Multidrug Resistant (MDR) bacterial infections: new treatments options

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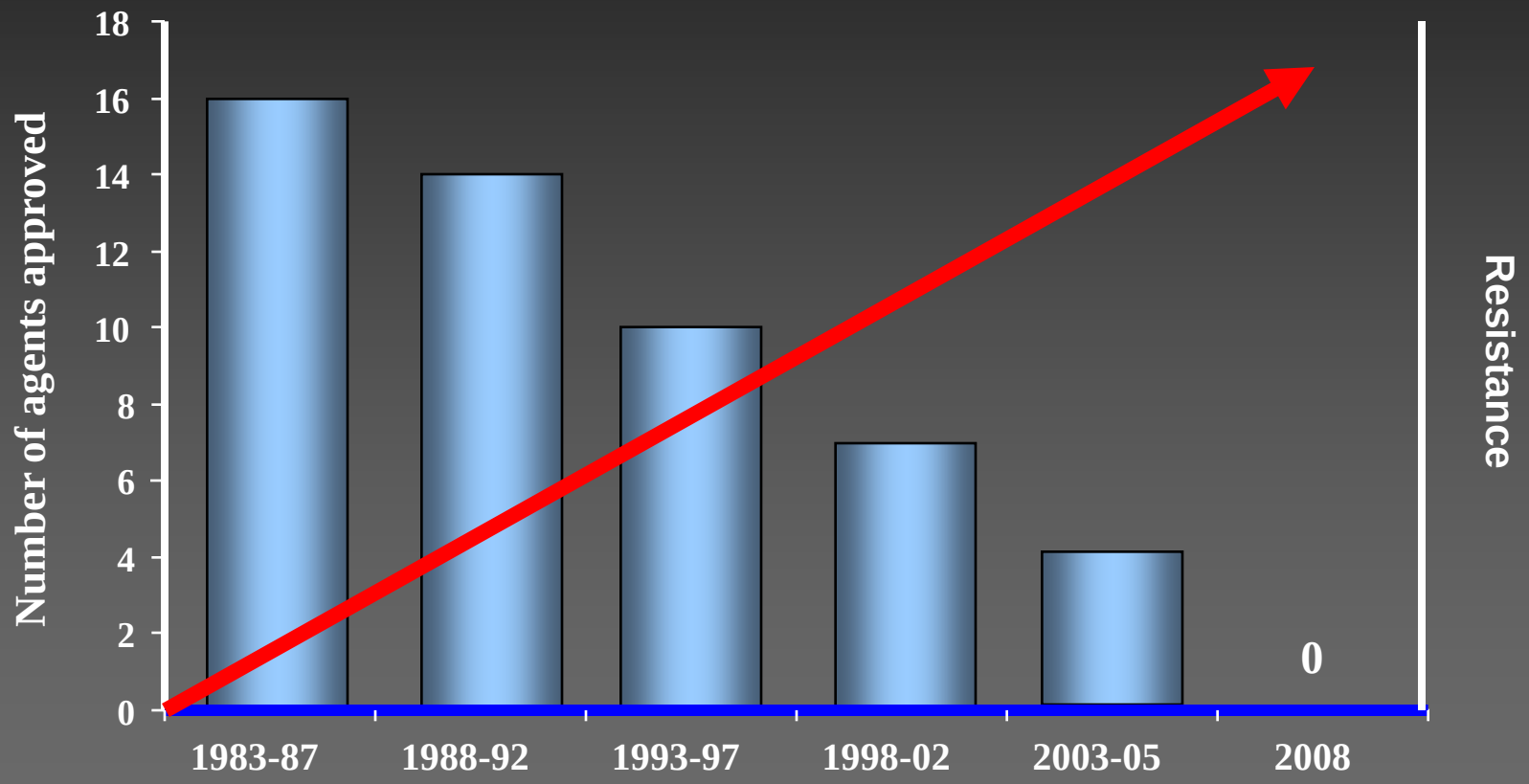
Bad bugs, no drugs: *No ESCAPE*

- Bad Bugs, No Drugs: No ESCAPE
  - *Enterococcus faecium* (E), *Staphylococcus aureus* (S), *Clostridium difficile* (C), *Acinetobacter baumannii* (A), *Pseudomonas aeruginosa* (P), and *Enterobacterobcteriaceae* (E)
- The late-stage clinical development pipeline remains unacceptably lean
  - Some important molecules for problematic pathogens such as MRSA
  - Few novel molecules for other ESCAPE pathogens
  - No new drugs for infection due to MDR Gram-negative bacilli
  - None represent more than an incremental advance over currently available therapies

Rice LB. *J Infect Dis*. 2008;197:1079-1081
Boucher HW, et al. *Clin Infect Dis*. 2009;48:1-12, Peterson LR. *Clin Infect Dis*. 2009;49:992

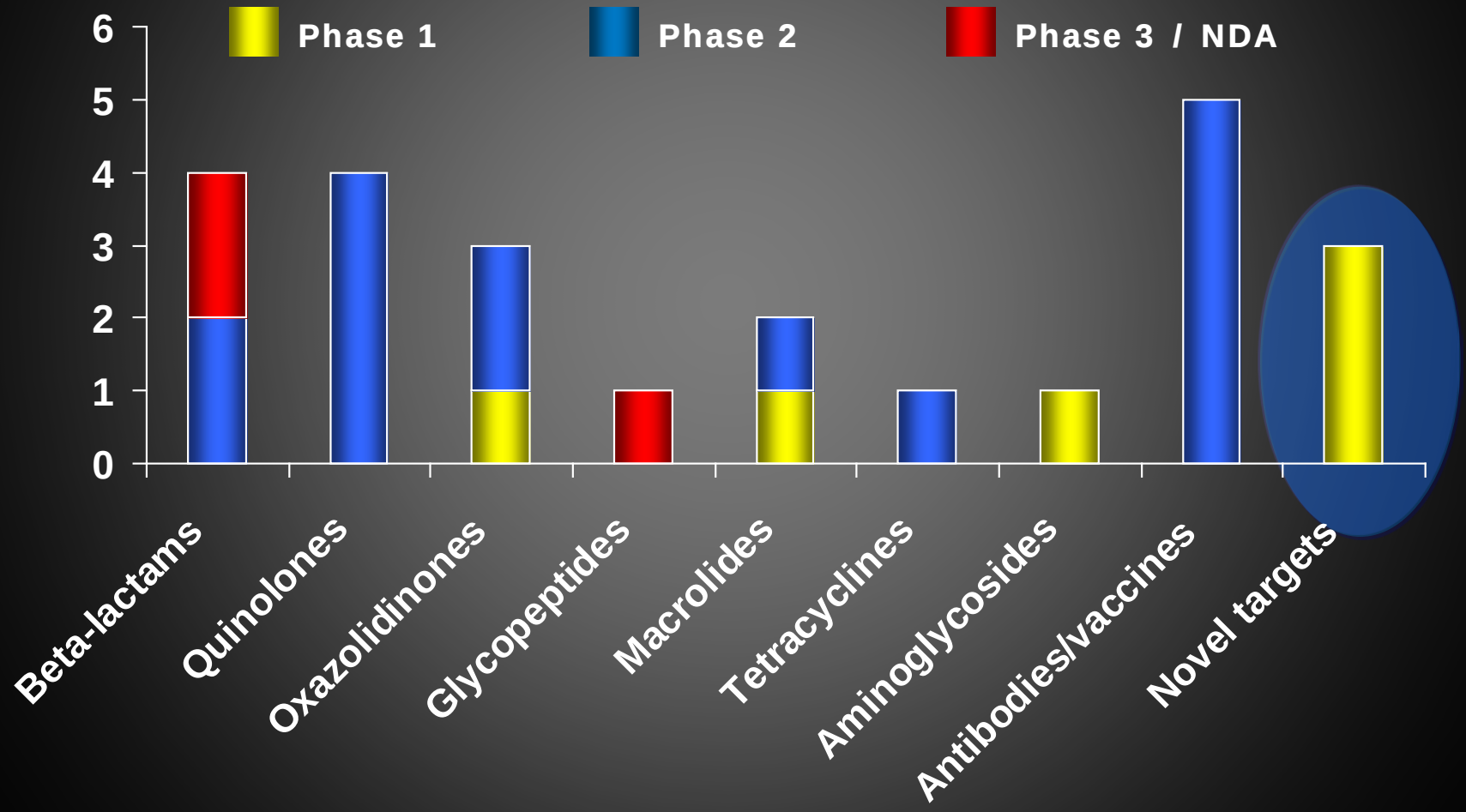
A Changing Landscape for Numbers of Approved Antibacterial Agents



Bars represent number of new antimicrobial agents approved by the FDA during the period listed.

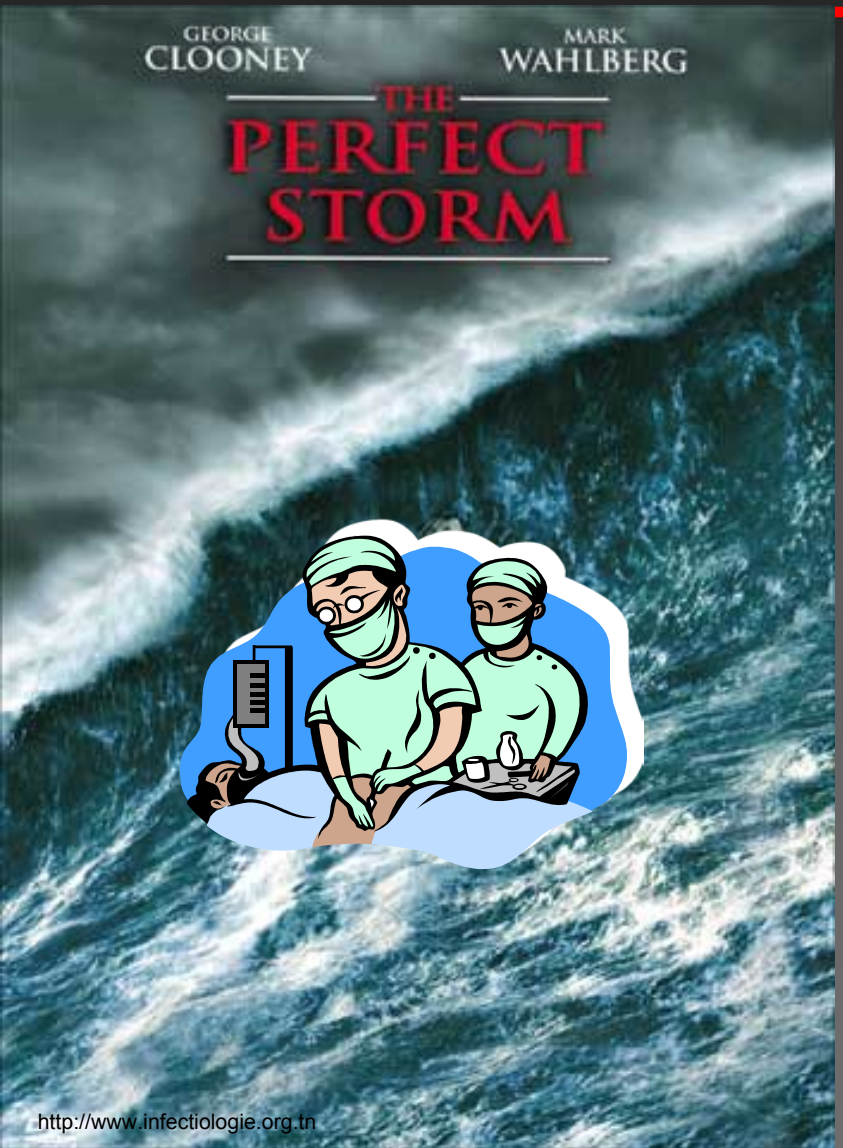
Infectious Diseases Society of America. *Bad Bugs, No Drugs*. July 2004; Spellberg B et al. *Clin Infect Dis*. 2004;38:1279-1286;
New antimicrobial agents. *Antimicrob Agents Chemother*. 2006;50:1912

Antibiotics in Clinical Development



Theuretzbacher U. Int J Antimicrob Agents. 2009;34:15-20

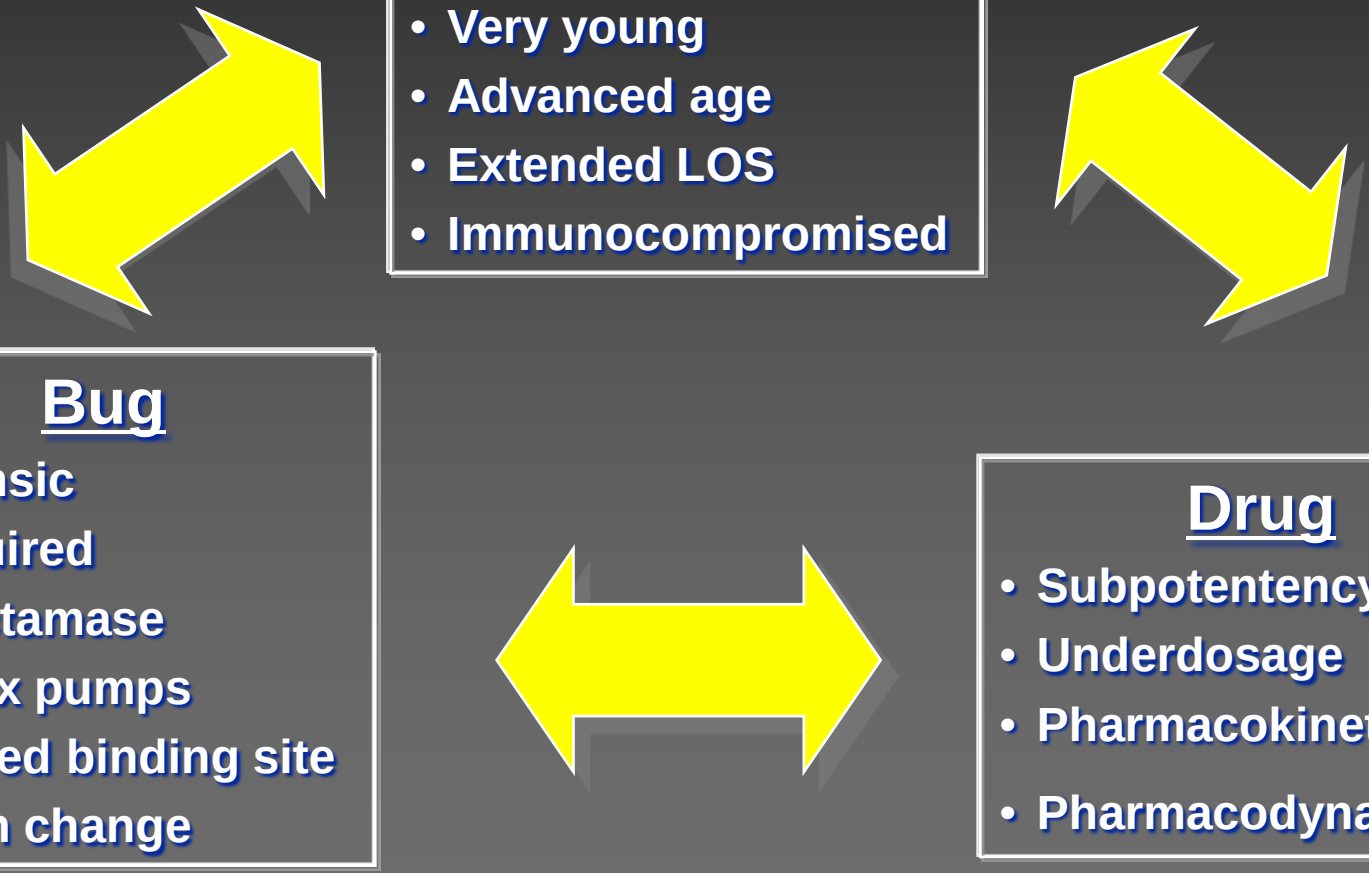
The hospital BACTERIAL "*perfect storm*"



