	morinidazole	nitroimidazolo	G+ve/G-ve ginecologiche e appendicite suppurativa
2014	finafloxacina	fluorochinolone	acute otitis externa
2015	zabofloxacina	fluorochinolone	G+ve/G-v CABP
2017	delafloxacina	fluorochinolone	G+ve/G-v ABSSSI e CABP
2018	plazomicina	aminoglicoside	G-ve UTI
2018	eravacyclina	tetraciclina	G+ve/G-ve IAI
2018	omadacyclina	tetraciclina	G+ve/G-v ABSSSI e CABP
2018	sarecyclina	tetraciclina	G+ve acne
2019	pretomanid	Nitroimidazolo	TB
2019	lefamulina	Pleuromutilina	G+ve/G-ve CABP
2019	lascufloxacina	fluorochinolone	G+ve/G-ve CABP e sinusite
2019	cefiderocol	cefalosporina siderofora	G-ve cUTI and bacterial NP infections
2020	levonadifloxacina	fluorochinolone	G+ve/G-ve ABSSSI
2020	contezolid acefosamil	oxazolidinone	G+ve cSSSI

Antibiotici registrati 2013 - 2022
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2014	nemonoxacina	chinolone	G+ve / G-ve SSSI
2014	morinidazole	nitroimidazolo	G+ve/G-ve ginecologiche e appendicite suppurativa
2014	finafloxacina	fluorochinolone	acute otitis externa
2015	zabofloxacina	fluorochinolone	G+ve/G-v CABP
2017	delafloxacina	fluorochinolone	G+ve/G-v ABSSSI e CABP
2018	plazomicina	aminoglicoside	G-ve UTI
2018	eravaciclina	tetraciclina	G+ve/G-ve IAI
2018	omadaciclina	tetraciclina	G+ve/G-v ABSSSI e CABP
2018	sareciclina	tetraciclina	G+ve acne
2019	pretomanid	nitroimidazolo	TB
2019	lefamulina	pleuromotilina	G+ve/G-ve CABP
2019	lascufloxacina	fluorochinolone	G+ve/G-ve CABP e sinusite
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2020	levonadifloxacina	fluorochinolone	G+ve/G-ve ABSSSI
2020	contezolid acefosamil	oxazolidinone	G+ve cSSSI

Antibiotici registrati a livello mondiale 2013 - 2022
Beta-lattamina / inibitore Beta-lattamina

Anno	Molecola	Classe	Indicazione
2014	ceftolozane-tazobactam	BL + BLI	G-ve cUTI, cIAI, HAP/VAP
2015	ceftazidime-avibacatm	DBO BL + BLI	G-ve cUTI, cIAI, HAP/VAP
2017	meropenem-vaborbactam	boronato Bl + BLI	G-ve cUTI, cIAI, HAP/VAP
2019	imipenem-cilastatina-relebactam	DBO BLI + BL + inibitore diidropeptidase renale	G+ve SSSI

Legenda. DBO: diaza biciclo ottano

Farmaci antibatterici non tradizionali

Anno	Molecola	Classe	Indicazione
2016	obiltoxaximab	mAb	G+ve Anthrax
2016	bezlotoxumab	mAb	*Clostridioides difficile* tox
2022	RBX2660	Microbio	*Clostridioides difficile*

Legenda. mAb: anticorpi monoclonali

Antibiotici registrati a livello mondiale 2013 - 2022
Beta-lattamina / inibitore Beta-lattamina

Anno	Molecola	Classe	Indicazione
2014	ceftolozane-tazobactam	BL + BLI	G-ve cUTI, cIAI, HAP/VAP
2015	ceftazidime-avibacatm	DBO BL + BLI	G-ve cUTI, cIAI, HAP/VAP
2017	meropenem-vaborbactam	boronato Bl + BLI	G-ve cUTI, cIAI, HAP/VAP
2019	imipenem-cilastatina-relebactam	DBO BLI + BL + inibitore diidropeptidase renale	G+ve SSSI

Legenda. DBO: diaza biciclo ottano

Farmaci antibatterici non tradizionali

Anno	Molecola	Classe	Indicazione
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2016	bezlotoxumab	mAb	*Clostridioides difficile* tox
2022	RBX2660	Microbio	*Clostridioides difficile*

Legenda. mAb: anticorpi monoclonali

Che fare?

