Protocolli di terapia delle infezioni da batteri multiresistenti

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Università degli Studi di Verona

VENEZIA 5.10. 2013

Presidente: Prof. Enzo Raise

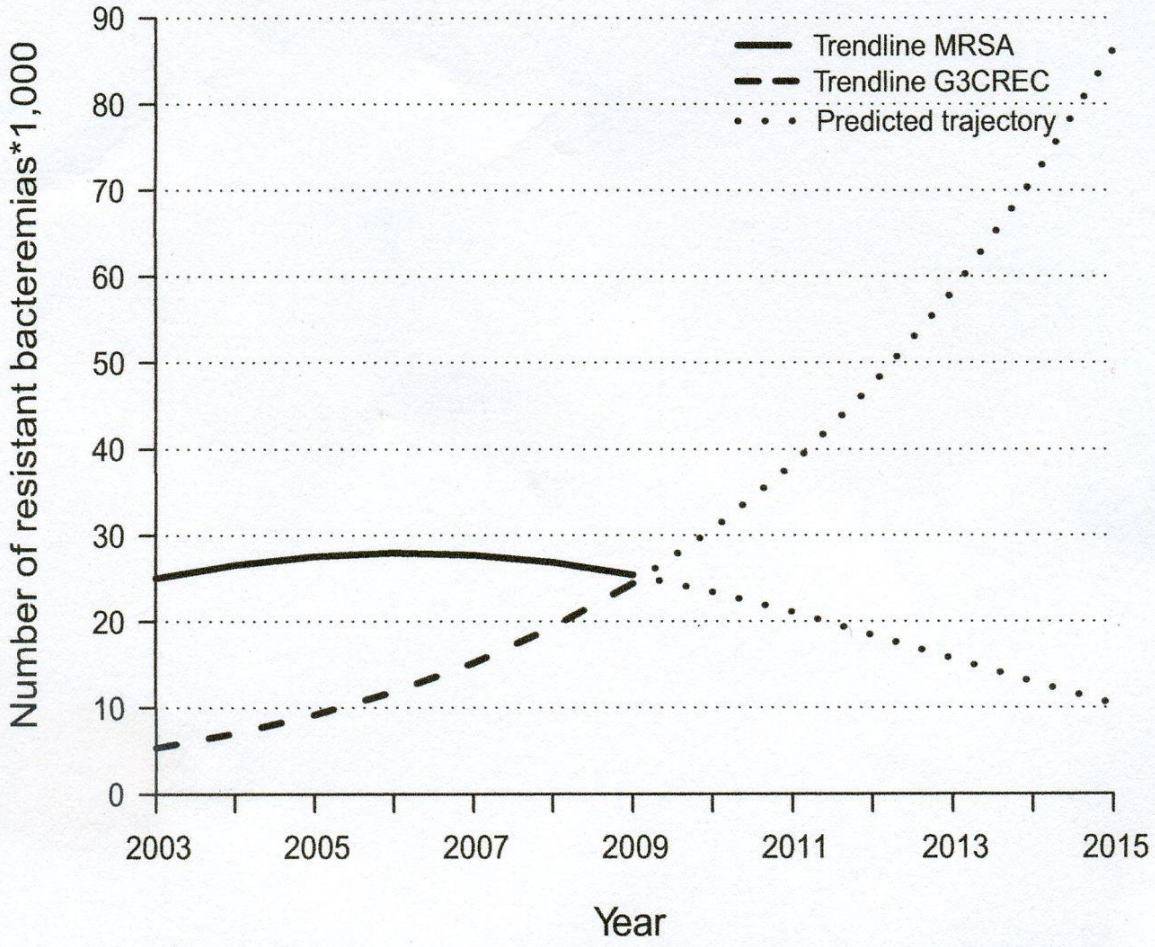


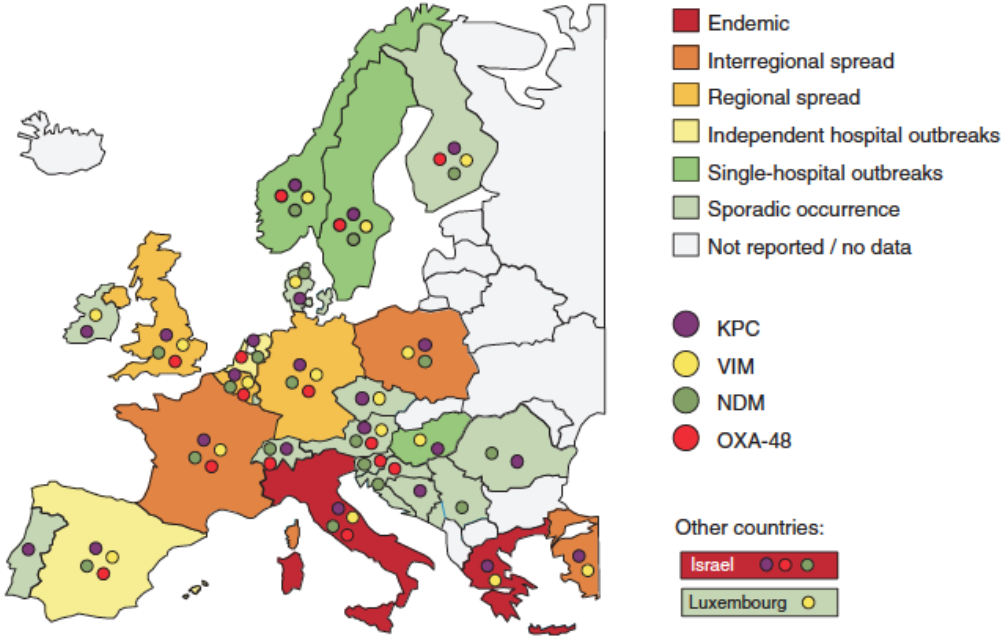
Figure 1. Trends in the estimated number of MRSA and G3CREC bacteremias in the European region. Extrapolated EARSS numbers for 2003–2009, and future trajectories based on regression analysis for 2010–2015.
doi:10.1371/journal.pmed.1001104.g001

Enterobacteriaceae non- suscettibili ai carbapenemici in Europa

- **2010**

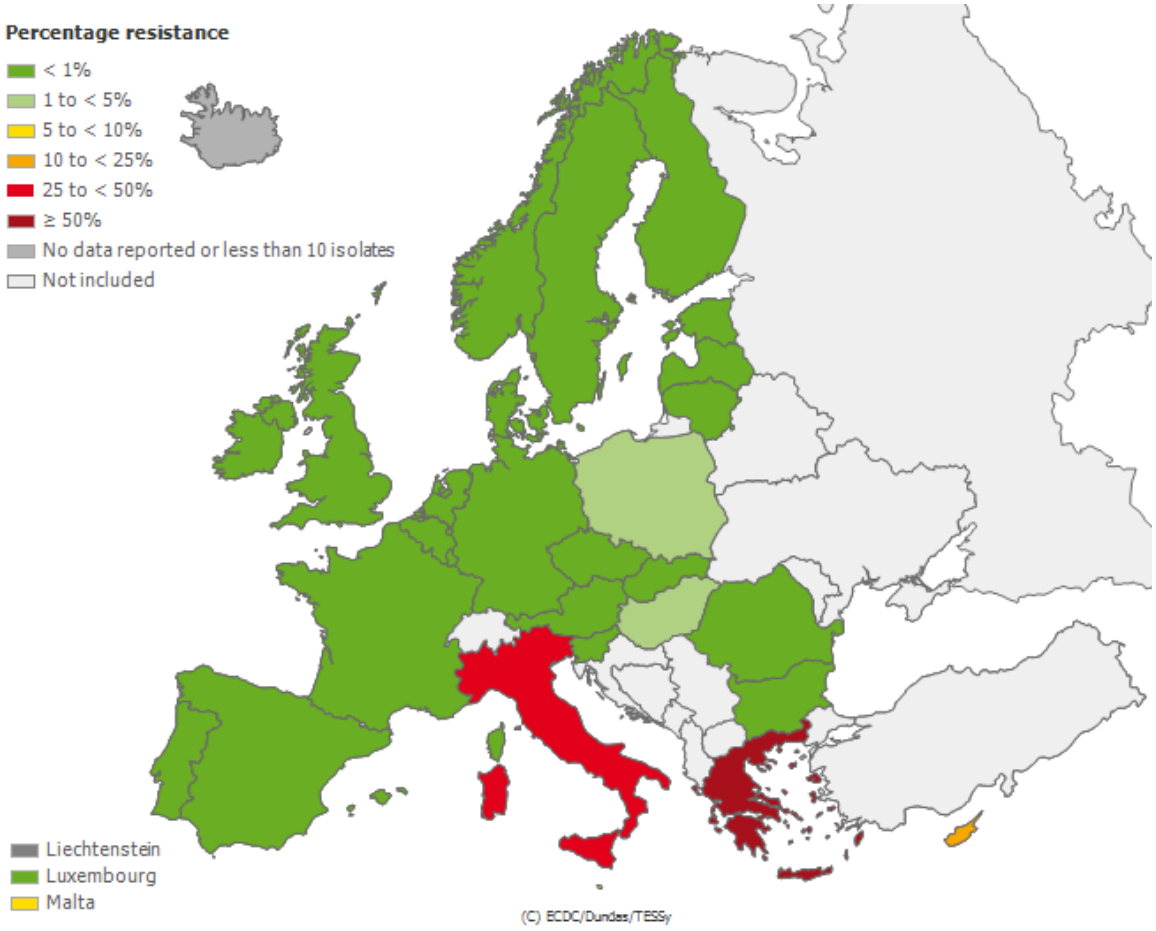
. 2011

- **Grado 5** (endemiche): Grecia e Israele
- **Grado 4** (diffusione inter-regionale): **Italia** e Polonia
- **Grado 3** (outbreaks regionali): Francia, Germania, Ungheria
- **Grado 2a** (singolo outbreak ospedaliero): Belgio, Spagna, Inghilterra/Galles
- **Grado 2b** (sporadici outbreaks ospedalieri): Cipro, Paesi Bassi, Svezia, Norvegia, Scozia
- **Grado 1** (segnalazioni sporadiche)
- Grado 0 (nessuna segnalazione)



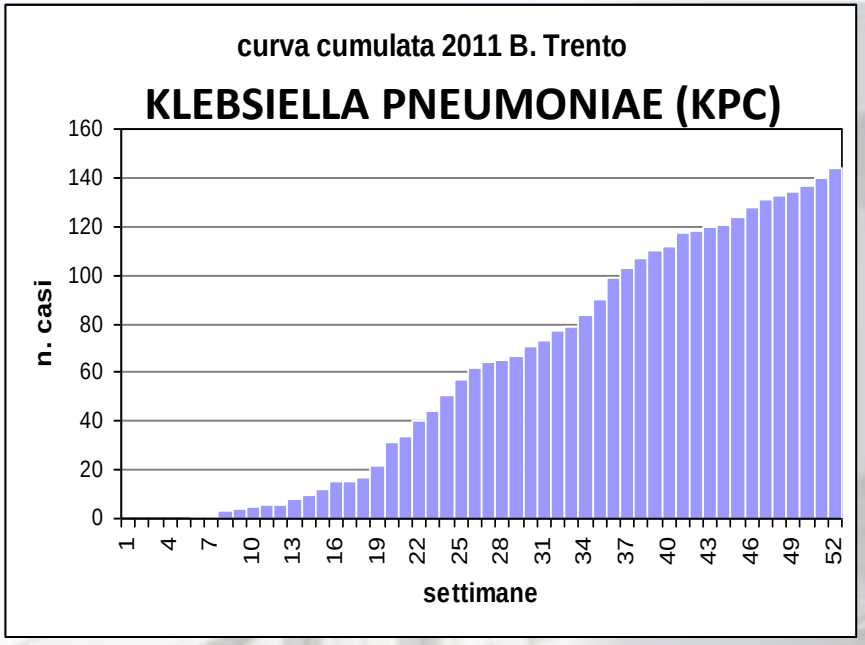
CMI 2012;18(5):413-31

Proporzione di *K.pneumoniae* resistente ai carbapenemici (R +I) (2011)

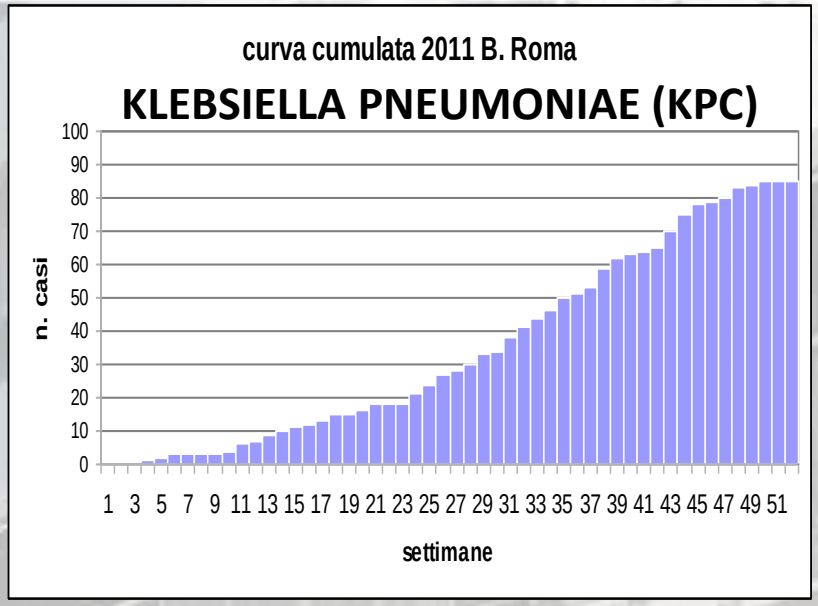


http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/maps_report.aspx (Aprile 2013)

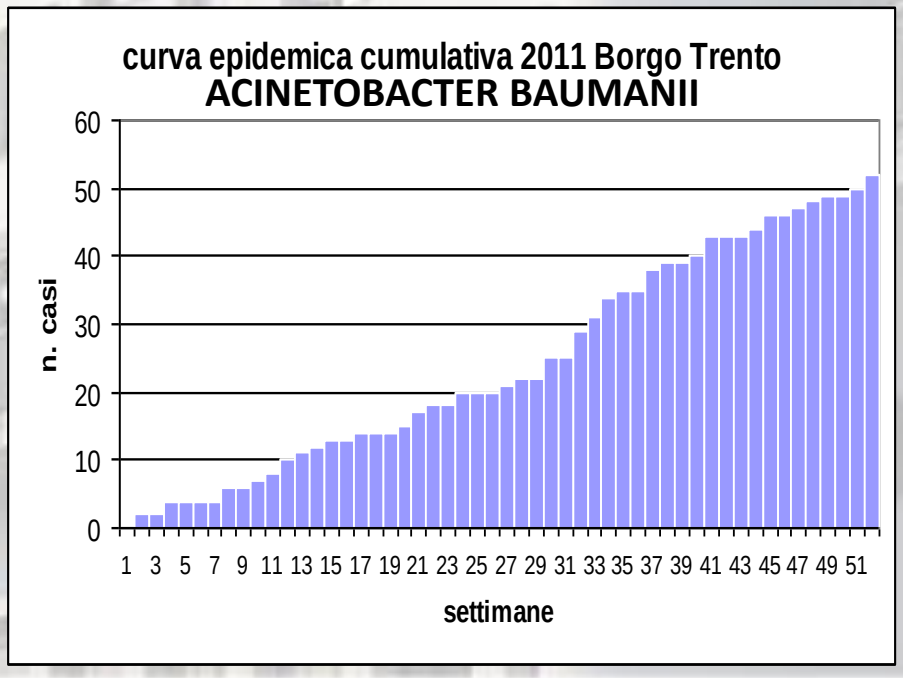
curva cumulata 2011 B. Trento



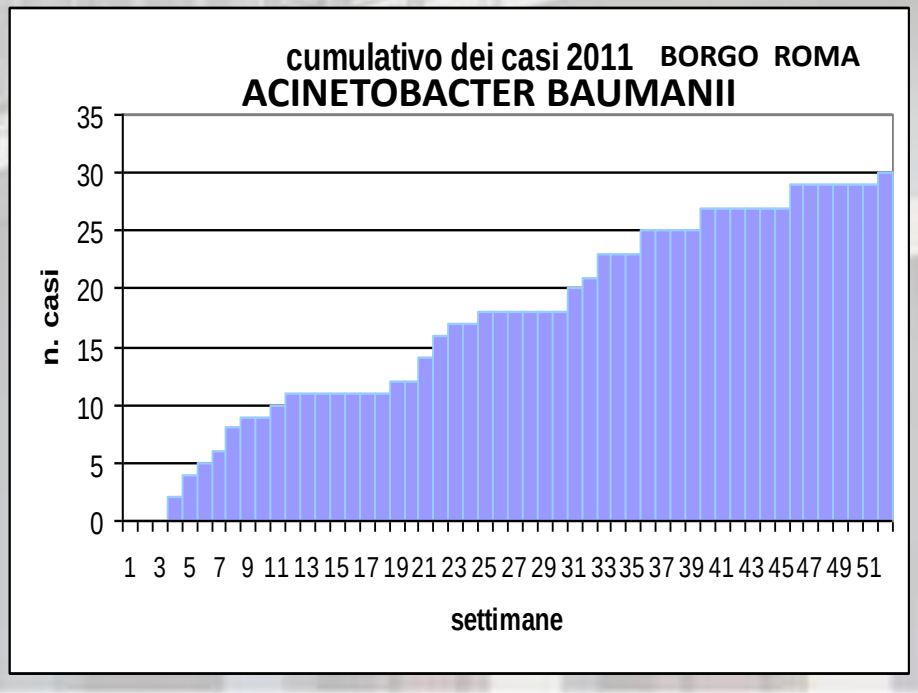
curva cumulata 2011 B. Roma



curva epidemica cumulativa 2011 Borgo Trento

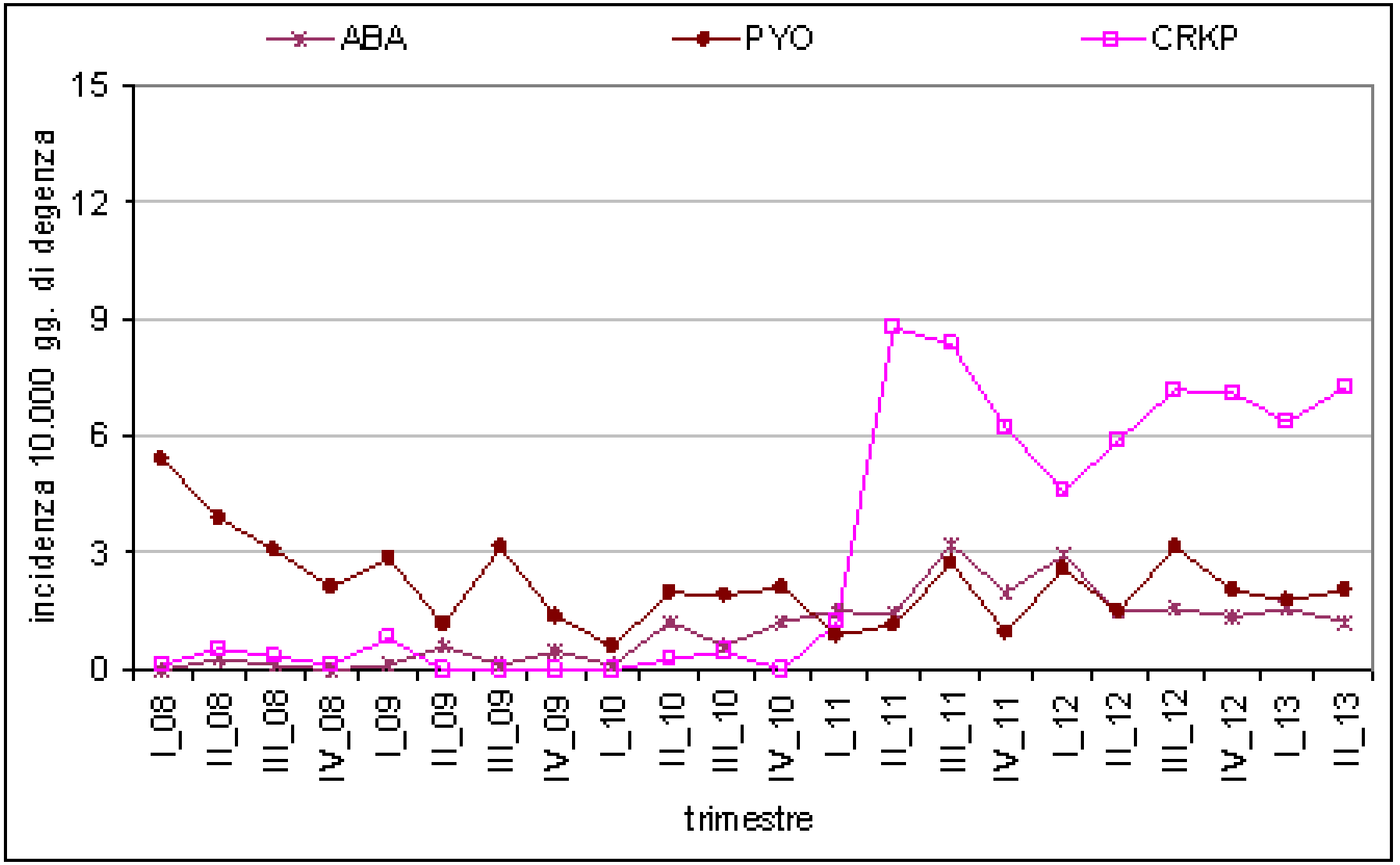


cumulativo dei casi 2011 BORGO ROMA



B. Trento

Acinetobacter baumani, Pseudomonas aeruginosa, Klebsiella pneumoniae



K. pneumoniae KPC: typical XDR phenotype

Antibiotic	MIC mg/L(S/I/R)
Amp/Sulb	>32 R
Pip/Tazo	>128 R
Ceftriaxone	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>32 R
Imipenem	>32 R
Meropenem	>32 R
Aztreonam	>64 R
Amikacin	>64 R
Gentamicin	2 S
Tobramycin	>16 R
Ciprofloxacin	>4 R
Fosfomycin	32 S
Tigecycline	1.5 I
Colistin	0.4 S