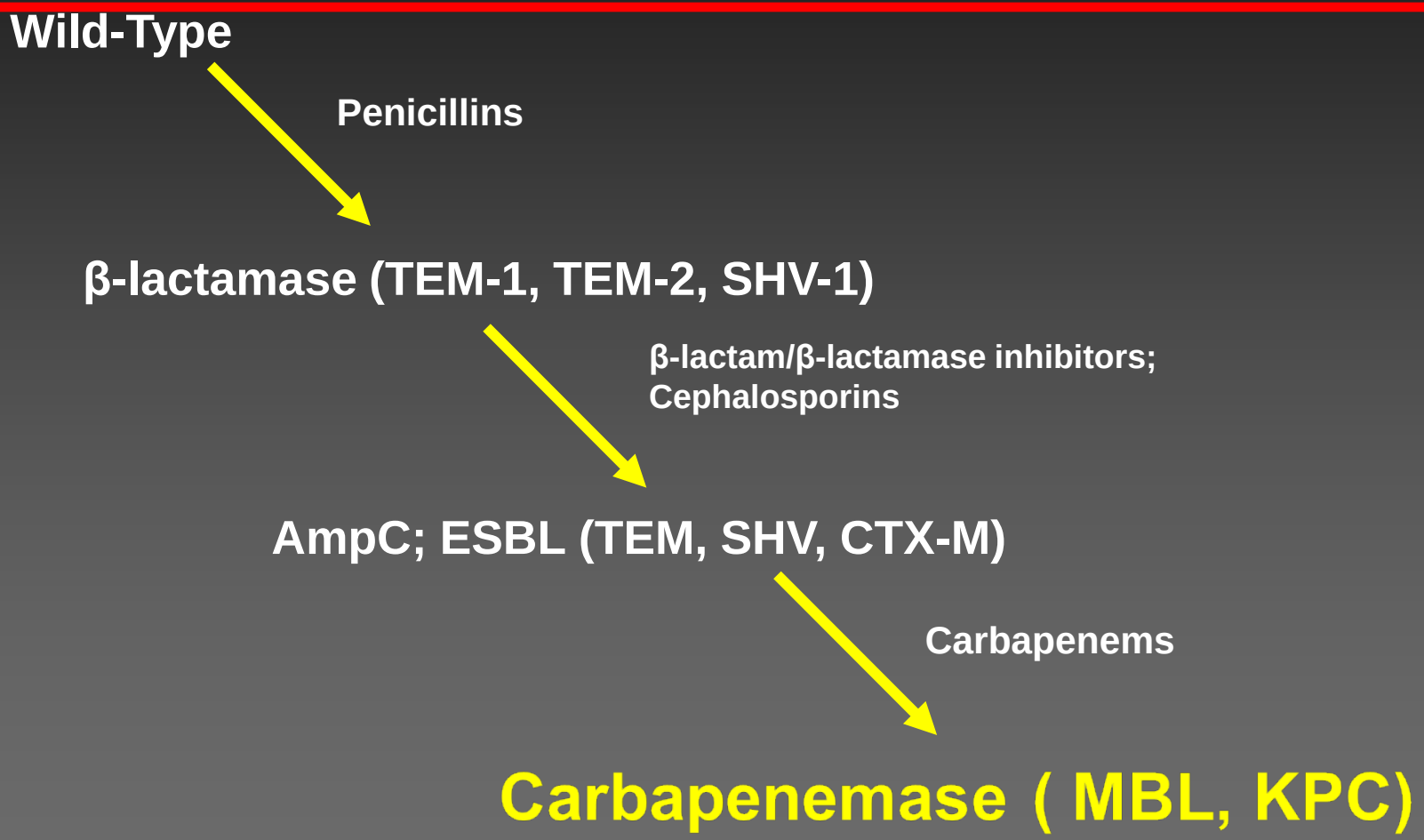
http://www.infectiologie.org.tn

- MRSA
  - hVISA
- Cons- MR
- MDR *A. baumannii*
- MDR *P. aeruginosa*
- KPC
- ESBL(+) *E. coli*
- ESBL(+) *K. pneumoniae*
- VRE
- ……

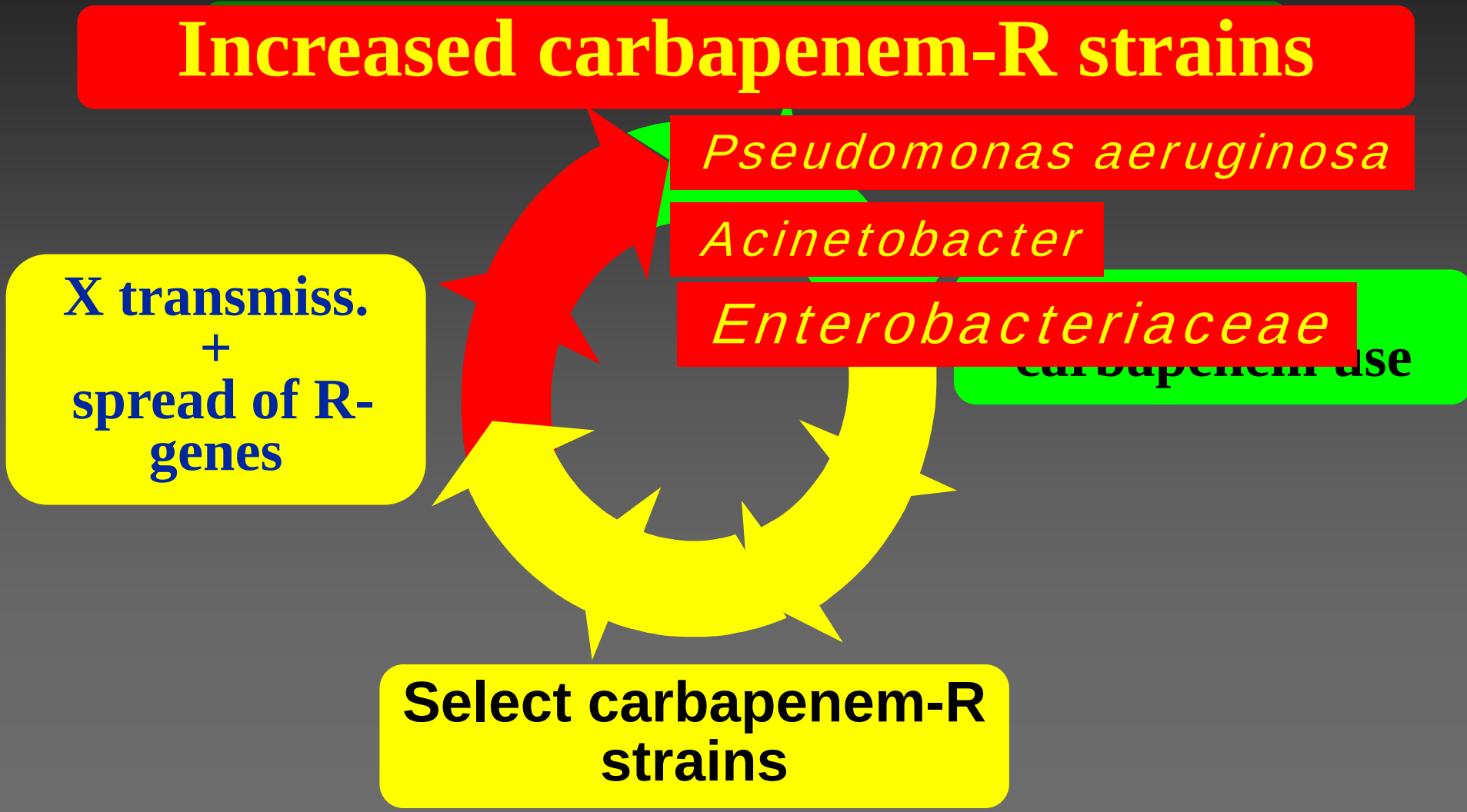
Drivers of Resistance



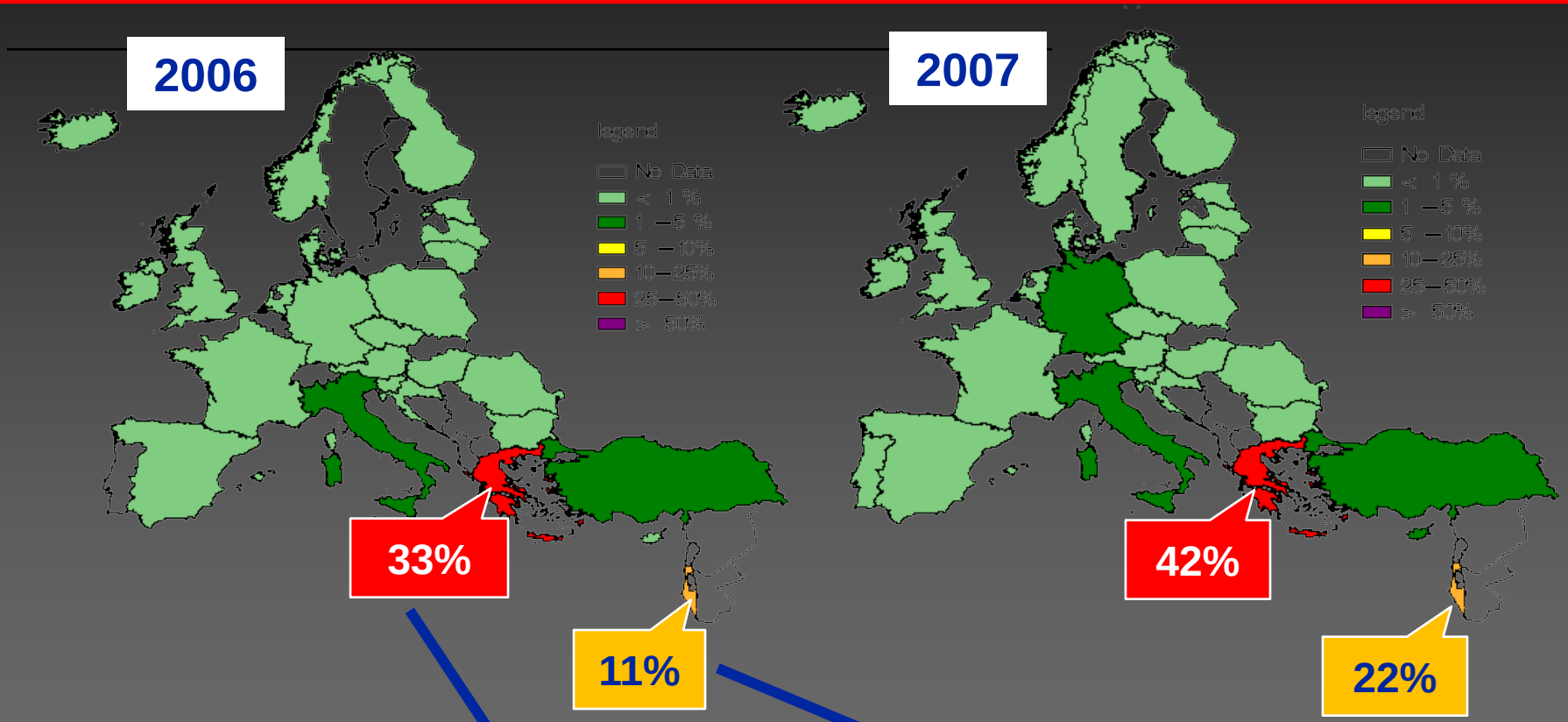
Evolution of β-Lactamases



Resistance driving resistance in the 2000s: the ESBL / carbapenem resistance loop

