MDRGN – Treatment Options and Challenges
Dr David Wareham, Queen Mary Universitys, UK
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Multi-drug Resistant Gram-negative Infections
Treatment Options and Challenges

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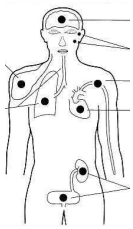
Infections with Gram-negative Bacilli

E. coli, Klebsiella, *Enterobacter*, *Serratia*, *Citrobacter*, *Pseudomonas*, *Acinetobacter*



Asymptomatic colonisation

Wound infection / Diabetic foot

Lower urinary tract infection

Upper urinary tract infection

Nosocomial pneumonia / VAP

Intra-abdominal / pelvic infection

Bacteraemia / septicaemia

Neurosurgical meningitis

SEVERITY

Problem Organisms

- Cephalosporin resistant and ESBL producing *Enterobacteriaceae*
  - *E. coli* , *K. pneumoniae*
    - CTX-M-14/15, TEM and SHV ESBL variants
    - Virulent epidemic clones – *E. coli* ST131, *K. pneumoniae* ST 258
  - *Enterobacter*, *Citrobacter, Serratia* spp
    - De-repressed chromosomal or plasmidic AmpC producers
- Carbapenem resistant Gram-negatives
  - *E. coli*, *K. pneumoniae* - KPC, OXA-48, NDM +/- ESBLs
  - *P. aeruginosa, A. baumannii* - IMP, VIM
- 'XDR' and 'Pan-drug' – resistant Gram-negatives
  - *P. aeruginosa* – MBLs +/- permeability and efflux lesions
  - *A. baumannii* – OXA-23/24/58 +/- MLBLs, ESBLs, permeability and efflux lesions

Treatment of ESBL Producing Enterobacteriaceae

Severe infections – Bacteraemia / Sepsis

Carbapenems v anything else if susceptible ?

Other β-lactams (BLI) - Cephalosporins / β-lactam/inhibitor combinations (BLICs)

Others - Quinolones / aminoglycosides / tigecycline / colistin

Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamases: a systematic review and meta-analysis

Konstantinos Z. Vardakas[1,2], Giannoula S. Tansarli[3], Petros I. Rafailidis[1,2] and Matthew E. Falagas[1,3]*

[1]Alfa Institute of Biomedical Sciences, 9 Neapoleos St. 151 23 Marousi, Athens, Greece; [2]Department of Medicine, Henry Dunant Hospital, 107 Mesogion Avenue, 115 26 Athens, Greece; [3]Tufts University School of Medicine, 145 Harrison Avenue, Boston, MA 02111, USA

Systematic review of 21 eligible studies favours....

Carbapenems > all other agents for definitive treatment of ESBL bacteraemia

Carbapenems > others for empirical treatment

Carbapenems = BLI and BLICs for empirical treatment

Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamases: a systematic review and meta-analysis

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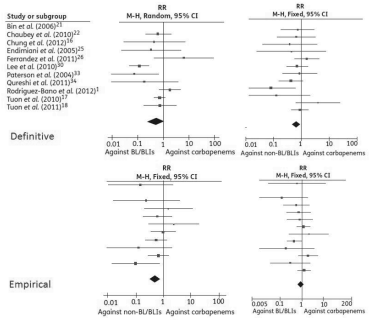

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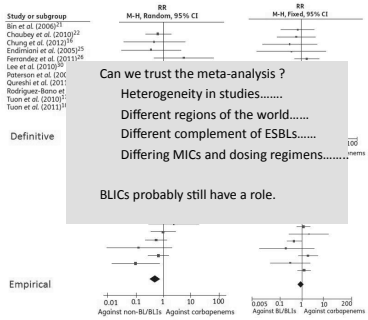

Can we trust the meta-analysis ?

Heterogeneity in studies.....

Different regions of the world.....

Different complement of ESBLs.....

Differing MICs and dosing regimens.....

BLICs probably still have a role.

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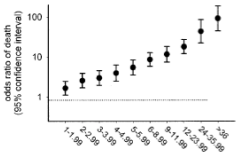
Do we overuse Carbapenems ?

- Initiatives to improve the treatment of sepsis
  - Highly active antimicrobial therapy saves lives[1]
- But de-escalation also important
  - Only 20 % of Gram-negative bacteraemias de-escalated[2]
- Generic carbapenems remove financial considerations
- 'Workhorse' antibiotics
  - Used earlier and wider
- Antimicrobial Stewardship.....



[1]Kumar et al Crit Care Med 2006, [2]Phee & Wareham ISICEM 2011

ESBL Producers: Other Options ?

