Terapia delle infezioni da *Acinetobacter baumannii* MDR

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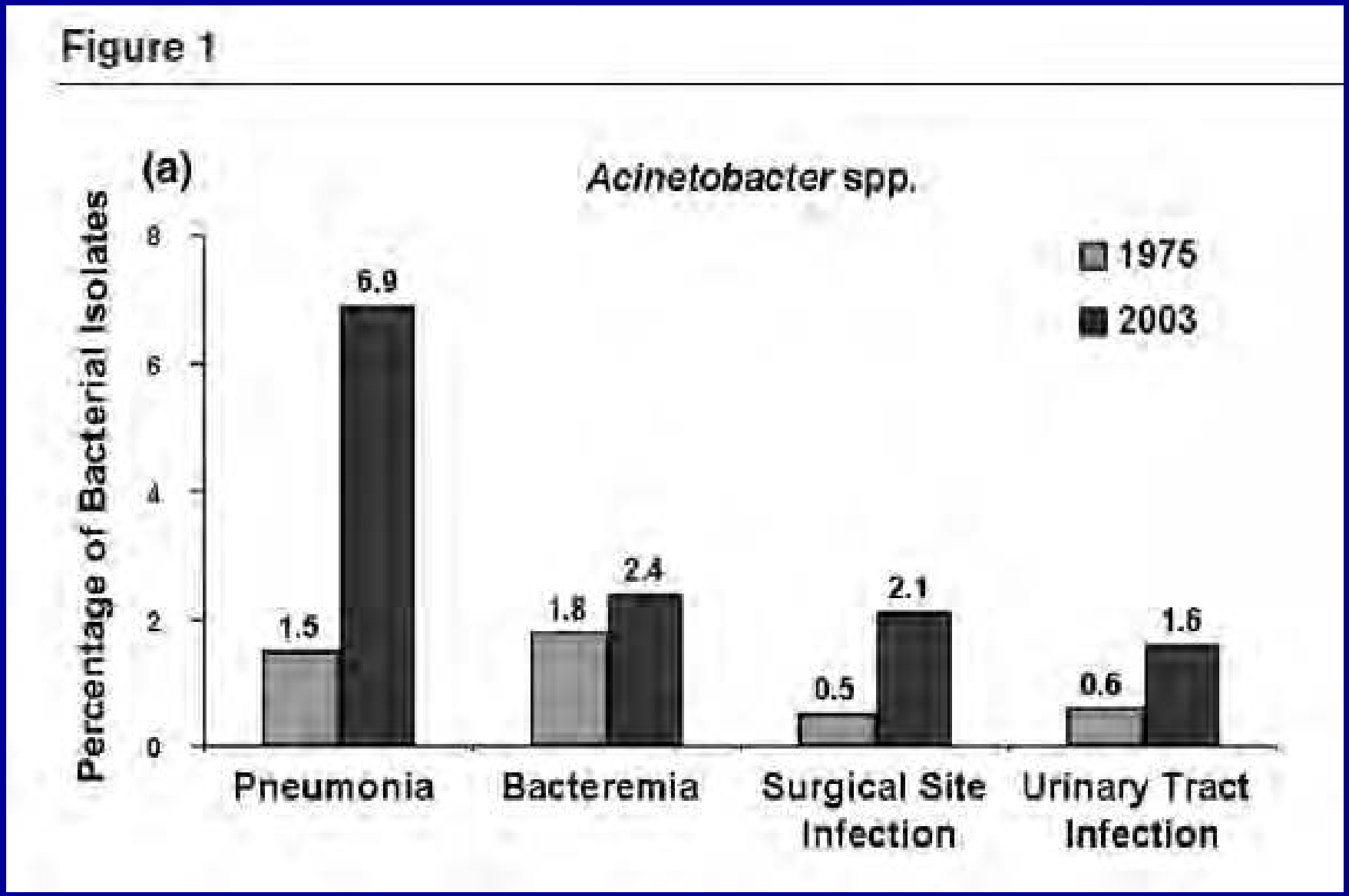
Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America

E: ***Enterococcus faecium*** **(VRE)**
S: ***Staphylococcus aureus*** **(MRSA)**
K: **ESBL-producing *E.coli* and *Klebsiella* spp.**
K. Pneumoniae **Carbapenemase-Hydrolyzing BLs**
A: ***Acinetobacter baumannii***
P: ***Pseudomonas aeruginosa***
E: ***Enterobacter*** **Species**

Clinical Infectious Diseases 2009; 48:1–12

Infezioni da *Acinetobacter* spp.



A. baumannii: evoluzione della resistenza al meropenem

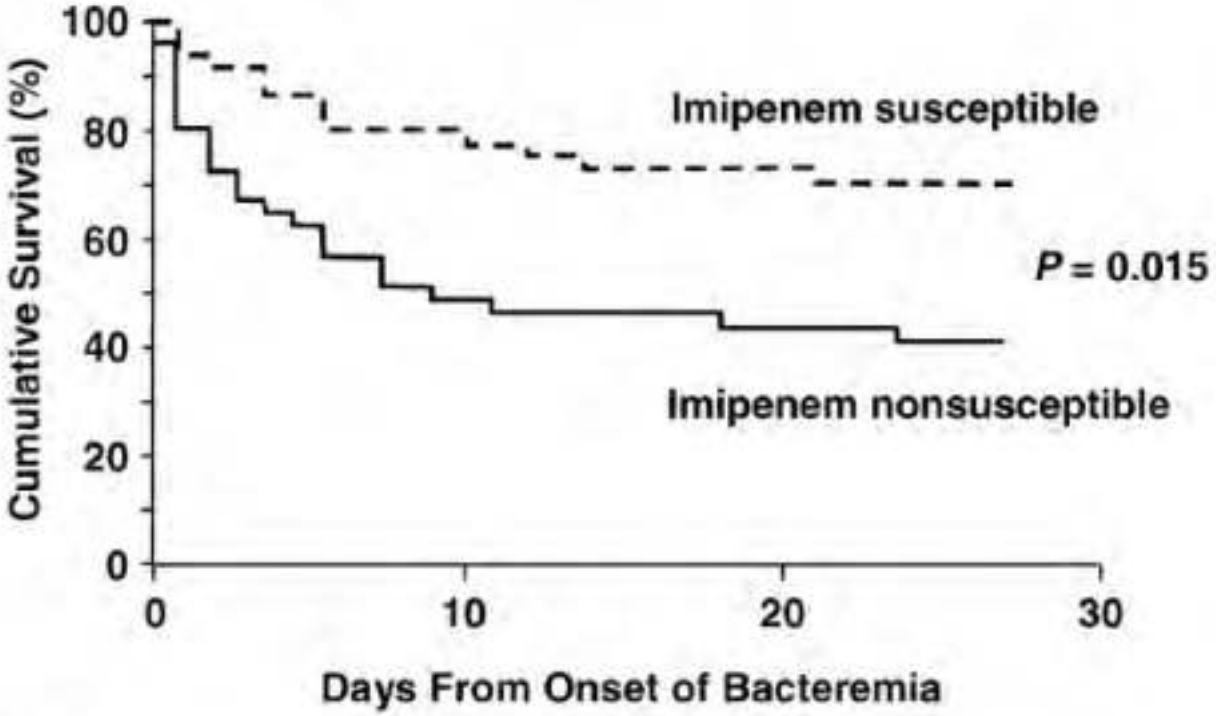
TABLE 2. Meropenem resistance in *Acinetobacter baumannii*[a]

Yr	No. of isolates	% of isolates that were:		
		Susceptible	Intermediate	Resistant
1998	171	84.8	9.4	5.9
1999	123	89.4	2.4	8.1
2000	309	76.4	4.5	19.1
2001	376	77.4	1.1	21.5
2002	437	72.5	4.4	23.1
2003	366	81.7	3.8	14.5
2004	554	75.3	6.1	18.6
2005	357	64.4	7.0	28.6

[a] Data were collected from the MYSTIC website (www.mystic-data.org).

Impatto sulla letalità delle batteriemie da *Acinetobacter* della resistenza ad imipenem

Figure 2



Impact of imipenem resistance on mortality of patients with *Acinetobacter* bacteremia. Reprinted with permission from Kwon and coworkers [12]. Copyright © 2007 Oxford University Press.

Acinetobacter baumannii: outbreaks da ceppi resistenti ai carbapenemi

< 2006

> 2006

Acinetobacter: meccanismi di resistenza

- Betalattamasi tipo OXA (Europa) che idrolizzano carbapenemici
- MBL tipo VIM ed IMP (Asia)
- OXA-58 + modifica porine di membrana = resistenza ai carbapenemici
- Se OXA da sola: MIC nel range della suscettibilità intermedia o ai limiti x carbapenemici
- Attività sinergica di colistina con RFP, sulbactam, carbapenemici

% MDR *Pseudomonas aeruginosa* & *Acinetobacter baumannii* isolates*

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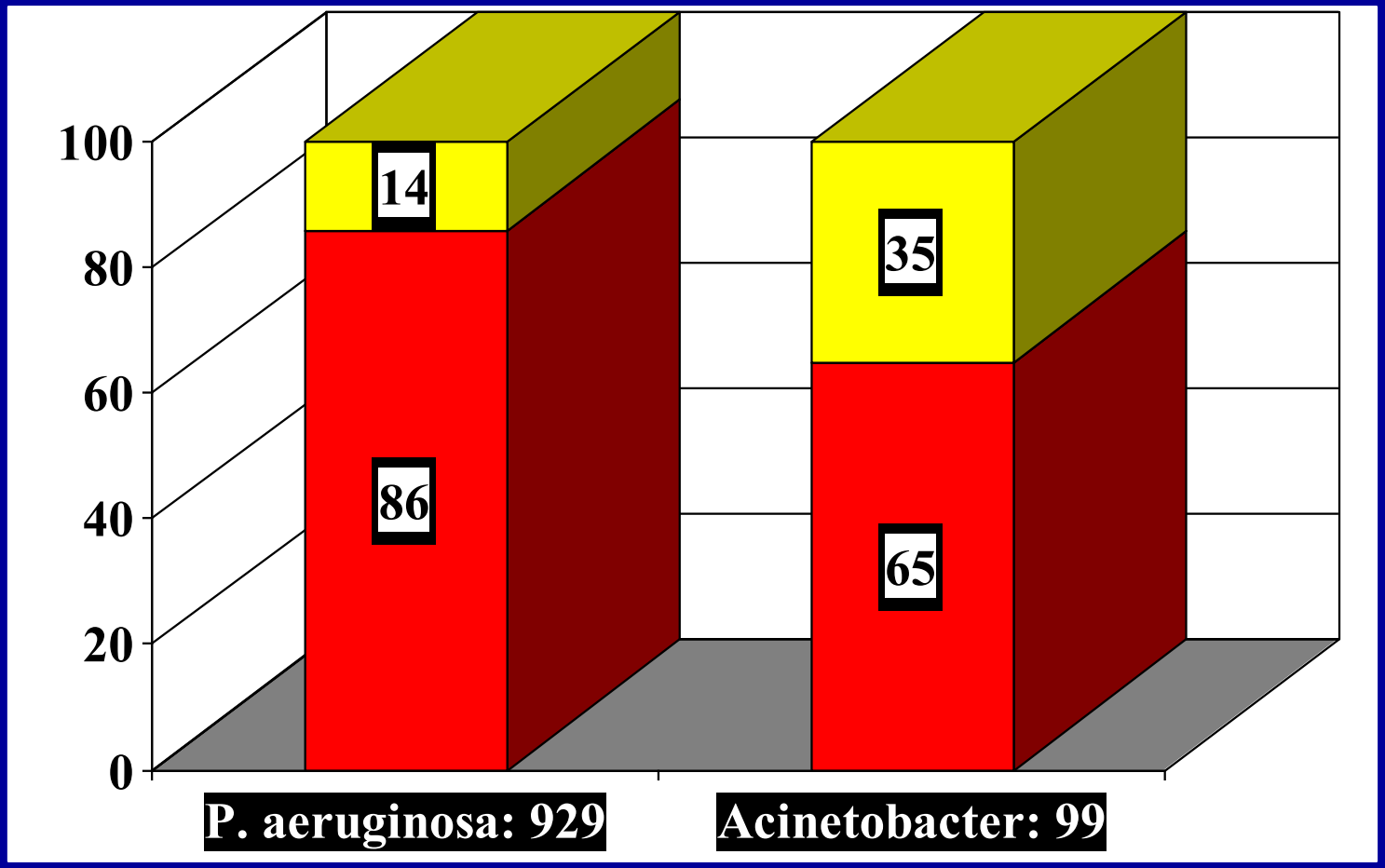