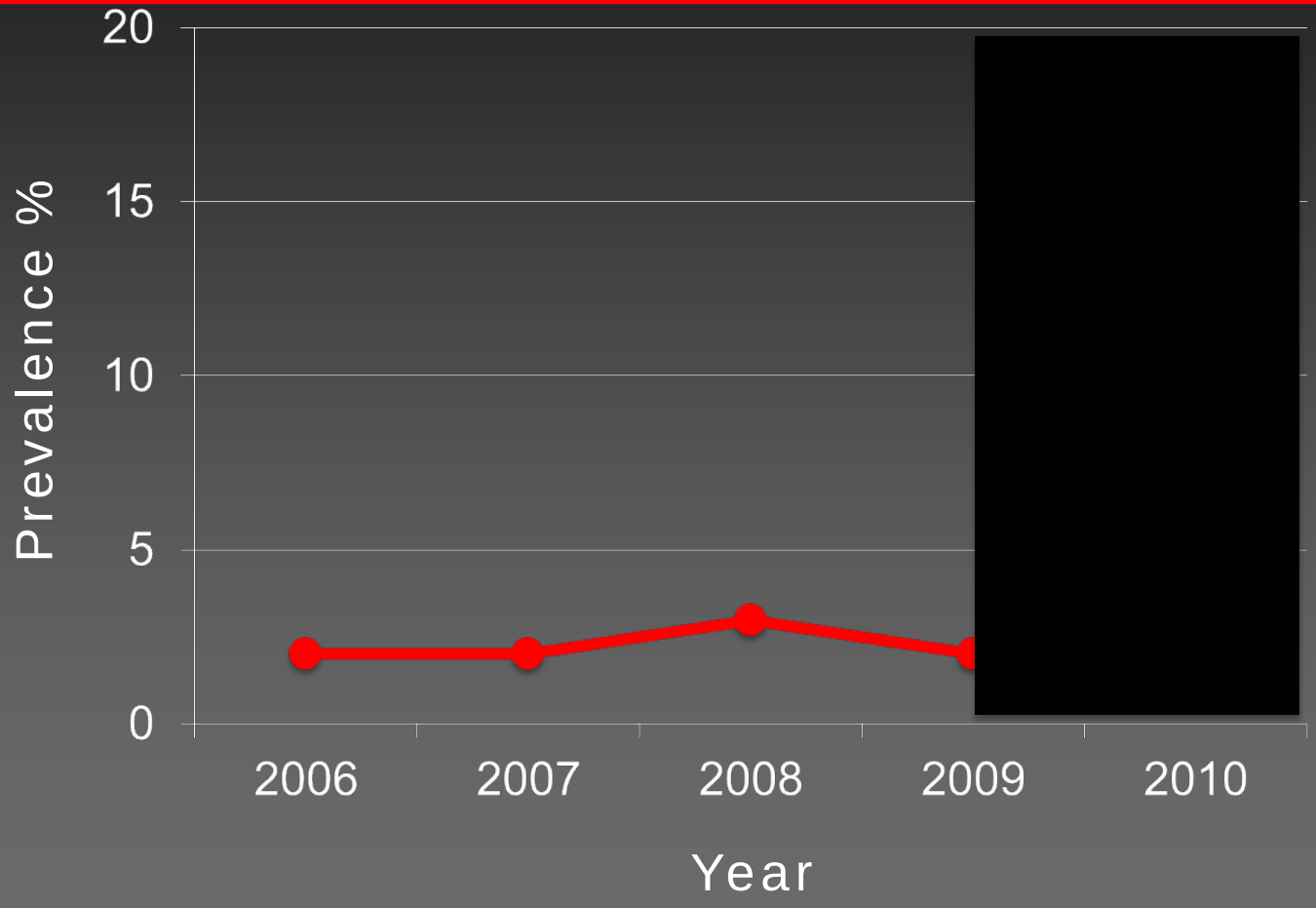


Carbapenemases in *K. pneumoniae*: Mediterrean area



EARSS database

Carbapenem-R *K. pneumoniae* Italy



EARS-NET

New Delhi Metallo-β-lactamase 1 (NDM-1): A New Menace

- Most *bla*$_{NDM-1}$ positive plasmids are readily transferable
- Multi-resistant to fluoroquinolones, β-lactams, and aminoglycosides

- The majority of Indian isolates were from community-acquired infections, suggesting that *bla*$_{NDM-1}$ is widespread in the environment
- Potential for worldwide endemicity

Kumarasamy KK, et al. *Lancet Infect Dis.* 2010;10:597-602.

Isolates with NDM-1: Susceptibility

Antibiotic	Proportion susceptible (%)		
	UK (n=37)	Chennai (n=44)	Haryana (n=26)
Meropenem	3	3	3
Aztreonam	11	0	8
Ciprofloxacin	8	8	8
Gentamicin	3	3	3
Tigecycline	64	56	67
Colistin	89	94	100

0% Susceptible

Imipenem

Pip-taz

Cefotaxime

Ceftazidime

Cefpirome

Tobramycin

Amikacin

Minocycline

Kumarasamy KK, et al. *Lancet Infect Dis.* 2010;10:597-602.

How to manage MDR pathogens in the daily practice

- Collateral damage of 3GC, FQ and carbapenems
- Adverse clinical outcomes in infections due to ESCAPE pathogens
- Need to preserve the carbapenems use
- Lack of clinical and PK/PD evidence to use polimyxins for MDR-Gram-negatives
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- Pilars of empiric antibacterial use

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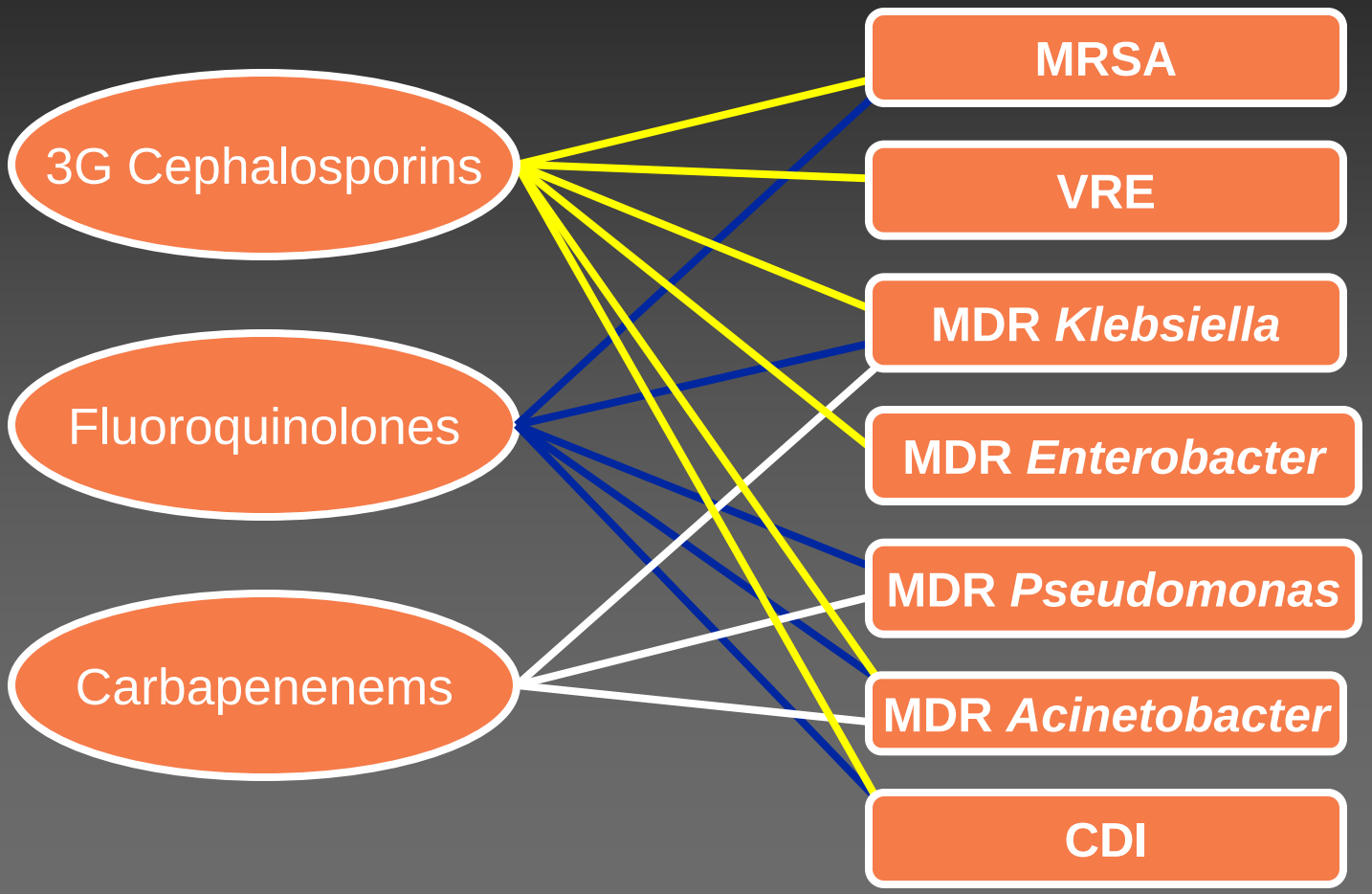
- *Pilars of empiric antibacterial use*

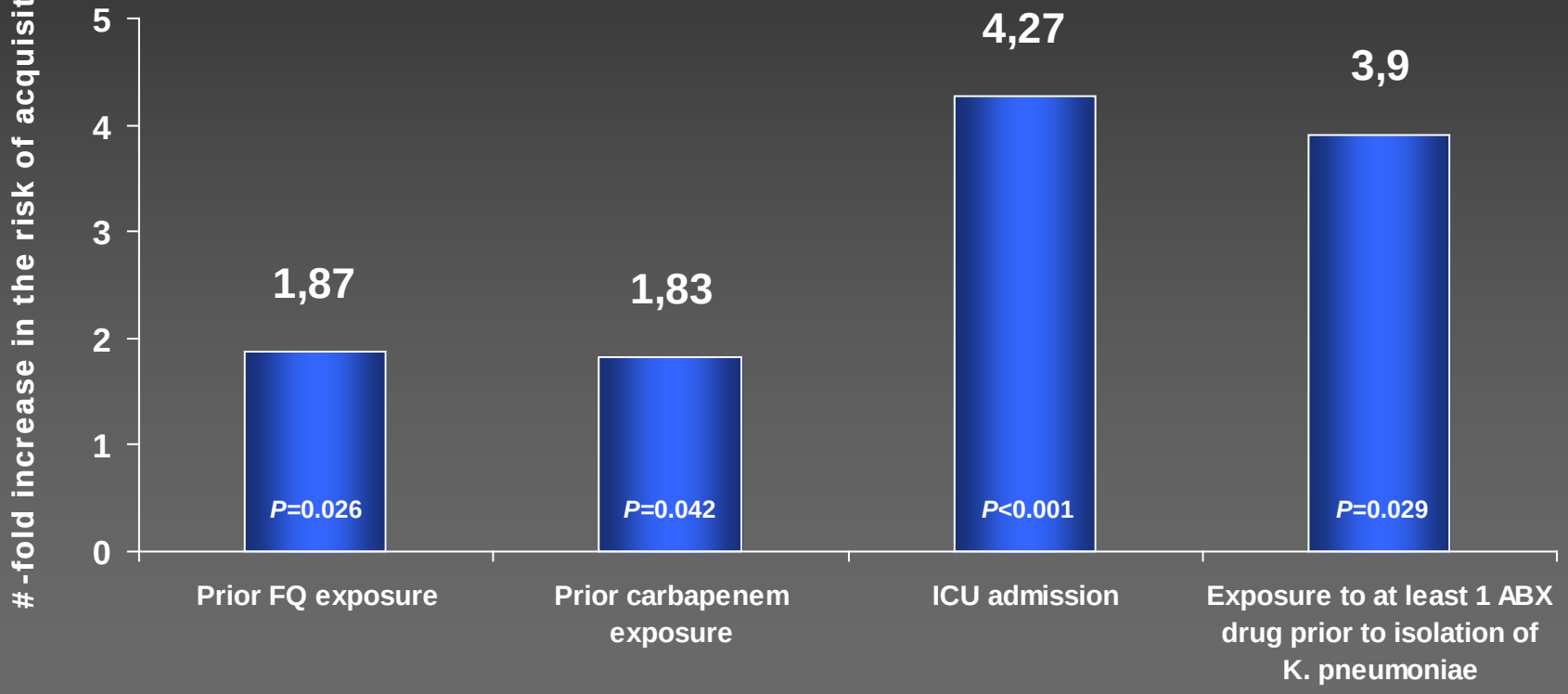
Antimicrobial use and Bacterial–Resistance : A Complex-Relationship



Landman et al. Arch Intern Med 2002;162:1515-20, Quale et al. Clin Infect Dis 2002;35:834-41, Manikal et al. Clin Infect Dis 2000;31:101-6, Saurina et al. J Antimicrob Chemother 2000 ;45 :895-8, Lautenbach et al. Clin Infect Dis 2001;33:1288-94., Paterson et al. Clin Infect Dis 2000;30:473-8., Lee et al. Antimicrob Agents Chemother. 2004 Jan;48(1):224-8, Lepper et al. Antimicrob Agents Chemother. 2002;46:2920-2925, Cao B, et al. J Hosp Infect. 2004;57:112-118, Mentzelopoulos SD, et al. Int Care Med. 2007;33:1524-1532, Soulí et al. Clin Infect Dis. 2008 Mar 15;46(6):847-54., Nelson et al. Infect Control Hosp Epidemiol 1994 ;15 :88-94, Lai et al. Infect Control Hosp Epidemiol 1997 ;18 :628-32, Yip et al. Infect Control Hosp Epidemiol 2001 ;22 :572-5, Gaynes 3et al. Clin Infect Dis 2004 ;38 :640-5,

