Difficoltà ed insuccessi nel trattamento delle infezioni da Gram-negativi MDR

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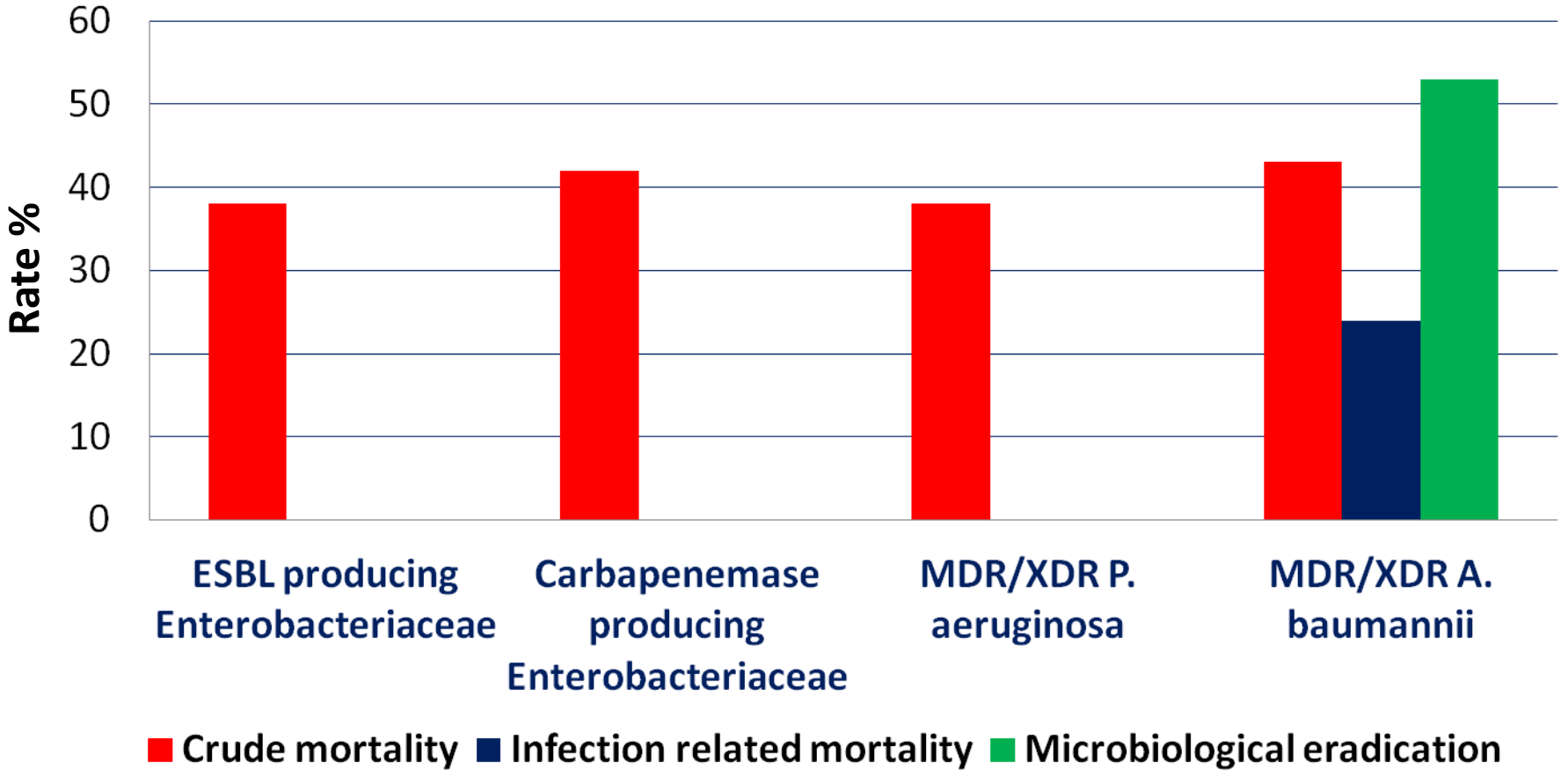
Summary

- Treatment failure
- Recurrence
- Emergence of further antibiotic resistance
- Adverse events

Treatment failure

- Crude mortality
- Infection related mortality
- Clinical success
- Microbiological eradication

Treatment failure



Tumbarello M et al. Antimicrob Agents and Chemother 2007: 51

Tumbarello M et al. Clin Infect Dis 2012:55

Pena C et al.Clin Infect Dis 2013:57

Durante Mangoni E et al. Clin Infect Dis 2013:57

Predictors of mortality in multidrug-resistant *Klebsiella pneumoniae* bloodstream infections

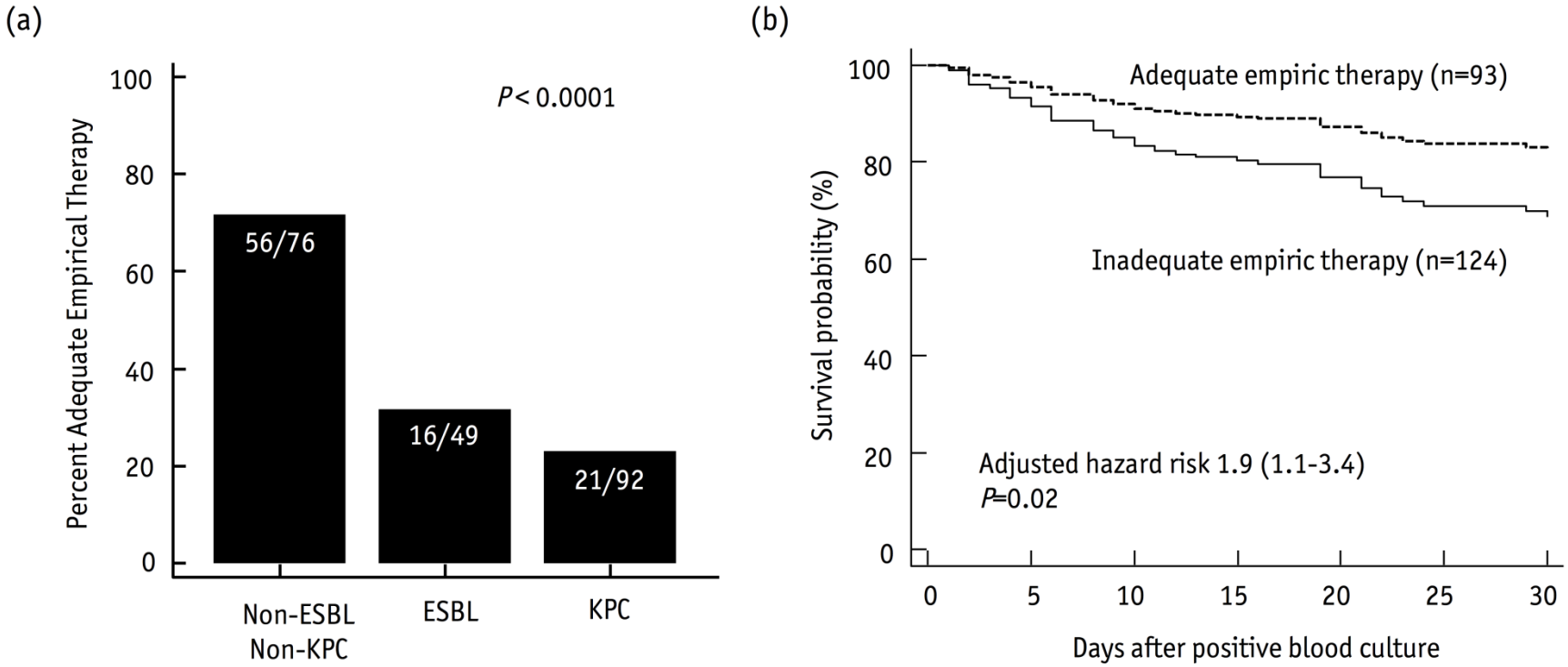
Viale P, Giannella M et al. Expert Opinion Infect Dis 2013

