GiViTI

Gruppo italiano per la Valutazione degli interventi in Terapia Intensiva

LE MULTIRESISTENZE: LE KPC NELLE TERAPIE INTENSIVE ITALIANE

Meeting GiViTI al sud, Lecce 8 e 9 aprile

Daniela Silengo San Giovanni Bosco Torino

ANTIBIOTIC RESISTANCE

Antibiotic resistance is the ability of a microorganism (like bacteria, viruses, and some parasites) to stop an antimicrobial (such as antibiotics, antivirals and antimalarials) from working against it. As a result standard treatments become ineffective, infection persist and may spread to others.

WHO

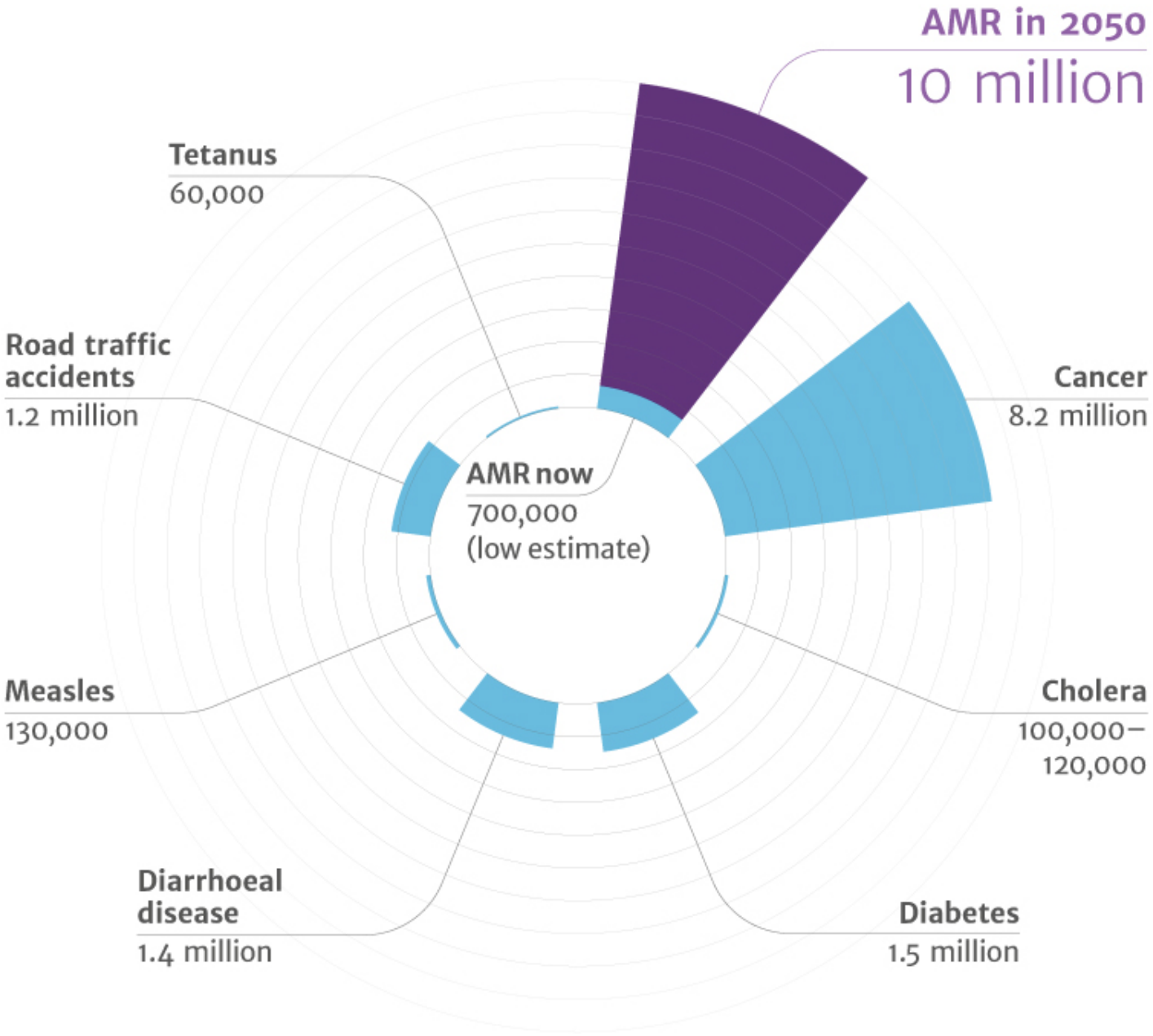
ANTIBIOTICO RESISTENZA

TABLE 6. **Definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria**

Bacterium	MDR	XDR	PDR
Staphylococcus aureus	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 1[a]	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1.	Non-susceptibility to all agents in all antimicrobial categories for each bacterium in Tables 1–5
Enterococcus spp.	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 2	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 2.	
Enterobacteriaceae	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 3	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 3.	
Pseudomonas aeruginosa	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 4	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 4.	
Acinetobacter spp.	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 5	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 5.	

[a]All MRSA isolates are defined as MDR because resistance to oxacillin or cefoxitin predicts non-susceptibility to all categories of β-lactam antimicrobials listed in this document, with the exception of the anti-MRSA cephalosporins (i.e. all categories of penicillins, cephalosporins, β-lactamase inhibitors and carbapenems currently approved up until 25 January 2011).
http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/public_consultation_clinical_microbiology_infection_article.aspx.

Clinical Microbiology and Infection, Volume 18 Number 3, March 2012



amr-review.org

Clinical Infectious Diseases

SUPPLEMENT ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Gram-Negative Bacterial Infections: Research Priorities, Accomplishments, and Future Directions of the Antibacterial Resistance Leadership Group

Yohei Doi,[1] Robert A. Bonomo,[2] David C. Hooper,[3] Keith S. Kaye,[4] James R. Johnson,[5] Cornelius J. Clancy,[1] Joshua T. Thaden,[6] Martin E. Stryjewski,[7] and David van Duin[8]; for the Gram-Negative Committee of the Antibacterial Resistance Leadership Group (ARLG)[a]

Antimicrobial resistance in gram-negative pathogens has implications beyond the immediate issues of morbidity and mortality. None of the advances of modern medicine such as complex surgery, transplantation, cancer chemotherapy, and intensive care are possible without reliable means to treat the infections that inevitably complicate them.

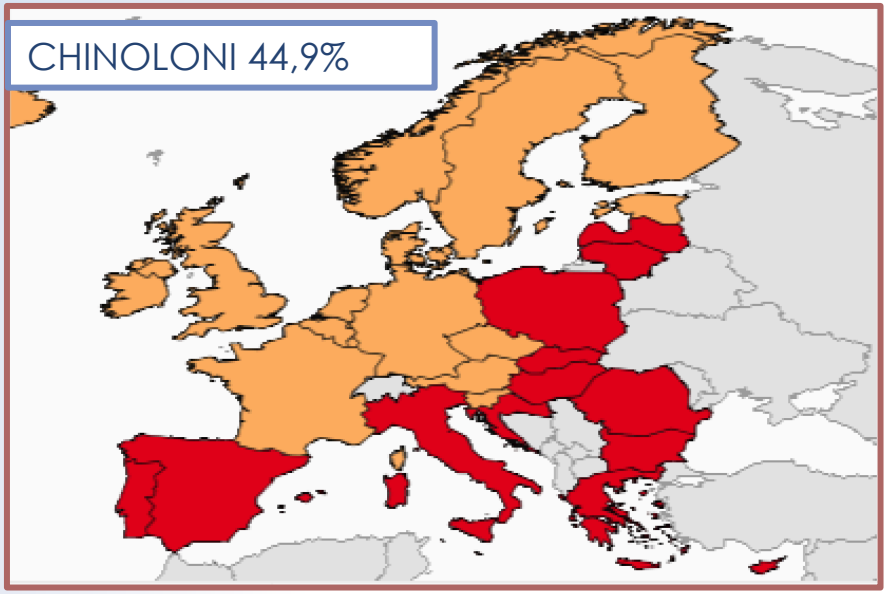
RESEARCH ARTICLE Open Access

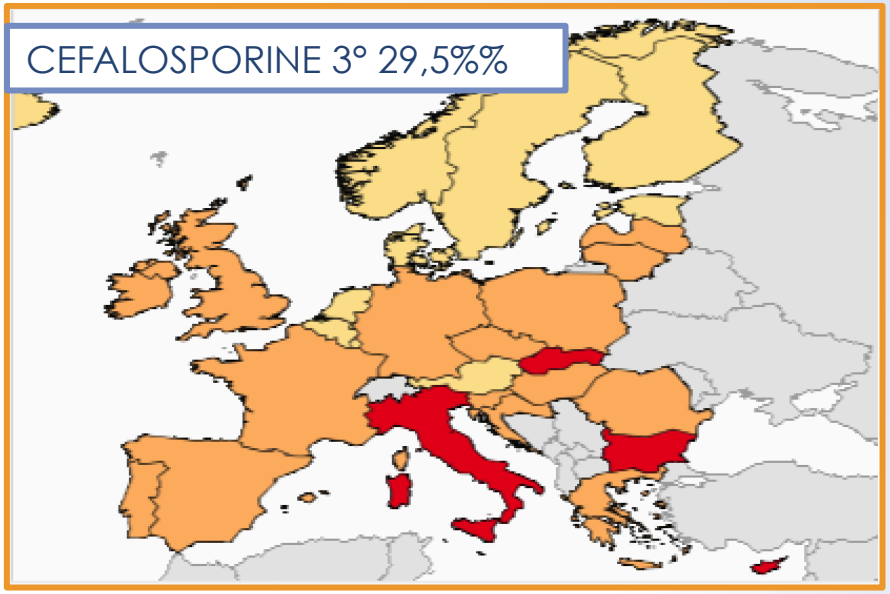
Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with Enterobacteriaceae urinary tract infection, pneumonia and sepsis

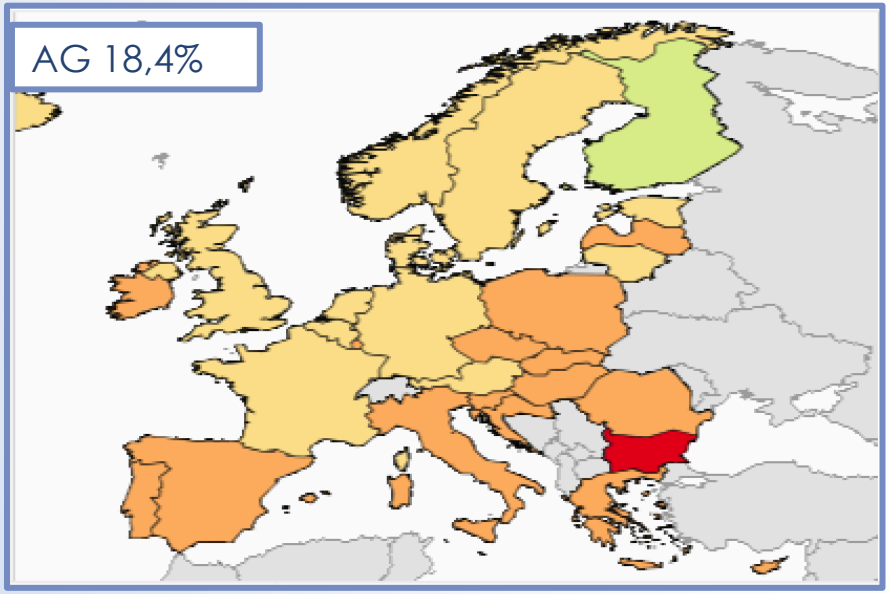
Marya D. Zilberberg[1*], Brian H. Nathanson[2], Kate Sulham[3], Weihong Fan[3] and Andrew F. Shorr[4]

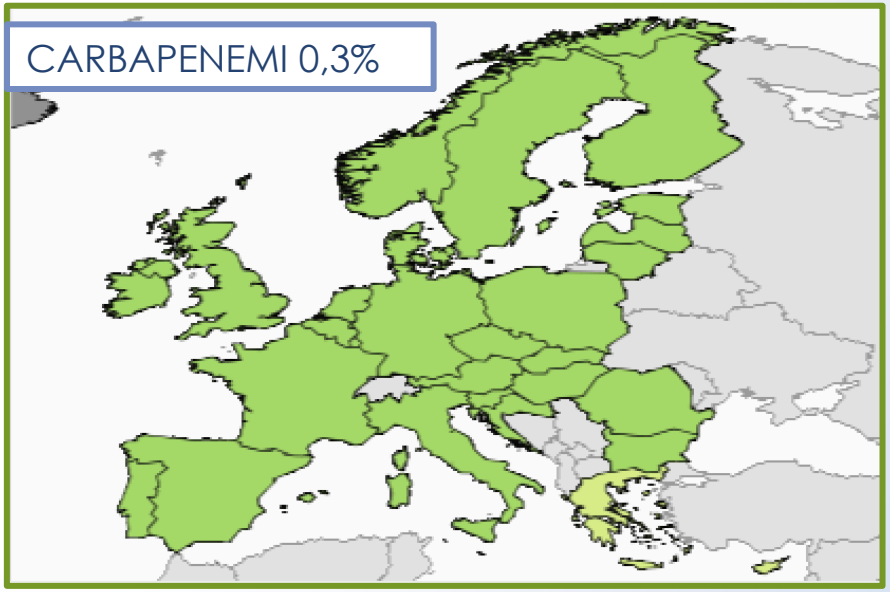
- ✓ Terapia empirica ha impatto sull'outcome:
  - Tempestiva
  - Attiva in vitro sul patogeno infettante
- ✓ Terapia empirica tardiva o non efficace aumenta rischio di morte da 2 a 5 volte