Risk Factors for the Acquisition of Carbapenem-Resistant *K. pneumoniae*

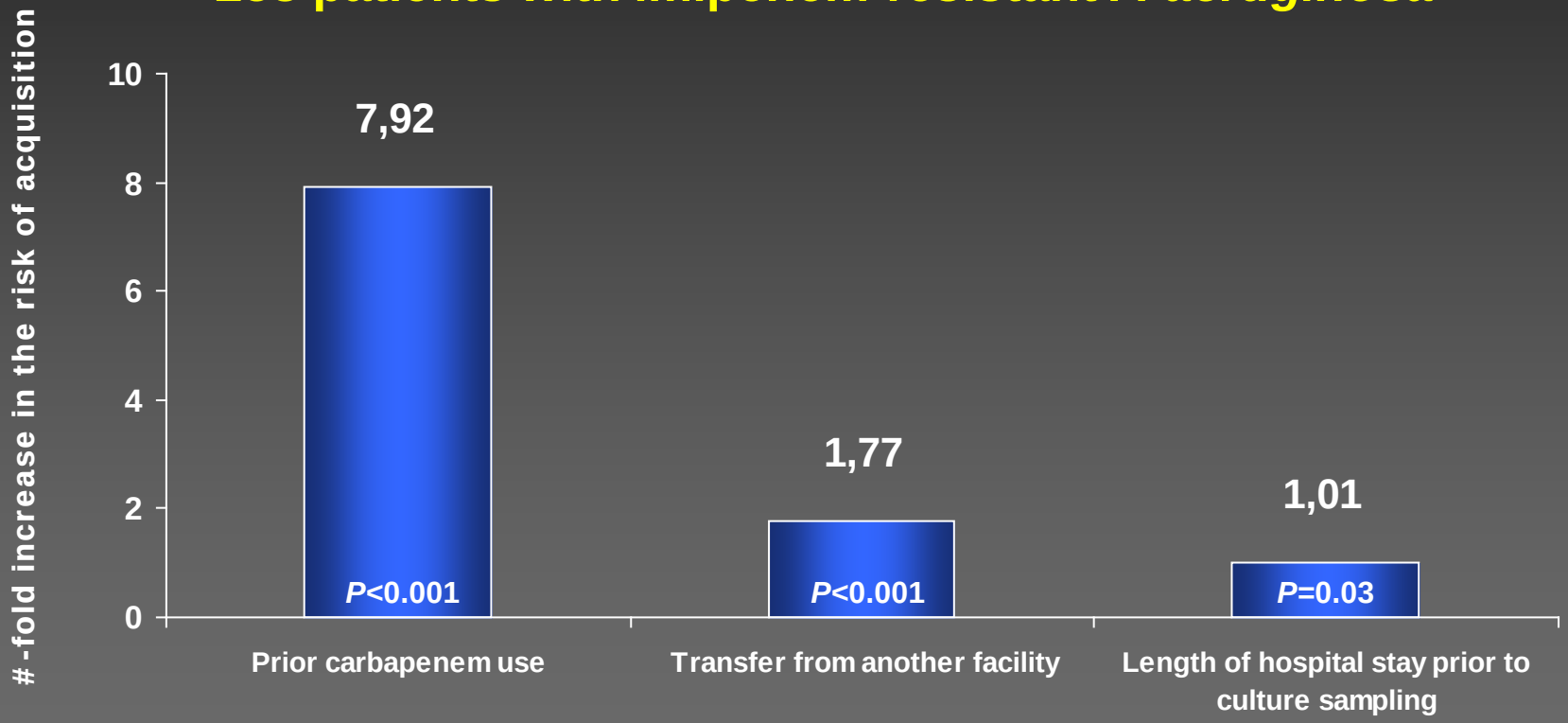
CRKP isolated from 88 patients
Carbapenem-susceptible *K. pneumoniae* in 373 patients



Hussein K, et al. *Infect Control Hosp Epidemiol*. 2009;30:666-671.

Risk Factors for the Acquisition of Imipenem-Resistant *P. aeruginosa*

2,534 patients with *P. aeruginosa* isolates
253 patients with imipenem-resistant *P. aeruginosa*



Lautenbach E, et al. *Infect Control Hosp Epidemiol*. 2010;31:47-53.

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"ESKAPE" Pathogens

Clinical Outcomes ➔ Increased Mortality

VRE[1]	VSE	
n=683	n=931	OR 2.52*
MRSA[2]	MSSA	
11.8% (n=382)	5.1% (n=433)	p<0.001
K. pneumoniae-ESBL+[3]	*K. pneumoniae*-ESBL-	
52% (n=48)	29% (n=99)	p<0.05
A. baumannii (IMP-R)[4]	*A. baumannii* (IMP-S)	
57.5% (n=40)	27.5% (n=40)	p=0.007
MDR-*P. aeruginosa*[5]	No-MDR-*P. aeruginosa*	
21% (n=40)	12% (n=40)	p=0.08
Enterobacter spp. (IMP-R)[6]	Enterobacter spp. (IMP-S)	
33% (n=33)	9% (n=33)	p=0.038
Bacteremic KPC[7]	Non-bacteremic KPC	
71.9% (n=32)	21.9% (n=32)	P<0.001

*95% CI, 1.9–3.4

1. DiazGranados et al. *Clin Infect Dis*. 2005; 41:327–33.
2. Melzer M, et al. *Clin Infect Dis*. 2003;37:1453-1460.
3. Tumbarello M, et al. *Antimicrob Agents Chemother*. 2006;50:498-504.
4. Kwon K. et al. *J Antimicrob Chemother*. 2007;59:525–530.
5. Aloush V. et al. *Antimicrob Agents Chemother*. 2006;50: 43–48.
6. Marchaim D. et al. *Antimicrob Agents Chemother*. 2008; 52:1413-1418.
7. Borer A, et al. Infect Control Hosp Epidemiol. 2009;30:972-6.

Estimated Annual Human Burden of Infections due to Antibiotic-Resistant (AR) Bacteria

2007 data includes EU Member States, Iceland, and Norway

AR bacteria	No. cases of infection†	No. extra deaths	No. extra hospital days
AR Gram-positives			
MRSA	171,200	5,400	1,050,000
VREF	18,100	1,500	111,000
PRSP	3,500	(–)	(–)
AR Gram-negatives			
3G-cephalosporin-resistant *E. coli*	32,500	5,100	358,000
3G-cephalosporin-resistant *K. pneumoniae*	18,900	2,900	208,000
Carbapenem-resistant *P. aeruginosa*	141,900	10,200	809,000
TOTAL	386,100	25,100	2,536,000

European Centre for Disease Prevention and Control (ECDC) / European Medicines Agency (EMeA) Joint Technical Report, Stockholm, September, 2009.

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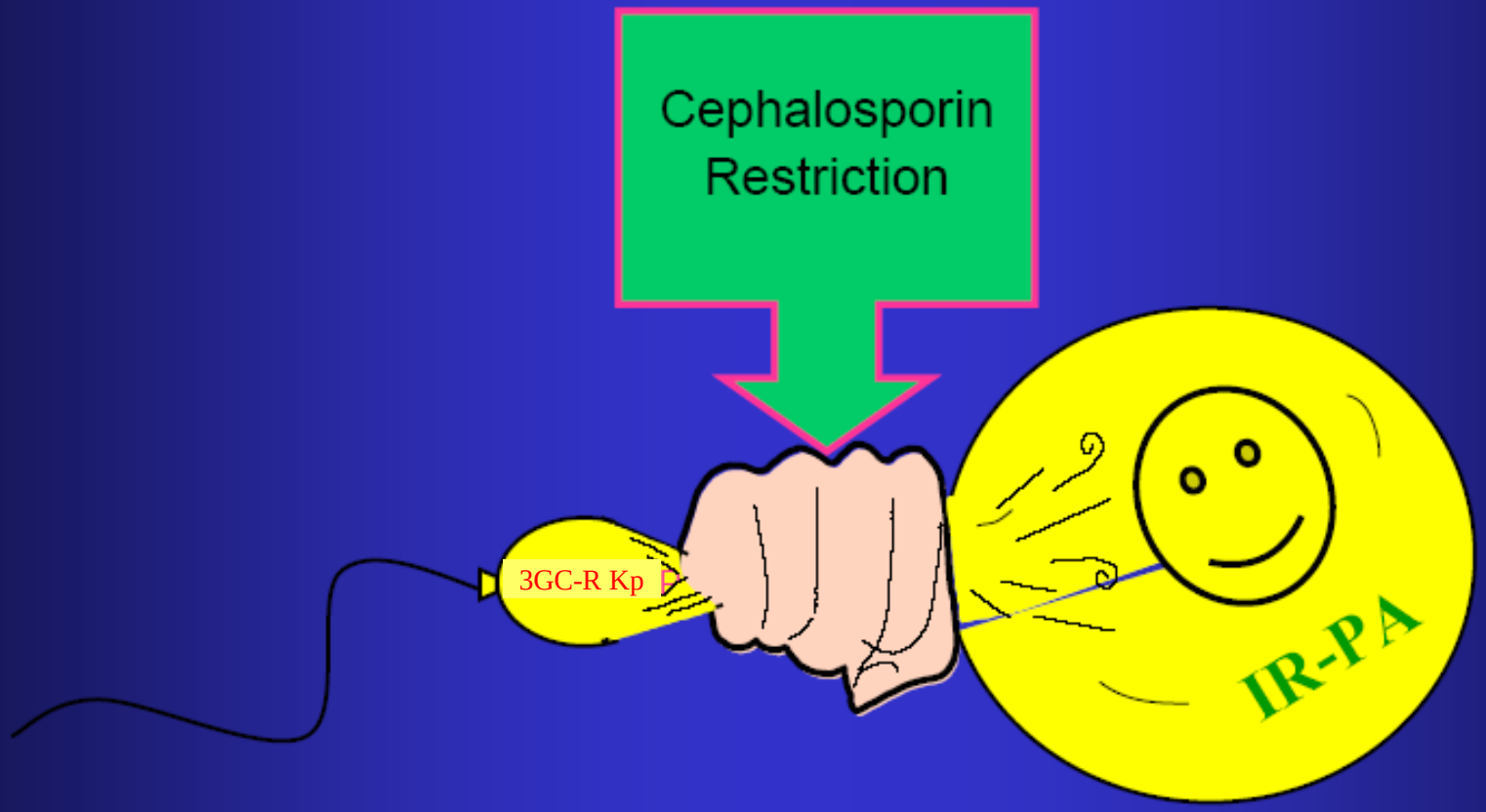
The Resistance Balloon



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Colistin Issues

- **Low level evidence on :**

1. Clinical efficacy in serious infections
2. Intraventricular or intrathecal administration
3. Inhaled administration
4. Co-administration of rifampicin

- **Disc susceptibility testing methods** and **Heteroresistance**
- **pK/pD controversy**
- **optimal dosing regimen remains unknown**
- **Mono or combo**

Resistance to colistin

- Rates of colistin resistance have been relatively low, probably because of its infrequent use. Nevertheless, resistance has recently been identified in several Gram-negative bacterial species.
- Resistance in MRAB increasingly described in some centers where colistin has been widely used
- Heteroresistance (i.e. the presence of colistin-resistant subpopulations within a microbial population that is susceptible according to its MIC) in MDR A. baumannii has been reported in 23–100% of clinical isolates
- Resistance of P. aeruginosa to colistin is a growing problem, and has been described most commonly in patients with cystic fibrosis (CF) who have received aerosolized colistin therapy
- Colistin resistance in KPC-producing K pneumoniae has been observed

Use the drug with caution

Yahav D et al. *Clin Microbiol Infect* 2012; **18**: 18–29

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New antibiotic pipeline analysis: potential utility of emerging agents

Review of the literature revealed 15 agents with a new mechanism of action or new target likely *and* systemic administration

A: Data supports in vitro activity

B: Assumed in vitro activity (known properties or mechanism of action)

	Gram-positive				Gram-negative		
	MRSA	VISA/ VRSA	PRSP	VRE	3GC R ENB	Carb R ENB	Carb R NF GNB
A	12	9	8	5	3	2	2
B	1	3	1	1	4	4	4
Total	13	12	9	6	7	6[a]	6[b]

3GC R ENB = 3rd generation cephalosporin-resistant *Enterobacteriaceae;* Carb R ENB = carbapenem-resistant *Enterobacteriaceae;* Carb R NF GNB = carbapenem-resistant non-fermentative Gram-negative bacilli

[a]phase I (2); phase II (3); phase III (1)
[b]phase I (2); phase II (3); phase III (1)

European Centre for Disease Prevention and Control (ECDC)/European Medicines Agency (EMeA) Joint Technical Report, Stockholm, September, 2009.

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Overview

- Clinical challenges of **ESCAPE**-pathogens
- Pharmacological profile
- Tigecycline clinical trials
- Tigecycline issues
  - Opportunities of use in approved indications
  - Mortality in RCTs
  - Use in not approved indications
  - Higher dose?

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  - Susceptibility tests

ESCAPE pathogens (Bad Bugs)

Enterococcus faecium
Staphylococcus aureus
Clostridium difficile
Acinetobacter baumannii

Pseudomonas aeruginosa

Enterobacteriaceae[1]

tigecycline spectrum

[1]included ESBL and carbapenemases producing

Rice LB. J Infect Dis. 2008;197:1079
Boucher HW, et al. Clin Infect Dis. 2009;48:1
Peterson, LR. Clin Infect Dis. 2009;49(6):992-3

Tigecycline: an extended broad-spectrum

Staphylococci
(incl. MRSA, VISA, VRSA)

Enterococci
(incl. VRE, LRE)

Streptococci
(incl. PRP)

Listeria

Corynebacterium

Enterobacteriaceae
(incl. ESBL, AmpC, MBL)

Acinetobacter
(incl. MDR)

S. maltophilia

H. influenzae

Moraxella

Pasteurella

Neisseria

Campylo

Anaerobes

Atypicals
- **Legionella**
- ***Mycoplasma***
- ***Chlamidia***
- ***M. fortuitum***

NOT Active
Proteus spp.
P.aeruginosa

Broad/Extended spectrum antimicrobials available for monotherapy

Antibiotic	Gram-negative	Gram-positive	Resistant Gram-negative	Resistant Gram-positive	Anaerobe	Pseudo
β-Lactam/ β-Lactamase Inhibitor						
3rd- Gen. Cephs						
Tigecycline			no proteus			
Glycopeptides						
Carbapenems						
Quinolones						

Varies by product within class

In Vitro Activity

No In Vitro Activity

Tigecycline: in vitro activity

	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	% Susceptible
E. coli	0.12	0.25	100
Klebsilella spp. ESBL+	0.5	1	97.9
Klebsiella spp. imi-R	0.5	1	98.2
Enterobacter spp.	0.5	1	98.4
Enterobacter spp. cefta-R	0.5	2	97.1
Acinetobacter spp.	0.5	2	94.4
Acinetobacter spp. carba-R	1	4	86.2

Sader HS et al. *Diagn Microbiol Infect Dis.* 2011;69:223-7

Susceptibility to tigecycline in hospitalized patients with secondary peritonitis undergoing surgery

- A total of 600 facultative/aerobic isolates (392 Gram negative, 208 Gram positive) and 100 anaerobes were tested

	n. ISOLATES	% S FDA breakpoint
E. coli	220	99.5
E. coli ESBL+	15	100
Klebsiella spp.	42	100
Streptococcus viridans		100
Staphylococcus aureus		100
Enterococcus spp.		100
Bacteroides fragilis	45	100