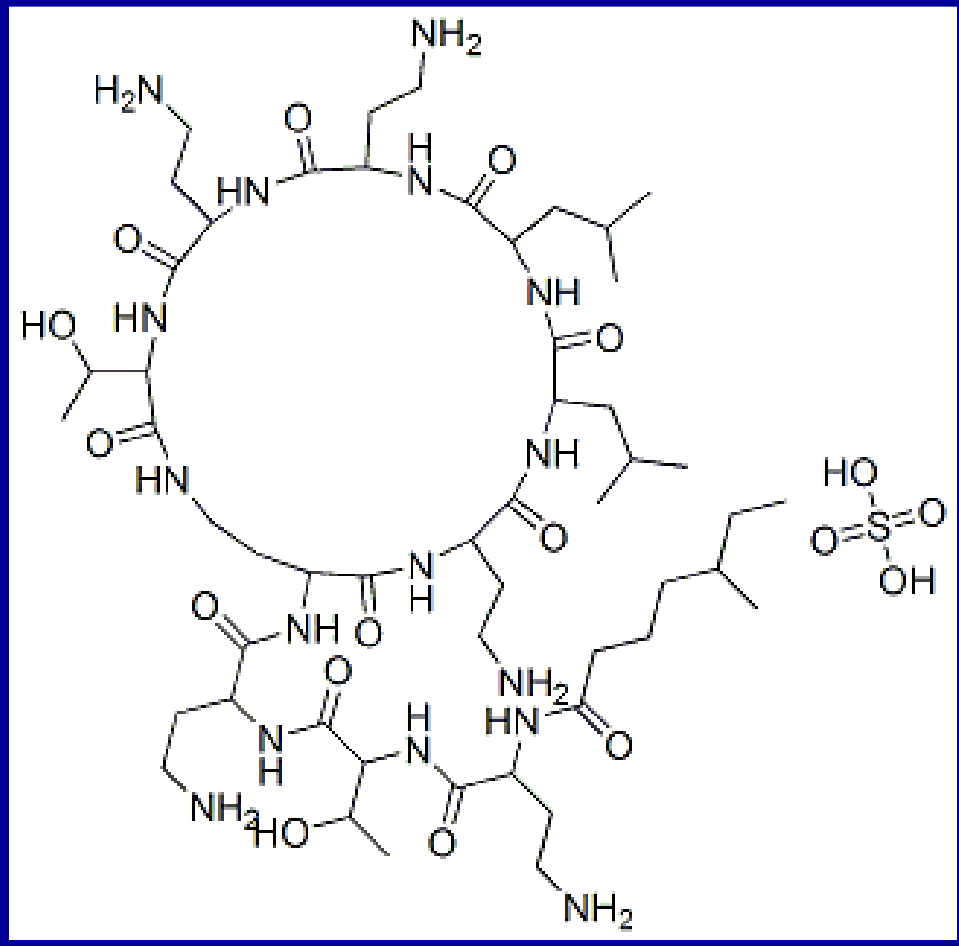
* Pisa Hospital, selected wards, 2001-2005

MDR *Acinetobacter baumannii*

Antibiotic	Non suscept.	Total	%
Aztreonam	34	34	100
Ciprofloxacin	35	35	100
Ceftazidime	32	32	100
Piperacillin	32	34	94
Cefepime	29	31	94
Pip/tazo	31	34	91
Meropenem	26	35	74
Imipenem	24	34	71
Amikacin	7	35	20

Colistin structure

- Cationic cyclic decapeptid linked to fatty acid chain (lipopetid) antibiotic of the polymyxin family
- **Colistin**: polymyxin E
- **Colistimethate sodium or colistin methanesulfonate**: hydrolisis to sulfomethil-derivatives and **colistin**



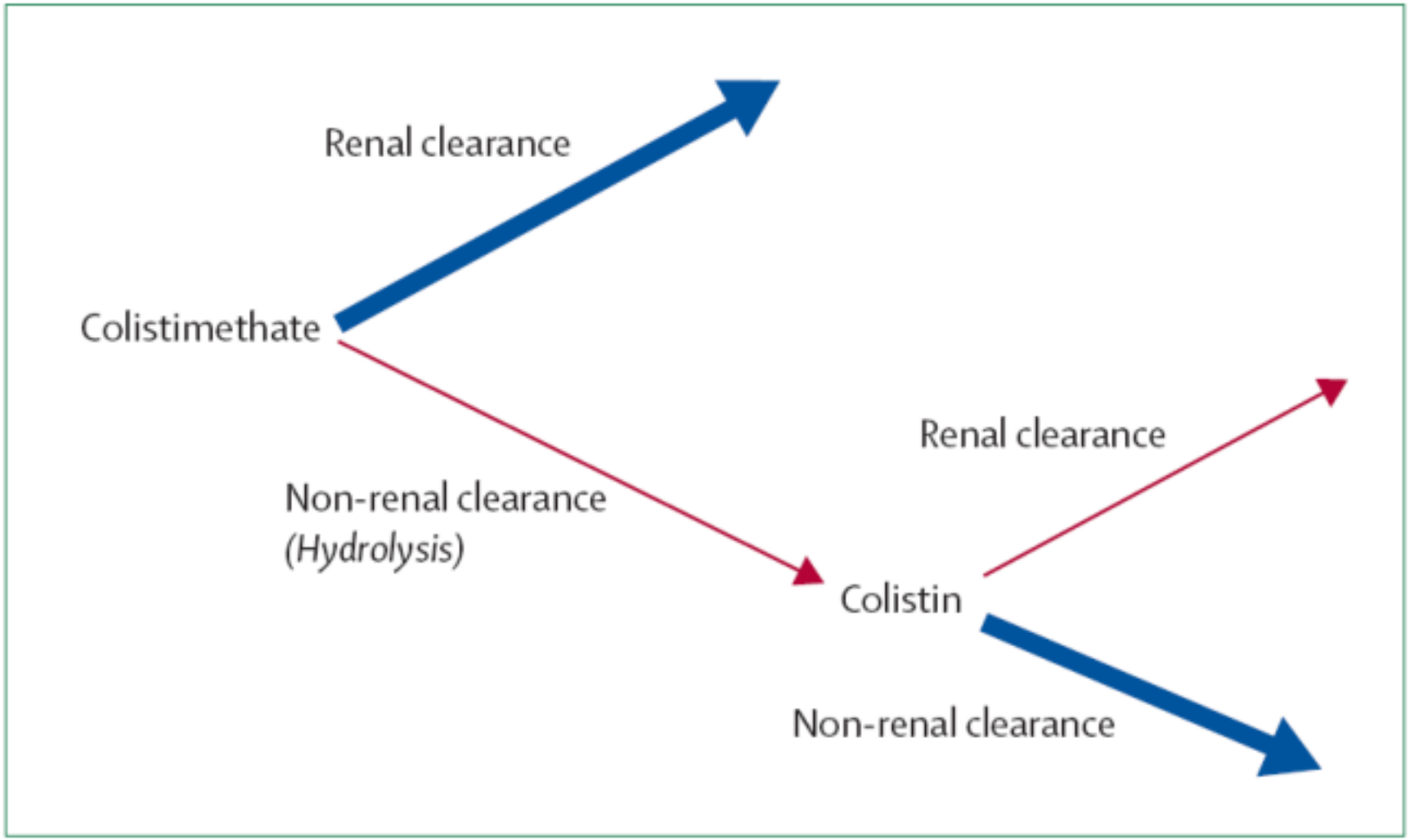


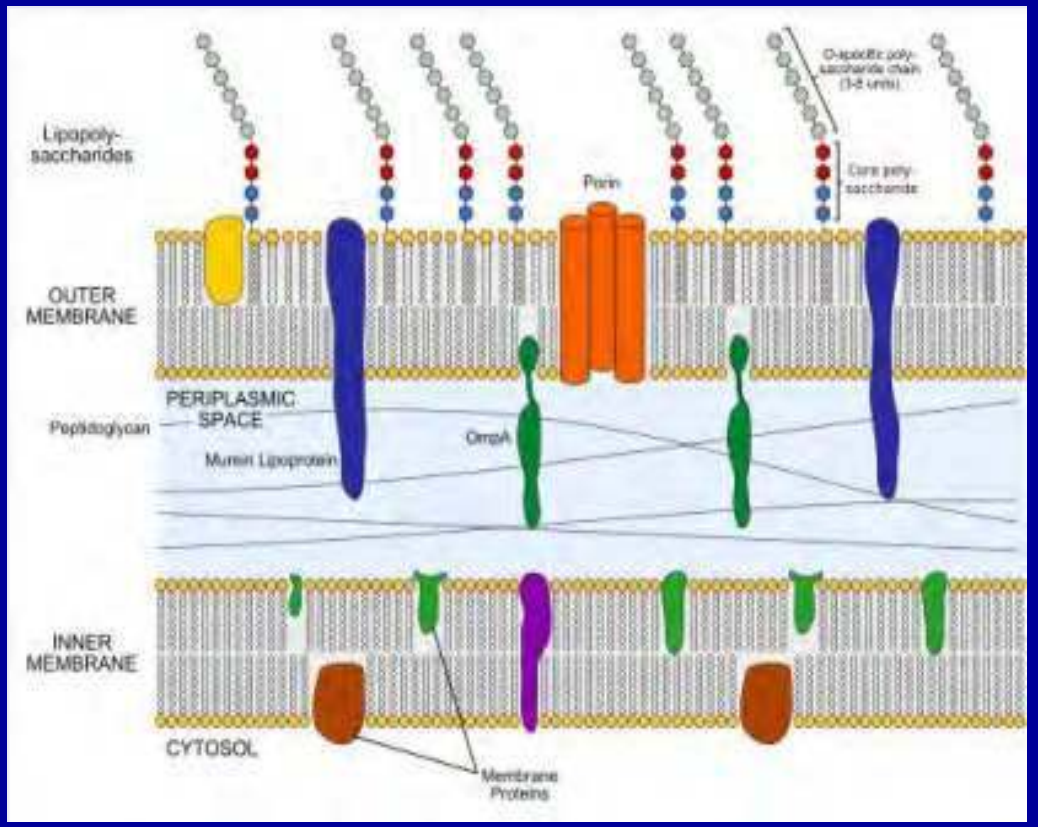
Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

