Treatment options for difficult-to-treat organisms: the case of MDR MDR Gram-negatives: *Enterobacteriaceae*, *P.aeruginosa* and *A. baumannii*

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OUTLINE

- Scope of the problem
- Risk factors for MDR infection
- Impact on mortality
- Antibiotic combinations
- An example
- How to use colistin

- Increased recognition of successful antibiotic-resistant clones appearing in multiple geographic regions.
- Patients with MDR GNB *are at an increased risk for inappropriate* empirical antimicrobial therapy, and studies have demonstrated that delays in appropriate antimicrobial treatment may be detrimental to patient outcomes
- In one study, growth rates of most MDR isolates (n=33) were similar to that of the wild type, and two isolates (11%) were found to be hypermutable (Tam VH et al. AAC 2010)

- Strains that are resistant to all antibiotics including polymixins are rare, although their incidence is increasing
- Antibiotic combinations that yield some degree of susceptibility in vitro are the only recourse in such situations.

Expansion of healthcare-associated carbapenem-non-susceptible *Enterobacteriaceae* *in Europe: epidemiological scale and* stages by country, as of July 2010

Country	Stage	Epidemiological scale	Documented introduction from abroad	Dominant class	Underreporting
Greece	5	Endemic	Yes	KPC/VIM	
Israel[a]				KPC	
Italy	4	Interregional spread	Yes	KPC	
Poland					Likely
France	3	Regional spread	Yes	KPC	
Germany				OXA-48/VIM	Likely
Hungary				KPC	Likely
Belgium	2b	Independent hospital outbreaks	Yes	VIM	Likely
Spain				KPC/VIM/IMP	Likely
England and Wales				NDM	
Cyprus	2a	Single hospital outbreak		VIM	
Netherlands			Yes	KPC	
Norway			Yes	KPC	
Scotland				KPC	
Sweden			Yes	KPC	
Bosnia Herzegovina	1	Sporadic occurrence	Yes	KPC	
Denmark				KPC/VIM	
Finland			Yes	KPC	
Croatia				VIM	
Czech Republic			Yes	VIM/KPC	
Ireland				KPC	Likely
Lithuania				?	Likely
Latvia				?	Likely
Malta				?	
Portugal				KPC	Likely
Romania				?	Likely
Switzerland				KPC	
Austria	0	Not reported		-	
Bulgaria					Likely
Estonia					Likely
Iceland					
Slovenia					

*Grundmann H et al. Euro Surveill. 2010

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Clinical Prediction Tool To Identify Patients with *P aeruginosa* Pneumonia at Greatest Risk for MDR infection

- Retrospective case-control study
- Multidrug resistance defined as resistance to at least four classes of antipseudomonal agents

Lodise TP et al. AAC2007

Bivariate analysis of the relationship between clinical features and MDR *P. aeruginosa*[a]

Clinical feature	MDR *P. aeruginosa* (n = 122)	No MDR *P. aeruginosa* (n = 229)	P value
Age of ≥61 yr[b]	93 (66.9)	104 (49.1)	0.001
Sex (male)	82 (67.2)	133 (58.1)	0.09
Admission for ≥72 h within 6-mo prior to culture	54 (44.3)	100 (43.7)	0.9
LOS prior to collection of ≥33 days[b]	73 (59.8)	58 (25.1)	<0.001
ICU at onset	107 (87.7)	180 (78.6)	0.04
ICU LOS of ≥27 days prior to culture[b]	73 (59.8)	55 (24.0)	<0.001
Mechanical ventilation at culture	109 (89.3)	172 (75.1)	0.001
Congestive heart failure	27 (22.1)	46 (20.1)	0.65
Diabetes mellitus	47 (38.5)	51 (22.3)	0.001
Chronic obstructive pulmonary disease	46 (37.7)	72 (31.4)	0.2
Hepatic dysfunction	5 (4.1)	15 (6.6)	0.35
Dialysis	26 (21.3)	18 (7.9)	<0.001
Decubitus ulcers	35 (28.7)	37 (16.2)	0.006
Prior antibiotic exposure			
Carbapenem, ≥3 days[b]	33 (27.0)	31 (13.4)	0.002
Fluoroquinolone, ≥4 days[b]	33 (27.0)	30 (13.0)	0.001
Aminoglycoside, ≥5 days[b]	39 (32.0)	36 (15.9)	<0.001
Cefepime, ≥9 days[b]	19 (15.6)	11 (4.8)	0.001
Piperacillin-tazobactam, ≥12 days[b]	41 (33.6)	37 (16.9)	<0.001

[a] *Resistance to at least four drug classes. All data are presented as number* (percentage) unless otherwise indicated.

[b] *CART-derived breakpoint.*

Lodise TP et al. AAC2007

Relationship between number of antipseudomonal antibiotic exposures and MDR *P. aeruginosa (n 351)*[a]

No. of antibiotic exposures[b]	MDR *P. aeruginosa* (n = 122)	No MDR *P. aeruginosa* (n = 229)	% MDR *P. aeruginosa* (n = 351)
0	34 (27.9)	122 (53.3)	21.8
1	39 (32.0)	74 (32.3)	34.5
2	28 (23.0)	29 (12.1)	49.1
3	16 (13.1)	3 (1.3)	84.2
4	3 (2.5)	1 (0.4)	75
5	2 (1.6)	0 (0)	100

[a] *All data are presented as number (percentage).*

[b] *Note that carbapenem exposure for 3 days, fluoroquinolone exposure for* 4 days, aminoglycoside exposure for 5 days, cefepime exposure for 9 days, and piperacillin-tazobactam exposure for 12 days were defined as antibiotic exposures prior to culture collection

Lodise TP et al. AAC2007

Predicted likelihood of MDR *P. aeruginosa in a patient* with a *P. aeruginosa respiratory culture (n = 351)*

LOS (days)	Predicted, actual MDR *P. aeruginosa* frequency, % (*n*), after following no. of prior antibiotic exposures:			
	0	1	2	≥3
<33	19.0, 20.0 (135)	25.2, 22.6 (62)	33.4, 34.8 (23)	NA,[a] 0 (0)
≥33	35.4, 33.3 (21)	47.0, 49.0 (51)	62.3, 58.8 (34)	82.7, 84.0 (25)

[a] *NA, not applicable. The predicted MDR P. aeruginosa likelihood is not* provided here because no patient in our sample had an LOS of 33 days prior to collection and three or more prior antibiotic exposures.

Lodise TP et al. AAC2007

Clinical Prediction Tool To Identify Patients with *P aeruginosa* Respiratory Tract Infections at Greatest Risk for MDR infection

- **A history of a prolonged hospital stay and exposure to antipseudomonal antibiotics predicts MDR among patients with *P. aeruginosa* respiratory tract infections at our institution.**
- **Identifying these risk factors enabled us to develop a prediction tool to assess the risk of resistance and thus guide empirical antibiotic therapy**

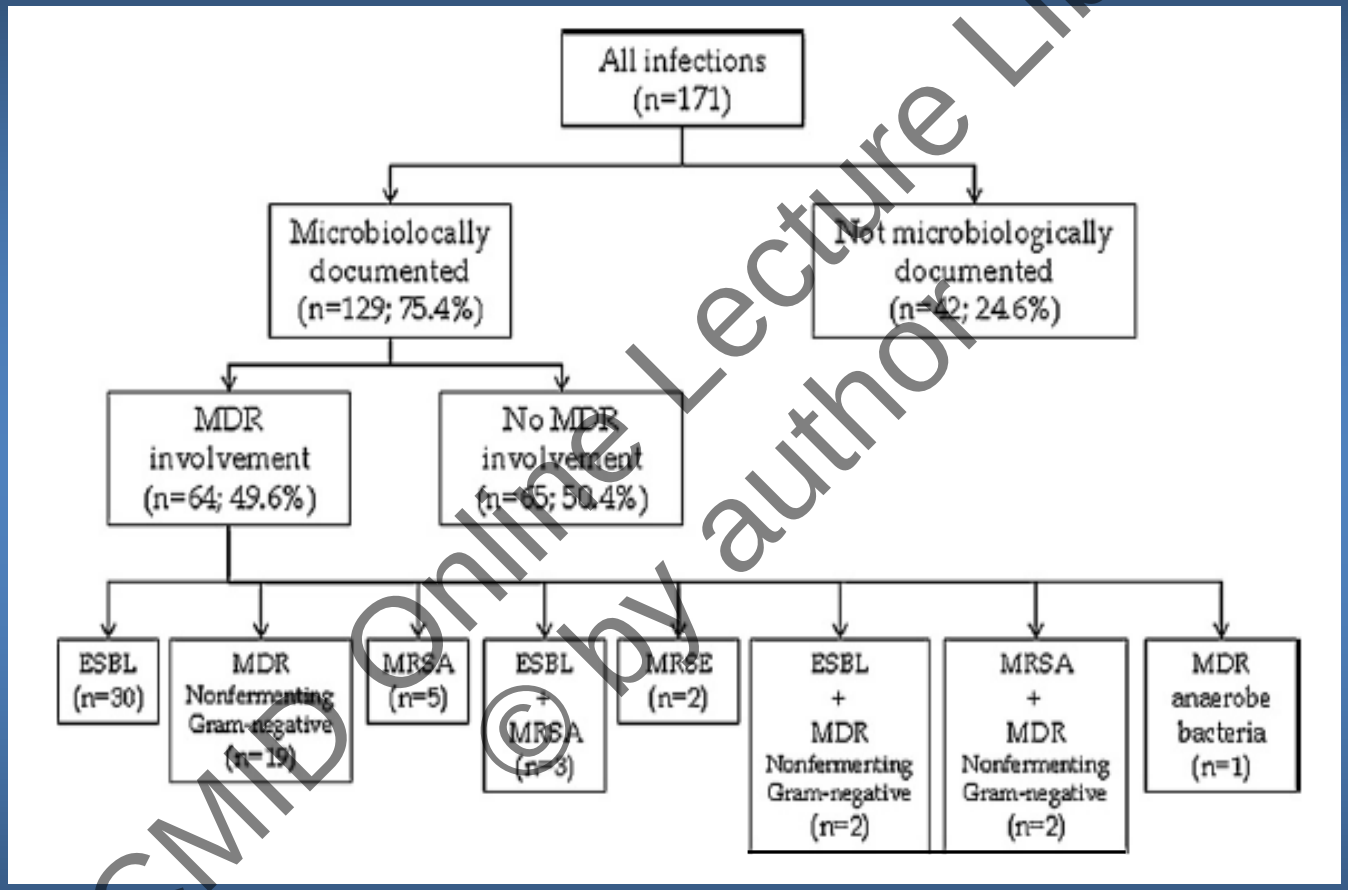
Lodise TP et al. AAC2007

Patterns of antimicrobial therapy in severe nosocomial infections: empiric choices, proportion of appropriate therapy, and adaptation rates—a multicentre, observational survey in critically ill patients