	Unmodifiable risk factors	Modifiable risk factors
ESBL KP BSI	• Rapidly fatal disease, ≥ 2 comorbidities, LOS before BSI, >2 antibiotics before BSI • ICU admission, MV, APACHE II • Nosocomial BSI • Deteriorated mental status, septic shock	• Delay > 72 h appropriate therapy • Carbapenem treatment (protective)
CR-KP BSI	• Age, Charlson index, cardiovascular and chronic liver disease, SOT • ICU stay, APACHE II • Pitt score, persistent BSI, pulmonary source, septic shock • Colistin resistant strain	• Source control (protective) • Combination carbapenem-containing therapy (protective)

Treatment failure

217 *Kp* BSI

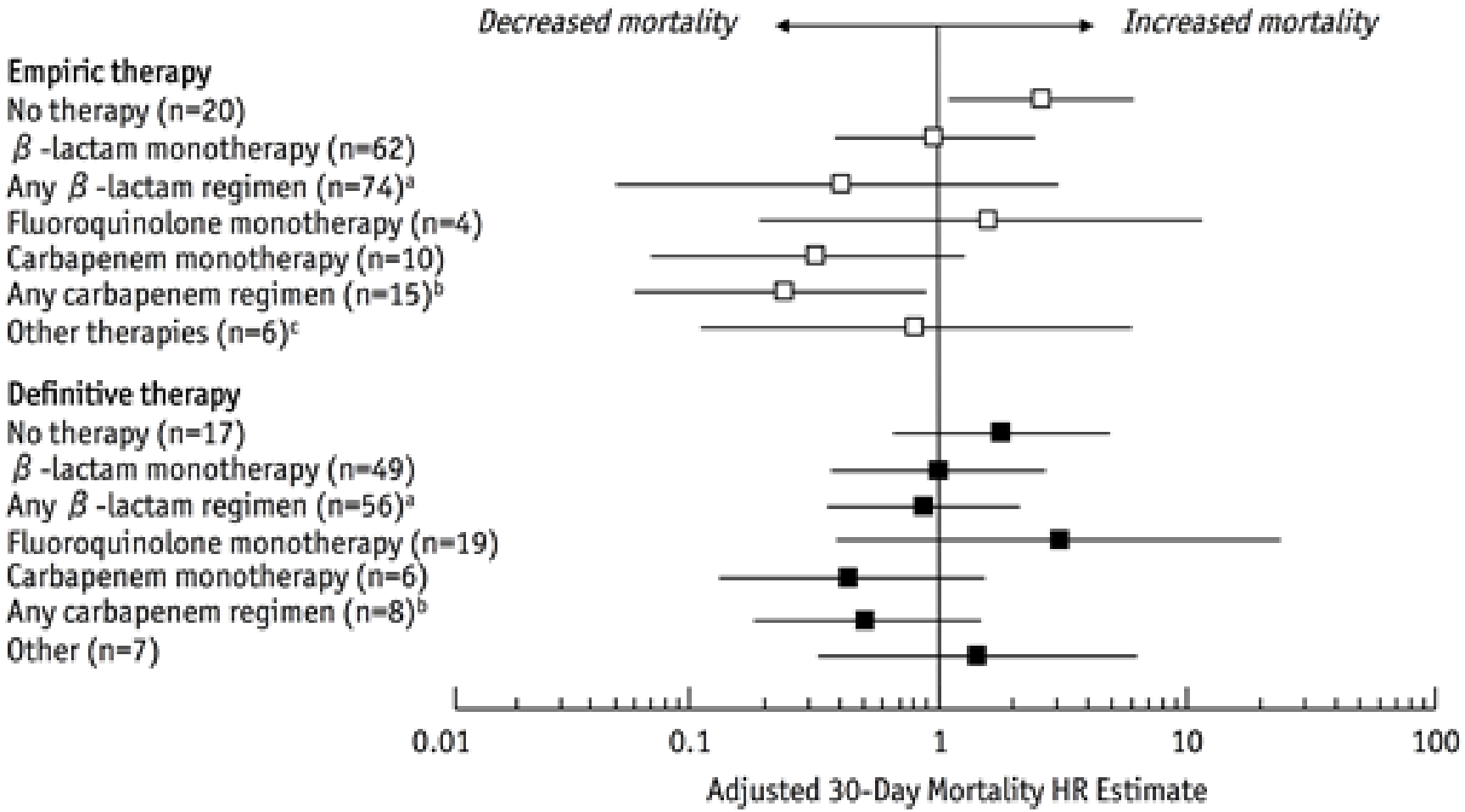
- Retrospective cohort 2010-2012
- 92 (42%) KPC-positive, 49 (23%) ESBL-positive, and 1 (0.5%) MBL positive isolates