E.COLI





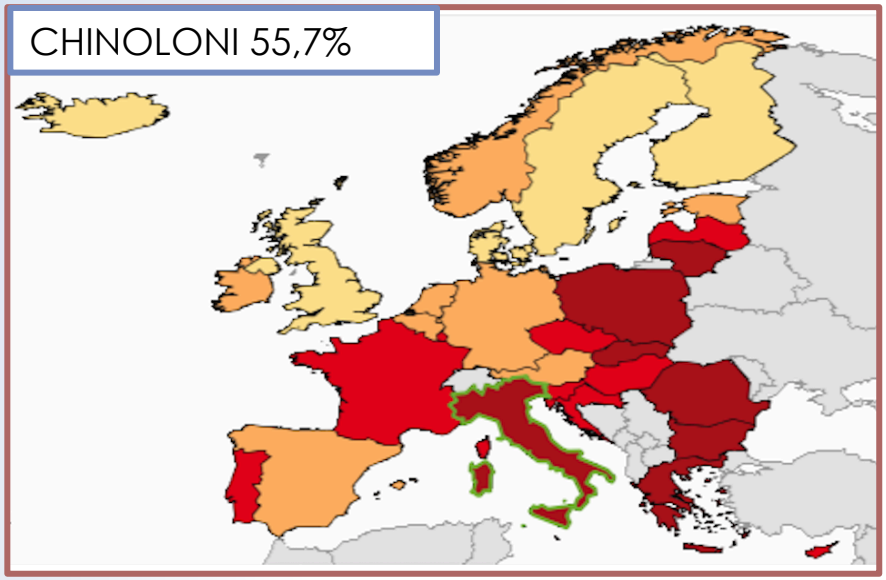




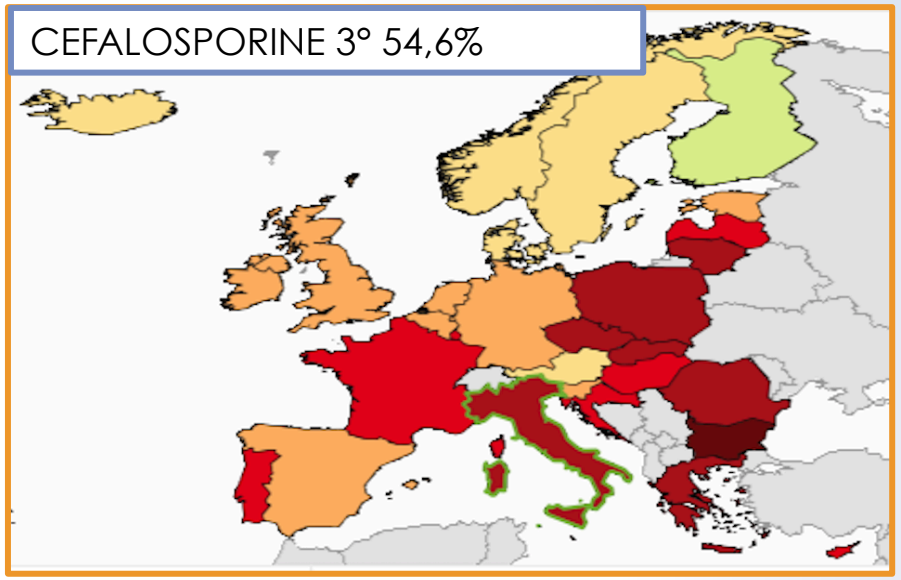
ECDC ATLAS DATI 2017

KLEBSIELLA PNEUMONIAE

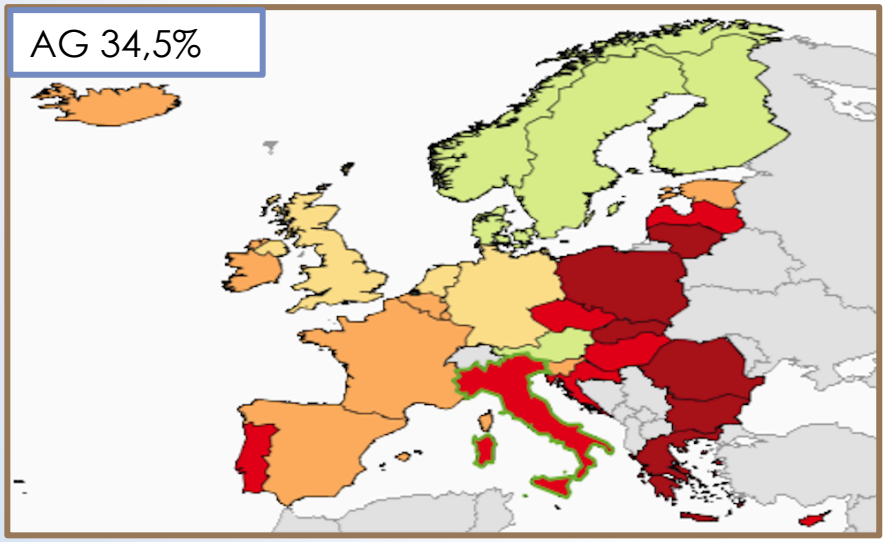
CHINOLONI 55,7%



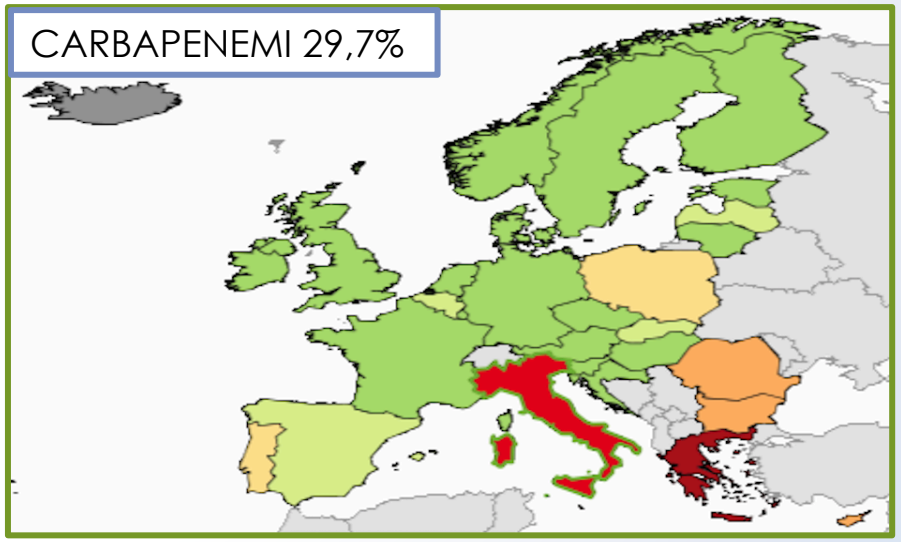
CEFALOSPORINE 3° 54,6%



AG 34,5%

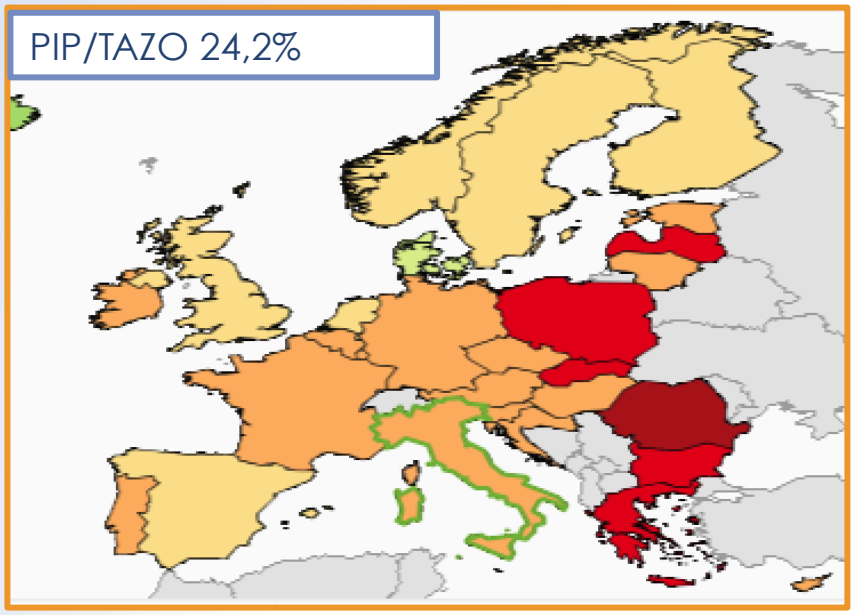


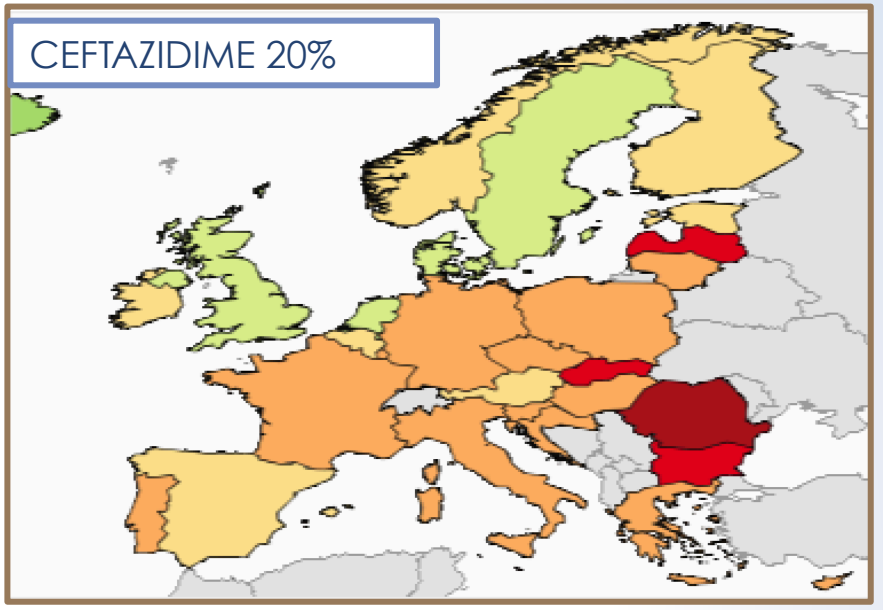
CARBAPENEMI 29,7%

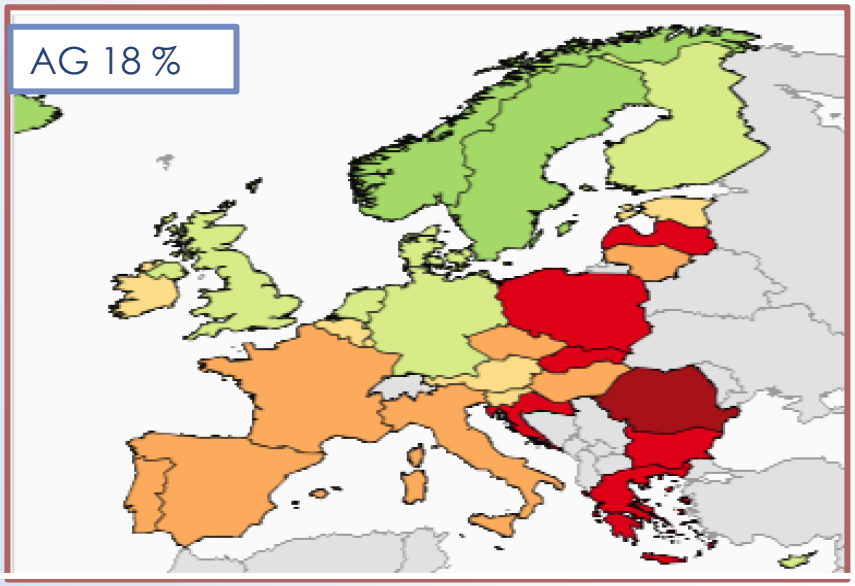


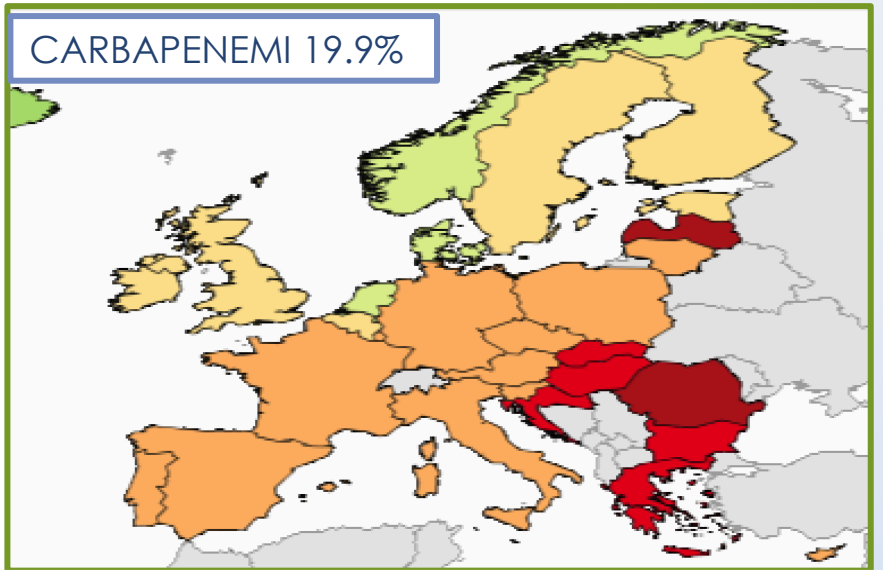
ECDC ATLAS DATI 2017

PSEUDOMONAS









ECDC ATLAS DATI 2017

ENTEROBATTERIACEE

Table 1 Individual CRE organisms and their frequencies

CRE organism name	CRE organism Count (*N* = 1938)	% of Total CRE (*N* = 1938)	% of the Total patients[a] (*N* = 1227)
Klebsiella pneumoniae	724	37.4%	59.0%
Proteus mirabilis	370	19.1%	30.2%
Escherishia coli	294	15.2%	24.0%
Enterobacter cloacae	128	6.6%	10.4%
Providencia spp	94	4.9%	7.7%
Serratia marcescens	87	4.5%	7.1%
Morganella morganii	87	4.5%	7.1%
Enterobacter aerogenes	40	2.1%	3.3%
Proteus spp.	27	1.4%	2.2%
Citrobacter freundii	27	1.4%	2.2%
Klebsiella oxytoca	22	1.1%	1.8%
Enterobacter other	13	0.7%	1.1%
Citrobacter other	14	0.7%	1.1%
Serratia other	6	0.3%	0.5%
Klebsiella other	5	0.3%	0.4%

[a]Sum adds up to >100%, as some patients had >1 CRE organism

Zilberberg et al. BMC Infectious Diseases (2017) 17:279

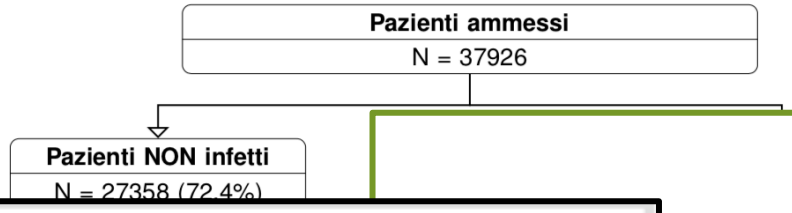
ICU CHALLENGE

- ICU sono spesso considerate l'epicentro delle infezioni: tra il 38% (SOAP) e il 50% (EPIC II) dei pazienti in ICU ha un'infezione
- 5%-15% dei posti letto vs 10%-25% di spesa
- La sepsi in ICU è la seconda causa di morte non-cardiaca, con una mortalità che si aggira intorno al 50%
- Ogni ora di ritardo nell'instaurare una terapia antibiotica efficace aumenta la mortalità del 7,6%

Crit Care Med 2006; 34: 344-353, JAMA 2009; 302: 2323-2329,
Crit Care Med 2011;39:2066-71

T.I. ITALIANE

Report nazionale (118 TI) - **Anno 2018** [TI Polivalenti]
Flow-chart



AMMISSIONE:

= 12609 (33,24%)

Pazienti infetti (N=12609)

Gravità massima dell'infezione	N	%
INFEZIONE SENZA SEPSI	2367	19.6
SEPSI	6198	51.4
SHOCK SETTICO	3501	29.0
Missing	543	

Mortalità per gravità dell'inf. (%)	In TI	In H
INFEZIONE SENZA SEPSI	12.5	19.8
SEPSI	18.4	27.2
SHOCK SETTICO	46.1	53.9

4

					3+4	2+4
					Pazienti infetti all'ammissione	Pazienti infetti in degenza
					N=10417 (27.5%)	N=3382 (8.9%)
					6; 2–12	19; 11–31
					18; 9–31	31; 18–49
					2665; 25.6% {24.8–26.5}	872; 25.9% {24.4–27.4}
					3344; 34.1% {33.2–35.1}	1047; 32.8% {31.2–34.5}
					1734; 17.4% (✞ 12.9; ✝ 20.2)	758; 23.3% (✞ 12.2; ✝ 19.7)
SEPSI		4415; 50.1% (✞ 16.5; ✝ 26.2)	564; 48.0% (✞ 25.0; ✝ 31.9)	1219; 58.5% (✞ 22.0; ✝ 28.7)	4979; 49.9% (✞ 17.5; ✝ 26.9)	1783; 54.7% (✞ 23.0; ✝ 29.8)
SHOCK SETTICO		2783; 31.6% (✞ 45.4; ✝ 53.2)	486; 41.4% (✞ 43.8; ✝ 52.0)	232; 11.1% (✞ 59.1; ✝ 67.3)	3269; 32.7% (✞ 45.2; ✝ 53.0)	718; 22.0% (✞ 48.7; ✝ 56.9)

