Antibiotico resistenza:
la salute unica alla prova

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AULA MAGNA

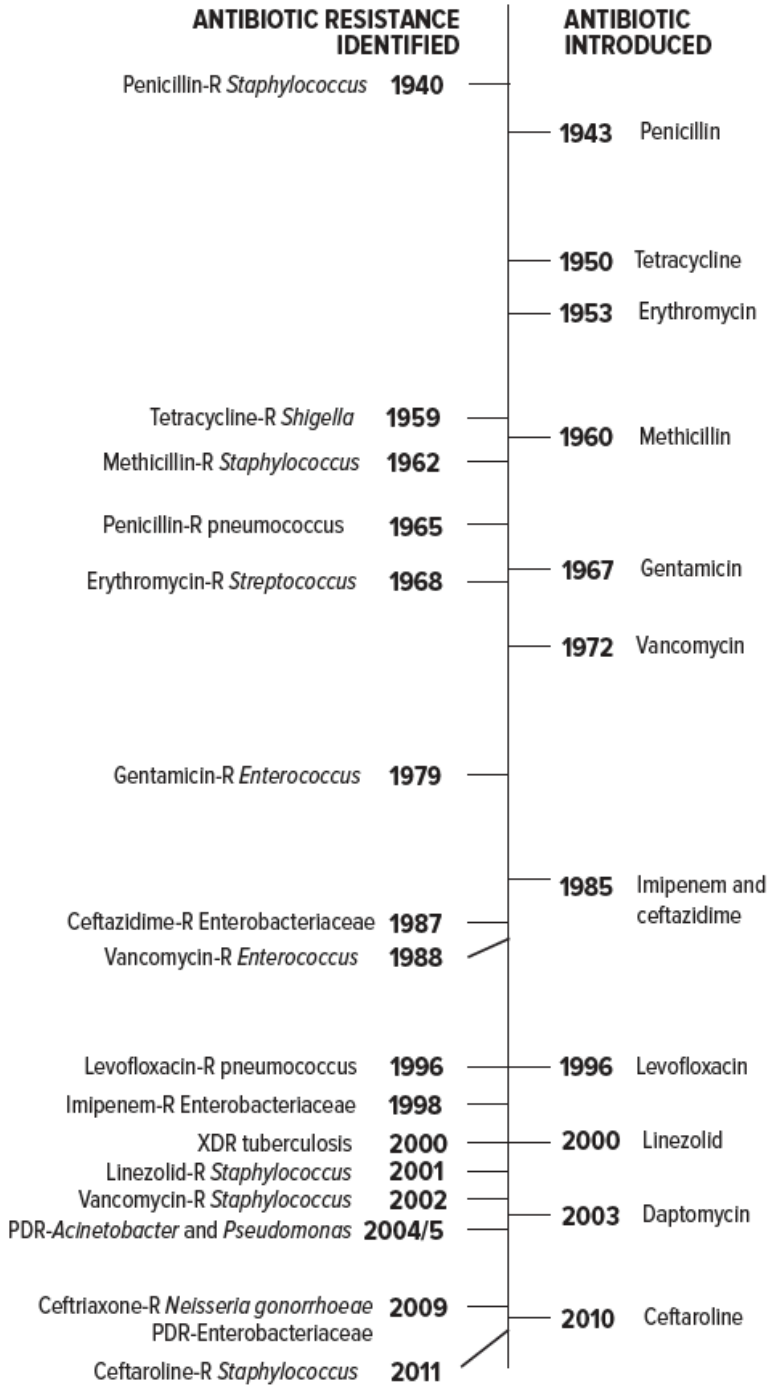
14 dicembre 2018

Antibiotico-resistenza in medicina umana

Antonello Di Paolo

Dipartimento di Medicina Clinica e Sperimentale, Università di Pisa

UO Farmacologia Clinica, AOU Pisana

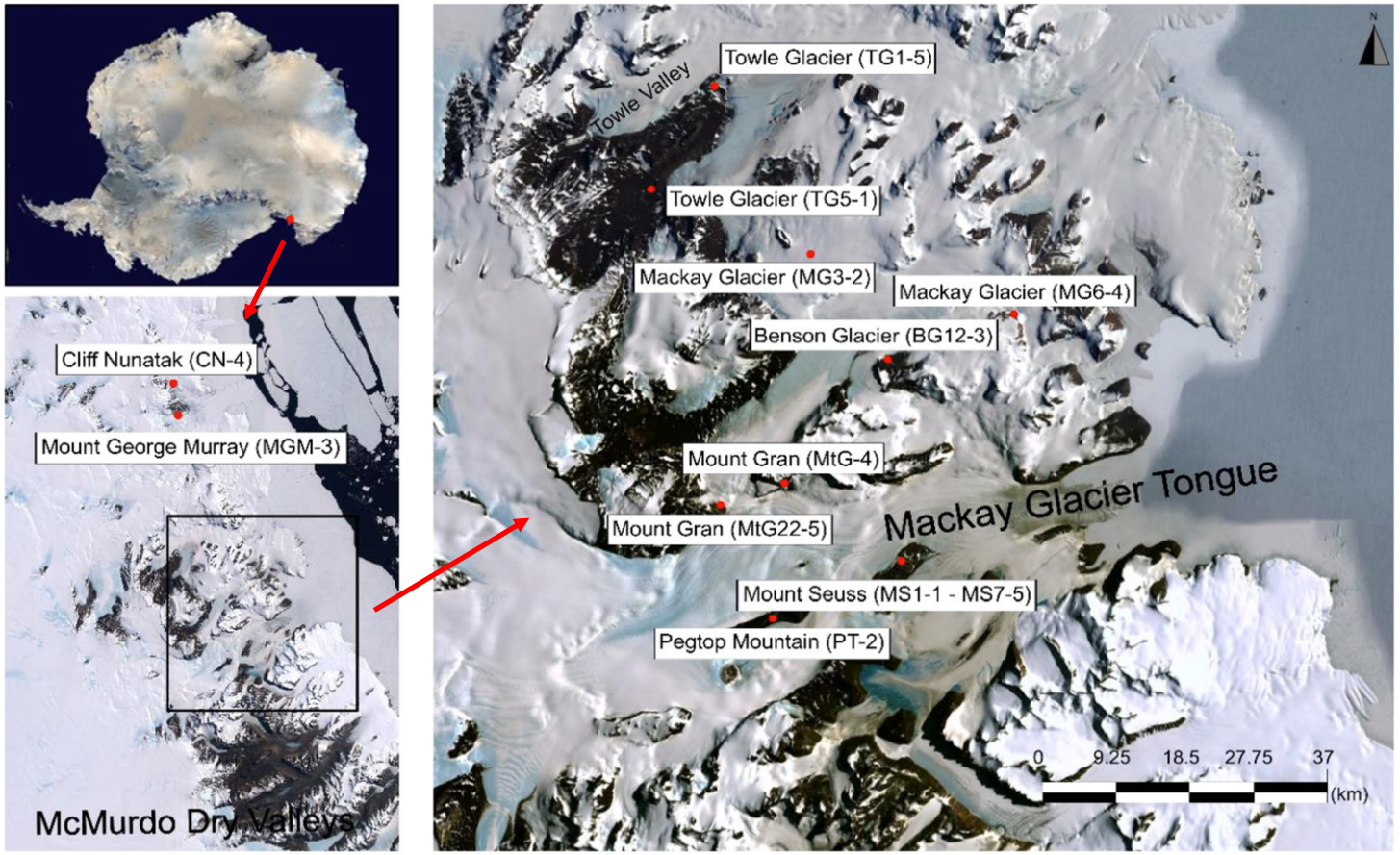


The Antibiotic Resistance Crisis

C. Lee Ventola

Vol. 40 No. 4 • April 2015 • P&T® 277

A reservoir of 'historical' antibiotic resistance genes in remote pristine Antarctic soils



Van Goethem et al. Microbiome (2018) 6:40

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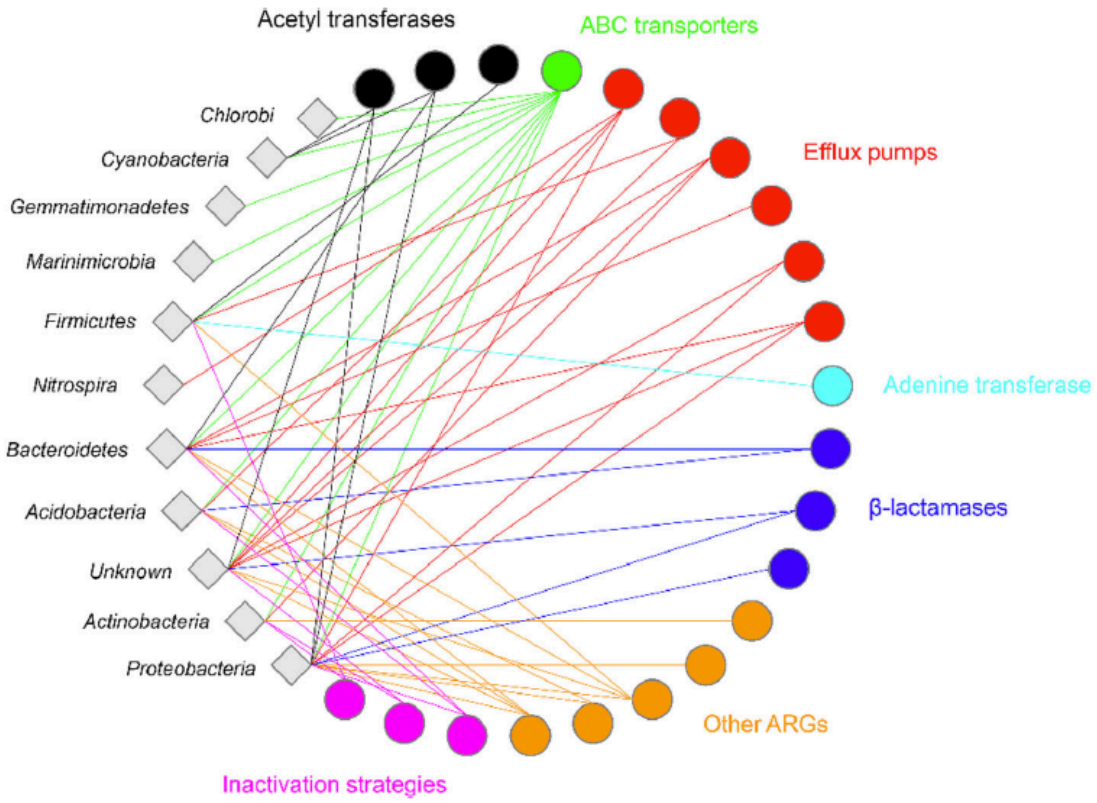

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Antimicrobial resistance (AMR)

Why should we be concerned?