- Prospective, observational multicentre (n = 24) in 171 ICU patients with severe nosocomial infections
- Patients had pneumonia (n = 127; 66 VAP), intra-abdominal infection (n = 23), and bloodstream infection (n = 21)
- Predominant pathogens were *Pseudomonas aeruginosa* (n = 29) *Escherichia coli* (n = 26), *Staphylococcus aureus* (n = 22), and *Enterobacter aerogenes* (n = 21).
- In 49.6% of infections MDR bacteria were involved, mostly EBSL-producing *Enterobacteriaceae* and MDR non-fermenting Gram-negative bacteria
- Prior antibiotic exposure and hospitalisation in a general ward prior to ICU admission were risk factors for MDR

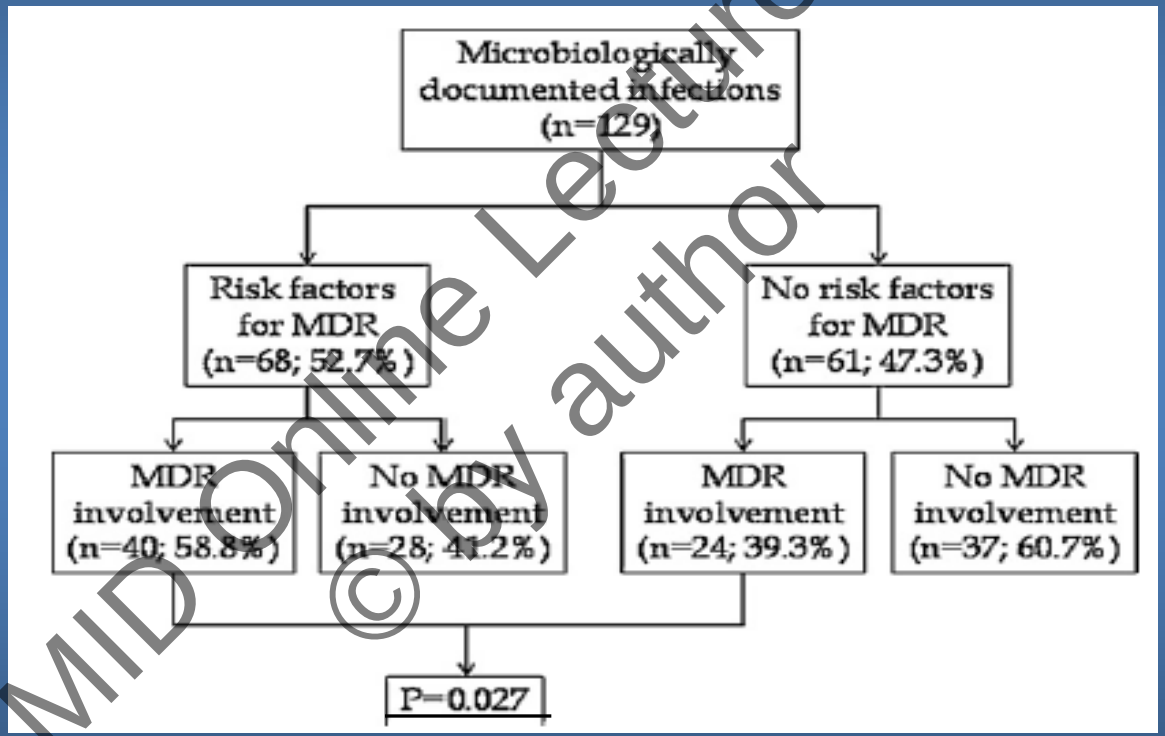
Vogelaers D et al. Int J antimicrob Agents 2010

Review of 171 nosocomial infections distributed for microbiological documentation and multidrug resistance involvement.



Vogelaers D et al. Int J antimicrob Agents 2010

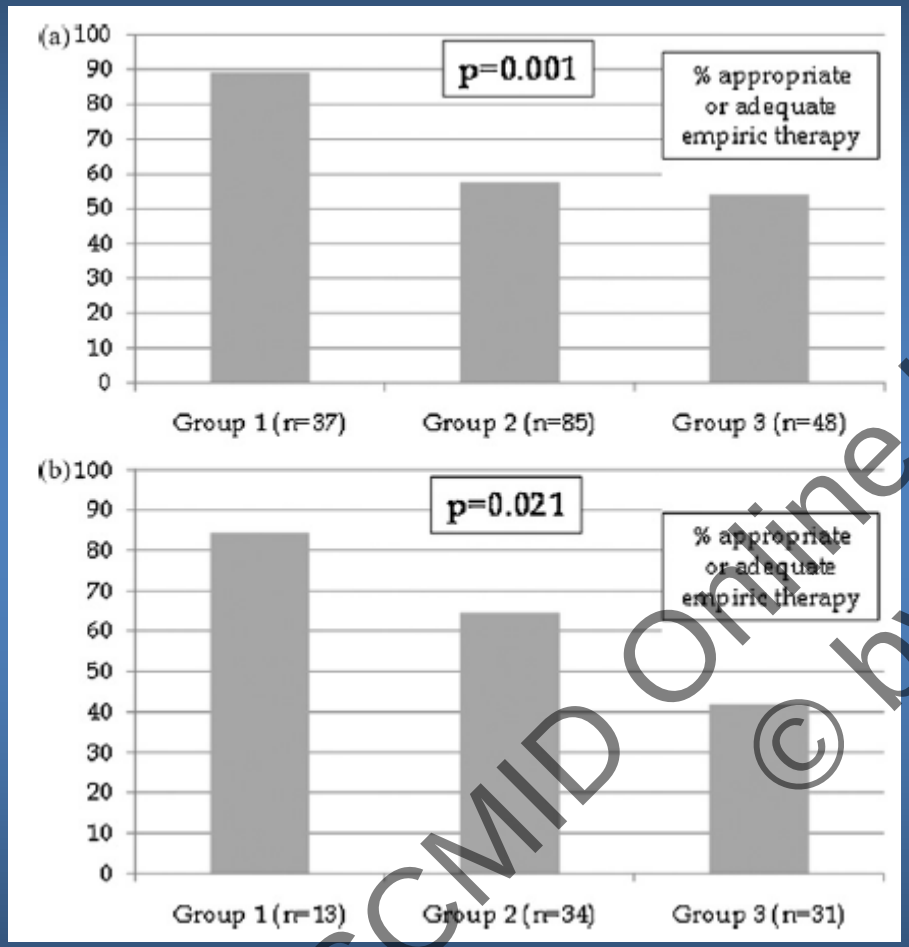
Breakdown of microbiologically documented infections according to the presence of risk factors for multidrug resistance, and multidrug resistance involvement.



Vogelaers D et al. Int J antimicrob Agents 2010

Rates of empiric appropriate therapy according to three major groups of empiric antibiotic regimens (coverage of meticillin-resistant pathogens not considered)

Vogelaers D et al. Int J antimicrob Agents 2010



(a) All patients considered (n = 170); in one patient no empiric therapy was initiated.

(b) Only patients considered without risk factors for multidrug resistance involvement (hospitalisation at a general ward prior to ICU Admission and prior antibiotic exposure) (n = 78)

Group 1: coverage of ESBL-producing and *Pseudomonas aeruginosa* (meropenem-based schemes).
Group 2: coverage of *P. aeruginosa* (schemes containing an antipseudomonal agent).
Group 3: no coverage of ESBL-producing, or non-fermenting, Gram-negative bacteria (first-line agents).

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Impact of Multidrug-Resistant *Pseudomonas aeruginosa* Bacteremia on Patient Outcomes

- **Retrospective cohort study of adult patients with *P. aeruginosa* bacteremia (N = 109) from 2005 to 2008.**
- **Logistic regression was used to explore independent risk factors for 30-day mortality**

Tam VH et al. AAC 2010

Logistic regression analysis of the risk factors for 30-day mortality

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.022 (0.984–1.060)	0.261		
Male	1.820 (0.641–5.170)	0.261		
Ethnic background				
Caucasian	1.170 (0.436–3.142)	0.755		
African American	0.506 (0.136–1.888)	0.311		
Hispanic	0.871 (0.226–3.348)	0.840		
Baseline serum creatinine concn	0.997 (0.722–1.376)	0.985		
Length of prior hospital stay	1.009 (0.998–1.021)	0.116		
Multidrug resistance	4.933 (1.748–13.922)	0.003	6.829 (1.945–23.984)	0.003
Appropriate empirical therapy	0.295 (0.093–0.943)	0.039		
Baseline APACHE II score	1.157 (1.062–1.260)	0.001		
Baseline APACHE II score ≥ 22	15.436 (3.539–67.329)	<0.001	29.034 (5.012–168.196)	<0.001
Comorbidities				
Cardiovascular conditions	0.658 (0.209–2.072)	0.474		
Respiratory conditions	3.039 (0.966–9.558)	0.057		
Central nervous system conditions	1.132 (0.288–4.455)	0.859		
Renal conditions	5.973 (2.065–17.280)	0.001		
Diabetes mellitus	0.981 (0.365–2.641)	0.970		
Immunosuppression	3.129 (1.157–8.462)	0.025	5.001 (1.430–17.495)	0.012
Source of bacteremia				
Line	0.338 (0.041–2.760)	0.311		
Lung	4.235 (1.522–11.787)	0.006		
Urine	0.194 (0.024–1.543)	0.121		
Wound	0.805 (0.211–3.097)	0.751		
Abdomen	1.773 (0.501–6.278)	0.375		

[a] Receiver operating characteristic value of the final model, 0.820.