Girometti N, Lewis R, Giannella M et al. *accepted in Medicine (Baltimore)*

Treatment failure

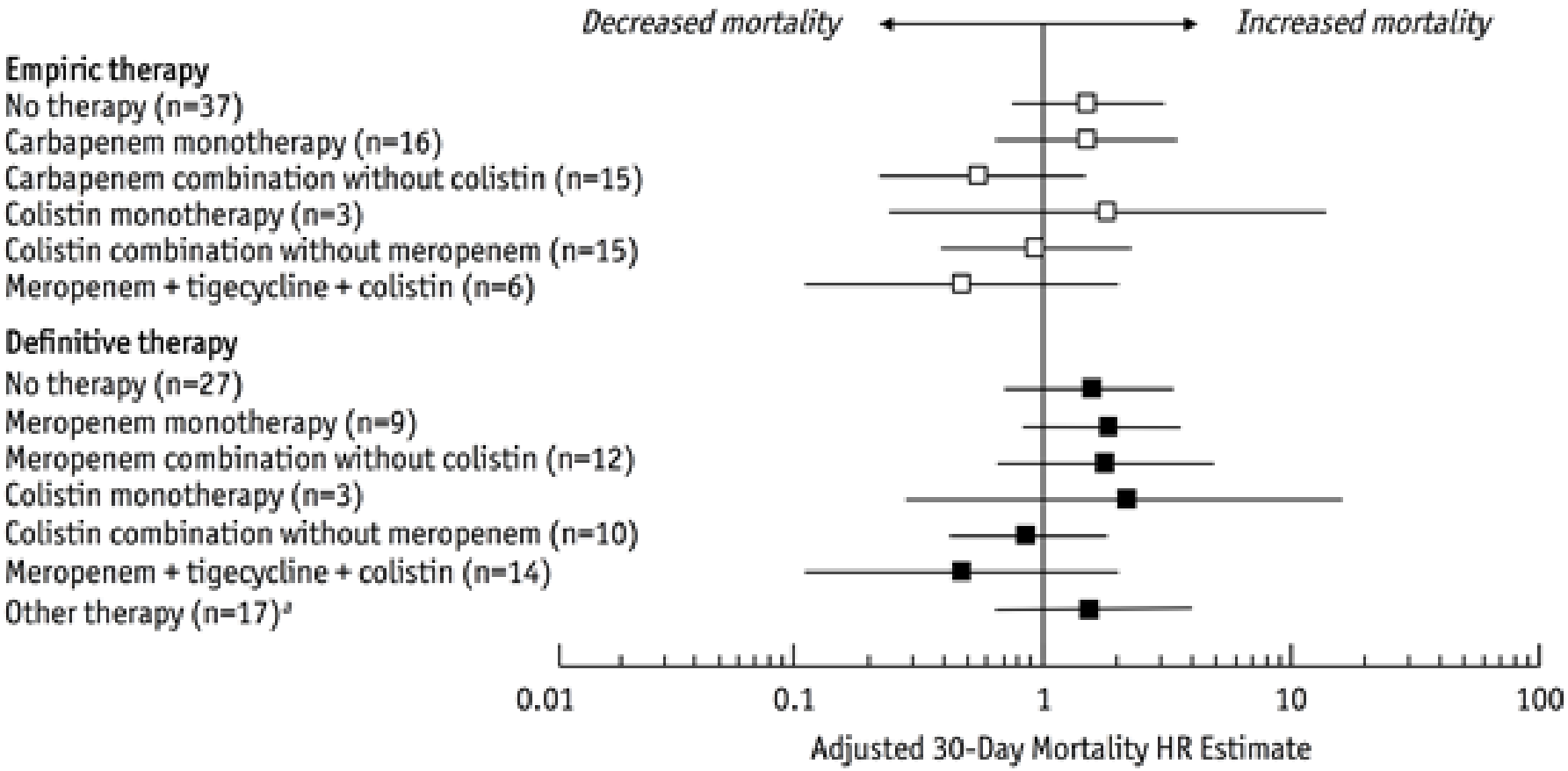
ESBL KP



Girometti N, Lewis R, Giannella M et al. *accepted in Medicine (Baltimore)*

Treatment failure

CR-KP



Girometti N, Lewis R, Giannella M et al. *accepted in Medicine (Baltimore)*

Treatment failure

	Unmodifiable risk factors	Modifiable risk factors
PA BSI	• Age ≥65 years, Charlson ≥3, immunosuppression • LOS prior BSI • High risk source, Pitt ≥2 • APACHE II ≥22 • MDR, XDR	• Inappropriate IAT • **No positive impact of combination therapy over appropriate monotherapy**
MDR/XDR AB infections	• Malignancy, CKD, Charlson >3 • APACHE II, SAPS II >40	• Inappropriate IAT • No ID consultation •**Higher microbiological eradication (61% vs 45%, p=.03) for colistin+rifampicin vs colistin alone**

Tam VH et al. AAC 2010:54; Hirsh EB et al. DMID 2012:72

Bowers DR et al. AAC 2013:57; Pena C et al. Clin Infect Dis 2013:57

Lee Y-T et al. Clin Infect Dis 2012:55; Khawcharoenporn T et al. IJAA 2014:43

Durante Mangoni E et al. Clin Infect Dis 2013:57

Appropriate initial antibiotic therapy

- Local epidemiology
- Individual patient factors
  - ✓ preexisting medical conditions
  - ✓ severity of illness
  - ✓ nature of infection
  - ✓ previous antibiotic and hospital exposure
  - ✓ presence of indwelling catheters
  - ✓ **colonization with antibiotic-resistant organisms**
- PK/PD issues

Risk factors for KPC-producing *Klebsiella pneumoniae* bloodstream infection among rectal carriers: a prospective observational multicenter study

Giannella M et al. *Submitted data*

- Matched case-control study of all adult CR-KP rectal carriers hospitalized in 5 tertiary teaching hospitals in Italy over 2 years
- **143 of 1,813 CR-KP rectal carriers (7.8%) developed BSI**
- 572 controls without a documented infection during their hospitalization

	OR (95% CI)	P-value	Risk score point
Admission to ICU	1.65 (1.05-2.59)	0.03	2
Invasive abdominal procedures	1.87 (1.16-3.04)	0.01	3
Chemotherapy/radiation therapy	3.07 (1.78-5.29)	<0.0001	4
Colonization at site besides stool (risk per each additional site)	3.37 (2.56- 4.43)	<0.0001	5 per site

Risk factors for KPC-producing *Klebsiella pneumoniae* bloodstream infection among rectal carriers: a prospective observational multicenter study