Dati GIViTI 2018

ESITI

	Mortalità T.I.	Mortalità H	Degenza T.I. (media)	Degenza H (media)
Totale pazienti	18%	24,4%	6,1 gg	19,3 gg
Pazienti non infetti	14,4%	20,1%	3,3 gg	16 gg
Pazienti infetti (totale)	25,1%	32,88 %		
Pazienti infetti polmoniti	28,9%	36,2%	11,4 gg	23,7 gg
Pazienti infetti peritoniti	28,9%	40,7%	8 gg	26,1 gg

Dati GIViTI 2018

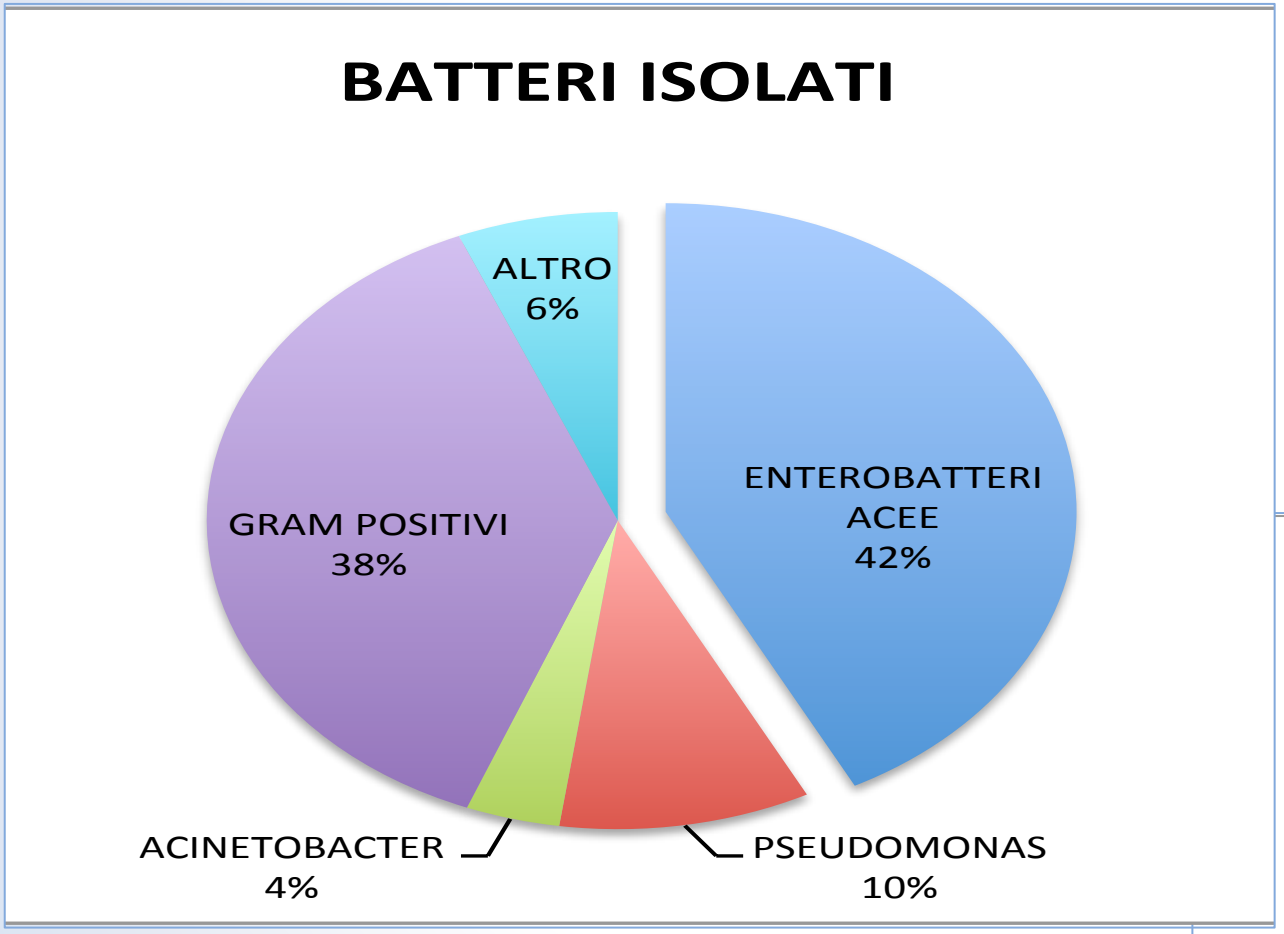
PAZIENTI INFETTI ALL'AMMISSIONE

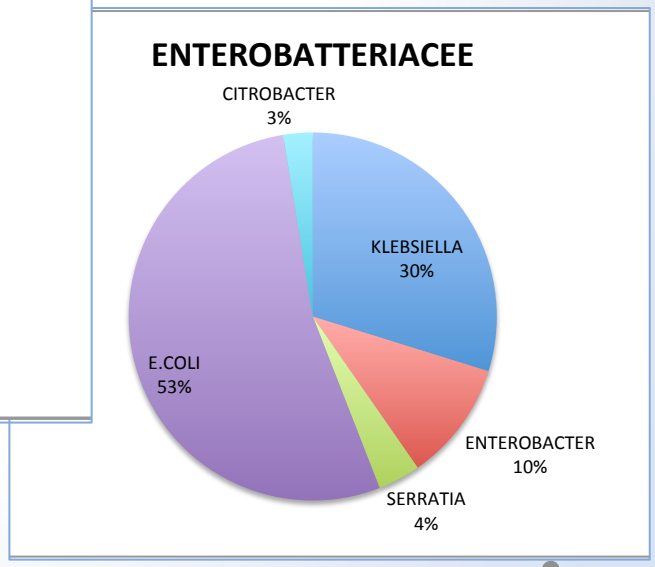
Infezioni all'ammissione (top 10)	N	%
Polmonite	4010	38.5
Peritonite secondaria NON chir.	1108	10.6
Infezione vie urinarie NON post-chir.	923	8.9
Inf. basse vie respiratorie NON polmonite	693	6.7
Peritonite post-chirurgica	686	6.6
Colecistite/colangite	501	4.8
Batteriemia primaria sconosciuta	478	4.6
Infezione cute/tessuti molli NON chir.	440	4.2
Sepsi clinica	402	3.9
Infezione del S.N.C. NON post-chirurgica	297	2.9
Missing	0	

Dati GIViTI 2018

MICRORGANISMI ISOLATI

PAZIENTI INFETTI ALL'AMMISSIONE

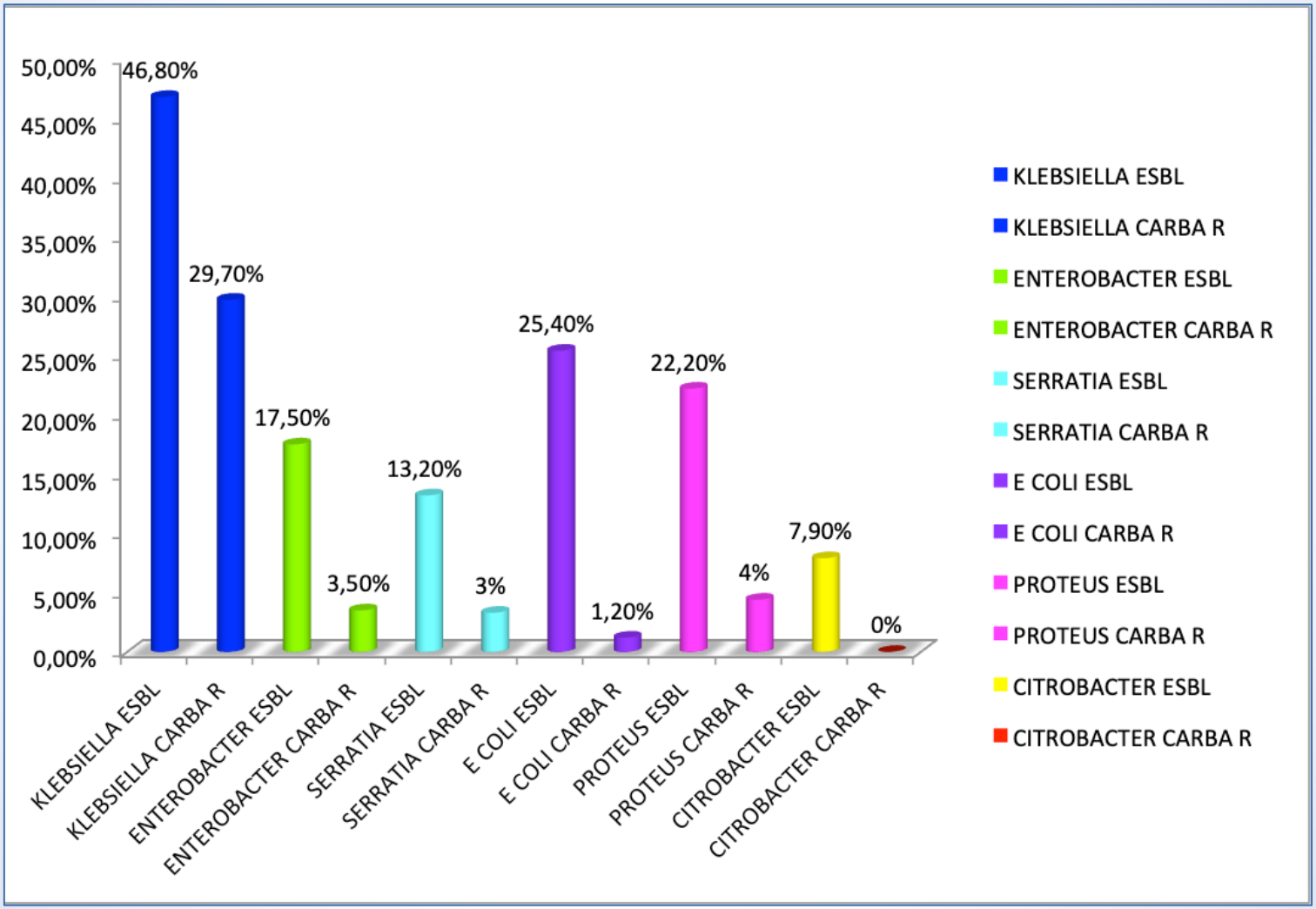




Dati GIViTI 2018

ENTEROBATTERIACEE MDR

INFEZIONI ALL'AMMISSIONE



Dati GIViTI 2018

Pazienti infetti in degenza (N): 3382

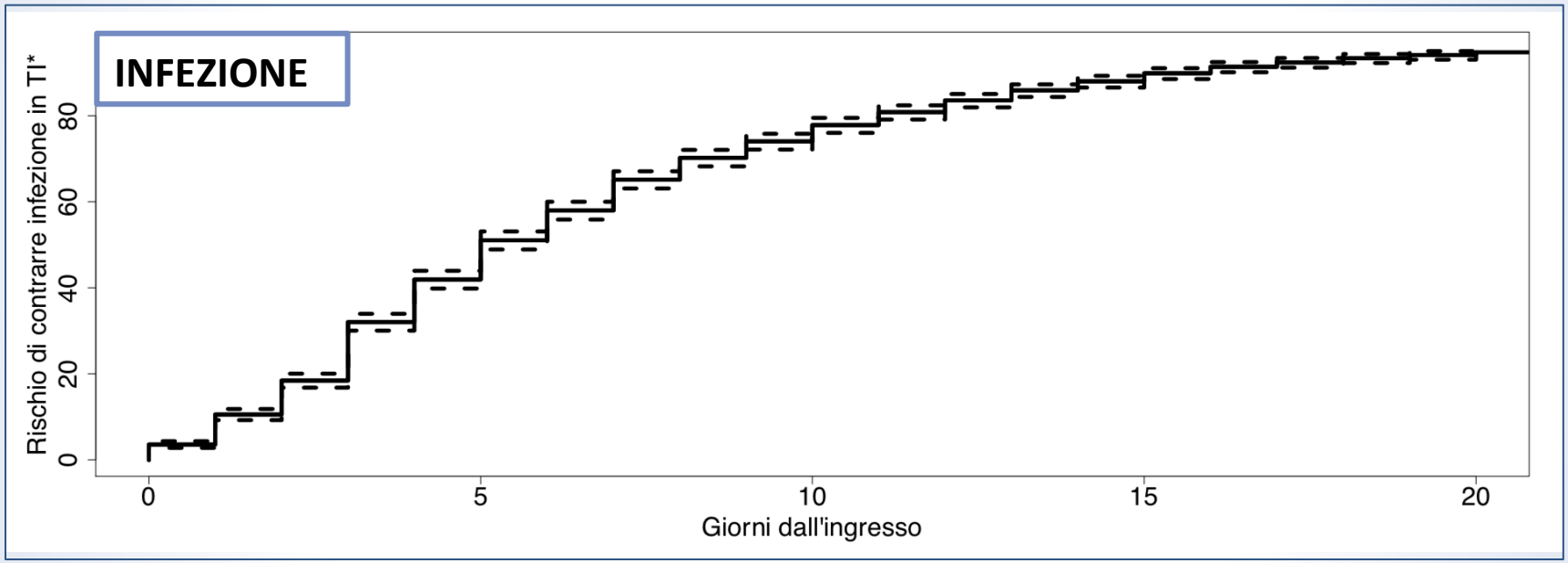
Infezioni in degenza (top 10)	N	%
Polmonite	1235	36.5
Inf. basse vie respiratorie NON polmonite	795	23.5
Infezione vie urinarie NON post-chir.	493	14.6
Batteriemia da catetere (CR-BSI)	444	13.1
Batteriemia primaria sconosciuta	379	11.2
Peritonite post-chirurgica	130	3.8
Infezione cute/tessuti molli post-chir.	123	3.6
Infezione delle alte vie respiratorie	117	3.5
Sepsi clinica	100	3.0
Infezione cute/tessuti molli NON chir.	85	2.5
Missing	0	

Giorni per contrarre infezione	
Media	8.3
DS	8.8
Mediana	6
Q1–Q3	3–11
Missing	0
Incidenza di infezioni in degenza (1) *(Paz. infetti in degenza/1000 gg. pre-infezione)*	
Stima	17.9
CI (95%)	17.3–18.5
Incidenza di infezioni in degenza (2) *(Paz. infetti in degenza/paz. ricoverati per 7 gg.)*	
Stima	12.5%
CI (95%)	12.1–13.0

Mortalità in TI	N	%
Vivi	2499	74.1
Deceduti	872	25.9
Missing	11	
Mortalità ospedaliera *	N	%
Vivi	2141	67.2
Deceduti	1047	32.8
Missing	46	
Degenza in TI (giorni)		
Media	23.4	
DS	18.8	
Mediana	19	
Q1–Q3	11–31	
Missing	11	
Degenza ospedaliera (giorni) *		
Media	37.5	
DS	28.6	
Mediana	31	
Q1–Q3	18–49	
Missing	45	

