MANAGEMENT OF DRUG RESISTANT INFECTIONS IN ICU

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22.01.21

OVERVIEW

- Current definition of drug resistance
- Various aspects related to P. aeruginosa
- Novel antipseudomonal drugs
- Various aspects related to Acinetobacter baumanni and Enterobacteriaceae
- Continuous infusion of Meropenem
- Pharmacokinetic issues of Colistin
- Rationale for change in cut off for Colistin sensitivity by CLSI
- Minocycline for MDR Acinetobacter
- Propylactic Use of Mupirocin

ANTIMICROBIAL-RESISTANT PHENOTYPE DEFINITIONS

- Extended-spectrum cephalosporin-resistant E. coli

Any Escherichia coli that has tested Intermediate (I) or Resistant (R) to atleast 1 of the following: cefepime, ceftriaxone, cefotaxime, or ceftazidime

- Carbapenem-resistant Enterobacteriaceae

Any Escherichia coli, Klebsiella aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae, or Enterobacter spp. that has tested Resistant (R) to at least 1 of the following: imipenem, meropenem, doripenem, or ertapenem

FROM CDC OFFICIAL SITE

RICU DATA 2018-2019

ORGANISMS CAUSING HAIs IN RICU 2018-19

	Respiratory secretions	Blood culture	Pleural fluid	Skin and soft tissue infection
	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)
Acinetobacter baumannii	**105 (43.4)**	31 (19.1)	**3 (20.0)**	10 (27.0)
Pseudomonas aeruginosa	56 (23.1)	16 (9.9)	1 (6.7)	2 (5.4)
Klebsiella pneumoniae	39 (16.1)	17 (10.5)	**3 (20.0)**	7 (18.9)
Staphylococcus aureus	19 (7.9)	20 (12.3)	**3 (20.0)**	12 (32.4)
Other *Staphylococcus spp. (CONS)*	-	**38 (23.5)**	1 (6.7)	
Escherichia coli	7 (2.9)	15 (9.3)	1 (6.7)	4 (10.8)
Other *Acinetobacter spp*	4 (1.7)	1 (0.6)	-	-
Serratia marcenses	4 (1.7)	1 (0.6)	-	-
Burkholderia cephacia	2 (0.8)	4 (2.5)	-	-
Candida	-	5 (3.1)	-	-
Enterococcus faecium	-	5 (3.1)	2 (13.3)	1 (2.7)
Enterobacter cloacae	2 (0.8)	-	1 (6.7)	-
Others	4 (1.7)	9 (5.6)	-	1 (2.7)
Total	242 (100)	162 (100)	15 (100)	37 (100)

	Urine	Genital tract	Intrabdominal drain
	Frequency (%)	Frequency (%)	Frequency (%)
Escherichia coli	22 (47.8)	**4 (50.0)**	2 (66.7)
Enterococcus faecium	10 (21.7)	2 (25.0)	1 (33.3)
Klebsiella pneumoniae	7 (15.2)	1 (12.5)	
Acinetobacter baumannii	3 (6.5)	1 (12.5)	
Pseudomonas aeruginosa	1 (2.2)		
Others	3 (6.5)		
Total	46 (100)	8 (100)	3 (100)

COURTESY – Dr. DEEPA SHRESTHA

SENSITIVITY PATTERN OF ORGANISM ISOLATED 2018-19

- ACB (n = 153)

- MDR 93.46%
- XDR 3.9%
- PDR 0.65%.
- PAN SENSITIVE 1.96%

Antibiotics	Sensitive (%)	Intermediate (%)	Resistant No. (%)	Data not available (%)
Ceftazidime	1 (0.7)	1 (0.7)	139 (90.8)	12 (7.84)
Cefepime	1 (0.7)	1 (0.7)	144 (94.11)	7 (4.57)
Cefoperazone+ Sulbactum	17 (11.1)	24 (15.7)	108 (70.58)	4 (2.61)
Piperacillin+ Tazobactum	3 (2.0)	1 (0.7)	147 (96.07)	2 (1.30)
Amikacin	7 (4.6)	2 (1.3)	65 (42.48)	79 (51.63)
Gentamicin	4 (2.6)	1 (0.7)	50 (32.7)	98 (64.1)
Ciprofloxacin	3 (2.0)	1 (0.7)	146 (95.42)	3 (1.96)
Levofloxacin	3 (2.0)	5 (3.3)	110 (71.89)	35 (22.87)
Imipenem	3 (2.0)	1 (0.7)	145 (94.77)	4 (2.61)
Meropenem	3 (2.0)	1 (0.7)	104 (67.97)	45 (29.41)
Colistin	134 (87.58)	-	6 (3.9)	13 (8.49)
Minocycline	64 (41.8)	26 (17.0)	47 (30.7)	16 (10.5)
Tigecycline	56 (36.6)	12 (7.8)	18 (11.8)	67 (43.8)

COURTESY – Dr. DEEPA SHRESTHA

SENSITIVITY PATTERN OF ORGANISM ISOLATED 2018-19

- Pseudomonas (n=76)