Tam VH et al. AAC 2010

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- Although combination therapy has been widely accepted for management of patients infected with *M. tuberculosis and HIV, it has* not been widely accepted for infections caused by MDR Gram-negative bacteria
- Studies performed *in vitro or* in animal models often demonstrate synergy with antibiotic combinations, but few translate this success to the clinical arena because of the lack of well-controlled studies

COMBINATION THERAPY VS. MONOTHERAPY IN MDR P AERUGINOSA

- Activity against multi-resistant *P aeruginosa* has been achieved by combinations of:
  - B-lactam + Ag + rifampin
  - Polimixin plus carbapenem (imipenem, meropenem, doripenem)
  - Polimixin B plus rifampin
  - Ceftazidime or cefepime plus FQ
  - Ceftazidime plus colistin
  - Clarithromycin plus tobramycin
  - Aztreonam/Amikacin
  - Azithromycin plus tobramycin, doxycycline, trimethoprim, or rifampin
  - Fosfomycin + B-lactam ± other

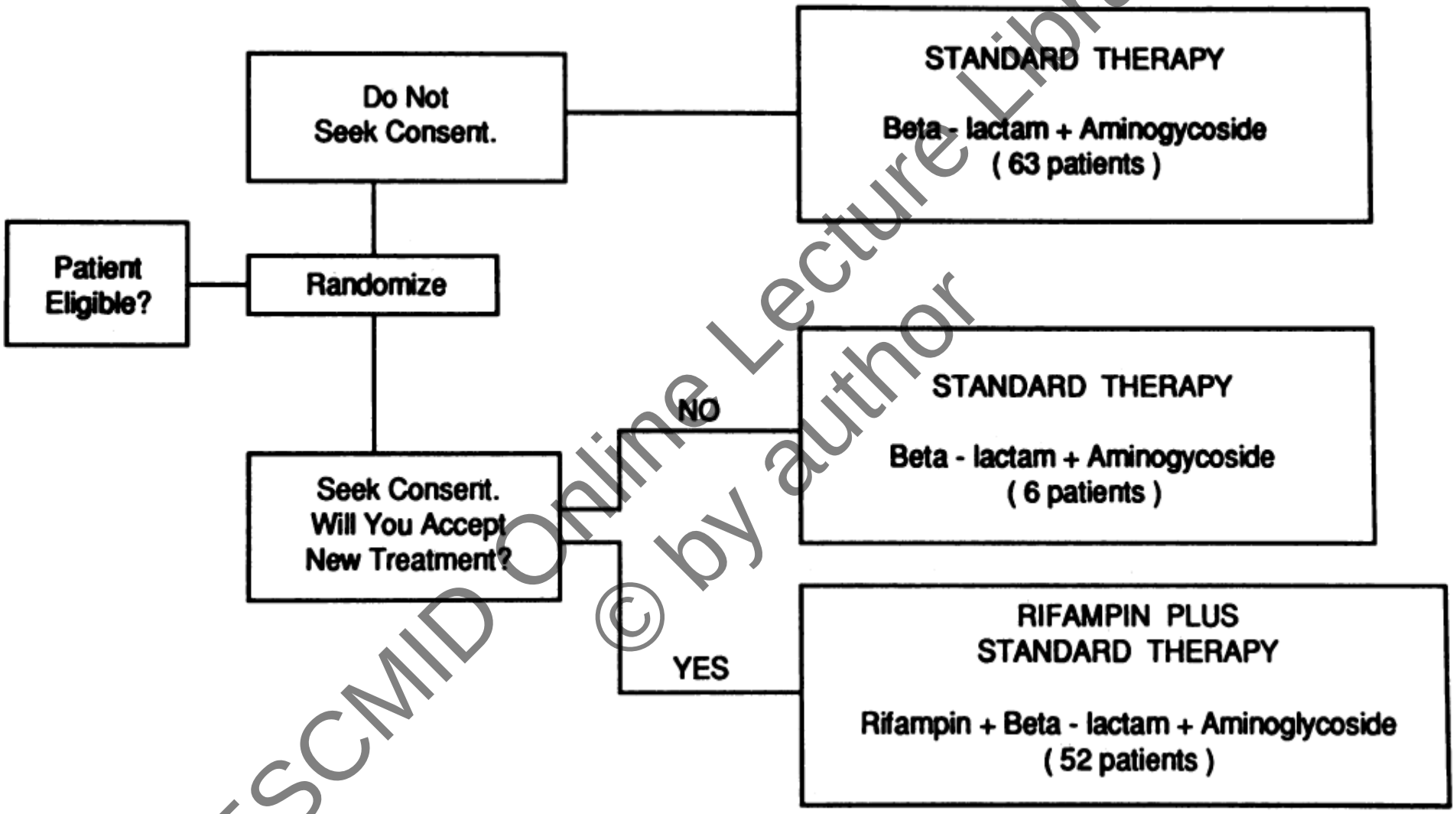
The mechanisms of positive interaction between these agents are not known , with few exceptions

COMBINATION THERAPY VS MONOTHERAPY FOR RESISTANT P AERUGINOSA

- *P aeruginosa* clinical isolates R to ticarcillin and tobramycin, alone and in combination, were killed by the addition of rifampin. Thus, despite the organism's R to each one of the drugs alone, killing was achieved with the combination[1]
- These results validated in a neutropenic mouse model of *P aeruginosa* infection[2]
- In humans with *P aeruginosa* bacteremia (121 patients), the triple antibiotic regimen was compared with double therapy (without rifampin). No significant diference in mortality occurred in the 2 groups: However, bacteriologic cure occurred more frequently in the triple therapy group, and breakthrough or relapsing bacteremia occurred in 2% of patients treated with triple therapy and in 14% of those treated with double therapy[3]

1. Zuravleff JJ et al, J Lab Clin Med 1983;101:896
2. Zuravleff JJ et al, J Lab Clin Med 1984;103:878
3. Korvick JA et al, AAC 1992;36:620

Addition of Rifampin to Combination Antibiotic Therapy for Pseudomonas aeruginosa Bacteremia: Prospective Trial Using the Zelen Protocol



Schematic allocation of patients by the Zelen protocol.

Korvick et al. AAC1992

Bactericidal experiments using double and triple antibiotic combination

- Time-kill studies at concentrations at ¼ of their MICs
- Doripenem, polymyxin B, and rifampin alone also tested at 1/4 MIC against each isolate
- For bactericidal assays, samples were taken at time zero and 2, 4, 8, and 24 h
- Bactericidal activity was defined as a 3-log CFU/ml decrease in 24 h.

Urban C et al. AAC 2010

Genotypic and phenotypic characteristics for carbapenem-resistant isolates[a]

Etest isolate	Modified Hodge test	MBL Etest	Carbapenem resistance mechanism(s)	MIC (μg/ml)					
				PB	RI	IP	MP	ERT	D
K. pneumoniae 1	−	−	Porin + ACT-1	2	>32	>32	16	>32	8
K. pneumoniae 2	−	−	Porin + ACT-1	1	>32	>32	32	>32	32
K. pneumoniae 3	−	−	Porin + ACT-1	0.75	>32	>32	6	>32	6
K. pneumoniae 4	+	−	KPC-2	1	>32	>32	>32	>32	>32
K. pneumoniae 5	+	−	KPC-2	0.75	>32	32	16	>32	24
A. baumannii 6	−	−	ND	1	8	>32	>32	>32	>32
A. baumannii 7	−	−	ND	0.75	>32	>32	>32	>32	>32
A. baumannii 8	−	−	ND	1.5	16	>32	>32	>32	>32
A. baumannii 9	−	−	ND	0.5	16	>32	>32	>32	>32
A. baumannii 10	−	−	ND	1	>32	>32	>32	>32	>32
P. aeruginosa 11	+	−	KPC + PCR	2	>32	>32	>32	>32	>32
P. aeruginosa 12	−	−	ND	1	>32	>32	>32	>32	8
P. aeruginosa 13	−	−	ND	1.5	>32	>32	>32	>32	>32
P. aeruginosa 14	−	−	ND	3	>32	>32	>32	>32	32
P. aeruginosa 15	−	−	ND	2	>32	>32	>32	>32	>32
E. coli 16	+	−	KPC-3	0.5	>32	>32	16	>32	4
E. coli 17	+	−	KPC-2	1	>32	6	3	>32	2
E. coli 18	+	−	KPC-2	0.5	>32	8	2	8	1.5
E. coli 19	+	−	KPC-2	1	>32	6	2	>32	1.5
E. coli 20	+	−	KPC-2	0.75	>32	6	4	16	1.5

[a] PB, polymyxin B; RI, rifampin; IP, imipenem; MP, meropenem; ERT, ertapenem; D, doripenem; ND, not determined; +, positive result; −, negative result.

Urban C et al. AAC 2010

Isolate	PB-D-RI		PB-D		PB-RI		D-RI	
	LogΔ (CFU/ml)	Fold change	LogΔ (CFU/ml)	Fold change	LogΔ (CFU/ml)	Fold change	LogΔ (CFU/ml)	Fold change
K. pneumoniae 1	≤−3.70[b]	≥5,000	≤−3.70[b]	≥5,000	≤−3.70[b]	≥5,000	≤−3.70[b]	≥5,000
K. pneumoniae 2	−2.70	500	−2.10	125	+3.54	35,000	≤−3.70[b]	≥5,000
K. pneumoniae 3	≤−3.70[b]	≥5,000	−0.84	7	−0.65	4.4	+1.51	32
K. pneumoniae 4	≤−3.70[b]	≥5,000	+3.79	6,100	+4.30	20,000	+4.30	20,000
K. pneumoniae 5	≤−3.70[b]	≥5,000	−2.70	500	+3.45	2,793	+3.07	1,188
A. baumannii 6	≤−3.70[b]	≥5,000	+0.19	1.5	≤−3.70[b]	≥5,000	≤−3.70[b]	≥5,000
A. baumannii 7	−2.0	100	+5.3	200,000	+0.87	7.4	+5.30	200,000
A. baumannii 8	−1.67	46	+0.56	3.7	+2.43	267	≤−3.70[b]	≥5,000
A. baumannii 9	≤−3.70[b]	≥5,000	≤−3.70[b]	≥5,000	≤−3.70[b]	≥5,000	+0.8	6.3
A. baumannii 10	≤−3.70[b]	≥5,000	+5.05	112,000	+5.30	200,000	+4.0	10,000
P. aeruginosa 11	≤−3.70[b]	≥5,000	+1.56	36.3	+2.95	886	+0.52	3.3
P. aeruginosa 12	≤−3.70[b]	≥5,000	+4.60	39,900	≤−3.70[b]	≥5,000	+4.17	14,700
P. aeruginosa 13	≤−3.70[b]	≥5,000	≤−3.70[b]	≥5,000	+4.30	20,000	≤−3.70[b]	≥5,000
P. aeruginosa 14	≤−3.70[b]	≥5,000	+5.30	200,000	+4.30	20,000	+2.66	460
P. aeruginosa 15	≤−3.70[b]	≥5,000	+4.75	56,000	+4.30	20,000	+3.93	8,600
E. coli 16	≤−3.70[b]	≥5,000	≤−3.70[b]	≥5,000	−1.81	63.8	+4.32	21,100
E. coli 17	≤−3.70[b]	≥5,000	≤−3.70[b]	≥5,000	≤−3.70[b]	≥5,000	+5.30	200,000
E. coli 18	≤−3.70[b]	≥5,000	≤−3.70[b]	≥5,000	+2.21	161	+5.03	106,000
E. coli 19	≤−3.70[b]	≥5,000	≤−3.70[b]	≥5,000	≤−3.70[b]	≥5,000	≤−3.70[b]	≥5,000
E. coli 20	≤−3.70[b]	≥5,000	+0.37	2.4	+1.72	53	+3.56	3,633

[a] PB, polymyxin B; D, doripenem; RI, rifampin.
[b] Maximum log reduction in CFU/ml detectable by assay = (standard inoculum) 5.7 $\log_{10}$ − (lower limit of detection) 2.0 $\log_{10}$.