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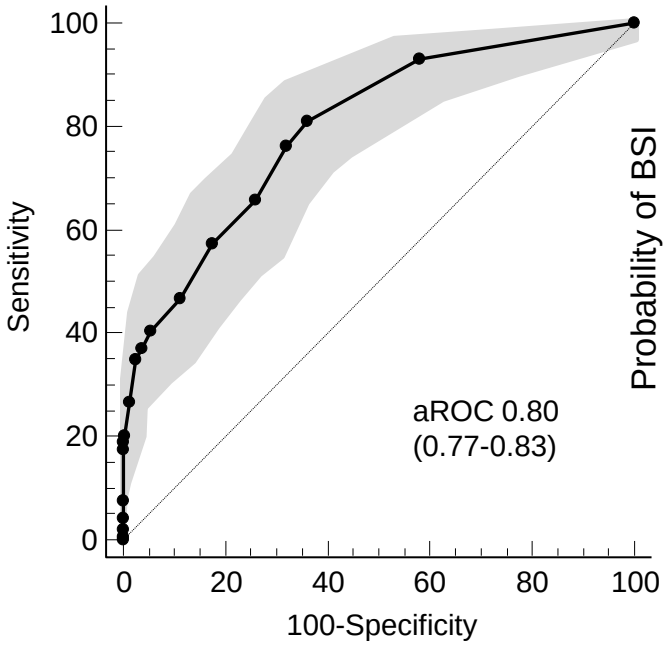
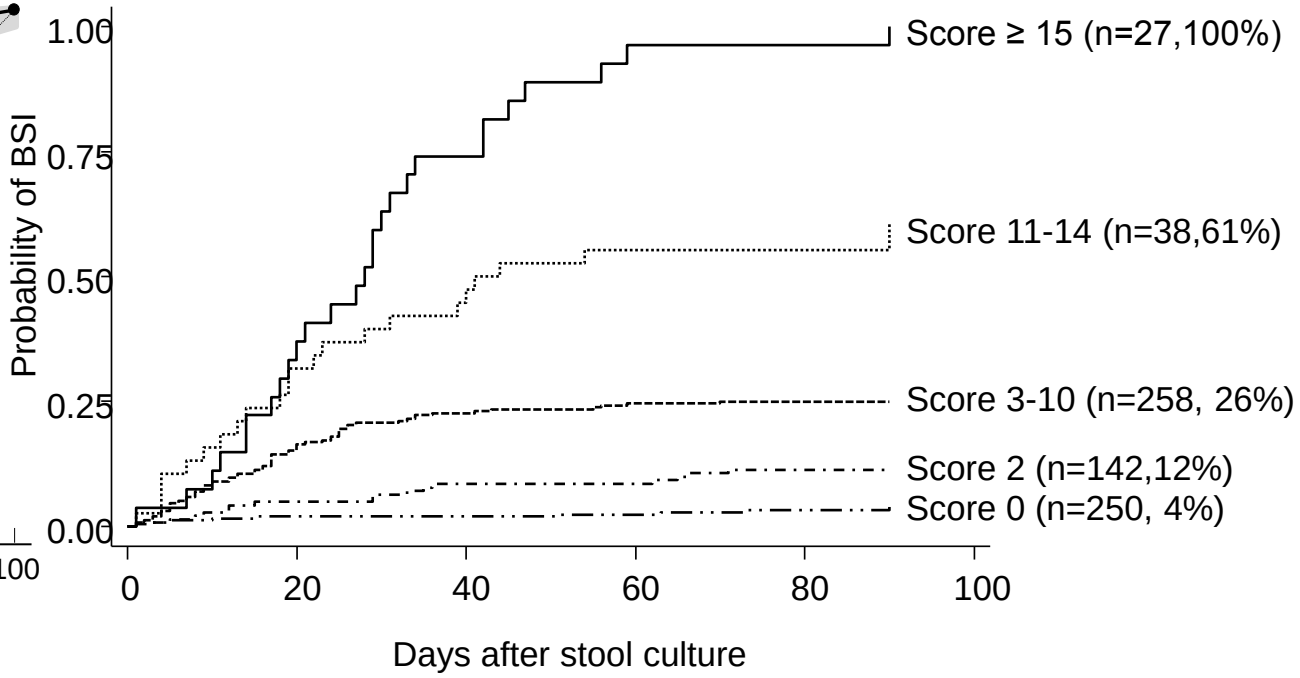


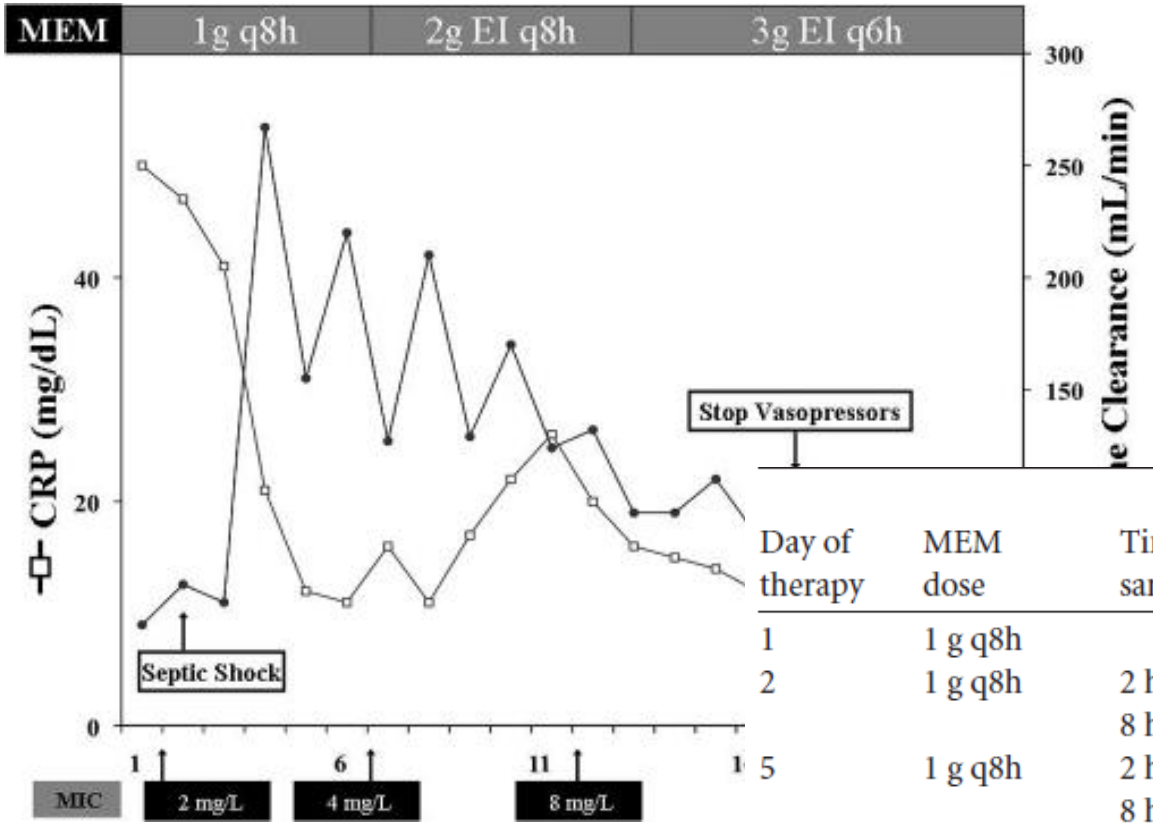


	Sens	Spec	PPV	NPV
Risk score ≥2	93%	42%	28.6%	96%

PK/PD issues

Optimal meropenem concentrations to treat MDR *Pseudomonas aeruginosa* septic shock

Taccone FS et al. Antimicrob Agents Chemother 2012



Day of therapy	MEM dose	Time of sampling	MEM concn (mg/liter)	MIC (mg/liter)	% T > 4× MIC
1	1 g q8h				
2	1 g q8h	2 h	12.3	2	37
		8 h	<2.0		
5	1 g q8h	2 h	13.4	2	39
		8 h	<2.0		
9	2 g EI q8h	3 h	17	4	39
		8 h	3		
15	3 g EI q6h	3 h	43	8	51
		6 h	19		