ONE treatment options are limited and sometimes nonexistent

TWO resistance has spread widely on several fronts

THREE dissemination and acquisition of AMR may be silent

FOUR infections are associated with increased mortality and economic costs

Vasoo et al. / Mayo Clin Proc. 2015;90(3):395-403

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Antimicrobial resistance (AMR)

Meccanismi

Pathogen and Resistance Strategy	Antibiotic	Gene(s) Involved
Staphylococci		
Drug inactivation	β-lactams (penicillins with or without cefazolin[a])	*blaZ*
Target replacement	β-lactams	*mecA*
	Vancomycin (VRSA)	*vanA* Gene cluster
Target modification	Linezolid	23S rRNA genes, L3/L4 ribosomal proteins *cfr*
	Ceftaroline	*pbp2a*
Changes in cell surface adaptation	Vancomycin (VISA)	*vraRS, yycFG, graRS, rpoB*
	Daptomycin	*mprF, dlt, vraRS, yycFG, pgsA, cls*

Pathogen and Resistance Strategy	Antibiotic	Gene(s) Involved
Enterococci		
Drug inactivation	β-lactams (penicillins)	*blaZ*
Target replacement	Vancomycin	*van* Gene clusters
Target modification	β-lactams (penicillin and ampicillin)	*pbp5*[b]
	Linezolid	23S rRNA genes, L3/L4 ribosomal proteins, *cfr*
Changes in cell surface adaptation	Daptomycin	*liaFSR, yycGF, gdpD, cls*
Streptococci		
Target modification	β-lactams (penicillin)	PBPs (*pbp2x, pbp2b* in pneumococci), *murM, cpoA, pdgA*
	Linezolid	23S rRNA genes, L3/L4 ribosomal proteins, *cfr*
Unknown	Daptomycin	Unknown

Munita et al. / Clin Infect Dis. 2015;61(S2):S48-57

Antimicrobial resistance (AMR)

Betalattamasi

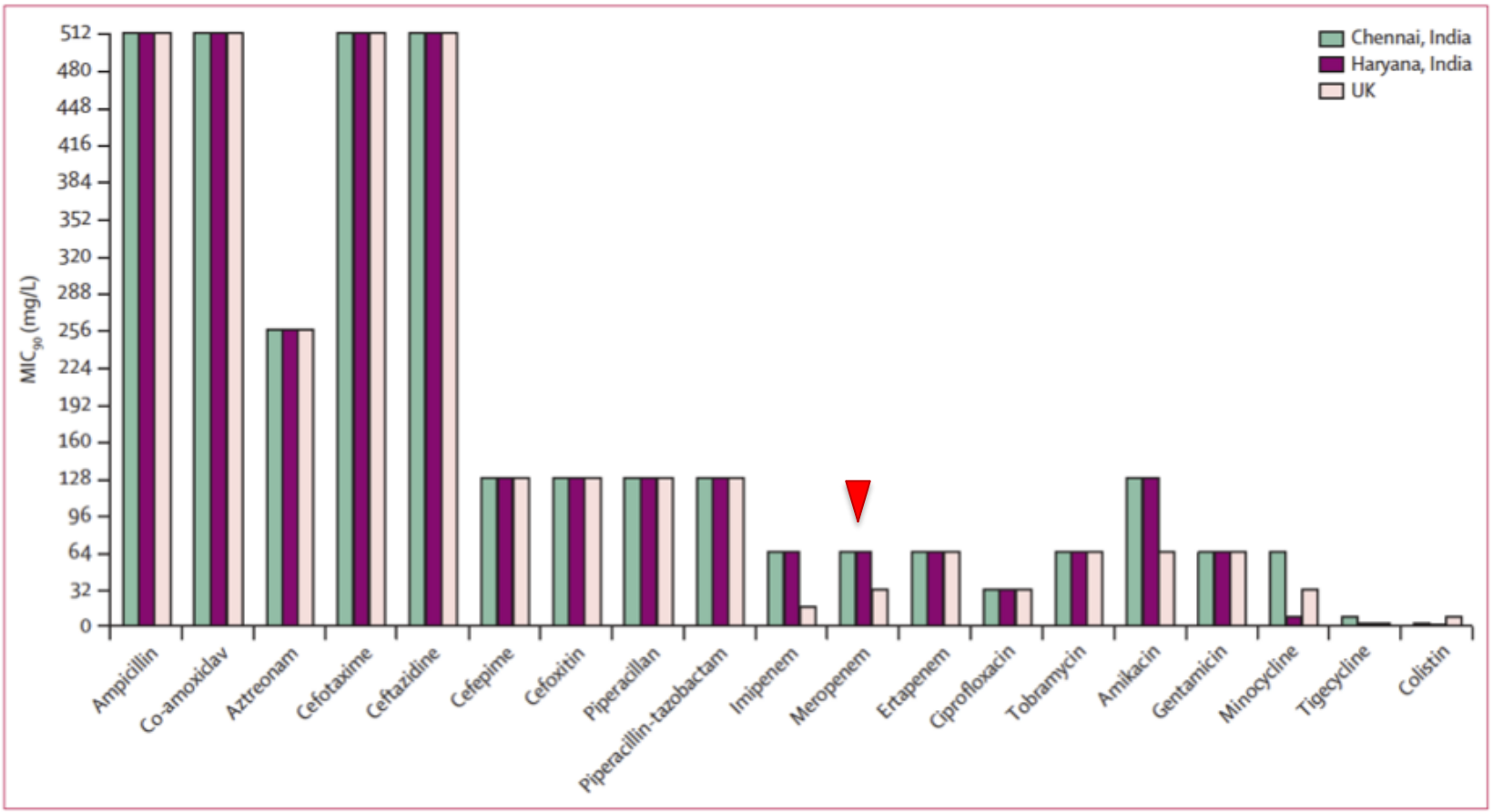
Enzyme	ESBL	AmpC	KPC	NDM	OXA-48 group
Activity	ESBL	Cephalosporinases	Carbapenemases		
Ambler class	A	C	A	B	D
Active site residue	Serine	Serine	Serine	Zinc	Serine
Resistance gene location	Plasmid	Chromosomal (inherent in some genera, such as *Enterobacter, Serratia, Citrobacter*), occasionally plasmid	Plasmid	Plasmid	Plasmid
β-lactams inactivated[b]	First-generation to fourth-generation cephalosporins, aztreonam, older BLBLIs	First-generation to third-generation cephalosporins, older BLBLIs, carbapenems	First-generation to fourth-generation cephalosporins, aztreonam, older BLBLIs, carbapenems	First-generation to fourth-generation cephalosporins, older BLBLIs, carbapenems	First-generation to fourth-generation cephalosporins, carbapenems; however, may have variable or diminished hydrolysis of third-generation or fourth-generation cephalosporins
Examples of current treatment options[c]	Carbapenems Possibly BLBLIs, such as piperacillin-tazobactam, in carefully select patients (low inoculum, nonsevere infections, such as cystitis)	Cefepime (in select patients, such as those needing only a short course of therapy, low-inoculum, nonsevere infections) Carbapenems	More data needed Polymyxins, tigecycline, and aminoglycosides Combination treatment, consider including a carbapenem Cystitis: fosfomycin (oral) nitrofurantoin	More data needed Polymyxins, tigecycline, and aminoglycosides Aztreonam[d] Combination treatment, consider including a carbapenem Cystitis: fosfomycin (oral), nitrofurantoin	More data needed Polymyxins, tigecycline, and aminoglycosides Consider using a β-lactam in combination with the above, choice dependent susceptibility testing; third-generation cephalosporin (eg, ceftazidime) may retain activity and may be preferable to carbapenems