Dati GIViTI 2018

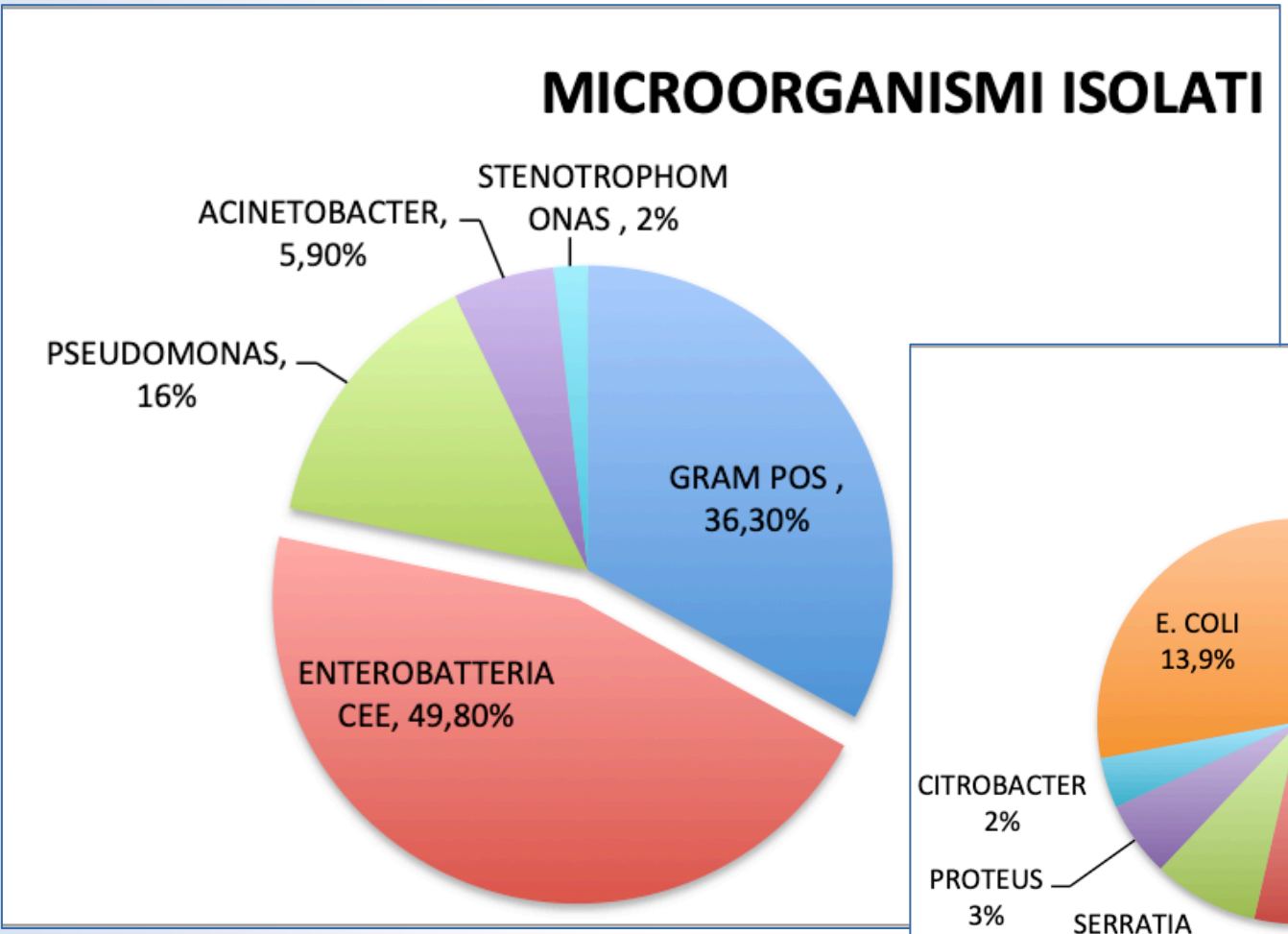
RISCHIO INFETTIVO

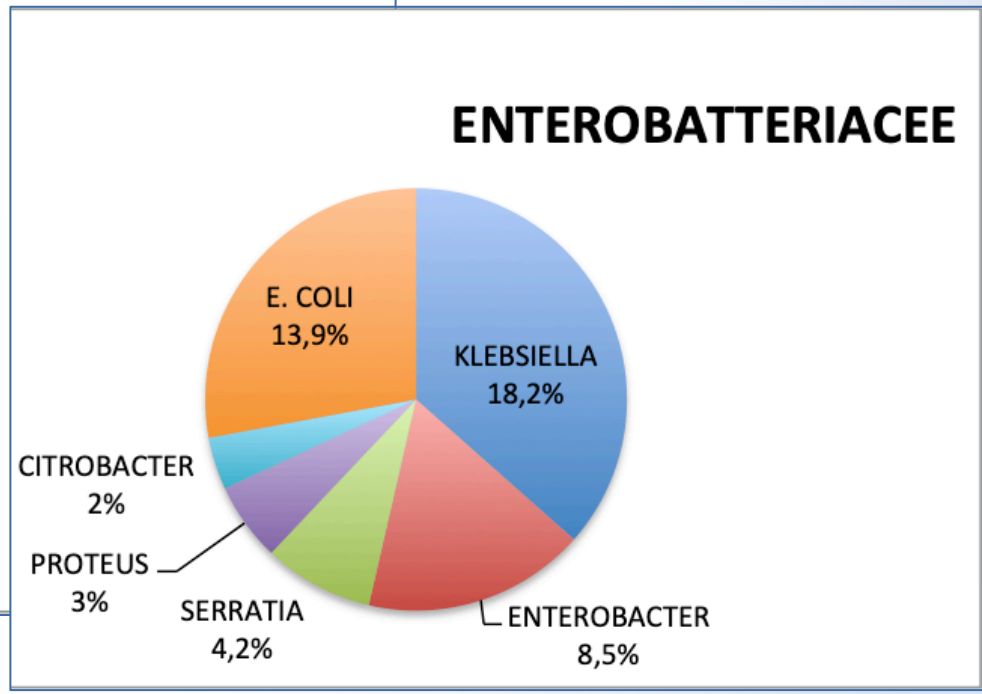


Dati GIViTI 2018

MICRORGANISMI ISOLATI

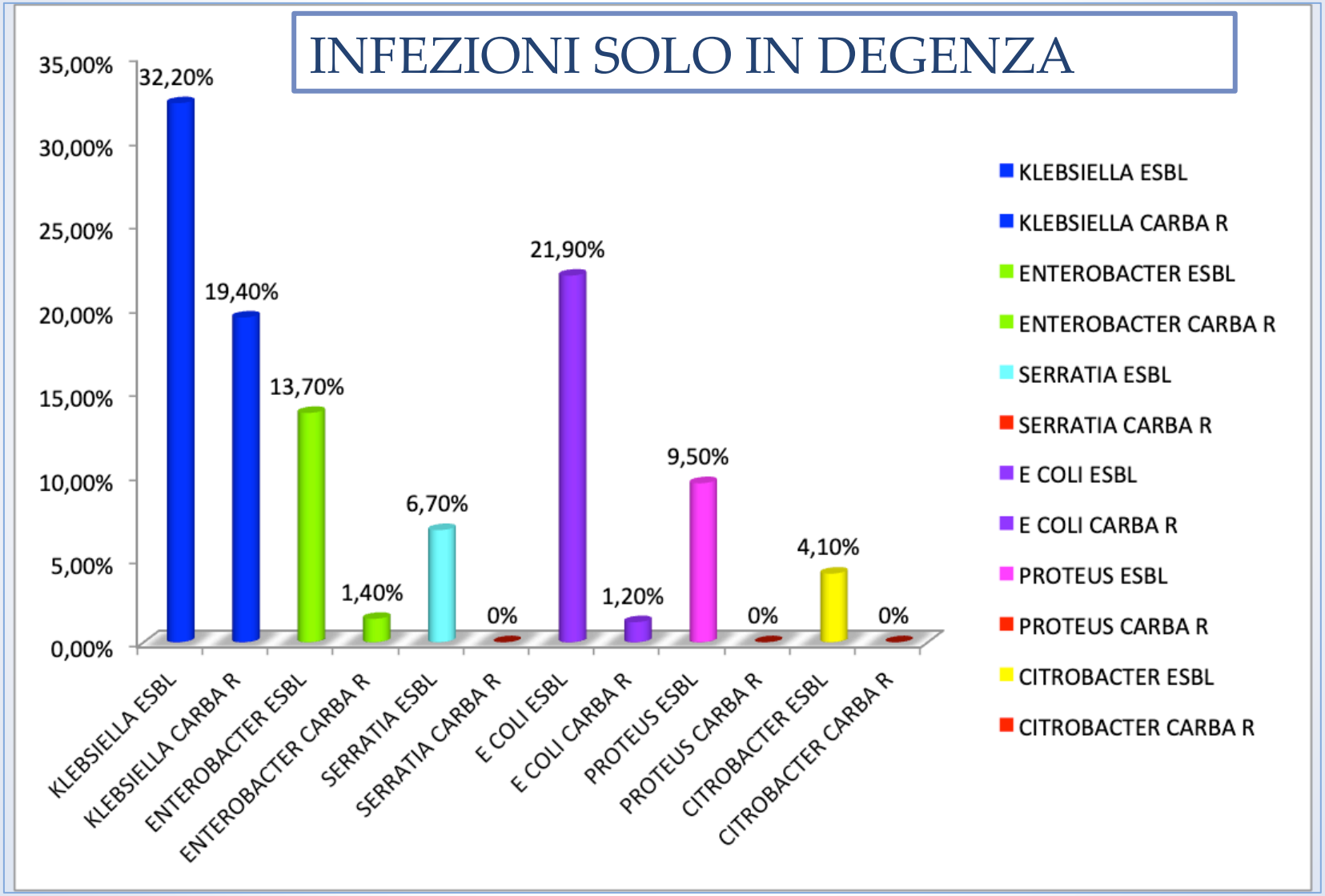
PAZIENTI INFETTI SOLO IN DEGENZA





Dati GIViTI 2018

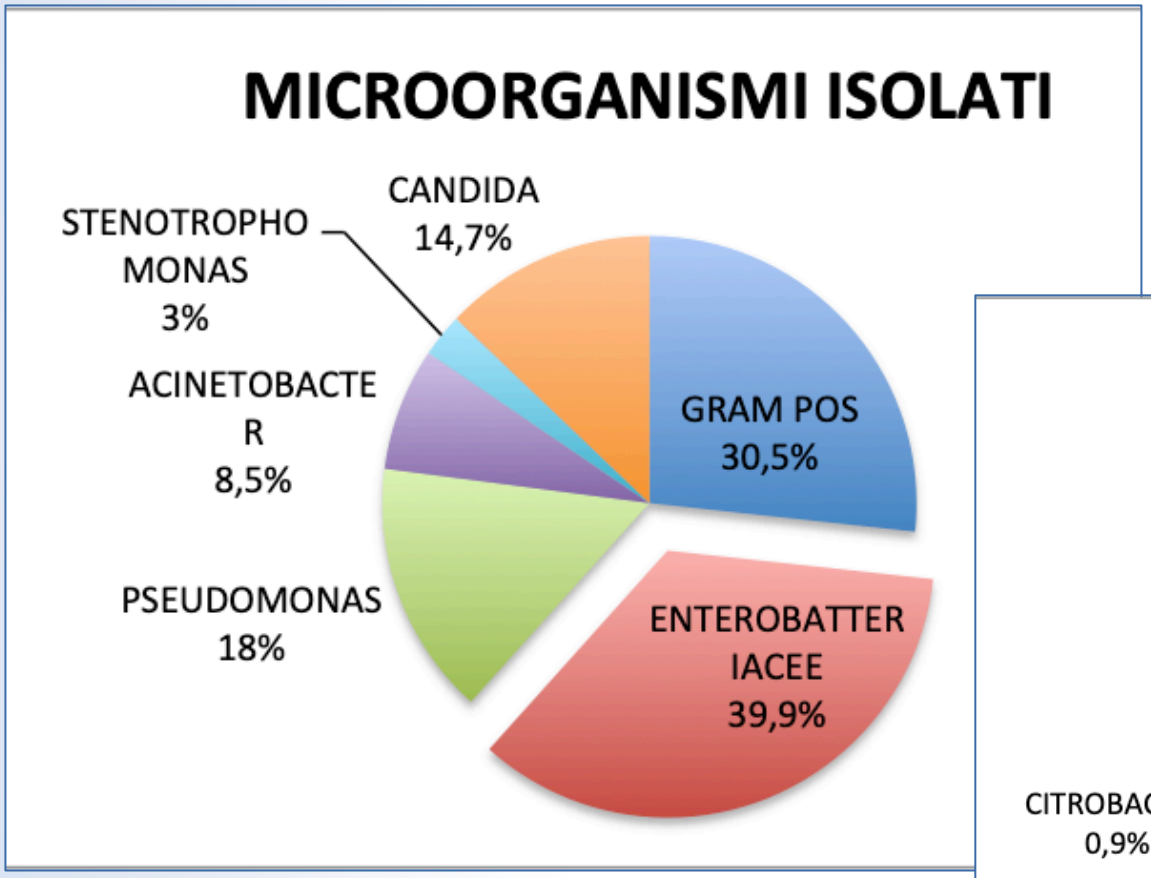
ENTEROBATTERIACEE MDR

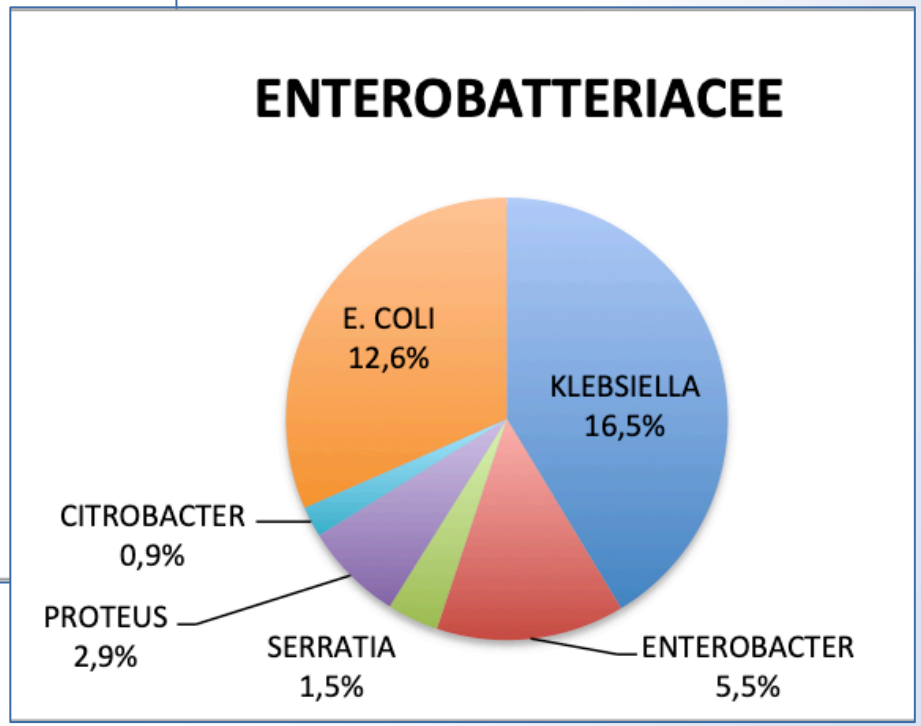


Dati GIViTI 2018

MICRORGANISMI ISOLATI

PAZIENTI INFETTI SIA IN AMMISSIONE CHE IN DEGENZA