Recurrence

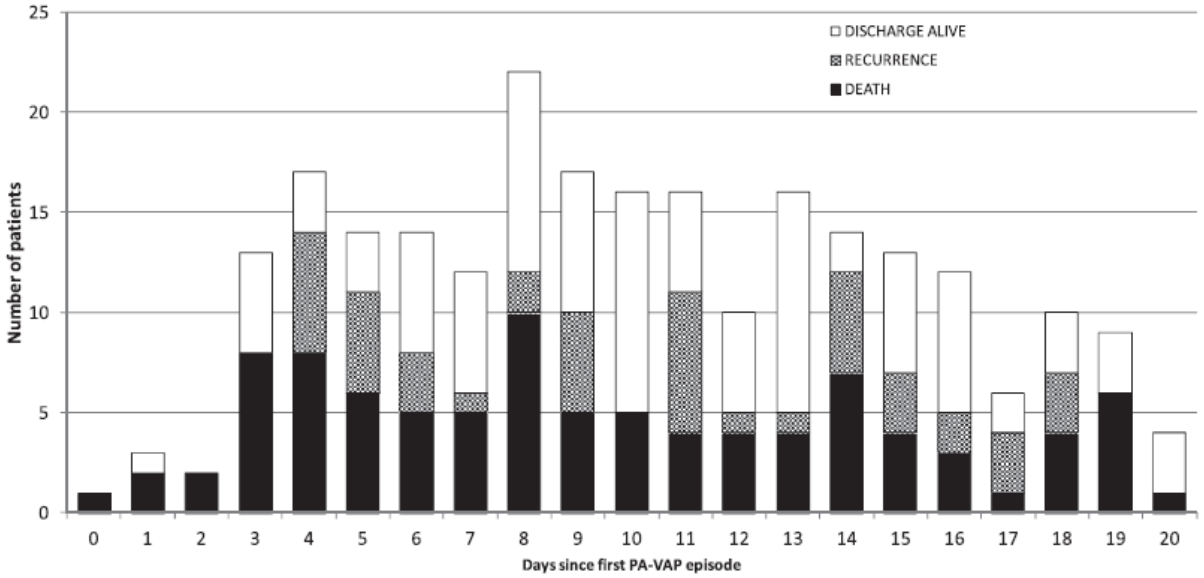
	Recurrence rate
ESBL producing Enterobacteriaceae	13-67%
Carbapenemase producing Enterobacteriaceae	--
MDR *P. aeruginosa*	20%
MDR *A. baumannii*	44%

Kanafani ZA et al. Am J Infect Control 2005; Cattaneo C. Ann Hematol 2014:93
Planquette B et al. Am J Resp Crit Care Med 2013:188
Shields RK et al. PLOSone 2012:7

Pseudomonas aeruginosa VAP
Predictive Factors of Treatment Failure

Planquette B et al. Am J Resp Crit Care Med 2013:188

- Retrospective analysis (1997-2011, 12 French ICUs) of 314 patients with 393 PA-VAP
- Main objective: **PA-VAP recurrence** (new suspicion of VAP with positive sample after a minimum of 4 days from the 1st PA-VAP episode)
- Recurrence 20%. median 14 (IQR 8-20) days after the 1st episode



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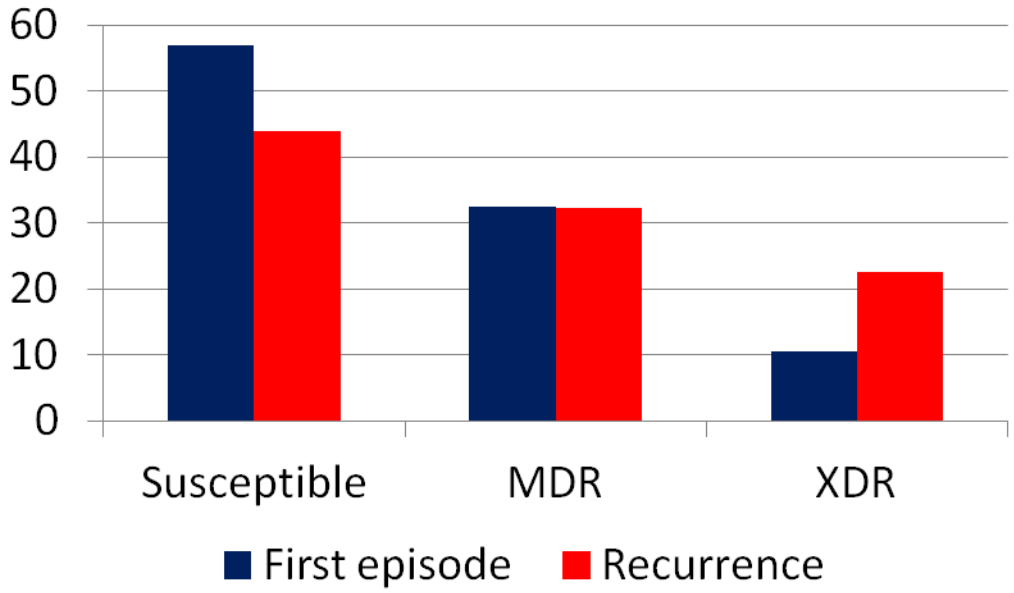


	Ceftazidime		Cefepime/ Cefpirome		Piperacillin		Ciprofloxacin		Amikacin		Penems	
	S (*n* = 51)	I/R (*n* = 11)	S (*n* = 54)	I/R (*n* = 8)	S (*n* = 54)	I/R (*n* = 8)	S (*n* = 54)	I/R (*n* = 8)	S (*n* = 53)	I/R (*n* = 9)	S (*n* = 51)	I/R (*n* = 11)
Use for the firstepisode during the first 2 wk, n (%)												
No	31 (88.6)	4 (11.4)	45 (89.9)	8 (15.1)	30 (100)	0 (0)	35 (97.2)	1 (2.8)	14 (100)	0 (0)	38 (95)	2 (5)
Yes	20 (74.1)	7 (25.9)*	9 (100)	0 (0)	24 (75)	8 (25)†	19 (73.1)	7 (26.9)†	39 (81.3)	9 (18.8)†	13 (59.1)	9 (40.9)†
Number of days of use during the first 2 wk (first episode), median (IQR)	6 (2–11)	9 (6–11)	6 (2–11)	—	8 (3–10)	8 (4–12)	4 (3–9)	8 (4–9)	4 (3–8)	4 (3–5)	3 (2–10)	5 (4–9)