Tubau F et al. *Diagn Microbiol Infect Dis* 2010 ;66:308-13

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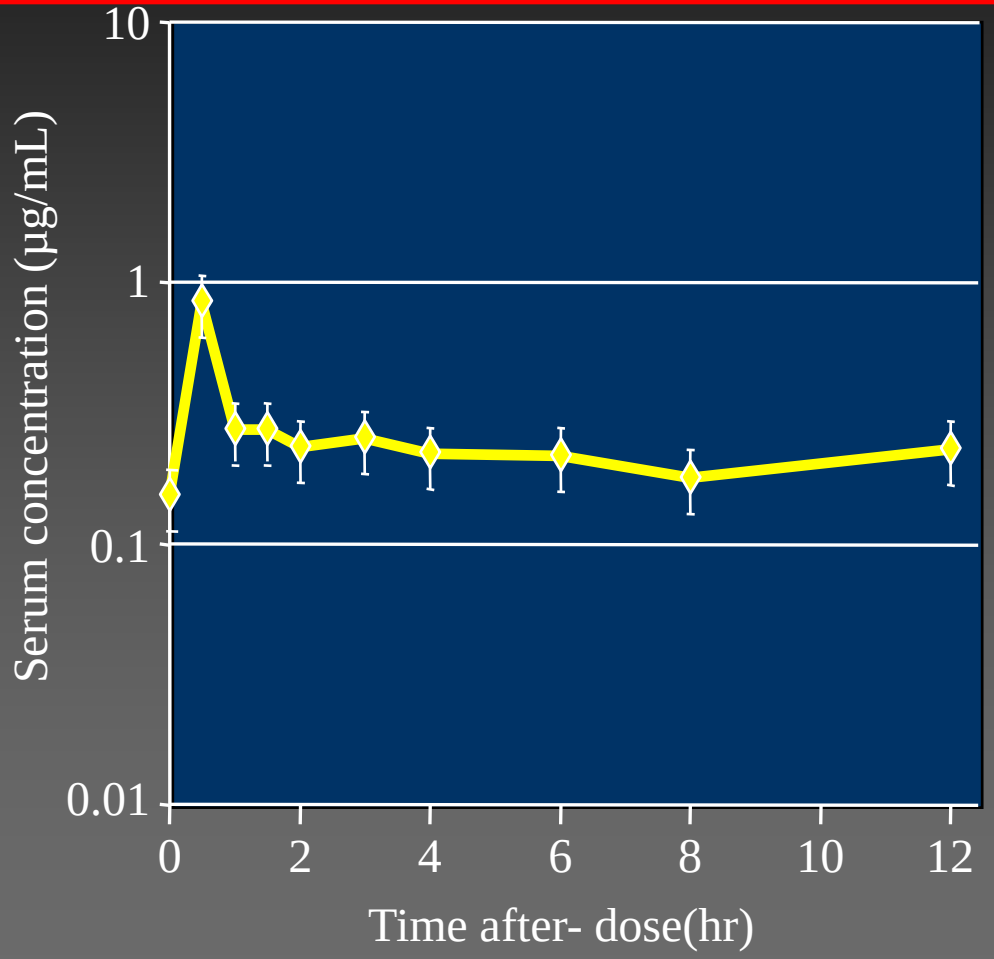
Tigecycline and Pharmacokintics and Pharmacodynamics

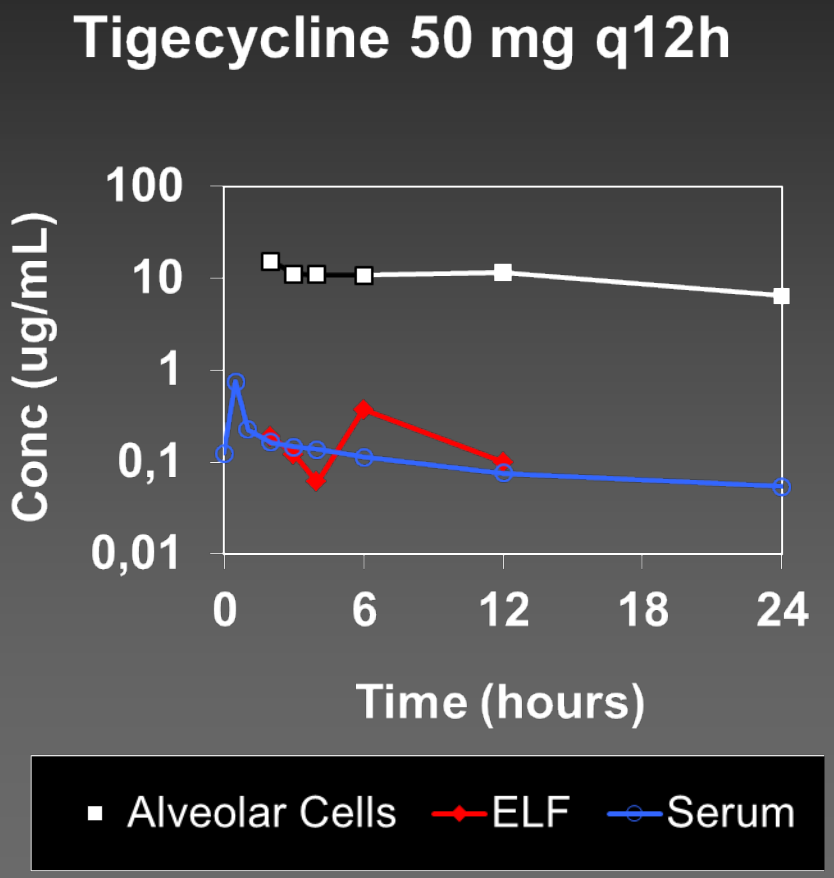


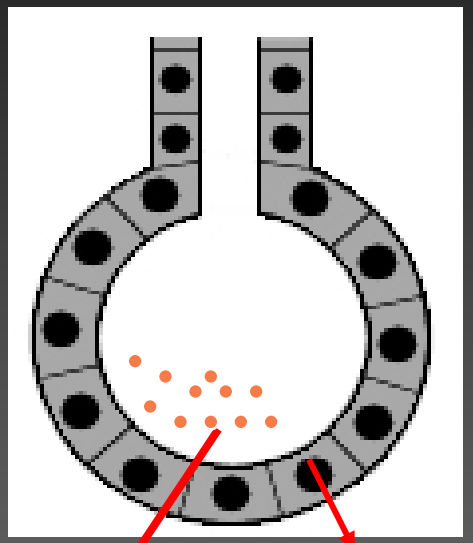
- **Lenear PK**
- **C_{max} = 0.911 µg/mL[1]**
  0.62 µg/mL[2]
- **C_{min} = 0.13 µg/mL**
- **$AUC_{0\text{-}24h}$ = 4.7 µg•h/mL**
- **$t_{½}$ = 42 hours**
- **V_{ss} = 639 L**

[1]After100mg
[2] After 10 days of 50 mg BID

Rello J. J Chemother. 2005;17(suppl 1):12-22.
Pfizer Pharma

Intrapulmonary Pharmacokinetics of Tigecycline





AUCAC/AUCserum = 77.5

AUCELF/AUCserum = 1.32

- infected patients?
- higher doses?

Conte et al. *Int J Antimicrob Agents*. 2005;**25**:523-9

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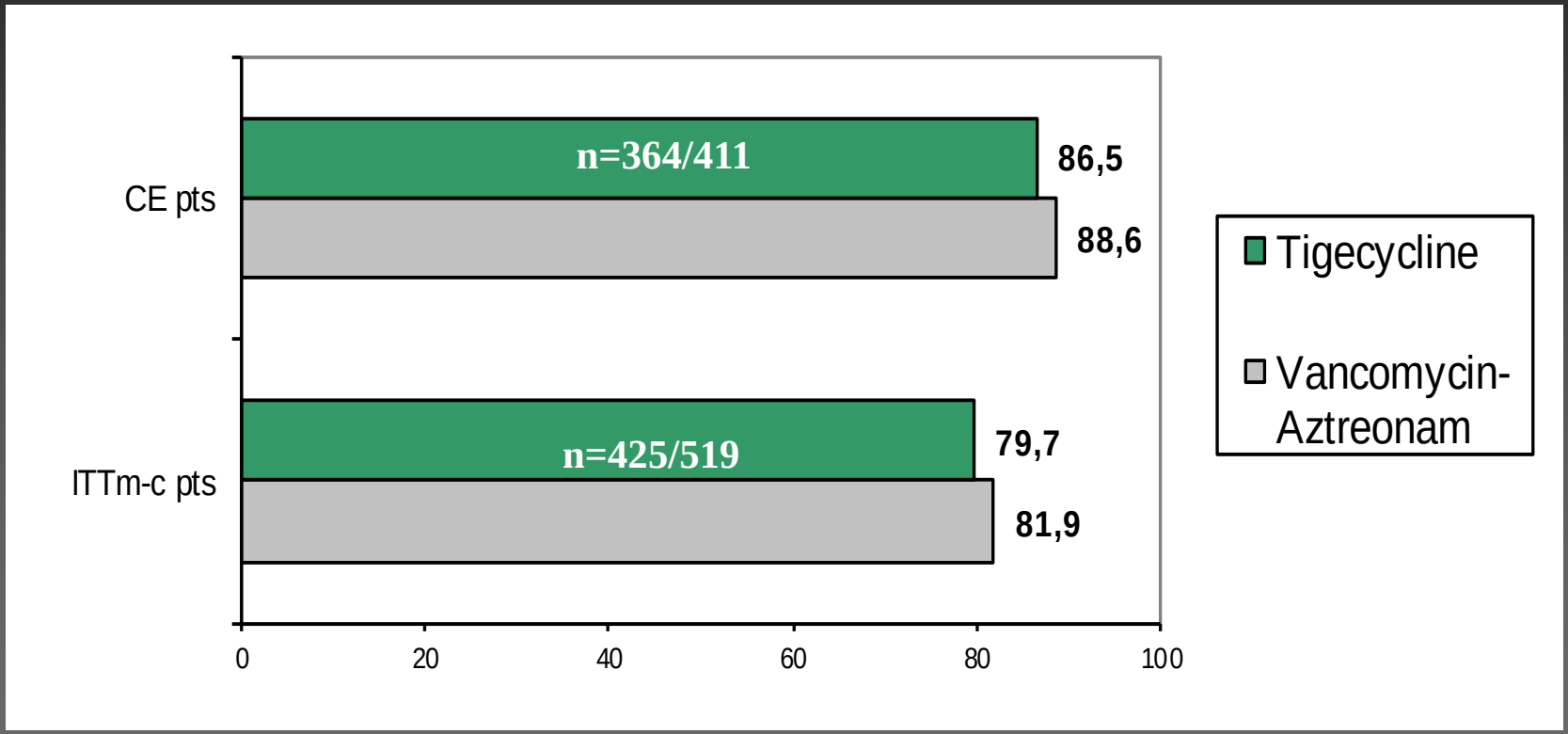
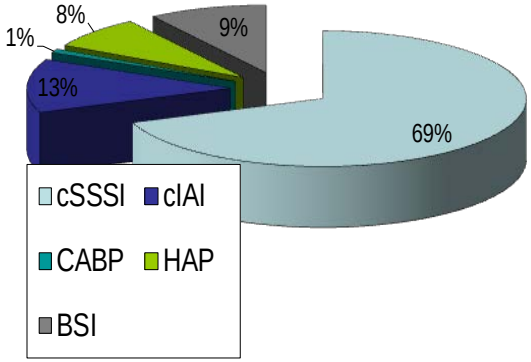
TIGECYCLINE-cSSSI
Clinical Outcomes (TOC)

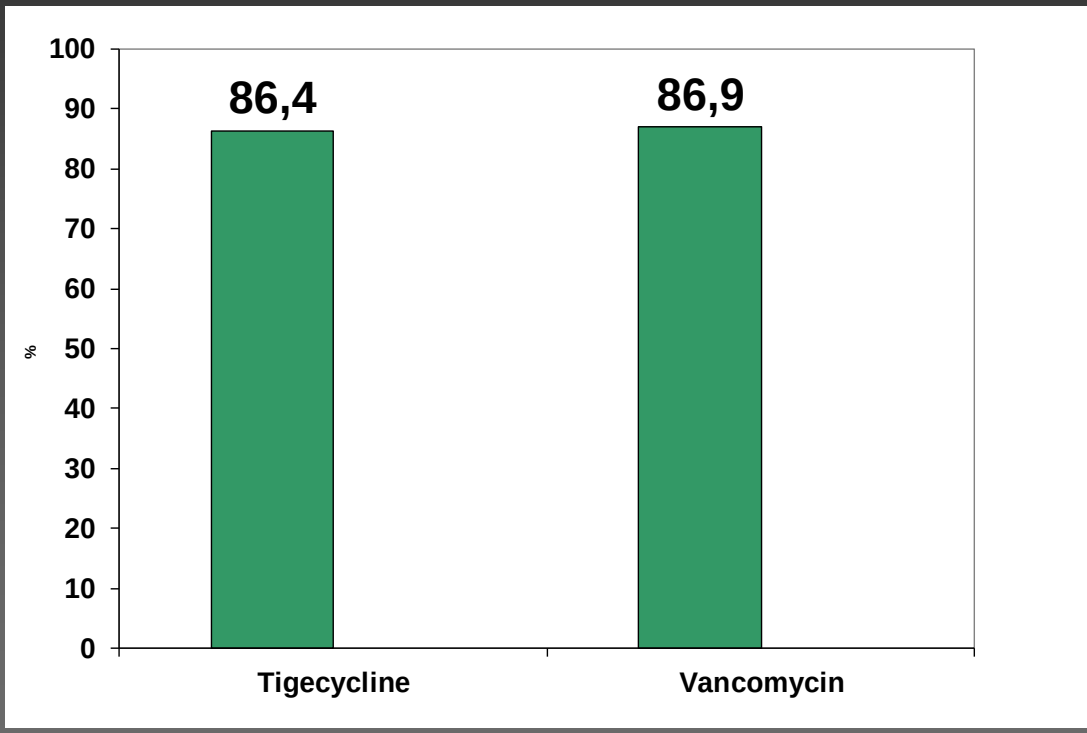


@ Difference = -2.1; **95% CI - 6.8, 2.7**
# Difference = -2.1; **95% CI - 7.1, 2.8**