La necessità delle metacompetenze

s. f. Competenza individuale che va oltre il bagaglio di competenze formative specifiche di un determinato settore, comprendendo le predisposizioni, le conoscenze e le esperienze acquisite.

TRECCANI

- Introduzione

- I dati epidemiologici

- Gli strumenti

- **I germi e le terapie**

- Conclusioni

Enterobacterales produttrici di ESBL
Infezioni non urinarie - gravi

	ESCMID 2021	AIFA 2022	IDSA 2023
Prima scelta	Meropenem Imipenem-cilastatina Ertapenem*	Meropenem Imipenem-cilastatina	Meropenem Imipenem-cilastatina
Terapia alternativa		Fosfomicina EV§ TMP-SMX	
Alternative (solo se prima e seconda scelta non sono possibili)		Ceftazidime-avibactam Ceftolozane-tazobactam	
Semplificazione/passaggio terapia orale	Piperacillina-tazobactam Amoxicillina-acido clavulanico TMP-SMX Ciprofloxacina Levofloxacina	Piperacillina-tazobactam Amoxicillina-acido clavulanico Ampicillina-sulabctam TMP-SMX Ciprofloxacina Levofloxacina	TMP-SMX Ciprofloxacina Levofloxacina

Note: * Pazienti non in shock§: solo in terapia di combinazione

MRSA

Clinical Infectious Diseases

VIEWPOINTS

Considerations for Clinical Trials of *Staphylococcus aureus* Bloodstream Infection in Adults

Thomas L. Holland,[1] Henry F. Chambers,[2] Helen W. Boucher,[3] G. Ralph Corey,[1] Rebecca Coleman,[4] Bibiana Castaneda-Ruiz,[4] and Vance G. Fowler Jr[1]

[1]Department of Medicine, Duke University Medical Center, Durham, North Carolina; [2]Department of Medicine, University of California San Francisco; [3]Department of Medicine, Tufts Medical Center, Boston, Massachusetts; and [4]Theravance Biopharma US, Inc., South San Francisco, California

Overall, there have been fewer than 2500 patients enrolled in published randomized clinical trials for *S. aureus* bacteremia in the past 20 years, and fewer than 450 for MRSA bacteremia.

Clin Infect Dis. 2019

JAMA
View Article

JAMA. 2020 Feb 11; 323(6): 527–537.
Published online 2020 Feb 11. doi: 10.1001/jama.2020.0103
PMCID: PMC7042887
PMID: 32044943

Effect of Vancomycin or Daptomycin With vs Without an Antistaphylococcal β-Lactam on Mortality, Bacteremia, Relapse, or Treatment Failure in Patients With MRSA Bacteremia

Vanco/dapto + flucloxa/cloxa 2 g q6h vs vanco/dapto

Outcomes	No./Total No. (%) Combination Therapy	Standard Therapy	Risk Difference, % (95% CI)	*P* Value
Primary Outcome[a,b]				
Primary analysis population	59/170 (35)	68/175 (39)	−4.2 (−14.3 to 6.0)	.42
Per protocol	47/144 (33)	68/175 (39)	−6.2 (−16.7 to 4.3)	.25
Secondary Outcomes[c]				
All-cause mortality[d]				
Day 14	13/170 (8)	13/174 (7)	0.2 (−5.4 to 5.8)	.95
Day 42	25/170 (15)	19/174 (11)	3.8 (−3.3 to 10.8)	.29
Day 90	35/170 (21)	28/174 (16)	4.5 (−3.7 to 12.7)	.28
Persistent bacteremia[e]				
Day 2	50/167 (30)	61/173 (35)	−5.3 (−15.3 to 4.6)	.29
Day 5	19/166 (11)	35/172 (20)	−8.9 (−16.6 to −1.2)	.02
Microbiological relapse[a]	14/169 (8)	18/175 (10)	−2.0 (−8.1 to 4.1)	.52
Microbiological treatment failure[a]	16/170 (9)	17/175 (10)	−0.3 (−6.5 to 5.9)	.92
Acute kidney injury[f]	34/145 (23)	9/145 (6)	17.2 (9.3 to 25.2)	<.001
Duration of intravenous antibiotics, mean (SD), d	29.3 (19.5)	28.1 (17.4)		.72