Pseudomonas aeruginosa VAP
Predictive Factors of Treatment Failure

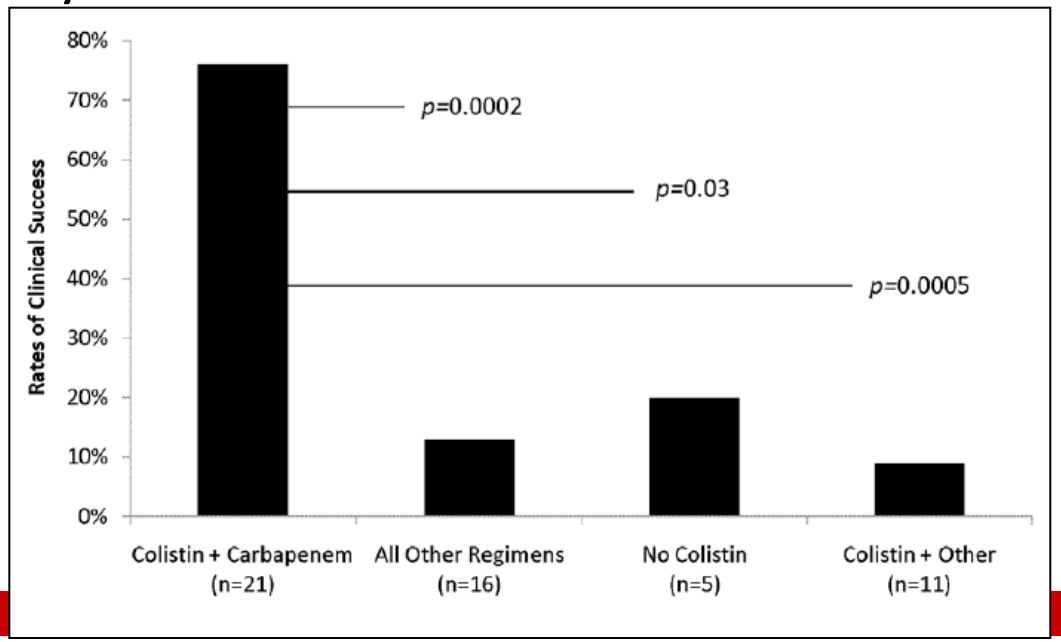
Planquette B et al. Am J Resp Crit Care Med 2013:188

	Dead or PA-VAP recurrence or in ICU at day 14 (n=239)	Discharged alive without PA-VAP recurrence within 14 days (n=75)	p	SHR (95%CI)
Limitation of life support in the first 48 h of ICU stay	10.5%	1.3%	0.05	0.1 (0.02-0.9)
Vasopressors	41.4%	25.3%	0.02	0.4 (0.2-0.7)
Delay to first PA-VAP onset <12 d	44.4%	60%	0.02	2.3 (1.4-3.7)
MDR/XDR PA	46.4%	32%	0.03	0.6 (0.4-1.0)
IAT			0.08	
None	19.2%	9.3%		
Monotherapy	25.9%	37.3%		
Combination therapy	54.8%	53.3%		

Epidemiology, Clinical Characteristics and Outcomes of Extensively Drug-Resistant *Acinetobacter baumannii* Infections among Solid Organ Transplant Recipients

Shields RK et al. PLOSone 2012:7

- Retrospective analysis of 69 SOT recipients: 28 colonized, 41 infected with XDR-Ab
- Median time to colonization and infection after SOT 121 and 172 days, respectively
- Main infection site: respiratory tract 98%
- 28-day survival rate among infected pts 54%



Epidemiology, Clinical Characteristics and Outcomes of Extensively Drug-Resistant *Acinetobacter baumannii* Infections among Solid Organ Transplant Recipients

Shields RK et al. PLOSone 2012:7

- 44% recurrence (signs and symptoms of infection with XDR-Ab isolation within the following 3 months), 28% multiple recurrences
- XDR-Ab colonization (p=0.04) and longher hospital stays (p=0.02) were associated with recurrence

Subject	Initial Disease	Rx (Duration, days)	First Recurrence	Rx (Duration, days)	Outcome	# of Additional Recurrences	Final Recurrence	Rx (Duration, days)	Outcome	Micro Eradication	Final Outcome
1	VAP	CD (28)	VAP	CD (28)	Success	0	–	–	–	Yes	Death 232 days after infection[1]
2	VAT	CD (5)	VAP	CDA (18)	Success, Recurrence	3	VAP	CDA (71)	Success	Yes	Death 250 days after infection[2]
3	VAP	CD (14)	VAP	CD (17)	Success, Recurrence	1	VAP	CDA (22)	Success	Yes	Alive
4	VAP	CD (21)	VAP	CD (14)	Success, Recurrence	1	VAP	No Rx[3]	Death	No	Death
5	VAP	CD (13)	VAP	CD (10)	Success, Recurrence	3	VAP	CDA (3)	Death	No	Death
6	VAP	CD (14)	VAP	CD (15)	Failure	1	VAP	CDA (15)	Success	Yes	Alive
7	VAP	CD (14)	Bacteremia	CD (10)	Success	0	–	–	–	Yes	Alive
8	VAP	CD (7)	VAP	CD (7)	Success	0	–	–	–	Yes	Death 107 days after infection[4]

Emergence of further resistance

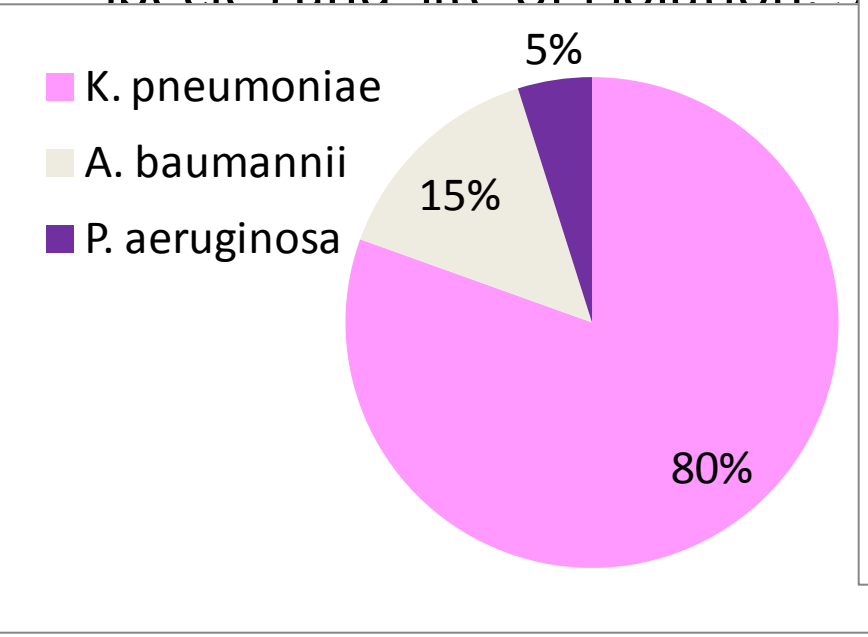
	Resistance to colistin	Resistance to tigecycline
CR-KP	7-36%	2-20%
MDR *P. aeruginosa*	6%	--
MDR *A. baumannii*	0.1-41%	14-66%