Ellis-Grosse et al. Clin Inf Dis 2005; 41: S341-S353

TIGECYCLINE /MRSA serious infectons Clinical Outcomes (TOC)

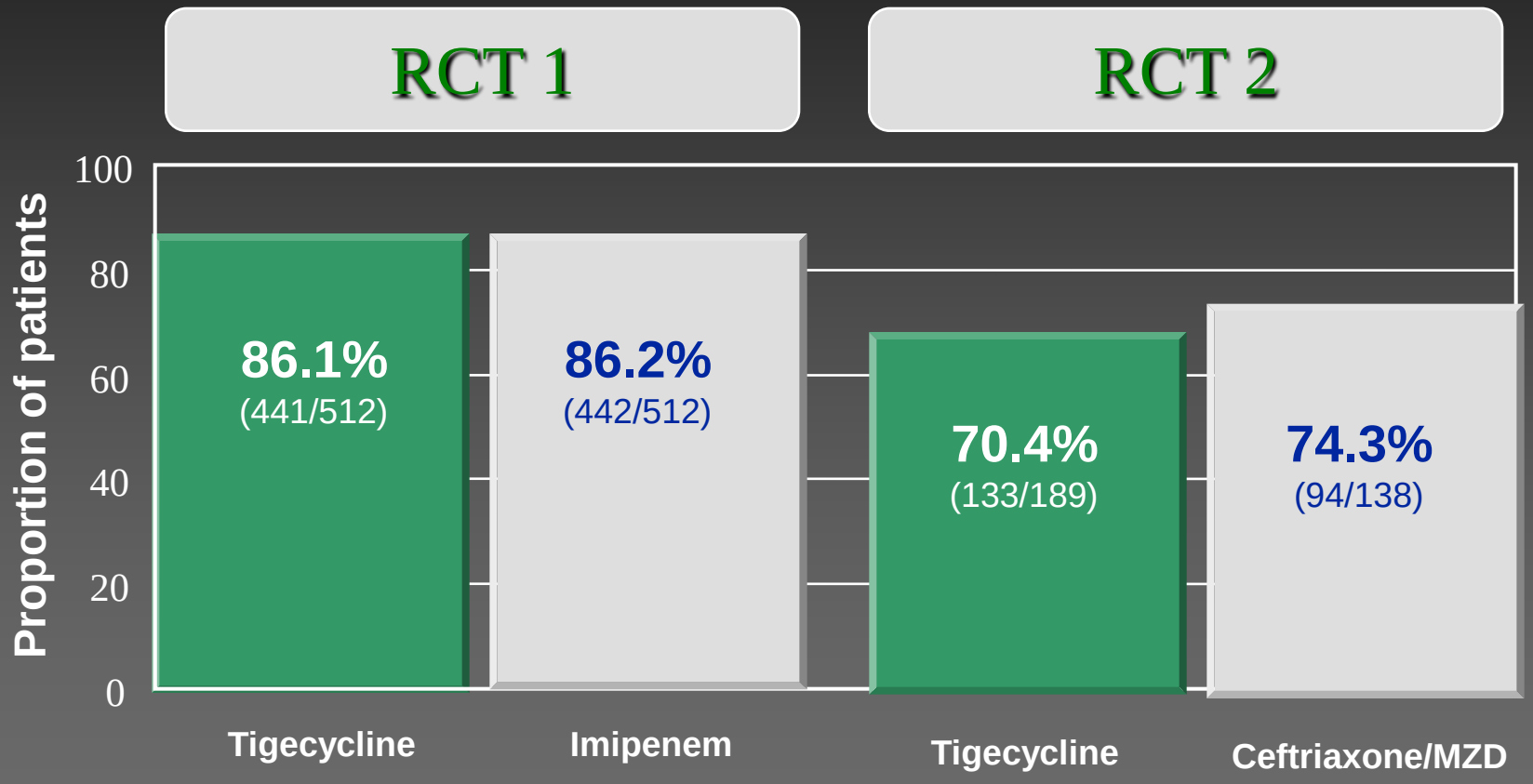




Flurescu et al. J Antimicrob Chemother. 2008;62:i17-28.

cIAI: Tigecycline Efficacy

Clinical Outcomes (TOC)

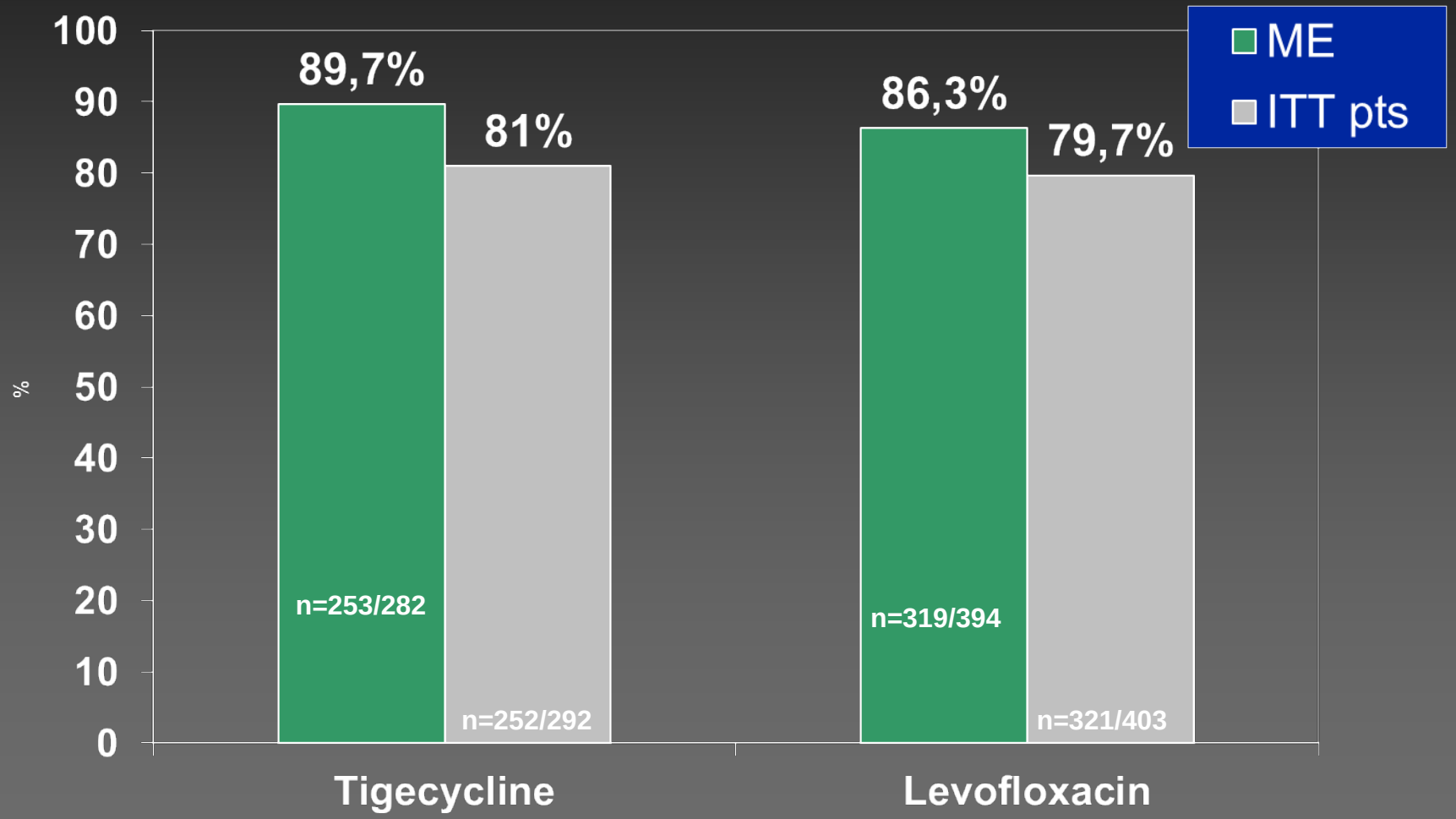


RCT=randomized clinical trial

Babinchak T et al. *Clin Inf Dis* 2005; **41**: S354-S367

Towfigh J et al *ECCMID* 2009: *R2132*

TIGECYCLINE-CABP
Clinical Outcomes (TOC)



Tanaseanu, et al. *Diagn Microbiol Infect Dis*. 2008;**61**:329-38

Tigecycline in secondary bacteremia: Pooled Results from 8 Phase III Clinical Trials

Table 3. Cure Rates, by Major Pathogen

Infectious agent	No. of cured subjects/no. of subjects in group (%)		*P*
	Tigecycline arm	Comparator arm	
Staphylococcus aureus			
All	16/20 (80.0)	12/15 (80.0)	>.99
Methicillin resistant[a]	5/6 (83.3)	3/4 (75.0)[b]	>.99
Streptococcus pneumoniae	22/24 (91.7)	13/19 (68.4)	.111
Gram-negative organisms[c]	17/21 (81.0)	20/22 (90.9)	.412

[a] Minimum inhibitory concentration of oxacillin, >4 μg/mL.
[b] All subjects were treated with vancomycin.
[c] *Klebsiella oxytoca, Klebsiella pneumoniae, Escherichia coli, Enterobacter cloacae,* and *Citrobacter freudii.*

Gardiner D et al. *Clin Infect Dis* 2010; 15;*50*:229-38.

Tigecycline vs. imipenem/cilastatin for treatment of HAP including VAP

Clinical cure rate at test of cure by population (%)		
	Tigecycline	Imipenem/ cilastatin
Clinically modified intent-to-treat (c-mITT)	62.7	67.6
Clinically evaluable (CE)	67.9	78.2
Non-ventilator-associated hospital-acquired pneumonia (non-VAP)	75.4	81.3
Ventilator-associated pneumonia (VAP)	48	70

- Tigecycline was non-inferior to imipenem/cilastatin in both the CE and c-mITT populations for non-VAP patients
- Tigecycline failed to achieve non-inferiority to imipenem/cilastatin in both the CE and c-mITT populations for VAP patients

Freire et al. *Diagn Microbiol Infect Dis.* 2010;**68**:140-51

Overview

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Tigecycline in critical-ill patients : Experience in the RCTs

	n	APACHE II (mean)	Subrrogate marker	Bacteremia
cSSSI	422 (CE)	no	Surgery/drainage 109 (25,8%)	23 (5,4%)
cIAI	631 (m-ITT)	6,3	Peritonitis 21 (3,3%)	40 (6,3%)
CABP	424 (m-ITT)	no	Fine IV-V 84 (19,8%)	22 (5,1%)
HAP	467 (m-ITT)	12,3	--	NA
MRSA	117 (m-ITT)	7,9	--	11 (9,4%)
MDR-GN	112 (m-ITT)	10,2	--	1 (2,8%)

cSSSI=complicated skin and skin structure infection;
cIAI=complicated intra-abdominal infections
CAP=community-acquired bacterial pneumonia
HAP=hospital acquired pneumonia
MRSA=methicillin-resistant *S.aureus*
MDR-GN=multidrug-resistant Gram-negatives

Babinchak T et al. Clin Inf Dis 2005; 41: S354-S367
Ellis-Grosse et al. Clin Inf Dis 2005; 41: S341-S353
Tanaseanu, et al. Diagn Microbiol Infect Dis. 2008;61:329-38
Florescu et al. J Antimicrob Chemother. 2008;62 Suppl 1:i17-28
Vasilev et al. J Antimicrob Chemother. 2008;62 Suppl 1:i29-40

cIAI Randomized Clinical Trials (RCT): where are the critical-ill patients?

	Drug	n	APACHE II
RCT 1	Ertapenem	203	≥15=9%
	Pip/Tazo	193	≥15=6.7%
RCT 2	Meropenem	71	Mean 5.8
	Imipenem	64	Mean 6.4
RCT 3	Doripenem	162	≤10=88%
	Meropenem	163	≤10=91.5%

RTC=randomized clinical trial

RCT 1=Solomkin et al. Annals Surg 2003;237:235-245
RCT 2=Zanetti et al. Int J Antimicrob Agents 1999;11:107-113
RCT 3=Lucasti et al. Clin Ther. 2008;30:868-83

2010 IDSA Guidelines on Anti-infective Agents for Complicated IAIs

Type of Therapy	Class	Complicated Community-Acquired Infections	
		Mild-to-moderate	High[illegible]
Single Agent	β-lactam/ β-lactamase inhibitor	Ampicillin/ Sulbactam Ticarcillin/Clav.	
	Carbapenem	Ertapenem	Imipenem, M[illegible]openem, doripenem
	Glycycycline	Tigecycline	Tigecycline
Combo Regimen	Cephalosporin-based	Cephalosporins + Metronidazole	3rd/4th Gen. Cephalosporin + Metronidazole
	Fluoroquinolone -based	Fluoroquinolone + Metronidazole	Ciprofloxacin/levo + Metronidazole

Why not?