JAMA 2020

RESEARCH Open Access

A randomized phase 2B trial of vancomycin versus daptomycin for the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia due to isolates with high vancomycin minimum inhibitory concentrations – results of a prematurely terminated study

Shirin Kalimuddin[1*], Yvonne F. Z. Chan[1], Rachel Phillips[2,3], Siew Pei Ong[4], Sophia Archuleta[5,6], David Chien Lye[7], Thuan Tong Tan[1] and Jenny G. H. Low[1]

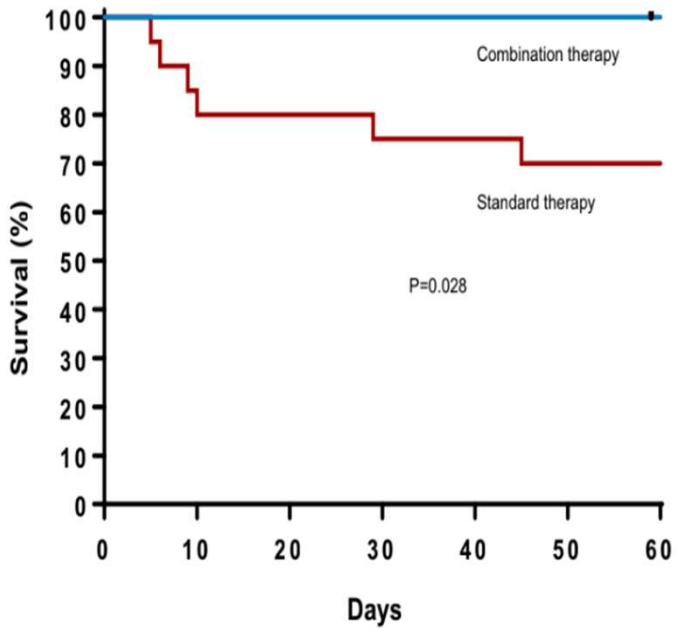
Trials 2018

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CLINICAL THERAPEUTICS

Clinical Data on Daptomycin plus Ceftaroline versus Standard of Care Monotherapy in the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Matthew Geriak,[a] Fadi Haddad,[b] Khulood Rizvi,[c] Warren Rose,[d] Ravina Kullar,[e] Kerry LaPlante,[f] Marie Yu,[b] Logan Vasina,[a] Krista Ouellette,[a] Marcus Zervos,[c] Victor Nizet,[f] George Sakoulas[a,g]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ceftobiprole for Treatment of Complicated *Staphylococcus aureus* Bacteremia

T.L. Holland, S.E. Cosgrove, S.B. Doernberg, T.C. Jenkins, N.A. Turner, H.W. Boucher, O. Pavlov, I. Titov, S. Kosulnykov, B. Atanasov, I. Poromanski, M. Makhviladze, A. Anderzhanova, M.E. Stryjewski, M. Assadi Gehr, M. Engelhardt, K. Hamed, D. Ionescu, M. Jones, M. Saulay, J. Smart, H. Seifert, and V.G. Fowler, Jr., for the ERADICATE Study Group*