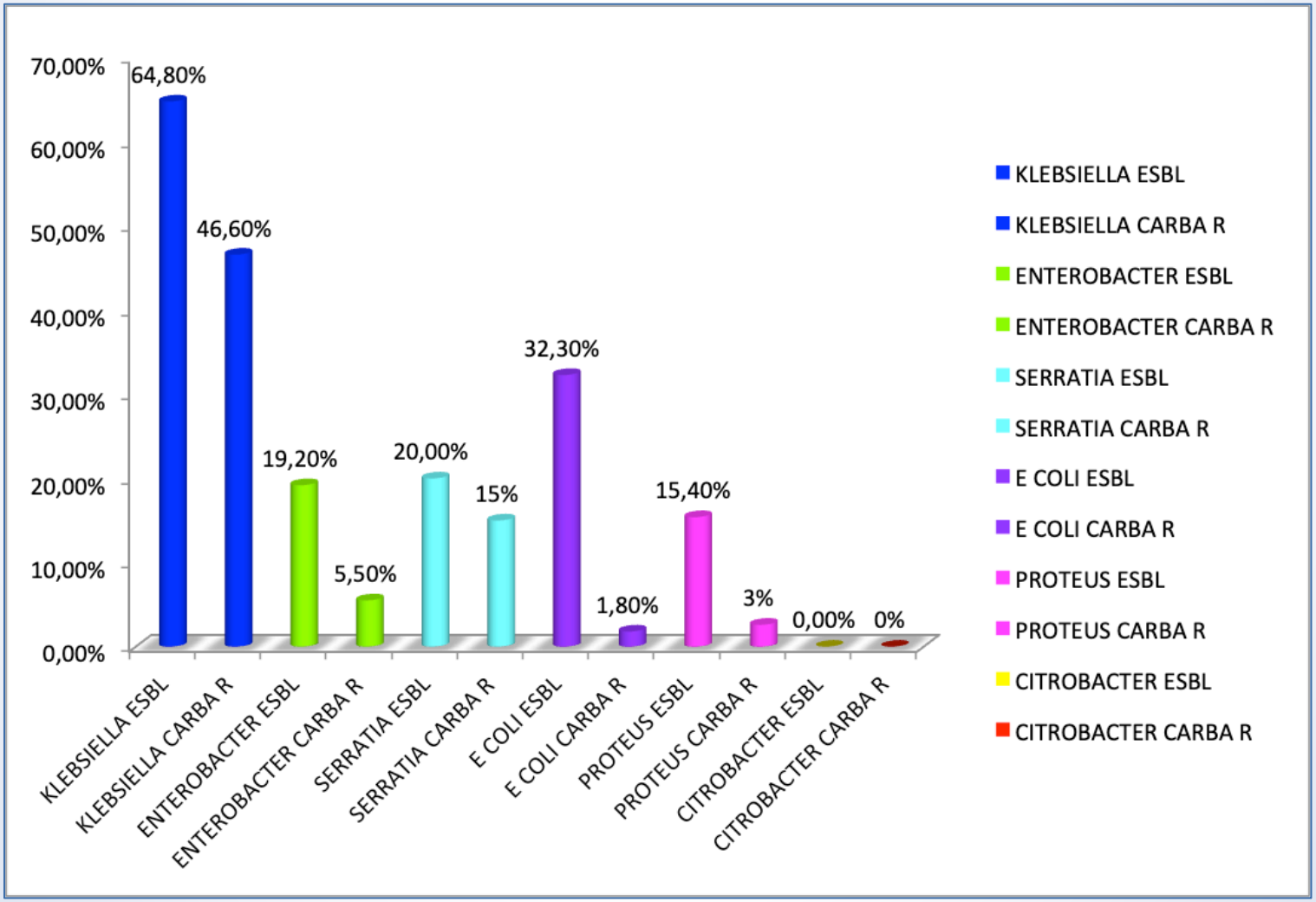




Dati GIViTI 2018

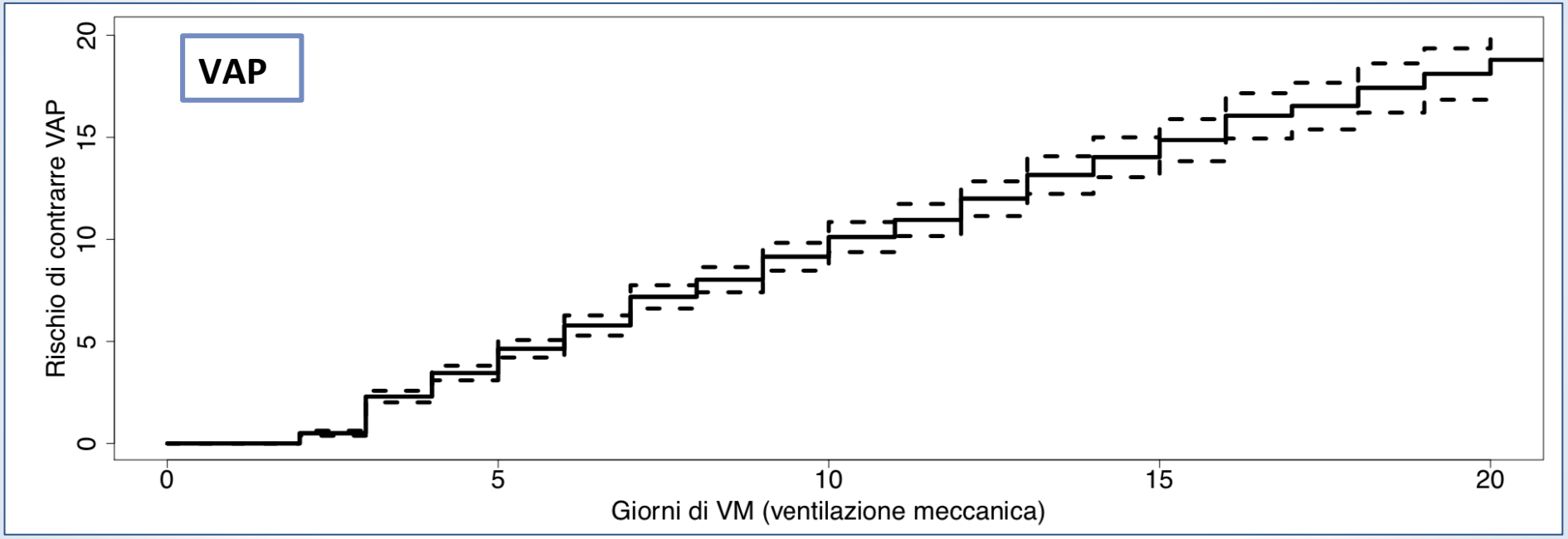
ENTEROBATTERIACEE MDR

INFEZIONI SIA IN AMMISSIONE CHE IN DEGENZA



Dati GIViTI 2018

RISCHIO VAP



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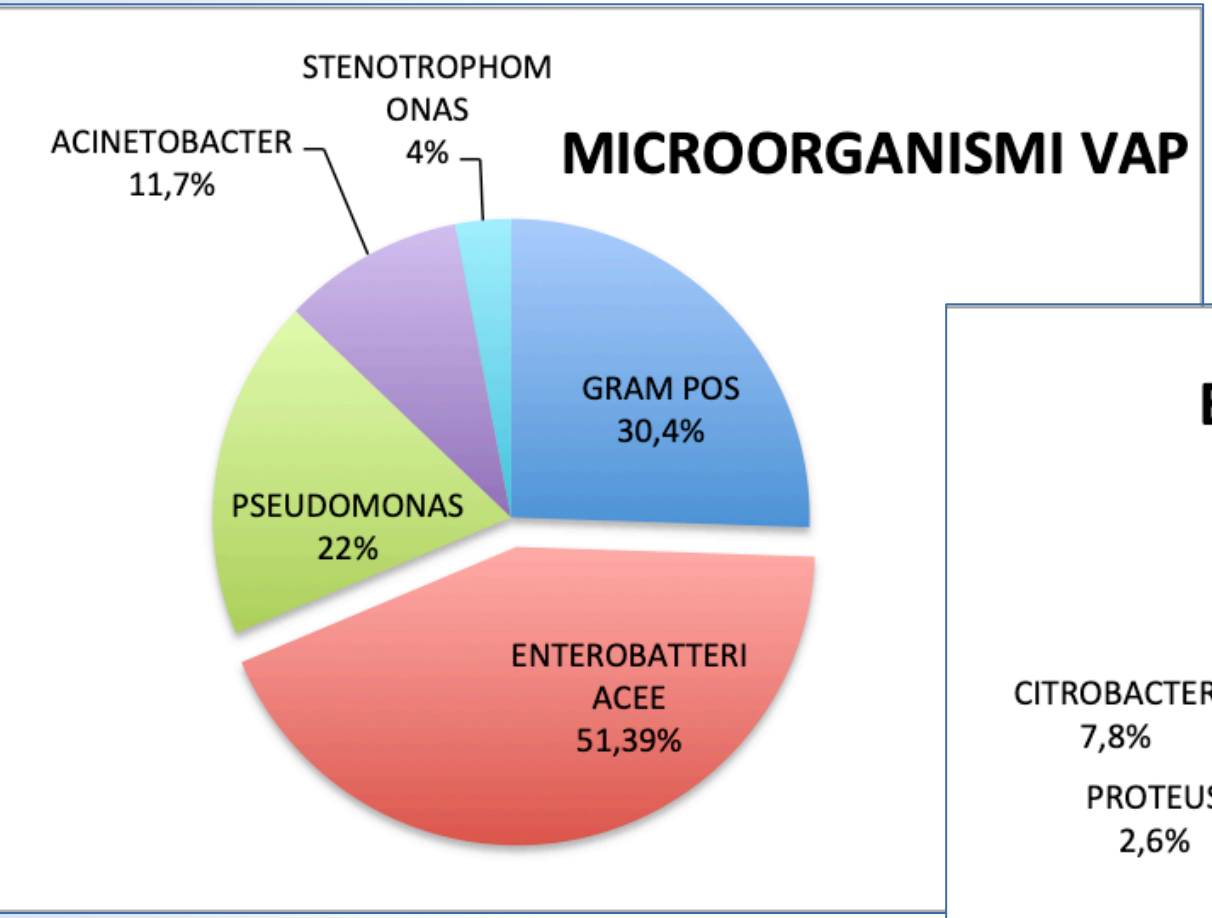

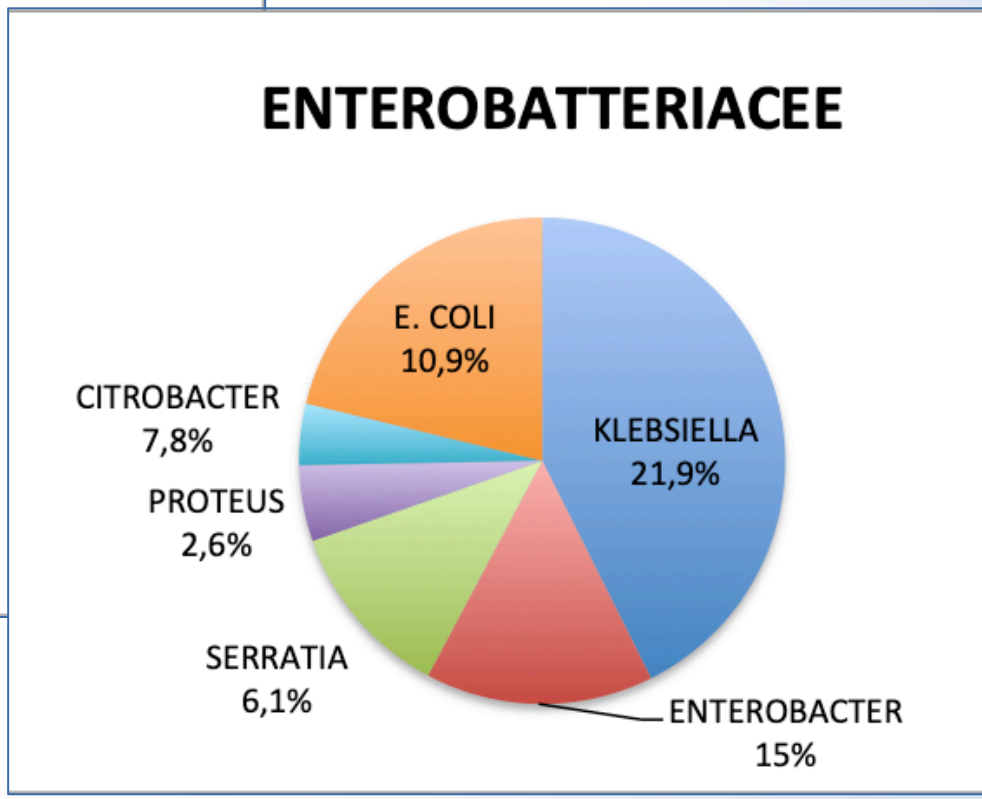

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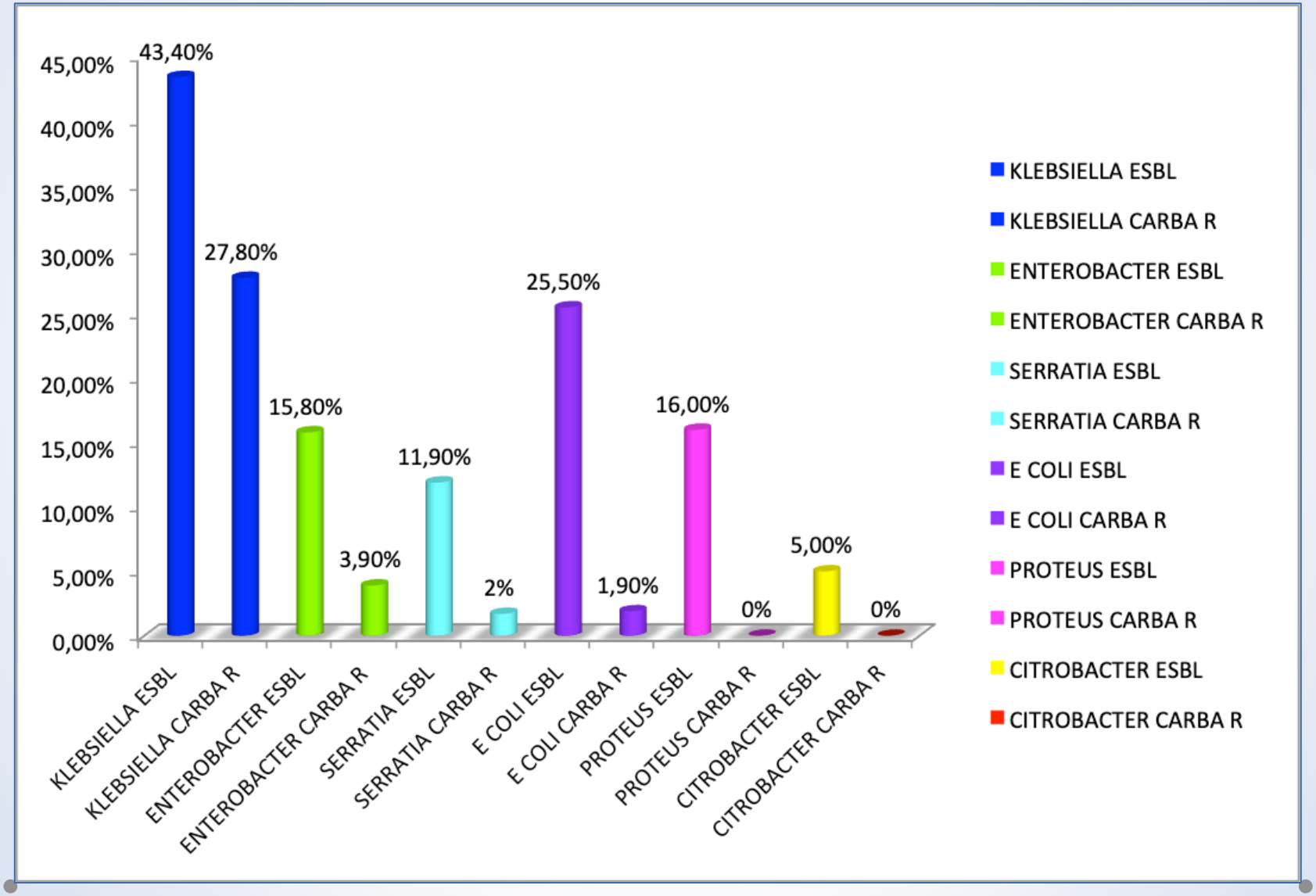
ENTEROBATTERIACEE MDR VAP