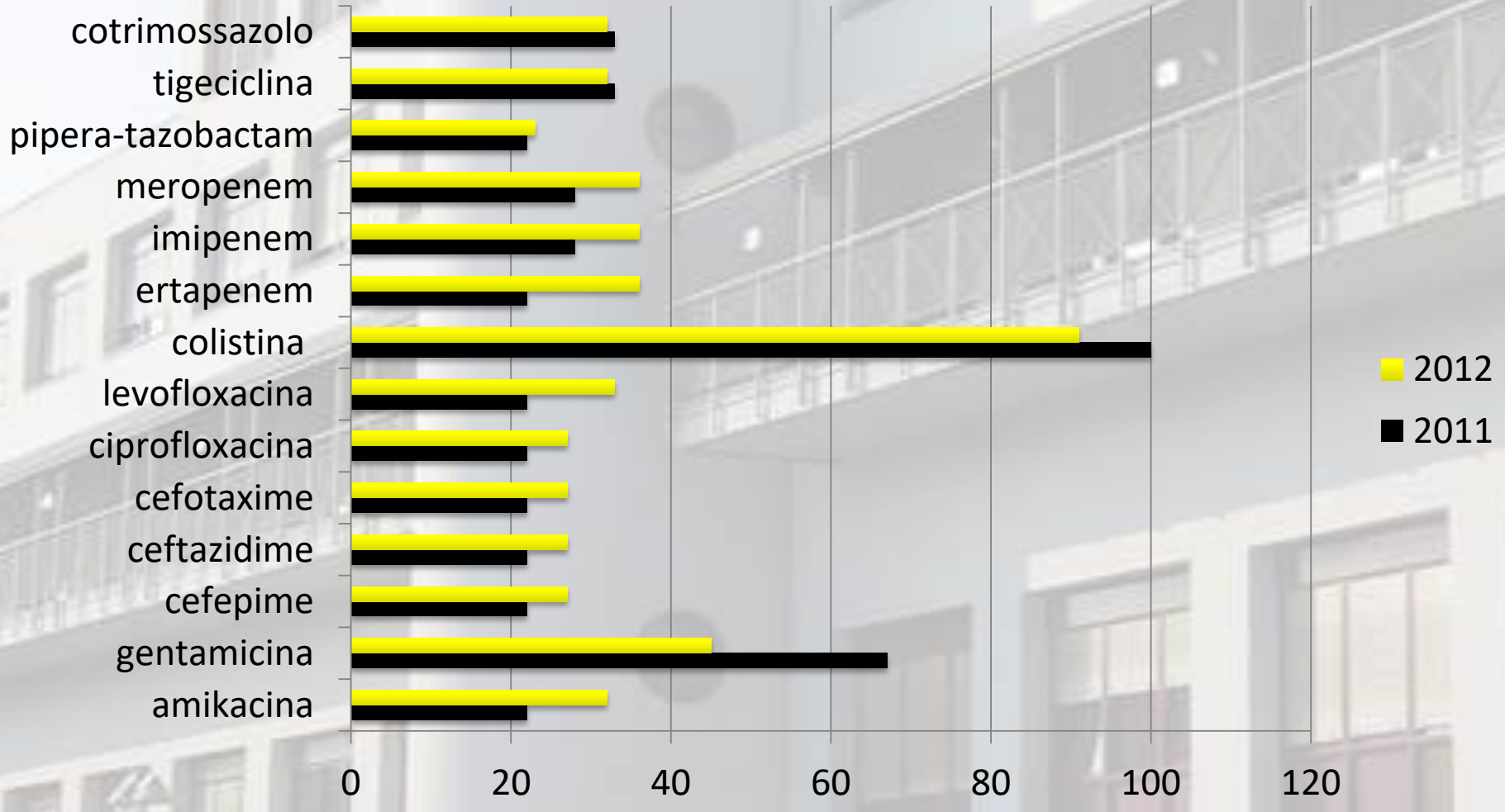
Treatment options:

- Colistin
- Carbapenem (especially if MIC relatively low)
- Tigecycline (HD)
- Gentamicin
- Fosfomycin HD
- Rifampin (test synergy)

Combination regimens (open issues)

Hirsch & Tam – JAC 2010
Qureshi *et al* – AAC 2012
Tumbarello *et al* - CID 2012

Sensibilità *K.pneumoniae* da materiali respiratori (UTI Borgo Roma)



Andamento dei casi di infezione / colonizzazione da K. pneumoniae produttore di carbapenemasi (CRKP) presso l'Azienda Ospedaliera Integrata di Verona

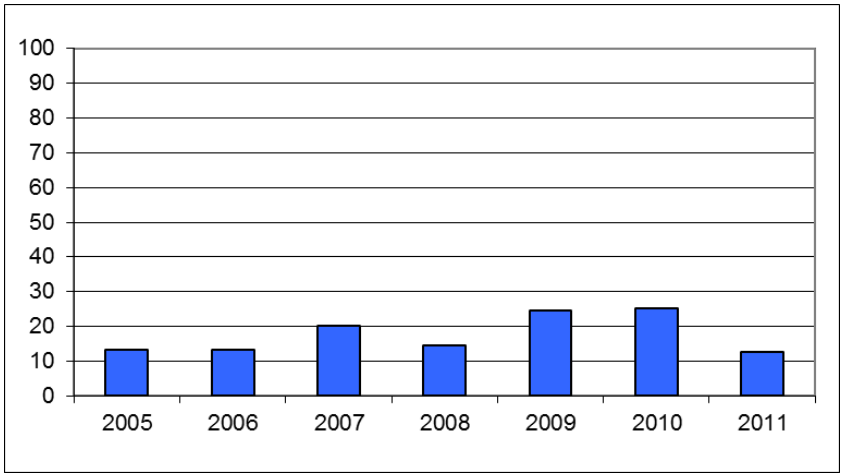
Caratteristiche dei pazienti con infezione/colonizzazione di *K. pneumoniae* produttore di carbapenemasi, alla 39ª settimana. Anno 2011.

	AOUI	B.go Trento	B.go Roma
Casi, N	174	111	63
Maschi, N(%)	81 (46.5)	45 (40.5)	36 (57.1)
Età			
media (range)	73.2 (21-97)	73.6 (21-97)	72.6 (22-93)
mediana (IQR)	78 (68-85)	78 (68.5-85)	77 (66-85)
Giorni dal ricovero			
media (range)	17.8 (0-79)	15.8 (0-68)	21.3 (1-79)
mediana (IQR)	13 (4-29)	12 (3.5-23.5)	17 (4-36)
Isolamento all'ingresso*, N(%)	37 (21.3)	25 (22.5)	12 (19.0)

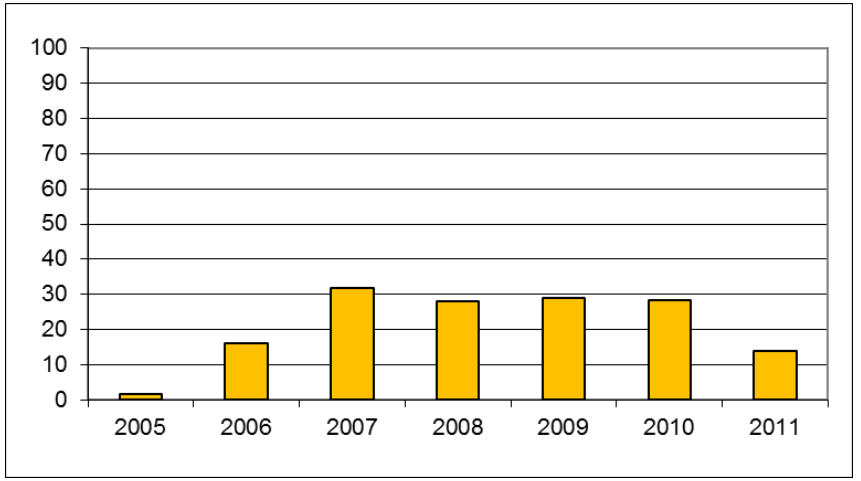
* isolamento di CRKP entro 2 giorni dal ricovero

Frequenza dei ceppi di E. coli e K. pneumoniae produttori di ESBL in Terapia Intensiva vs Geriatria

Terapia Intensiva



Geriatrie



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DIPARTIMENTO RIABILITATIVO
U.O.C. RIABILITAZIONE

U.O.S. Riabilitazione Pneumologica

Alla c.a. dei Direttori delle Terapie
Intensive,
al Direttore della 1°, 2° e 3° Geriatria,
della Geriatria Clinicizzata,
della Pneumologia
dell'**Ospedale di Borgo Trento**

e al direttore dell'UTI
del **Policlinico di Borgo Roma**

e al Direttore dell'UTI,
della geriatria
e della Lungodegenza
POLO UNICO
San Bonifacio

In ordine ai recenti casi di contaminazione da K Pneumoniae e di Clostridium difficilis su Pazienti trasferiti dalle sedi indicate, in accordo con la Direzione Medica di questa Azienda e per protocollo interno, comunico che *temporaneamente non saranno più accolti Pazienti senza documentazione laboratoristica di negatività per i batteri indicati.*
Rimango a disposizione per ogni chiarimento nell'auspicata e prevista risoluzione del problema.

Verona, 01/07/2011

rischio di infezione da parte di questo germe è basso negli adulti e nei bambini sani (maggiore attenzione va posta nei confronti dei neonati e bambini con deficit del sistema immunitario). Non saranno necessarie precauzioni particolari per il lavaggio di indumenti e stoviglie. Ricordi comunque a tutti di lavarsi le mani frequentemente. È necessario lavarsi le mani sempre prima di mangiare e dopo essere andato al bagno. Se a casa c'è una persona ammalata, chieda al suo medico se devono essere prese particolari precauzioni per prevenire la trasmissione di questo germe.

- **QUESTO GERME PUÒ ESSERE ELIMINATO?** In genere questo germe viene eliminato spontaneamente dall'organismo in un tempo variabile. Si può eseguire un esame per vedere se si è ancora portatori di questo germe nell'intestino (tampone rettale "per ricerca Klebsiella MDR"). I farmaci utilizzati per la cura delle infezioni dovute a questo germe non sono ritenuti utili per accelerare l'eliminazione del batterio in caso di semplice colonizzazione.
- **COME MI DEVO COMPORTARE IN CASO DI UN ULTERIORE RICOVERO?** Se lei dovesse avere in futuro bisogno di cure mediche o necessitasse di altri ricoveri in strutture sanitarie, informi i sanitari della positività per "Klebsiella pneumoniae produttore di carbapenemasi" che le è stata riscontrata durante l'attuale ricovero. Se Lei dovesse ancora risultare positivo, probabilmente verranno di nuovo usate queste precauzioni.

GRAZIE PER L'ATTENZIONE!

POSITIVITÀ PER KLEBSIELLA PNEUMONIAE RESISTENTE AI CARBAPENEMICI
INFORMAZIONI PER PAZIENTI E LORO FAMILIARI

Uno degli esami eseguiti durante il ricovero ha evidenziato che Lei è portatore di un germe (Klebsiella pneumoniae) resistente a molti degli antibiotici attualmente a nostra disposizione.

- **COS'È UN GERME RESISTENTE AGLI ANTIBIOTICI?** gli antibiotici sono medicinali utilizzati per combattere ed eliminare i batteri che causano infezioni. Un **batterio resistente** ad un antibiotico non viene ucciso da quello specifico antibiotico. Questo comporta la necessità di usare antibiotici alternativi che a volte possono avere maggiori effetti collaterali. In particolare, la Klebsiella pneumoniae isolata dal Suo organismo produce una sostanza (chiamata carbapenemasi) che è in grado di distruggere gli antibiotici carbapenemici, rendendoli inefficaci. Questo batterio si chiama per tanto "Klebsiella pneumoniae produttore di carbapenemasi".
- **CHE COSA È LA KLEBSIELLA PNEUMONIAE?** È un germe che, come altri batteri, **fa parte della normale flora intestinale** e quindi è necessario per mantenere la

Sede Legale Azienda Ospedaliera Universitaria Integrata: P.le A. Stefani, 1 - 37126 VERONA - Tel 045/812 1111 - Fax 045/916735
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Table 1. Antibiotic options for the treatment of MDROs (multidrug-resistant organisms)

MDRO type	Resistance pattern	Therapeutic options
MRSA	R to all β-lactam antibiotics—penicillins, cephalosporins, carbapenems	Glycopeptides (e.g., vancomycin or teicoplanin), oxazolidinone (e.g., linezolid), glycylcycline (e.g., tigecycline) and lipopeptide (e.g., daptomycin)
VRE	R to glycopeptides	Oxazolidinone (e.g., linezolid), glycylcycline (e.g., tigecycline) and lipopeptide (e.g., daptomycin)
ESBL	R to all cephalosporins and aztreonam	Carbapenems (e.g., imipenem, meropenem, ertapenem), aminoglycosides (e.g., gentamicin, amikacin based on susceptibility), BL-BLI (e.g., piperacillin-tazobactam in selected cases), polymyxin (e.g., colistin) and glycylcycline (e.g., tigecycline)
AmpC	Inducible cephalosporin resistance	Carbapenems (e.g., imipenem, meropenem), polymyxin (e.g., colistin) and glycylcycline (e.g., tigecycline)
MBL	R to carbapenems, penicillins, cephalosporins	Polymyxin (e.g., colistin) and glycylcycline (e.g., tigecycline)
Colistin R GNB	R to carbapenems, penicillins, cephalosporins, polymyxins	Glycylcycline (e.g., tigecycline, in few cases), fosfomycin (in few cases), no effective agent for serious systemic infections in neutropenic patients

R, resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant Enterococci; ESBL, extended spectrum β-lactamase producers; MBL, metallo-β-lactamase or carbapenemase producers; GNB, Gram-negative bacilli; BL-BLI, β-lactam + β-lactamase inhibitor.

S. Bhattacharya – Virulence 2013

TABLE 3. Clinical Risk Factors Associated With Mortality Among Patients With Carbapenem-Resistant *Klebsiella pneumoniae* Infection, From July 1, 2004, to June 30, 2006

Risk factor	Patients who died ($n = 48$)	Patients who survived ($n = 51$)	Univariable analysis OR (95% CI)	Univariable analysis *P*	Multivariable analysis OR (95% CI)	Multivariable analysis *P*
Patient-specific risk factor						
Age, mean ± SD, years				.24		
Diabetes				.97		
HIV infection				.99		
Heart disease				.02	4.56 (1.26–16.55)	.02
Liver disease				.20	2.36 (0.80–6.91)	.12
Renal insufficiency				.02	2.75 (0.93–8.17)	.07
Transplant recipient				.96		
Healthcare-associated risk factor						
Length of stay before infection, mean ± SD, days				.35		
Use of CVC				.10	2.41 (0.26–17.43)	.50
Receipt of mechanical ventilation				.06	0.51 (0.10–2.66)	.15
ICU stay				.009	11.10 (1.85–66.95)	.009
Therapeutic intervention						
Use of antibiotics with in vitro activit				.20	2.30 (0.73–7.24)	.15
Delay in antibiotic therapy with in vitro activity, mean ± SD, days				.98		
Adjunctive therapy[a]				.004	0.14 (0.04–0.49)	.002

MORTALITA' CRUDA:
KPC +: 48%
KPC - :20%

MORTALITA' ATTRIBUIBILE:
KPC +: 38%
KPC-: 12%

I pts con infezione da KPC+ hanno una probabilità **4 volte maggiore** di morire per l'infezione rispetto ai pazienti con infezione da KPC -

NOTE. Data are no. (%) of patients, unless otherwise indicated. Univariable and multivariable analyses were performed by conditional logistic regression. Only those variables that achieved a *P* value of .02 or less in the univariable analysis were included in the multivariable analysis. CI, confidence interval; CVC, central venous catheter; HIV, human immunodeficiency virus; ICU, intensive care unit; OR, odds ratio; SD, standard deviation.

[a] Procedure employed to treat the infection by removing the probable focus of the infection (eg, debridement, drainage, or catheter removal).