Prevalence and mechanisms of cephalosporin resistance in Enterobacteriaceae in London and South-East England

Nicola A. C. Potz[1]*, Russell Hope[2], Marina Warner[2], Alan P. Johnson[1] and David M. Livermore[2] on behalf of the London & South East ESBL Project Group

Percentage resistant (intermediate)

	FOX	CIP[a]	CIP[b]	GEN	NIT[a]	TMP[a]	TMP[b]	MEC[a]	IPM	MEM	ERP
CTX-M-producers											
Enterobacteriaceae (n = 502; urine n = 395, non-urine n = 107)	*39.2*	89.4	96.3 (0)	60.2 (1.2)	51.6	88.6	87.9 (2.8)	28.9	0.0	0.0	0.4
E. coli (n = 292; urine n = 239, non-urine n = 53)	*34.9*	91.6	96.2 (0)	46.9 (1.4)	25.1	87.4	83.0 (0)	7.5	0.0	0.0	0.3
K. pneumoniae (n = 190; urine n = 138, non-urine n = 52)	*42.1*	91.3	96.2 (0)	80.0 (1.1)	96.4	90.6	92.3 (5.8)	61.6	0.0	0.0	0.5
ESBL-producers (non-CTX-M)											
Enterobacteriaceae (n = 149; urine n = 120, non-urine n = 29)	*49.0*	67.5	48.3 (0)	59.7 (1.4)	37.5	84.2	55.2 (10.3)	49.2	0.0	0.0	0.7
E. coli (n = 89; urine n = 79, non-urine n = 10)	*30.3*	74.7	NC	57.3 (2.2)	13.9	84.8	NC	36.7	0.0	0.0	0.0
K. pneumoniae (n = 25; urine n = 20, non-urine n = 5)	*60.0*	70.0	NC	44.0 (0)	85.0	75.0	NC	75.0	0.0	0.0	0.0
AmpC-producing *Enterobacter, Citrobacter, Morganella, Serratia* spp. (n = 144; urine n = 71, non-urine n = 73)	95.8	7.0	16.4 (5.5)	15.3 (1.4)	64.8	36.6	26.0 (15.1)	28.2	0.0	0.0	4.2
AmpC-producing *E. coli* (n = 41; urine n = 38, non-urine n = 3)	100.0	36.8	NC	22.0 (2.4)	21.1	57.9	NC	13.2	0.0	0.0	0.0

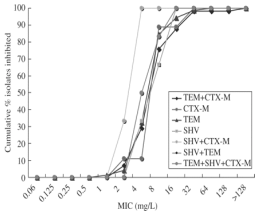
Temocillin for ESBLs?

- Ticarcillin derivative
  - Stable to ESBL's and AmpC
  - No activity versus *Pseudomonas* or Gram positives
- Rodriguez-Villalobos 2006
  - Breakpoint < 16 mg/L – 92 % of isolates susceptible
  - Wide range of ESBLs
- Livermore 2006
  - Good activity versus UK ESBL and AmpC hyperproducing Enterobacteriaeciae
  - Modal MIC 8 mg/L

In vitro activity of temocillin against extended spectrum β-lactamase-producing *Escherichia coli*

Hector Rodríguez-Villalobos*, Vincent Malaviolle, Joëlle Frankard, Ricardo de Mendonça, Claire Nonhoff and Marc J. Struelens

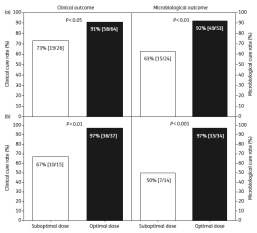
Microbiology Department, Erasme Hospital–Université Libre de Bruxelles, Brussels, Belgium



Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum and/or derepressed AmpC β-lactamase-producing Enterobacteriaceae

Indran Balakrishnan[1*], F. Mustafa Awad-El-Kariem[2], Adnan Aali[3], Prasanna Kumari[4], Rohinton Mulla[5], Benny Tan[6], Daniel Brudney[1], David Ladenheim[1], Anan Ghazy[1], Imran Khan[5], Nilangi Virginkar[6], Shabnam Iyer[6], Stephane Carryn[7] and Sebastien Van de Velde[7]

Retrospective outcome study
- n = 92 – 42 BSI, 42 UTI, 8 VAP
- '*Clinical cure Rate*'
- Overall efficacy 86 %
- No difference in efficacy v AmpC producers
- Significantly more effective at *higher dose* (2 mg 12hrly)



Treatment of Carbapenemase Producers

What remains against carbapenem-resistant Enterobacteriaceae? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline

David M. Livermore*, Marina Warner, Shazad Mushtaq, Michel Doumith, Jiancheng Zhang, Neil Woodford

International Journal of Antimicrobial Agents

Table 2
Minimum inhibitory concentrations (MICs) of antibiotics in relation to bacterial species[a,b].