- MDR 26.3%
- XDR 1.31%
- Pansensitive 72.3%

Antibiotics	Sensitive (%)	Intermediate (%)	Resistant No. (%)	Data not available (%)
Ceftazidime	53 (69.7)	4 (5.3)	17 (22.4)	2 (2.6)
Cefepime	32 (42.1)	6 (7.9)	14 (18.4)	24 (31.6)
Cefoperazone+ Sulbactum	34 (44.7)	4 (5.3)	9 (11.8)	29 (38.2)
Piperacillin+ Tazobactum	51 (67.1)	9 (11.8)	7 (9.2)	9 (11.8)
Amikacin	58 (76.3)	3 (3.9)	12 (15.8)	3 (3.9)
Gentamicin	39 (51.3)	1 (1.3)	8 (10.5)	28 (36.8)
Ciprofloxacin	50 (65.8)	1 (1.3)	20 (26.3)	5 (6.6)
Levofloxacin	44 (57.9)	4 (5.3)	17 (22.4)	11 (14.5)
Imipenem	51 (67.1)	-	20 (26.3)	5 (6.6)
Meropenem	25 (32.9)	2 (2.6)	14 (18.4)	35 (46.1)
Colistin	29 (38.2)	-	2 (2.6)	45 (59.2)
Tigecycline	3 (3.9)	1 (1.3)	18 (23.7)	54 (71.1)

COURTESY – Dr. DEEPA SHRESTHA

SENSITIVITY PATTERN OF ORGANISM ISOLATED 2018-19

- Klebsiella (n= 74)

- MDR 64.86%
- PDR 5.41%
- Pansensitive 29.73%

Antibiotics	Sensitive (%)	Intermediate (%)	Resistant No. (%)	Data not available (%)
Cefotaxime	5 (6.8)	1 (1.4)	28 (37.8)	40 (54.1)
Ceftazidime	6 (8.1)	3 (4.1)	29 (39.2)	36 (48.6)
Cefepime	16 (21.9)	3 (4.1)	43 (58.1)	12 (16.2)
Cefoperazone+ Sulbactum	20 (27.0)	-	46 (62.2)	8 (10.8)
Piperacillin+ Tazobactum	21 (28.4)	1 (1.4)	52 (70.3)	-
Amikacin	28 (37.8)	1 (1.4)	39 (52.7)	6 (8.1)
Gentamicin	6 (8.1)	5 (6.8)	6 (8.1)	57 (77)
Ciprofloxacin	16 (21.6)	9 (12.2)	44 (59.5)	5 (6.8)
Imipenem	27 (36.5)	9 (12.2)	36 (48.6)	2 (2.7)
Meropenem	15 (20.3)	-	33 (44.6)	26 (35.1)
Ertapenem	14 (18.9)	1 (1.4)	14 (18.9)	45 (60.8)
Colistin	43 (58.1)	1 (1.4)	4 (5.4)	26 (35.1)
Minocycline	8 (10.8)	3 (4.1)	17 (23.0)	46 (62.2)
Tigecycline	19 (25.7)	2 (2.7)	1 (1.4)	52 (70.3)

COURTESY – Dr. DEEPA SHRESTHA

SENSITIVITY PATTERN OF ORGANISM ISOLATED 2018-19

- E. coli (n=55)
- MDR 69.09%
- PDR 2%
- Pan-sensitive 29%

Antibiotics	Sensitive (%)	Intermediate (%)	Resistant No. (%)	Data not available (%)
Cefotaxime	1 (1.8)	-	22 (40.0)	32 (58.2)
Ceftazidime	1 (1.8)	1 (1.8)	16 (29.09)	37 (67.27)
Cefepime	6 (10.9)	-	24 (43.64)	25 (45.45)
Cefoperazone+ Sulbactum	18 (32.7)	9 (16.4)	19 (34.5)	9 (16.4)
Piperacillin+ Tazobactum	14 (25.5)	6 (10.9)	28 (50.90)	7 (12.72)
Amikacin	41 (74.54)	-	10 (18.2)	4 (7.27)
Gentamicin	11 (20.0)	-	13 (23.6)	31 (56.4)
Ciprofloxacin	2 (3.6)	-	49 (89.09)	4 (7.27)
Nalidixic acid	1 (1.9)	-	20 (37.0)	33 (61.1)
Imipenem	31 (56.4)	4 (7.3)	14 (25.5)	6(10.9)
Meropenem	18 (32.7)	-	11 (20.0)	26 (47.3)
Ertapenem	23 (41.8)	1 (1.8)	7 (12.7)	24 (43.6)
Cotrimoxazole	1 (1.8)	-	20 (36.4)	34 (61.8)
Colistin	27 (49.1)	-	2 (3.6)	26 (47.3)
Tigecycline	14 (25.5)	-	-	41 (74.5)
Nitrofurantoin	11 (20.0)	4 (7.3)	5 (9.1)	35 (63.6)

COURTESY – Dr. DEEPA SHRESTHA

PSEUDOMONAS AERUGINOSA

Review

β-Lactam plus aminoglycoside or fluoroquinolone combination versus β-lactam monotherapy for *Pseudomonas aeruginosa* infections: A meta-analysis

Vardakas et. al.

- Till April 2012
- Nineteen articles (8 RCTs), 1721 patients

RESULTS:

- Patients receiving combination therapy no difference in mortality compared with b lactam monotherapy as definitive (risk ratio = 0.97, 95% CI 0.77-1.22) or as empirical treatment (1.02, 0.78-1.34)
- In definitive treatment group, no difference in mortality between combination and monotherapy for patients with bacteraemia (0.95, 0.67-1.34) or severe infections (0.96, 0.75-1.24)