Urban C et al. AAC 2010

- Combinations of polymyxin B-doripenem-rifampin at 1/4 MICs for each antibiotic were bactericidal for 4/5 *K. pneumoniae, 3/5 A. baumannii, 5/5 P. aeruginosa,* and 5/5 *E. coli isolates*
- Bactericidal activity was achieved in 85% of all bacteria assayed using combinations of polymyxin B-doripenem-rifampin

Urban C et al. AAC 2010

In Vitro Evaluation of Antibiotic Synergy for Polymyxin B-Resistant Carbapenemase-Producing *Klebsiella pneumoniae*

- **We investigated several antimicrobial agents for potential synergy with polymyxin B against 12 clinical strains of carbapenemase-producing *K. pneumoniae. A broth microdilution assay using a* 96-well plate was developed in which graded dilutions of polymyxin B and the study drug were incubated with resistant isolates in a checkerboard pattern.**
- **All *K. pneumoniae strains tested* positive for *K. pneumoniae carbapenemase (KPC) genes had elevated polymyxin B MIC* values ranging from 16 to 128 g/ml.**

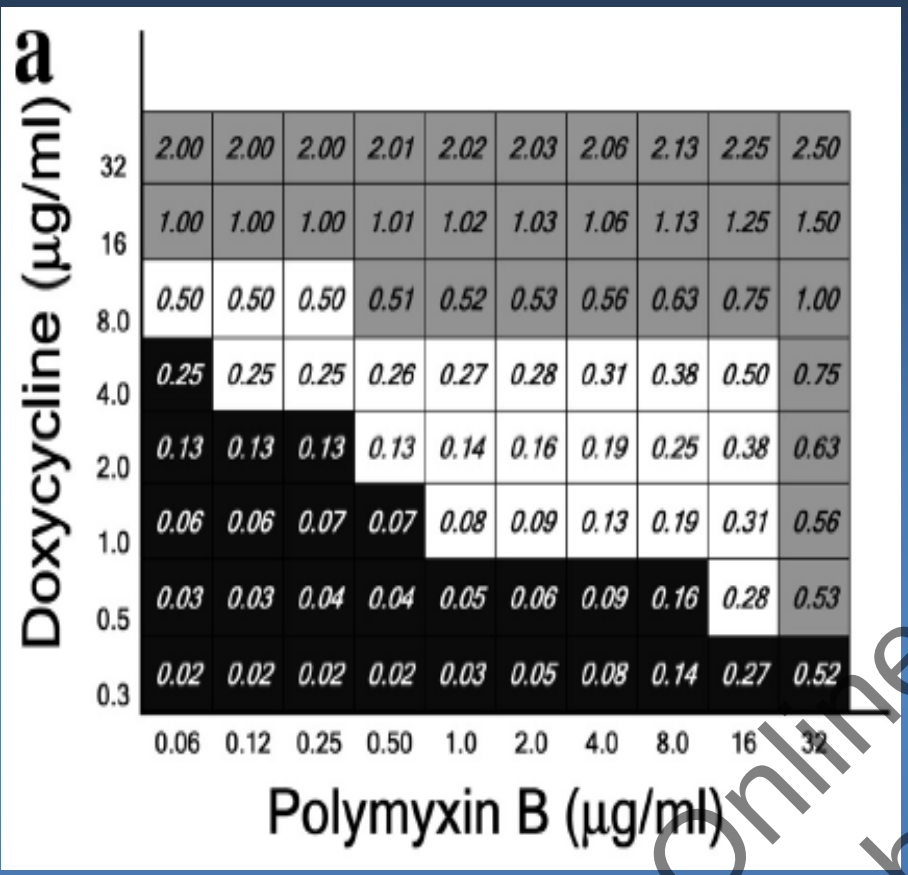
Elemam A et al. JCM 2010

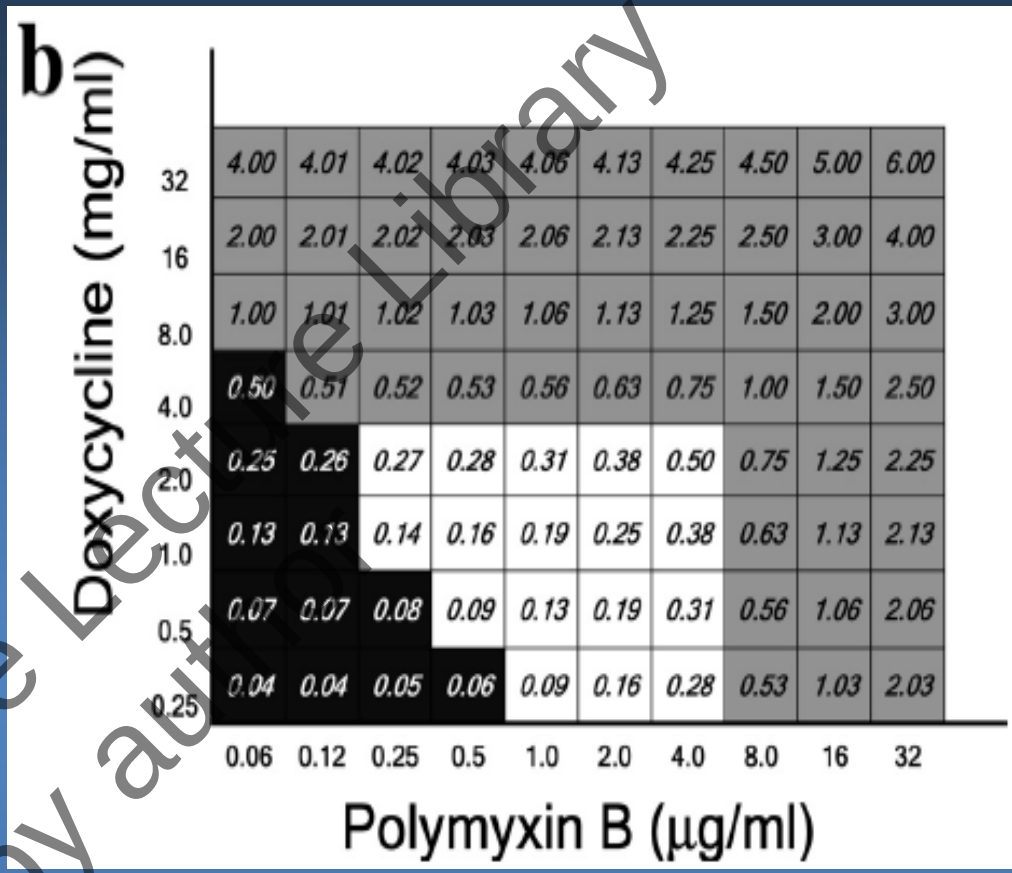
Sources of isolates and MICs of various antibiotics

Isolate	Source	MIC (μg/ml)									
		PB	RIF	Doxy	FEP	IMI	CZ	CRO	GM	TG	CL
1	Sputum	32	>32	8	32	16	≥64	≥64	≥16	2	8
2	Tracheal aspirate	32	32	8	64	16	≥64	≥64	≥16	2	8
3	Tracheal aspirate	128	32	4	64	16	≥64	≥64	≥16	2	8
4	Sputum	32	32	4	128	16	≥64	≥64	≥16	2	6
5	Axilla	64	32	4	64	32	≥64	≥64	≥16	2	8
6	Tracheal aspirate	32	32	4	32	16	≥64	32	≥16	2	8
7	Urine	64	>32	8	>128	64	≥64	≥64	≥16	8	4
16	Tracheal aspirate	16	32	4	32	32	≥64	≥64	≥16	2	12
17	Urine	32	>32	8	64	32	≥64	≥64	8	2	8
29	Urine	32	32	8	32	32	≥64	≥64	≥16	2	12
32	Sputum	64	>32	8	32	32	≥64	≥64	8	8	12
35	Catheter tip	128	>32	16	32	32	≥64	≥64	8	4	12

[a] *The isolates were tested against polymyxin B (PB), rifampin (RIF), doxycycline (Doxy; susceptible MIC S 4 g/ml, intermediate MIC I 8 g/ml, resistant* MIC R 16 g/ml), cefepime (FEP; S 8 g/ml, I 16 g/ml, R 32 g/ml), imipenem (IMI; S 4 g/ml, I 8 g/ml, R 16 g/ml), cefazolin (CZ; S 8 g/ml, I 16 g/ml, R 32 g/ml), ceftriaxone (CRO; S 8 g/ml, I 16 to 32 g/ml, R 64 g/ml), gentamicin (GM; S 4 g/ml, I 8 g/ml, R 16 g/ml), tigecycline (TG; S 4 g/ml, I 8 g/ml, R 16 g/ml), and colistin (CL).

Elemam A et al. JCM 2010





Total fractional inhibitory concentrations of polymyxin B combined with doxycycline-resistant (a) and doxycycline-susceptible (b) isolates. Data obtained for isolates 35 (a) and 3 (b) are presented

Elemam A et al. JCM 2010

In Vitro Evaluation of Antibiotic Synergy for Polymyxin B-Resistant Carbapenemase-Producing *Klebsiella pneumoniae*

- **Synergy was observed with the combination of polymyxin B and rifampin as well as with polymyxin B and doxycycline, resulting in at least a 4-fold decrease in the polymyxin B MIC.**
- **For both combinations, this effect occurred at physiologically achievable concentrations. Less pronounced synergy was noted with tigecycline and polymyxin B.**

Elemam A et al. JCM 2010

Pharmacodynamic Studies of Meropenem Alone or in Combination with Colistin-Sulphate against *Pseudomonas aeruginosa* and *A baumannii* in an In Vitro Kinetic Model*

To evaluate the potential synergistic effect of low doses of colistin-sulphate (CS) with meropenem (M) against strains of *P. aeruginosa* and *A. baumannii* in an in vitro kinetic model.