Antibiotic/species	No. isolates with indicated MIC (mg/L):											
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	≥256
Chloramphenicol													
Klebsiella spp.[c]							9	7	1	4	8	7	16
Enterobacter spp./Citrobacter freundii[d]							1	3	6	3	2	5[e]	
Escherichia coli[c]								1	1			4	
Ciprofloxacin													
Klebsiella spp.	5[f]	1			2	2	8	5	1	1	6	7	7	7
Enterobacter spp./C. freundii	4[f]			1		1	1	1	2	5	1	2	1	
E. coli								1			4	1	1	
Colistin													
Klebsiella spp.					36[f]	13				1	2			
Enterobacter spp./C. freundii					16[f]	3			1					
E. coli					6[f]	1								
Fosfomycin													
Klebsiella spp.							2[f]	2	7	5	9	10	7	10
Enterobacter spp./C. freundii							2[f]	3	3	4	4	3	1	
E. coli							5[f]	1	1					
Nitrofurantoin														
Klebsiella spp.								1[f]		2	1		9	35[g]
Enterobacter spp./C. freundii										1		4	4	11[g]
E. coli										2		1	3	2[g]
Minocycline														
Klebsiella spp.							3	10	22	10	6	1[g]		
Enterobacter spp./C. freundii							1	5	5	3	1	5[g]		
E. coli						1	1		3		1	1[g]		
Tigecycline														
Klebsiella spp.					6	15	22	9						
Enterobacter spp./C. freundii					1	9	5	3	2					
E. coli				1	3	3								

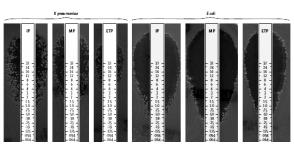
Can We Use Carbapenems ?

Carbapenemase-producing *Klebsiella pneumoniae:* (when) might we still consider treating with carbapenems?

G. L. Daikos[1] and A. Markogiannakis[2]

1) *First Department of Propaedeutic Medicine, University of Athens and 2) Department of Pharmacy, Lakan General Hospital, Athens, Greece*

Isolates with a meropenem MIC of ≤ 4 mg/L may be treatable with high dose prolonged infusions of meropenem



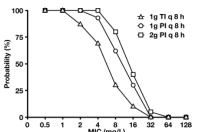


FIG. 2. Simulated target attainment probabilities for 50% time above the MIC (50% T > MIC) of three different regimens of meropenem. TI, traditional 30-min infusion; PI, prolonged 3-h infusion. Adapted from [36].

[1]Nordmann et al, 2009

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Possible Treatment Options From the Antibiogram

Most KPC producers sensitive to aminoglycosides
ST258 usually susceptible to gent – others only amikacin
16S methylases rare in these strains

Some MBL (IMP / VIM) producers sensitive to aztreonam
Mostly non-fermenters – Enterobacteria usually have co-resident ESBL ?

OXA-48 producers may be susceptible to cephalosporins
Mostly Enterobacteria and usually have co-resident ESBL ?

Most Enterobacteria and Acinetobacter *'sensitive'* to tigecycline

Almost all *'sensitive'* to polymyxins

Some NDM-1 producers resistant to all….

Tigecycline or Colistin ?

Experience with Tigecycline (TGC)

- Good in-vitro activity v most Carbapenem R Enterobacteria and MDRAB
- Bacteriostatic - Very low serum levels 0.8 mg/L

A review of clinical and microbiological outcomes following treatment of infections involving multidrug-resistant *Acinetobacter baumannii* with tigecycline

N. C. Gordon[1] and D. W. Wareham[1,2]*

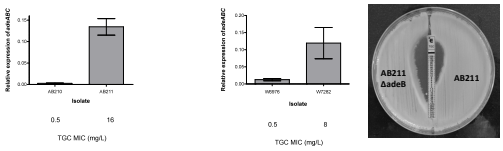
[1]*Division of Infection, Barts and The London NHS Trust, London, UK;* [2]*Centre for Infectious Disease, Institute of Cell and Molecular Science, Barts and The London, Queen Mary's School of Medicine and Dentistry, London, UK*

- Case series of infections involving MDRAB treated with tigecycline[1]
  - 68 % clinical response rate
  - 41 % overall mortality
  - Recurrent episodes of bacteraemia with development of frank resistance in 3 cases

Emergence of TGC resistance during TGC therapy

AdeABC-mediated efflux and tigecycline MICs for epidemic clones of *Acinetobacter baumannii*

Michael Hornsey[1a], Matthew J. Ellington[1b], Michel Doumith[1], Claire P. Thomas[2], Nicola C. Gordon[2], David W. Wareham[3], John Quinn[4,5], Karen Lolans[4], David M. Livermore[1] and Neil Woodford[1]



Rapid emergence of resistance due to overexpression of efflux pumps

Seen with *Enterobacter, Klebsiella, Serratia, …….*

Emergence of AcrAB-mediated tigecycline resistance in a clinical isolate of *Enterobacter cloacae* during ciprofloxacin treatment

Michael Hornsey[a,*], Matthew J. Ellington[a,1], Michel Doumith[a], Geoff Scott[b], David M. Livermore[a], Neil Woodford[a]