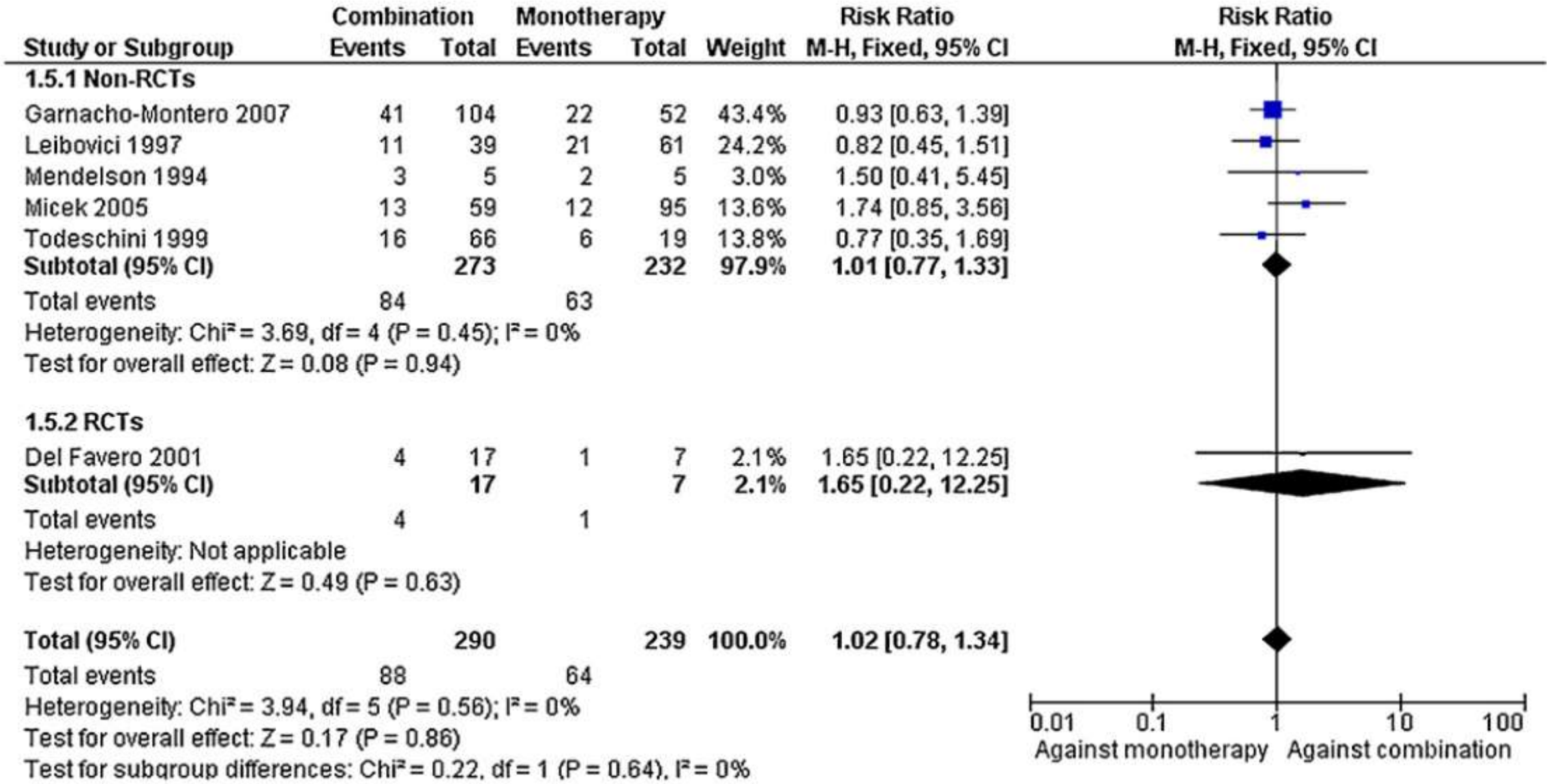
Vardakas et al. International Journal of Antimicrobial Agents 2013

- Patients receiving definitive combination therapy non significantly higher clinical cure compared with patients receiving beta lactam monotherapy (**1.36, 0.99-1.86**)
- Higher clinical cure rate for patients receiving empirical treatment with combination therapy (1.23, 1.05-1.43)
- No difference in clinical cure either for RCTs (1.29, 0.91-1.83) or for non randomized studies (1.18, 0.97-1.45)