Vasoo et al. / Mayo Clin Proc. 2015;90(3):395-403

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study

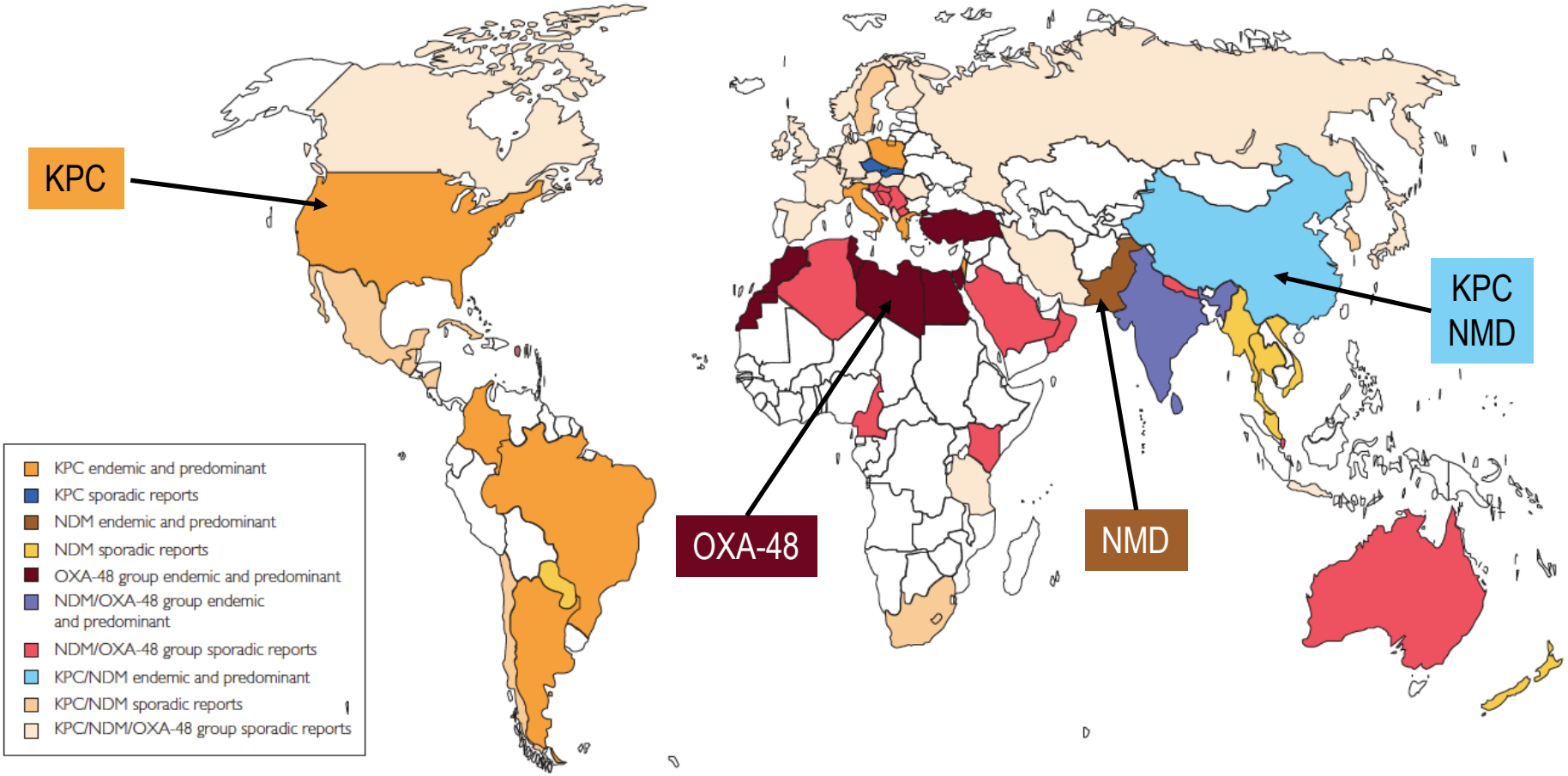
Lancet Infect Dis 2010; 10: 597–602

Karthikeyan K Kumarasamy, Mark A Toleman, Timothy R Walsh, Jay Bagaria, Fafhana Butt, Ravikumar Balakrishnan, Uma Chaudhary, Michel Doumith, Christian G Giske, Seema Irfan, Padma Krishnan, Anil V Kumar, Sunil Maharjan, Shazad Mushtaq, Tabassum Noorie, David L Paterson, Andrew Pearson, Claire Perry, Rachel Pike, Bhargavi Rao, Ujjwayini Ray, Jayanta B Sarma, Madhu Sharma, Elizabeth Sheridan, Mandayam A Thirunarayan, Jane Turton, Supriya Upadhyay, Marina Warner, William Welfare, David M Livermore, Neil Woodford



Antimicrobial resistance (AMR)

Diffusione di betalattamasi



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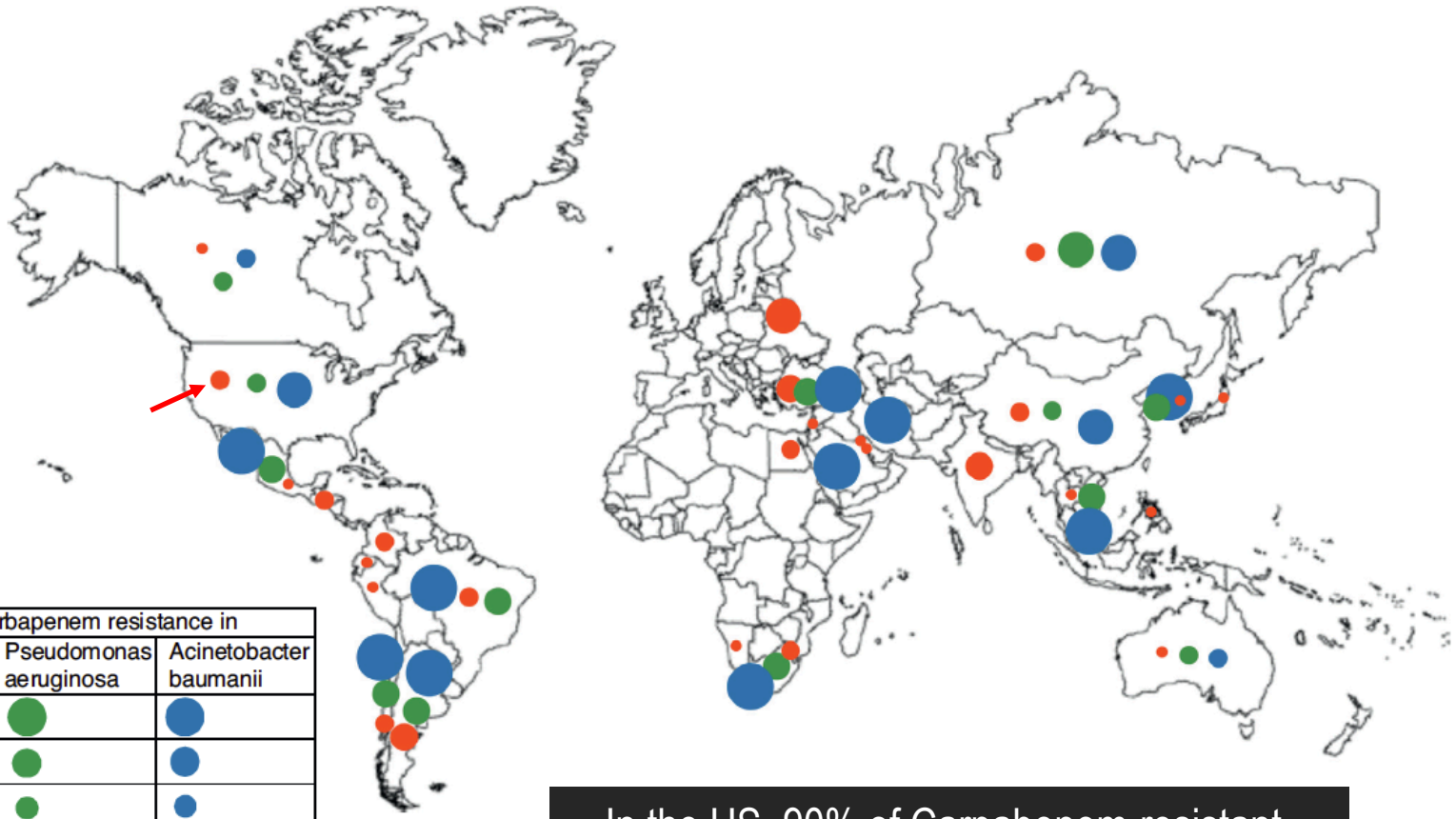
Global antimicrobial resistance in Gram-negative pathogens and clinical need

Ursula Theuretzbacher

Current Opinion in Microbiology 2017, **39**:106–112



Prevalence of carbapenem resistance in			
	Klebsiella pneumoniae	Pseudomonas aeruginosa	Acinetobacter baumanii
≥75			
50-<75			
25%-<50			
5-<25			
<5%			

…In the US, 90% of Carpabenem-resistant *Enterobacteriaceae* are *K. pneumoniae* and 92% of them produce a carbapenemase…

Global antimicrobial resistance in Gram-negative pathogens and clinical need

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Current Opinion in Microbiology 2017, 39:106–112

- ***K. pneumoniae***: In Europe, the rate of resistance to **third generation cephalosporins** with co-resistance to **fluoroquinolones** and **aminoglycosides**, the most common multi-drug resistance (MDR) phenotype, ranges from 0 to 60%... A similar wide range is seen with the rate of resistance to **carbapenems**.
- ***P. aeruginosa (PA)***: Rates of resistance to **carbapenems** in European countries ranged from 0% (Iceland) to 66% (Romania) in 2015... Combined resistance in PA was common in European countries: about **14%** of the isolates were resistant to at least **three antimicrobial groups**, and **5.5%** were resistant to **all five antimicrobial groups**.
- ***A. baumanni (AB)***: **carbapenem** resistant (CR) AB is the most common CR organism associated with nosocomial infection, followed by CR PA. In most cases CR is combined with resistance to **fluoroquinolones** and **aminoglycosides**… Generally, CR AB strains have a high potential for being XDR or even pan-drug resistance (PDR) where no active antibiotic exists.