Results: The MICs of CS were 1 mg/l for all strains. The MICs for the M susceptible strains of P*. aeruginosa* were 1 mg/l. For the M resistant strains the MICs were 32 mg/l

For the M susceptible *P. aeruginosa*, the combination of M and CS and M alone gave similar results with a 99.9% kill at 2h but regrowth appeared and at 8 h only a reduction of one log10 CFU was seen from the initial inoculum.
CS alone was less effective. Also for the M resistant strains, the combination of M and CS gave the best results with a 5 log10 decrease after 3 h. However, regrowth occurred thereafter both for the combination and for CS alone.

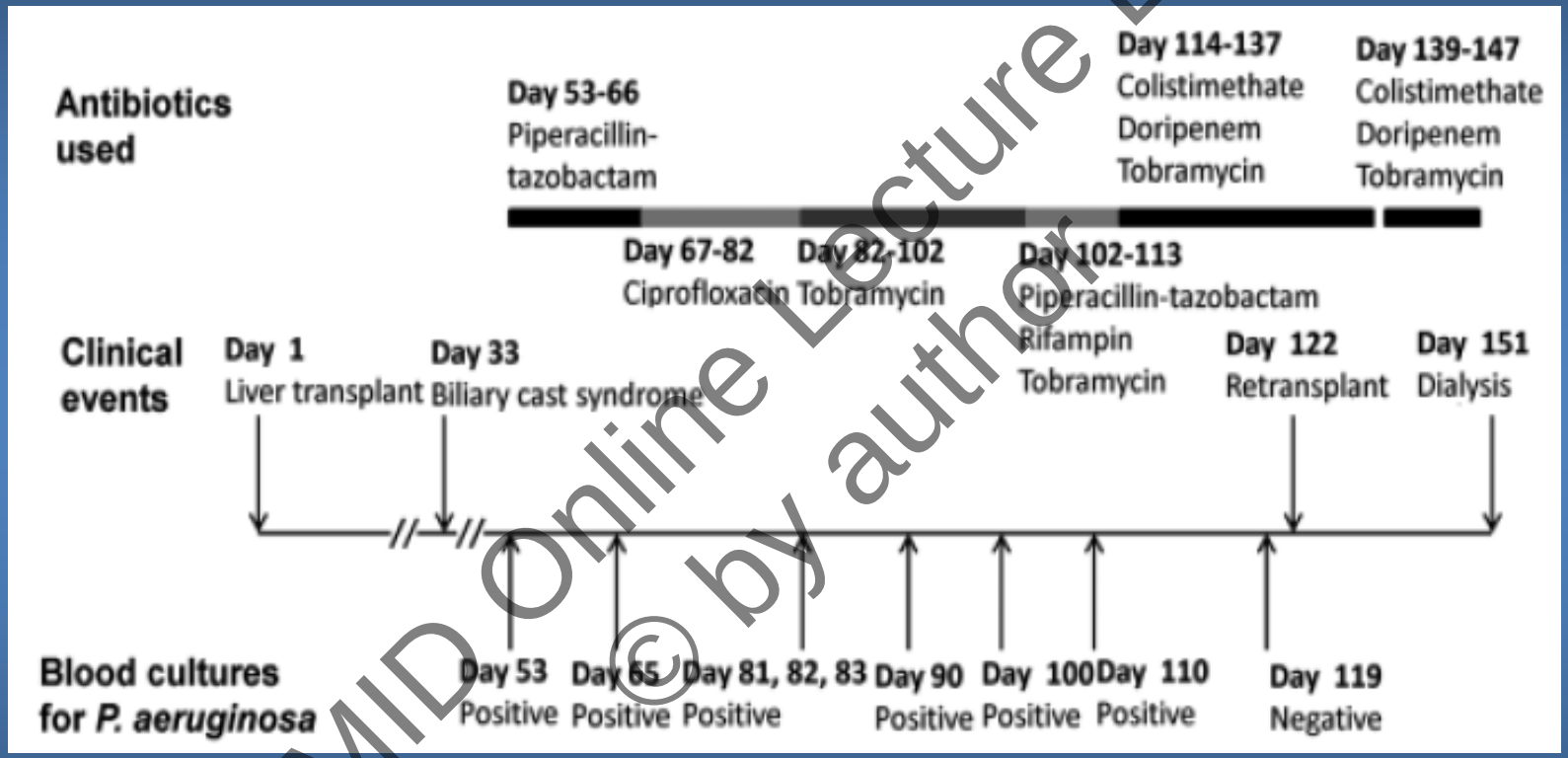
Conclusions: Although two of the strains were M resistant, the combination with subinhibitory concentrations of CS gave a higher degree of killing in comparison to CS alone.

*Karvanem M et al, A-9, 46th ICAAC, San Francisco, 2006

OUTLINE

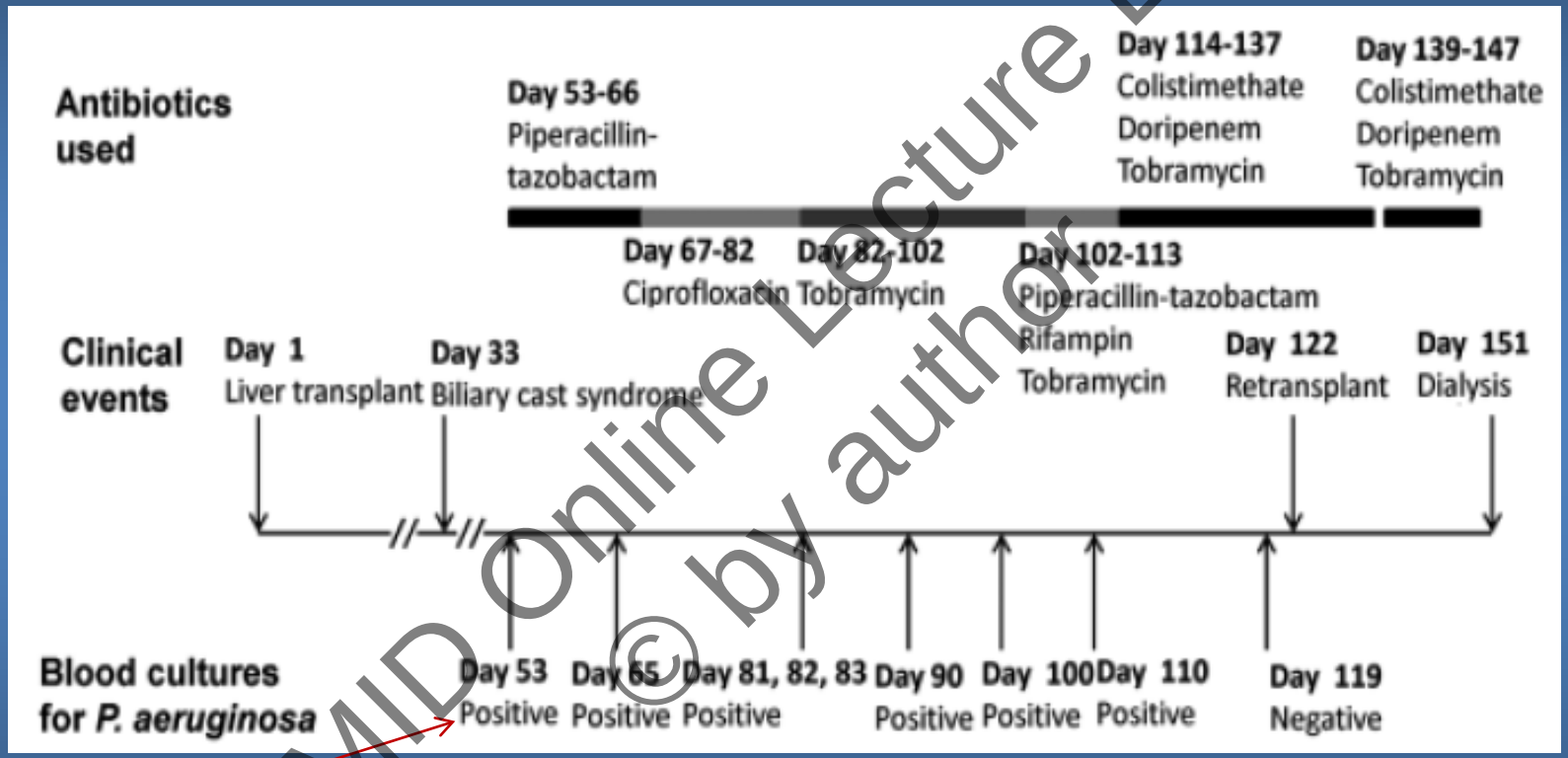
- Scope of the problem
- Risk factors for MDR infection
- Impact on mortality
- Antibiotic combinations
- **A real case**
- How to use colistin

Clinical course and antimicrobial therapy for a liver transplant recipient with persistent bacteremia due to MDR *Pseudomonas aeruginosa*.