Colimicina

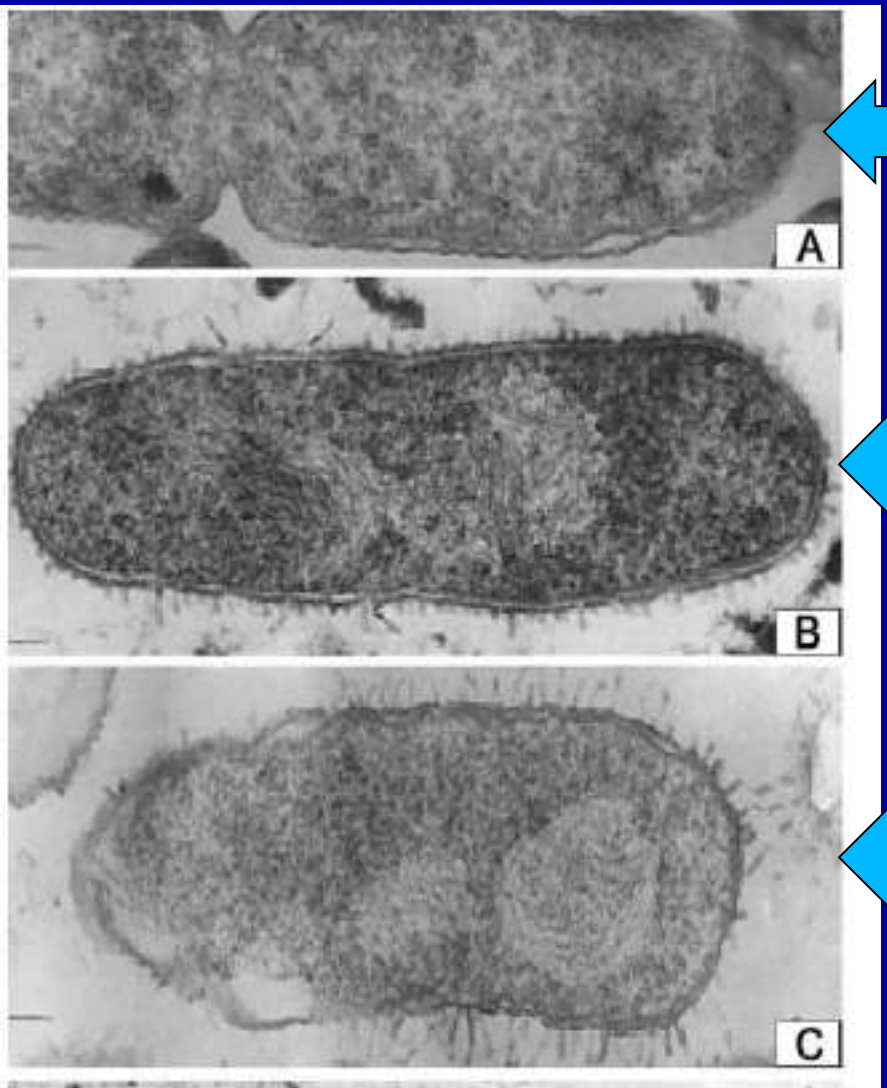
- **Colimicina**: nome del preparato commerciale che contiene **colistina metansulfonato o colistimetato**
- **Colimicina Ucb**: ogni flacone contiene 1 milione di colistimetato in polvere da ricostituire con 4 ml di SF
- Il colistimetato si trasforma in colistina e derivati solfometilati
- Il rapporto colistimetato/colistina è approssimativamente di 2-3:1
- 1 milione di colimicina contiene cioè da 300.000 a 500.000 UI di colistina base

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



Effetto di polimixina B e colistina metanesolfato su *P. Aeruginosa*



Cellula non trattata

Cellula trattata con polimixina B (25 μg/ml per 30 min)

Cellula trattata con colistina metanesolfato (250 μg/ml per 30 min)

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.

Colistin: susceptibility criteria

- Disk diffusion method (10μg colistin disk): susceptible if the **inhibition zone ≥11mm** (falsely susceptible results for some *S. maltophilia* and *Acinetobacter* spp.)

Breakpoints di suscettibilità e resistenza

	S	R
CLSI		
***Acinetobacter* spp.**	**≤ 2 mg/l**	**≥ 4 mg/l**
P.aeruginosa	**≤2 mg/l**	**≥ 8 mg/l**
EUCAST		
***Acinetobacter* spp.**	**≤ 2 mg/l**	**> 2 mg/l**
P.aeruginosa	**≤ 4 mg/l**	**> 4 mg/l**

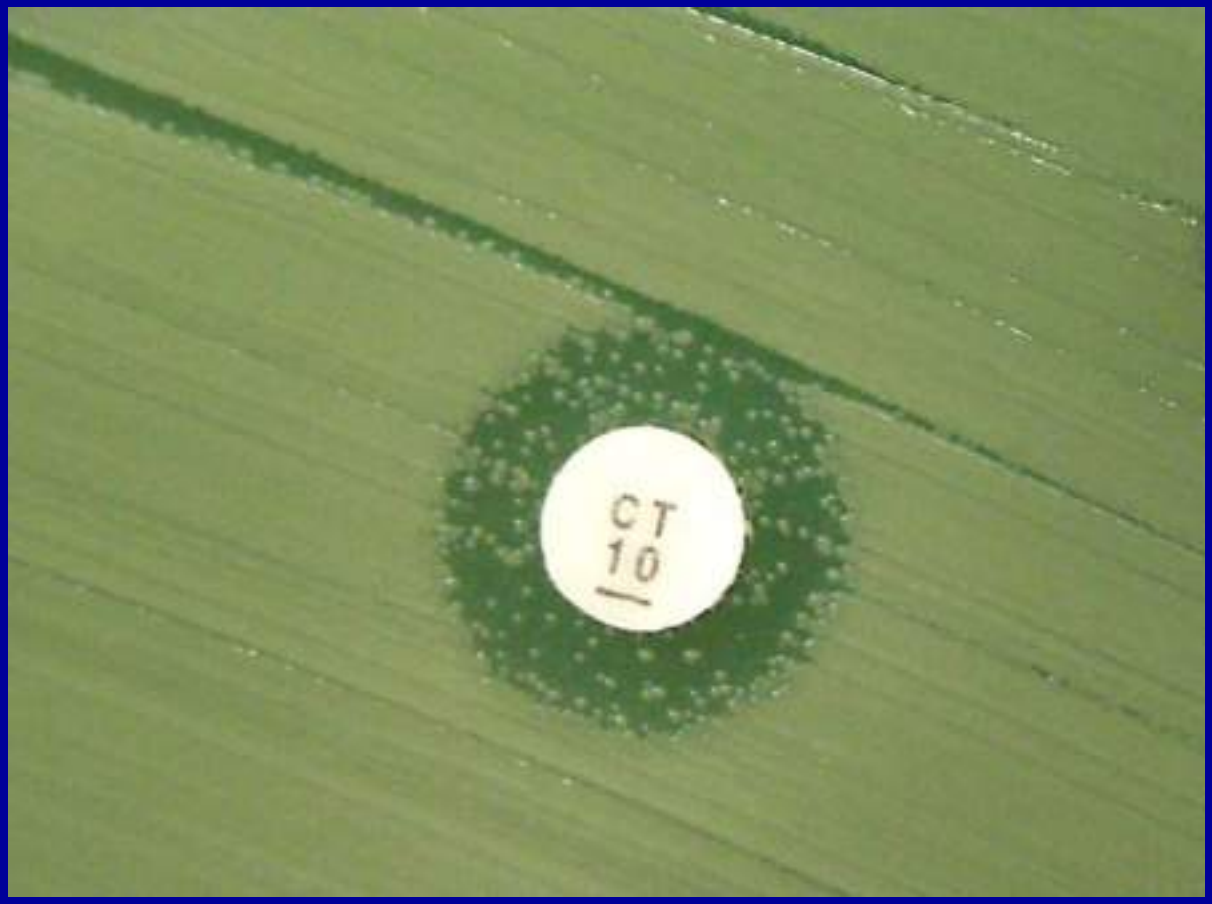
Colistina: attività verso i gram-negativi non fermentanti

Table 2. Antimicrobial activity of polymyxin B against non-fermentative Gram-negative bacteria and Enterobacteriaceae isolates[a]

Organism (number of isolates				% resistant
Non-fermentative Gram-nega				
Acinetobacter spp. (2621)				2.1
Aeromonas spp. (368)				28.3
Alcaligenes spp. (121)				36.4
B. cepacia (153)				88.2
P. aeruginosa (8705)				1.3
Pseudomonas spp. (non-*aeruginosa*; 282)	≤1	4	≤1 to >8	11.7
S. maltophilia (1256)	1	8	≤0.12 to >8	27.6
other non-enteric Gram-negative bacilli (302)	4	>4	≤1 to >8	55.6

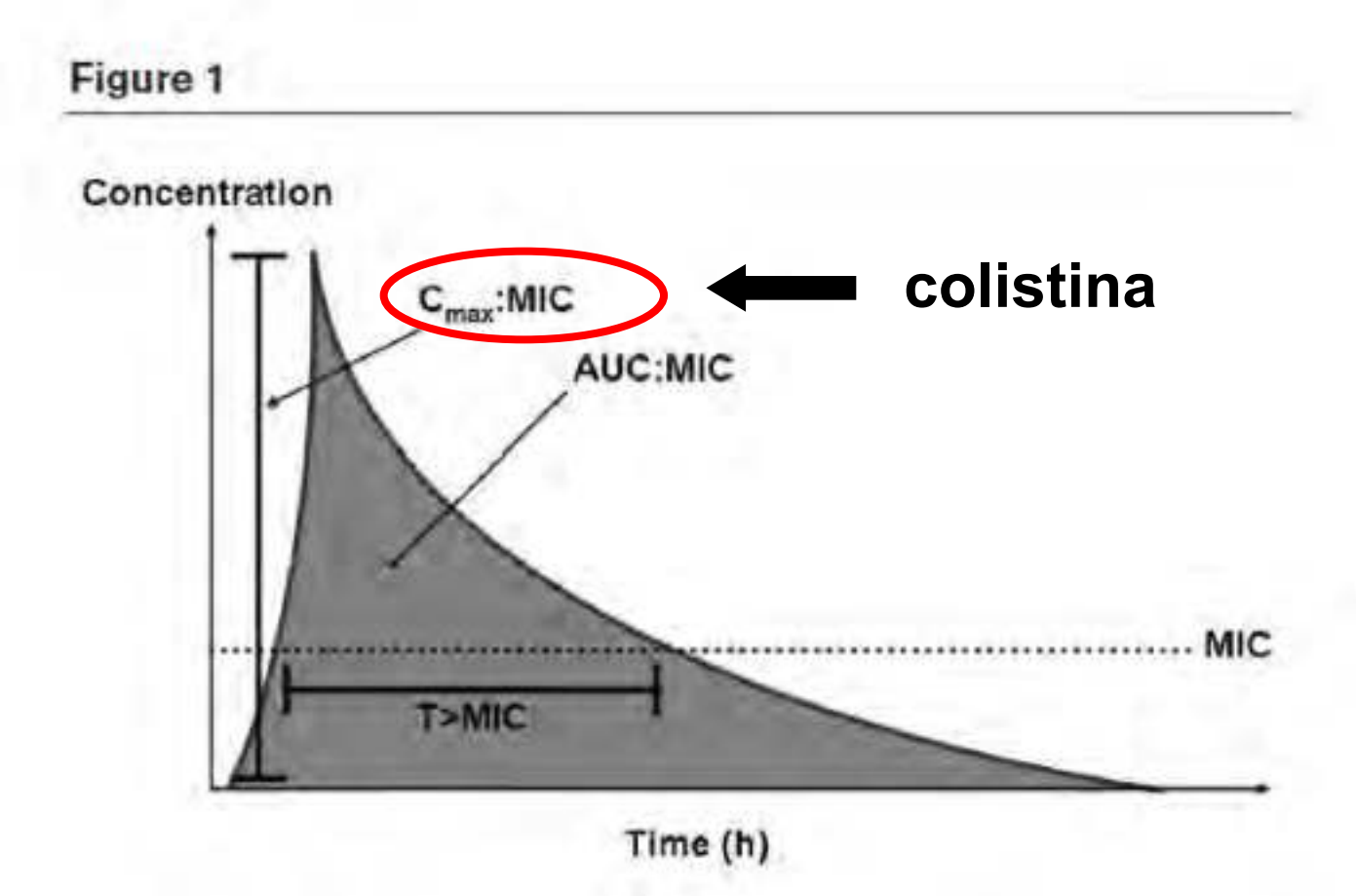
Attività contro gram-negativi non fermentanti