CONCLUSION-

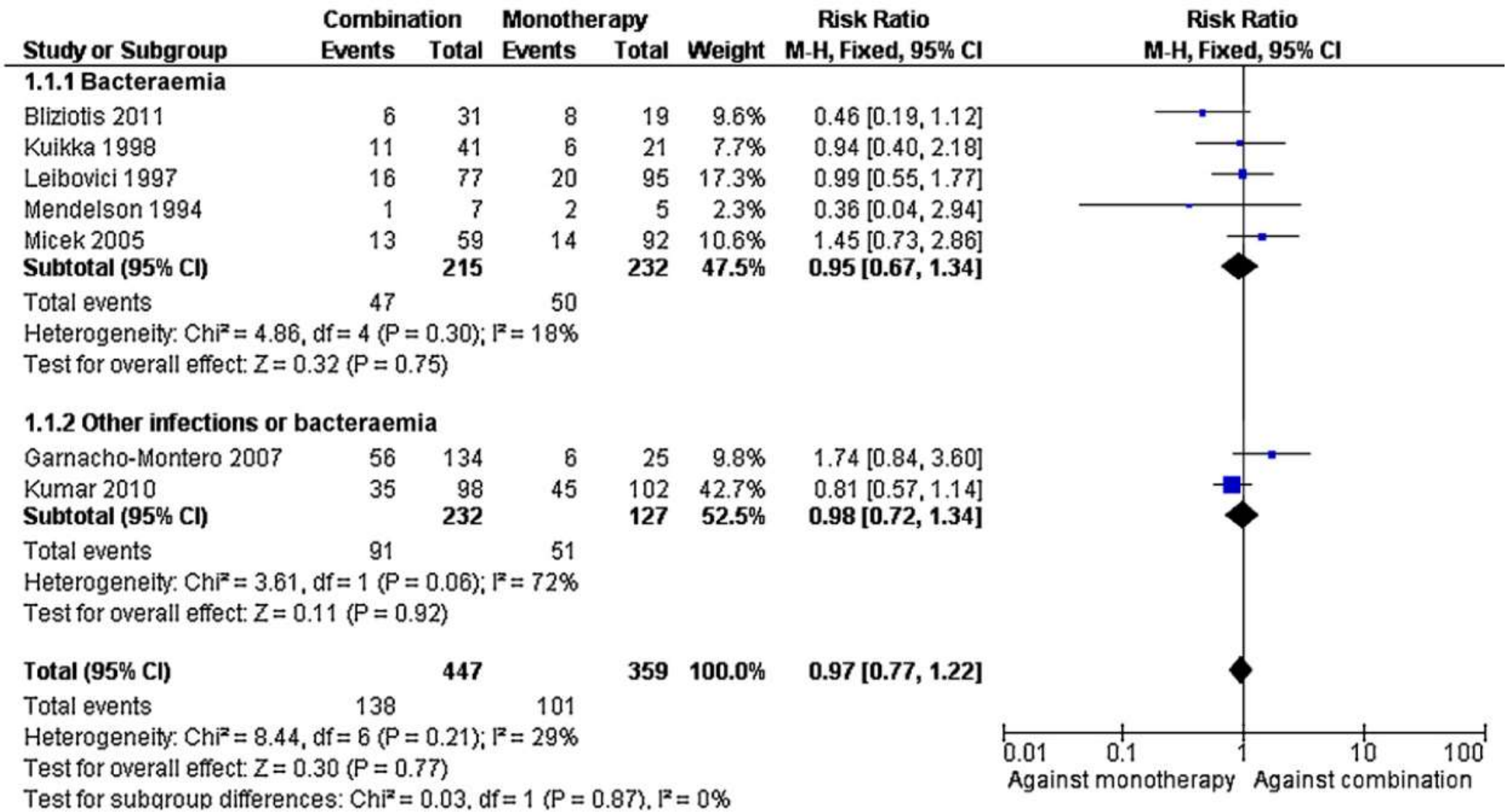
No benefit in mortality in patients receiving combination therapy for P.aeruginosa infections

Vardakas et al. International Journal of Antimicrobial Agents 2013



Forest plot depicting the risk ratios of all-cause mortality of patients with Pseudomonas aeruginosa infections treated empirically with beta-lactam/aminoglycoside or fluoroquinolone combination versus beta-lactam monotherapy

Vardakas et al. International Journal of Antimicrobial Agents 2013



Risk ratios of all-cause mortality of patients with Pseudomonas aeruginosa infections treated definitively with -lactam/aminoglycoside or fluoroquinolone combination versus -lactam monotherapy

Vardakas et al. International Journal of Antimicrobial Agents 2013

RESEARCH ARTICLE

Combination therapy for treatment of *Pseudomonas aeruginosa* bloodstream infections

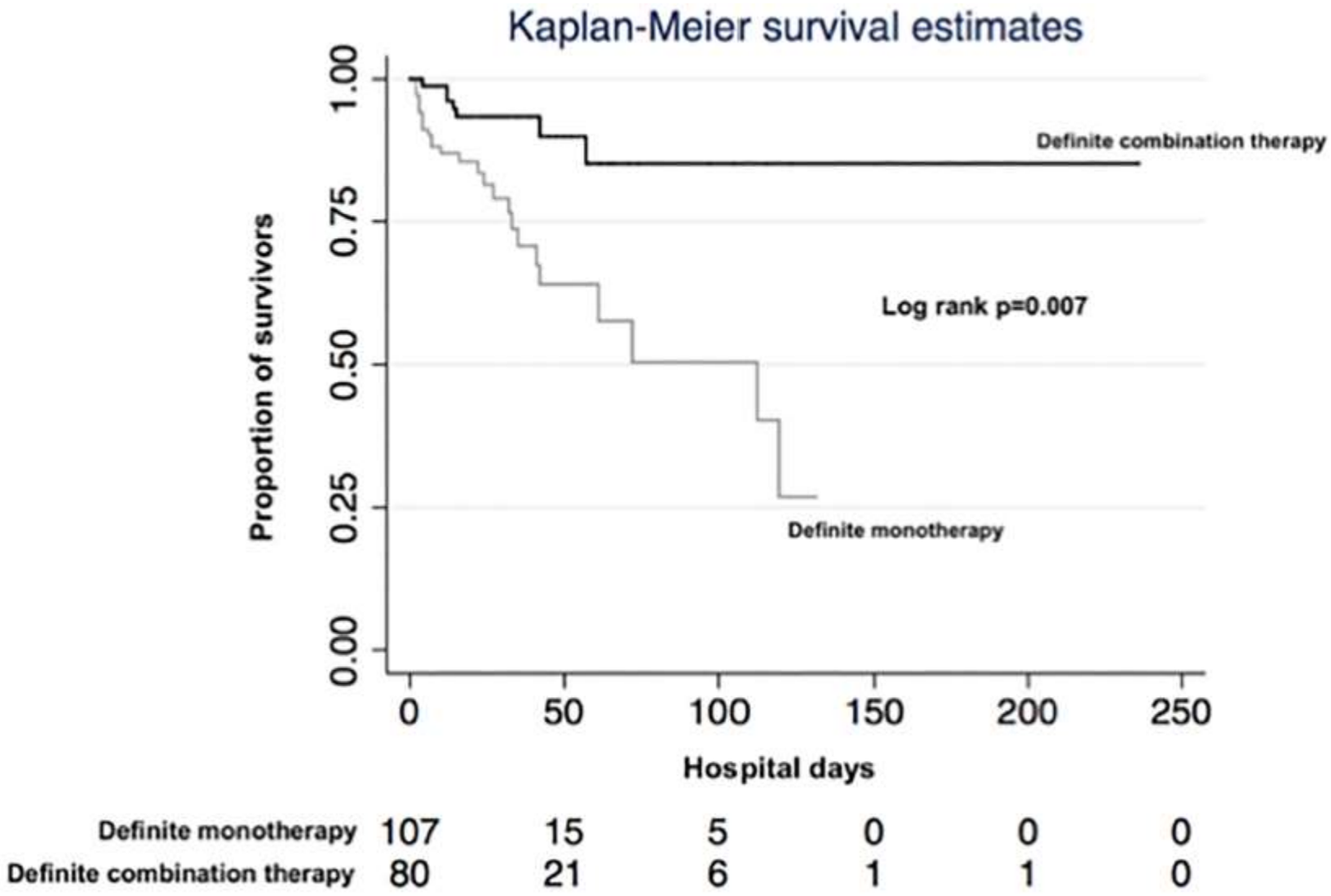
Sutter et.al.