EUROPEAN ANTIBIOTIC AWARENESS DAY

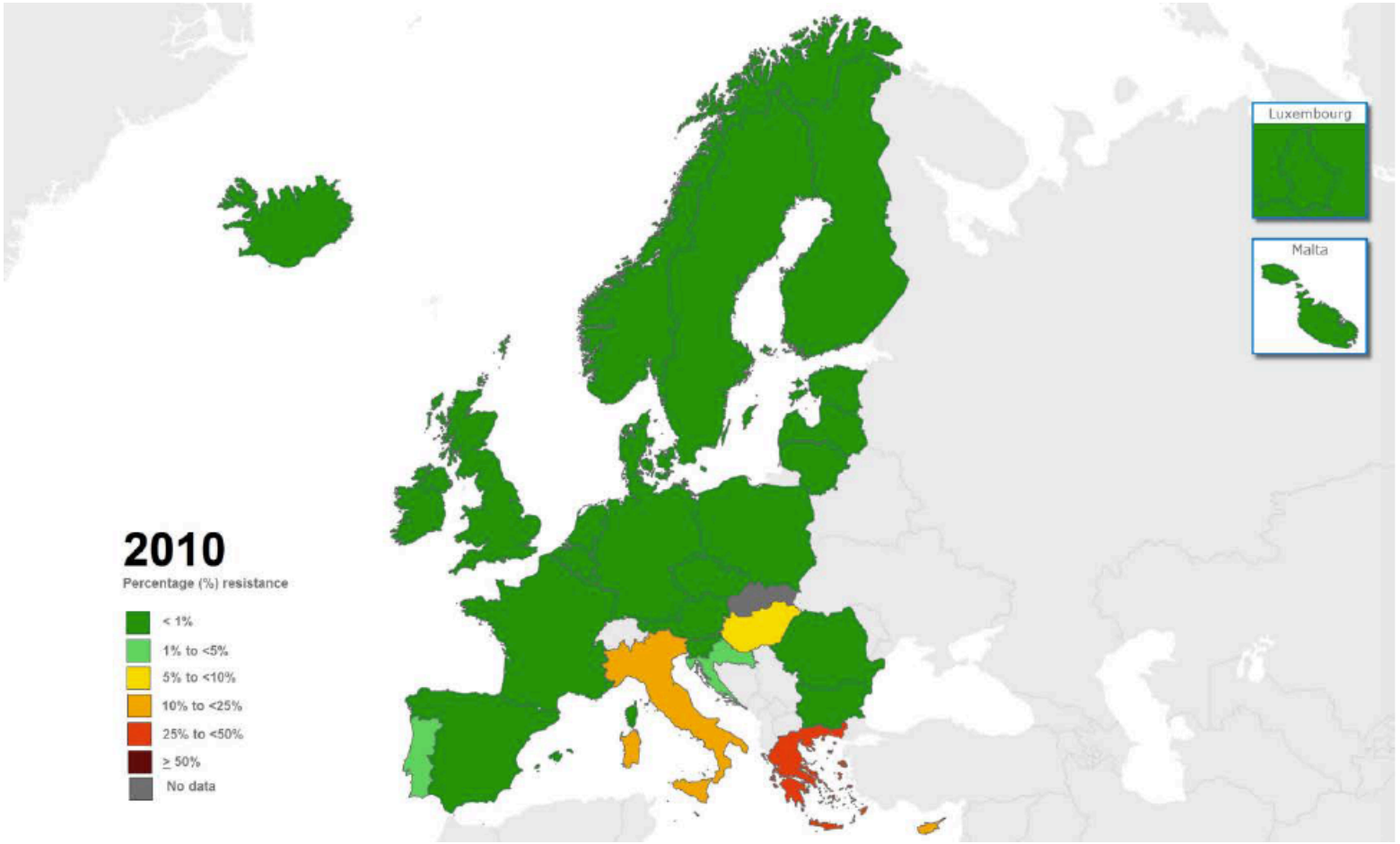
A European Health Initiative

Klebsiella pneumoniae

Percentage of invasive isolates with resistance to carbapenems

ecdc

EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL



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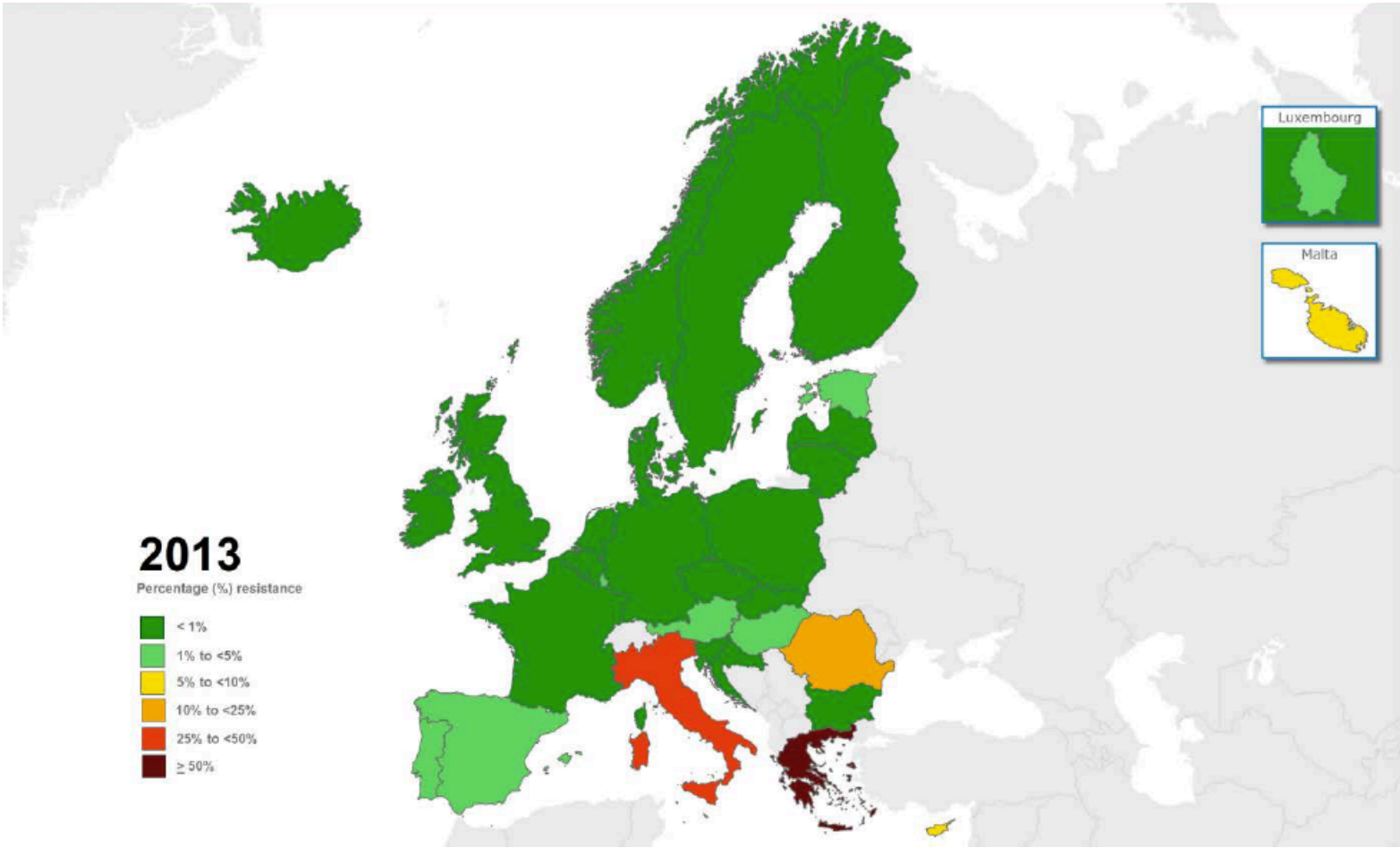


Klebsiella pneumoniae

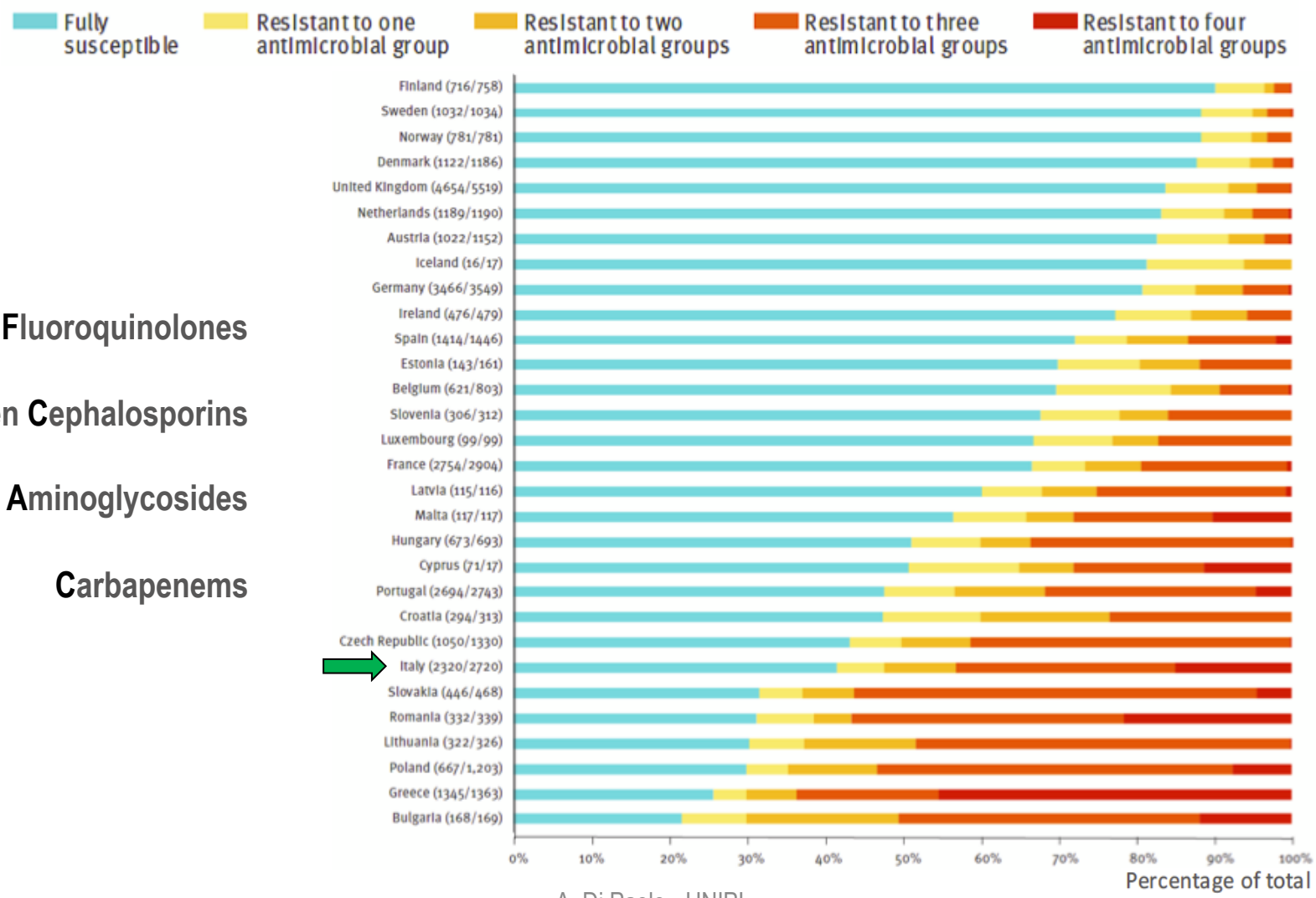
Distribuzione degli isolati, EU, EEA, 2017