Subgroup	Ceftobiprole	Daptomycin	Percentage-Point Difference (95% CI)
	no. of patients/total no. (%)		
All patients	132/189 (69.8)	136/198 (68.7)	2.0 (–7.1 to 11.1)
Age at written informed consent			
18 to <65 yr	98/131 (74.8)	101/135 (74.8)	0.6 (–9.8 to 10.9)
≥65 yr	34/58 (59)	35/63 (56)	6.9 (–10.5 to 24.3)
Sex			
Male	93/128 (72.7)	92/140 (65.7)	8.0 (–2.8 to 18.8)
Female	39/61 (64)	44/58 (76)	–11.3 (–27.7 to 5.1)
Baseline category of complicated *S. aureus* bacteremia			
Soft-tissue infection	81/116 (69.8)	80/121 (66.1)	4.5 (–7.3 to 16.3)
S. aureus bacteremia excluding soft-tissue infection	51/73 (70)	56/77 (73)	–1.7 (–15.9 to 12.6)
Osteoarticular infection	23/32 (72)	24/35 (69)	2.9 (–19.7 to 25.6)
Abdominal abscess	18/26 (69)	22/29 (76)	–9.7 (–33.3 to 13.9)
Hemodialysis	13/24 (54)	15/25 (60)	–4.6 (–32.5 to 23.3)
Persistent *S. aureus* bacteremia	8/16 (50)	8/16 (50)	–0.0 (–35.9 to 35.9)
Infective endocarditis on right side of heart	10/15 (67)	7/10 (70)	–6.6 (–40.1 to 27.0)
Baseline *S. aureus* infection			
Methicillin-susceptible	100/141 (70.9)	97/146 (66.4)	4.8 (–5.9 to 15.5)
Methicillin-resistant	31/45 (69)	38/49 (78)	–8.3 (–25.3 to 8.6)
Previous antibiotic use			
Yes	92/139 (66.2)	85/134 (63.4)	2.9 (–8.4 to 14.2)
No	40/50 (80)	51/64 (80)	–0.2 (–15.0 to 14.6)
Trial cohort			
Cohort 1	68/97 (70)	62/96 (65)	7.6 (–5.6 to 20.8)
Cohort 2	64/92 (70)	74/102 (72.5)	–3.4 (–16.1 to 9.3)

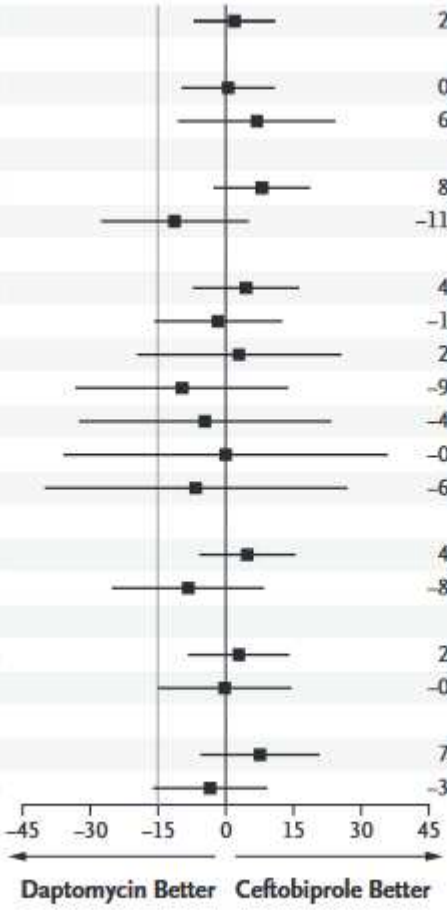


Figure 2. Overall Treatment Success at the Post-Baseline Evaluation Visit, According to Patient Characteristics at Baseline (Modified Intention-to-Treat Analysis Population).

Pseudomonas aeruginosa CR

CRPA

Resistenza

- Più facile con
  - Ceftolozano-tazobactam: mutazioni PDC
  - Ceftazdime-avibactam: mutazioni PDC
  - Resistenza a Cefta-azi dopo terapia con Cefto-tazo in 80% isolati
- Anche per
  - Imipenem-relebactam: ? Forse PDC
  - Cefiderocol: TonB e PDC

Pseudomonas aeruginosa DTR
Infezioni non urinarie - gravi

	ESCMID 2021	SEIMC 2022	SIMIT 2022	AIFA 2022	IDSA 2023
CR ma sensibile ad altri B lattamici					Cefto-tazo Cefta-avi Imi-rele
Prima scelta	Cefto-tazo	Cefto-tazo	Cefto-tazo Cefta-avi	Cefto-tazo	Cefto-tazo Cefta-avi Imi-rele
Alternativa/Seconda scelta	Polimixine* Aminoglicosidi* Fosfomicina*	Cefta-avi Imi-rele Cefto-tazo/cefta-avi + aminogl/colist Fosfomicina*	Imi-rele Colistina*	Cefta-avi Imi-rele	Cefiderocol
Prima scelta MBL				Cefiderocol	Cefiderocol
Prima scelta GES, ESBL+OprD		Cefta-avi			
Alternativa (se prima o seconda scelta non possibili)		Colistina aerosol^ Colistina intratecale^		Cefiderocol Colistina* Colistina intratecale^	

Note: * solo in combinazione- ^ in associazione alla terapia endovenosa.