- Prospective study from January 2003 to December 2013
- Cohort – 187 patients
- Definitive combination therapy in 42.8% (80/187) of all patients, 76% (61/80) received combination (beta lactam and aminoglycosides) and 24% (19/80) received betalactam and quinolone
- Remaining 52.7% (107/187) treated with betalactam monotherapy

RESULTS:

Mortality lower in patients receiving definite combination therapy in univariable and multivariable cox regression analysis (HR 0.26, 95% CI 0.11- 0.6, p=0.002 and HR 0.3, 95% CI 0.13-0.7, p=0.006 respectively) adjusted for age, neutropenia at diagnosis, PITT bacteremia score, and inadequate empirical treatment

Sutter et.al. PLoS ONE



Sutter et.al. PLoS ONE 2018

Duration of Exposure to Antipseudomonal β-Lactam Antibiotics in the Critically Ill and Development of New Resistance

Teshome et. al.

- Retrospective study
- COHORT – 7118 adults with discharge diagnosis of severe sepsis and septic shock who received atleast 1 dose of cefepime, meropenem or piperacillin-tazobactam between 2010-2015
- PLAN – Entry defined as first day of any antipseudomonal initiation and exposure as cumulative days of antipseudomonal beta-lactam exposure during 60 days of follow up
- RESULTS – Each additional day of any antipseudomonal beta lactam resulted in adjusted hazard ratio of 1.04 (95% CI 1.04-1.05) for new resistance development

Teshome et.al. Pharmacotherapy Mar 2019

Duration of Exposure to Antipseudomonal β-Lactam Antibiotics in the Critically Ill and Development of New Resistance

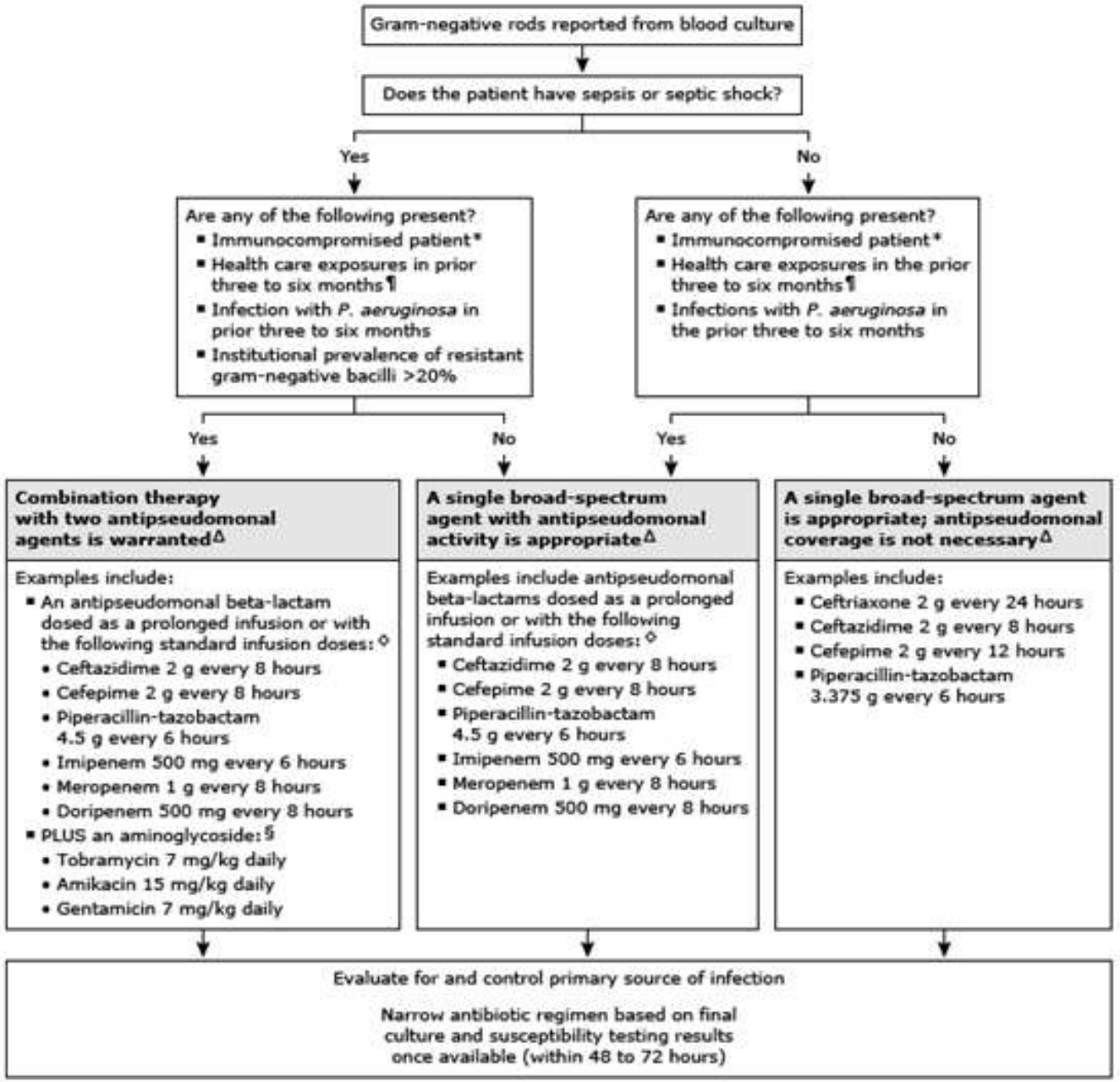
Teshome et. al.