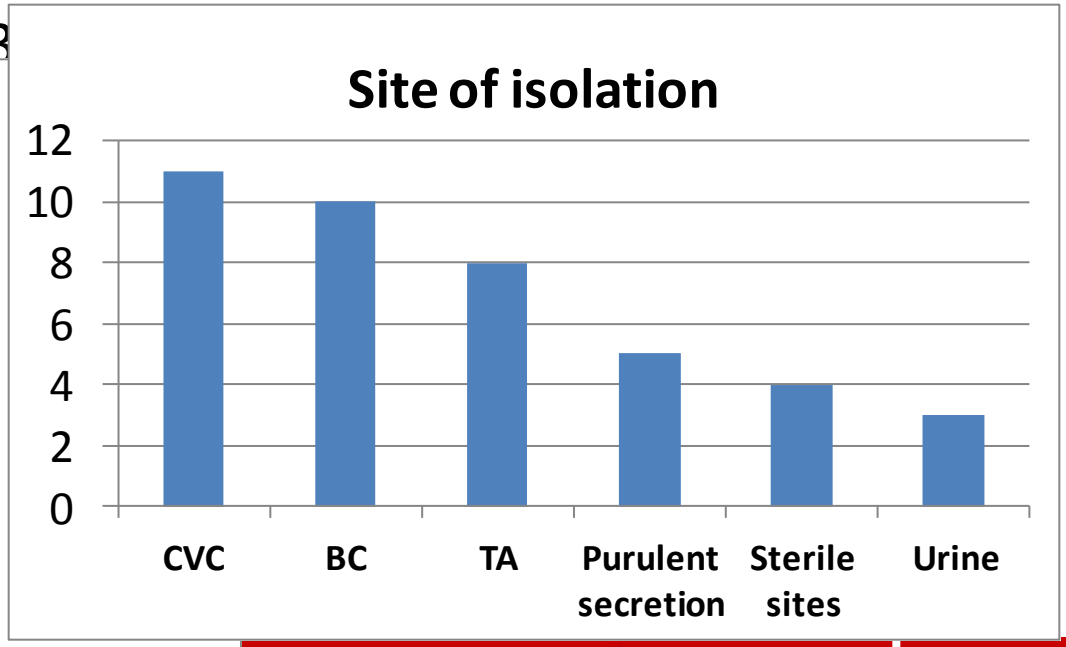
Hirsh EB et al. J Antimicrob Chemother 2010; Capone et al. Clin Microbiol Infect 2013
Cai Y et al. J Antimicrob Chemother 2012:67
Sader HS et al. DMID 2011:69; Navon-Venezia S et al. JAC 2007:59

Risk factors associated with the isolation of colistin-resistant Gram-negative bacteria: A matched case-control study

Matthaiou DL et a. Crit Care Med 2008

- Retrospective matched 1:1 case-control study at a 450-bed hospital in Athens, 2006-2007
- 41 patients with isolation of a colistin-resistant GNB, 35 (85.4%) were deemed as having infection
- 41 controls who were all matched to case patients for bacterial species and site of isolation. 3





Risk factors associated with the isolation of colistin-resistant Gram-negative bacteria: A matched case-control study

Matthaiou DL et a. Crit Care Med 2008

	CR	CS	p
Age	57±17	66±19	0,005
LOS prior to isolation of GNB	37±32	28±36	0,08
APACHE II score	30±26	18±22	0,02
Prior use of colistine	83%	37%	<0,001
Days of prior colistin	25±24	16±20	<0,001

- Multivariate analysis : **prior use of colistin OR 7.78**, p=0.002
- In-hospital mortality 37% CR vs 44% CS (p=0.58)

Combination therapy and emergence of resistance

Combination Therapy for Treatment of Infections with Gram-Negative Bacteria

Pranita D. Tamma,[a] Sara E. Cosgrove,[b] and Lisa L. Maragakis[b]

The Johns Hopkins Medical Institutions, Department of Medicine, Division of Pediatric Infectious Diseases, Baltimore, Maryland, USA,[a] and The Johns Hopkins Medical Institutions, Department of Medicine, Division of Infectious Diseases, Baltimore, Maryland, USA[b]

Potential advantages:

- increased likelihood that the infective pathogen will be susceptible to at least one of the components of an empiric combination regimen
- synergistic effect afforded by the use of two agents
- **protection against emergence of resistance with combination therapy**

Clin Microbiol Rev 2012;25:450-70

Ref	Study type	MO	Treatment	Outcome
Lee J et al. JCM 2009	Case series	CR-KP	Colistin alone 12 Colistin+tigecycline 4	Colistin R during treatment 25% vs 0
Lister PD et al. CID 2005	*In vitro*	*P. aeruginosa*	Imipenem+levofloxacin	Effective combination for preventing emergence of resistance even when subpopulations resistant to both drugs are present
Rodriguez CH et al. JInfectDevCtries 2010	*In vitro*	XDR *A. baumannii*	Colistin+rifampicin Colistin+imipenem	Synergistic against heteroresistant isolates and prevented colistin-resistant mutants
Shields RK et al. PLOSone 2012	Retrospective study	XDR *A. baumannii*	Colistin+carbapenem 21 Colistin+tigecycline 3	Colistin R during treatment 18% vs 100%

Proposed treatments for coli-R strains

- Colistin + doripenem

Jernigan MG et al Antimicrob Agents Chemother 2012

- Colistin + doripenem + ertapenem

Hong JH et al Antimicrob Agents Chemother 2013

- Colistin + rifampicin

Tascini C et al Antimicrob Agents Chemother 2013
Gaibani P et al J Antimicrob Chemother 2014

- Doripenem or meropenem + ertapenem

Bulik CC and Nicolau DP Antimicrob Agents Chemother 2011
Giamarellou H et al. Antimicrob Agents Chemother. 2013
Ceccarelli G et al. Antimicrob Agents Chemother. 2013
Olivia A et al J Antimicrob Chemother 2014