[a] *Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, London NW9 5EQ, UK*
[b] *University College London Hospitals, Windeyer Institute, London W1T 4JF, UK*

Tigecycline resistance in *Serratia marcescens* associated with up-regulation of the SdeXY-HasF efflux system also active against ciprofloxacin and cefpirome

Michael Hornsey[1*], Matthew J. Ellington[1§], Michel Doumith[1], Sue Hudson[2], David M. Livermore[1] and Neil Woodford[1]

[1]*Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK;* [2]*Gateshead Health NHS Foundation Trust, Queen Elizabeth Hospital, Sheriff Hill, Gateshead NE9 6SX, UK*

***Klebsiella pneumoniae*: development of a mixed population of carbapenem and tigecycline resistance during antimicrobial therapy in a kidney transplant patient**

C. Rodríguez-Avial[1], I. Rodríguez-Avial[2], P. Merino[1] and J. J. Picazo[1,2]

1) *Departamento de Microbiología, Facultad de Medicina, Universidad Complutense de Madrid, Madrid,* 2) *Servicio de Microbiología, Hospital Clínico San Carlos, Madrid, Spain*

Efficacy and safety of tigecycline: a systematic review and meta-analysis

Dafna Yahav[1,2]*, Adi Lador[1,2], Mical Paul[2,3] and Leonard Leibovici[2,3]

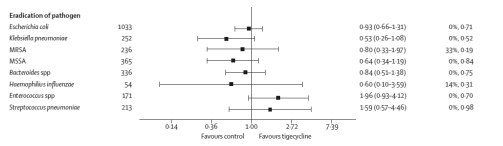
[1]*Department of Medicine E, Rabin Medical Center, Beilinson Hospital, Petah-Tiqva, Israel;* [2]*Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel;* [3]*Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital, Petah-Tiqva, Israel*

Conclusions: In the light of the increased mortality, probably explained by decreased clinical and microbiological efficacy, clinicians should avoid tigecycline monotherapy in the treatment of severe infections and reserve it as a last-resort drug.

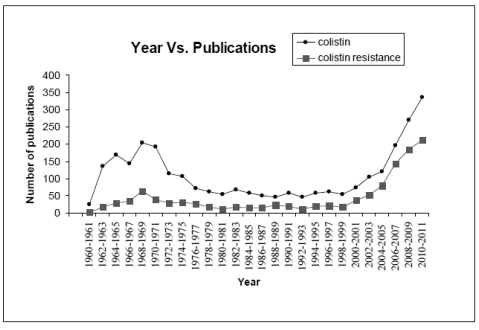
Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis

Efthimia Tasina, Anna-Bettina Haidich, Stamatia Kokkali, Malamatenia Arvanitidou

Interpretation Tigecycline is not better than standard antimicrobial agents for the treatment of serious infections. Our findings show that assessment with unpublished studies is needed to make appropriate decisions about new agents.



The Rebirth of Colistin ?



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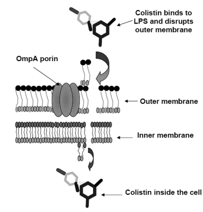
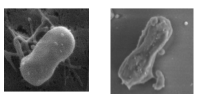
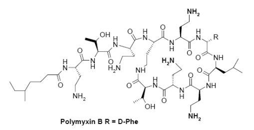
Colistin / Polymyxins

Unique Mode of Action





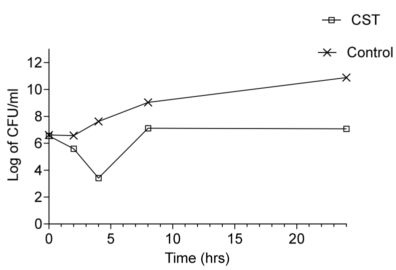
- *'How to carry out susceptibility testing ?'*
- *'Is colistin effective?'*
- *'Is colistin safe ?'*
- *'How should it be adminstered ?'*



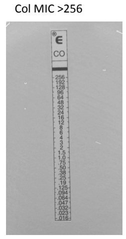
Colistin MIC breakpoints and Susceptibility Testing

- MIC determination highly method dependent
  - Poor diffusion in agar – compromises discs / Etests
  - Poor reproducibility in broth – adhesion to glass / plastic ?
  - Not evaluated with automated systems – Vitek, Phoenix, MicroScan
- Breakpoints: CLSI: ≤ 2 mg/L, EUCAST: < 4 mg
- No molecular target for PCR gold standard
- Time Kill methodology as gold standard ?