- Risk of developing new resistance to cefepime, meropenem and pipaercillin-tazobactam for each additional day of exposure resulted in HR of 1.08 (95% CI 1.07-1.09), 1.02 (95% CI 1.01-1.03) and 1.08 (95% CI 1.06-1.09) respectively

- CONCLUSION – Among critically ill patients each additional day of exposure to cefepime, meropenem and piperacillin-tazobactam associated with increased risk of new resistance development

Teshome et.al. Pharmacotherapy Mar 2019

Algorithm for empiric antimicrobial selection for gram-negative bacillary bacteremia



AMINOGLYCOSIDES

- Active against P. aeruginosa but not used as single agent because of inadequate clinical efficiency at most sites (except lower UTI)
- Not to be used as monotherapy for pneumonia because they perform poorly in acidic environment
- Use as monotherapy for bacteremia associated with high mortality rates
- Tobramycin over gentamicin because of greater intrinsic antipseudomonal activity

Antimicrobial combination treatment including ciprofloxacin decreased the mortality rate of *Pseudomonas aeruginosa* bacteraemia: a retrospective cohort study

Paulsson et.al.

- Cases pf P. aeruginosa bacteremia (n=292)
- Retrospective study from Sweden

RESULTS:

- No difference in mortality between empiric monotherapy or combination therapy
- Definitive combination therapy including ciprofloxacin correlated to lower mortality than monotherapy (p=0.006) whereas combinations including tobramycin did not

CONCLUSION:

P. Bacteraemia to be treated with antimicrobial combination including ciprofloxacin when susceptible

Paulsson et.al. Eur J Clin Microbiol Infect Dis 2017

NOVEL ANTIPSEUDOMONAL DRUGS

- Beta lactam – beta lactamase inhibitor combinations:
- Ceftolozane-tazobactam
- Ceftazidime-avibactam

- Novel cephalosporins:
- Cefiderocol – siderophore cephalosporin – only for UTI

- Novel carbapenem-beta-lactamase combination-
- Imipenem-cilastin-relebactam

CEFTAZIDIME/AVIBACTAM

- Broad gram negative activity including Enterobacteriaceae and P. aeruginosa
- Avibactam additionally protects against class A (TEM, SHV, CTX-M, KPC), class C (Amp C) and some class D (OXA) beta lactamases
- No inhibitory activity against MBLs (NDM-1, IMP and VIM)
- First BL/BLI combination to retain activity against KPC-2 carbapanemase producing and most OXA-48 carbapenemase producing strains
- Minimal activity against Acinetobacter spp, anaerobic or gram-positive organisms

Sader et. al. Antimicrob Agents Chemother 2015

CURRENT STATUS

- Ceftazidime/avibactam similar efficacy to carbapenems in abdominal and complicated UTI, the former requiring combination of ceftazidime/avibactam with metronidazole

Sader et. al. Antimicrob Agents Chemother 2015

CEFTOLOZANE/TAZOBACTAM

- Oxyimino-cephalosporin
- Active against gram negative organisms including enterobacteriaceae and

  P. aeruginosa
- Most active against P. aeruginosa, with resistance confined to MBLs and unusual ESBLs (VEB and GES)
- Caution on clinical outcome necessary because of the potential, as with ceftazidime/avibactam for superinfection with C. difficile

Sader et.al. J Infect 2014

CURRENT STATUS

- Use ceftolozane/tazobactam to treat susceptible P. aeruginosa infections resistant to ceftazidime
- Use ceftolozane/tazobactam (alternative to carbapenems) to treat urinary or intra-abdominal infection involving ESBL producing E. coli
- Can offer clinical advantages where MDR Pseudomonas infections are problem, such as in cystic fibrosis
- Caution needed treating infection due to ESBL-producing Klebsiella spp. owing to a higher resistance rate

Hawkey et. al. J Antimicrob Chemother 2018

- Relebactam in combination with imipenem/cilastatin is entering Phase 3 trials with trials against imipenem-resistant bacteria compared with a combination of colistin and imipenem/cilastatin and a comparative study against piperacillin/tazobactam in ventilator-associated pneumonia

Lapuebla A, Antimicrob Agents Chemother 2015

COMBINATION USE AS EMPIRIC THERAPY

- In patients with signs of severe shock or septic shock present
- Neutropenic patients with bacteremia
- Risk factors for MDR-PA, namely prior intravenous antibiotic use within 90 days (mostly broad-spectrum cephalosporins, carbapenems, quinolones)
- In other settings, where incidence of resistance to chosen antibiotic is high

CONCLUSION

- Use of combination therapy with two agents remains controversial because of paucity of well-compared comparative trials using clinically important end points
- Early use of combination therapy diminishes likelihood of inappropriate therapy but from available data choice of monotherapy or combination treatment as definitive therapy does not impact on mortality