ICHE 2008;29(12):1099-106

Pazienti con isolamenti di batteri multiresistenti

1. Non trattare mai i pazienti colonizzati
2. Non usare mai la colimicina o la fosfomicina da sole
3. Nelle infezioni da germi multiresistenti la scelta dell'antibiotico e anche le dosi devono essere basate sul valore delle CMI in rapporto al breakpoint.
4. In caso di panresistenze occorre chiedere al laboratorio studi di sinergia in vitro
5. I tentativi di decolonizzare con antibiotici per via orale (gentamicina 80 mg x 3 /die) non hanno, a tutt'oggi, sufficiente ed adeguata documentazione

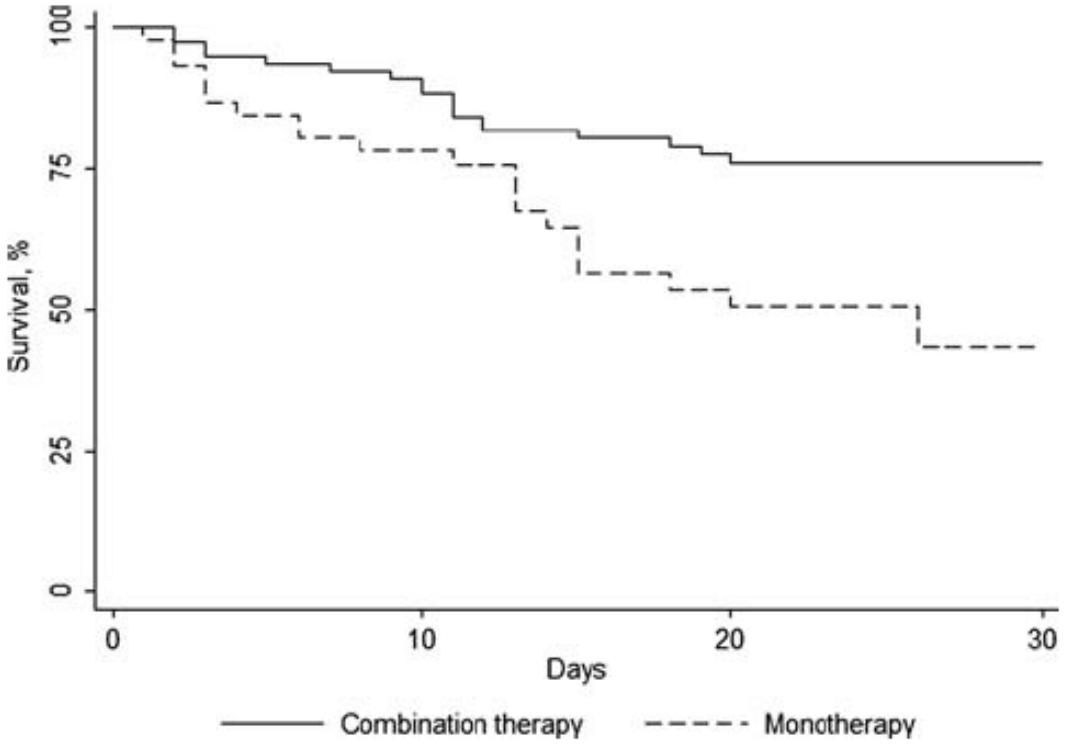

Figure 2. Kaplan-Meier curves showing the impact of combination therapy (solid line) versus monotherapy (dotted line) on 30-day mortality of patients with *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae* isolate bloodstream infections ($P = .002$).

Tumbarello M et al. CID 2012;55:943-50

Table 4. Outcomes of the 36 Bloodstream Infections Treated With Combination Therapy Including Meropenem Stratified by Meropenem Minimum Inhibitory Concentration

		No. (%)	
Meropenem MIC (mg/L)	Total	Nonsurvivors	Survivors
1	1	0	1 (100)
2	4	0	4 (100)
4	10	2 (20)	8 (80)
8	4	1 (25)	3 (75)
≥16	17	6 (35.2)	11 (64.7)
Total	36	9 (25)	27 (75)

Abbreviation: MIC, minimum inhibitory concentration.

Tumbarello M et al. CID 2012;55:943-50

T. Halaby AAC 29 april 2013

- Emergence of colistin resistance in Enterobacteriaceae after the introduction of selective digestive tract decontamination in an intensive care unit

- “In conclusion colistin resistance among ESBL –Kp isolates emerged rapidly after SDD. In addition both the occurence and the proportion of tobramycin resistance among CIR increased under the use of SDD”.

Pazienti con isolamenti di batteri multiresistenti

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2. Non usare mai la colimicina o la fosfomicina da sole
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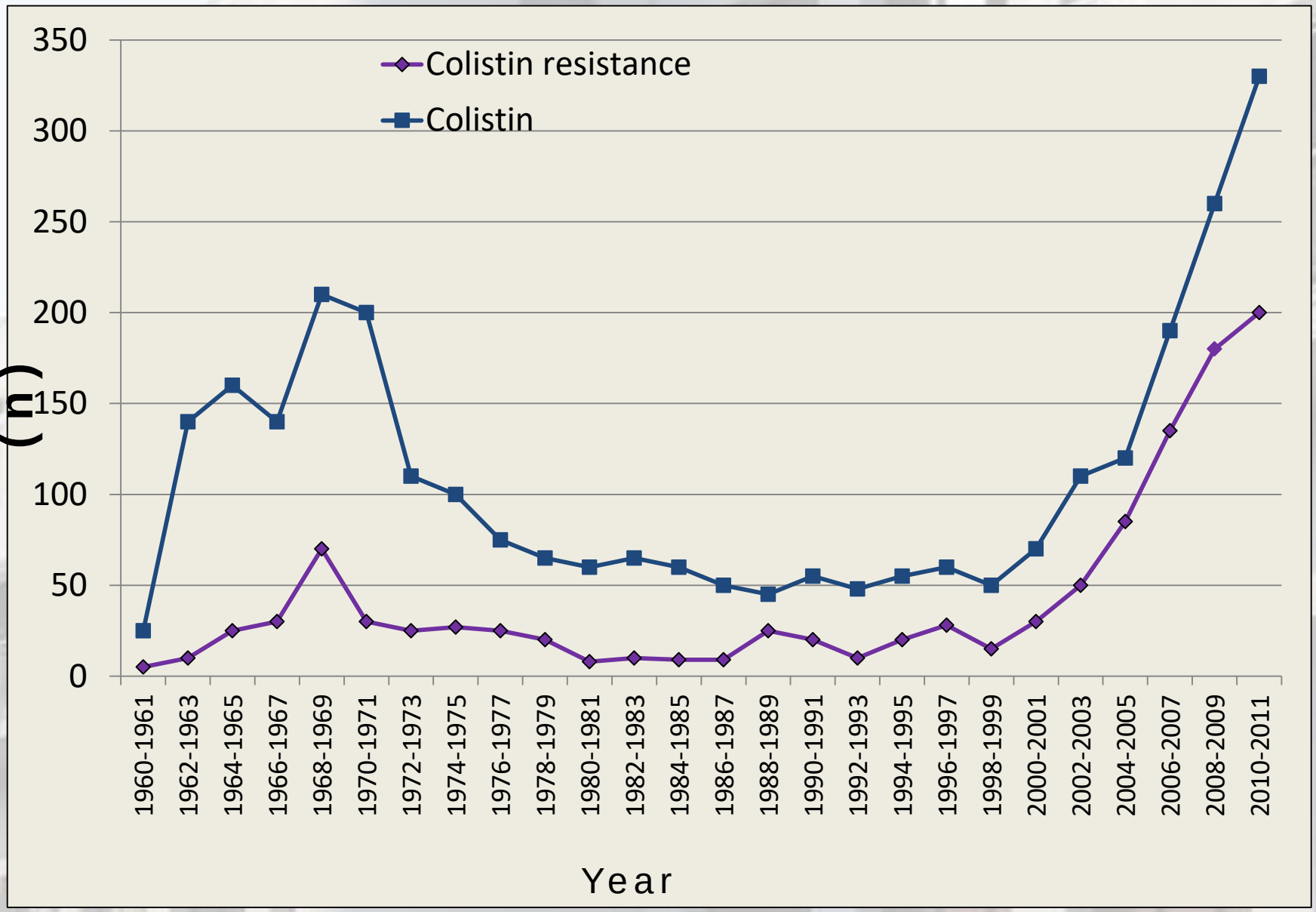
- Paziente di anni 62 affetto da cirrosi epatica esotossica scompensata con ascite refrattaria. Viene messo in lista per trapianto di fegato. Si riscontra positività colturale per KPC al tampone rettale e faringeo. ??????
- Si decide di eseguire decolonizzazione, prima del trapianto, con COLIMICINA soluzione orale (1 M x 4 al dì) + GENTAMICINA soluzione orale (80 mg x 4 al dì) per 7 giorni.

- Alla fine del ciclo i tamponi risultarono negativi. Il paziente venne sottoposto a trapianto in data 10.7.2013 (fu profilassato con colimicina, meropenem e tigeciclina)
- In seguito il paziente ridivenne positivo per KPC al tampone rettale; non sviluppò comunque patologie sistemiche batteriche.
- Attualmente (23.09.13) il paziente è ancora colonizzato ma gode di buona salute.

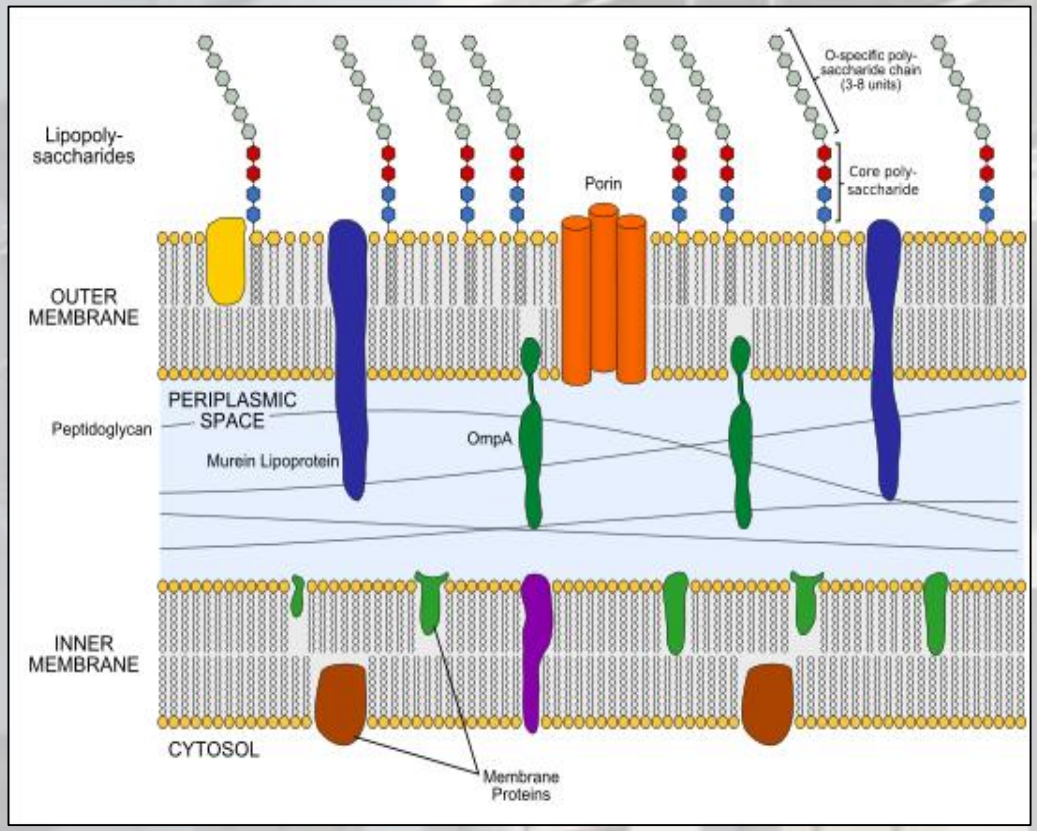
COLIMICINA

Colistin : increased trend in n° pubblications



Colistin: mechanism of action

- **Si lega al LPS anionico della membrana cellulare esterna dei gram-negativi spiazzando ioni calcio e magnesio e così determinando alterazioni della permeabilità nell'envelope cellulare, fuoriuscita del contenuto e conseguente morte cellulare**



Spettro d'attività in vitro della colistina

	Entérobactéries	Pseudomonas	Autres bacilles à Gram négatif	Anaérobies
Germes sensibles	*E. coli* *Citrobacter* *Klebsiella* *Enterobacter* *Morganella* *Salmonella* *Shigella*	*P. aeruginosa* *P. fluorescens* *P. putida* *P. maltophilia*	*Acinetobacter* *S. maltophilia* *Moraxella* *H. influenzae* *Bordetella* *Pasteurella* *L. pneumophila*	*B. melaninogenicus* *B. oralis*
Germes résistants	*Proteus* *Providencia* *Serratia* *Brucella* *Nocardia* *Camplylobacter*	*P. pseudomallei* *P. cepacia* *P. picketti*	*V. cholerae* *V. el tor*	*B. fragilis*

Sono naturalmente resistenti cocchi Gram-negativi e Gram-positivi, bacilli aerobi Gram-positivi, anaerobi, funghi e parassiti.

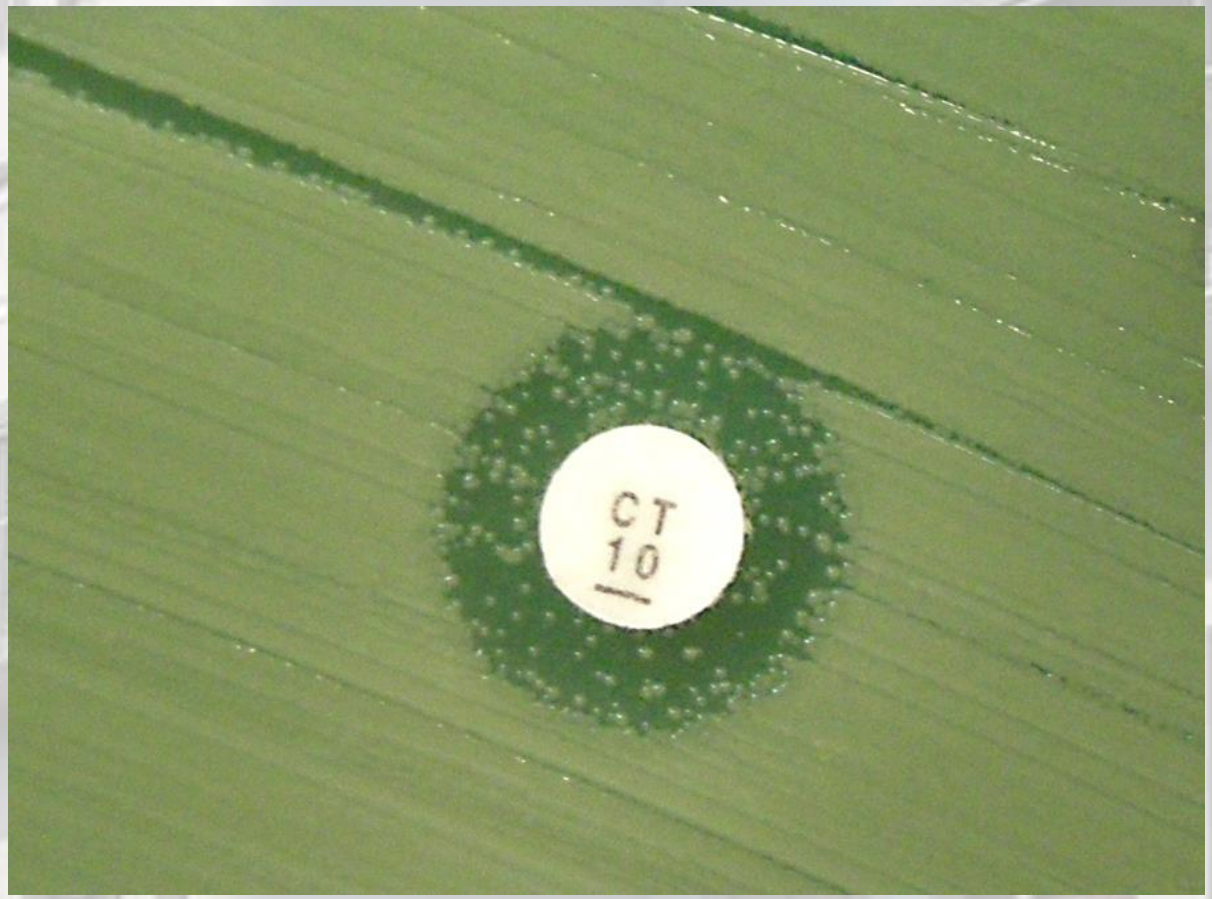
F. Menichetti – Infection 2010

Colistin heteroresistance

- The emergence of resistance to colistin by a subpopulation from an otherwise susceptible (MIC≤2 mg/L) population
- The proportion on cells exhibiting heteroresistance is significantly higher among *Acinetobacter* isolates recovered from patients treated with colistin

AAC (08)52:351

Eteroresistenza alla colistina in *Serratia*



- Colistin-resistant *K. pneumoniae, P. aeruginosa and A. baumanii* have steadily increased in the last years
- A high percentage of heteroresistant *A. baumanii* strains can be found, although the clinical implication of this phenomenon is not yet known
- Although the mechanism of action of colistin is due to a detergent effect that disrupts membrane integrity, another cytoplasmatic target can not be ruled out
- The main mechanism of resistance to colistin is mainly the modification of the LPS, although changes in OMP can not be discarded
- Acquisition of resistance to colistin can impair the virulence in *A. baumannii*.

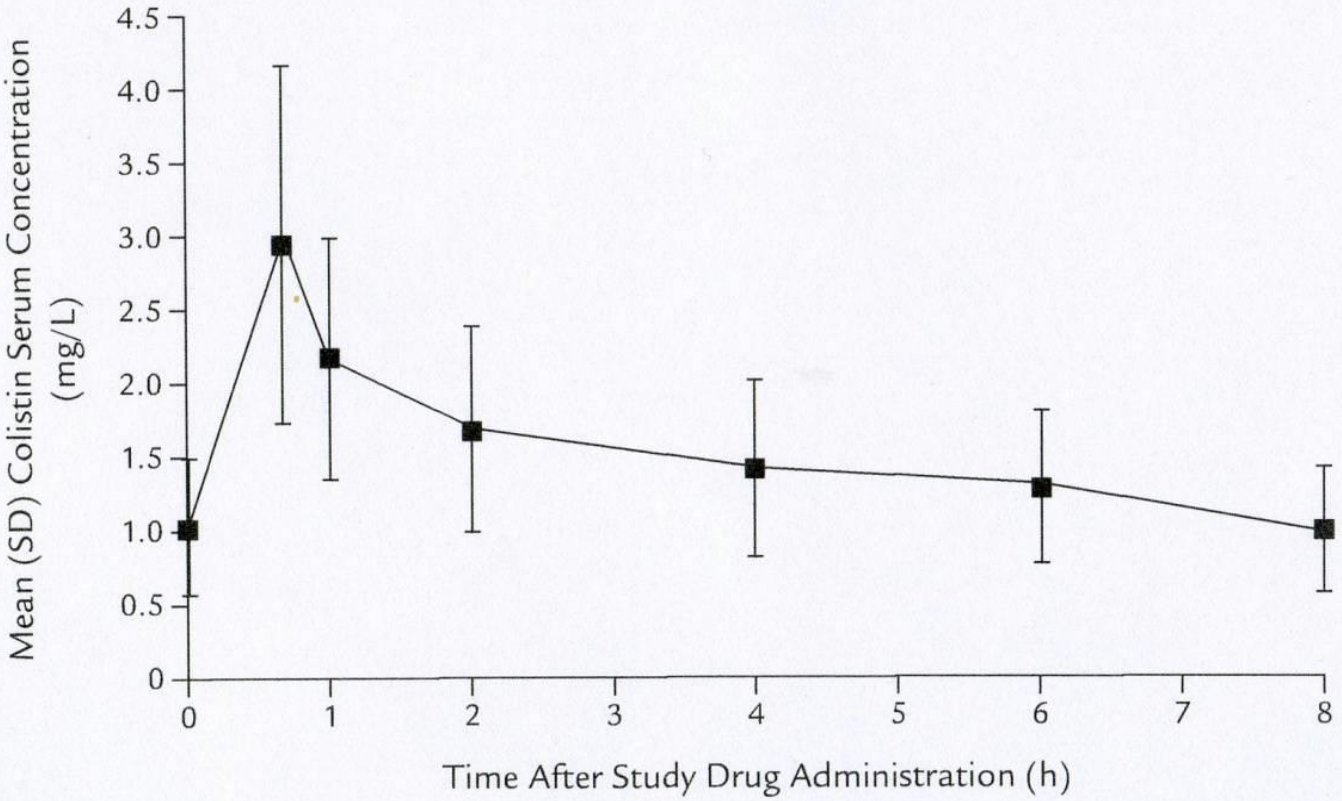


Figure. Mean (SD) colistin serum concentration versus time curve under steady-state conditions with colistin methanesulfonate 225 mg q8h (n = 11).