Colistin is not sufficiently bactericidal versus many GNRs



OXA-23 clone 1
Col MIC >256



Regrowth after 24 – 48 hrs in time kill assays at up to 32 x MIC[1]

[1]Li, AAC 2006

Heteroresistance to Colistin in Multidrug-Resistant *Acinetobacter baumannii*

Jian Li,[1]* Craig R. Rayner,[1] Roger L. Nation,[1] Roxanne J. Owen,[1] Denis Spelman,[2] Kar Eng Tan,[1] and Lisa Liolios[2]

Facility for Anti-infective Drug Development and Innovation, Victorian College of Pharmacy, Monash University, Parkville, Victoria, Australia,[1] and Department of Microbiology and Infectious Diseases Unit, Alfred Hospital, Melbourne, Victoria, Australia[2]

- A sub-population of bacteria recovered from growth of a 'susceptible' strain at colistin concentrations above breakpoint of 2mg/L[1]
- Also reported in *K. pneumoniae, P. aeruginosa* and *Enterobacter*

Colistin heteroresistance in carbapenemase-producing *Klebsiella pneumoniae*

Georgios Meletis[1]*, Egki Tzampaz[1], Effrosyni Sianou[1], Ioannis Tzavaras[2] and Danai Sofianou[1]

[1]*Department of Clinical Microbiology, Hippokration General Hospital, Thessaloniki, Greece;* [2]*3rd Army Veterinary Hospital, Thessaloniki, Greece*

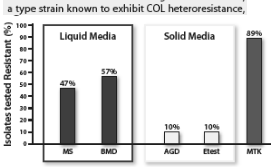
Table 1. Characteristics of the 20 *K. pneumoniae* isolates studied

Strain	Colistin treatment	Carbapenemase type	Broth MIC (mg/L)	Highest concentration of growth in PAPs (mg/L)	Proportion of resistant subpopulations	Resistant colonies MIC before daily passages onto colistin-free medium (mg/L)	Resistant colonies MIC after 2 week daily passages onto colistin-free medium (mg/L)	Susceptibility
1	yes	VIM-1	2	8	4.4×10^{-7}	16	16	heteroresistant
2	yes	VIM-1	2	8	8×10^{-7}	16	16	heteroresistant
9	no	VIM-1	1	8	4.1×10^{-7}	64	32	heteroresistant
3	yes	KPC	2	8	2.6×10^{-6}	32	32	heteroresistant
6	yes	KPC	1	8	1.7×10^{-5}	32	16	heteroresistant
12	no	KPC	1	8	1.5×10^{-5}	64	64	heteroresistant
17	no	KPC	1	8	1.2×10^{-6}	16	16	heteroresistant
18	no	KPC	1	8	2×10^{-6}	32	16	heteroresistant
19	no	KPC	1	8	3.6×10^{-7}	16	16	heteroresistant
8	yes	KPC	1	8	3.5×10^{-5}	4	1	heteroresistant
5	yes	KPC	4	8	NA	NA	NA	resistant
7	yes	KPC	4	8	NA	NA	NA	resistant
13	no	VIM-1	4	8	NA	NA	NA	resistant
10	no	VIM-1	2	8	3.2×10^{-7}	32	32	heteroresistant
20	no	VIM-1	2	8	4.2×10^{-7}	16	16	heteroresistant
4	yes	KPC	4	8	NA	NA	NA	resistant
11	no	KPC	0.5	0.5	NA	NA	NA	susceptible
14	no	KPC	0.5	0.5	NA	NA	NA	susceptible
15	no	KPC	0.5	0.5	NA	NA	NA	susceptible
16	no	VIM-1	0.5	0.5	NA	NA	NA	susceptible

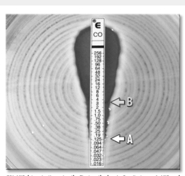
Susceptibility of Multi-drug Resistant Strains of *Acinetobacter baumannii* to Colistin: A Comparison of Disk Diffusion, Agar Dilution, Etest, Broth Microtitre Dilution, Automated and Time-kill methodologies

L Phee [1,2], Hornsey M [2], Wareham DW [1,2]

Acinetobacter baumannii isolates consisted of the ATCC 19606 type strain and 28 multi-drug resistant (MDR) clinical isolates. *Pseudomonas aeruginosa* ATCC 27853, a type strain known to exhibit COL heteroresistance,



MTK = Modified Time-kill, MS = MicroScan WalkAway, BMD = Broth Microtitre Dilution, AGD = Agar Dilution,



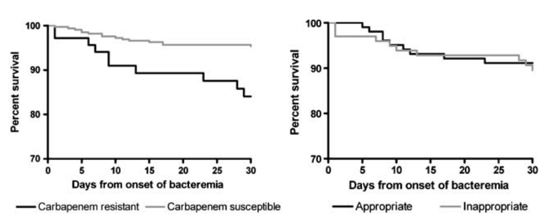
COL MIC determination using the Etest method on IsoSensitest agar. A: MIC read as per manufacturer's guidelines (bioMérieux). B: Suggested MIC reading by extrapolated ellipse method

The most sensitive method for detecting resistance was MTK – only 3 isolates (including Acinetobacter baumannii (AB) type ATCC 19606) showed >3 log reduction in colony counts at 24h.