MARAOLO et al. EXPERT REVIEW OF ANTI-INFECTIVE THERAPY, 2017

BREAKPOINTS

ORGANISM	ANTIBIOTICS	EUCAST	CLSI
Enterobacteriaceae	Piperacillin/tazobactam	Susceptible ≤ 8mg/L Resistant >16mg/L	Susceptible ≤ 16 + 4 mg/L Resistant ≥ 128+4 mg/L
	Amoxicillin/clavulanate	Susceptible ≤ 8 + 2 mg/L Resistant > 8 mg/L	Susceptible ≤ 8 + 4 mg/L Resistant ≥ 32 + 16 mg/L
Pseudomonas aeruginosa	Piperacillin tazobactam	Susceptible ≤ 16 + 4 mg/L	
	Cefepime	Susceptible ≤ 2 mg/L 1 gm twice daily doses	MICs 4 or 8 mg/L susceptible but dose dependent

Outcomes of Bacteremia due to *Pseudomonas aeruginosa* with Reduced Susceptibility to Piperacillin-Tazobactam: Implications on the Appropriateness of the Resistance Breakpoint

Tam et.al.

- Retrospective cohort study of pseudomonal bacteremia from 2002 to 2006
- Total of 34 bacteremia episodes involving isolates with reduced susceptibility to piperacillin-tazobactam (minimum inhibitory concentration, 32 or 64 mg/L)
- Thirty-day mortality was found to be 85.7% in the piperacillin-tazobactam group and 22.2% in the control group p value - 004)
- Time to hospital mortality found to be shorter in the piperacillin tazobactam group (P = 0.001)
- In the multivariate analysis, 30-day mortality was found to be associated with empirical piperacillin-tazobactam therapy (odds ratio, 220.5; 95% confidence interval, 3.8–12707.4;009), after adjustment for differences in age and APACHE II score

- **Do not use imipenem to treat susceptible Pseudomonas infections**

EVIDENCE:

- Total of 109 imipenem-non-susceptible (MIC >4 mg/L) strains of P. aeruginosa were collected in June 2010 from the ICUs of 26 French public hospitals
- Their resistance mechanisms characterized by phenotypic, enzymatic, western blotting and molecular methods
- RESULTS:
- Single or associated imipenem resistance mechanisms were identified among the 109 strains

Fournier et.al. J Antimicrob Chemother 2013

- Seven isolates (6.4%) were found to produce metallo-b-lactamase
- Porin OprD was lost in 94 (86.2%) strains as a result of mutations or gene disruption by various insertion sequences

CONCLUSION:

- Diversity of resistance mechanisms allows P. aeruginosa, more than any other nosocomial pathogen, to rapidly adapt to carbapenems in ICUs

Fournier et.al. J Antimicrob Chemother 2013

ACINETOBACTER BAUMANNII AND ENTEROBACTERIACEAE

Ambler Class	Bush-Jacoby Medeiros Class	Active Site	Key Features	Genetics	Common Species	Enzyme Type
Class A	2b, 2be, 2br, 2c, 2e, 2f	Serine	• Resistance to monobactams and third-generation cephalosporin • Inhibited by clavulanate or tazobactam in vitro (except KPC)	• ESBLs arise from mutations in "parent" narrow-spectrum β-lactamase. Highly transmissible on mobile genetic elements (eg, plasmids) often carrying multiple resistance determinants	• *Escherichia coli* • *Klebsiella* spp • *Proteus* spp	Broad-spectrum β-lactamases: • TEM • SHV ESBLs: • TEM • SHV • CTX-M Carbapenemases: • KPC • GES • SME
Class B	3	Bivalent metal ion (primarily Zn++)	• Able to hydrolyze penicillins, cephalosporins, and carbapenems • Not inhibited by clavulanate/tazobactam	• Highly transmissible on plasmids carrying multiple other resistance determinants	• *E coli* • *Klebsiella* spp Described in many Enterobacteriaceae	Carbapenemases: • IMP • VIM • NDM
Class C	1	Serine	• Broad cephalosporinase activity including hydrolysis of third-generation cephalosporins and cephamycins • Limited inhibition by clavulanate • Limited effect of tazobactam	• Chromosomally encoded in several species • May be inducible by exposure to β-lactams • Mutations in key regulatory genes may lead to transcription and increased production of AmpC • Increasing plasmid transmission seen	• Enterobacter cloacae • *Enterobacter aerogenes* • *Serratia marcescens* • *Citrobacter freundii* • *Providencia* spp • *Morganella morganii* Plasmid-mediated AmpC increasing in *E coli*, *Klebsiella* spp	Cephalosporinases: • CMY • DHA • MOX • FOX
Class D	2d	Serine	• Oxacillinases may demonstrate activity against carbapenems • Weakly inhibited by clavulanate	• May be acquired or through naturally occurring chromosomal genes • May be colocated on plasmids with other β-lactamases (eg, OXA-48 and CTX-M-15)	• *K pneumoniae* (OXA-48)	Carbapenemases: • OXA types

NDM-1

Encoded by blaNDM-1 gene found among members of Enterobacteriaceae and Pseudomonas species. Particularly hazardous because

(i) Most plasmids detected in these bacteria are transferable and capable of wide rearrangement, suggesting widespread horizontal transmission and flexibility among bacterial populations

(ii) There is lack of a routine standardized phenotypic test for metallo-beta-lactamase (MBL) detection

Khan et al. BMC Microbiology 2017

NDM-1

(iii) There is consequent probable high prevalence of unrecognized asymptomatic carriers

(iv) Highly resistant to all antibiotics including carbapenems and aminoglycosides because of co-existence of rmtF methylase gene in most of the isolates but susceptible to tigecycline and colistin

Khan et al. BMC Microbiology 2017

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu et. al.