Eteroresistenza alla colistina in *Acinetobacter* (usualmente S)

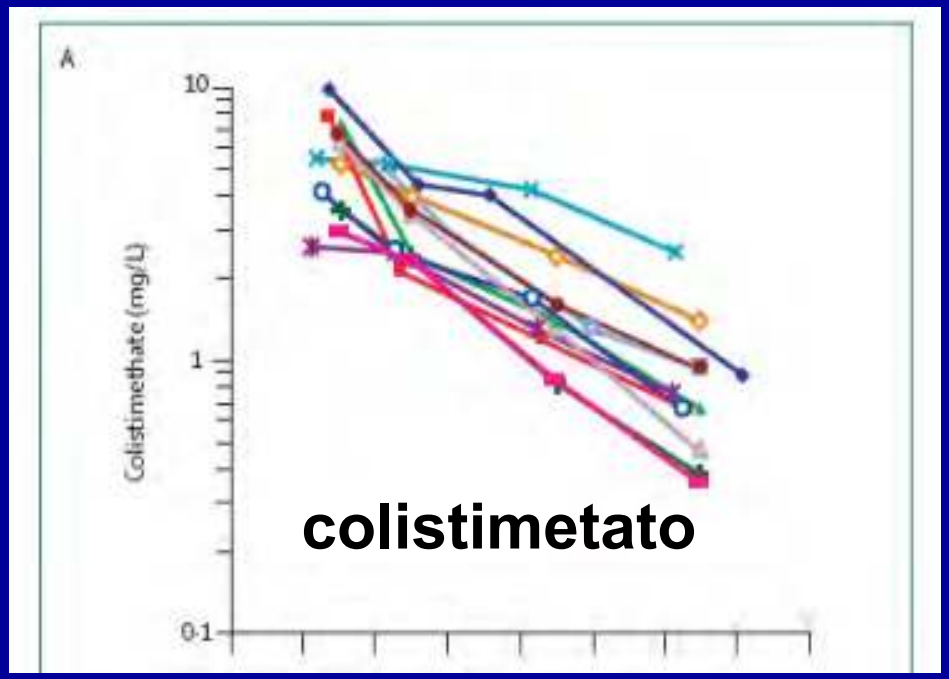


Resistenza piena alla colistina in *Klebsiella* (usualmente S)

Indice farmacodinamico: rapporto tra un parametro PK ed un parametro microbiologico



PK di colistimetato e colistina nella fibrosi cistica: steady-state con 1,5-3 Milioni ogni 8 ore



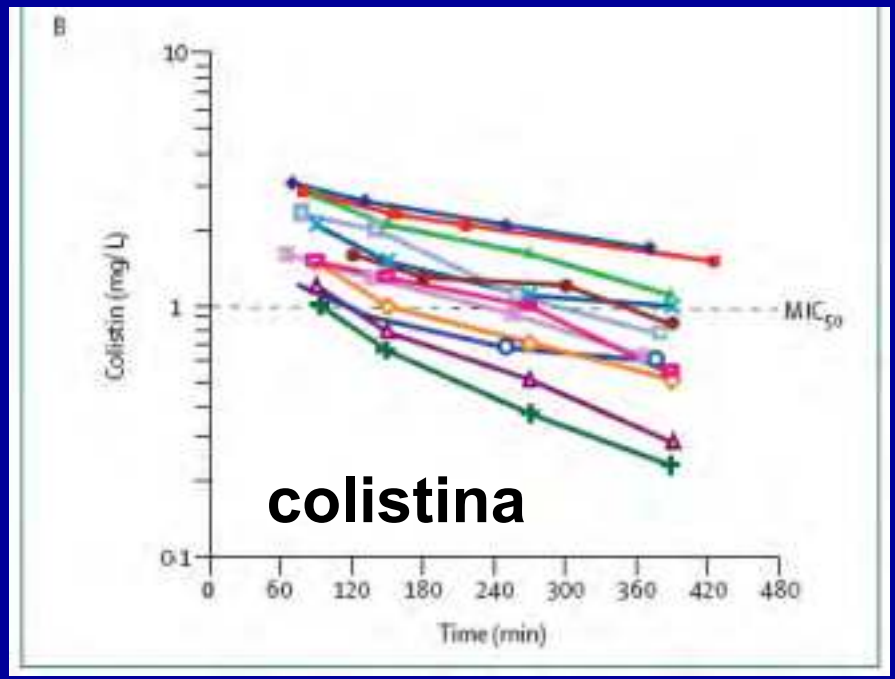


Figure 3: **Pharmacokinetics of colistimethate and colistin in cystic fibrosis patients**

Concentrations of colistimethate (A) and colistin (B) in plasma from patients with cystic fibrosis at steady state administered doses of colistimethate sodium (Colomycin) ranging from 1·63–3·11 mg/kg every 8 h of Colomycin (n=12).[31]

Colistin serum concentrations after iv administration in critically ill pts with serious MDR, gram-negative bacilli infections.

2.8 MIU CMS every 8 or 12 hrs for at least 2 days

At steady state:

mean (SD) colistin maximum concentrations were 2.93 (1.24) mg/L, minimum concentrations were 1.03 (0.44) mg/L

Apparent VD was 139,9 L and t 1/2 was 7.4 hours

Colistin-related nephrotoxicity was not observed

CMS dosage regimens were associated with suboptimal Cmax/MIC ratios for many strains of gram-negative bacilli currently reported as sensitive (MIC < or = 2 microg/mL).

Markou N. et al. Clin Ther 2008, 30 (1): 143-51

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2009, p. 3430–3436 Vol. 53, No. 8
0066-4804/09/$08.00+0 doi:10.1128/AAC.01361-08

Population Pharmacokinetic Analysis of Colistin Methanesulfonate and Colistin after Intravenous Administration in Critically Ill Patients with Infections Caused by Gram-Negative Bacteria▽†

D. Plachouras,[1]* M. Karvanen,[2] L. E. Friberg,[3] E. Papadomichelakis,[4] A. Antoniadou,[1] I. Tsangaris,[4] I. Karaiskos,[1] G. Poulakou,[1] F. Kontopidou,[1] A. Armaganidis,[4] O. Cars,[2] and H. Giamarellou[1]

3 Million unit every 8 hrs of CMS
Blood levels of CMS and Colistin
Colistin C.max after first dose: 0.60 mg/L
Colistin C.max at steady state: 2.3 mg/L
Time for steady state: 4 days
Usual MIC for *Ps.aeruginosa and A.baumannii*: 2 mg/L
Need for a loading dose ?

Dosaggio per via endovenosa

1 mg colistimetato sodico o colimicina = 12.500 UI

4-6 mg [illegible] in 3 dosi [illegible] g 60

80-160 [illegible] er adul[illegible]

Insuffi[illegible]

Creatinina 1.3-1.5 mg/dl: 2 milioni ogni 12 h

Creatinina 1.6-2.5 mg/dl: 2 milioni ogni 24 h

Creatinina > 2.6 mg/dl: 2 milioni ogni 36 h

Dose colistina: questione aperta

Journal of Antimicrobial Chemotherapy (2008) **61**, 636–642
doi:10.1093/jac/dkm511
Advance Access publication 28 January 2008

JAC

Comparison of once-, twice- and thrice-daily dosing of colistin on antibacterial effect and emergence of resistance: studies with *Pseudomonas aeruginosa* in an *in vitro* pharmacodynamic model

Phillip J. Bergen[1], Jian Li[1], Roger L. Nation[1]*, John D. Turnidge[2], Kingsley Coulthard[3,4] and Robert W. Milne[4]

No difference in overall bacterial kill was observed when the recommended maximum daily dose was adminestered at 8,12 or 24 h intervals.

However, the 8 hourly regimen appeared most effective at minimizing emergence of resistance

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

Journal of Antimicrobial Chemotherapy (2007) **59**, 473–477
doi:10.1093/jac/dkl512
Advance Access publication 8 February 2007

JAC

In vitro pharmacodynamics of colistin against *Acinetobacter baumannii* clinical isolates

Roxanne J. Owen[1], Jian Li[1]*, Roger L. Nation[1] and Denis Spelman[2]

Monotherapy with colistin and long dosage intervals (ie 24h) may be problematic for treatment of infections caused by colistin heteroresistant *A.baumannii*

Effetti avversi

Nefrotossicità (necrosi tubulare acuta)

Neurotossicità: vertigini, debolezza, parestesie faciali, disturbi visivi, confusione, atassia, blocco neuromuscolare che può portare ad insufficienza respiratoria od apnea

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

Colistin for MDR *P.aeruginosa* & *Acinetobacter* spp. infections

Cystic Fibrosis (IV or nebulized)

VAP & bacteremia in ICU & SOT

Meningitis (case reports)

Monotherapy or combination therapy

Esperienze cliniche con colimicina

Reference	Number of patients	Conditions treated (%)	Pathogens (%)	Colistimethate sodium dose*	Therapy duration (SD)	Outcome
Reina et al[31]	55	Ventilator-associated pneumonia (53%), primary bacteraemia (16%), urinary tract infection (18%), and other infections (13%)	*P aeruginosa* (35%), *A baumannii* (65%)	5·0 mg/kg per day (maximum daily dose of 300 mg) divided into three doses; colistimethate sodium from Laboratory Bristol-Myers Squibb (Argentina); product information not available.	13 (5) days	Clinical cure on day 6 of treatment, 15%. Bacteriological cure not assessed
Michalopoulos et al[17]	1	Bacteraemia	*A baumannii*	160 mg per 24 h by continuous intravenous infusion; product information not available.	14 days	Cured
Michalopoulos et al[18]	43	Various intensive care unit-acquired infections, pneumonia (72%), bacteraemia (33%), sinusitis (2%), urinary tract infection (5%), catheter-related infection (7%), and surgical wound infection (5%)	*P aeruginosa* (81%), *A baumannii* (19%)	240 mg every 8 h; Colomycin or colistimethate sodium from Norma (13 333 units/mg; Athens, Greece)	18·6 (5·8) days	Clinical cure of infection observed in 69·8% of patients, clinical improvement in 4·7%, and clinical failure in 25·6%
Falagas et al[32]	17	Pneumonia (68%), bacteraemia (5%), urinary tract infection (11%), meningitis (11%), and surgical site infection (5%)	*P aeruginosa* (60%), *A baumannii* (25%), *K pneumoniae* (10%), *Enterobacter cloacae* (5%)	Daily dose 352 ± 168 mg Colomycin or colistimethate sodium from Norma (Athens, Greece)	43·4 (14·6) days	Cured 52·6%, improvement 21·1%, unresponsiveness 26·3%
Levin et al[19]	59	Pneumonia (33%), urinary tract infection (20%), primary bloodstream infection (15%), central nervous system infection (8%), peritonitis (7%), catheter-related infection (7%), surgical site infection (7%), and otitis media (2%)	*P aeruginosa* (35%), *A baumannii* (65%)	6·67–13·3 mg/kg per day up to a maximum dose of 800 mg; Coly-Mycin or colistimethate sodium from Bellon (Rhône-Poulenc Rorer, France; product information not available.	12·6 (6·8) days	A good outcome occurred for 58% of the patients with 25% in pneumonia, 83% in urinary tract infection, 78% primary bloodstream infection, 80% in central nervous system infection, 50% in peritonitis, 75% in catheter-related infection, 60% in surgical site infection, and in 100% with the patient with otitis media infection