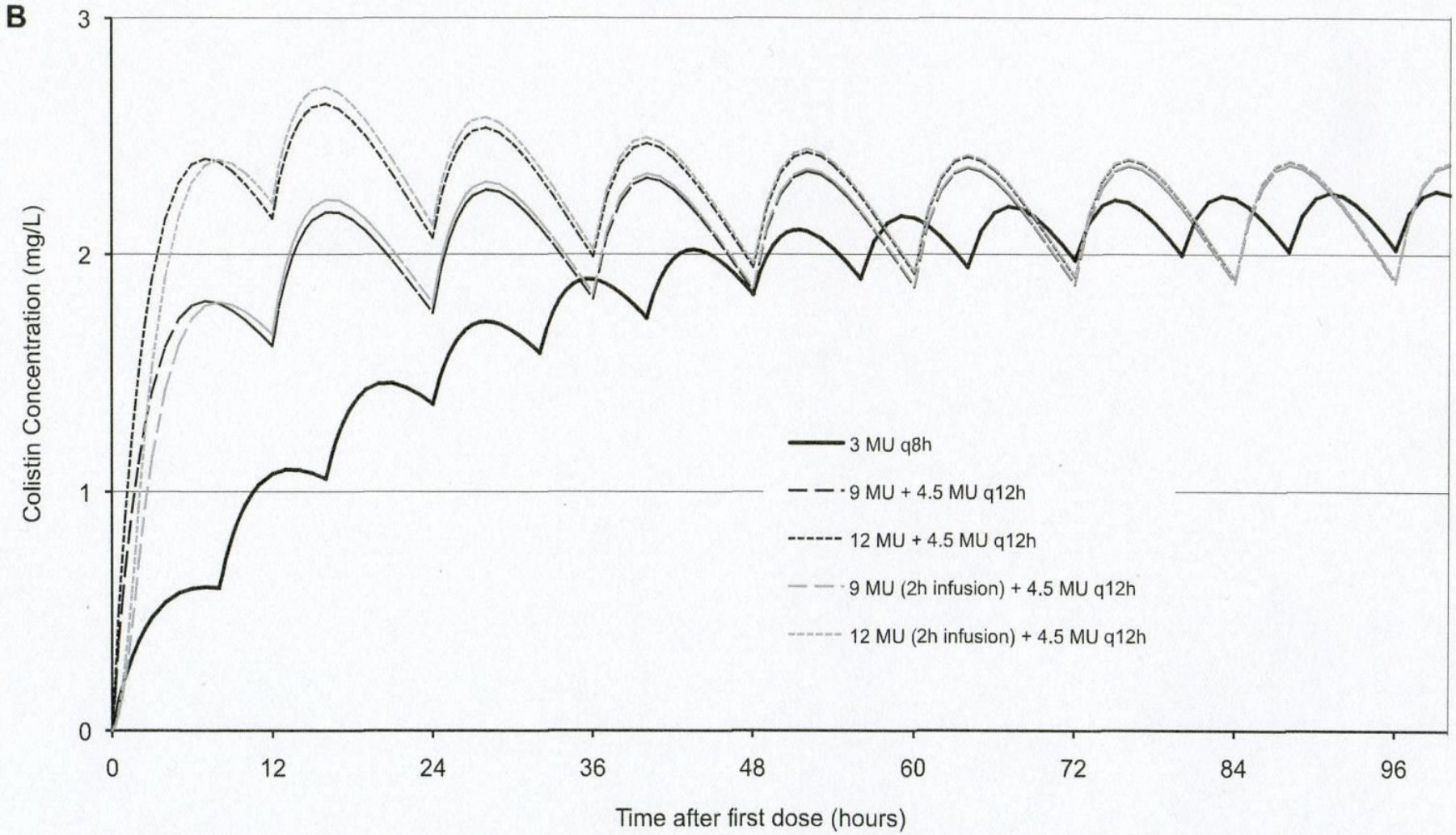


FIG. 4. Model-predicted CMS (A) and colistin (B) concentrations in a typical patient following the use of the current dosing regimen (3 MU as a 15-min infusion of CMS every 8 h [q8h]) and alternative dosing regimens with loading doses of 9 or 12 MU CMS as infusions of 15 min or 2 h and a maintenance dose of 4.5 MU CMS every 12 h (q12h).

Pharmacokinetics of Three Different Dosing Regimens of Colistin with Meaning for Optimum Use

A. SKIADA et al.; Laikon Hosp., Univ. of Athens, Athens, Greece.

Parameters	Substance	Treatment regimens		
		3MU q 8h	4.5 MU q 12h	9 MU q 24h
AUC (mg.h/L)	CMS Colistin	12.38±2.41 11.42±1.91	13.34±3.05 13.70±2.27	23.48±3.72 22.43±3.88
$t_{1/2}$ (h)	CMS Colistin	8.3±1.3 7.8±1.7	9.2±1.4 8.8±1.6	11.4±1.5 9.6±1.4
Cmax (mg/L)	CMS Colistin	4.38±1.56 3.34±0.89	4.75±1.37 2.98±0.74	8.23±2.58 5.63±1.97
Cmin (mg/L)	CMS Colistin	2.66±0.79 2.07±0.38	3.43±1.12 1.64±0.53	2.63±0.88 2.61±0.84
Vd (L)	CMS Colistin	124.7±16.8 142.4±31.8	135.8±20.7 118.8±23.2	156.4±19.6 154.2±2.74

ABSTRACT

Background. Colistin-only susceptible (COS) Gram Negative Bacteria (GNB) are emerging causes of severe nosocomial infections, reviving interest in the use of colistin. However, consensus on the most effective way to administer colistin has not yet been reached.

Methods. All patients with sepsis due to COS or minimally susceptible GNB, who received intravenous colistin were prospectically enrolled. Colistimethate sodium (CMS) dosing schedule was based on a loading dose of 9 MU, and a 9 MU two-daily fractioned maintenance dose, titrated on renal function. For each CMS course, clinical cure, bacteriological clearance, daily serum creatinine and estimated creatinine clearance were recorded.

Results. Twenty-eight infectious episodes due to *A. baumannii* (46.4%), *K. pneumoniae* (46.4%), and *P. aeruginosa* (7.2%) were analyzed. Main types of infection were bloodstream infections (64.3%) and ventilator-associated pneumonia (35.7%). Clinical cure was observed in 23 (82.1%) cases. Acute kidney injury developed during 5 treatment courses (17.8%), did not require renal replacement therapy, and subsided within 10 days from CMS discontinuation. No correlation was found between serum creatinine variation (baseline-peak) and daily and cumulative doses of CMS, and between serum creatinine variation (baseline-peak) and duration of CMS treatment.

Conclusions. Our study shows that in severe infections by COS-GNB, the high-dose extended interval CMS regimen has a high efficacy, without significant renal toxicity.

CID 2012

Effetto sinergico della polimixina con altri antimicrobici (checkerboard methods)

Organism (no. of isolates)	Polymyxin studied	Combined-drug synergy (% of isolates with synergy)	Reference
A. baumannii (13)	Colistin	Rifampin (85)	74
A. baumannii (5)	Polymyxin B	Rifampin (60); ampicillin-sulbactam (0)	172
A. baumannii (55)	Polymyxin B	Rifampin (76); imipenem (58)	26
A. baumannii (24)	Polymyxin B	Azithromycin (83); rifampin (54); meropenem (38); cotrimazole (25)	113
A. baumannii (5)	Colistin	Rifampin (80), meropenem (60), azithromycin (60)	174
A. baumannii (8)	Colistin	Rifampin (100)	104
A. baumannii (6)	Colistin	Rifampin (100)	16
P. aeruginosa (55)	Polymyxin B	Rifampin (0); imipenem (0)	26
P. aeruginosa (5)	Colistin	Rifampin (40); meropenem (0), azithromycin (0)	174
P. aeruginosa (7)	Colistin	Rifampin (14)	171
P. aeruginosa (10)	Polymyxin B	Azithromycin (60); imipenem (20); rifampin (10)	93
P. aeruginosa (40)	Polymyxin B	Rifampin (not stated)	165
K. pneumoniae (55)	Polymyxin B	Rifampin (46); imipenem (15)	26
S. marcescens (12)	Polymyxin B	Rifampin (100)	177
S. marcescens (12)	Polymyxin B	Rifampin (100)	134
S. marcescens (13)	Colistimethate	Cotrimazole (not stated); rifampin (not stated); chloramphenicol (not stated)	173

Landman D. et al. Clin Microb Reviews, 2008; 21: 449-465

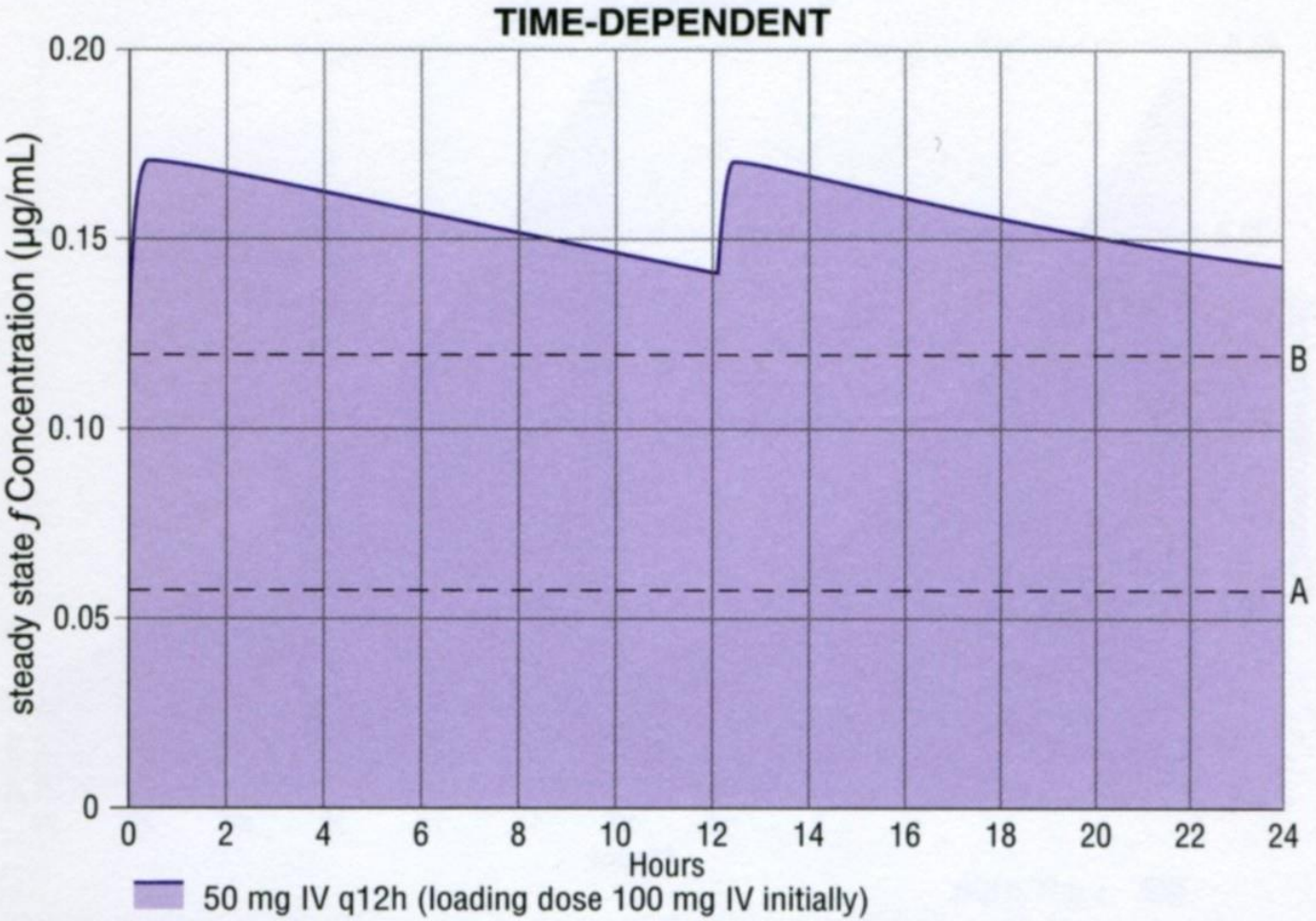
Terapia delle KPC (Kebsiella pneumoniae produttrice di carbapenemasi o altri enterobatteri produttori di carbapenemasi= CRE)

•COLIMICINA dose da carico 9 milioni poi 4,5 milioni x 2/die
+
MEROPENEM 2 gr x 3/die oppure IMIPENEM 1 gr x 3-4/die
+
TIGECICLINA 100-150 mg x 2/die

•COLIMICINA dose come sopra
+
MEROPENEM* o IMIPENEM dosi come sopra
+
FOSFOMICINA 4 gr x 4/die

* Scelta basata sul valore della CMI ; il carbapenemico deve essere utilizzato anche nei casi in cui le CMI superino, non di molto, il breakpoint di resistenza

Tigecycline IV



	MIC_{90}	Pathogen
A	0.06	*Streptococcus pyogenes*
B	0.12	*Staphylococcus aureus* MSSA
	0.25	*Staphylococcus aureus* MRSA

HD Tigecycline?

TABLE 1. Tigecycline: dose-related serum and urinary concentrations

Tigecycline initial i.v. dose (mg)	Serum concn[d] (μg/ml)	Urinary concn[d] (μg/ml)
100[a]	~1.5	~0.3
200[b]	~3.0	~0.6
400[c]	~6.0	~1.2

[a] Maintenance dose, 50 mg (i.v.) q12h.
[b] Maintenance dose, 100 mg (i.v.) q24h.
[c] Maintenance dose, 200 mg (i.v.) q24h.
[d] Values represent estimates.

B.A. Cunha JOURNAL OF CLINICAL MICROBIOLOGY, May 2009, p. 1613

Background: **Infections caused by multidrug-resistant gram-negative bacteria have caused a resurgence of interest in colistin. To date, information about pharmacokinetics of colistin is very limited in critically ill patients, and no attempts have been made to evaluate its concentration in BAL.**
Methods: **In this prospective, open-label study, 13 adult patients with ventilator-associated pneumonia caused by gram-negative bacteria were treated with colistin methanesulfonate (CMS) IV, 2 million International Units (174 mg) q8h, a usually recommended dose, for at least 2 days. Blood samples were collected from each patient at time intervals after the end of infusion. BAL was performed at 2 h. Colistin was measured by a selective, sensitive high-performance liquid chromatography-based method. Pharmacokinetic parameters were determined by noncompartmental analysis.**
Results: **Patients received 2.19 ± 0.38 mg/kg (range, 1.58-3.16) of CMS per dose. At steady state, mean ± SD plasma colistin maximum (Cmax) and trough (Ctrough) concentrations were 2.21 ± 1.08 and 1.03 ± 0.69 μg/mL, respectively. Mean ± SD area under the plasma concentration-time curve from 0 to 8 h (AUC_{0-8}), apparent elimination half-life, and apparent volume of distribution were 11.5 ± 6.2 μg × h/mL, 5.9 ± 2.6 h, and 1.5 ± 1.1 L/kg, respectively. Cmax/minimum inhibitory concentration (MIC) ratio and AUC_{0-24}/MIC ratio (MIC = 2 μg/mL) were 1.1 ± 0.5 and 17.3 ± 9.3, respectively. Colistin was undetectable in BAL. Nephrotoxicity was not observed.**
Conclusions: **Although the pharmacodynamic parameters that better predict the efficacy of colistin are not known in humans, in critically ill adult patients the IV administration of CMS 2 million International Units (174 mg) q8h results in apparently suboptimal plasma concentrations of colistin, which is undetectable in BAL. A better understanding of the pharmacokinetic-pharmacodynamic relationship of colistin is urgently needed to determine the optimal dosing regimen.**

CHEST 2010; 138(6):1333–1339

Abbreviations: AUC = area under the plasma concentration-time curve; CF = cystic fibrosis; CL/fm = apparent total body clearance of formed colistin; Cmax = maximum concentration; CMS = colistin methanesulfonate; Ctrough = minimum concentration at predose; HPLC = high-performance liquid chromatography; Kel = apparent elimination rate constant; MIC = minimum inhibitory concentration; $t_{1/2}$ = apparent elimination half-life; Vd/fm = apparent volume of distribution of formed colistin

Table 2—*Pharmacokinetics Parameters*

Patient	Dose, mg/kg per Dose	Sampling Day	Cmax, µg/mL	Ctrough, µg/mL	$AUC_{(0-8)}$ µg × h/mL	Kel, per h	$t_{1/2}$, h	CL/fm, L/h/kg	Vd/fm, L/kg
1	3.16	6	2.52	0.66	14.76	0.09	7.9	0.21	1.77
2	2.26	3	1.93	0.66	6.94	0.30	1.4	0.33	1.08
3	2.32	4	0.68	0.23	2.96	0.25	1.7	0.78	3.10
4	2.18	6	1.93	0.25	8.77	0.18	5.6	0.25	1.35
5	2.48	5	3.85	1.93	20.88	0.49	7.4	0.12	0.61
6	1.93	3	1.33	1.20	7.51	0.13	3.9	0.26	1.94
7	2.00	5	1.77	0.58	9.15	0.26	6.9	0.22	0.83
8	2.04	4	2.54	0.33	6.77	1.10	10	0.30	0.27
9	2.34	3	2.49	1.55	15.58	NC	NC	0.15	NC
10	1.58	3	2.4	1.67	13.43	0.12	7.9	0.12	0.99
11	1.97	6	4.65	2.43	25.08	0.12	5.8	0.08	0.51
12	1.87	3	1.39	1.03	9.84	0.05	6.9	0.19	3.80
13	2.34	7	1.29	0.90	8.3	0.14	5	0.33	1.89
Mean	2.19	4.5	2.21	1.03	11.54	0.27	5.9	0.26	1.51
SD	0.38	1.4	1.08	0.69	6.20	0.29	2.6	0.18	1.06

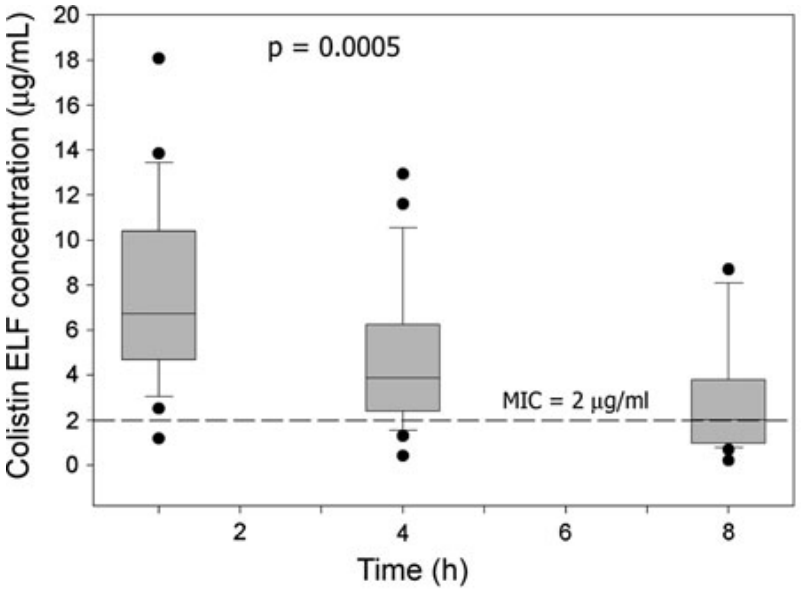
AUC = area under the plasma concentration-time curve; CL/fm = apparent total body clearance of formed colistin; Cmax = maximum plasma colistin concentration; Ctrough = minimum plasma colistin concentration at predose; Kel = apparent elimination rate constant; NC = not calculated; $t_{1/2}$ = apparent elimination half-life; Vd/fm = apparent volume of distribution of formed colistin.