* Severe physiologic disturbance, advanced age, immunocompromized

Solomkin JS et al *Clin Infect Dis* 2010;*50*:133-64

Complicated intra-abdominal infection (cIAI): Tigecycline Experience

Clinical Trials

cIAI study -301ww-[1]	
Treatment	**Clinical success**
Tigecycline	86.1%
Imipenem	86.2%[a]

cIAI study -400ww-[2]	
Treatment	**Clinical success**
Tigecyline	70.4%
CRO+MZD	74.3%[a]

[a]p<.0001 for noninferiority
[b]p=.009 for noninferiority

Case series

	n	APACHE II	Outcome
Swoboda et al[3]	48	27	Mortality 30%
Curcio et al.[4]	18	13.5	Success 78%

[1]Babinchak T et al. Clin Inf Dis 2005;41:S354-S367
[2]Towfigh et al Clin Microbiol Infect. 2009 [Epub ahead of print]
[3]Swoboda et al. J Antimicrob Chemother. 2008;61:729-33
[4]Curcio et al. J Antimicrob Chemother. 2009;64:1344-6

Tigecycline Treatment of Critically Ill Patients

	Spain	Italy	LA[1]
N	44	207	209
APACHE II (mean)	22	21	18
Type of infection			
• *pneumonia (%)*	*51,2*	*27*	*47*
• *cSSSI[2] (%)*	*13,6*	*8*	*18*
• *cIAI[3] (%)*	*13,6*	*48*	*8,5*
• *BSI[4] (%)*	*9,1*	*11*	*0*
• *Other (%)*	*12,5*	*6*	*26,5*
Monotherapy, (%)	25,6	78	76
Combination, (%)	74,4[5]	22[6]	24[7]
Clinical success, (%)	67,4	73	69

Balsera et al. Med Intensiva. 2010

Bassetti et al. BMC Infect Dis. 2010;10:287

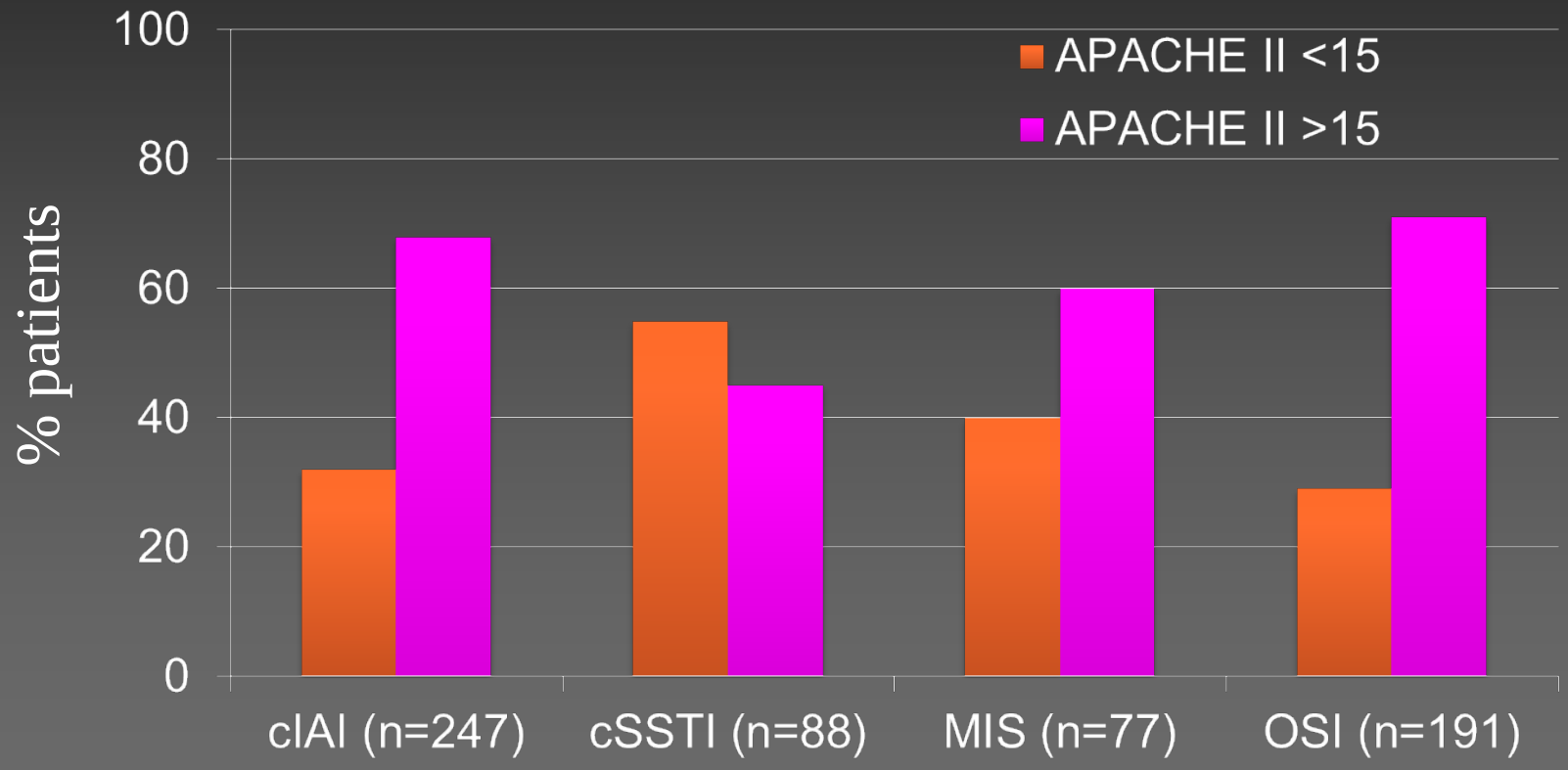
Curcio D et al. Curr Clin Pharmacol. 2011;6:18-25.

Tigecycline in Severly Ill Patients

- Prospective, multicenter, non-interventional study
  - Hospitalized, severly ill patients with
    - cIAIs (41%)
    - cSSTIs (16%)
    - Multiple infection sites (13%)
    - Other severe infections (31%)
- 656 patients
  - Mean APACHE II score 19.1
  - 66% patients with hospital-acquired infections

Eckmann C, et al. Chemotherapy 2011;57:275

APACHE II Score According to Type of Infection



Eckmann C, et al. Chemotherapy 2011;57:275

Rates of Cure or Improvement

Patient group	Patients cured/improved
Intra-abdominal infection	201 (75)
Community acquired	71 (84)
Hospital acquired	129 (72)
Peritonitis	164 (76)
Skin and soft tissue infection	84 (82)
Community acquired	55 (87)
Hospital acquired	29 (74)
Multiple infection sites	55 (67)
Community acquired	16 (73)
Hospital acquired	31 (65)
Other infections	156 (76)
Community acquired	44 (83)
Hospital acquired	111 (74)
Antibiotic-resistant pathogen	
ESBL[1]	49 (77)
MRSA[1]	77 (72)
VRE[1]	27 (82)
Disease severity (APACHE II)[2]	
APACHE II ≤15	177 (83)
APACHE II >15	279 (72)

MRSA = Methicillin-resistant *Staphylococcus aureus*.
[1] Percentages based on all patients with at least 1 pathogen of this type present at the start of treatment.
[2] Based on all patients.

Eckmann C, et al. Chemotherapy 2011;57:275

Tigecycline use in serious nosocomial infections: a drug use evaluation

	n, 207
Gender, *n* (%) Male	 118 (57)
Age, yrs Median Range	 63 14-89
Apache II score Mean (± SD) Range	 21 ± 8.8 8-45
Admitted to ICU, *n* (%)	83 (40)
Co-morbid conditions, *n* (%) Solid tumor Hematologic malignancy Diabetes mellitus Neutropenia (< 500 mm^3)	 79 (38) 50 (24) 48 (23) 29 (14)

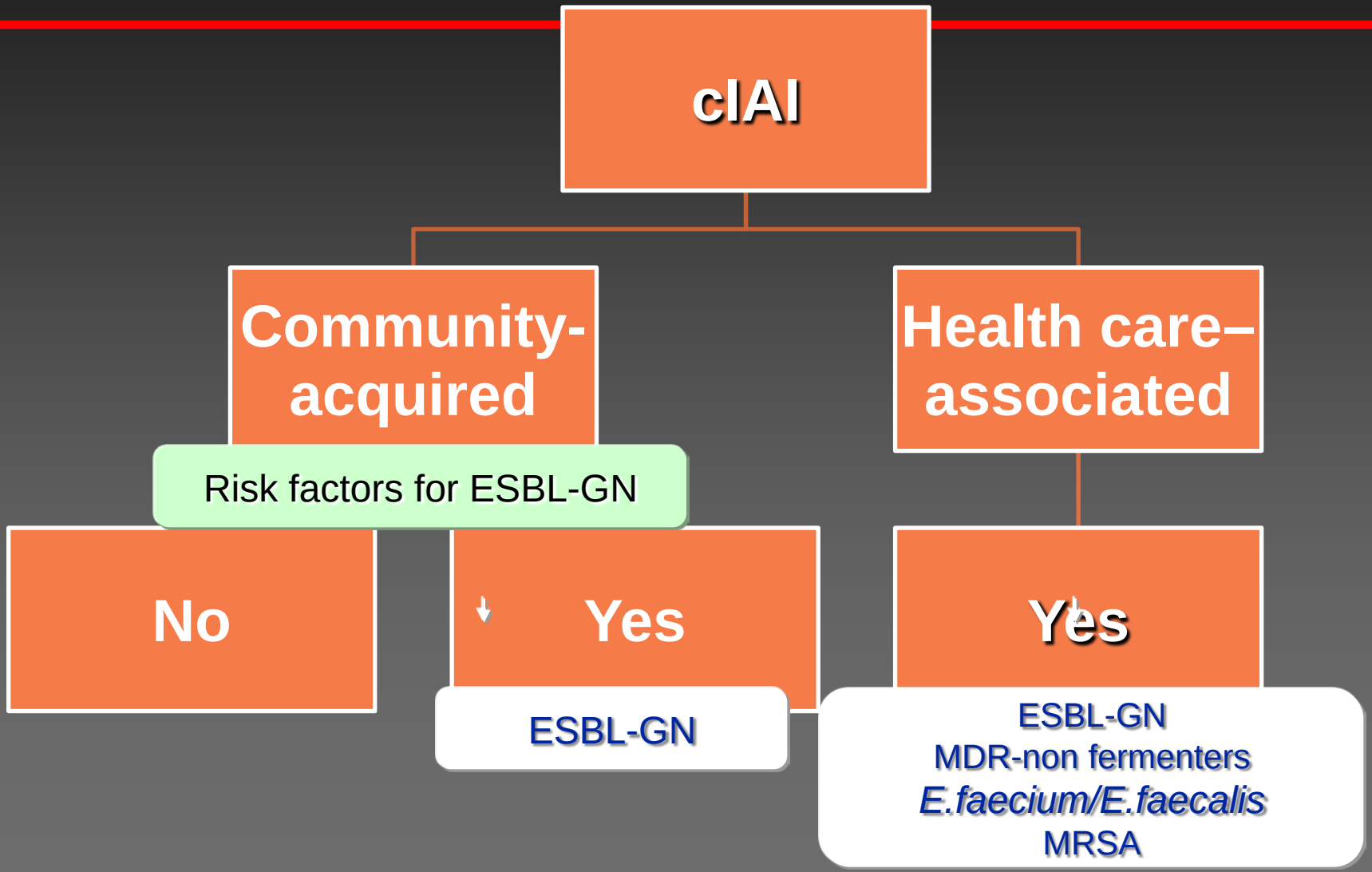
Bassetti M et al. BMC Infect Dis 2010 Sep 29;10:287

Tigecycline use in serious nosocomial infections: a drug use evaluation

Type of infections	*n* (%)	*Duration of treatment, days Median (range)*	Clinical efficacy *n* (%)	Clinical failure *n* (%)
Secondary peritonitis	46 (22)	9 (6- 18)	40 (88)	6 (12)
Tertiary peritonitis	41 (20)	15 (11-28)	32(78)	9 (22)
Other abdominal infections	12(6)	11 (7-17)	5 (42)	7 (58)
Pneumonia (HAP, HCAP, VAP)	27 (13)	12 (8-21)	18 (67)	9 (33)
Pneumonia and bloodstream infections	29 (14)	17 (13-24)	19 (66)	10 (34)
Bloodstream infections	23 (11)	15 (12-18)	16 (70)	7 (30)
Complicated skin and soft tissue infections	17 (8)	11 (7-18)	13(76)	4 (24)
Empiric use in neutropenic	12 (6)	14 (9-17)	7 (58)	5(42)
Total	207 (100)		151 (73)	56 (27)

Bassetti M et al. BMC Infect Dis 2010 Sep 29;10:287

Rational to use tigecycline in cIAI



Tigecycline in Abdominal Infections

Monotherapy

Combination Treatment

CA and HA sec peritonitis

Tertiary peritonitis

Paul-Ehrlich-Society (Germany) 2010 – recommendation diffuse secondary peritonitis

Diagnosis	Antibiotic agent	duration	Level of Recom.	Level of evidence
Community acqui. diffuse ± Risk factores	**Acylaminopenicillin/BLI**	**3-5 days**	**A**	**I**
	Cephalosporin Gr. 3a/4		**A/B**	**I**
	Fluorquinolon Gr. 2/3 o.		**A/B**	**I**
	+ Metronidazol			
	Carbapenem group 1		**A**	**I**
	Carbapenem group 2		**A**	**I**
	Tigecycline		**B**	**I**
Nosocomial postoperative (change of antibiotic class!)	**Carbapenem group 1**	**7 days**	**A**	**I**
	Carbapenem group 2		**A**	**I**
	Acylaminopenicillin/BLI		**A**	**I**
	Tigecycline		**A**	**II**
	Fluorquinolon group 4		**B**	**I**

Eckmann C et al. Chemother J 2010

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Tigecycline FDA Drug Safety Communication (Sep 2010)

Infection Type	Tigecycline deaths/total pts	Comparator Antibiotics deaths/total pts	Risk Difference* (95% Confidence Interval)
cSSSI	12/834 (1.4%)	6/813 (0.7%)	0.7 (-0.3, 1.7)
cIAI	42/1382 (3.0%)	31/1393 (2.2%)	0.8 (-0.4, 2.0)
CAP	12/424 (2.8%)	11/422 (2.6%)	0.2 (-2.0, 2.4)
HAP	66/467 (14.1%)	57/467 (12.2%)	1.9 (-2.4, 6.3)
Non-VAP†	41/336 (12.2%)	42/345 (12.2%)	0.0 (-4.9, 4.9)
VAP†	25/131 (19.1%)	15/122 (12.3%)	6.8 (-2.1, 15.7)
RP	11/128 (8.6%)	2/43 (4.7%)	3.9 (-4.0, 11.9)
DFI	7/553 (1.3%)	3/508 (0.6%)	0.7 (-0.5, 1.8)
Overall Adjusted	150/3788 (4.0%)	110/3646 (3.0%)	0.6 (0.1, 1.2) **

cSSSI = Complicated skin and skin structure infection; cIAI = Complicated intra-abdominal infections; CAP = Community-acquired pneumonia; HAP = Hospital-acquired pneumonia; VAP = Ventilator-associated pneumonia; RP = Resistant pathogens; DFI = Diabetic foot infection.

*Risk Difference = the difference between the percentage of patients who died in the tigecycline and comparator antibiotic groups. The 95% CI for each infection type was calculated using the normal approximation method without continuity correction.