Sun H-Y et al. Transplant Infectious Disease 2010

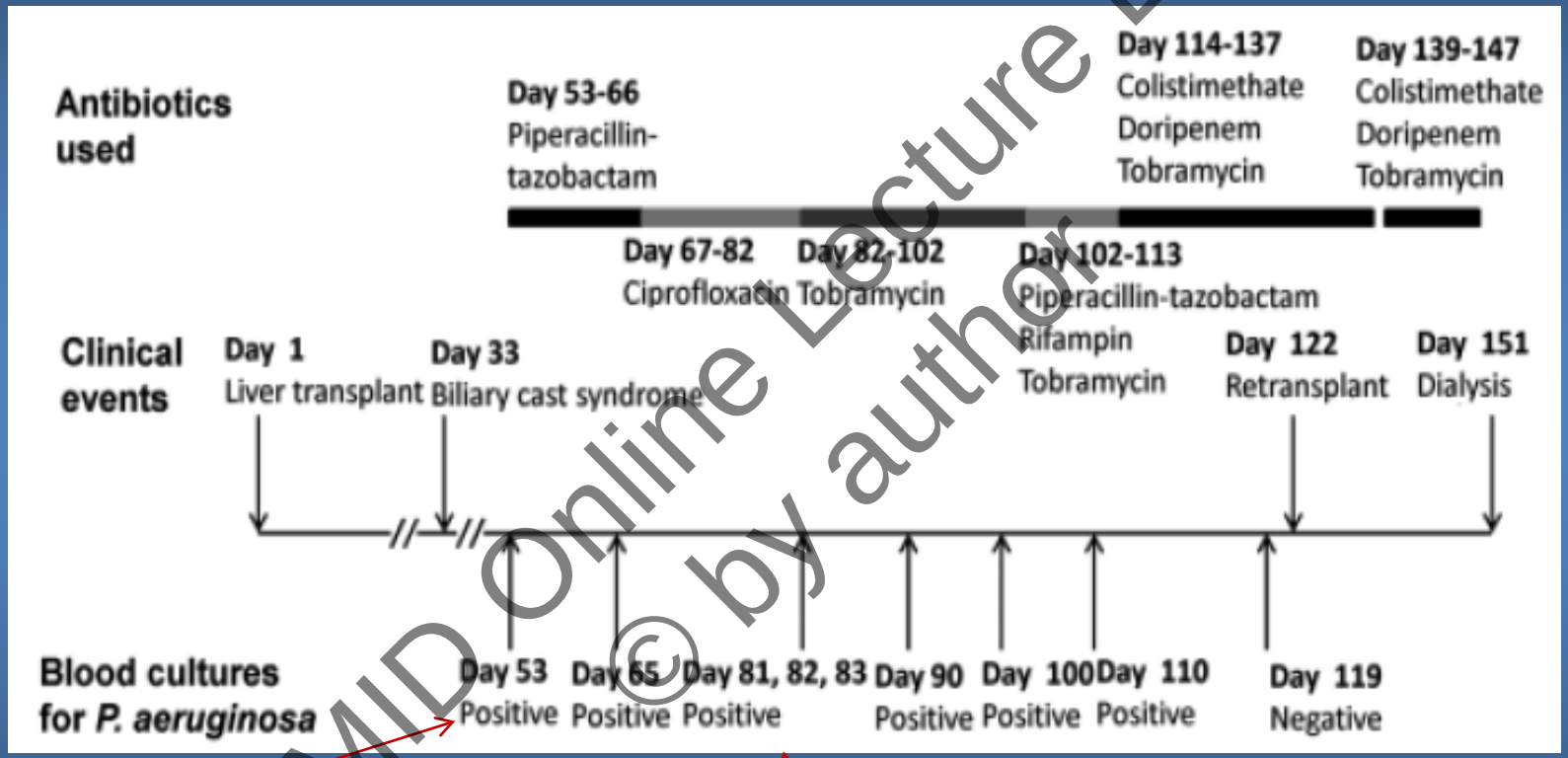
Clinical course and antimicrobial therapy for a liver transplant recipient with persistent bacteremia due to MDR *Pseudomonas aeruginosa*.



P. aeruginosa, resistant only to imipenem

Sun H-Y et al. Transplant Infectious Disease 2010

Clinical course and antimicrobial therapy for a liver transplant recipient with persistent bacteremia due to MDR *Pseudomonas aeruginosa*.



P. aeruginosa, resistant only to imipenem

susceptible only to the aminoglycosides

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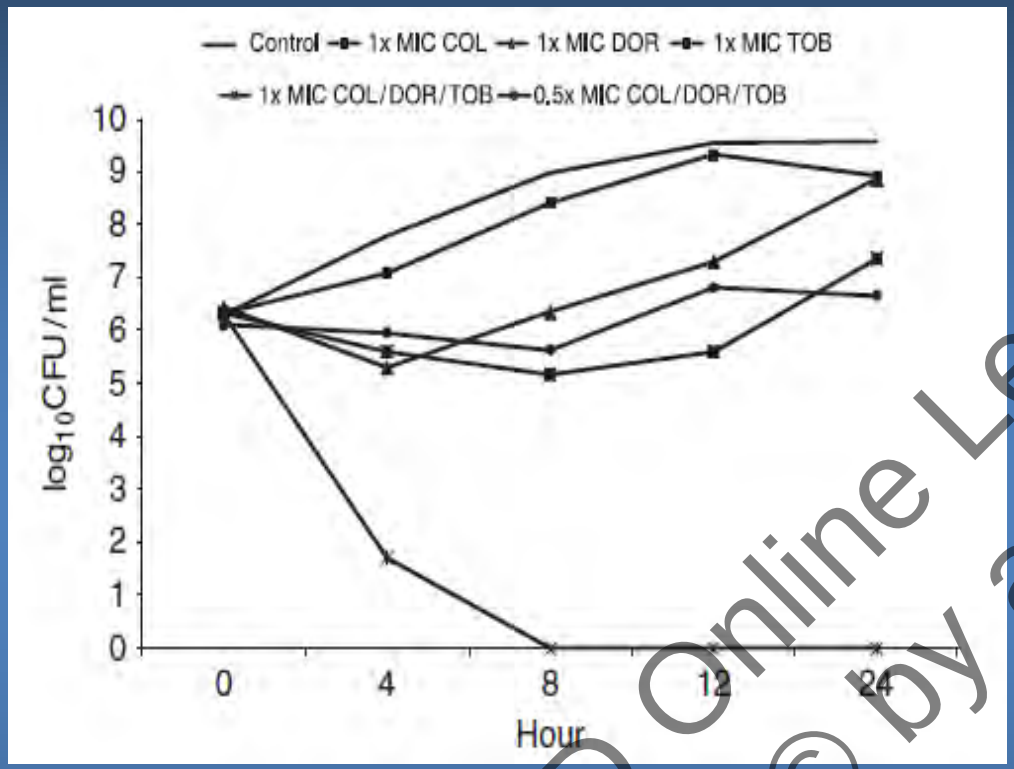
Results of time-kill assay, testing colistin (COL), Doripenem (DOR), and tobramycin (TOB) alone and in combination against the MDR P aeruginosa



Antimicrobial concentrations tested in combination include COL 0.5 mg/L, DOR 4 mg/L, and TOB 1 mg/L

Results of in vitro susceptibility and synergy testing by checkerboard microdilution

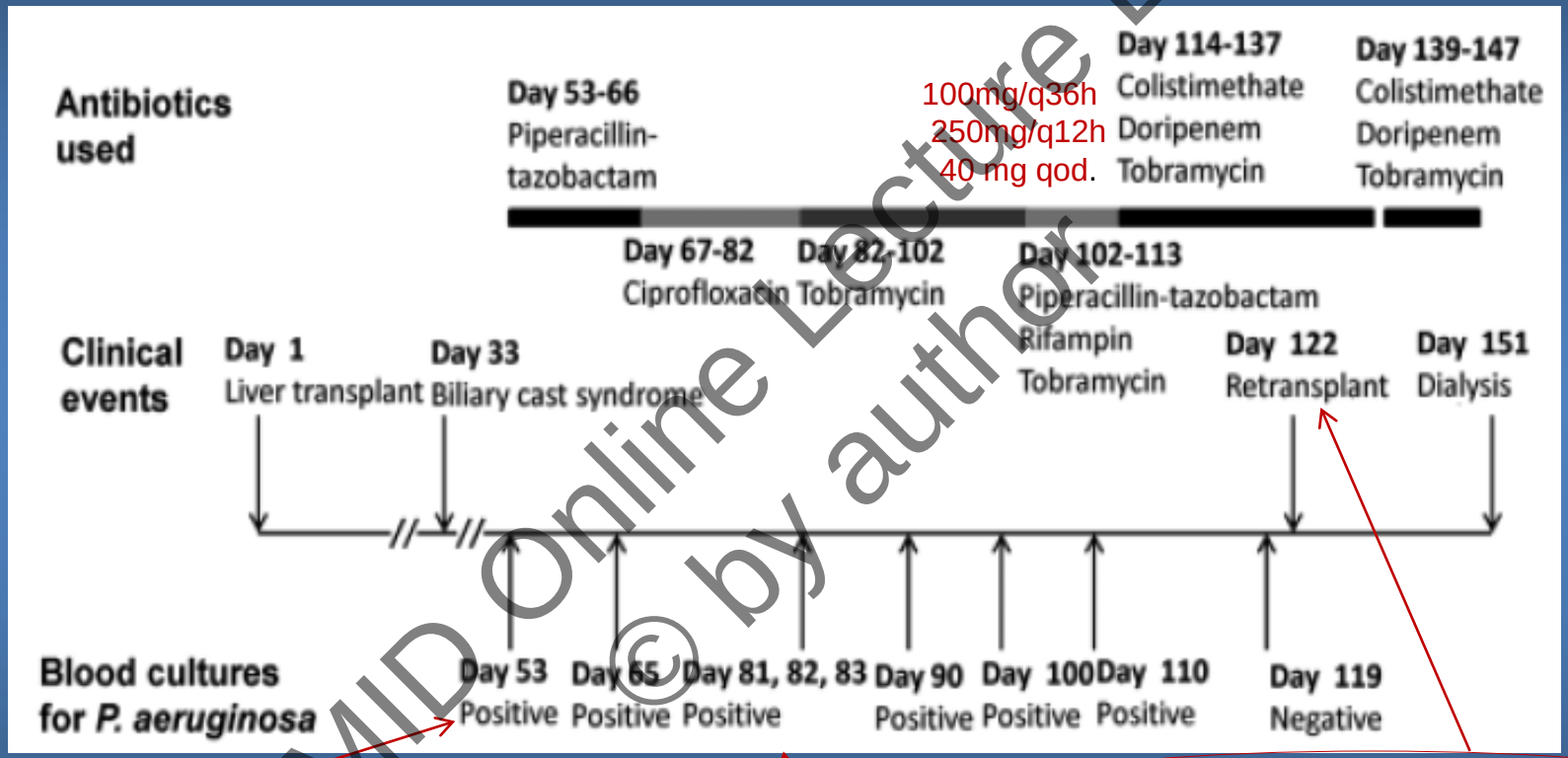
Antimicrobial agent	Minimum inhibitory concentration (μg/mL)	Interpretation
Colistin	1	Susceptible
Doripenem	8	Resistant
Tobramycin	2	Susceptible
Antimicrobial combination	ΣFIC[1]	Interpretation
Colistin and doripenem	1	Indifferent
Colistin and tobramycin	2	Indifferent
Doripenem and tobramycin	0.75	Additive

[1]ΣFIC, fractional inhibitory concentration index.

Synergy was defined as SFIC ≤ 0.5

Sun H-Y et al. Transplant Infectious Disease 2010

Clinical course and antimicrobial therapy for a liver transplant recipient with persistent bacteremia due to MDR *Pseudomonas aeruginosa*.



P. aeruginosa, resistant only to imipenem

susceptible only to the aminoglycosides

after 3 days of persistently negative cultures.

Sun H-Y et al. Transplant Infectious Disease 2010

Clinical course and antimicrobial therapy for a liver transplant recipient with persistent bacteremia due to MDR *Pseudomonas aeruginosa.*

- Not all combinations are created equal.
- Initially, our patient was started on a regimen of piperacillin-tazobactam, rifampin, and tobramycin (Zuravleį JJ et al. J Lab Clin Med 1983; Zuravleį JJ et al. Lab Clin Med 1984), (Yu VL et al. Addition of rifampin to carboxypenicillin-aminoglycoside combination for the treatment of *P aeruginosa* infection: clinical experience with four patients. AAC 1984) and (Korvick JA et al. Addition of rifampin to combination antibiotic therapy for P aeruginosa bacteremia: prospective trial using the Zelen protocol. AAC 1992)

- Unfortunately, our patient did not respond to this triple-drug combination for *P. aeruginosa* bacteremia and all potential options for therapy employing conventional antimicrobial agents were considered to have been exhausted.