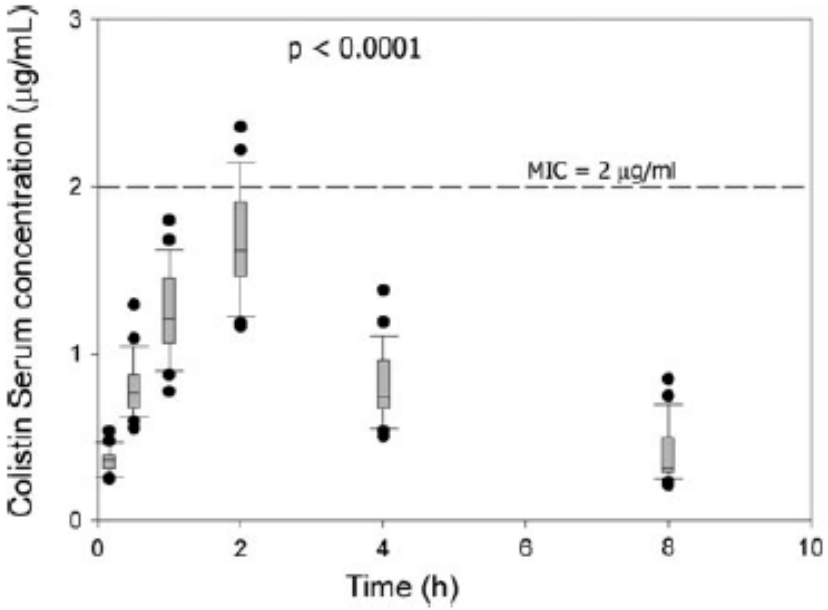
Cmax/MIC = 1,1 $\pm$ 0.5

Concentrazione nel BAL dopo 2h dall'inizio dell'infusione: UNDETECTABLE

CHEST;2010;138(6):1333-9

Pharmacokinetics of inhaled colistimethate sodium (CMS) in mechanically ventilated critically ill patients





20 pazienti
VAT da Gram negativi sensibili al CMS
CMS aerosol: 80 mg ogni 8 h per 7 giorni

Concentrazione mediana nell'ELF (µg/mL)
(25-75% intervallo interquartile): 6.7 (4.8-10.1) a 1h

Concentrazione mediana nel siero (µg/mL)
(25-75% intervallo interquartile): 1,2 ((1.1-1.4) a 1h

Int Care Med 2012;38:1779-86

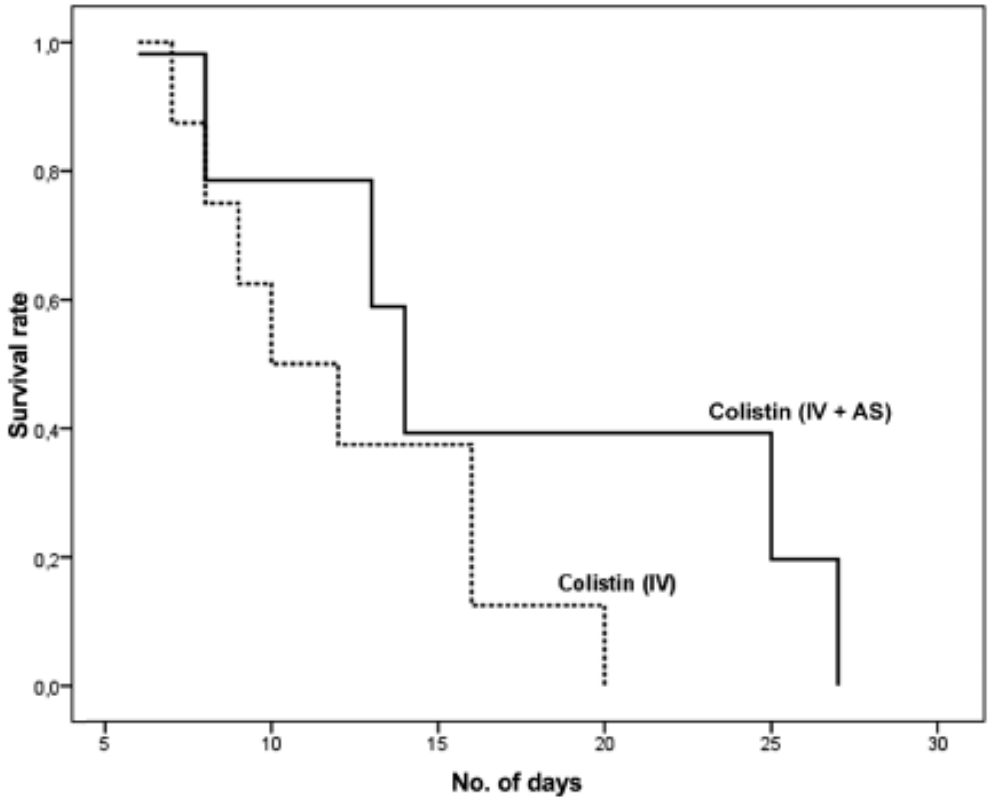


Figure 2. Ventilator-associated pneumonia–related mortality in the 2 treatment groups. AS, aerosolized; IV, intravenous.

Treatment Regimen

The daily dose of AS colistin was 2 million international units (IU) divided into 2 doses, whereas the daily dose of IV colistin was 9 million IU divided into 3 doses in patients with normal renal function.

CID 2010;51(11):1238-44

La colistina aerosol:

Problemi aperti e conclusioni

- Nebulizzazione antibiotico→ selezione R ambientali?
- Maggior studi su efficacia e sicurezza della somministrazione aerosol (finora studi piccoli)
- Maggior dati su sinergie con altri AB/ colistina EV
- Quale posologia?
- Standardizzazione internazionale delle unità di misura

Concludendo:

- La colistina aerosol può essere uno strumento efficace, in cosomministrazione, nella terapia delle polmoniti da Gram-negativi MDR
- La somministrazione aerosol potrebbe essere più sicura ed efficace della somministrazione EV, e comunque più sicura di quello comunemente ritenuto

In caso di VAP o HAP

La colimicina deve essere somministrata anche per via aerosolica alla dosi di

1.000.000 per 3 /die

(esiste la possibilità di broncospasmo)

In caso di meningite la colimicina deve essere somministrata anche per via intraventricolare alla dose di 5-10 mg.

Ceppi colimicino resistenti: spesso i sistemi automatici sovrastimano la resistenza alla colimicina. Tali ceppi sono parzialmente sensibili alla fosfomicina, alla gentamicina e talora alla tigeciclina.

Colimicina in corso di insufficienza renale

1. CrCl 20-50 : 75 % della dose ogni 12-24 ore
2. CrCl 10-20 : 50% della dose ogni 24 ore
3. C rCl <10 : 25 % della dose ogni 36 ore

Incidenza di nefrotossicità e neurotossicità durante trattamento con colistina

First author [reference], year	Incidence of nephrotoxicity, no./total (%)	Incidence of neurotoxicity, no./total	Treatment discontinuation
Levin [9], 1999	4/21 (19)[a]	None	None
Garnacho-Montero [10], 2003	5/14 (36)[b]	None	None
Linden [12], 2003	NA[c]	1/23	In 1 patient, because of neurotoxicity
Markou [11], 2003	3/21(14)[d]	None	None
Kasiakou [13], 2005	4/50 (8)[e]	None	None

Linden et al. CID 2006

FOSFOMICINA

- Derivato dell'acido fosfonico isolato nel 1969 da colture di *Streptomyces spp*., attualmente prodotta in forma sintetica
  - fosfomicina-trometamina o fosfomicina sale calcico: **formulazione orale**
  - fosfomicina di-sodica: **formulazione parenterale**

- **Battericida**, inibisce la sintesi di peptidoglicano ad uno stadio più precoce rispetto alle β-lattamine

- **Ampio spettro d'azione**
  - Gram positivi: *S.aureus* anche *MR, S. epidermidis, S.pneumoniae, E.faecalis anche VR*
  - Gram negativi: *E.coli, Proteus spp, K.pneumoniae, Enterobacter spp, Serratia marcescens, Salmonella typhi*
  INATTIVA: *L. monocytogenes, Bacteroides fragilis.*
  Acinetobacter baumannii e *P.aeruginosa* tendenzialmente resistenti, ma se associata ad altre classi antibiotiche può manifestare effetto sinergico

- Meccanismo d'azione **concentrazione-dipendente o tempo-dipendente non chiaro**, secondo alcuni studi
  - concentrazione-dip. per *E.coli, Proteus mirabilis* (vitro) e *S.pneumoniae* (vivo)
  - tempo-dip per *S.aureus* (vitro)

CID 2008;46:1069-77
Int J Antimicrob Agents 2009;34:506-15

Sensibilità alla fosfomicina di Enterobacteriacee ESBL + isolate in corso di infezioni diverse da UTI e tratto gastro-enetrico

	Studies showing susceptibility to fosfomycin of 90% or more compared with total number of studies	Cumulative susceptibility of isolates according to the CLSI criteria†
All Enterobacteriaceae isolates		
Any advanced antimicrobial drug resistance profile	11 of 17 (64·7%)[18-34]	3891 of 4478 (86·9%)[18-25,27,29,31]
ESBL-producing	11 of 17 (64·7%)[18-34]	3569 of 3911 (91·3%)[18-25,27,29,31]
Isolates from urinary tract	8 of 10 (80·0%)[19-21,23-28,30]	2061 of 2227 (92·5%)[19-21,23-25,27]
Isolates from mixed sites‡	5 of 8 (62·5%)[18,22,25,29,31-34]	1508 of 1684 (89·5%)[18,22,25,29,31]
Isolates from outpatients	3 of 3 (100·0%)[20,21,24]	292 of 297 (98·3%)[20,21,24]
Isolates from hospitalised patients	4 of 8 (50·0%)[21,22,25,28,29,31,33,34]	1344 of 1519 (88·5%)[21,22,25,29,31]
***Escherichia coli* isolates**		
Any advanced antimicrobial drug resistance profile	11 of 12 (91·7%)[18,20,21,24-32]	1672 of 1725 (96·9%)[18,20,21,24,25,27,29,31]
ESBL-producing	11 of 12 (91·7%)[18,20,21,24-32]	1604 of 1657 (96·8%)[18,20,21,24,25,27,29,31]
Isolates from urinary tract	6 of 7 (85·7%)[20,21,24-28]	704 of 721 (97·6%)[20,21,24,25,27]
Isolates from mixed sites‡	5 of 6 (83·3%)[18,25,29-32]	900 of 936 (96·2%)[18,25,29,31]
Isolates from outpatients	3 of 3 (100%)[20,21,24]	292 of 297 (98·3%)[20,21,24]
Isolates from hospitalised patients	4 of 5 (80·0%)[21,25,28,29,31]	864 of 909 (95·0%)[21,25,29,31]
***Klebsiella pneumoniae* isolates**		
Any advanced antimicrobial drug resistance profile	3 of 6 (50·0%)[18,22,29-31,33]	608 of 748 (81·3%)[18,22,29,31]
ESBL-producing	3 of 6 (50·0%)[18,22,29-31,33]	608 of 748 (81·3%)[18,22,29,31]
Isolates from mixed sites‡	2 of 5 (40·0%)[18,22,29,31,33]	608 of 748 (81·3%)[18,22,29,31]
Isolates from hospitalised patients	2 of 4 (50·0%)[22,29,31,33]	480 of 610 (78·7%)[22,29,31]

ESBL=extended-spectrum β-lactamase. CLSI=Clinical and Laboratory Standards Institute. *Multidrug resistance, carbapenem-resistance, or production of ESBLs, AmpC β-lactamases, serine carbapenemases, or metallo-β-lactamases. †CLSI fosfomycin susceptibility criteria refer specifically to urinary isolates of *Escherichia coli*. ‡Urinary tract isolates are potentially included.

SUCCESSO CLINICO

Pts trattati 1604
- guariti 81.1%
- migliorati 2.9%

RIDOTTO rischio di selezionare R in corso di trattamento

Lancet Inf Dis 2010;10:43-50

FOSFOMICINA

VIA DI SOMMINISTRAZIONE :	E.V.
DOSE UNITARIA :	4 gr.
PICCO SERICO :	123 ± 16 mg/l
POSOLOGIA:	12-16 gr. in 3-4 dosi
METABOLIZZAZIONE:	assente
LEGAME PROTEICO:	< 10
VOLUME DISTRIBUZIONE:	0,3 l/kg
ESCREZIONE URINARIA:	> 85 %
ELIMINAZIONE BILIARE:	modesta
DIFFUSIONE NEL LCR :	20% dei valori serici

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Review

What is the relevance of fosfomycin pharmacokinetics in the treatment of serious infections in critically ill patients? A systematic review

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ABSTRACT

As treatment options for critically ill patients with multidrug-resistant bacteria diminish, older antibiotics such as fosfomycin are being investigated for use as last-resort drugs. Fosfomycin is a broad-spectrum antibiotic with activity both against Gram-positive and Gram-negative bacteria. The aim of this review was to examine the effectiveness of current fosfomycin dosing strategies in critically ill patients. These patients can be subject to pathophysiology that can impact antibiotic pharmacokinetic (PK) profiles and potentially the effectiveness of their treatment. As a hydrophilic drug with negligible protein binding, fosfomycin is eliminated almost entirely by glomerular filtration and is subject to patient renal function. If altered as seen in augmented renal clearance, renal function in a critically ill patient may lead to low blood concentrations and predispose patients to the risk of treatment failure. If altered as seen in acute kidney injury, toxic blood concentrations may develop. Fosfomycin has a volume of distribution comparable with β-lactams and aminoglycosides and may therefore increase in critically ill patients. Altered dosing strategies may be required to optimise dosing given these PK changes, although the current paucity of data on fosfomycin in critically ill patients prevents accurate dosing guidance being recommended at this time.

Table 1
Review of literature for pharmacokinetic (PK) data on intensive care unit (ICU) patients receiving fosfomycin.

Reference	Study population	No. of patients	Fosfomycin dose	PK parameter					
				V_d (L)	$t_{1/2}$ (h)	CL (L/h)	C_{max} (mg/L)	T_{max} (h)	AUC (mg h/L)
Bergan et al. [13]	Healthy volunteers	12	3 g i.v.	20.6[a]	2.1 ± 0.1	6.8[b]	370.6 ± 92	0.02 ± 0	443.6 ± 48.9
Frossard et al. [4]	Healthy volunteers	6	4 g i.v., once	nd	nd	9.0[b] (serum)	97 ± 13 (muscle) 144 ± 1 (subcutis) 202 ± 20 (serum)		201.7 ± 56.7 (muscle) 313.3 ± 43.3 (subcutis) AUC_{0-8}, 443.3 ± 41.7 (serum)
			8 g i.v., once	nd	nd	9.0[b] (serum)	156 ± 16 (muscle) 209 ± 30 (subcutis) 395 ± 46 (serum)		460 ± 40 (muscle) 596.7 ± 48.3 (subcutis) 886.7 ± 70 (serum)
Gattringer et al. [33]	Anuric ICU patients (CVVH)	12	8 g (CVC)	33.7 ± 12.7	12.1 ± 5.2	6.4 ± 7.6 (total) 1.1 ± 0.2 (HF)[c]	442.8 ± 124.0	0.4 ± 0.1	AUC_{0-12}, 2159.4 ± 609.8
Joukhadar et al. [23]	Sepsis	9	8 g i.v.	31.5 ± 4.5	3.9 ± 0.9 4.1 ± 0.6 (muscle)	7.2 ± 1.3	357 ± 28 (plasma) 247 ± 38 (muscle)	0.4 ± 0.1 (plasma) 1.2 ± 0.2 (muscle)	AUC_{0-4}, 721 ± 66 (plasma) AUC_{0-4}, 501 ± 69 (muscle)
Pfausler et al. [14]	Bacterial ventriculitis	6	8 g i.v.	30.8 ± 10.2	3.0 ± 1.0	7.4 ± 2.3	260 ± 85 (plasma) 43 ± 20 (CSF)	1.2 ± 0.4 (plasma) 3.8 ± 1.8 (CSF)	929 ± 280 (plasma) 225 ± 131 (CSF)
			8 g t.i.d.	26.3 ± 9.7	4.0 ± 0.5	5.0 ± 2.0	307 ± 101 (plasma) 62 ± 38 (CSF)	1.5 ± 1.2 (plasma) 4.5 ± 2.7 (CSF)	1035 ± 383 (plasma) 295 ± 179 (CSF)
Pfeifer et al. [26]	Perioperative neurosurgical patients	39	5 g i.v.	15.4	2	7.2	253 ± 108 9–10 (CSF)	0.25 3–6	
			10 g i.v.	nd	nd	nd	14–17 (CSF)	2–6	
			5 g i.v. t.i.d.	nd	nd	nd	32 (CSF)	Between 2 days and 5 days	
Matzi et al. [19]	Sepsis	7	4 g i.v.	31.7[a]	2.5 ± 0.5 (plasma)	8.8[b]	243.3 ± 58.5 (plasma)	0.3 ± 0 (plasma)	AUC_{0-4}, 453.0 ± 113.4 (plasma)
		n = 7 healthy lung		nd	2.2 ± 0.8[d]	nd	131.6 ± 110.6[d]	1.1 ± 0.4[d]	AUC_{0-4}, 242.4 ± 101.6[d]
		n = 5 infected lung		nd	2.7 ± 1.5[e]	nd	107.5 ± 60.2[e]	1.4 ± 0.5[e]	AUC_{0-4}, 203.5 ± 118.4[e]

V_d, volume of distribution; $t_{1/2}$, terminal elimination half-life; CL, clearance; C_{max}, maximum concentration; T_{max}, time to reach C_{max}; AUC, area under the concentration–time curve; i.v., intravenous; nd, not described; AUC_{0-x}, AUC from time 0–x h; CVVH, continuous venovenous haemofiltration; CVC, central venous catheter; HF, haemofiltration; t.i.d., three times daily; CSF, cerebral spinal fluid.

[a] Calculated based on the approximation that $k_e = 0.693/t_{1/2} = CL/V_d$.

[b] Calculated based on the approximation CL = dose/AUC.

[c] The clearance of haemofiltration (CL_{HF}) was calculated with the formula $CL_{HF} = (UFR \times C_{UF})/C_A$, where UFR refers to the ultrafiltration rate and C_{UF} and C_A refer to the ultrafiltrate and arterial (dialyser inlet) serum fosfomycin concentrations, respectively.

[d] Healthy lung.

[e] Infected lung.