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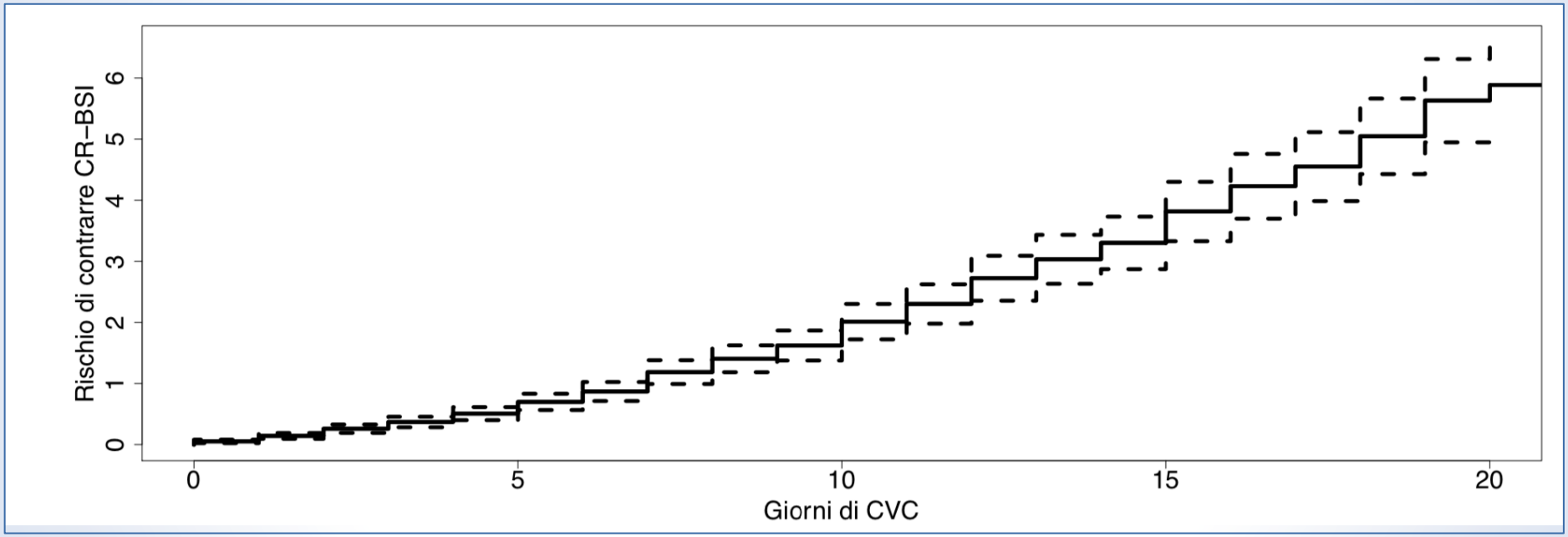
RISCHIO CR-BSI



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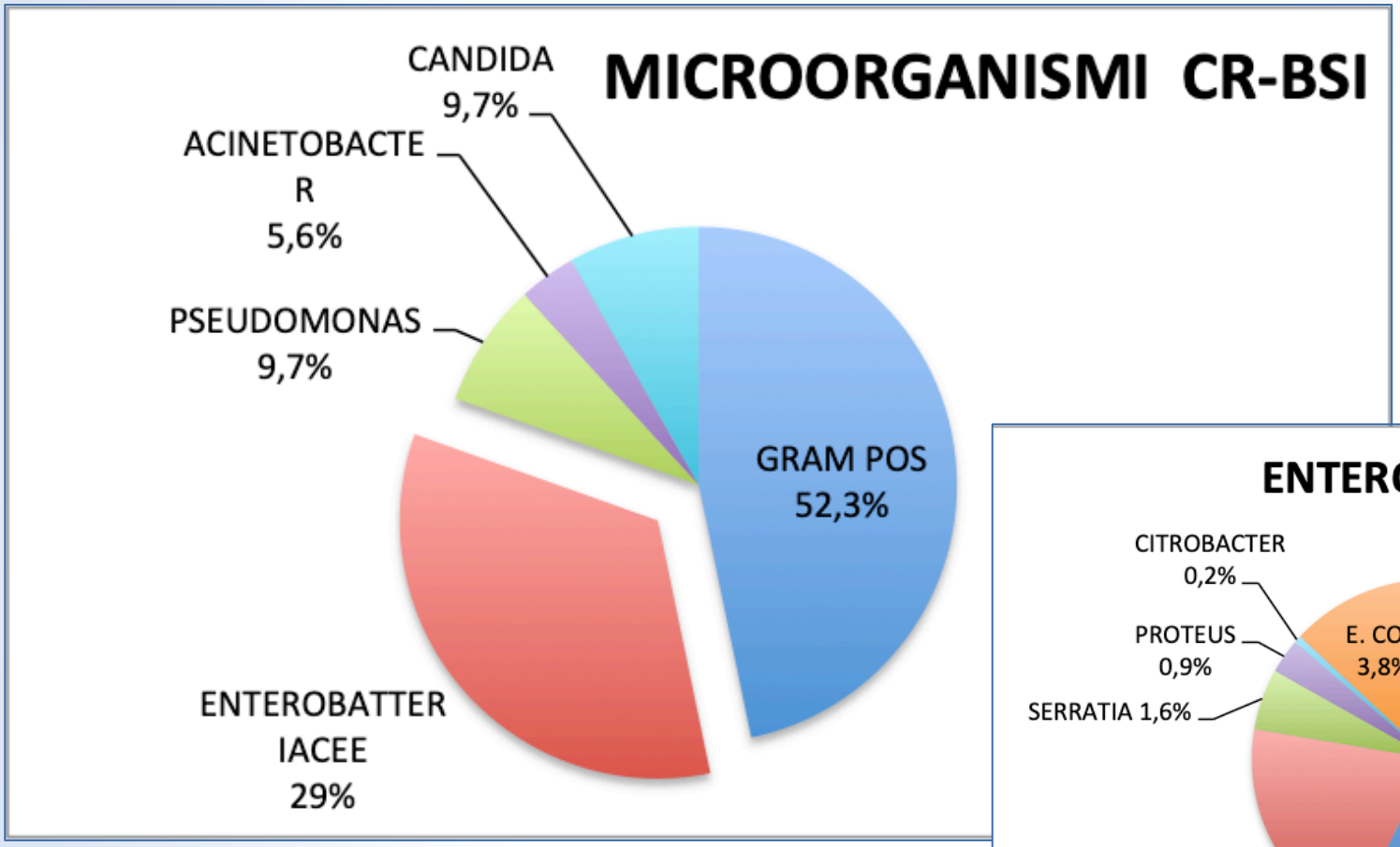
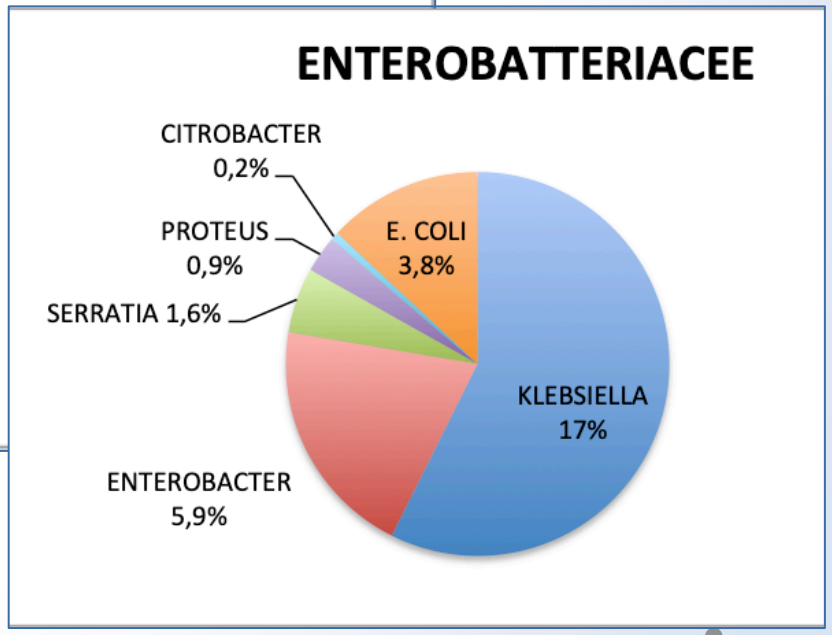
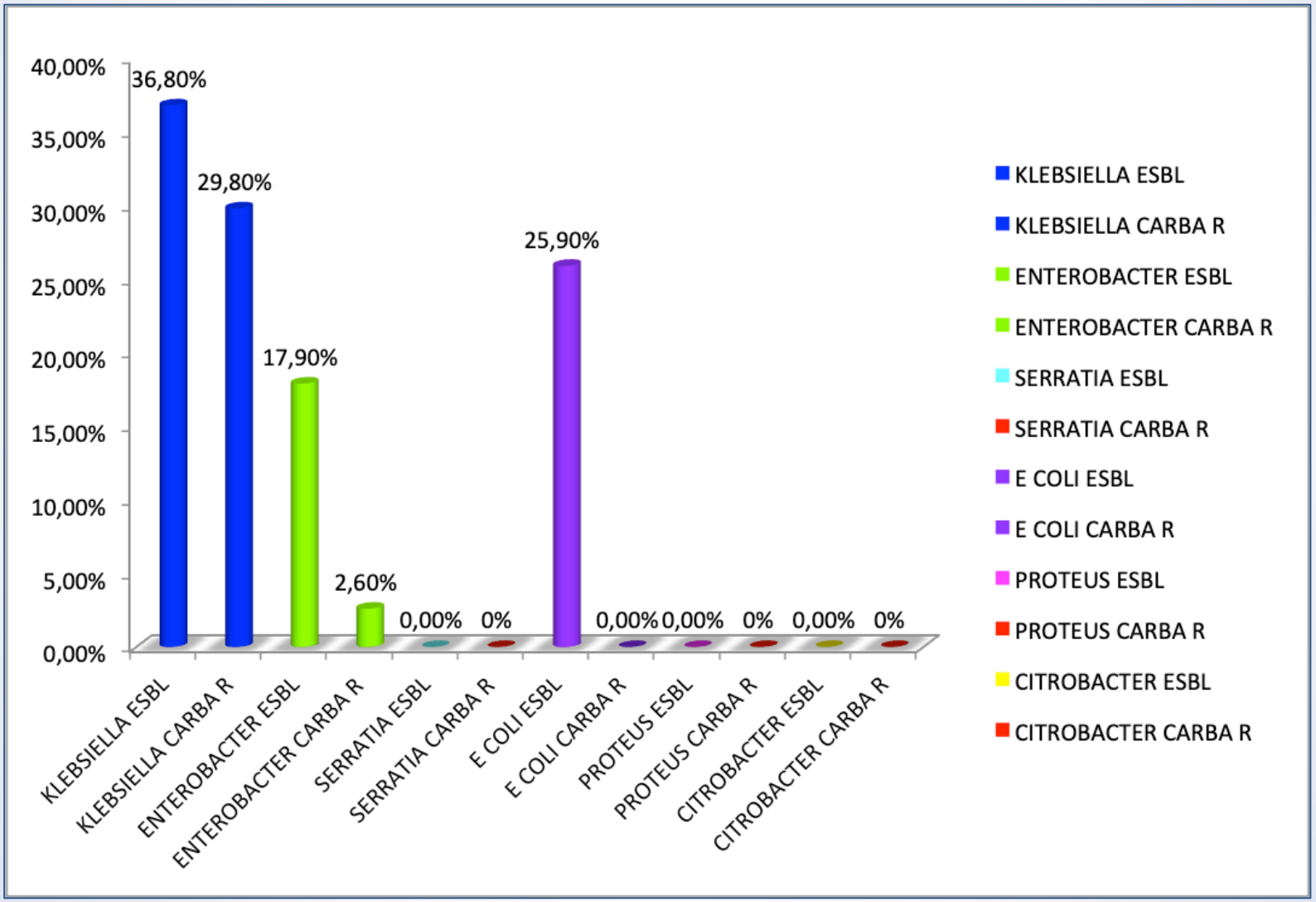
MICRORGANISMI CR-BSI





Dati GIViTI 2018

ENTEROBATTERIACEE MDR BATTERIEMIE



Dati GIViTI 2018

ANTIBIOTICO RESISTENZA

- ✓ **ENTEROBATTERIACEE**
- ✓ PSEUDOMONAS AERUGINOSA
- ✓ ACINETOBACTER BAUMANII

✓ MECCANISMI DI RESISTENZA:

- PRODUZIONE DI ENZIMI CHE IDROLIZZANO L'ANELLO β-LATTAMICO
- RIDUZIONE DELLA PERMEABILITA' DELLA PARETE BATTERICA
- PRESENZA DI POMPE DI EFFLUSSO
- MODIFICAZIONI DELLE PBP

Drawz and Bonomo 2010; Papp-Wallace et al. 2011

β-LATTAMASI

TABLE 1. β-Lactamase classification schemes[a]

Ambler class	Bush-Jacoby-Medeiros class	Preferred substrates	Inhibited by clavulanate	Representative enzyme(s)
A (serine penicillinases)	2a	Penicillins	+	PC1 from *S. aureus*
	2b	Penicillins, narrow-spectrum cephalosporins	+	TEM-1, TEM-2, SHV-1
	2be	Penicillins, narrow-spectrum and extended-spectrum cephalosporins	+	SHV-2 to SHV-6, TEM-3 to TEM-26, CTX-Ms
	2br	Penicillins	−	TEM-30, SHV-72
	2c	Penicillins, carbenicillin	+	PSE-1
	2e	Extended-spectrum cephalosporins	+	FEC-1, CepA
	2f	Penicillins, cephalosporins, carbapenems	±	KPC-2, SME-1, NMC-A
B (metallo-β-lactamases)	3	Most β-lactams, including carbapenems	−	IMP-1, VIM-1, CcrA, and BcII (B1); CphA (B2); L1(B3)
C (cephalosporinases)	1	Cephalosporins	−	AmpC, CMY-2, ACT-1
D (oxacillinases)	2d	Penicillins, cloxacillin	±	OXA-1, OXA-10
Not classified	4			

clinical microbiology reviews, Jan. 2010, p. 160–201

β-LATTAMASI

Table 3. Classification of most frequent extended-spectrum b-lactamases and carpapenemase

Molecular class	Enzymes	Substrates of hydrolysis
A	ESBL (TEM, SHV, CTX-M, others)	Penicillins, cephalosporins (except cefamycins), aztreonam
A	KPC	Penicillins, cephalosporins, aztreonam, carbapenems
B	MBLs (VIM, IMP, NDM, others)	Penicillins, cephalosporins, and carbapenems. Monobactams are susceptible
D	OXA (OXA-48, OXA-23, others)	Penicillin, aztreonam, and carbapenems

ESBL, extended-spectrum b-lactamases; IMP, imipenemase metallo-beta-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-betalactamase; OXA-48, oxacillinase-48; OXA-23, oxacillinase-23; VIM, Verona integron-encoded metallo-beta-lactamase.