Fluoroquinolones

3rd-gen Cephalosporins

Aminoglycosides

Carbapenems



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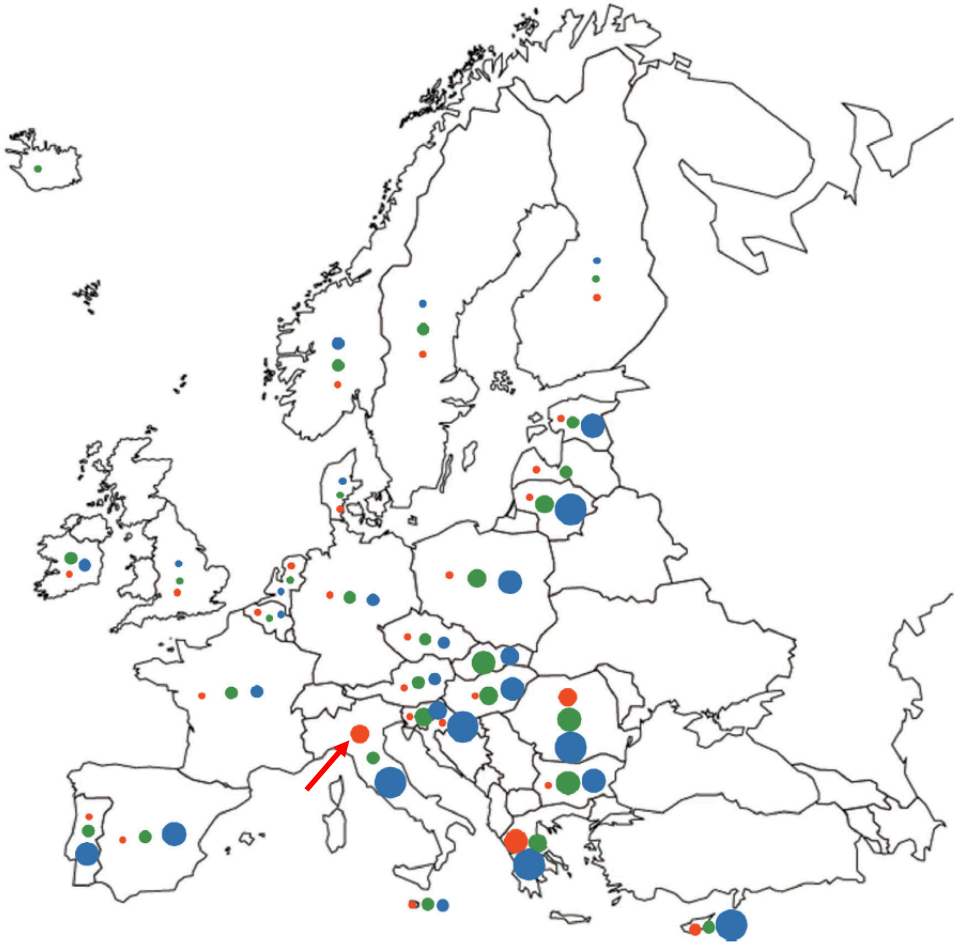
Current Opinion in Microbiology 2017, **39**:106–112

… **Italy** has a high rate of Carbapenem-resistance in *K. pneumoniae* (36%), of which 97% carry the gene for KPC (mostly KPC-3)…



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≥75			
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<5%			

Resistenze antimicrobiche in Italia

Pathogen	Resistance rate	
	Italy	European Union countries
ESBL-producing *Escherichia coli*	30%	12%
MDR *Escherichia coli*	13%	5%
ESBL-producing *Klebsiella pneumoniae*	56%	26%
CR *Klebsiella pneumoniae*	40%	6%
MDR *Klebsiella pneumoniae*	32%	16%
CR *Pseudomonas aeruginosa*	23%	15%
CR *Acinetobacter* spp.	78%	35%
Meticillin-resistant *Staphylococcus aureus*	34%	14%
Vancomycin-resistant *Enterococcus faecium*	13%	12%

ESBL, extended-spectrum beta-lactamase; CR, carbapenem-resistant; MDR, multidrug-resistant (resistant to third-generation cephalosporins, fluoroquinolones and aminoglycosides)

F. Menichetti et al. / Int J Antimicrob Agents 52 (2018) 127–134

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Vasoo et al. / Mayo Clin Proc. 2015;90(3):395-403

Carbapenemases in *Klebsiella pneumoniae* and Other *Enterobacteriaceae*: an Evolving Crisis of Global Dimensions

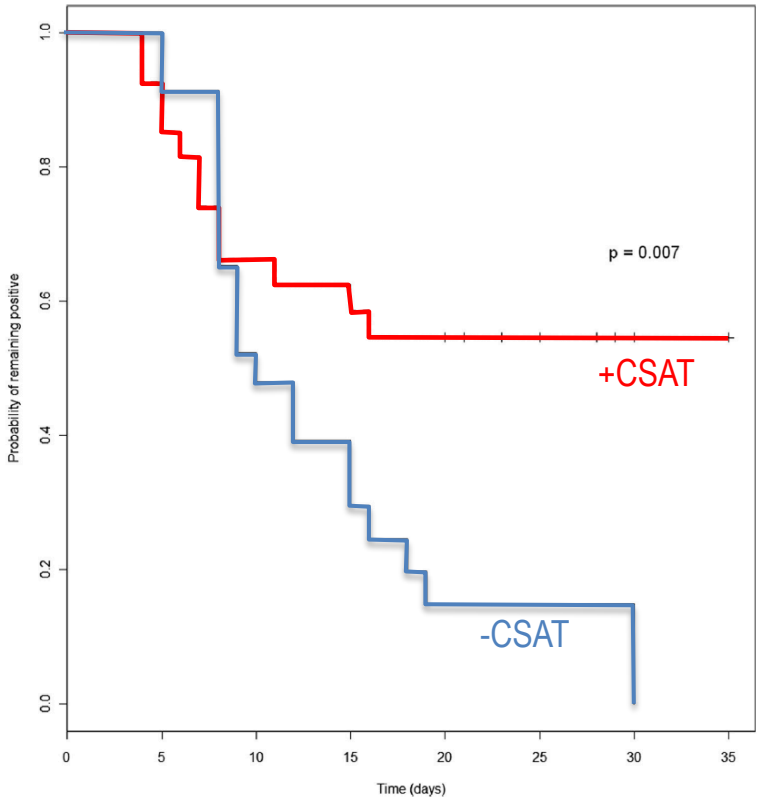
- *Klebsiella pneumoniae* is encountered as a **saprophyte** in humans and other mammals, colonizing the gastrointestinal tract, skin, and nasopharynx; it is also found in various environmental niches (soil, water, etc.)…
- …it is found in the gastrointestinal tracts of patients, at frequencies as high as 80%, but high carriage rates have also been recorded for patient nasopharynges and hands.
- This **considerable efficiency of colonization**, enhanced by acquired resistance to antibiotics, enables *K. pneumoniae* to persist and spread rapidly in health care settings.
- *K. pneumoniae* is a notorious "**collector**" of multidrug resistance plasmids.

Touvelekis et al. / Clin Microbiol Rev 2012;25(4):682-707

Oral Gentamicin Gut Decontamination for Prevention of KPC-Producing *Klebsiella pneumoniae* Infections: Relevance of Concomitant Systemic Antibiotic Therapy

Carlo Tascini,[a] Francesco Sbrana,[b] Sarah Flammini,[a] Enrico Tagliaferri,[a] Fabio Arena,[c] Alessandro Leonildi,[a] Ilaria Ciullo,[a] Francesco Amadori,[a] Antonello Di Paolo,[d] Andrea Ripoli,[b] Russell Lewis,[e] Gian Maria Rossolini,[c,f,g] Francesco Menichetti,[a] the GENGUT Study Group

Antimicrobial Agents and Chemotherapy p. 1972–1976
April 2014 Volume 58 Number 4



Decontamination rate: 96% (22/23) patients receiving oral gentamicin only, compared to 44% (12/27) of those treated with oral gentamicin and concomitant systemic antibiotic therapy (CSAT) (P<0.001).

The multivariate analysis confirmed CSAT and KPC-Kp infection as the variables associated with gut decontamination.

Oral gentamicin was shown to be potentially useful for gut decontamination and prevention of infection due to KPC-Kp, especially in patients not receiving CSAT.

The risk of emergence of gentamicin-resistant KPC-Kp should be considered.