Does Colistin work ?

Retrospective cohort study of 399 *Acinetobacter* spp bacteraemia (MDRAB n=78)

Impact of carbapenem R, colistin Rx (1 mu 8 hrly)



78 MDRAB

[1]Wareham, EJCMID 2008

MDRGN – Treatment Options and Challenges
Dr David Wareham, Queen Mary Universitys, UK
Broadcast live from the HIS/FIS conjoint conference www.hisconference.org.uk

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doi:10.1093/jac/dkq069 Advance publication 18 March 2010

Journal of Antimicrobial Chemotherapy

Effectiveness and safety of colistin: prospective comparative cohort study

Micol Paul[1,2]*, Jihad Bishara[1,2], Ariela Levcovich[1,2], Michal Chowers[2,3], Elad Goldberg[1,2], Pierre Singer[2,4], Shaul Lev[2,4], Perla Leon[5], Maria Roskin[1,2], Dafna Yahav[2,6] and Leonard Leibovici[2,6]

[1]Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; [2]Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [3]Unit of Infectious Diseases, Meir Medical Center, Kfar Saba, Israel; [4]Intensive Care Unit, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; [5]Department of Anesthesiology, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; [6]Department of Medicine E, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel

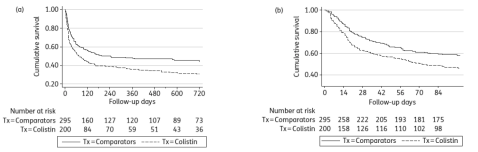


Figure 1. Kaplan–Meier survival analysis, by study arm. (a) Two years of follow-up. (b) Three months of follow-up.

Conclusions: The need for colistin treatment is associated with poorer survival. Adjusted analyses suggest that colistin is less effective and more toxic than β-lactam antibiotics.

Is Colistin safe ?

Research Open Access

Toxicity of polymyxins: a systematic review of the evidence from old and recent studies

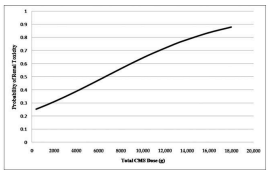
Matthew E Falagas[1,2,3] and Sofia K Kasiakou[1]

- Nephrotoxicty ?

Conclusion New evidence shows that polymyxins have less toxicity than previously reported. The avoidance of concurrent administration of nephrotoxic and/or neurotoxic drugs, careful dosing, as well as more meticulous management of fluid and electrolyte abnormalities and use of critical care services may be some of the reasons for the discrepancy between data reported in the old and recent literature.

Nephrotoxicity Associated with Intravenous Colistin (Colistimethate Sodium) Treatment at a Tertiary Care Medical Center

Joshua D. Hartzell,[1] Robert Neff,[2] Julie Ake,[1] Robin Howard,[2] Stephen Olson,[2] Kristopher Paolino,[1] Mark Vishnepolsky,[2] Amy Weintrob,[1] and Glenn Wortmann[1]



- Neurotoxocity
  - Neuromuscular blockade
  - Paraathesia
  - Confusion / Seizures

Rare to non-existent with modern use

How should we administer colistin ?

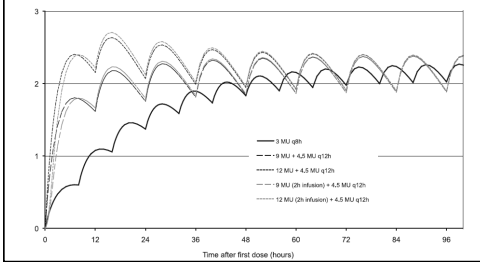
BNF October 2012

NHS National Institute for Health and Clinical Excellence

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

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

- Colistin Methanesulfonate Sodium 1- 2 million units / 8 hrly ?



Colistin Dosage Recommendations

Population Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in Critically Ill Patients from a Multicenter Study Provide Dosing Suggestions for Various Categories of Patients†

S. M. Garonzik,[1] J. Li,[2] V. Thamlikitkul,[3] D. L. Paterson,[4] S. Shoham,[5] J. Jacob,[5] F. P. Silveira,[5] A. Forrest,[5] and R. L. Nation[1]*

Patient category	Dose (mIU) to target or Css, avg 2 mg/\L
	Loading dose
All patients	**BW* (kg) / 7.5** (max 10)
	Maintenance dose
Not on renal replacement	**(C_{Cr}/10)+2** in 2-3 doses 1st dose 24 h after loading dose
Intermittent hemodialysis	**2** (in two doses) + 30% on the day of hemodialysis after session
Continuous renal replacement	**12** In 2-3 doses

*1 million IU of CMS ~ 30 mg of CBA ~ 80 mg of CMS
**Lower of ideal or actual body weight in kg

Garonzik SM et al. AAC 2011 (modified)

Combination Treatments for MDR, XDR and PDR strains ?