ACINETOBACTER MDR

Terapia delle infezioni da Acinetobacter multiresistente

1. Ampicillina /Sulbactam 3 gr x 4 /die*
2. Colimicina 9 milioni dose da carico
   poi 4,5 milioni x 2
   +
   Rifampicina 600-900 mg / die
   +/-
   Imipenem o Meropenem**
   anche se resistenti ma con CMI relativamente basse
3. Colimicina dose come sopra
   +
   Tigeciclina 100 mg poi 50 mg x 2 ***
   (la dose può essere aumentata sino a 100/150 mg x 2 / die)
4. Colimicina (dose come sopra)
   +
   Ampicillina/Sulbactam 3 gr x 4 / die*

*** Alcuni autori consigliano 16 g di Ampicillina/sulbactam (3 gr x 6)**

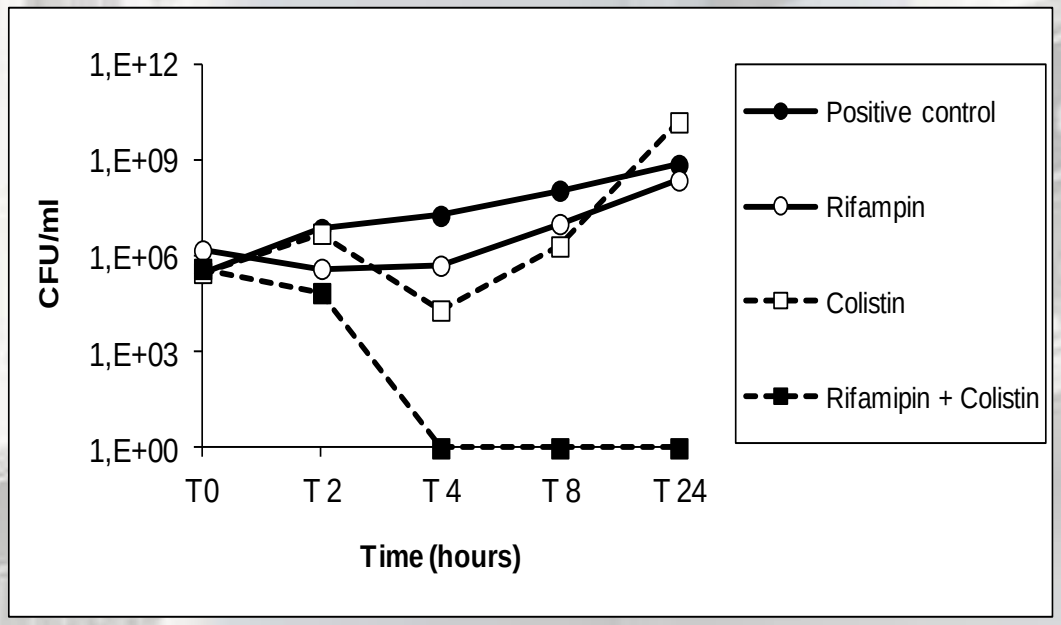
**** La triplice terapia (colimicina + rifampicina + carbapenemico è consigliabile nel caso di un grave quadro settico).**

**** * L'associazione colimicina + tigeciclina non è consigliata nel caso di HAP o VAP**

Table 2. Clinical outcomes of patients with severe carbapenem-resistant *Acinetobacter* spp. infections treated with ampicillin/sulbactam or polymyxins, in two large teaching hospitals, from 1996 to 2004

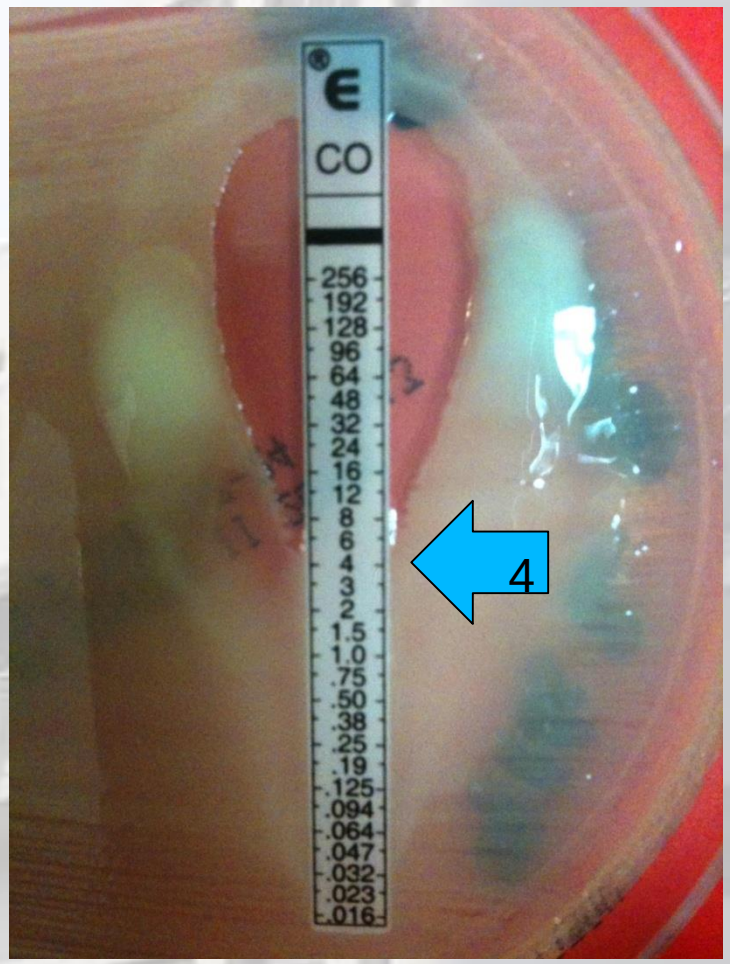
Outcome	Patients treated with polymyxins ($n = 82$)	Patients treated with ampicillin/sulbactam ($n = 85$)
Cure (%)	15 (18)	25 (29)
Improvement (%)	17 (21)	26 (31)
Failure (%)	30 (37)	29 (34)
Indeterminate (%)	20 (24)	5 (6)
Death during treatment (%)	41 (50)	28 (33)
Death during hospitalization (%)	63 (77)	54 (64)

Rifampin plus Colistin time-kill curve vs. MDR *P. aeruginosa*



Tascini C. et al: Microbiological activity and clinical efficacy of a colistin and rifampin combination in multidrug-resistant *Pseudomonas aeruginosa* infections.
J Chemother. 2004 Jun;16(3):282-7.

Colistin MIC vs KPC-Kp with Etest on MHB agar alone (left) and supplemented with Rifampin 32 mg/L (right)



Colistin susceptibility breakpoint 2 mg/L

Rifampin peak serum level 4-32 mg/L (600 mg po

Effetto sinergico della polimixina con altri antimicrobici (checkerboard methods)

Organism (no. of isolates)	Polymyxin studied	Combined-drug synergy (% of isolates with synergy)	Reference
A. baumannii (13)	Colistin	Rifampin (85)	74
A. baumannii (5)	Polymyxin B	Rifampin (60); ampicillin-sulbactam (0)	172
A. baumannii (55)	Polymyxin B	Rifampin (76); imipenem (58)	26
A. baumannii (24)	Polymyxin B	Azithromycin (83); rifampin (54); meropenem (38); cotrimazole (25)	113
A. baumannii (5)	Colistin	Rifampin (80), meropenem (60), azithromycin (60)	174
A. baumannii (8)	Colistin	Rifampin (100)	104
A. baumannii (6)	Colistin	Rifampin (100)	16
P. aeruginosa (55)	Polymyxin B	Rifampin (0); imipenem (0)	26
P. aeruginosa (5)	Colistin	Rifampin (40); meropenem (0), azithromycin (0)	174
P. aeruginosa (7)	Colistin	Rifampin (14)	171
P. aeruginosa (10)	Polymyxin B	Azithromycin (60); imipenem (20); rifampin (10)	93
P. aeruginosa (40)	Polymyxin B	Rifampin (not stated)	165
K. pneumoniae (55)	Polymyxin B	Rifampin (46); imipenem (15)	26
S. marcescens (12)	Polymyxin B	Rifampin (100)	177
S. marcescens (12)	Polymyxin B	Rifampin (100)	134
S. marcescens (13)	Colistimethate	Cotrimazole (not stated); rifampin (not stated); chloramphenicol (not stated)	173

Landman D. et al. Clin Microb Reviews, 2008; 21: 449-465

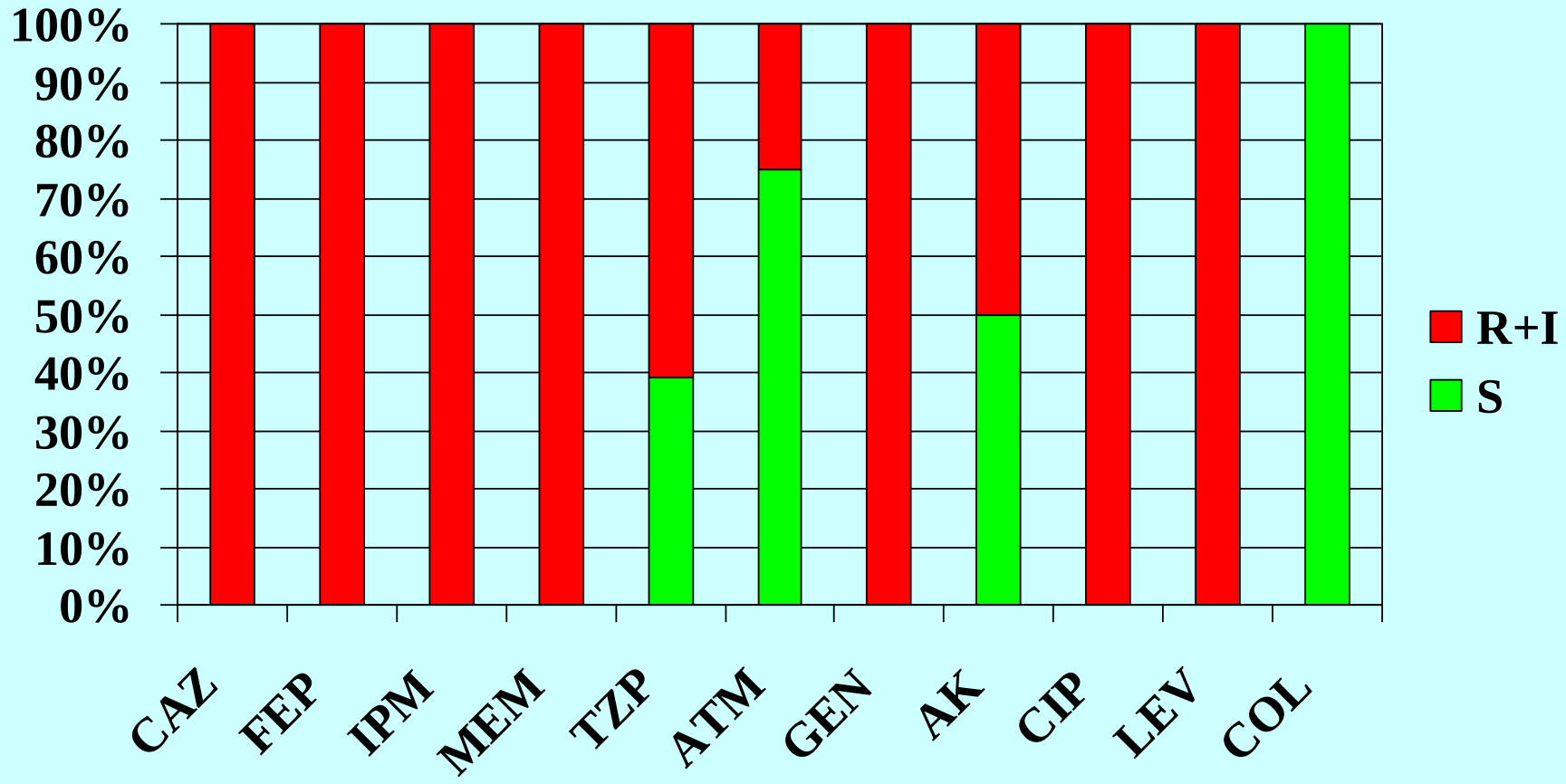
PSEUDOMONAS AERUGINOSA MDR

Fenotipo di sensibilità di *Ps.aeruginosa* MBL-produttore

Antibiotic	Susceptible	Intermediate	Resistant	Not tested
IPM	2	4	94	
MEM	2	1	97	
CAZ	6		91	3
PIP	2		95	3
TZP	6		90	4
ATM	31		62	7
GEN	3		94	3
TOB	5		79	16
AMK	14	5	78	3
CIP	12		85	3
CST	95		2	3

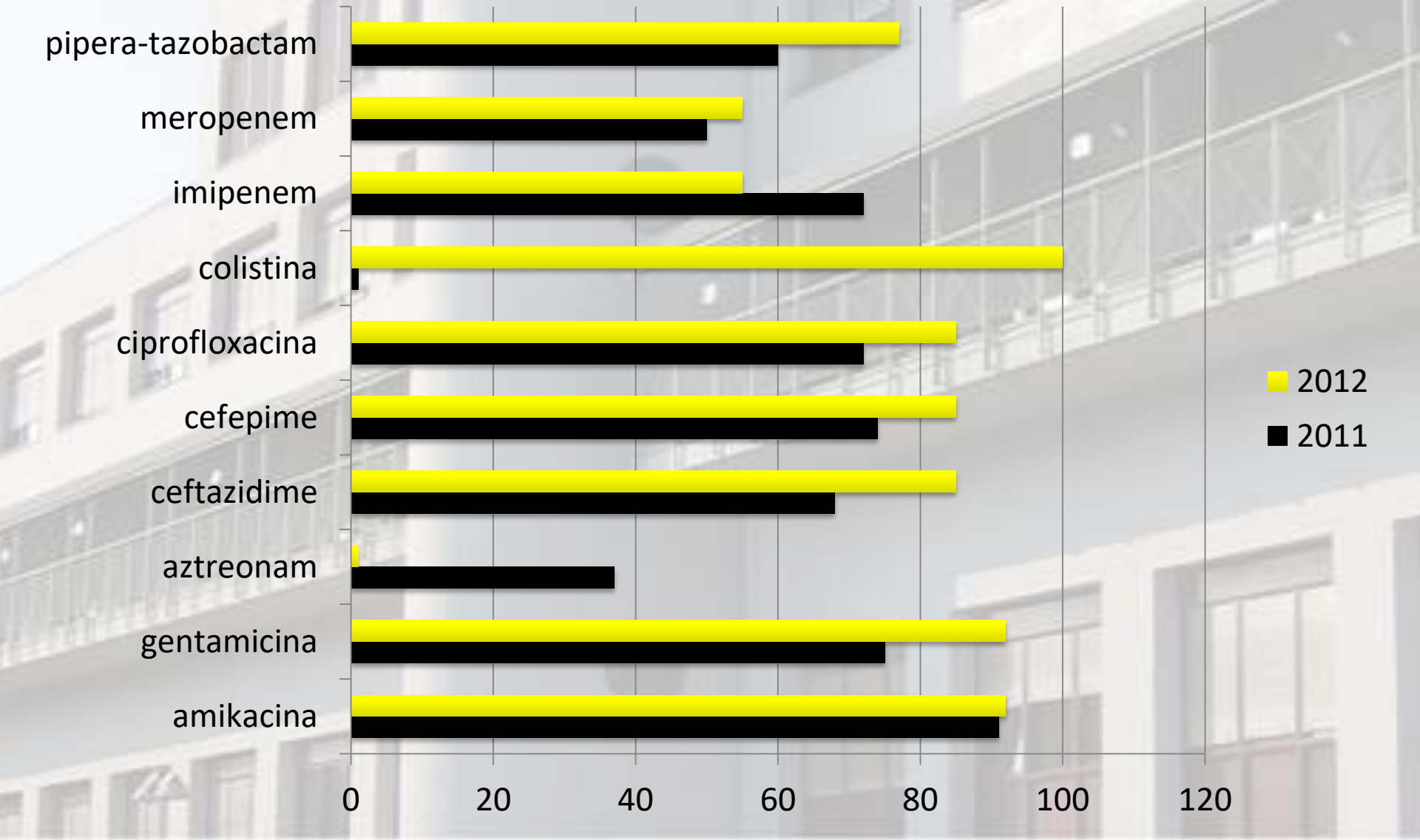
AMK, amikacin; ATM, aztreonam; CAZ, ceftazidime; CIP, ciprofloxacin; CST, colistin; GEN, gentamicin; IPM, imipenem; MEM, meropenem; PIP, piperacillin; TOB, tobramycin; TZP, piperacillin/tazobactam.

Antimicrobial susceptibility of MBL-producing *P. aeruginosa* from the first Italian nationwide survey



Rossolini et al. - unpublished

Sensibilità *P.aeruginosa* da materiali respiratori (UTI Borgo Roma)



Terapia delle infezioni da Pseudomonas aeruginosa MDR

1. COLIMICINA (9 milioni dose da carico poi 4,5 milioni x 2 / die)
   +
   RIFAMPICINA 600 -900 mg /die (l'uso prescinde dalla sensibilità in vitro)

2. COLIMICJNA (dose come sopra)
   +
   FOSFOMICINA (4 gr x 4 / die) (solo se è dimostrata una sensibilità in vitro)

3. CEFTAZIME (2 gr x 3 /die),
   CEFEPIME (2 gr x 3 /die),
   PIPERACILLINA/TAZOBACTAM (4 gr x 4 / die),
   IMIPENEM (1 gr x 3-4/die),
   MEROPENEM (1gr x 3-4, 2 gr x 3 /die)
   +
   CIPROFLOXACINA (400 mg x 3 / die)
   oppure
   LEVOFLOXACINA (500 mg x 2 / die)
   oppure
   AMIKACINA (1 gr / die, nelle polmoniti 1,5 gr/die)
   (richiedere studio in vitro di sinergia)

Terapia derivante da test di sinergia in vitro

Terapia delle infezioni da Stenotrophomonas maltophilia

1. COTRIMOXAZOLO 3 fiale (80 mg Trimetoprim x fiala) x 4 / die

2. TICARCILLINA/CLAVULANATO 3,1 gr x 4 / die

3. TIGECICLINA 100 mg poi 50 mg x 2 / die
   (aumentare la dose se scarsa risposta clinica)

Table 1. Antimicrobial activity of various antimicrobial agents against *S. maltophilia* by the agar dilution method

Antimicrobial	MIC (μg/mL)			Susceptibility (%)		
	Range	50%	90%	S	I	R
Cotrimoxazole	≤ 0.06-128	1	2	96	-	4
Levofloxacin	0.12-64	2	16	64	16	20
Moxifloxacin	≤ 0.06-32	0.5	8	-	-	-
Minocycline	0.12-16	0.5	2	99	< 1	< 1
Tigecycline	≤ 0.06-8	1	4	-	-	-
Ceftazidime	1- > 128	64	> 128	21	8	71
Ticarcillin-clavulanate	1-16	32	> 128	38	38	24
Chloramphenicol	8-128	16	64	7	45	49
Amikacin	≤ 1- > 128	> 128	> 128	-	-	-

S, susceptible; I, intermediate; R, resistant.

http://dx.doi.org/10.3346/jkms.2013.28.1.62

Chung H-S, et al Antimicrobial Synergies for S. malfophilia

CONSIDERAZIONI FINALI

1. Fenomeno irreversibile
2. Uso corretto e limitato degli antibiotici (terapia-profilassi)
3. Precauzioni universali per il controllo della trasmissione (lavaggio mani, precauzioni standard e da contatto, isolamento respiratorio e/o da contatto, strumentazioni ecc…)
4. Screening? (malato proveniente da RSA)
5. Mobilità all'interno dell'ospedale
6. Dimissioni precoci
7. Scheda paziente
8. Non abituarsi all'emergenza

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doi:10.1093/jac/dkp255

JAC

Has the era of untreatable infections arrived?