† Subgroups of the HAP population

** Overall adjusted (random effects model by trial weight) risk difference estimate

http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm last access Sep 09, 2010

Systematic Review and Meta-Analysis of the Effectiveness and Safety of Tigecycline for Treatment of Infectious Diseases

- ".. To compare the efficacy and safety of Tigecycline….. with those of empirical antibiotic regimens …. with good efficacy against cSSTIs, cIAIs, CAP & other infections by MRSA or VRE"
- 8 RCTs with 4651 patients included
- → Tige monotherapy effective as comparison for cSSTIs, cIAIs, CAP and infections by MRSA or VRE
- However, because of the high risk for mortality, adverse effects and emergence of resistant isolates, prudence with tigecycline monotherapy is required

Cai Y et al AAC 2011; 55 (3): 1162 - 72

Death definitions

1. Death not due to the primary infection under study.

In order to summarize these cases, what is the best understanding as to the antecedent cause(s) of death (e.g. died of PE)?

2. Death with primary infection under study.

In order to summarize these cases, what is the best understanding as to the antecedent cause(s) of death (e.g. died of myocardial infarction while being actively treated for primary infection)?

3. Death due to primary infection under study.

a. death without confounding factor.

b. death with confounding factors - In order to summarize the cases, what are the confounding factor(s) that that affected the outcome (e.g. entered into the trial in severe sepsis or septic shock, inadequate source control, surgical complication)?

Bassetti M, Holtom P, Wenisch C. Data per EMA February 2011

Death analysis

N=86	Comparator (n=37)	Tigecycline (n=49)	Chi-square (df=1)
Death not due to infection	25 (67.6)	24 (49.0)	p=0.08
Death with infection	1 (2.7)	8 (16.3)	p=0.04
Death due to infection	**11 (29.7)**	**17 (34.7)**	**p=0.6**
no confounding factor	9 (24.3)	2 (4.1)	p=0.0002*
confounding factor	2 (5.4)	15 (30.6)	p=0.0002*

Bassetti M, Holtom P, Wenisch C. Data for EMA February 2011

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  - Higher dose?

Ventilator-associated pneumonia (VAP): Tigecycline experience

	Poulakou et al.[1]	Anthony et al.[2]	Schafer et al.[3]	Curcio et al.[4]	Curcio et al.[5]
n VAP	18	6	22	73	117
n VAP + BSI[a]	11%	NA	14%	8%	19.5%
APACHE II (mean)	18	NA	NA	NA[e]	18
A.baumannii	83%	83%	100%	100%	48%
Monotherapy	50%	16%	22%	63%	37%
Combination	50%	84%	78%[c]	27%	63%
Colistin	77%	40%[b]	35%[d]	30%	NA
Clinical success					
Total	88%	50%	81%	69,9%	63%

[a]bloodstream infections, [b]1 pt. nebulized, [c]9 pts. with imipenem, [d]nebulized, [e]median MPM II=58

[1]Poulakou et al. Journal of Infection. 2009;58:273-284.
[2]Anthony et al. Clin. Infect. Dis.2008;46:567-570.
[3]Schafer et al. Pharmacotherapy. 2007;27:980-7.
[4]Curcio et al. J Chemother. 2009;21:58-62.
[5]Curcio et al. Infez Med. 2010;18:27-34.

Tigecycline in the treatment of infections from multi-drug resistant Gram-negative pathogens

- TIG for >5 days either as monotherapy (M group) or as presumed active monotherapy (PAM group). In the PAM group, all co-administered antimicrobial(s) were resistant in vitro against the targeted pathogen(s) or had been clinically and microbiologically failing after 5 days of therapy despite in vitro susceptibility.
- 45 pts (35 in ICU)
  - 28 *Acinetobacter baumannii*
  - 23 *Klebsiella pneumoniae* infections
  - 21 VAP/HCAP, 10 BSI, 14 surgical infections (SI)
  - Successful overall clinical outcome was 80%
    - 81.8% in M group,
    - 78.3% in PAM group,
    - 90.5% in VAP/ HCAP, 80% in BSI, 64.3% in SI

Tigecycline is not currently approved for the treatment of HAP and bacteremia

Poulakou et al. J Infection 2009;58: 273-284

Univariate analysis of factors associated with death among patients with bloodstream infection due to KPC producing Klebsiella pneumoniae

Variable	Non survivors (n=52)	Survivors (n=73)	*P* value	OR (95% CI)
Monotherapy	25 (48.1)	21 (28.7)	0.02	1.59 (1.06-2.38)
Tigecycline	10 (19.2)	9 (12.3)	0.28	1.32 (0.81-2.16)
Colistin	11 (21.5)	11 (15.1)	0.37	1.25 (0.77-2.03)
Gentamicin	4 (7.6)	1 (1.3)	0.09	1.98 (1.21-3.23)
Combination therapy	27 (51.9)	52 (71.2)	0.02	0.62 (0.41-0.94)
Tigecycline & Colistin	7 (13.4)	16 (21.9)	0.22	0.68 (0.35-1.32)
Tigecycline & Gentamicin	6 (11.5)	6 (8.2)	0.53	1.22 (0.66-2.25)
Colistin & Gentamicin	4 (7.7)	3 (4.1)	0.39	1.40 (0.71-2.76)
Tigecycline & Meropenem	2 (3.8)	2 (2.7)	0.55	1.21 (0.44-3.29)
Colistin & Meropenem	1 (1.9)	3 (4.1)	0.44	0.59 (0.10-3.27)
Gentamicin & Meropenem	3 (5.7)	3 (4.1)	0.48	1.21 (0.53-2.78)
Tigecycline & Colistin & Meropenem	**2 (3.8)**	**14 (19.2)**	**0.009**	**0.27 (0.07-1.01)**
Tigecycline & Gentamicin & Meropenem	1 (1.9)	5 (6.8)	0.20	0.38 (0.06-2.35)
Other combinations	1 (1.9)	2 (2.7)	0.62	0.79 (0.15-4.01)
Inadequate initial treatment	39 (75)	36 (49.3)	0.003	2.00 (1.19-3.34)
Shock	13 (25)	4 (5.5)	0.002	2.11 (1.47-3.04)
APACHE II score (mean ± SD)	40±22	24±15	<0.001	-

Multivariate analysis of factors associated with death among patients with bloodstream infection due to KPC producing Klebsiella Pneumoniae.

Shock	-	-	0.008	7.17 (1.65-31.03)
Inadequate initial treatment	-	-	0.003	4.17 (1.61-10.76)
APACHE III score (mean ± SD)	-	-	<0.001	1.04 (1.02-1.07)
Tigecycline & Colistin & Meropenem	-	-	0.01	0.11 (0.02-0.69)

Bassetti M et al. Clin Infect Dis 2012 in press

Refractory *Clostridium difficile* Treated with Tigecycline

- Vancomycin and metronidazole are the only effective agents readily available at this time for treatment of severe, refractory *C. difficile* infection (CDI)
- Standard therapy for CDI becomes less effective as hypervirulent strains become more prevalent
- In 3 of the 4 patients, colectomy was considered; after initiation of tigecycline, all patients recovered quickly, and surgery was no longer indicated
- Favorable outcomes suggest tigecycline may be a feasible alternative for severe, refractory CDI

Herpers BL, et al. *Clin Infect Dis.* 2009;48:1732-1735.

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  - Higher dose?

Tigecycline in VAP: why the RCT failed?

- Low concentrations in ELF[1]
- Low AUC/MIC (we need more than >8.8 for *Acinetobacter* spp. MR)[2]
- Clinical trial ongoing with higher dose…[3]

[1]Burkhardt et al. Int J Antimicrob Agents. 2009;34:101-2.
[2]Koomanachai et al. J Antimicrob Chemother. 2009;63:982-7.
[3]www.clinicaltrial.gov (último acceso 5 de Julio 2009)

Tigecycline HAP RCT: AUC/MIC ratios

	VAP patients (n=22)	Non-VAP patients (n=38)
Mean	**2.644**	**8.907**
SD	3.018	13.01
Minimum	0.0035	0.048
Median	1.730	4.389
Maximum	11.53	55.56

Freire et al. Diagn Microbiol Infect Dis. 2010;68:140-51

Pharmacokinetic/pharmacodynamic parameters of the three tigecycline twice-daily regimens.

	Day 1			Day 2			
	50mg*	100mg	150mg	50mg*	100mg	150mg	*p*
AUC_{0-24}/MIC	27.76	32.16	50.56	25.60	53.76	79.52	<0.01

*100 mg as loading dose following by 50mg q 12h

MRSA showing heteroresistance to vancomycin MIC/MBC 0.12/0.25_g/mL
Enterococcus faecium MIC/MBC 0.12/0.25_g/mL
ESBLproducing *E. coli* MIC/MBC 0.12/0.25_g/mL

Sevillano et al. International J of Antimicrob Agents 2010;36:137–144

Tigecycline in HAP: pKpD considerations

- The PD target most closely associated with tigecycline efficacy is the AUC/MIC ratio.
- AUC/MIC of 8.78 were required to produce 2 log kill, in a pneumonia murine model by *A. baumannii* (MIC 1.0 mg/L) respectively.
- 50mg tigecycline twice daily is probably underdosed for the treatment of pneumonia caused by typical, extracellular-acting bacteria (low ELF concentrations).
- Tigecycline doses of up to 200 mg/day may be required to provide adequate exposure for microorganisms with MIC ≥1.0 mg/L

Ambrose et al. Clin. Infect. Dis. 2007;44:79–86.
Koomanachai et al. J Antimicrob Chemother. 2009;63:982-7.
Burkhardt et al. Int J Antimicrob Agents. 2009;34:101-2.

Tigecycline
Its Role in the Hospital

1-Surgical site infection

2-cSSSI in patients with MDR-pathogens risk factors

3-cIAI in high risk patients (ie. nosocomial peritonitis)

4. Not approved uses (VAP, bacteremia, other): in combination

Please Do Not Forget

- **Tigecyline as a tool to save carbapenems, either as a primary treatment or de-escalation**
- **Tigecycline to avoid «*collateral damage*»**

How to manage MDR pathogens in the daily practice

- Collateral damage of 3GC, FQ and carbapenems
- Adverse clinical outcomes in infections due to ESCAPE pathogens
- Need to preserve the carbapenems use
- Lack of clinical and PK/PD evidence to use polimyxins for MDR-Gram-negatives
- Lack of new antibiotics with activity against MDR-*Acinetobacter* spp., *P. aeruginosa and carba-R enterobacteraceae*
- *Role of tigecycline*
- *Pilars of empiric antibacterial use*

Pillars of Empiric Therapy for Serious (Nosocomial) Infection

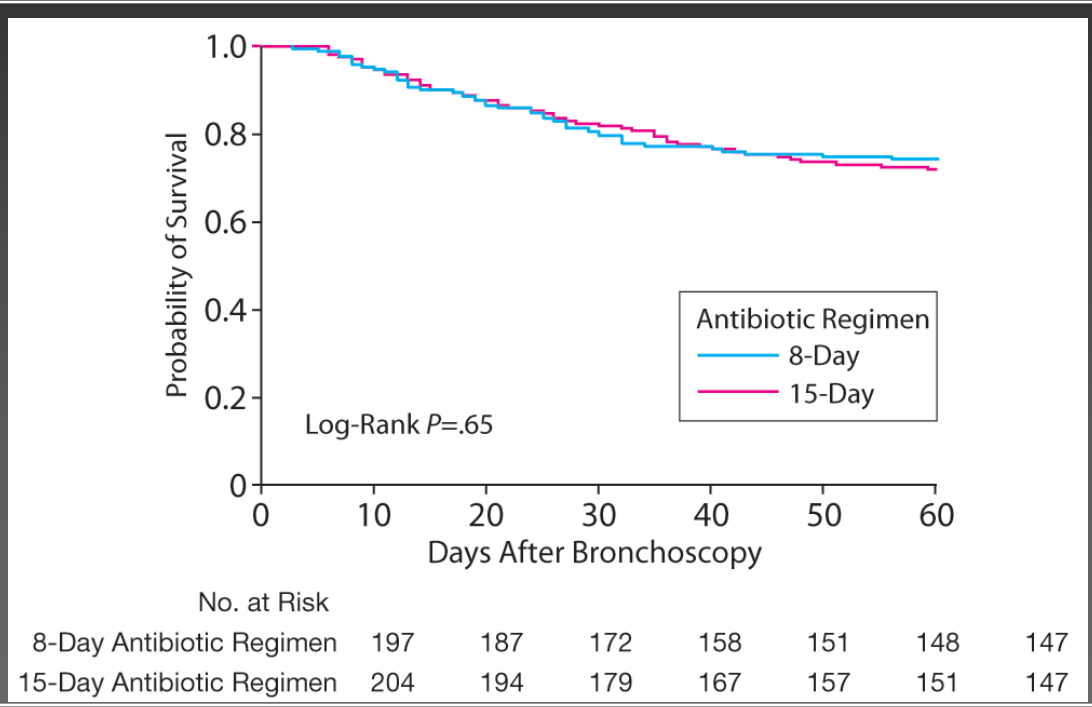
- Timely
  - Any delay in initiation potentially lethal
- Appropriate
  - All isolated pathogens susceptible to ≥ of the administered antibiotics
- Administered at adequate dosage and intervals consistent with PK/PD parameters
- Timely streamlining based on clinical response and microbiological data
- Prompt discontinuation when practical

Deresinski S. *Clin Infect Dis*. 2007;45:S177-S183.

Opal SM, et al. JAMA. 2009;302:2367-2368.

Antibiotic Care Bundle Appropriate Duration of Therapy: Longer is Not Necessarily Better

Kaplan-Meier estimates of probability of survival in VAP patients on 8 days vs 15 days of therapy



No. at Risk							
8-Day Antibiotic Regimen	197	187	172	158	151	148	147
15-Day Antibiotic Regimen	204	194	179	167	157	151	147

In ventilator-associated pneumonia, patients treated for 8 days compared to 15 days had:

- No excess mortality
- No more recurrent infections
- Had more antibiotic-free days

Chastre J, et al. *JAMA*. 2003;290:2588-2598.

Summary

Summary of the Antibiotic Care Bundle

Right drug
Right time
Right dose
Right duration

+

Infection Control