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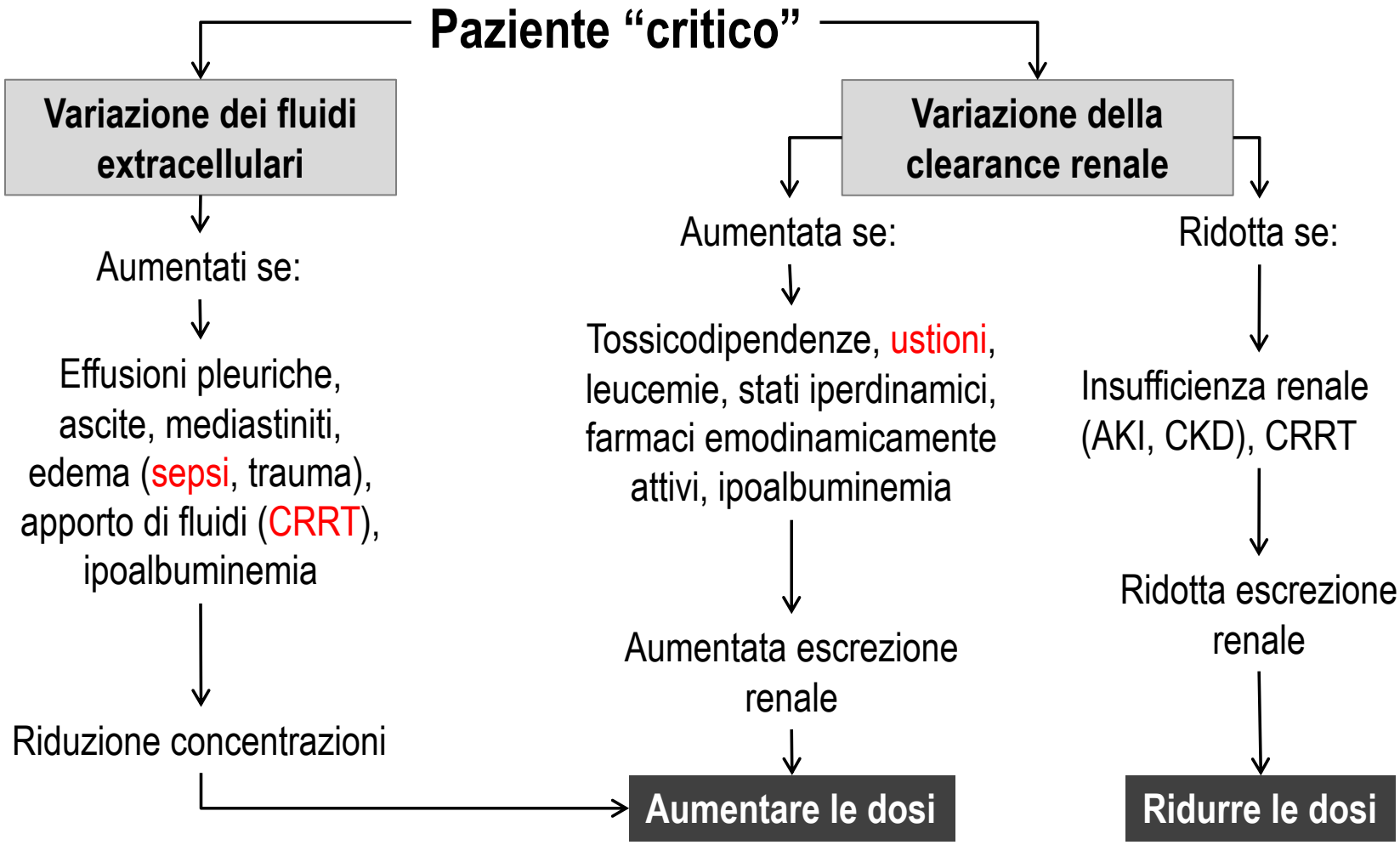
Variabilità PK degli antibiotici nel paziente critico



Pea et al. *Clin Pharmacokinet* 2005;44:1009-1034

Caratteristiche generali degli antimicrobici

idrofili

β-lattamici
Glicopeptidi
Aminoglicosidi
Oxazolidinoni

- Limitato volume di distribuzione
- Prevalentemente eliminati immodificati dal rene

liposolubili

Macrolidi
Fluorochinoloni
Tetracicline
Rifampicina

- Ampio volume di distribuzione, diffondono attraverso le membrane cellulari
- Prevalentemente eliminati dal fegato previa biotrasformazione

Pea et al. *Clin Pharmacokinet* 2005;44:1009-1034

Short- and long-term outcomes in infective endocarditis patients: a systematic review and meta-analysis

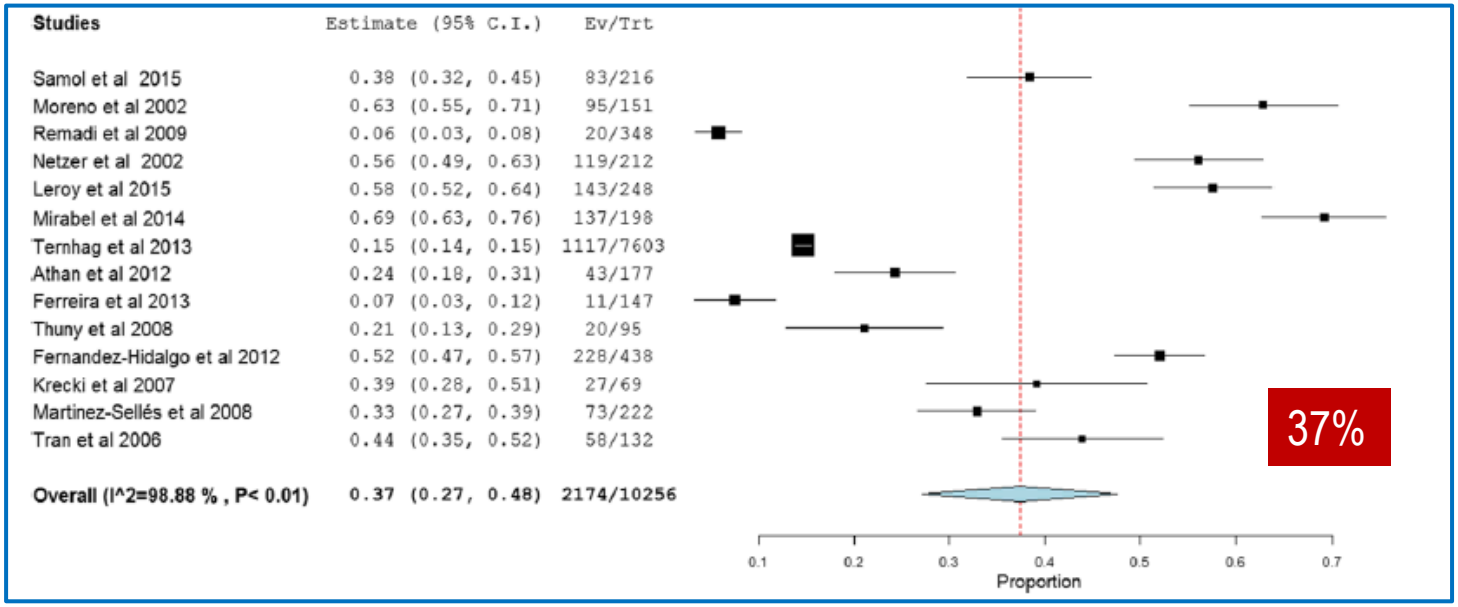
Abegaz *et al. BMC Cardiovascular Disorders* (2017) 17:291

Common pathogens involved in the pathogenesis of infective endocarditis

Pathogens/culture	Patients with pathogens	Total number of patients	Overall estimate, 95% CI
Culture positive	1320	2012	0.63(0.37–0.88)
Culture negative	1049	12,508	0.21(0.09–0.42)
Staphylococcus aureus	2894	13,768	0.27(0.22–0.33)
Streptococcus aureus	2426	13,768	0.23(0.18–0.29)
Enterococci bacteria	313	2731	0.11(0.10–0.28)
HACEK and others	628	11,936	0.10(0.10–0.11)

Abbreviation: HACEK Haemophilus, Aggregatibacter, Cardiobacterium hominis, Eikenella corrodens, Kingella species

Long-term outcome of infective endocarditis (**mortality rate**)



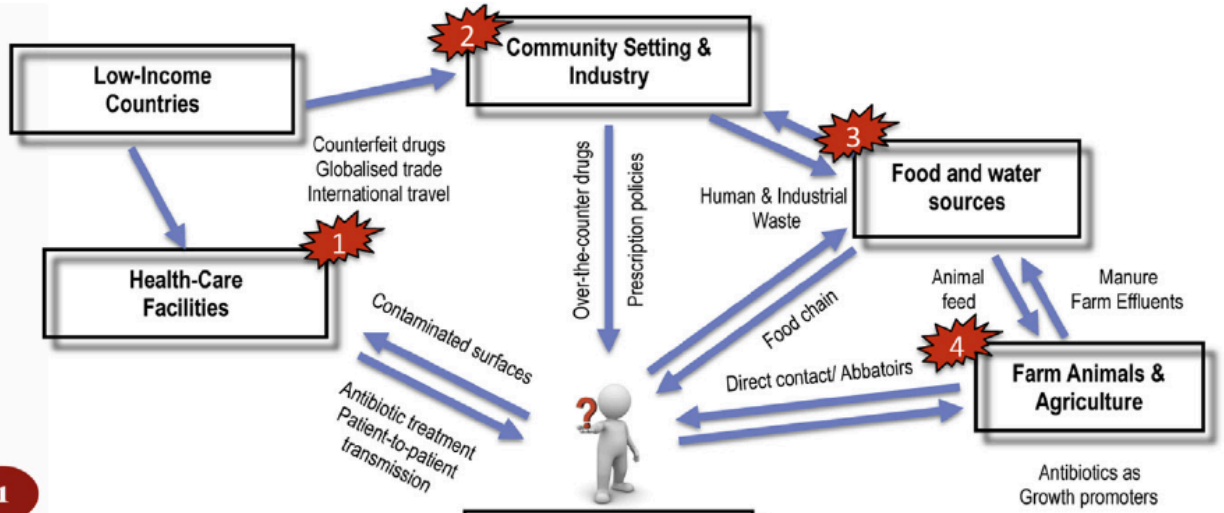
Epidemiology of severe sepsis

Florian B Mayr[1,2,3], Sachin Yende[1,2,*], and Derek C Angus[1,2]

Virulence 5:1, 4–11; January 1, 2014

	Frequency (%)	OR (95% CI)
Gram-positive	46.8	
Staphylococcus aureus	20.5	0.8 (0.6–1.1)
MRSA	10.2	1.3 (0.9–1.8)
Enterococcus	10.9	1.6 (1.1–2.3)
S. epidermidis	10.8	0.9 (0.7–1.1)
S. pneumoniae	4.1	0.8 (0.5–1.4)
Other	6.4	0.9 (0.7–1.2)
Gram-negative	62.2	
Pseudomonas species	19.9	1.4 (1.2–1.6)
Escherichia coli	16.0	0.9 (0.7–1.1)
Klebsiella species	12.7	1.0 (0.8–1.2)
Acinetobacter species	8.8	1.5 (1.2–2.0)
Enterobacter	7.0	1.2 (0.9–1.6)
Other	17.0	0.9 (0.7–1.3)
Anaerobes	4.5	0.9 (0.7–1.3)
Other bacteria	1.5	1.1 (0.6–2.0)