Acinetobacter baumannii CR
CRAB

- Prevenzione aggressiva
- Gestione dei pazienti
- Gestione dell’ambiente

Acinetobacter baumannii CR
Infezioni non urinarie - gravi

	ESCMID 2021	SEIMC 2022	SIMIT 2022	AIFA 2022	IDSA 2023
Prima scelta	Almeno 2 farmaci: Ampicillina-sulbactam Polimixina B Colistina Tigeciclina	Ampicillina-sulbactam HD* + ≥1 altro farmaco: Colistina Minociclina HD Tigeciclina HD Gentamicina Amikacina	Non ci sono abbastanza dati per identificare una terapia ottimale	Ampicillina-sulbactam HD* Colistina* Tigecilina*	Ampicillina-sulbactam HD* + ≥1 altro farmaco: Minociclina HD Polimixina B Tigeciclina HD Cefiderocol
Alternativa/Seconda scelta	Colistina Polimixina B Tigeciclina HD	Colistina Colistina aerosol^ Colistina intratecale^	Cefiderocol	Cefiderocol	
Alternativa (se prima o seconda scelta non possibili)	Meropenem§ + un altro farmaco	Cefiderocol + Colistina Colistina + Meropenem HD + Ampicillina-sulbactam HD		Colistina aerosol^ Colistina intratecale^	Sulbactam-durlobactam Eravaciclina

Note: HD: alte dosi. * Solo in combinazione. ^ Solo insieme a colistina endovenosa. § Se MIC <8 mg/L.

Enterobacterales CR

Enterobacterales
Resistenze ai nuovi farmaci

Nuovo farmaco	Rischio di resistenza
Ceftazidime-avibactam	10-20%
Ceftolozane-tazbactam	10-20?
Cefiderocol	?
Meropenem-vaborbactam	3%
Imipenem-relebactam	?

Indagini molecolari



GiViTI Report infection full 2022

Enterobacterales produttrici di carbapenemasi
Infezioni non urinarie - gravi

	ESCMID 2021	SEIMC 2022	SIMIT 2022	AIFA 2022	IDSA 2023
Prima scelta Non CP o nessun dato	Mero-vabor Cefta-avi			Mero-vabor Cefta-avi	Mero-vabor Cefta-avi Imi-rele
Prima scelta KPC	Mero-vabor Cefta-avi	Mero-vabor Cefta-avi	Mero-vabor Cefta-avi	Mero-vabor Cefta-avi Meropenem HD*	Mero-vabor Cefta-avi Imi-rele
Prima scelta MBL	Cefiderocol Aztreonam + Cefta-avi	Aztreonam + Cefta-avi	Aztreonam + Cefta-avi	Cefiderocol Aztreonam + Cefta-avi	Cefiderocol Aztreonam + Cefta-avi
Prima scelta OXA-48	Cefta-avi	Cefta-avi	Cefta-avi	Meropenem HD* Cefta-avi	Cefta-avi
Seconda scelta		Imi-rele§ Cefiderocol	Imi-rele§ Cefiderocol	Colistina¶ Fosfomicina¶ Tigeciclina¶ Meropenem¶§	Cefiderocol Aztreonam + Cefta-avi^

Note. CP: produttore carbapenemasi. HD: dose elevata. * Se MIC <2 mg/L. ^ Senza identificazione CP o in assenza di dati, in caso di alta prevalenza o pregresso isolamento MBL. ¶ Solo in terapia di combinazione. § se MIC >2 - <8 mg/L.

Conclusioni

- I germi continuano ad evolvere
- La prevenzione innanzitutto
- Pochi dati veramente solidi
- Impariamo dalla pandemia
- Metacompetenze
- Lavoro di rete: gruppo multidisciplinare