- Numerous *In-vitro* studies of colistin containing combinations
  - Polymyxin B + imipenem + rifampicin – Synergy
  - Colistin + rifampicin – Synergy
  - Colistin + minocycline – Synergy
  - Colistin + ceftazidime – Synergy
  - Polymyxin B + meropenem / rifampicin azithromycin – Synergy
- In-vivo studies of colistin containing combinations
  - Colistin + rifampicin – effective in mouse pneumonia and rat model
- Case reports
  - Colistin + rifampicin – 'favourable response'

Treatment Outcome of Bacteremia Due to KPC-Producing *Klebsiella pneumoniae*: Superiority of Combination Antimicrobial Regimens

Zubair A. Qureshi,[a] David L. Paterson,[a,b] Brian A. Potoski,[a,c] Mary C. Kilayko,[d] Gabriel Sandovsky,[d] Emilia Sordillo,[d,e] Bruce Polsky,[d,e] Jennifer M. Adams-Haduch,[a] and Yohei Doi[a]

Division of Infectious Diseases,[a] Department of Pharmacy,[c] University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA; University of Queensland UQ Centre for Clinical Research and Royal Brisbane and Women's Hospital, Brisbane, Australia[b]; and Divisions of Infectious Diseases and Epidemiology,[d] Department of Pathology,[e] St. Luke's-Roosevelt Hospital Center, New York, New York, USA

TABLE 3 Definitive antimicrobial therapy and mortality in 17 patients who received combination therapy and 19 patients who received monotherapy

Definitive treatment	*n* (%)	Mortality *n* (%)
Combination therapy	15 (44)	2 (13.3)
Colistin–polymyxin B combined with:		
Carbapenem	5 (33)	1 (20)
Tigecycline	1 (7)	0
Fluoroquinolone	1 (7)	0
Tigecycline combined with:		
Carbapenem	3 (20)	0
Aminoglycoside	2 (12)	0
Carbapenem-fluoroquinolone	1 (7)	1 (100)
Aztreonam-fluoroquinolone	1 (7)	0
Cefepime-gentamicin	1 (7)	0
Monotherapy	19 (46)	11 (57.8)
Colistin–polymyxin B	7 (36.8)	4 (57.1)
Tigecycline	5 (26.3)	4 (80)
Carbapenem	4 (21)	2 (50)
Gentamicin	1 5.2)	0
Ampicillin-sulbactam	1 (5.2)	0
Piperacillin-tazobactam	1 (5.2)	1 (100)
Total	34 (83)	13 (38.2)

Combination treatment superior
Best combinations
Colistin with tigecycline
Colistin with carbapenems

In conclusion, mortality associated with bacteremia due to KPC-producing *K. pneumoniae* continues to be high. The use of a combination therapy, in particular with either colistin–polymyxin B or tigecycline and a carbapenem, seems to have a survival benefit in this critically ill population.

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In-vitro 'Synergy'

- Multiple methods
  - Checkerboards / Etest / Time Kill
- 'Synergy' by established criteria
  - Fractional Inhibitory concentration index ≤ 0.5

(MIC of A in combination with B / MIC A alone)
+
(MIC of B in combination with A / MIC of B alone)

- Susceptible Breakpoint Index (SBPI) as a better parameter ?[1]

(Susceptible Breakpoint of A / MIC of A in combination with B)
+
(Susceptible Breakpoint of B / MIC of B in combination with A)

- SBPI >2 = clinically relevant synergy

[1]Milne and Gould, JAC 2010

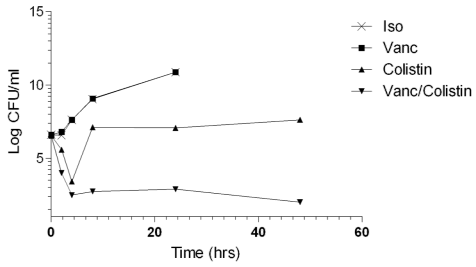
Colistin Combined with Vancomycin

- Potent synergy when colistin is combined with vancomycin
- Vancomycin combined with colistin prevents re-growth of A. baumannii in time-kill assays[1]

OXA-23 clone 1 vanc MICs

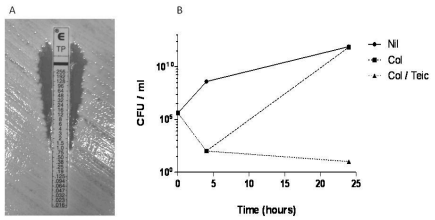
+ colistin 0.5 x MIC

Time Kill Kinetics of Vancomycin 20 mg/L and Colistin 1 mg/L v MDRAB[1]



[1] Gordon & Wareham AAC 2010

Effective with other glycopeptides

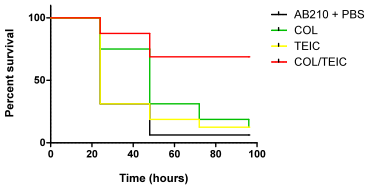


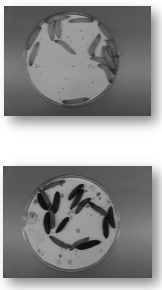
Telavancin , daptomycin..... But very species dependent – lack of target ?