Sun H-Y et al. Transplant Infectious Disease 2010

OUTLINE

- Scope of the problem
- Risk factors for MDR infection
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- Antibiotic combinations
- A real case
- **How to use colistin**

Clinical and microbiological response rates from recent clinical studies of colistin for the treatment of pneumonia due to *P. aeruginosa* or *A. baumannii*

First author, year	Infecting organism (n of patients)	Comparator	Clinical response n/total(%)	Microbiological response n/total (%)
Levin, 1999	P. aeruginosa (6) A. baumannii (1)	None	5/20 (25)	NA for pneumonia
Linden, 2003	P. aeruginosa (18)	None	11/18 (61)	6/18 (33)
Markou, 2003	P. aeruginosa (11) A. baumannii (4)	None	9/15 (60)	8/15 (53)
Kasiakou, 2005	P. aeruginosa (8) A. baumannii (10)	None	10/18 (56)	NA
Kallel, 2006	P. aeruginosa and A. baumannii (78)	None	11/17 (66) 60/78 (76,9)	NA NA
Pleczkowski, 2006	P. aeruginosa (10)			
Falagas, 2006	P. aeruginosa (17) A. baumannii (12)	None	23/27 (85)	NA
Furtado, 2007	P. Aeruginosa (74)	None	35 (47,3%)	NA

Aerosolized plus IV Colistin vs. IV Colistin Alone for the Treatment of VAP: A Matched Case-Control Study

- Purpose: to compare the efficacy and safety of AS plus IV colistin versus IV colistin alone for patients with MDR VAP due to gram-negative bacteria.
- ***A retrospective matched case-control study***, 2005 to 2008.
- Forty-three patients with VAP due gram-negative MDR pathogens received AS plus IV colistin and were matched on the basis of age and APACHE II score with 43 control patients who had received IV colistin alone.

Kofteridis DP et al. CID 2010; 51:1238–1244

Demographic and Clinical Characteristics of Study Patients

Characteristic	IV colistin (n = 43)	AS-IV colistin (n = 43)	P
Age, mean years ± SD	62.35 ± 14.92	62.60 ± 15.14	.890
Sex, male/female	30/13	28/15	.645
Mean APACHE II score ± SD	17.74 ± 7.61	16.95 ± 6.59	.852
Reason for admission			
Acute respiratory failure	16 (37)	12 (28)	.357
Shock	7 (16)	5 (12)	.532
Postoperative resuscitation	3 (7)	8 (19)	.106
Multiple trauma	5 (12)	3 (7)	.713
Underlying disease			
Diabetes mellitus	5 (12)	4 (9)	.725
Chronic obstructive pulmonary disease	12 (28)	7 (16)	.194
Malignancy	9 (21)	3 (7)	.117
Renal failure	5 (12)	1 (2)	.202
Prior receipt of antibiotic therapy	40 (93)	38 (88)	.458
Immunosuppressive therapy	10 (23)	5 (12)	.115
Prior blood transfusion	12 (28)	15 (35)	.486
Presence of fever	38 (88)	34 (79)	.243
Septic shock	3 (7)	4 (9)	.693
Microorganism			
Acinetobacter baumannii	31 (72)	35 (81)	
Klebsiella pneumoniae	7 (16)	5 (12)	.584
Pseudomonas aeruginosa	5 (12)	3 (7)	
Duration of ICU stay, median days (range)	18 (3–78)	20.5 (3–93)	.676
Duration of MV, median days (range)	16.5 (5–62)	15 (3–97)	.840
Duration of colistin therapy, median days (range)	10 (4–36)	13 (5–56)	.080

NOTE. Data are no. (%) of patients, unless otherwise indicated. APACHE II, Acute Physiology and Chronic Health Evaluation; AS, aerosolized; ICU, intensive care unit; IV, intravenous; MV, mechanical ventilation; SD, standard deviation.

Kofteridis DP et al. CID 2010; 51:1238–1244

Aerosolized plus IV Colistin vs. IV Colistin Alone for the Treatment of VAP: A Matched Case-Control Study

Outcome	No. (%) of patients		P
	IV colistin group (n = 43)	AS-IV colistin group (n = 43)	
Clinical outcome			
Clinical cure	14 (32.5)	23 (54)	.05
Clinical improvement	12 (28)	9 (21)	.451
Clinical failure	14 (32.5)	7 (16)	.126
Recurrence	3 (7)	4 (9)	>.99
Bacteriological outcome[a]			
Eradication	17 (50)	19 (45)	.679
Persistent	12 (35)	10 (24)	.272
Recurrence	2 (6)	5 (12)	.450
Colonization	3 (9)	8 (19)	.208
Mortality			
All-cause	18 (42)	10 (23)	.066
VAP-related	11 (26)	7 (16)	.289
Adverse events			
Nephrotoxicity	8 (19)	8 (19)	>.99
Neurotoxicity	0	0	

NOTE. AS, aerosolized; IV, intravenous; VAP, ventilator-associated pneumonia

[a] Bacteriological outcome was evaluated in 34 patients in the IV colistin group and in 42 patients in the AS-IV colistin group.

Kofteridis DP et al. CID 2010; 51:1238–1244

Aerosolized plus IV Colistin vs. IV Colistin Alone for the Treatment of VAP: A Matched Case-Control Study

- Demographic characteristics, clinical status, and gram-negative isolated pathogens were similar between the 2 treatment groups.
- *Acinetobacter baumannii (66 cases [77%]), the most common pathogen, followed by Klebsiella pneumoniae (12 cases [14%]) and Pseudomonas aeruginosa (8 cases [9.3%]). No colistin-resistant strains* were isolated from patients in either group.
- No significant differences between the 2 groups were observed regarding eradication of pathogens (*P= 0.679), clinical cure (P= 0.10), and mortality (P= 0.289). Eight patients (19%) in each* treatment group developed reversible renal dysfunction. No AS colistin–related adverse events were recorded.

Addition of AS colistin to IV colistin did not provide additional therapeutic benefit to patients

Kofteridis DP et al. CID 2010; 51:1238–1244

Limitatiosn of Kofteridis' study

- The study was underpowered to truly show a significant difference between the 2 treatment options.
- Diagnosis of VAP is always difficult, even when quantitative cultures are used. Airway colonization may have been labeled as VAP; a real chance of bias toward the null hypothesis, because the outcomes for patients with airway colonization should not be affected by therapy, thereby necessitating an even greater sample size to show a real difference.
- Dosages of colistin not based on modern PK analyses, and it is possible that dosing regimens were not optimal.
- Few details are provided about the mode of aerosolization of colistin.

Population PK analysis of colistin methanesulphonate and colistin after IV administration in critically ill patients with Gram-negative bacterial infections.

Parameter	CMS (RSE %)	Colistin (RSE %)
$t_{½}$ (h)	2.3	14.4
C_{max} predicted (mg/L)		
first dose		0.60
steady state		2.3
CL (L/h)	13.7 (10)	9.09 (19)
Vd (L)	28.9 (22)	189 (12)

CL = total body clearance; **C_{max}** = maximum concentration; **RSE** = relative standard error; **$t_{½}$** = half life; **Vd** = volume of distribution.

- Following repeated administration of 3 million IU every 8 hours.
- Without a loading dose, it takes 2–3 days before the steady-state concentration of colistin is obtained.

Plachouras D et al. AAC 2009

A loading dose of 9 million IU CMS and a maintenance dose of 4.5 million IU CMS q12h would result in the same steady-state concentration of colistin as the current dosing schedule, but would achieve the target faster.

Future studies with colistin

1. large prospective, possibly comparative, trials in MDR infections of ICU patients under well-designed protocols and reliable susceptibility testing;
2. Further PK/PD exploitation;
3. Clarification in vivo of the possible benefits of coadministering colistin with other antimicrobials, such as the carbapenems and rifampicin;
4. Evaluation of nebulized colistin as single VAP therapy vs. combination with parenteral colistin;
5. Better monitoring and elucidation of resistance mechanisms;
6. Larger experience in the febrile neutropenic host.

We must explore ways for maintaining the activity and usefulness of colistin.

Giamarellou H et al. Drugs 2009

CONCLUSIONS

- Therapy for MDR organisms will continue to be regarded as an off-label use, with clinicians persisting to use therapy without data from randomized, controlled trials
- Desperate need of randomized, controlled trials in the field of treatment of infections with MDR-gramnegative bacilli.
- Double or triple combinations, only available weapon against panresistant organisms
- Antibiotic stewardship, a temporary solution to an unstoppable process
- New antimicrobials needed!!

Back-up slides

Clinical course and antimicrobial therapy for a liver transplant recipient with persistent bacteremia due to MDR *Pseudomonas aeruginosa*.

- One combination showing promise in recent studies is colistin with rifampin (Aoki N et al. JAC 2009) in a mouse model of pneumonia cased by multidrug-resistant *P aeruginosa*. JAC 2009)
- The use of rifampin is extremely difficult in SOT patients receiving immunosuppressive agents owing to significant drug- drug interactions.
- A potential alternative to rifampin in combination with colistin may be the carbapenems. Although this combination has not been studied extensively for MDR Pseudomonas, it has been for MDR Acinetobacter infections.
- In our study, combination with doripenem and colistin demonstrated in vitro synergistic activity against Acinetobacter and also improved outcomes of SOT recipients with MDR Acinetobacter infections.
- Other centers have found similar results both for Acinetobacter and for Pseudomonas by using meropenem with colistin (Pankuch GA et al. Activity of meropenem with and without ciprofloxacin and colistin against *P aeruginosa* and *A baumannii*. AAC 2008)

Sun H-Y et al. Transplant Infectious Disease 2010

IV polymyxin B for the treatment of nosocomial pneumonia caused by MDR *P aeruginosa*

- Analysis of 74 patients with nosocomial pneumonia caused by MDR *P. aeruginosa who were treated with polymyxin B.*
- *A favourable outcome observed in 35 patients (47.3%).*
- *ARSD* (OR = 11.29, 95% CI 2.64–48.22; *P = 0.001) and septic shock (OR = 4.81, 95% CI 1.42–16.25, P = 0.01)* were independently associated with an unfavourable outcome.