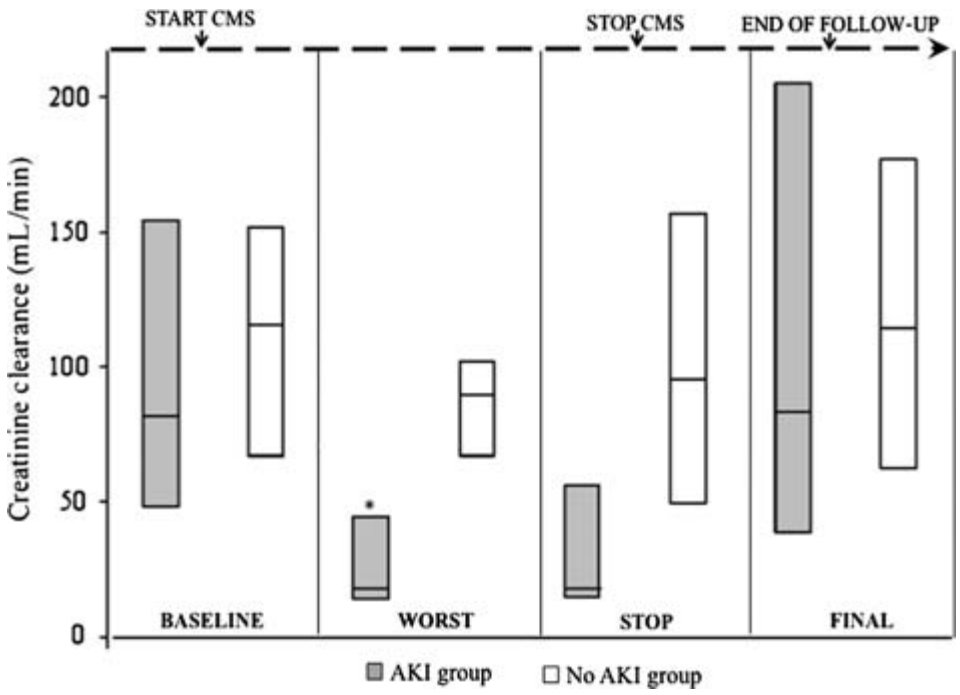
Adverse events

	Colistin	Polymyxin B	Tigecycline
Nephrotoxicity	6-60%	20-40%	--
Neurotoxicity paresthesia	27%	--	--
Respiratory failure	Anedoctal	--	--
Vomiting and nausea	--	--	≈25%
Pancreatitis	--	--	<1%

Yahav D et al. Clin Microbiol Infect 2011
Tasina E et al Lancet Infect Dis 2011

Risk factors for nephrotoxicity

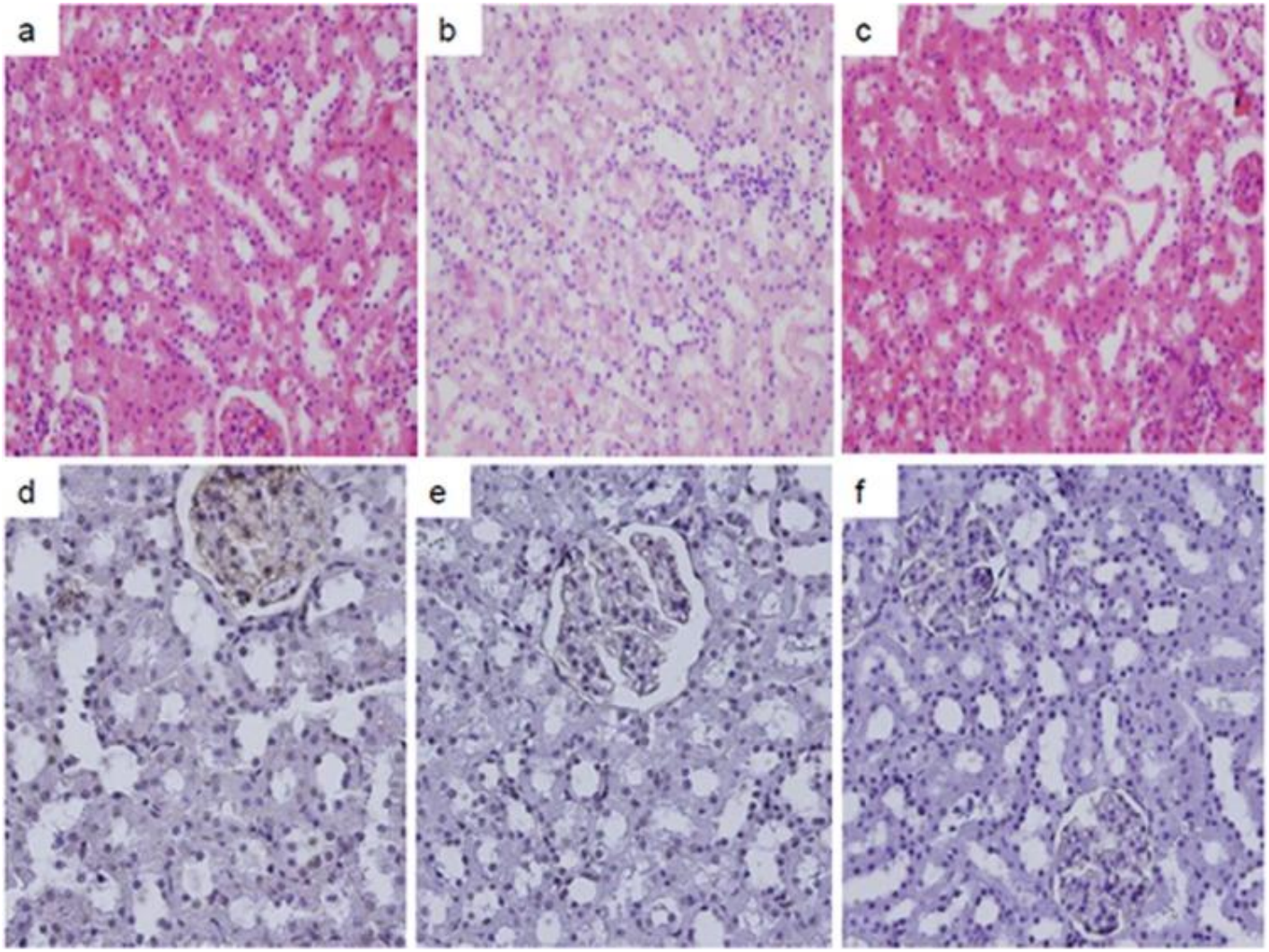
- Older age
- Colistin vs. polymyxin B
- Pre-existing renal insufficiency
- Concomitant use of other potentially nephrotoxic agents (NSAD, vancomycin, aminoglycosides, loop diuretics, vasoppressors, contrast, amphotericin B)
- Receipt of concomitant rifampicin
- Hypoalbuminemia
- **Higher dosing (cumulative or daily dose)**



Yahav D et al Clin Microbiol Infect 2011
Pogue JM et al. Clin Infect Dis 2011
Dalfino L et al. Clin Infect Dis 2012
Akajabor DS et al. Clin Infect Dis 2013
Tuon FF Int J Antimicrob Agents 2014

How Does Colistin-Induced Nephropathy Develop and Can It Be Treated?

Ozkan G et al. Antimicrob Agents Chemother 2013



Conclusions

- Predictive models for MDR GNB (true) infections are needed to guide IAT in different patient settings
- Large RCTs to assess the impact of combination therapy over monotherapy for MDR GNB (mainly CR-KP) are needed
- Antibiotic administration according with PK/PD characteristics allows to obtain better outcome even against MDR strains
- Incidence and risk factors for CR-KP recurrence have yet to be determined
- Impact of combination therapy on further resistance emergence should be determined in clinical studies
- Anti-oxidant agents may be used to prevent nephrotoxicity in patients treated with colistin

Grazie