Li J. et al. Lancet Infect Dis 2006; 6: 589-601

Esperienze cliniche con colimicina

Reference	Number of patients	Conditions treated (%)	Pathogens (%)	Colistimethate sodium dose*	Therapy duration (SD)	Outcome
Conway et al[47]	53	Acute respiratory exacerbations in patients with cystic fibrosis	*P aeruginosa*	160 mg every 8 h, Colomycin	12 days	All patients showed clinical improvement
Markou et al[48]	24	Ventilator-associated pneumonia (62·5%), empyema thoracis (4%), post-traumatic meningitis (4%), sinusitis (4%), urinary tract infection (4%), catheter-related sepsis (12·5%), and sepsis of unknown primary origin (17%)	*P aeruginosa* (76%), *Acinetobacter* spp (24%)	3 million units every 8 h, colistimethate sodium from Norma (Athens, Greece)	13·5 days (range 4–24)	Clinical response 73%, survival at 30 days 57·7%
Jimenez-Mejias et al[49]	1	Meningitis	*A baumannii*	5 mg/kg every day in four doses; product information not available	15 days	Cured
Garnacho-Montero et al[51]	21	Ventilator-associated pneumonia (100%)	*A baumannii*	2·5–5·0 mg/kg every 8 h, colistimethate sodium from Bellon (Rhône-Poulenec Rorer, France); product information not available	14·7 (4·1) days	Cured 57%
Linden et al[52]	23	Pneumonia (78%), bacteraemia (35%), wound infections (13%), intra-abdominal infections (26%), endocarditis (4%), and other infection (22%)	*P aeruginosa*	All patients required dose adjustment for diminished or absent renal function; Coly-Mycin	Median 17 days (range 7–36)	Favourable therapeutic outcome 61%, unfavourable therapeutic outcome 39%, died while receiving therapy 30%, experienced relapse 13%, survived through end of therapy 70%, and through end of hospitalisation 39%
Kasiakou et al[53]	2	Fixation device-related orthopaedic infections	*A baumannii*	A bolus intravenous injection of 80 mg colistimethate sodium followed by 480 mg in a continuous 24 h infusion (patient 1); 160 mg every 8 h (patient 2); Colomycin	36 and 22 days	Cured
Jimenez-Mejias et al[54]	1	Meningitis	*A baumannii*	5 mg/kg every day in four doses; product information not available	30 days	Cured
Fulnedy et al[55]	1	Post-surgical meningitis	*A baumannii*	1·25 mg/kg every 12 h; product information not available	10 days	CSF remained free of *A baumannii* throughout the rest of the hospitalisation

*Doses were for patients with normal renal function. Administration route was short intravenous infusion (5–30 min) unless specified otherwise. In cases where the product information is not available, it is uncertain whether the dose is in terms of colistimethate sodium or colistin base activity.

Li J. et al. Lancet Infect Dis 2006; 6: 589-601

Combination antibiotic therapy

- May be the (only) answer for MDR bugs
- “In vitro“ synergism
- “In vivo” increase of SBA
- “In vivo” increase of antibacterial activity in infected tissue (?)
- Control of the emergence of resistance to any single drug (?)
- Toxicity, cost

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

Effetto sinergico della polimixina con altri antimicrobici (time-kill methods)

Organism (no. of isolates)[a]	Polymyxin studied	Combined-drug synergy (% of isolates with synergy/% with bactericidal activity)	Reference
A. baumannii (NA)	Polymyxin B	Rifampin (100/100); imipenem (100/100)	26
A. baumannii (6)	Colistimethate	Rifampin (100/100)	60
A. baumannii (8)	Polymyxin B	Rifampin (88/88); imipenem (88/88); rifampin + imipenem (100/100)	186
A. baumannii (8)	Colistimethate	Rifampin (100/100)	160
A. baumannii (13)	Colistin	Minocycline (92/69)	170
P. aeruginosa (5)	Polymyxin B	Rifampin (100/100)	139
P. aeruginosa (17)	Colistimethate	Rifampin (12/12)	59
P. aeruginosa (2)	Colistin	Ceftazidime (100/100); ciprofloxacin (0/0)	67
P. aeruginosa (2)	Colistin	Rifampin (100/100)	171
P. aeruginosa (13)	Polymyxin B	Azithromycin (70/70)	19
P. aeruginosa (10)	Polymyxin B	Azithromycin (40/40); imipenem (80/80); rifampin (90/90); rifampin + imipenem (100/100)	93
S. maltophilia (24)	Colistimethate	Rifampin (63/not stated); cotrimazole (42/not stated)	58
K. pneumoniae (16)	Polymyxin B	Rifampin (89/89); imipenem (44/44)	20
S. marcescens (4)	Polymyxin B	Rifampin (100/100)	134
S. marcescens (13)	Colistimethate	Cotrimazole (85/85), rifampin (not stated/not stated); chloramphenicol (not stated/not stated)	173

[a] NA, not available.

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

“Colistin plus Rifampin combination was synergic or partially synergic against 5 *A. baumannii* strains tested by chekerboard method”

Evaluation of the activities of two-drug combinations of rifampicin, polymyxin B and ampicillin/sulbactam against *Acinetobacter baumannii.*

Tascini C, Menichetti F, Bozza S, Del Favero A, Bistoni F.

J Antimicrob Chemother. 1998 Aug;42(2):270-1.

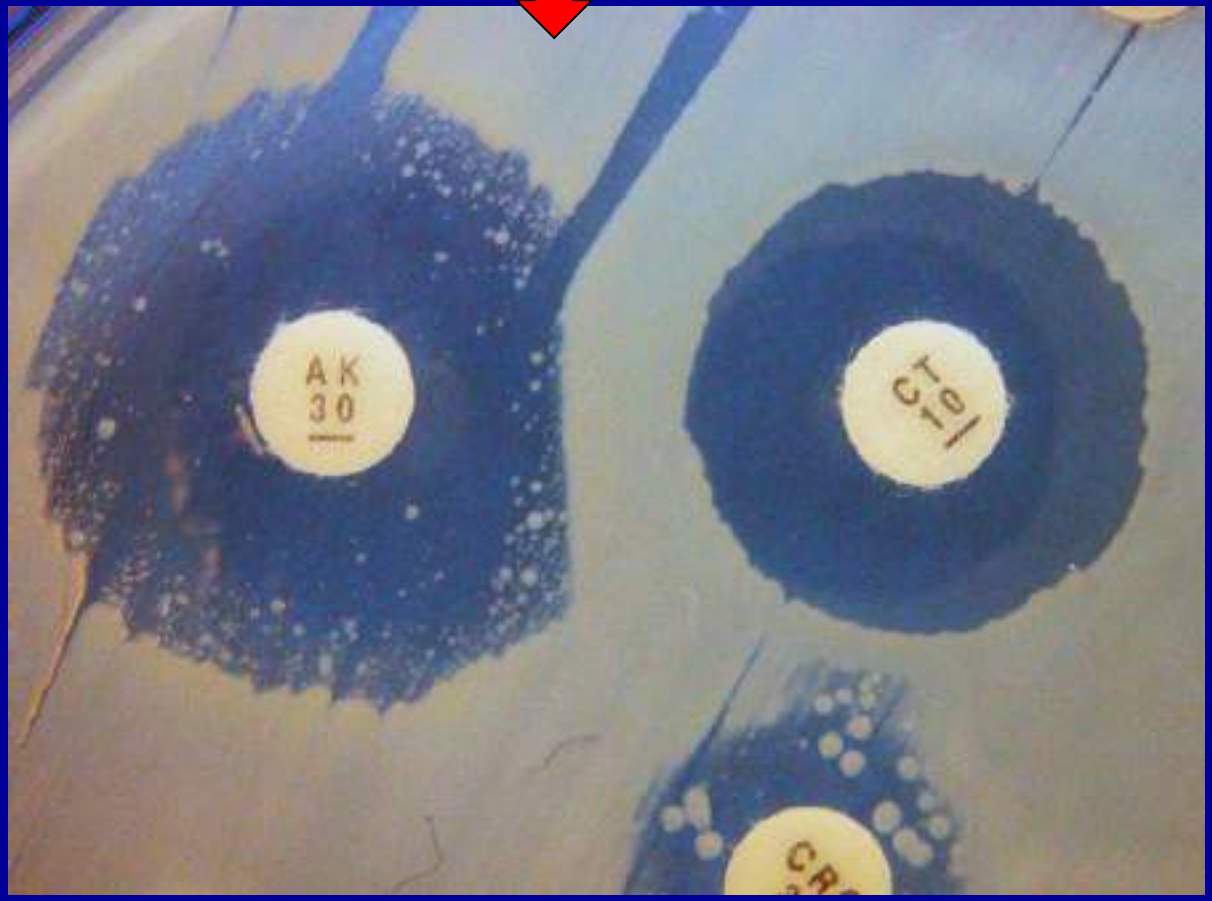
A.baumannii

Coli MIC: 0,25 mg/l (S)
RFP MIC: 6 mg/l (R)
Coli (+RFP): 0,125 mg/l
RFP (+Coli): 4 mg/l

Sinergismo colistina-rifampicina

Sinergismo colistina + ampicillina/sulbactam

Antagonismo colistina-amikacina



Why Colistin plus Rifampin ?