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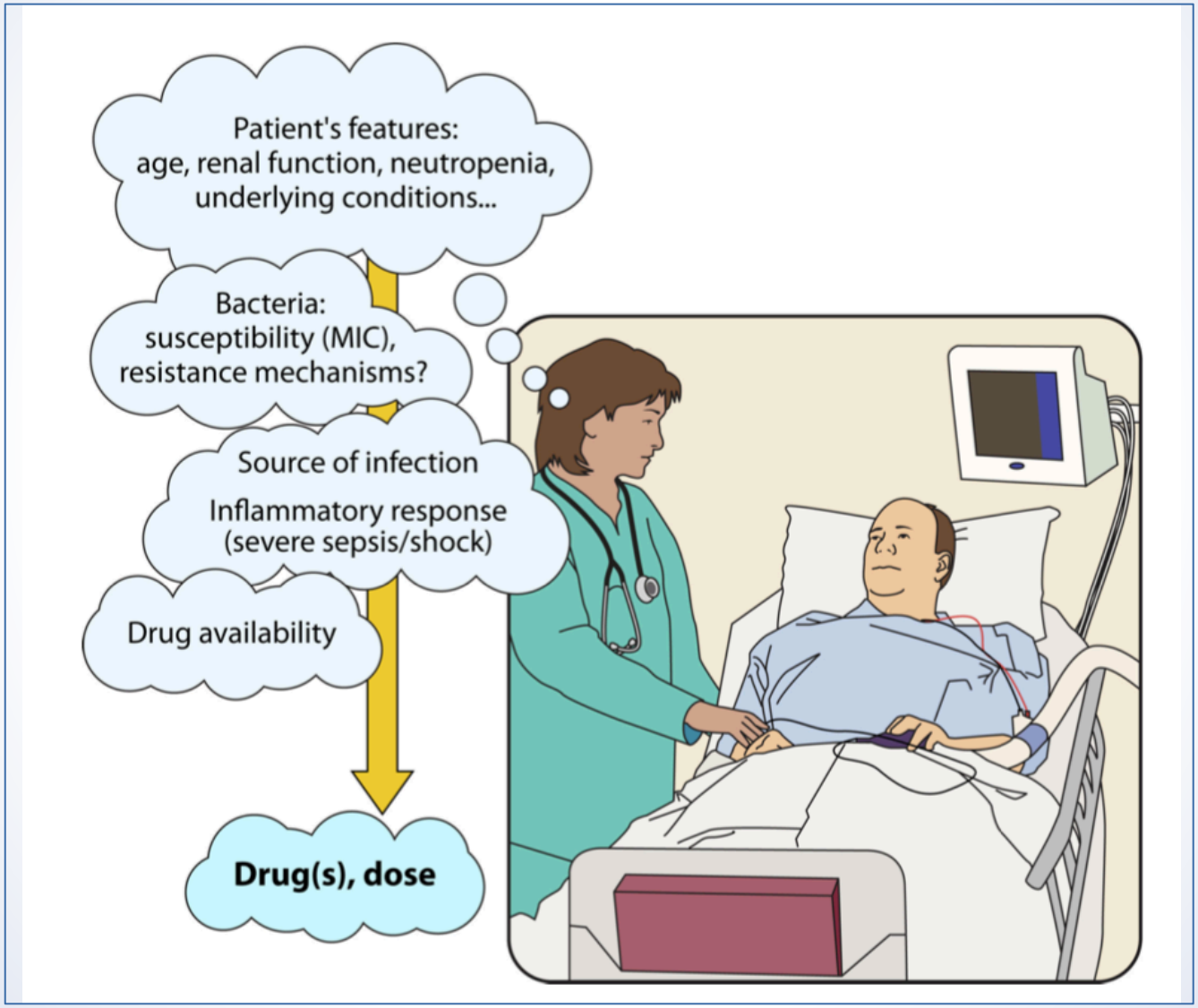
BLI

	TAZOBACTAM	AVIBACTAM	RELEBACTAM	VABORBACTAM
CLASSE A ESBL	+	+	+	+
CLASSE A KPC	-	+	+	+
CLASSE B	-	-	-	-
CLASSE C	+	+	+	+
CLASSE D		+		

TERAPIA



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TERAPIA ESBL

TABLE 1 Summary of positive and negative aspects and dosing of potentially useful drugs in the treatment of infections with ESBL- and AmpC-producing *Enterobacteriaceae*[b]

Drug	Positive aspects	Negative aspects	Dosing (for adults with normal renal function) and comments
Meropenem, imipenem, doripenem	Reference drugs, usually active	Ecological impact; less experience with doripenem	Standard dosing is recommended
Ertapenem	Not active against *P. aeruginosa*[a]; usually active; convenient for outpatient therapy and deescalation from other carbapenems	Ecological impact if CPE endemicity/outbreak; doubts in cases of septic shock (insufficient dosing?); anecdotal failures described with development of resistance (porin loss)	1 g/day in most situations; for septic shock or high-inoculum infections with borderline MIC isolates, use other alternatives or increase dose to 2 g/day
Piperacillin-tazobactam	Probably noninferior to carbapenems in UTI and biliary tract infections	False susceptibility with some automated systems; inoculum effect (unrelated to ESBLs); heterogeneous resistance rates (5 to 30% among ESBL producers, higher among AmpC producers); doubts in cases of septic shock, pneumonia (CLSI susceptibility breakpoint too high)?	4.5 g every 8 h (extended infusion) or every 6 h
Amoxicillin-clavulanic acid	No inoculum effect; probably noninferior to carbapenems in UTI and biliary tract infections; not active against *P. aeruginosa*[a]; convenient for oral switch	Not available for i.v. use in many countries; heterogeneous resistance rates, usually >40% among ESBL producers; AmpC producers are resistant	Intravenous, 2.2 g/8 h; oral, at least 1.250 g/8 h for UTI
Ceftolozane-tazobactam	Areas with large proportions of susceptible isolates	Reserve drug for MDR *P. aeruginosa* infection; scarce experience so far; 10–30% resistance rates among ESBL producers, lower rates in AmpC producers	1.5 g/8h; approved for cUTI and cIAI (with metronidazole); consider 3 g/8 h for pneumonia
Ceftazidime-avibactam	Large proportion of susceptible isolates	Reserve drug for KPC- or OXA-48-producing *Enterobacteriaceae*	2.5 g/8 h; approved for cUTI and cIAI (with metronidazole); in Europe, also approved for HAP in case of limited options
Cefotaxime, ceftriaxone, ceftazidime, cefepime	Some ESBL-E may be susceptible; cefepime is usually active against AmpC producers	Most isolates are resistant (except to cefepime in the case of AmpC producers); inoculum effect; ecological impact; clinical data are scarce and contradictory	If used, high doses are recommended (cefotaxime, 1 g/6 h to 2 g/8 h; ceftazidime or cefepime, 2 g/8 h)
Cefoxitin, cefotetan, cefmetazole, moxalactam, flomoxef	Not active against *P. aeruginosa*[a]; areas with large proportions of susceptible isolates (ESBL producers); probably useful against UTI for stable patients	AmpC producers are resistant; inoculum effect; observational studies with contradictory results; anecdotally described development of resistance during therapy	High doses; close follow-up needed
Temocillin	Active against ESBL and AmpC producers; not active against *P. aeruginosa*[a]	Not available in many countries; comparative studies are lacking	Probably 2 g every 8 h
Gentamicin, tobramycin, amikacin	Active against many ESBL and AmpC producers; useful for UTI	Nephrotoxicity; less efficacious in non-UTI infections; heterogeneous resistance rates	Standard dosing (see Table 2); may be considered empirically as carbapenem-sparing agents (in monotherapy or in combination with a lower-spectrum β-lactam) until microbiological data are available
Tigecycline	Active against most ESBL and AmpC producers; not active against *P. aeruginosa*[a]	FDA and EMA warnings for use only if other options are unavailable/unsuitable; probably not a good option for UTI or HAP	100-mg loading dose, 50 mg/12 h; may be an alternative in cIAI
Fosfomycin (i.v.)	Noninferior to piperacillin-tazobactam in cUTI (pending publication of data)	Not available in many countries; scant experience; risk of emergence of resistant subpopulations with monotherapy	4 g/6 h to 6–8 g/8 h
Ciprofloxacin, levofloxacin	Potentially useful for fully susceptible isolates; convenient for oral switch	Ecological impact; most isolates are resistant; failures for isolates with MICs of 0.5–1 mg/liter have been described	For i.v. ciprofloxacin, 400 mg/8–12 h; for oral ciprofloxacin, 500–700 mg/12 h; for levofloxacin (i.v., oral), 750 mg/24 h
Trimethoprim-sulfamethoxazole	Convenient for oral switch	Most isolates are resistant; scant published experience	i.v. or oral, 160/800 mg/8–12 h

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TERAPIA CRE

Drug	Usual/standard dose(s)	Dosing for CRE and comments
Meropenem	1 g/8 h	2 g/8 h by EI (isolates with MICs of 2–8 mg/liter; for isolates with higher MICs, it is probably not efficacious)
Ertapenem	1 g/24 h	Consider 2 g/day for double-carbapenem regimens
Colistin[b]	From the EMA, loading dose, 6–9 MU, and then 9 MU/day in 2–3 doses; from the FDA, 2.5–5 mg of colistin base activity/kg/day	EMA dose is recommended for severe CRE infections; the need for a loading dose and high continuation dose in patients without severe infection/shock is controversial
Polymyxin B[c]	From the FDA, 1.5–2.5 mg/kg/day in 2 doses	For mild infections and isolates with MICs of ≤1 mg/liter, the FDA dose is probably appropriate; for severe infections and isolates with MICs of up to 4 mg/liter, a loading dose of 2–2.5 mg/kg followed by 3 mg/kg/day in 2 doses is recommended (controversially)
Tigecycline	100-mg loading dose and then 50 mg/12 h	For HAP, cUTI, BSI, or shock, consider a 200-mg loading dose and then 100 mg/12 h
Gentamicin, tobramycin	5–7 mg/kg/day	For HAP or shock without other options, higher doses (10–15 mg/kg) might be considered, but the risk of toxicity is high; TDM is recommended
Amikacin	15–20 mg/kg/day	For HAP or shock without other options, higher doses (25–30 mg/kg) might be considered, but the risk of toxicity is high; TDM is recommended
Fosfomycin	4 g/6 h to 8 g/8 h	Use in combination; high sodium concn
Temocillin	2 g/8–12 h	KPC producers are occasionally susceptible; continuous infusion improves PK-PD target attainment
Aztreonam	1–2 g/8 h	MBL producers are susceptible if they are not ESBL or AmpC producers
Ceftazidime	1–2 g/8 h	OXA-48 producers are susceptible if they are not ESBL or AmpC producers
Ceftazidime-avibactam	2.5 g/8 h	KPC and OXA-48 producers are frequently susceptible
Meropenem-vaborbactam	2/2 g/8 h	KPC producers are frequently susceptible

[a]Please refer to the text for explanations and references. EI, extended infusion; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; HAP, hospital-acquired pneumonia; cUTI, complicated urinary tract infection; BSI, bloodstream infection; MU, million units; TDM, therapeutic drug monitoring; MBL, metallo-β-lactamase.

[b]One million units of colistimethate sodium = 80 mg colistimethate sodium = 34 mg of colistin base activity.

[c]One million units of polymyxin B = 100 mg of colistin base activity.

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TERAPIA KPC

Antimicrobial agents against KPC-KP

Drug	Loading dose	Daily dose for normal renal function	Comments
Polymyxins [30–41]			
Colistin[a]	9 million IU	4.5 million IU IV every 12 hours Intrathecal/intraventricular: 125 000–250 000 IU Inhaled: 1 to 3 million IU every 8 hours	For infections caused by organisms with MIC >0.5 mg/L, it is advisable to use colistin as part of combination therapy. For dosage adjustment in patients with renal failure, see Nation et al. [41].
Polymyxin B[b]	Not required	7500–12 500 IU/kg every 12 hours every 12 hours Intrathecal/intraventricular: 50 000 IU every 24 hours	No dose adjustment for renal failure.
Aminoglycosides [42–44] (https://www.uptodate.com/contents/manifestations-of-and-risk-factors-for-aminoglycoside-nephrotoxicity)			Aminoglycosides can be useful as part of combination regimens for treating KPC-KP infections, especially if colistin resistance is documented. Pulse dosing is preferable to multiple daily doses; desired peak serum levels are about 10 times the MIC of the organism. Adjust doses according to Hartford nomogram [43].
Gentamicin	Not required when administered in pulse dosing schemes	5 to 7 mg/kg infused over 1 hour	—
Amikacin	Not required when administered in pulse dosing schemes	15 to 20 mg/kg infused over 1 hour	
Tigecycline	100–200 mg	50–100 mg every 12 hours IV	For BSIs or pneumonia or when tigecycline MIC >0.5 mg/L, higher doses are recommended (loading dose, 200 mg followed by 100 mg every 12 hours), preferably in combination with another agent. Not to be used in urinary tract infections; no concentrations in urine.
Fosfomycin	Not required	18 to 24 g IV in 3 to 4 doses	Fosfomycin could be used in combination treatment for KPC-KP infections administered as 6 to 8 g every 8 hours. Resistance can occur during treatment and should be monitored. Potential of fosfomycin to select resistant mutants precludes use as single agent.
Ceftazidime/avibactam	Not required	2.5 g every 8 hours IV infused over 2 hours	Approved for Hospital and Ventilator acquired pneumonia, complicated intra-abdominal and urinary tract infections and for the treatment of infections due to aerobic Gram-negative organisms in adult patients when other treatments might not work.; active in vitro against Enterobacteriaceae-producing ESBLs, AmpC, KPC, OXA-48. Clinical experience for carbapenem-resistant Enterobacteriaceae is currently limited to case series [55–58]. Despite concerns of resistance selection raised by a few reports that might support the used of ceftazidime/avibactam in combination with other agents for treating KPC-KP infections, whether it should be ultimately used alone or combined remain unclear, and requires further dedicated investigation.
Meropenem	1–2 g	2 g every 8 hours IV infused over 3–6 hours	Meropenem should be used in combination with another active agent; the probability of response is higher when meropenem MIC ≤8 mg/L. Salvage therapy with association of 2 carbapenems, e.g. ertapenem plus either meropenem or doripenem, can be considered when other options are not suitable or available.

BSI, bloodstream infection; ESBL, extended-spectrum β-lactamase; KPC-KP, *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*; MIC, minimum inhibitory concentration.

[a] One milligram of colistin base activity is contained in 2.4 mg colistimethate, which is equivalent to 30 000 IU.

[b] One milligram of polymyxin B is equivalent to 10 000 IU.