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Antibiotic resistance is a major public health concern, with fears expressed that we shortly will run out of antibiotics. In reality, the picture is more mixed, improving against some pathogens but worsening against others. Against methicillin-resistant *Staphylococcus aureus* (MRSA)—the highest profile pathogen—the range of treatment options is expanding, with daptomycin, linezolid and tigecycline all launched, and telavancin, ceftobiprole, ceftaroline and dalbavancin anticipated. There is a greater problem with enterococci, especially if, as in endocarditis, bactericidal activity is needed and the isolate has high-level aminoglycoside resistance; nevertheless, daptomycin, telavancin and razupenem all offer cidal potential. Against Enterobacteriaceae, the rapid and disturbing spread of extended-spectrum β-lactamases, AmpC enzymes and quinolone resistance is forcing increased reliance on carbapenems, with resistance to these slowly accumulating via the spread of metallo-, KPC and OXA-48 β-lactamases. Future options overcoming some of these mechanisms include various novel β-lactamase-inhibitor combinations, but none of these overcomes all the carbapenemase types now circulating. Multiresistance that includes carbapenems is much commoner in non-fermenters than in the Enterobacteriaceae, depending mostly on OXA carbapenemases in *Acinetobacter baumannii* and on combinations of chromosomal mutation in *Pseudomonas aeruginosa*. No agent in advanced development has much to offer here, though there is interest in modified, less-toxic, polymyxin derivatives and in the siderophore monobactam BAL30072, which has impressive activity against *A. baumannii* and members of the *Burkholderia cepacia* complex. A final and surprising problem is *Neisseria gonorrhoeae*, where each good oral agent has been eroded in turn and where there is now little in reserve behind the oral oxyimino cephalosporins, to which low-level resistance is emerging.

Keywords: β-lactamases, MRSA, *Escherichia coli*, *Acinetobacter baumannii*, *Neisseria gonorrhoeae*

NUOVI ANTIBIOTICI

Table 1. Activity of β-lactamase inhibitors

β-Lactamase	Inhibitor (IC_{50} μM)		
	Tazobactam	Avibactam	MK7655
TEM-1	0.01	0.01	0.03
KPC-2	43.00	0.17	0.21
SHV-1	0.07	NR	0.03
SHV-4	0.06	0.003	NR
SHV-5	0.01	NR	0.36
CTX-M15	0.01	0.01	NR
AmpC (*P. aeruginosa*)	1.49	0.13	0.47
P99	12.00	0.10	0.13
Oxa (*A. baumannii*)	58.00	NR	>50

Adapted from Refs. 8–10.
NR = not reported.

D M Shales 2013

Table 3. Antimicrobial activity of β-lactam–β-lactamase inhibitor combinations against key pathogens[15,19–23]

Pathogen	Ceftazidime	Ceftazidime–avibactam	Ceftaroline	Ceftaroline–avibactam	Ceftolozane	Ceftolozane–tazobactam	(MIC_{90} μg/mL) Imipenem	Imipenem-MK7655
E. coli ESBL	32	0.5	>32	0.25	>32	16		
K. pneumoniae ESBL	>32	2	>32	1	>32	>16		
K. pneumoniae NS to carbapenem	>32	2	>32	2	>32	>16	64	1
E. cloacae Ceftazidime-R	>32	2	>32	1	>32	>16		
Enterobactereaceae Multiple β-lactamases	>256	4	>64	0.5				
CTX-M (538)			>32	0.25				
KPC (118)			>32	1				
SHV (50)			>32	0.5				
AmpC + CTX-M (43)			>32	2				
SHV + CTX-M (28)			>32	0.25				
SHV + KPC (18)			>32	4				
Pseudomonas aeruginosa	32	8	Not expected	Not expected	8	8	32	4

Blank cell = not reported. Not expected = not expected to be active.

D M Shales 2013

NXL-104 (Avibactam)

- NXL-104 (Novexel, now AstraZeneca) is a non-β-lactam β-lactamase inhibitor .
- It restores β-lactam activity against Enterobacteriaceae producing:
  - class A enzymes (including many ESBLs)
  - class C enzymes (derepressed AmpC)
  - some class D enzymes
- NXL-104 is not active against class-B enzyme producers.

Table 3 continued

	β-lactamase enzyme[a]	MIC		MIC reduction (fold)
		Ceftazidime	Ceftazidime-avibactam[b]	
Klebsiella pneumoniae				
Extended-spectrum β-lactamases	CTX-M-3	16	0.5	32
	CTX-M-14	16	1	16
	CTX-M-15[c]	>128	1	>128
	SHV-2	>64	0.5	>128
	SHV-3	>64	0.5	>128
	SHV-4	>256	4	>64
	SHV-5	64	0.5	128
	SHV-6	4	1	4
	SHV-18	64	2	32
	SHV-38	8	2	4
	TEM-4	32	0.5	64
	CTX-M-2, TEM-1B	128	2	64
	CTX-M-16, OXA-1	256	1	256
	SHV-5, TEM-10	>128	2	>64
	CTX-M-2, SHV-5, TEM-12	>128	2	>64
	CTX-M-2, SHV-2, TEM-12	>128	4	>32
	CTX-M-3, SHV-1, TEM-1B	256	2	128
	CTX-M-15, TEM-1, OXA-1	256	2	128
	SHV-1, TEM-2, PER	256	4	64
Carbapenemases	KPC-2[c]	>128	1	>128
	KPC-3[c]	256	0.5	512
	KPC-2, SHV-11, SHV-12, TEM-1	512	≤0.06	≥8192
Metallo-β-lactamases	VIM-1, SHV-5	256	256	1
Ambler class C β-lactamases	AmpC + SHV-11	64	2	32
	DHA-2	256	2	128
	ACC-1, TEM-1	128	1	128
	LAT-4, SHV-11 variant	32	1	32
	CMY-4, TEM-1	256	0.5	512
	DHA-1, SHV-2a, TEM-1	>128	1	>128
	MOX-2, SHV-5, TEM-1	256	1	256

[a] Isolates may contain genes encoding other β-lactamases

[b] Fixed avibactam concentration of 4 mg/L

[c] Modal MIC values derived from MIC data for ten or more unique isolates

MIC minimum inhibitory concentration

DRUGS 2013

CEFTAZIDIME-AVIBACTAM: a novel cephalosporin/betalactase inhibitor combination

- Ceftazidime is a third generation cephalosporin; resistance, especially with gram negative bacilli, is increasing globally
- Avibactam (NXL 104) is a non betalactam betalactamase inhibitor active in vitro against class A and C and some class D betalactamases
- Avibactam is being developed in combination with cefatzidime and with ceftaroline
- Ceftazidime-avibactam is currently in phase III clinical trials for treatment of **UTI and IAI complicated**

11 Place of Ceftazidime/Avibactam in Therapy

The addition of avibactam restores the activity of ceftazidime against Gram-negative bacilli that achieve β-lactam resistance through expression of the Ambler class A ESBLs, chromosomal or mobile class C β-lactamases, serine carbapenemases, or some class D β-lactamases. Safety and pharmacokinetic results published to date suggest that no additional considerations need to be taken when dosing ceftazidime-avibactam compared with ceftazidime alone. Ceftazidime-avibactam has demonstrated clinical efficacy similar to that of carbapenem therapy in phase II studies of complicated intra-abdominal infection and complicated urinary tract infection (including acute pyelonephritis). The extensive clinical experience with ceftazidime and the knowledge that avibactam broadens the spectrum of ceftazidime versus ß-lactamase-producing Gram-negative bacilli, will provide clinicians with confidence in using this agent. To date, no data are available on the efficacy of ceftazidime-avibactam for the treatment of difficult-to-treat infections such as hospital-acquired and ventilator-acquired pneumonia. The exact roles for ceftazidime-avibactam in the treatment of infectious diseases will, in part, depend on the development of other β-lactam/β-lactamase inhibitor combinations including ceftaroline-avibactam, imipenem-MK7655 and ceftolozane-tazobactam. An important advantage of ceftazidime-avibactam is that its development is furthest along and it may be first to market.

Potential future roles for ceftazidime-avibactam include the treatment of suspected or documented infections caused by resistant Gram-negative bacilli-producing ESBL, KPC and/or AmpC β-lactamases. In addition, ceftazidime-avibactam may be used in combination (with metronidazole) for suspected polymicrobial infections. Finally, the increased activity of ceftazidime-avibactam versus *P. aeruginosa* may be of clinical benefit in patients with suspected or documented *P. aeruginosa* infections.

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Journal of Antimicrobial Chemotherapy

Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, Phase II trial

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Objectives: Avibactam, a novel non-β-lactam β-lactamase inhibitor, restores the *in vitro* activity of ceftazidime against class A, C and some class D β-lactamase-producing pathogens, including those commonly associated with complicated intra-abdominal infections (cIAIs). This randomized, active-controlled, double-blind, Phase II trial (NCT00752219) aimed to evaluate the safety and efficacy of ceftazidime/avibactam plus metronidazole compared with meropenem in hospitalized patients with cIAI.

Methods: Adults with confirmed cIAI requiring surgical intervention and antibiotics were randomized 1:1 to receive intravenously either (i) 2000 mg of ceftazidime plus 500 mg of avibactam plus a separate infusion of 500 mg of metronidazole or (ii) 1000 mg of meropenem plus placebo every 8 h for a minimum of 5 days and a maximum of 14 days. The primary efficacy endpoint was the clinical response in microbiologically evaluable (ME) patients at the test-of-cure (TOC) visit 2 weeks after the last dose of study therapy.

Results: Overall, 101 patients received ceftazidime/avibactam plus metronidazole; 102 received meropenem. The median duration of treatment was 6.0 and 6.5 days, respectively. Favourable clinical response at the TOC visit in the ME population was observed in 91.2% (62/68) and 93.4% (71/76) of patients in the ceftazidime/avibactam plus metronidazole and meropenem groups, respectively (observed difference: −2.2%; 95% CI: −20.4%, 12.2%). The incidence of treatment-emergent adverse events was similar for ceftazidime/avibactam plus metronidazole (64.4%) and meropenem (57.8%).

Conclusions: Ceftazidime/avibactam plus metronidazole was effective and generally well tolerated in patients with cIAI, with a favourable clinical response rate in the ME population of >90%, similar to that of meropenem.

Keywords: ceftazidime non-susceptible, appendix, stomach/duodenum, *Escherichia coli*

Introduction

Complicated intra-abdominal infections (cIAIs), defined as those extending into the peritoneal space and associated with peritonitis or abscess formation,[1] are common infections that can be extremely serious and life-threatening, with most patients requiring surgical intervention. The pathogens associated with cIAIs result from perforation of the gastrointestinal tract and, thus, one or more aerobic or facultative anaerobic Gram-negative species is usually involved.

Ongoing surveillance studies have demonstrated an increasing frequency of antibiotic resistance among Gram-negative pathogens,[2] with one of the most common resistance mechanisms being the production of extended-spectrum β-lactamases (ESBLs).[3] Carbapenems are currently the antibiotic group of choice for the treatment of serious infections likely to be caused by ESBL-producing organisms.[3] However, resistance to carbapenems involving the production of serine carbapenemases is now emerging in some Gram-negative pathogens [e.g. *Klebsiella pneumoniae* carbapenemase (KPC)][4,5] and there

Display Settings: Abstract

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Curr Med Res Opin. 2012 Dec;28(12):1921-31. doi: 10.1185/03007995.2012.748653. Epub 2012 Nov 21.

Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study.

Vazquez JA, González Patzán LD, Stricklin D, Duttaroy DD, Kreidly Z, Lipka J, Sable C.

Division of Infectious Diseases, Henry Ford Hospital, Detroit, MI 48202, USA. JVAZQUE1@hfhs.org

Abstract

OBJECTIVES: The aim of this prospective phase II, randomized, investigator-blinded study (NCT00690378) was to compare the efficacy and safety of **ceftazidime-avibactam** and imipenem-cilastatin in hospitalized adults with serious complicated urinary tract infection (cUTI) due to Gram-negative pathogens.

PATIENTS AND METHODS: Patients aged between 18 and 90 years with cUTI were enrolled and stratified by infection type (acute pyelonephritis or other cUTI) and randomized 1:1 to receive intravenous **ceftazidime** 500 mg plus **avibactam** 125 mg every 8 hours or imipenem-cilastatin 500 mg every 6 hours. Patients meeting pre-specified improvement criteria after 4 days could be switched to oral ciprofloxacin. Patients were treated for a total of 7-14 days. The primary efficacy objective was a favorable microbiological response at the test-of-cure (TOC) visit 5-9 days post-therapy in microbiologically evaluable (ME) patients.

RESULTS: Overall, 135 patients received study therapy (safety population); 62 were included in the ME population (**ceftazidime-avibactam**, n = 27; imipenem-cilastatin, n = 35). The predominant uropathogen was Escherichia coli. Favorable microbiological response was achieved in 70.4% of ME patients receiving **ceftazidime-avibactam** and 71.4% receiving imipenem-cilastatin at the TOC visit (observed difference -1.1% [95% CI: -27.2%, 25.0%]). Among ME patients with **ceftazidime**-resistant uropathogens, response was observed in 6/7 (85.7%) receiving **ceftazidime-avibactam**. Adverse events were observed in 67.6% and 76.1% of patients receiving **ceftazidime-avibactam** and imipenem-cilastatin, respectively. Limitations of the study include the small number of patients in the ME population.

CONCLUSION: The results suggest that the efficacy and safety of **ceftazidime-avibactam** may be similar to that of imipenem-cilastatin.

PMID: 23145859 [PubMed - in process]

MK-7655

- **MK-7655 is a novel compound active against class A and class C carbapenemases with a good in vitro and in vivo activity in combination with imipenem**
- In a phase I randomized, double-blind, placebo-controlled study, MK-7655 was shown to have a favorable pharmacokinetics profile when administered in combination with cilastatin and imipenem.

CB-182,804

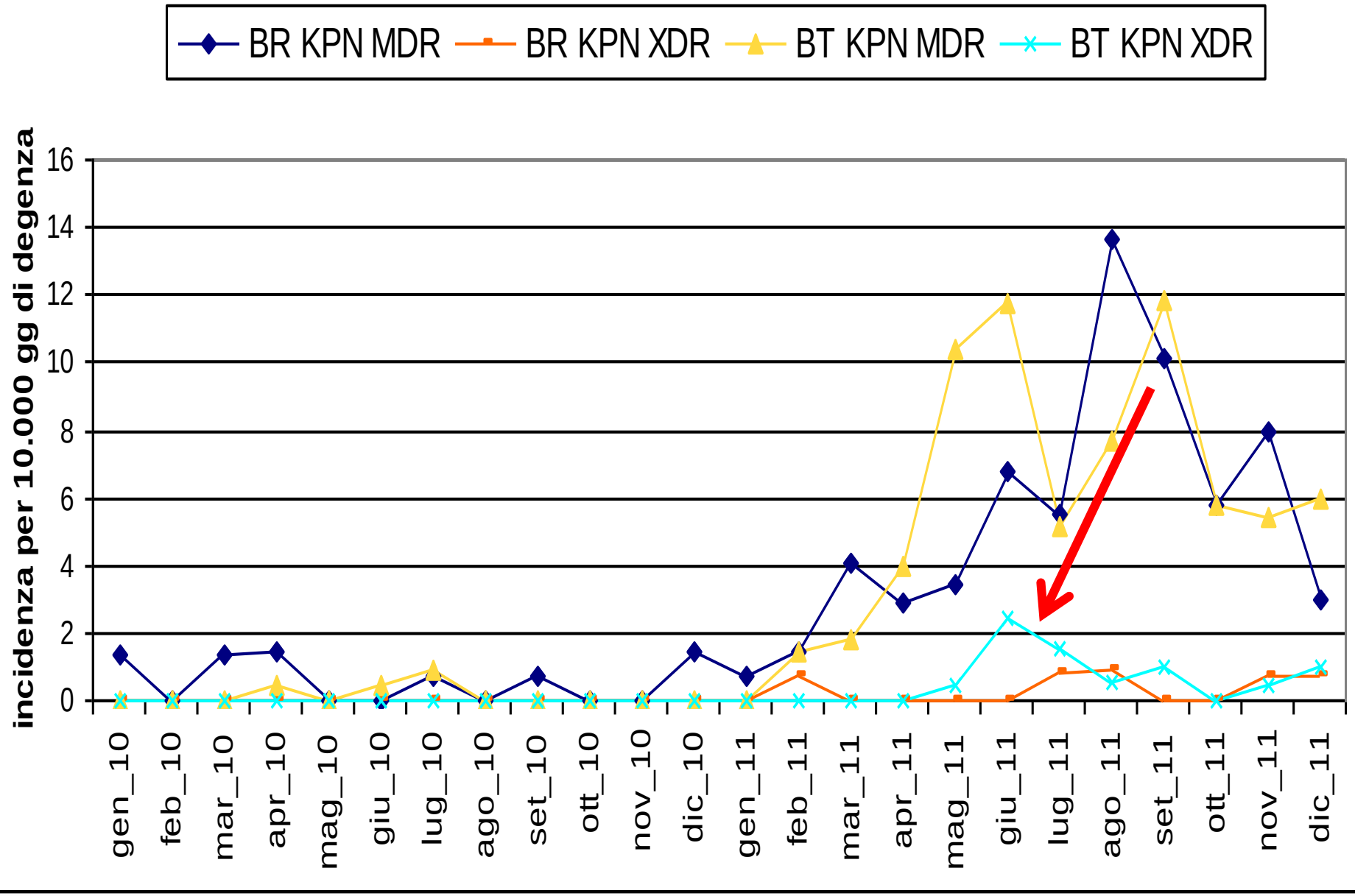
- Cubist has initiated in 1Q09 a phase I study of a **new polymyxin**, CB-182,804.
- The compound is described as rapidly bactericidal in vitro against *P. aeruginosa, Enterobacteriaceae* (including strains known to produce ESBLs and KPCs) and *A. baumannii.*
- Some strains had elevated MICs for colistin and polymyxin B, but in some other strains resistance to CB-182,804 arose more frequently than to polymyxin B.

Empiric antibiotic therapy in wards wth KPC-Kp epidemic

- Sepsis syndrome, site of infection defined or not
- Intestinal colonization UK
- Blood cultures, TA, BAL, urine, etc.
- Meropenem ev 2 g tid (100 ml SF in 4 hrs)
- Gentamicin ev 240 mg od (100 ml SF in 1 h)
- Tigecycline ev 100 mg bid (250 ml SF in 4 hrs)

MICRORGANISMI PANRESISTENTI

AOUI Verona


BR KPN MDR
BR KPN XDR
BT KPN MDR
BT KPN XDR
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0
2
4
6
8
10
12
14
16
gen_10
feb_10
mar_10
apr_10
mag_10
giu_10
lug_10
ago_10
set_10
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ago_11
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ott_11
nov_11
dic_11

Analisi dei primi 20 casi di *K. pneumoniae* pan-resistenti

- Riscontrati prevalentemente presso il presidio di B.go Trento (80%)
- 95% dei pazienti era stato esposto ad almeno 1 classe di antibiotici nei 30 giorni precedenti l'isolamento
- 15/5 (75%) aveva un precedente isolamento di CRKP (colistina sensibile)
- Mortalità cruda in ospedale del 27%
- Nessuna negativizzazione dopo terapia

Effectiveness of a Double-Carbapenem Regimen for Infections in Humans Due to Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae*

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6th Department of Internal Medicine, Hygeia General Hospital, Athens, Greece

Ertapenem plus doripenem or meropenem were given in three patients suffering from pandrug-resistant, KPC-2-positive *Klebsiella pneumoniae* bacteremia (2 patients) and urinary tract infection (1 patient), respectively. All responded successfully, without relapse at follow-up. The results obtained should probably be attributed to ertapenem's increased affinity for the carbapenemases hindering doripenem/meropenem degradation in the environment of the microorganism.