- Two-steps, sequential mechanism of action
- Colistin disrupt the outer bacterial cytoplasmic membrane
- Rifampin inhibit DNA-dependent RNA-polymerase at the ribosomal β-subunit
- Some preliminary experience on *A. baumannii*

Colimicina + rifampicina od altri antibiotici nel trattamento di gravi infezioni da gram-negativi MDR

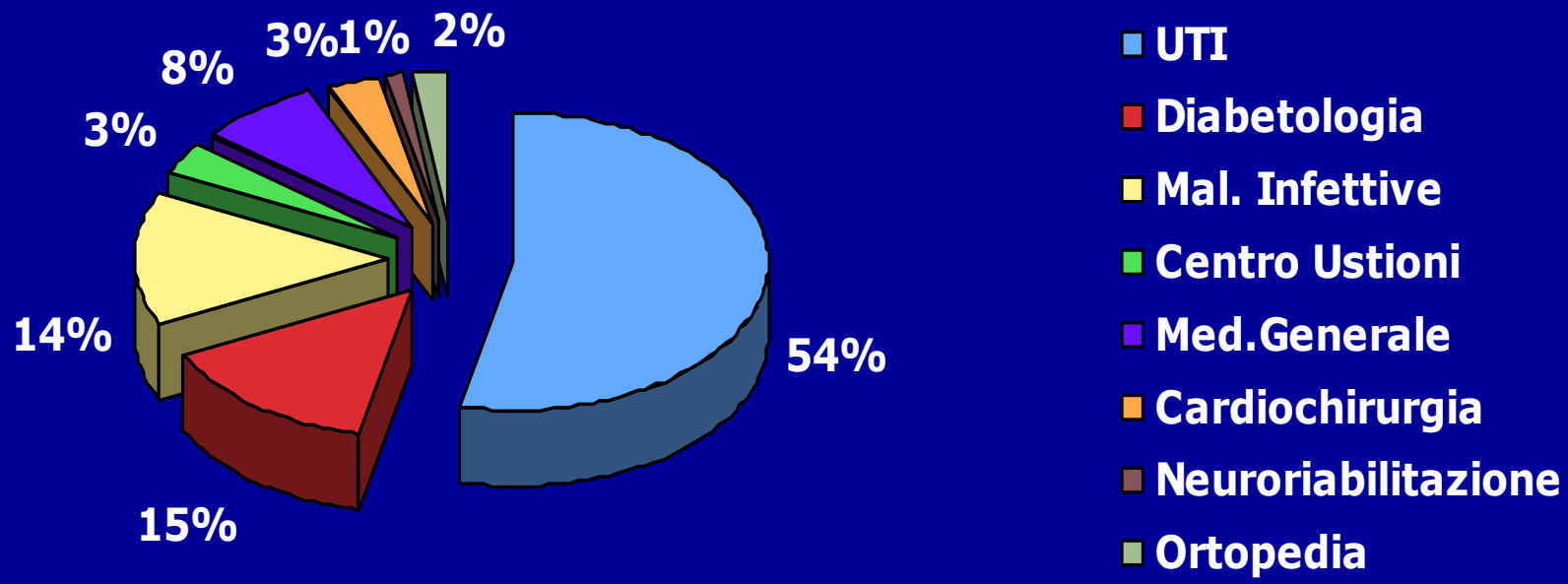
Serena Fondelli, Carlo Tascini,
Francesco Menichetti

ECCMID 2010

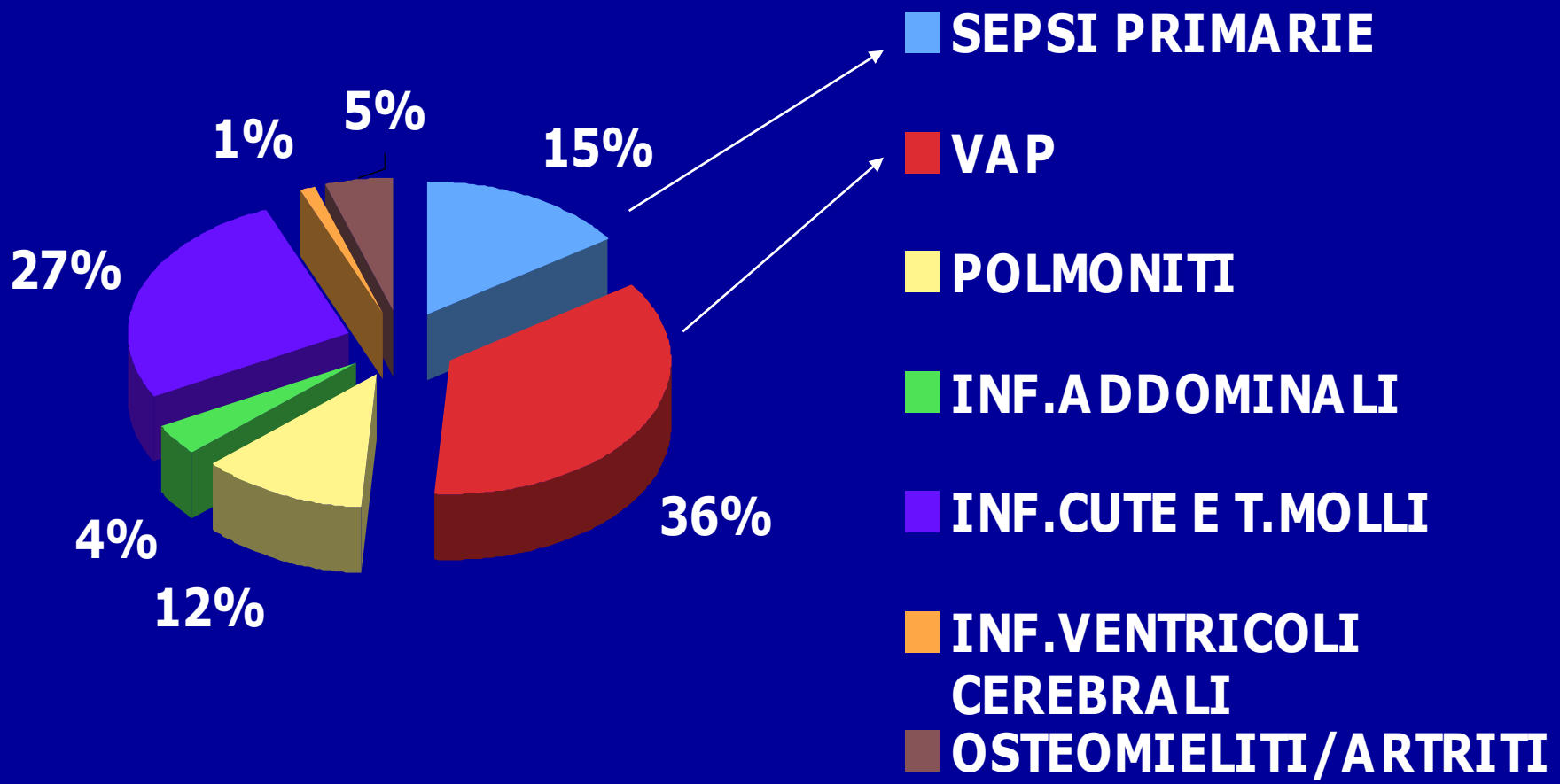
Caratteristiche dei pazienti

Popolazione trattata (2001-2009)	tot pz = 90
Maschi, n° (%)	67 (74)
Femmine, n ° (%)	23 (26)
Età media, (DS)	57.6 (±15)
Insufficienza renale presistente, n° (%)	4/84 (5)
Neuropatia periferica presistente, n° (%)	4/85 (5)
Fattori di rischio per infezioni da GNB MDR	
Comorbidità, n° (%)	69/85 (81)
Precedenti ricoveri, n° (%)	59 (66)
Precedenti terapie antibiotiche, n° (%)	82 (91)

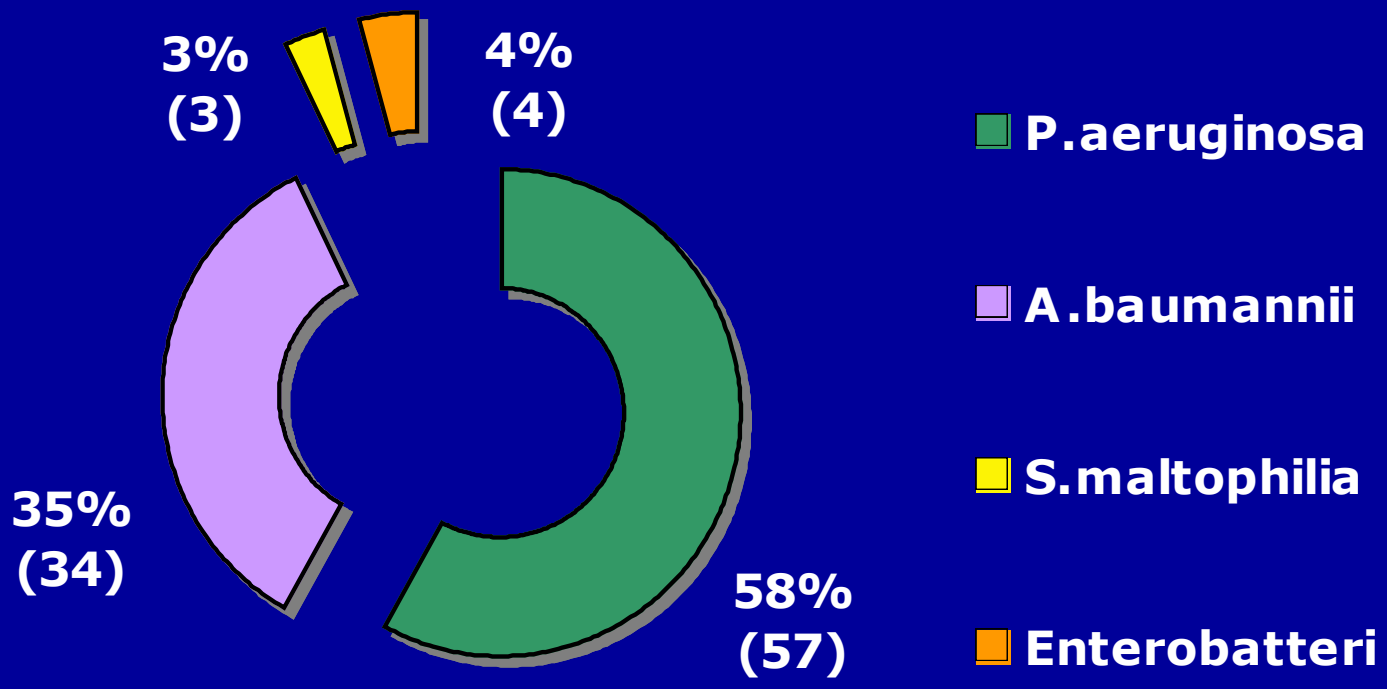
Reparti di ricovero dei pazienti



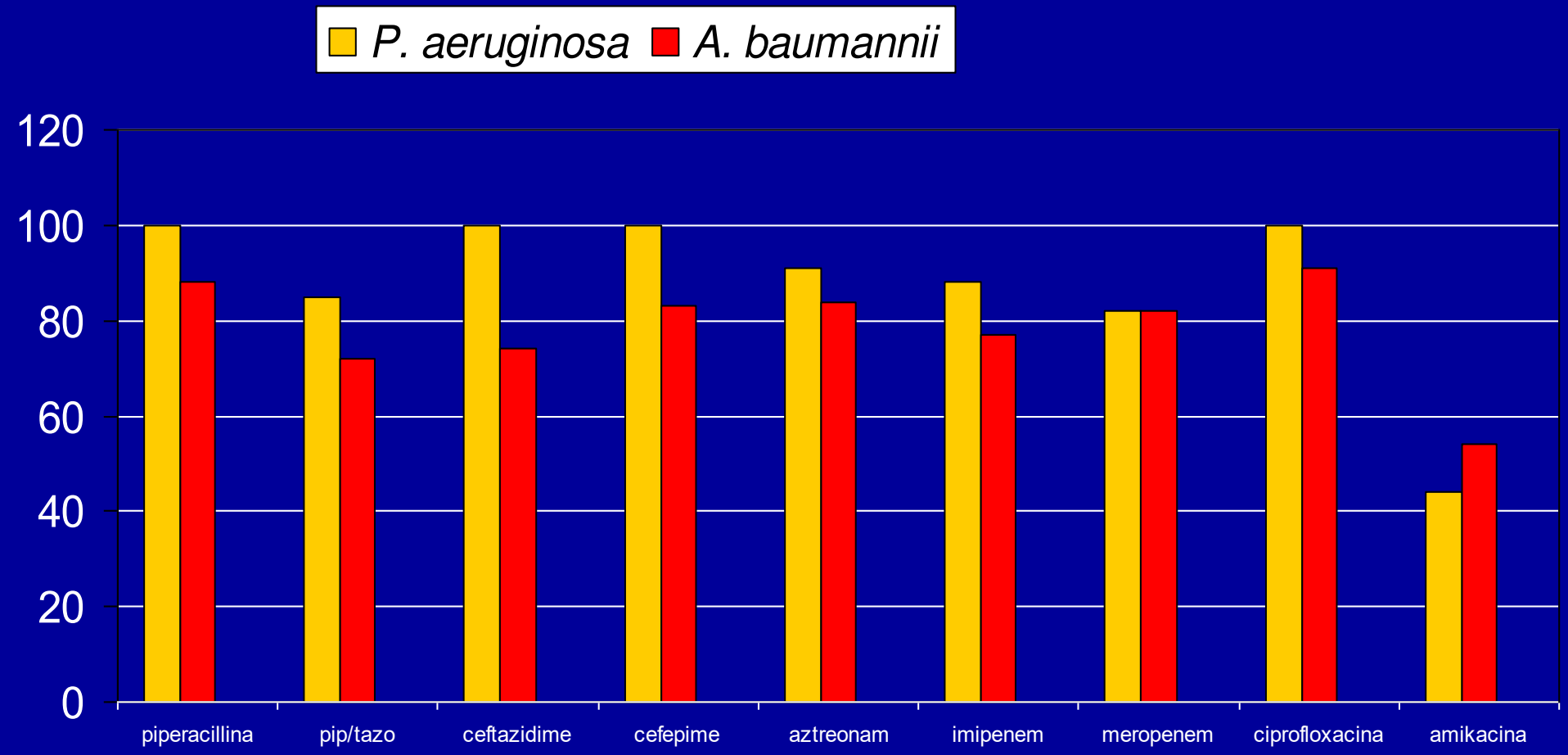
Sedi d'infezione (98)