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NUOVE MOLECOLE

ANTIBIOTICO	CLASSE	ATTIVITA'	NO ATTIVITA'
CEFTAZIDIME/ AVIBACTAM	BL/BLI	KPC,ESBLs, OXA, AmpC	CLASSE B
CEFTAROLINE/ AVIBACTAM	BL/BLI	KPC, ESBLs, AmpC, OXA	ACINETOBACTER, PSEUDOMONAS, CLASSE B
IMIPENEM/ RELEBACTAM	CARBAPENEMICO/BLI	CLASSI A, C, D	CLASSE B
MEROPENEM/ VABORBACTAM	CARBAPENEMICO/BLI	CLASSI A, C	CLASSE B
PLAZOMICINA	NEOGLICOSIDE	GRAM + E GRAM -	NDM
CEFIDEROCOL	CEFALOSPOSRINA, SIDEROFORO	ESBLs, KPC, NDM, OXA	
ERAVACICLINA	TETRACICLINA	ESBL, KPC, NDM, OXA E.Coli e Klebsiella	PSEUDOMONAS

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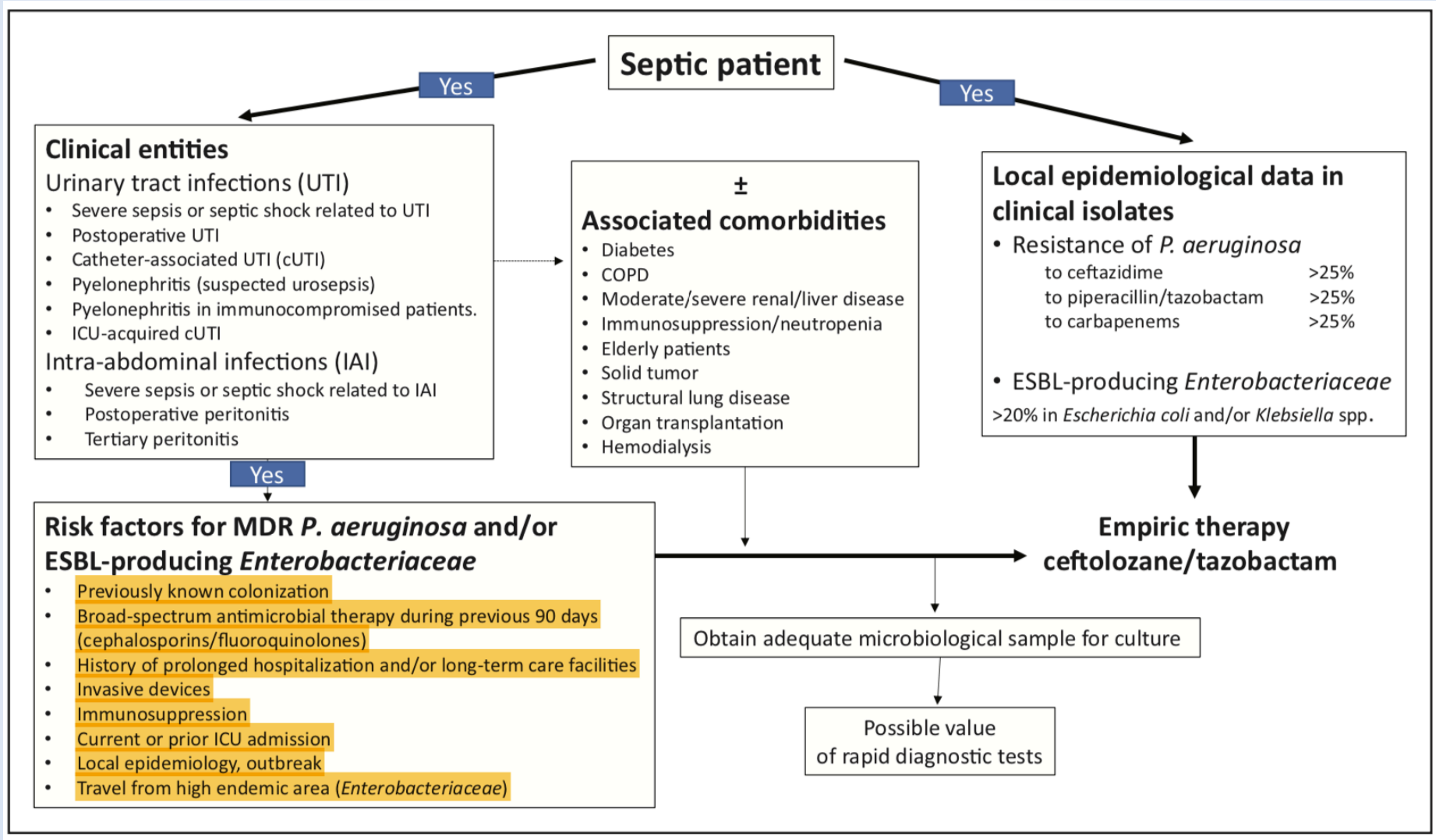
TERAPIA EMPIRICA



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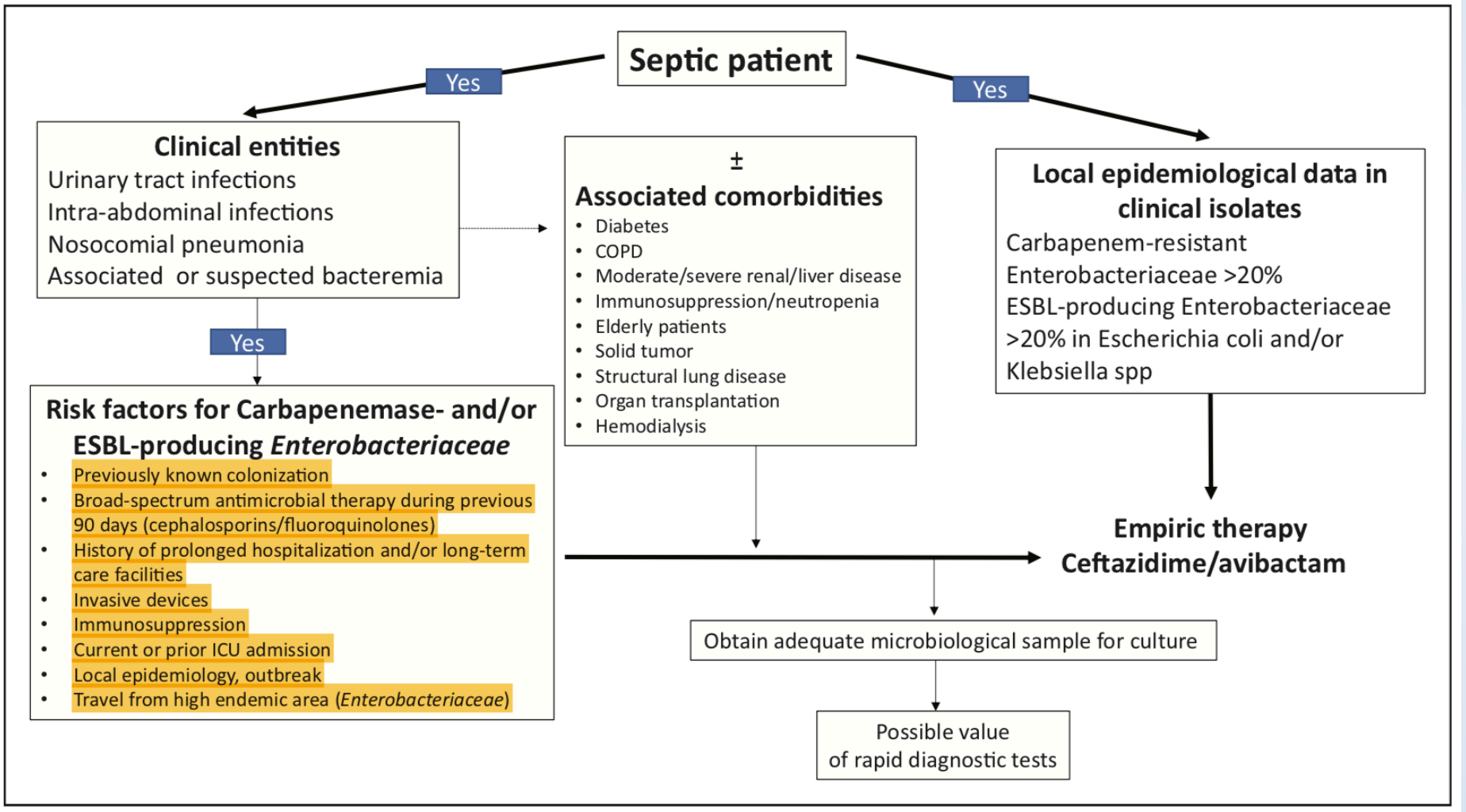
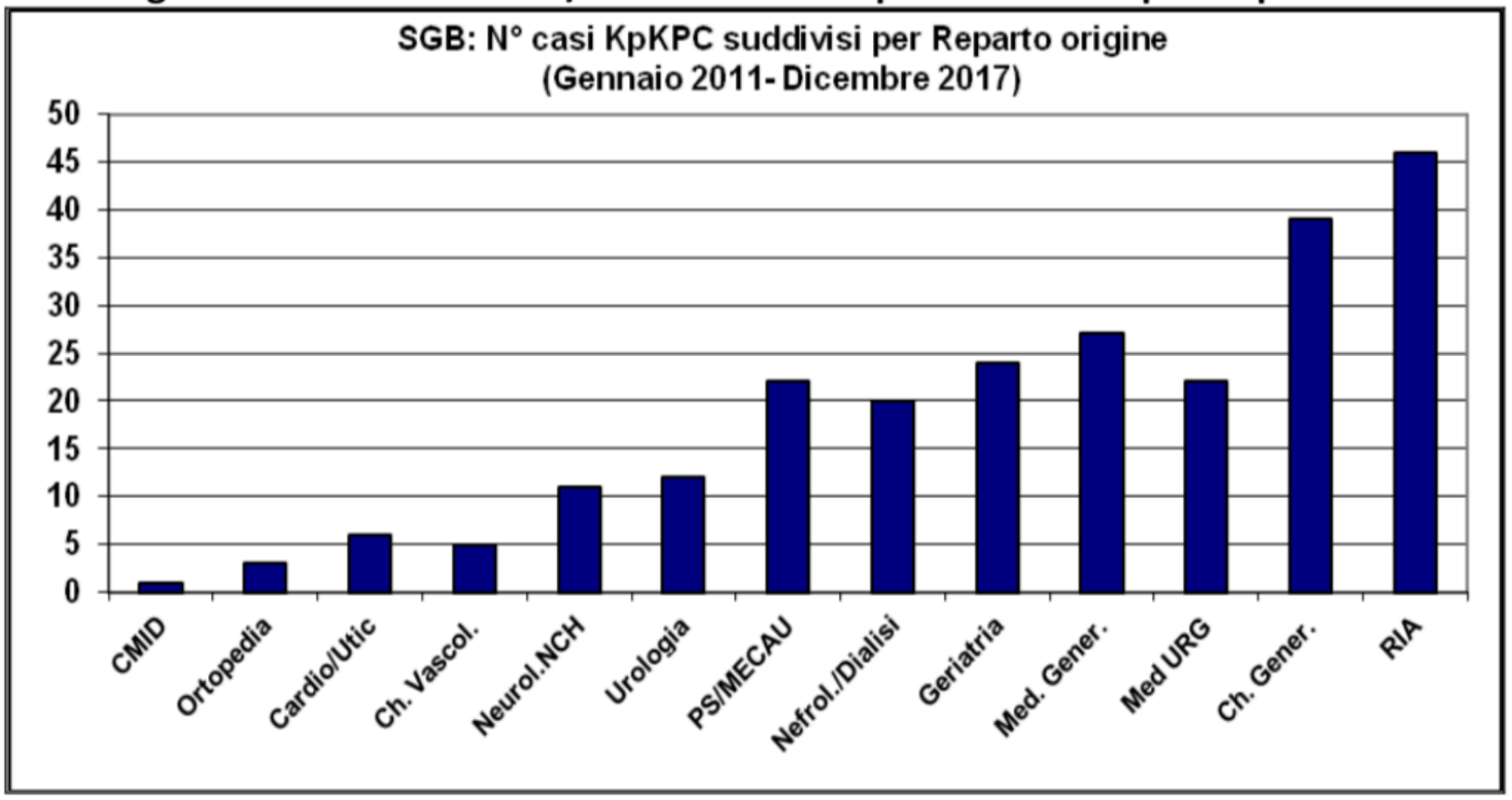


EPIDEMIOLOGIA LOCALE

Tabella 9

	%
SA MR	50,7
SCN MR	72,2
PA CIP-R	11,1
PA CARBA	0
PA CAZ -	16,7
PA PIP- R	N.V.
ENT CF-R	46,1
KLEB CA	12,8
KLEB CF-	41,3
E. coli CF	31,9
E. coli CI	46,9
E. coli ES	34,1
Pneumo	0
VRE	11,5
ACINE CF	93,3
SERR CF	0

Figura 2. Casi di infezione/colonizzazione KpKPC suddivisi per Reparto



Dati regione Piemonte 2017

INFECTION CONTROL

Table 4 Core infection prevention and control measures to minimize risk of spread of CRE within and between healthcare settings

Intervention (Evidence source)	Comments on measure and implementation
Antimicrobial stewardship (SR)	✓ Healthcare settings should have a formally defined antimicrobial stewardship programme for assuring appropriate antimicrobial use [54] ✓ Healthcare settings should have facility-specific treatment (and prophylaxis) recommendations, based on national guidelines and local microbial susceptibility, to assist with empiric antimicrobial selection [54] ✓ Should be part of a multimodal, integrated programme, along with IPC
Environmental cleaning (SR) Equipment reprocessing (SR)	✓ Responsibilities for environmental cleaning and equipment reprocessing must be well-defined and described in hospital internal procedures ✓ Hospitals should review the processes for environmental cleaning and equipment reprocessing, follow instructions of manufacturers, and consider screening (or auditing) to ensure quality of processes
Faecal and medical waste management (EO)	✓ Adequate toilet facilities should be available for all patients ✓ When patients are incontinent or have diarrhoea, bedpans or commodes may be indicated
Guidelines and processes (EO)	✓ Adherence to evidence-based guidelines, processes and pathways for the prevention of healthcare-associated infections (EO)
Hand hygiene (SR)	✓ There is evidence for the effectiveness of hand hygiene, as part of a multimodal strategy, for the reduction of transmission of MDROs [56–58] ✓ Patients should be encouraged to perform hand hygiene, as suggested by WHO guidelines [58]
Infrastructure and capacity for patient accommodation (EO)	✓ Healthcare managers should ensure that the ward occupancy does not exceed the capacity for which it is designed [72] ✓ Healthcare managers should ensure that infection prevention and control building recommendations are followed
Microbiological capacity (EO)	✓ Healthcare settings should have access to microbiology laboratories with capacity to detect CRE from both clinical and screening specimens ✓ Healthcare settings should have systems in place to ensure that potentially significant results are communicated by the microbiology laboratory in a timely manner to the relevant staff in the healthcare setting ✓ Should be part of a multimodal, integrated programme, along with IPC and antimicrobial stewardship
Staff education (SR)	✓ On-going education and training should be provided to all staff with patient contact, with specific reference to CRE
Staffing (EO)	✓ Staffing, appropriate skill level and workload of frontline healthcare workers must be adapted to acuity of care and the number of pool/agency nurses and physicians minimised [72]
Surveillance (EO)	✓ Routine surveillance of healthcare-associated infections

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COLONIZZAZIONE

In conclusion, ICU patients are at high risk for becoming colonized with ESBL-PE and colonization is associated with significantly higher incidence of subsequent infection. Early identification of colonization may help the selection of appropriate empiric treatment and future studies should focus on the evaluation of protocols that monitor for colonization, and the development of preventive measures that may halt spread of ESBL-PE in this setting.

Crit Care Med 2017; 45:705–714

GRAZIE PER L'ATTENZIONE