AAC 2013;57(6):2900

Successful Ertapenem-Doripenem Combination Treatment of Bacteremic Ventilator-Associated Pneumonia Due to Colistin-Resistant KPC-Producing *Klebsiella pneumoniae*

Giancarlo Ceccarelli,[a] Marco Falcone,[b] Alessandra Giordano,[a] Maria Lina Mezzatesta,[c] Carla Caio,[c] Stefania Stefani,[c] Mario Venditti[a]

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Antimicrobial Agents and Chemotherapy

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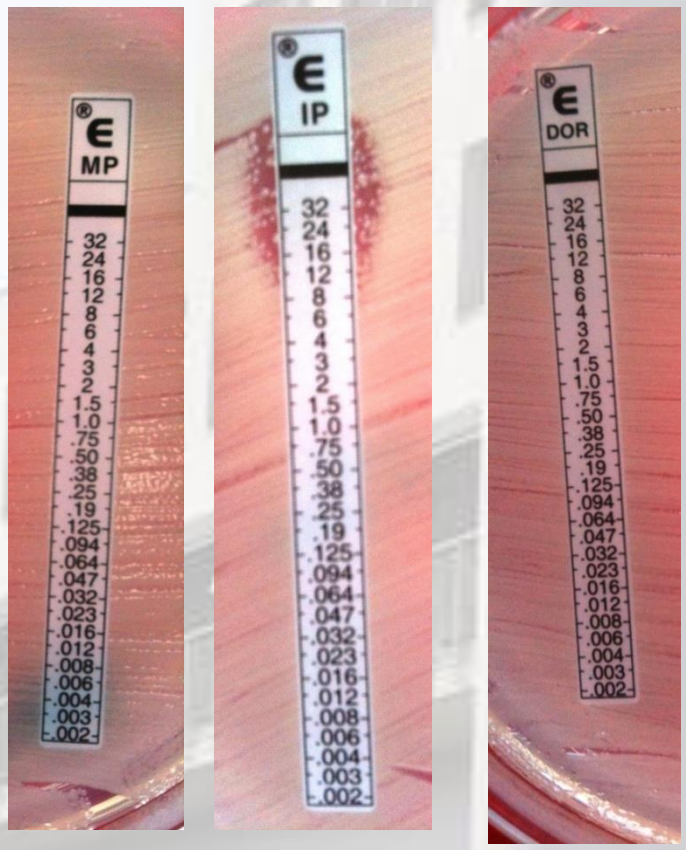
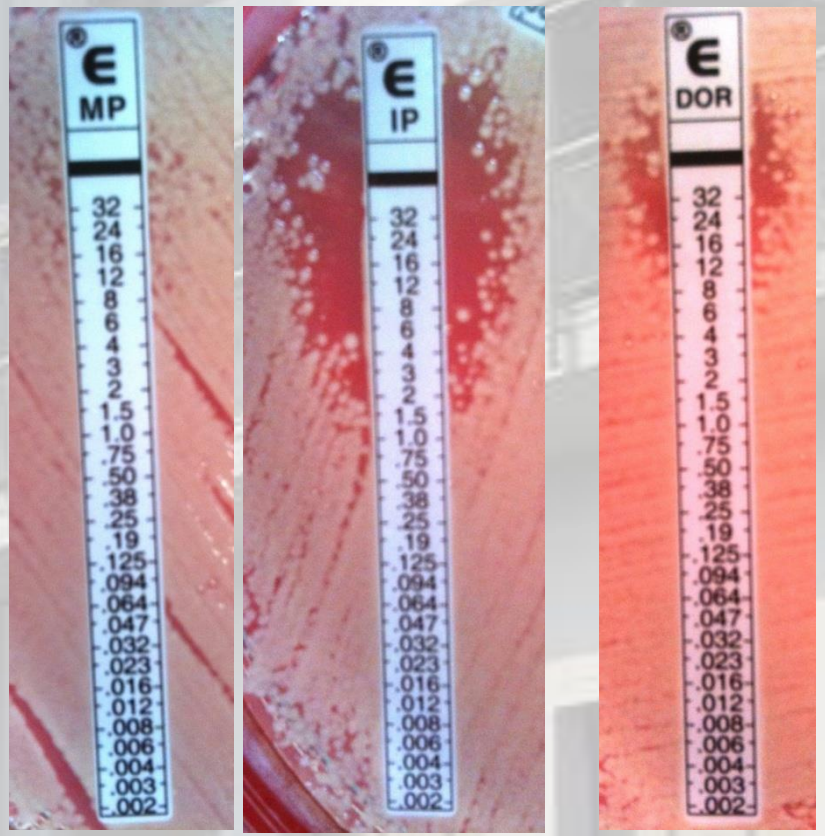
Antimicrob. Agents Chemother. 2013, 57(6):2900. DOI: 10.1128/AAC.00188-13.
Published Ahead of Print 9 April 2013.

MIC of carbapenems vs KPC-Kp with Etest on MHB agar alone (left) and with ertapenem 75 mg/L (right)





Imipenem S ≤ 2 mg/L,R > 8 mg/L
Meropenem S ≤ 2 mg/L,R > 8 mg/L
Doripenem S ≤ 1 mg/L,R > 4 mg/L
Ertapenem peak serum level 154 mg/L (1g IV dose)

Paziente di anni 65 affetta da cirrosi su base alcolica ed insufficienza renale cronica venne sottoposta a **trapianto di fegato** a settembre 2012.

Nei giorni successivi al trapianto sviluppò un quadro settico da E. faecium; trattata con adeguata terapia antibiotica gradualmente migliorò e fu dimessa 46 giorni dopo il trapianto.

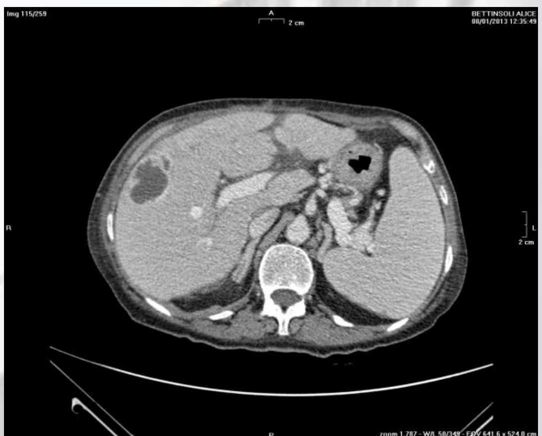
Dai tamponi di sorveglianza fu isolata una KPC

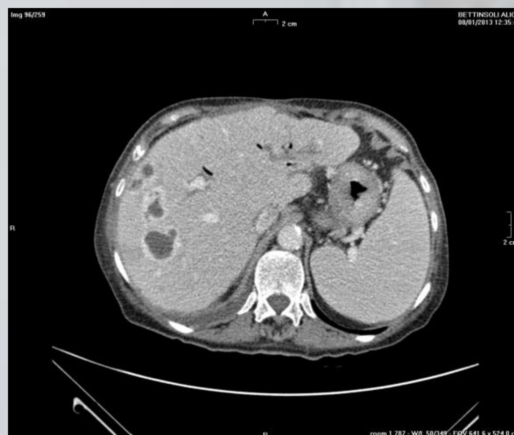
Fu nuovamente ricoverata alla fine di dicembre per insorgenza di quadro settico. Una TAC dell'addome rilevò una presenza di **multipli ascessi epatici** il maggiore di 3,5 cm. Di diametro. Le emoculture risultarono positive sia per E. coli che per KPC; iniziò una terapia con Meropenem, Tigeciclina e Gentamicina.

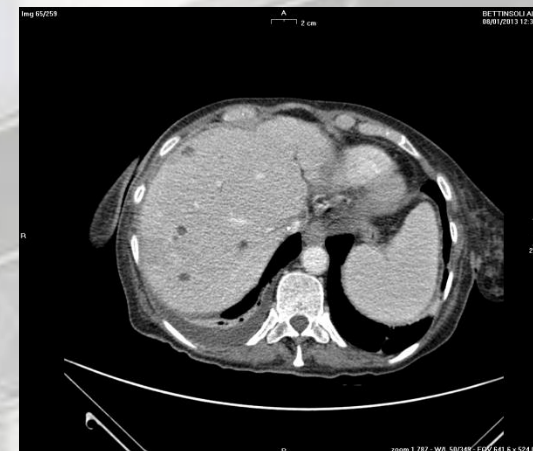
Le due lesioni maggiori furono drenate per via percutanea. Il ceppo isolato di K. Pneumoniae risultò ***panresistente***. Si instaurò terapia con ***Ertapenem + Meropenem***. Una PET TAC eseguita dopo un mese evidenziò un netto miglioramento. Un nuovo esame eseguito dopo tre mesi rilevò un ulteriore miglioramento.

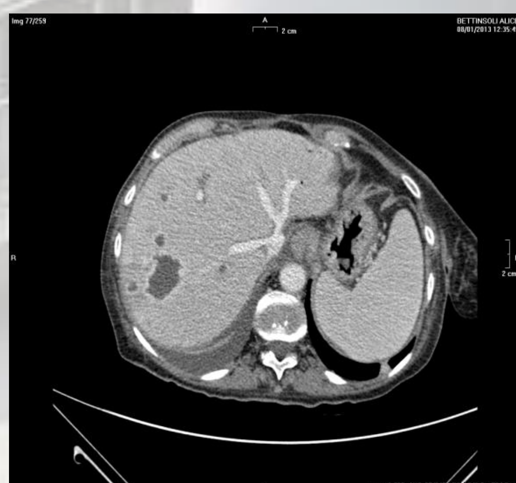
Attualmente la paziente, da più di 4 mesi dalla sospensione della terapia è a domicilio senza segni di infezione.

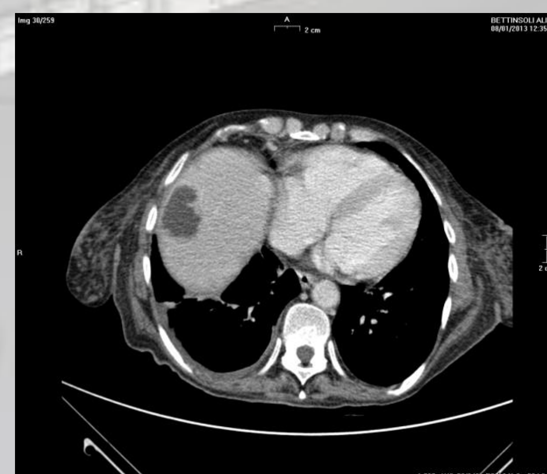
TAC Addome 8/01/13



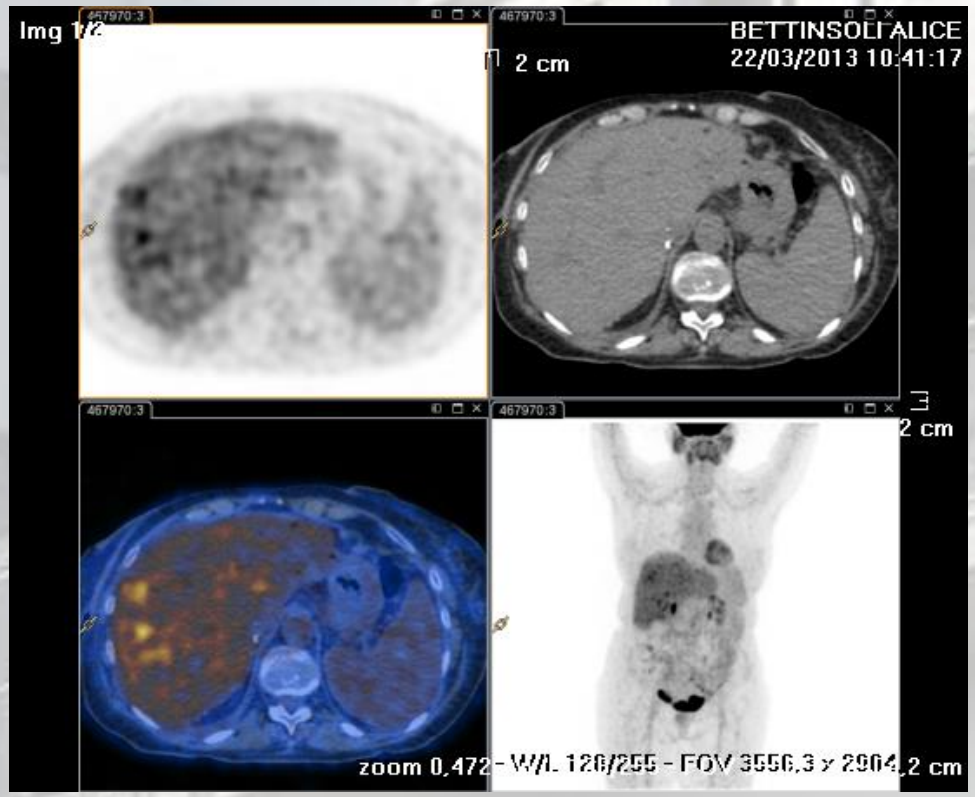








PET-TAC 22/03/13



La tomografia per emissione di positroni, eseguita con apparecchiatura PET-TC time of flight e scansioni dalla base cranica alla radice delle cosce un'ora dopo la somministrazione del fluorodesossiglucosio in presenza di valori di glicemia pari a 89 mg/dl, evidenzia discreta riduzione del metabolismo glucidico nelle note areole ascessuali epatiche. Attualmente si rileva moderata captazione in area mal definita alla TC di repere tra VII e VI segmento epatico (SUV max 5.2 vs 10.7), mentre non sono più apprezzabili metabolicamente le altre areole ubiquitarie nel fegato.
Non altre aree di aumentato metabolismo glucidico a livello dei restanti distretti corporei esaminati.

CONCLUSIONI: buona rispota alla terapia con modesto residuo ascessuale tra VI e VII segmento epatico

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Amikacin monotherapy for pan-resistant *Pseudomonas aeruginosa* sepsis

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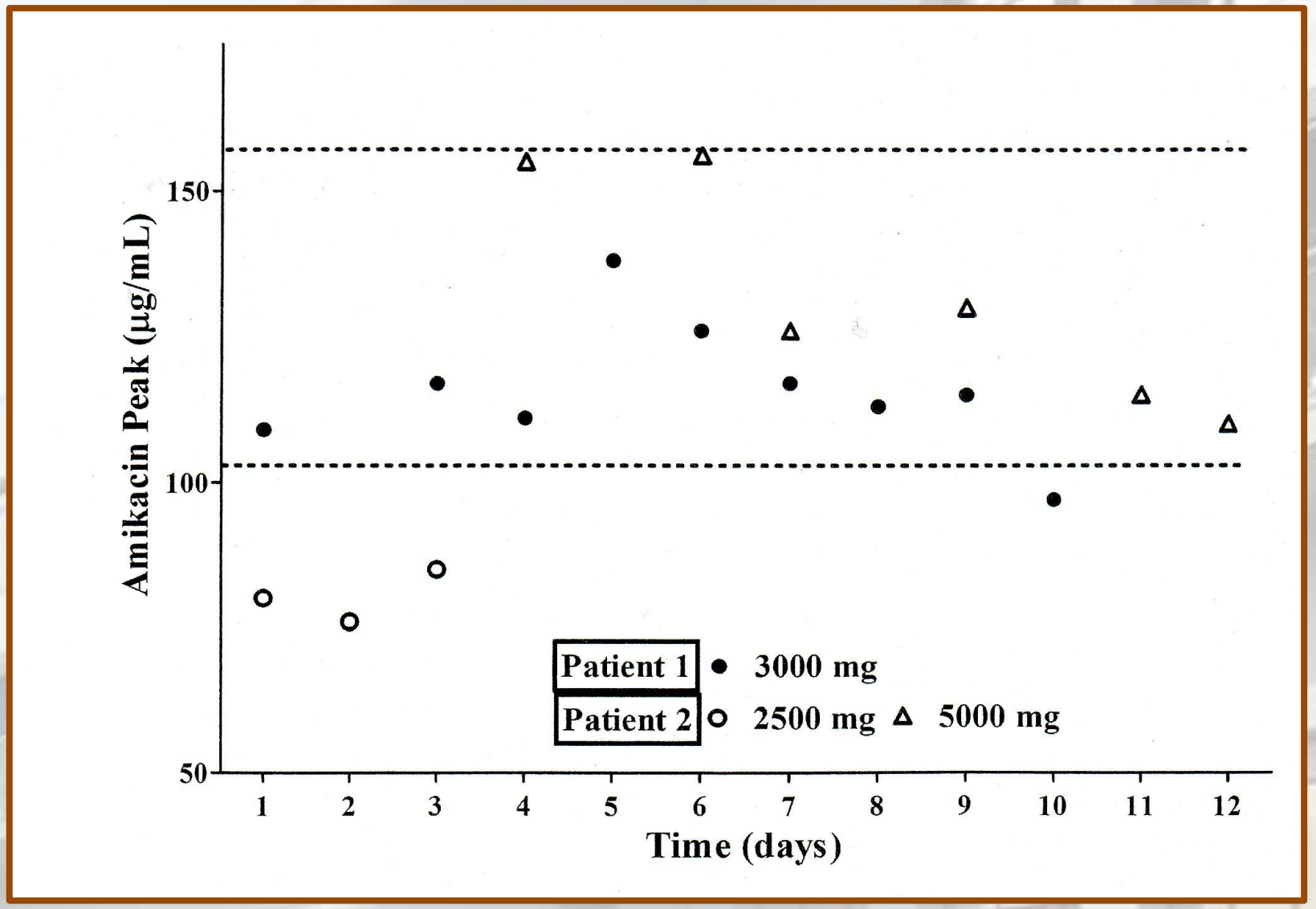
Amikacin Peak (µg/mL)
150
100
50
1
2
3
4
5
6
7
8
9
10
11
12
Time (days)
Patient 1
3000 mg
Patient 2
2500 mg
5000 mg

Table 1: Persistence of clinically relevant bacteria on dry inanimate surfaces.

Type of bacterium	Duration of persistence (range)	Reference(s)
Acinetobacter spp.	3 days to 5 months	[18, 25, 28, 29, 87, 88]
Bordetella pertussis	3 – 5 days	[89, 90]
Campylobacter jejuni	up to 6 days	[91]
Clostridium difficile (spores)	5 months	[92–94]
Chlamydia pneumoniae, C. trachomatis	≤ 30 hours	[14, 95]
Chlamydia psittaci	15 days	[90]
Corynebacterium diphtheriae	7 days – 6 months	[90, 96]
Corynebacterium pseudotuberculosis	1–8 days	[21]
Escherichia coli	1.5 hours – 16 months	[12, 16, 17, 22, 28, 52, 90, 97–99]
Enterococcus spp. including VRE and VSE	5 days – 4 months	[9, 26, 28, 100, 101]
Haemophilus influenzae	12 days	[90]
Helicobacter pylori	≤ 90 minutes	[23]
Klebsiella spp.	2 hours to > 30 months	[12, 16, 28, 52, 90]
Listeria spp.	1 day – months	[15, 90, 102]
Mycobacterium bovis	> 2 months	[13, 90]
Mycobacterium tuberculosis	1 day – 4 months	[30, 90]
Neisseria gonorrhoeae	1 – 3 days	[24, 27, 90]
Proteus vulgaris	1 – 2 days	[90]
Pseudomonas aeruginosa	6 hours – 16 months; on dry floor: 5 weeks	[12, 16, 28, 52, 99, 103, 104]
Salmonella typhi	6 hours – 4 weeks	[90]
Salmonella typhimurium	10 days – 4.2 years	[15, 90, 105]
Salmonella spp.	1 day	[52]
Serratia marcescens	3 days – 2 months; on dry floor: 5 weeks	[12, 90]
Shigella spp.	2 days – 5 months	[90, 106, 107]
Staphylococcus aureus, including MRSA	7 days – 7 months	[9, 10, 16, 52, 99, 108]
Streptococcus pneumoniae	1 – 20 days	[90]
Streptococcus pyogenes	3 days – 6.5 months	[90]
Vibrio cholerae	1 – 7 days	[90, 109]