The global threat of antimicrobial resistance: science for intervention



1

- Implementation of antimicrobial stewardship programs and infection control measures
- Universal screening of patients for MDRB upon admission
- Evaluation of duration and regimes of antibiotic treatment
- International harmonization of breakpoints
- Development of rapid and affordable diagnostic technologies
- Active surveillance
- Re-launching discovery and development of new antimicrobial drugs
- Reinforce International/National regulations

2

- Educational programs for prescribers and users
- Assessing antibiotic consumption
- Assessing prevalence of MDR strains
- Update local antibiotic prescribing guidelines
- Active surveillance
- Improved sanitation
- Reinforce International/National regulations

3

- Assessment of antibiotic concentrations of sewages and wastewater treatment plants
- Improved sanitation of industrial systems
- Decontamination of hospital sewage water
- Reinforce International/National regulations

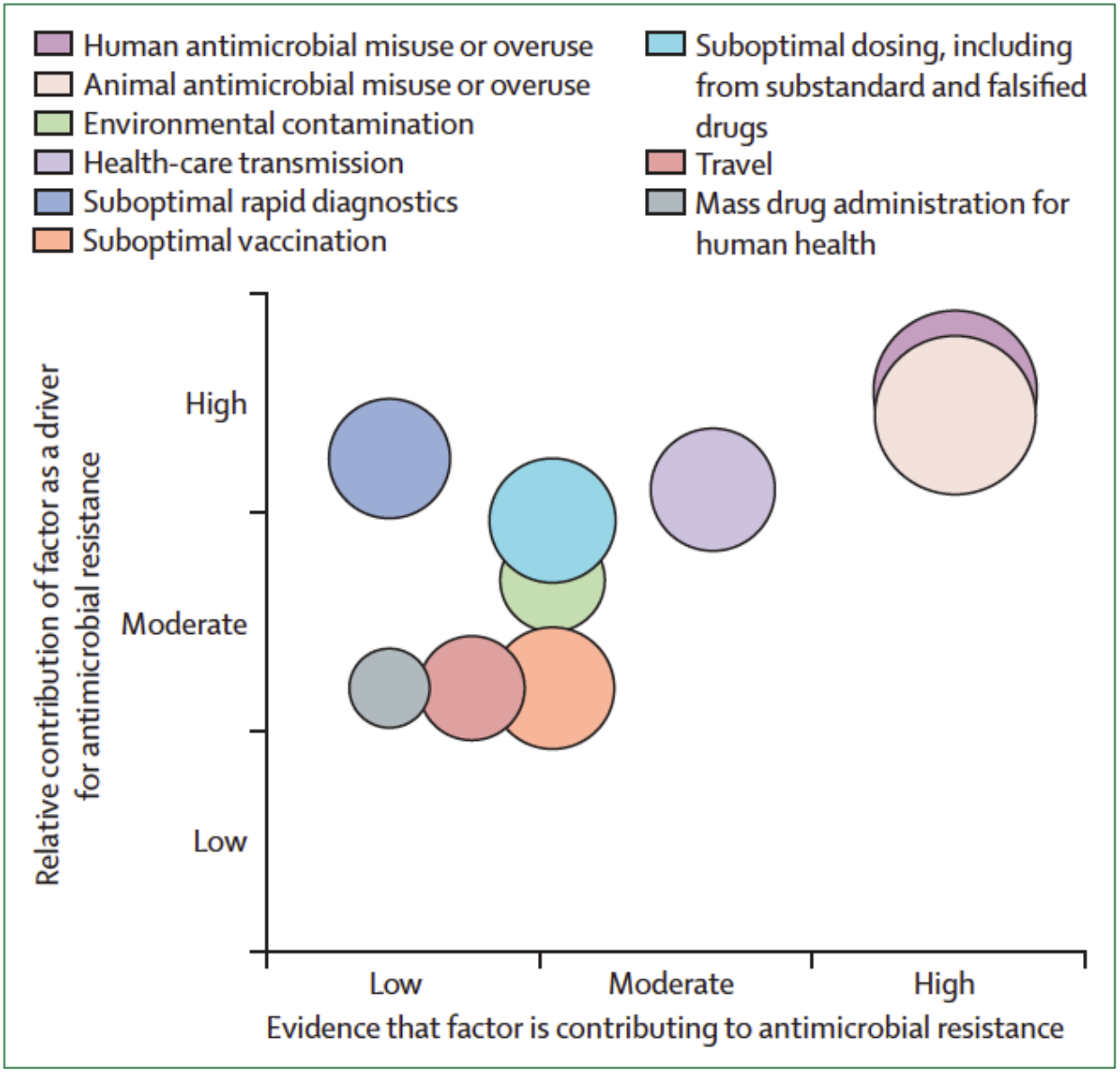
4

- Banning/regulating antibiotic use as growth promoters
- Improving Farm Biosecurity
- Enforcing joint surveillance systems in humans and animals
- The harmonisation of epidemiological cut-off values
- Reinforce International/National regulations

Roca et al. / New Microbe New Infect 2015;6:22-29

Understanding the mechanisms and drivers of antimicrobial resistance

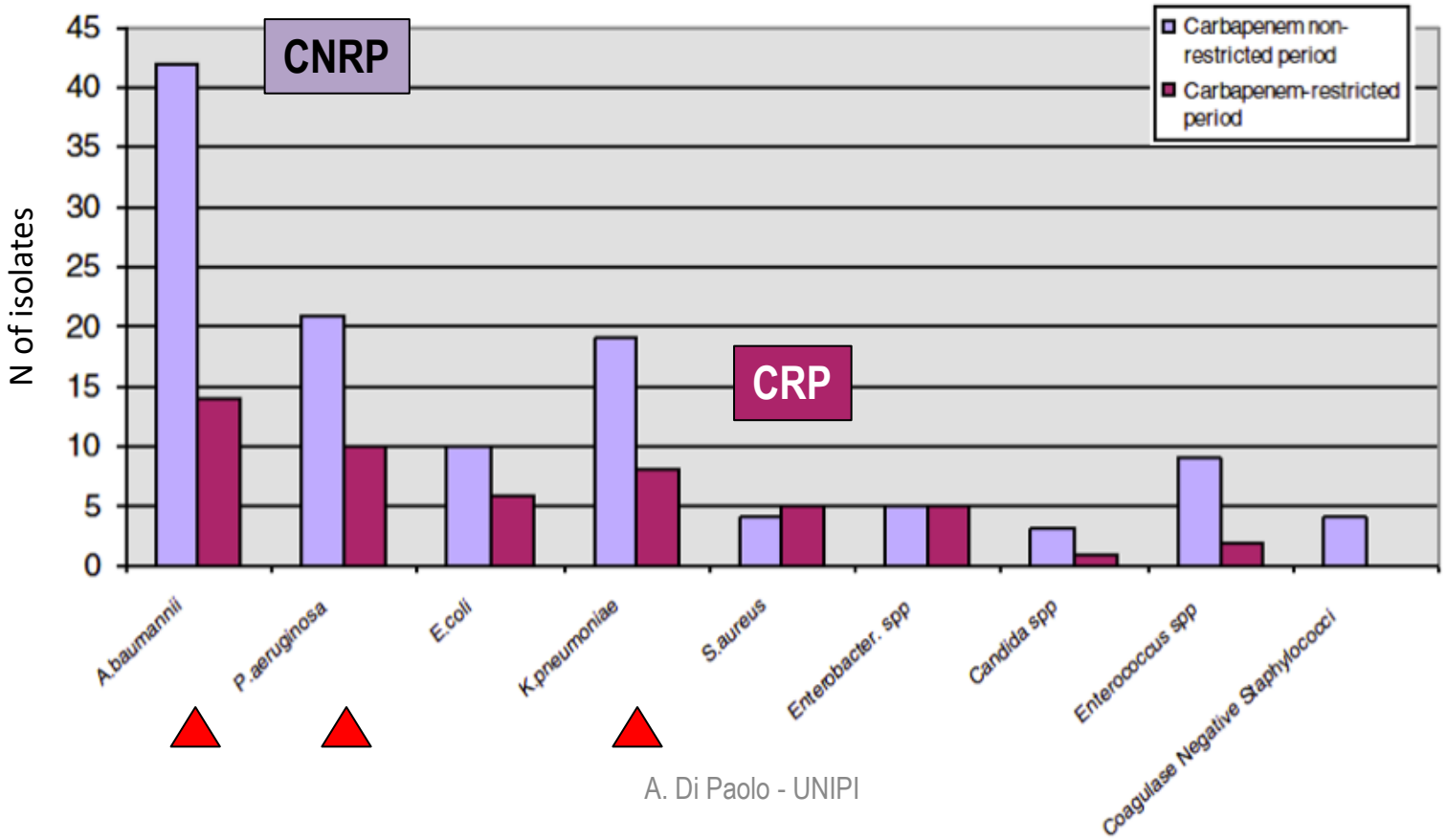
Holmes et al. / Lancet 2016;387:176-87



Effects of Carbapenem consumption on the prevalence of Acinetobacter infection in intensive care unit patients

Ogutlu *et al. Annals of Clinical Microbiology and Antimicrobials* 2014, **13**:7

The prevalence of MDR-*A. baumanni* strains isolated in the carbapenem non-restricted period (**CNRP**) was 2.24-fold higher than the prevalence in the carbapenem restricted period (**CRP**).
The prevalence of Acinetobacter infections can be reduced by taking strict isolation measures as well as by implementing good antibiotics usage policy



The Role of Human Health and Animal Health in Antimicrobial Resistance

- The common finding across all the research, including studies in Canada, is that 50% of the antimicrobials dispensed in the outpatient/community setting are deemed inappropriate or unnecessary

- Public awareness of the threat of AMR is also increasing, particularly with respect to intensive agriculture on 'factory farms' and the use of antimicrobials for animal growth promotion to increase cheap food production

- Resistant pathogens do not respect geographical borders, thus these interests must be met on a global scale, with an intelligent globally-coordinated response

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Reflection paper on use of aminoglycosides in animals in the European Union: development of resistance and impact on human and animal health

- Resistance [to AG] can be due to chromosomal mutations, but resistance determinants are often located on **mobile elements** such as transposons, integrons and plasmids.