Eziologia: GNB MDR



Profili di resistenza



Response in different type of infections

	Clinical Response N (%)	Microbiol. Response N (%)	Mean duration of therapy
VAP	25/35 (71)	18/35 (51)	15 days
SSTis	19/26 (73)	17/23 (73)	38 days
Sepsis	8/15 (53)	9/15 (60)	17 days
Other infections	15/22 (68)	9/22 (40)	44 days
Total	67/98 (69)	53/98 (55)	28.5 days

Patogeni e risposta alla terapia

	Risposta clinica N (%)	Risposta microbiologica N (%)
P.aeruginosa (57)	42/57 (74)	33/57 (58)
A.baumannii (34)	23/34 (68)	15/34 (44)
Altre (7) (*S.maltophila, enterobatteri)*	2/7 (28)	5/7 (71)
Totale	67/98 (69)	53/98 (55)

Response with different colistin combinations

	Colistin + Rifampin	Colistin + other antibiotics
Clinical response	32/45 (71%)	35/53 (66%)
Microbiol response	27/45 (60%)	26/53 (50%)
Mean duration of therapy	32 days	24 days

Acinetobacter baumannii: risposta clinica e microbiologica a diverse associazioni

	Colistina + rifampicina	Colistina + altri
Risposta clinica	12/16 (75%)	11/18 (61%)
Risposta microbiologica	9/16 (56%)	6/18 (33%)

Tigecycline (Tygacil)

Semi-synthetic glycylcycline

9-t-butylglyclamido derivative of minocycline

Bacteriostatic, act binding to 30S ribosomal subunit

Overcome the 2 major determinants of tetracycline resistance: active efflux of drug from inside the bacterial cell & protection of ribosomes

Tygacil chemical structure

“not simply a new parenteral tetracycline, but a new antibiotic with peculiar mechanisms of defense from bacterial resistance”

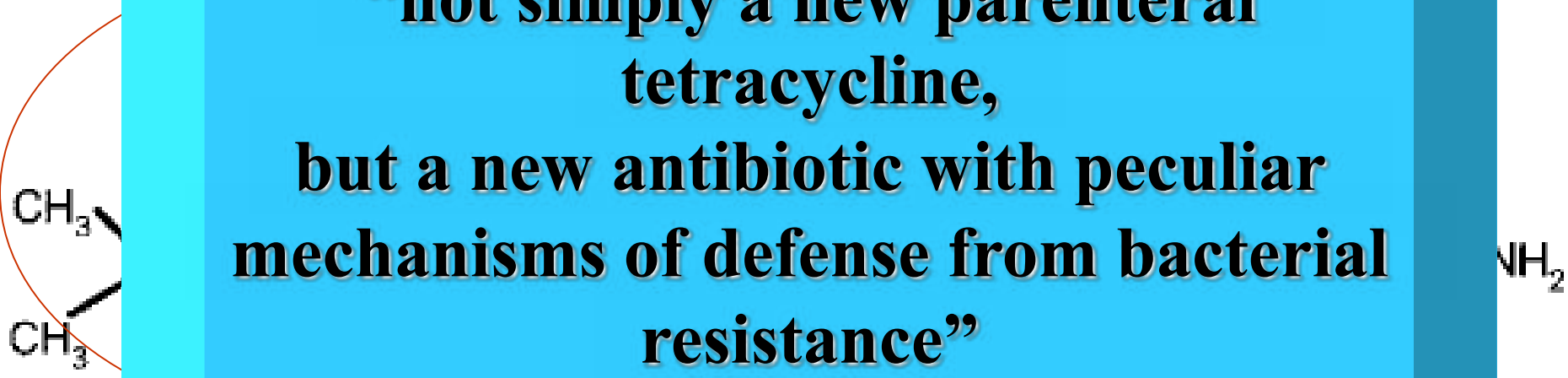


Figure 2. Structure of tigecycline [8]

9-t-butylglyclamido-glycylcycline

PK profile of Tigecycline

Table 1. Values for pharmacokinetic parameters for subjects in 5 phase 1 trials.

Dose regimen, parameter	Tigecycline dose, mg						
	12.5	25	50	75	100	200	300
Single dose							
C_{max},[a] μg/mL	0.11 ± 0.01	0.25 ± 0.06	0.38 ± 0.06	0.57 ± 0.08	0.93 ± 0.22	1.79 ± 0.53	2.82 ± 0.48
V_{ss}, L/kg	2.8 ± 0.95	6.4 ± 1.3	6.5 ± 2.0	7.5 ± 0.77	6.8 ± 2.5	13 ± 3.3	12 ± 2.4
AUC,[b] μg·h/mL	0.75 ± 0.52	2.26 ± 1.02	2.56 ± 0.53	3.66 ± 1.00	4.87 ± 1.41	13.2 ± 2.80	17.3 ± 2.18
CL_T, L/h/kg,	0.29 ± 0.20	0.20 ± 0.10	0.28 ± 0.04	0.29 ± 0.04	0.30 ± 0.08	0.23 ± 0.04	0.25 ± 0.03
$t_{1/2}$, h	11 ± 10	32 ± 20	18 ± 3.6	22 ± 5.3	22 ± 10	52 ± 12	44 ± 7.8
Multiple doses[c]							
C_{max},[a] μg/mL	…	0.32 ± 0.05	0.62 ± 0.09	…	1.17 ± 0.18	…	…
V_{ss}, L/kg	…	8.6 ± 1.98	7.2 ± 0.50	…	9.1 ± 2.91	…	…
AUC,[b] μg·h/mL	…	1.48 ± 0.26	3.07 ± 0.38	…	4.98 ± 0.93	…	…
CL_T, L/h/kg	…	0.20 ± 0.04	0.20 ± 0.02	…	0.24 ± 0.05	…	…
$t_{1/2}$, h	…	49 ± 35	37 ± 12	…	66 ± 23	…	

NOTE. Data are mean ± SD. AUC, area under the concentration–time curve; CL_T, total clearance; C_{max}, maximum concentration; $t_{1/2}$, elimination half-life; V_{ss}, apparent volume of distribution at steady state.

Tygecicline: PK/PD

Dos ed by
5
C_{ma}
V_{ss}
AU
AU s):
s
Pro
$T_{½}$:
Bili overy
No dose adjustment in renal failure or HD

Linear PK.
PK/PD index: AUC/MIC ratio relationship with clinical efficacy (?)

Tigeciclina: distribuzione tissutale

Tessuto/fluido	Concentrazione nel tessuto vs siero
Colecisti	38 volte superiore
Colon	più del doppio
Fluido di bolla cutanea	74% della concentrazione sierica
Macrofago alveolare	78 volte superiore
ELF (liquido bronchiolo-alveolare)	32% della concentrazione sierica
Polmone	8,6 volte superiore
Liquido sinoviale	58% della concentrazione sierica
Osso	35% della concentrazione sierica

Tigeciclina: eventi avversi

Eventi avversi	Tigeciclina (N = 1,415)	Comparatore (N = 1,382)	*P* value
Nausea	29.5	15.8	<0.001
Vomito	19.7	10.8	<0.001
Diarrea	12.7	10.8	0.127
Trombocitemia	6.1	6.2	0.937
Flebite	1.8	3.8	0.002
Rash	2.4	4.1	0.011
Infezione	8.3	5.4	0.003
Iperbilirubinemia	2.3	0.9	0.004
↑ALT	5.6	4.7	0.305
↑AST	4.3	4.4	0.926

Tigecycline: an extended broad-spectrum activity

Staphylococci
(incl. MRSA, VISA, VRSA)

Enterococci
(incl. VRE, LRE)

Streptococci (β-haemol., *viridans*, pneumo incl. PRP)

Listeria
Corynebacteria
Leuconostoc
Lactobacillus
Bacillus

Anaerobes

Atypicals
- *Mycoplasma*
- *Chlamydia*
- NT Mycob.
- *Nocardia*

Enterobacteriaceae
(ex. *Proteeae*)
(incl. ESBL, carbapenemases)

Acinetobacter
(incl. MDR)

S. maltophilia

H. influenzae

Moraxella

Pasteurella

Neisseria

Campylobacter

Vibrio

Aeromonas

Legionella

Brucella

Tigeciclina
Breakpoints di suscettibilità e resistenza

	S	R
CLSI		
Enterobacteriaceae	**?**	**?**
***Acinetobacter* spp.**	**?**	**?**
EUCAST		
Enterobacteriaceae	**≤ 1 mg/l**	**> 2 mg/l**
***Acinetobacter* spp.**	**?**	**?**