Study shows that polymyxin B is a reliable antimicrobial drug, but only as salvage therapy, for nosocomial pneumonia caused by MDR *P. aeruginosa.*

Furtado et al. International J Antimicrob Agents 2007

COMBINATION THERAPY VS. MONOTHERAPY-RESISTANT P AERUGINOSA

- *P aeruginosa* clinical isolates R to ticarcillin and tobramycin, alone and in combination, were killed by the addition of rifampin. Thus, despite the organism's R to each one of the drugs alone, killing was achieved with the combination[1]
- These results validated in a neutropenic mouse model of *P aeruginosa* infection[2]
- In humans with *P aeruginosa* bacteremia (121 patients), the triple antibiotic regimen was compared with double therapy (without rifampin). No significant diference in mortality occurred in the 2 groups: However, bacteriologic cure occurred more frequently in the triple therapy group, and breakthrough or relapsing bacteremia occurred in 2% of patients treated with triple therapy and in 14% of those treated with double therapy[3]

1. Zuravleff JJ et al, J Lab Clin Med 1983;101:896
2. Zuravleff JJ et al, J Lab Clin Med 1984;103:878
3. Korvick JA et al, AAC 1992;36:620

COMBINATION THERAPY VS MONOTHERAPY-RESISTANT P AERUGINOSA

- Reports of clinical trials of these and other drug combinations are extremely rare
- In a nosocomial outbreak of pulmonary infection with mutidrug-resistant *P aeruginosa*, cefepime plus amikacin were found to be “the least inactive” antibiotics ant to be highly sinergistic by checkerboard and killing curve methods. All patients were treated with this combination, and 44 out of 64 (75 %) recovered[1]
- In another cohort study, 25 critically ill patients with respiratory tract infections due to multidrug-resistant P aeruginosa or A baumannii were treate with aerosolized and/ or intavenous Polymixin B in combination with ≥ of the following imipenem or meropenem, amikacin, tobramycin, cefepime, ampicillin-sulbactam, ciprofloxacin, or aztreonam. 12/25 resistant to all agents except polymixin B. 79% survived to the end of therapy and 41% achieved microbiological clearance[2]

1. Dubois V et al, J Clin Microbiol 2001;39:2072
2. Sobieszckyk ME et al, JAC 2004;54:566

THERAPY OF P AERUGINOSA INFECTIONS-DOSING STRATEGIES

Time-dependent antibiotics

- 40% of the interval vs. 80-100%
- Increasing popularity of constant infusions (ceftazidime, 4 g/day) or prolonged intermittent dosing (meropenem, 2 g/q8h-3 hours infusion)

Concentration-dependent antibiotics

- AUC/MIC ratio, Cmax/MIC RATIO
- Ags: single daily dose (amikacin, 15 mg/Kg/day)
- FQs, ciprofloxacin preferred (400 mg/q8h)

SUMMARY

- For infections with susceptible *P aeruginosa*, combination therapy is preferable for patients with pneumonia and neutropenia
- Against infections with *P aeruginosa* isolates resistant to all antibiotics except the polymixins, several novel antibiotic combinations demonstrate increased activity. Whether these combinations yield outcomes that are improved over those seen with polymixins or other agents alone, remains to be determined
- In panresistant strains some antibiotic combinations are synergic in vitro

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

Organism (number of isolates)	MIC (mg/L) 50%	90%	range	% resistant
Non-fermentative Gram-negative bacteria				
Acinetobacter spp. (2621)	≤1	2	≤1 to >8	2.1
Aeromonas spp. (368)	≤1	>8	≤1 to >8	28.3
Alcaligenes spp. (121)	2	>8	≤1 to >8	36.4
B. cepacia (153)	>8	>8	0.5 to >8	88.2
P. aeruginosa (8705)	≤1	2	≤1 to >8	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
Enterobacteriaceae				
Citrobacter spp. (895)	≤1	≤1	≤1 to >8	0.9
Enterobacter spp. (4693)	≤1	>8	≤1 to >8	16.7
E. coli (18 325)	≤1	≤1	≤1 to >8	0.5
Klebsiella spp. (8188)	≤1	≤1	≤1 to >8	1.8
indole-positive *Proteus* spp. etc. (895)[b]	>8	>8	≤1 to >8	98.7
Proteus mirabilis (1931)	>8	>8	≤1 to >8	99.3
Salmonella spp. (2909)	≤1	4	≤1 to >8	24.0
Shigella spp. (828)	≤1	≤1	≤1 to >8	1.0
Serratia spp. (1919)	>8	>8	0.25 to >8	94.6
other enteric Gram-negative bacilli (340)	≤1	8	≤1 to >8	24.1

[a]Data from SENTRY antimicrobial surveillance programme, 2001–04.
[b]Includes: M. morganii (n = 507), Proteus spp. (n = 64), Proteus vulgaris (n = 179), Providencia alcalifaciens (n = 1), Providencia rettgeri (n = 41), Providencia spp. (n = 18) and Providencia stuartii (n = 85).

Zavascki AP et al. JAC 2007

Combination of polymyxin B with other antibiotics- *Acinetobacter baumannii*

- Seven studies have evaluated the potential synergistic activity of polymyxin B with other antibiotics, most of them against A. baumannii.55 – 61

  - Polymyxin B-Rifampin

  - Polymyxin B-Rifampin-Imipenem

  Time–kill curves using 0.25 mg/L polymyxin B, 0.5 mg/L rifampicin and 8 mg/L imipenem showed that all isolates were killed within 24 h, a result that was not achieved with each antibiotic alone (Yoon J et al. AAC 2004)

- Polymyxin B and azithromycin or rifampicin (chequerboard) 24 *A. baumannii* isolates. The combination of azithromycin with polymyxin B showed synergy (FICI range 0.18-0.5) against 20 isolates, including two polymyxin-resistant isolates, and additive effect against the remaining 4 (FICI range 0.5-1.0)
- The combination of 1 mg/L rifampicin and polymyxin B demonstrated synergy against half of the isolates (FICI range,0.1820.5) and an additive effect (FICI range, 0.5-1.0) against the remainder (Manikal VM et al. CID 2000)
- In another study, combinations of polymyxin B with imipenem, azithromycin or rifampicin were assessed using Etest agar dilution and combined Etest strip methods against five unrelated MDR A. baumannii isolates, which encoded OXA-23 carbapenemase and were only susceptible to polymyxins.61. **Synergy was not observed with polymyxin B in combination with any drug against four of the isolates**. Borderline synergy (FICI = 0.5) was shown against one strain with polymyxin B in combination with rifampicin or imipenem. (Wareham DW et al. Ann Clin Microbiol Antimicrob 2006)

Combination of polymyxin B with other antibiotics- *Klebsiella pneumoniae*

- Another study examined the combination of polymyxin B and rifampicin against 16 *K. pneumoniae* which produced KPC-2 carbapenemase; these isolates comprised 6 distinct strains and 10 isolates representative of another 2 different ribotypes.
- 59 The combination of 1 mg/L polymyxin B plus 1 mg/L rifampicin was synergistic against 15 out of the 16 isolates.
- For a polymyxin B-resistant isolate (MIC of 16 mg/L), a decrease of 2 log cfu/mL was observed with the combination of subinhibitory polymyxin B and rifampicin.
- The combination of polymyxin B (0.5 MIC) with 4 mg/L imipenem was synergistic against 10 out of 16 isolates but antagonistic for three isolates.
- The addition of 4 mg/L imipenem to the combination of polymyxin B (0.5 MIC) and 1 mg/L rifampicin had no effect.59

Combination of polymyxin B with other antibiotics- *Pseudomonas aeruginosa*

- Landman et al.57 analysed synergism of polymyxin B with imipenem, azithromycin and rifampicin against 10 MDR P. aeruginosa isolates.
- Chequerboard studies revealed synergy of polymyxin B combined with 4 mg/L azithromycin for six isolates, with 4 mg/L imipenem for two and with 1 mg/L rifampicin for one.57 In the time–kill studies, the combinations of polymyxin B with either rifampicin or imipenem were bactericidal against most of the isolates, and the three-drug combination against all isolates. The three-drug combination was most rapidly bactericidal.57 The same group of authors also investigated the combinations with time–kill method against 13 MDR P. aeruginosa isolates.58
- The addition of 4 mg/L azithromycin to the lower concentration of polymyxin B (2 mg/L) produced a .2 log kill against most isolates and prevented regrowth in all but two isolates.58

- Although combination therapy of polymyxin B with other antibiotics seems to be an attractive option, there are no firm clinical data showing superiority of this strategy over polymyxin B monotherapy.
- Nevertheless, given that no new antibiotics will be available in the next few years for MDR Gram-negative bacteria, in particular *P. aeruginosa* and *A. baumannii*, novel combinations of the currently available antibiotics have to be investigated.

Carbapenem-non-susceptible Enterobacteriaceae in Europe: conclusions from a meeting of national experts*

Epidemiological scale	Description	Stage
No cases reported	No cases reported	0
Sporadic occurrence	Single cases, epidemiologically unrelated	1
Single hospital outbreak	Outbreak defined as two or more epidemiologically related cases in a single institution	2a
Sporadic hospital outbreaks	Unrelated hospital outbreaks with independent, i.e. epidemiologically unrelated introduction or different strains, no autochthonous inter-institutional transmission reported	2b
Regional spread	More than one epidemiologically related outbreak confined to hospitals that are part of a regional referral network, suggestive of regional autochthonous inter-institutional transmission	3
Inter-regional spread	Multiple epidemiologically related outbreaks occurring in different health districts, suggesting inter-regional autochthonous inter-institutional transmission	4
Endemic situation	Most hospitals in a country are repeatedly seeing cases admitted from autochthonous sources	5

Epidemiological scale and stages of nationwide expansion of healthcare-associated carbapenem-non-susceptible *Enterobacteriaceae*

*Grundmann H et al. Euro Surveill. 2010

Recommended doses of i.v. colistin (CMS) in critically ill patients

Normal renal function
3 million IU (240 mg CMS) every 8 h
Manufacturers of European colistin products recommend 50,000 to 75,000 IU/kg/day of CMS in 2-3 divided doses
Manufacturers of the U.S. colistin product, Coly-Mycin, recommend a dose of 2.5 to 5 mg/kg colistin base activity daily divided in 2 to 4 doses
Renal Failure
For serum creatinine level 1.3-1.5 mg/dl, 1.6-2.5 mg/dl, or ≥ 2.6 mg/dl, the recommended dosage of intravenous colistin is 2 million IU (160 mg CMS) every 8 h, 12 h, or 24 h, respectively
Renal replacement therapy
2 million IU (160 mg CMS) after each hemodialysis
2 million IU (160 mg CMS) daily during peritoneal dialysis

Michalopoulos and Falagas. Annals of Intensive Care 2011