- Livestock-associated MRSA CC398 (LA-MRSA) carriage was significantly associated with contact with livestock. This indicates that **LA-MRSA resistant to AGs can be transmitted** between animals and humans.

- CR *P. aeruginosa* isolates found in Ohio contained the metallo-beta-lactamase gene *bla*VIM-2 within a class 1 integron. Genomic sequencing and assembly revealed that the integron was part of a novel 35-kb region that also included a Tn*501*-like transposon and Salmonella genomic island 2 (SGI2)-homologous sequences indicative of **a recombination event** between *Salmonella* spp. and *P. aeruginosa.*

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SCIENCE MEDICINES HEALTH

Reflection paper on use of aminoglycosides in animals in the European Union: development of resistance and impact on human and animal health

- Altogether, these data show that the probability of transfer of AG resistance from animals to humans is high, especially in *Enterobacteriaceae* and enterococci.

Substance	Prevalence of resistance*	Mobile genetic element-mediated transfer of resistance[a]	Vertical transmission of resistance gene(s)[b]	Co-selection of resistance[c]	Potential for transmission of resistance through zoonotic and commensal food-borne bacteria[d]	Evidence of similarity of resistance: genes / mobile genetic elements / resistant bacteria[e]	Overall probability of resistance transfer
kanamycin, gentamicin, amikacin, apramycin, tobramycin, paromomycin, framycetin, neomycin	low	3	3	3	3	3	high
spectinomycin, (dihydro)streptomycin,	high	3	3	3	3	3	high

gene is on a mobile genetic element, e.g. plasmid

it may be co-mobilised

transmission of resistance through food-borne zoonotic pathogens and commensal food-borne bacteria

genes and mobile genetic elements similar between animals and humans

Strumenti per contrastare i fenomeni di resistenza antimicrobica

1. Impiego appropriato di farmaci
    - Antibiogramma / terapia mirata *vs*. empirica
    - PK/PD
    - Monitoraggio terapeutico dei farmaci
    - Limitazioni alla prescrizione (infettivologi)
    - Vecchi farmaci (fosfomicina, colistina)
    - Combinazioni chemioterapiche (*double carbapenem,* nuovi BLI*)*
2. Sviluppo di nuovi farmaci

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Terapia antimicrobica e PK/PD

Antibatterici	Farmacodinamica	Dosaggio
Penicilline **Cefalosporine**	Killing tempo-dipendente Breve o assente PAE Correlazione PD-PK:**T>MIC**	Prolungare il tempo di esposizione all'antibiotico Mantenere i livelli sierici >alle MIC (ridurre gli intervalli o infusione continua)
Carbapenemici **Glicopeptidi** **Eritromicina**	Killing tempo-dipendente Prolungato PAE Correlazione PD-PK:**T>MIC**	Prolungare il tempo di esposizione all'antibiotico Livelli sierici possono essere < alle MIC (ridurre gli intervalli)
Aminoglicosidi **Fluorochinoloni** **Claritromicina** **Azitromicina**	Killing concentrazione dipendente Prolungato PAE Correlazione PD-PK: **Picco/MIC** o **AUC/MIC**	Ottenere alti livelli sierici ed elevate concentrazioni tissutali (aumentare le dosi e prolungare gli intervalli)

Population pharmacokinetics and probability of target attainment of meropenem in critically ill patients

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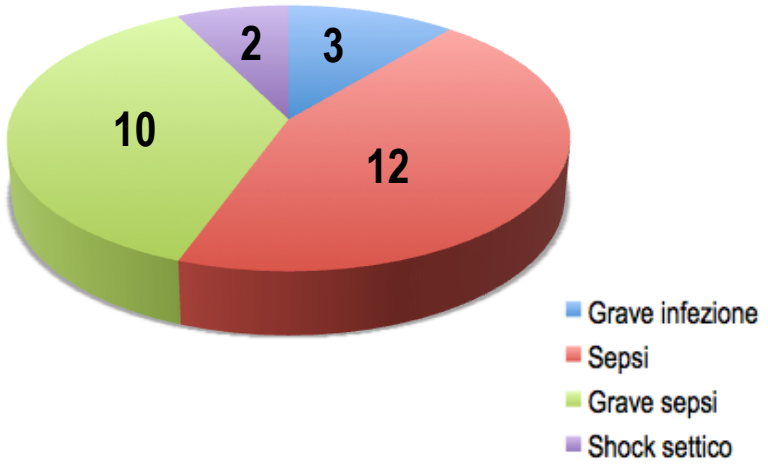
Parametro	Pazienti (n=27)
Età (anni)	62±12 (61)
Peso corporeo (kg) *	76,2±30,3 (68)
Altezza (cm) *	170,3±7,3 (170)
BSA (m^2) *	1,9±0,3 (1,8)
BMI (kg/m^2)	26,1±8,9 (23,4)
Creatininemia (mg/dL)	1,3±1,0 (0,9)
Albuminemia (g/L)	24,3±6,6 (23,1)
Diuresi (mL/die)	2032±950 (2000)

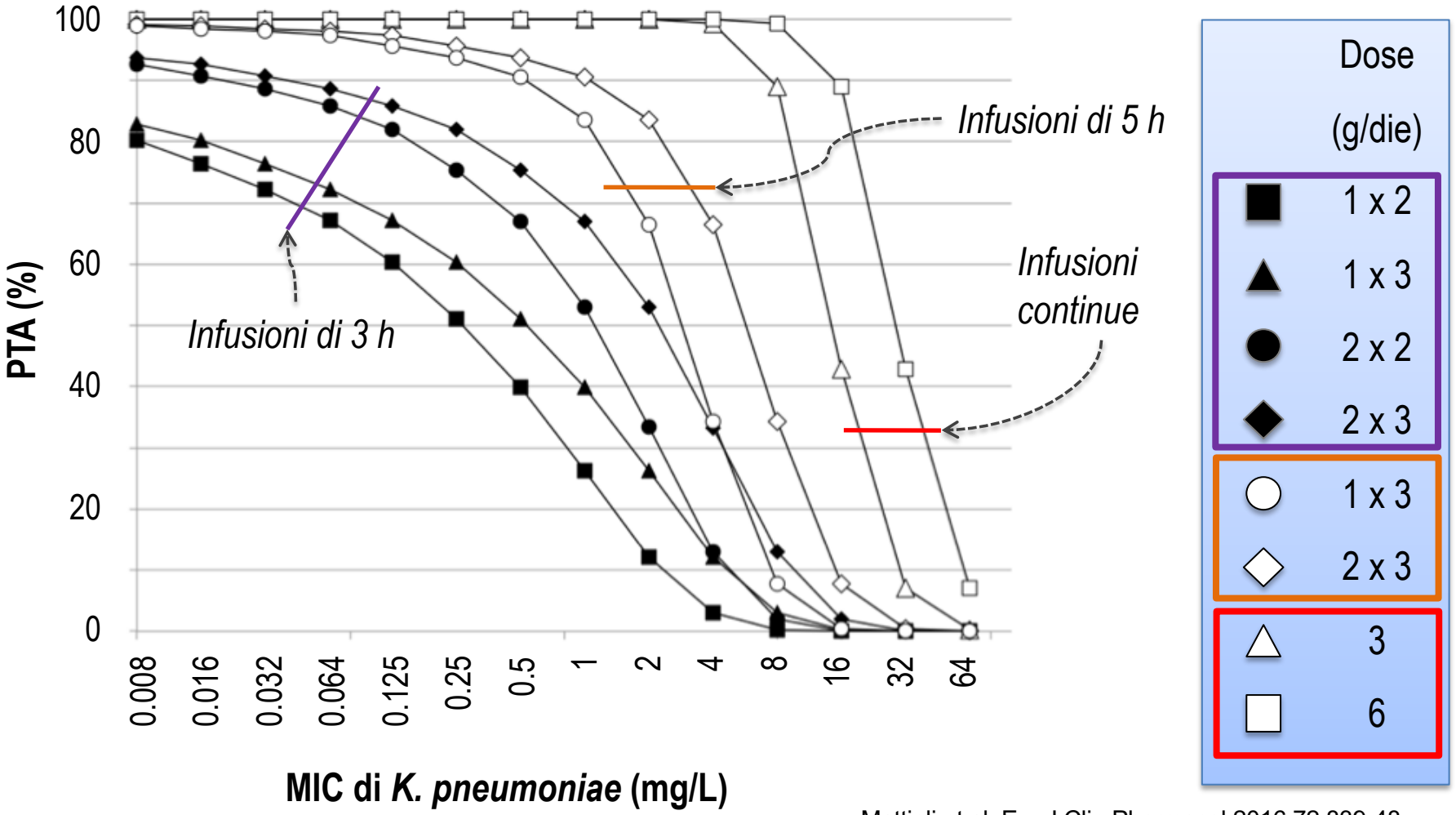


Meropenem	Pazienti
1g x 2	2
1g x 3	2
2g x 2	5
2g x 3	17
3g x 3	1

Note. I valori sono espressi come media±deviazione standard (mediana); *, differenze statisticamente significative per genere (test *t* di Student). **Abbreviazioni**: BSA, superficie corporea; BMI; indice di massa corporea

Probabilità di raggiungere l'obiettivo (PTA)

C_{min}>4xMIC



Mattioli et al. Eur J Clin Pharmacol 2016;72:839-48

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Antibiotic Kinetics

FARMACOCINETICA DEGLI ANTIBIOTICI NEI PAZIENTI CRITICI

CODICE: NCT02609646

Conclusioni

- La resistenza ai farmaci antimicrobici è un fenomeno di rilievo per la diffusione sempre maggiore di ceppi resistenti e la ridotta disponibilità di trattamenti farmacologici efficaci
- Numerosi fattori possono concorrere all'instaurarsi di resistenze e alla loro diffusione
- L'adozione di comportamenti appropriati può rappresentare un'efficace soluzione (seppur parziale in alcuni contesti)