Tigeciclina: indicazioni cliniche

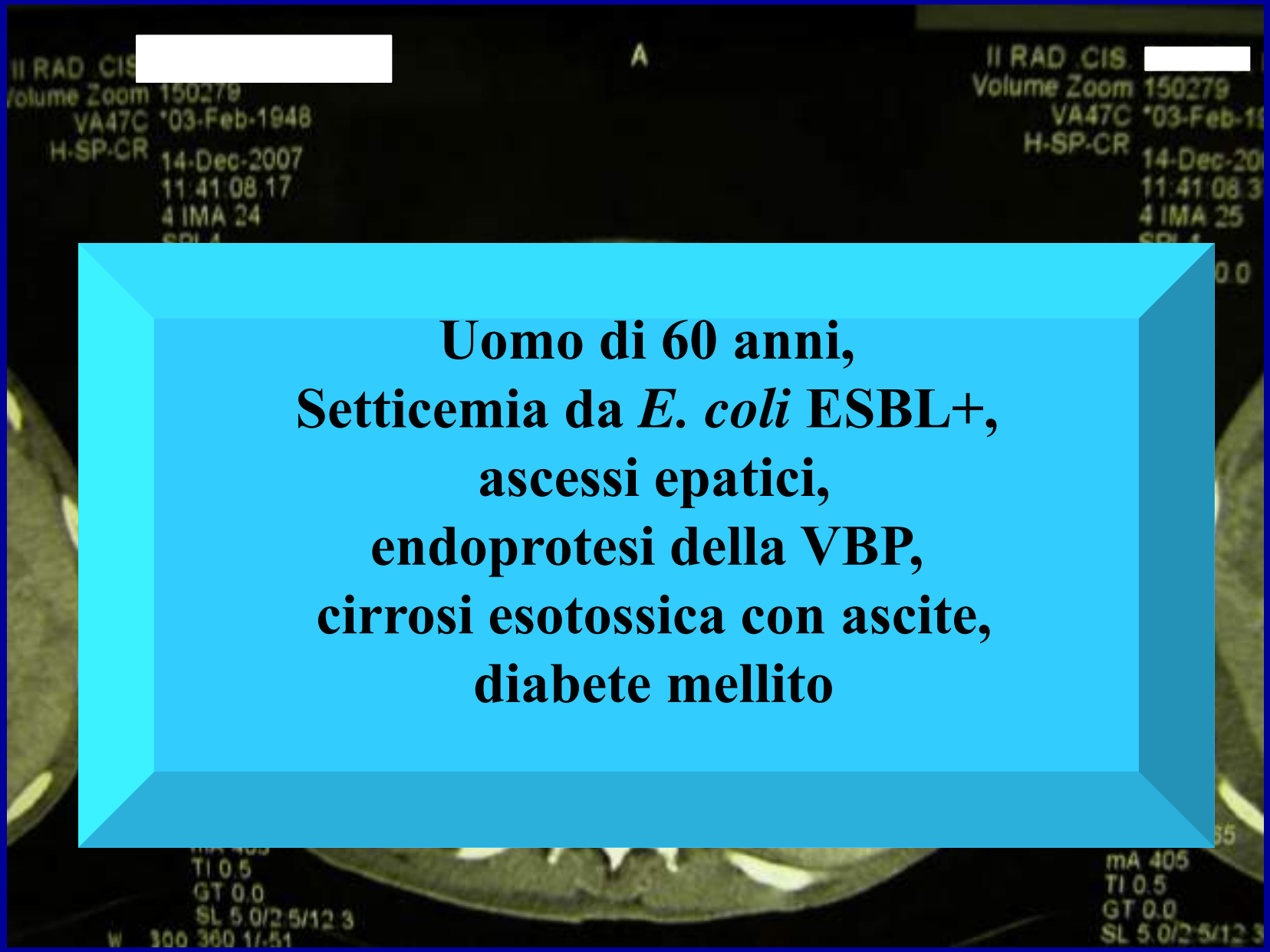
Indicazioni registrate (FDA/EMEA)

Complicated Intra-abdominal Infections

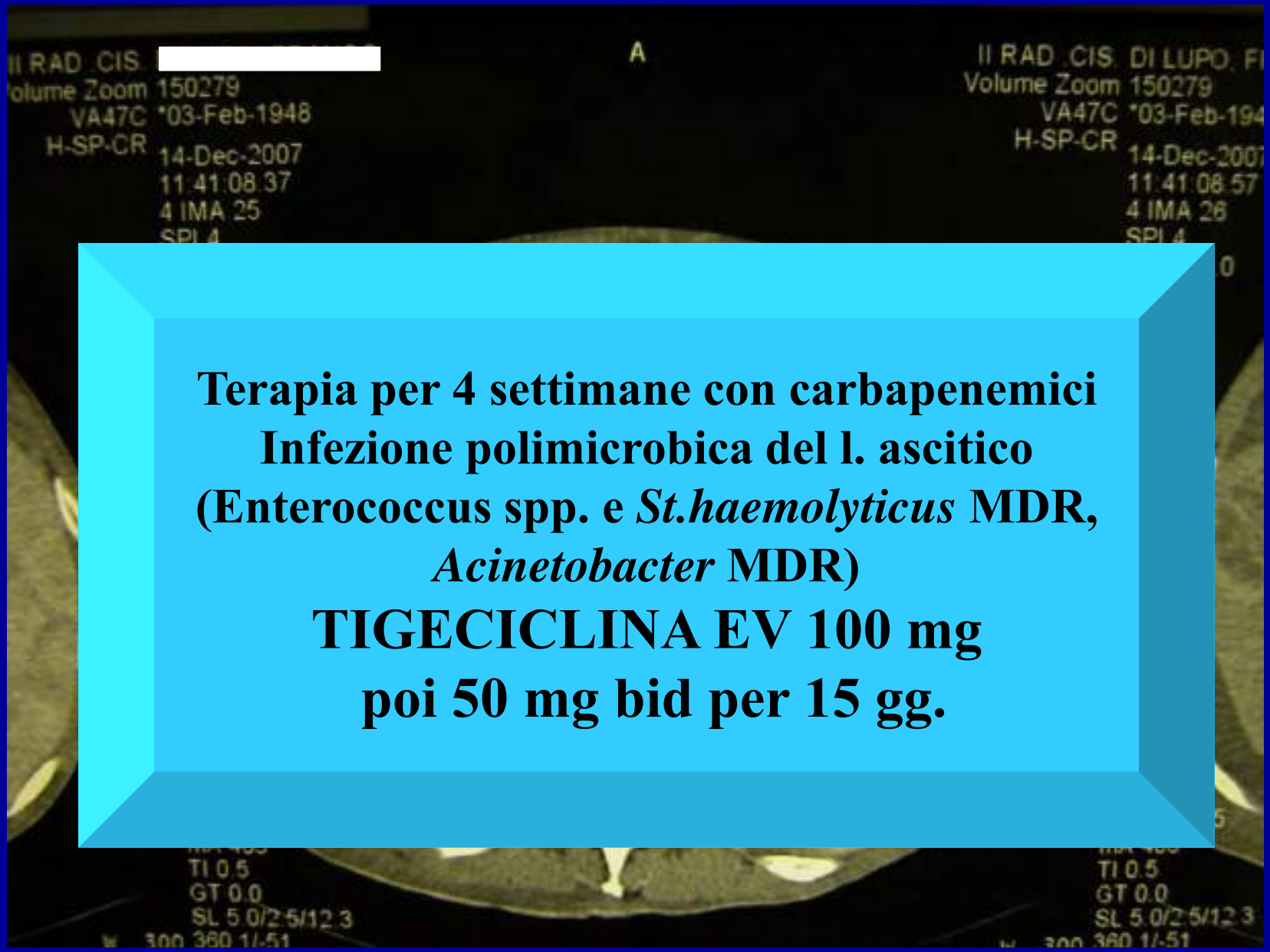
(2 trials, vs. imipenem/cilastatin)

Complicated Skin & Skin-Structure Infections

(2 trials, vs. VANCO/AZT)



Uomo di 60 anni,
Setticemia da *E. coli* ESBL+,
ascessi epatici,
endoprotesi della VBP,
cirrosi esotossica con ascite,
diabete mellito



Terapia per 4 settimane con carbapenemici
Infezione polimicrobica del l. ascitico
(Enterococcus spp. e *St.haemolyticus* MDR, *Acinetobacter* MDR)
TIGECICLINA EV 100 mg
poi 50 mg bid per 15 gg.

UTI catetere-relata
da *Proteus vulgaris* Amp-C e
***Ps.aeruginosa* FQ-R:**
rimozione catetere vescicale

Treatment of Community-Acquired c-IAI

Type of therapy	Mild-to- moderate	High-severity
Single agent		
β-lactam/ β-lactamase inhibitor	Ampi/sulbactam* Ticar/Clavulanic acid	Pipera/tazobactam
Carbapenems	Ertapenem Tigeciclina	Imipenem/Cilastatin Meropenem
Combination regimen		
Cephalosporin based	Cefuroxime, (Cefazolin) plus MNZ	CRO, CTX, Cefepime, (CAZ), plus MNZ
Fluoroquinolone based	Cipro, (Levo, Moxi) plus MNZ #	Cipro plus MNZ
Monobactam based		AZT plus MNZ

**E. coli* ampi/sulbactam resistant; # *B fragilis* FQ resistant

Tigeciclina: altre sperimentazioni cliniche

CAP, 2 studies, 800 pts, vs. LEVO: non inferiorità

HAP/VAP, 1 study, 866 pts, vs. imipenem/cilastatin: insuccesso

Ruolo di tigeciclina nelle HAP/VAP da meglio definire !!!!

Tigecycline and *Acinetobacter*

Source*	No. isolates	MIC_{90} (μg/ml)	% S**	References
Global	427	1	ND	Hoban DMID 2005
USA	851	1	ND	Waites AAC 2006
Greece	103	1	99	Souli AAC 2006
USA	282	2	ND	Hoban DMID 2007
Italy	107	2	93	Mezzatesta ACMA 2008
USA	225	2	97	Draghi Chemother 2008
Asia-Pacific	544	2	99	Mendes JAC 2008

* including MDR/XDR strains

** breakpoint for S = ≤2 μg/ml

Tigecycline and *Acinetobacter*

Source*	No. isolates	MIC_{90} (μg/ml)	% S**	References
EU-USA	215	4	85	Seifert JAC 2006
Spain	142	3	88	Insa JAC 2007
Iraq/USA	170	8	ND	Moland AAC 2008
Israel	82	32	22	Navon-Venezia JAC 2007
Turkey	66	12	53	Dizbay IJAA 2008

* including MDR/XDR strains

** breakpoint for S = ≤2 μg/ml

Tigecycline and *Acinetobacter* infections

Journal of Antimicrobial Chemotherapy (2008) 62, Suppl. 1, i29–i40
doi:10.1093/jac/dkn249

JAC

A Phase 3, open-label, non-comparative study of tigecycline in the treatment of patients with selected serious infections due to resistant Gram-negative organisms including *Enterobacter* species, *Acinetobacter baumannii* and *Klebsiella pneumoniae*

Krasimir Vasilev[1], Galina Reshedko[2], Remus Orasan[3], Miguel Sanchez[4], Juri Teras[5], Tim Babinchak[6]*, Gary Dukart[6], Angel Cooper[6], Nathalie Dartois[7], Hassan Gandjini[7], Russ Orrico[6] and Evelyn Ellis-Grosse[6]* on behalf of the 309 Study Group

Hospitalized patients (cSSSI, cIAI HAP/VAP, BSI/CR-BSI)

Acinetobacter, clinical response at TOC

ME	m-mITT
14/17 (82.4%)	17/32 (53.1%)

Acinetobacter, microbiological response at TOC

ME	m-mITT
11/17 (64.7%)	14/32 (43.8%)

Journal of Antimicrobial Chemotherapy (2008) **62**, 45–55
doi:10.1093/jac/dkn165
Advance Access publication 24 April 2008

JAC

Tigecycline for the treatment of multidrug-resistant (including carbapenem-resistant) *Acinetobacter* infections: a review of the scientific evidence

Drosos E. Karageorgopoulos[1], Theodore Kelesidis[1,2], Iosif Kelesidis[1,3] and Matthew E. Falagas[1,4,5]*

Tigecycline for the Treatment of *Acinetobacter* Infections: A Case Series

Ann Pharmacother 2008

Jason C Gallagher and Heather M Rouse

- Successes but also failures have been reported
- Data to support its clinical use in this setting are still limited
- Additional clinical experience is needed, especially for VAP

Vecchi e nuovi antibiotici

	Vecchi	Nuovi	Partner
ESBLs-Amp-C	carbapenemi	Tigeciclina	AK; FQs
KPC	Colisitina	Tigeciclina	
A. baumannii	Colistina	Tigeciclina	RFP
P. aeruginosa	Colistina	Doripenem (?)	RFP; AK; Fosfo