Colistin / Glycopeptide combinations in-vivo

Galleria mellonella infection model

'Treated' with human mg/kg doses





[1]Hornsey & Wareham AAC 2011

'How to Use Colistin Combinations: A Case… ?'

- 66 yr M admitted ITU with acute renal failure following failed TURP
  - Obstructive nephropathy due to BPH – dialysis dependent
- 44 days in ICU
  - 3 courses of antibiotics – aug / taz / imp
  - Colonised with MDRAB day 27
- Discharged with Ureteric MemoKath and JJ stent –
  - Urine sample cultured MDRAB
- Gradual decline in renal function over 18 months
  - Urine persistently cultures MDRAB
  - MemoKath changed twice – colistin 1 MU given as prophylaxis
  - Dialysis dependent – MDRAB cultured X 4

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Antibiogram of *A. baumannii* OXA-23 clone 1

Amoxicillin	R	>256
Co-Amoxiclav	R	>256
Cefuroxime	R	>256
Gentamicin	R	>64
Piperacillin/Tazobactam	R	>256
Ciprofloxacin	R	>256
Ceftazidime	R	>256
Amikacin	R	>64
Aztreonam	R	>256
Imipenem	R	>32
Trimethoprim	R	>256
Meropenem	R	>32
Minocycline	R	>32
Sulbactam	R	>32
Tobramycin	R	>64
Tigecycline	I	2
Colistin	S	0.38

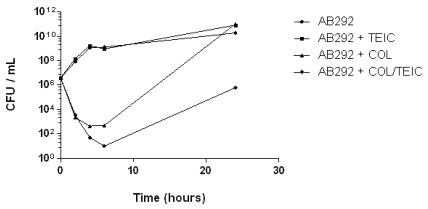
'How to Use Colistin Combinations: A Case… ?'

- Month 22….. Change of MemoKath urine still +ve for MDRAB
  - Col MIC – MicroScan > 4, Etest 0.38, broth microtitre 16 mg/L
- Decision to try colistin / glycopeptide combination therapy
  - Synergy studies (checkerboards)
  - Col / Teic FICI - 0.062 SBPI - 4.1
  - Col / Vanc FICI - 0.78 SBPI – 2.5
- Dosing regimen optimised according to Garonzik protocol

Antimicrobial	Dose of drug			
	Day 1 (Loading)	Day 2	Day 3	With each dialysis session (3x/wk)
Colistin	7.5 mu	1 mu am / 1.3 mu pm	1 mu BD	1 mu am / 1.3 mu pm
Teicoplanin	400mg BD	400mg OD	400mg OD	400mg OD

'How to Use Colistin Combinations: A Case… ?'

- Treatment continued for 9 days
- Pre-dialysis colistin trough levels – 1.3 – 3.1 mg/L
- Teicoplanin trough levels – 15 – 22 mg/L
- Time kill with Col 2 mg/L / Teic 20 mg/L



- Urine samples 2 x week for 3 weeks – negative for MDRAB

Anything New Coming ?'

- New β-lactam inhibitors
  - Avibactam (NXL 104) – Astra-Zeneca
  - MK-7655 - Merck +/- imipenem
- Siderophore monobactams - subvert efflux and porin lesions ?
  - BAL30072 – Basilea +/- meropenem
  - MC-1 – Pfizer
- Neoglycosides
  - 'next generation' aminoglycosides but not v 16s methylases...
  - Plazomcin (ACHN-490) - Achaogen
- 'Next generation' polymyxins
  - NAB 739 – Northern Antibiotics
- Lpx inhibitors – LPS biosynthesis inhibitors
  - Lpx-C1 - Pfizer
- To be used alone or in combinations ?

Summary

- Cephalosporin resistant and ESBL producing *Enterobacteriaceae*
  - Severe infections – bacteraemia / sepsis / VAP
    - Carbapenems
    - Possibly BLICs or temocillin
  - Other infections – based on antibiogram
    - BLICs
    - Nitrofurantoin
    - Trimethoprim
- Carbapenem resistant Gram-negatives
  - Aminoglycosides if susceptible
  - Colistin – (correctly dosed) +/- rifampcin
  - High dose carbapenems +/- colistin
- 'XDR' and 'Pan-drug' – resistant Gram-negatives
  - Cocktails based on MIC and in-vitro synergy studies ?
  - Colistin +/- rifampicin / carbapenems / tigecycline / glycopeptides ?

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