- Prevalence of mcr-1 was investigated in E coli and Klebsiella pneumoniae strains collected from five provinces between April, 2011, and November, 2014
- Polymyxin resistance shown to be singularly due to the plasmid-mediated *mcr-1* gene
- MCR-1 is member of phosphoethanolamine transferase enzyme family, with expression in *E coli* resulting in the addition of phosphoethanolamine to lipid A negating effect of colistin
- MCR-1 carriage in *E coli* isolates collected from 78 (15%) of 523 samples of raw meat and 166 (21%) of 804 animals during 2011–14, and 16 (1%) of 1322 samples from inpatients with infection

Yi-Yun Liu et. al. *Lancet Infect Dis*

Emergence of Chromosome-Borne Colistin Resistance Gene *mcr-1* in Clinical Isolates of *Klebsiella pneumoniae* from India

Sanjay Singh et. al.

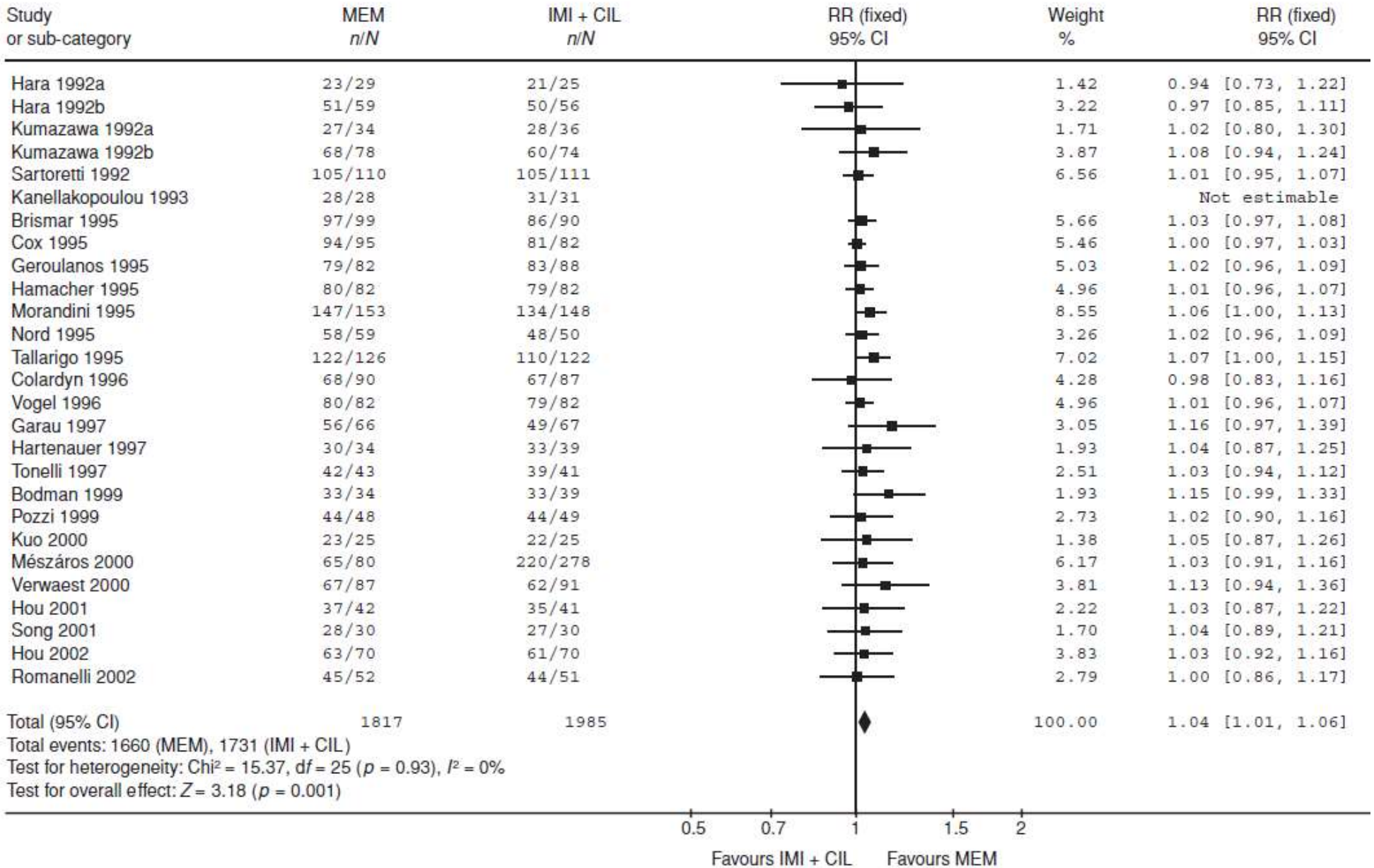
- COHORT - 200 K. pneumonia isolates between January and February 2016 from various clinical isolates, like pus, blood, sputum, and urine, at the Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow
- E-strip test followed by antibiotic susceptibility profiling revealed that a total of 21 isolates (10.5%) were resistant to colistin
- PCR screening and Sanger sequencing revealed that 4 isolates (designated CRL3, CRL5, CRL7, and CRL8) harbored the mcr-1 gene
- Strains CRL5, CLR7, and CLR8 were negative when screened for the presence of additional carbapenemases (NDM, KPC, and OXA-48) by PCR; however, CRL4 was found to carry the *bla*NDM-1 gene
- Antibiotic susceptibility testing by the broth microdilution method demonstrated that all mcr-1-positive isolates were resistant to carbapenems, third-generation cephalosporins, aminoglycosides, and ciprofloxacin but susceptible to tigecycline

Sanjay Singh et. al. Antimicrobial Agents and Chemotherapy 2018

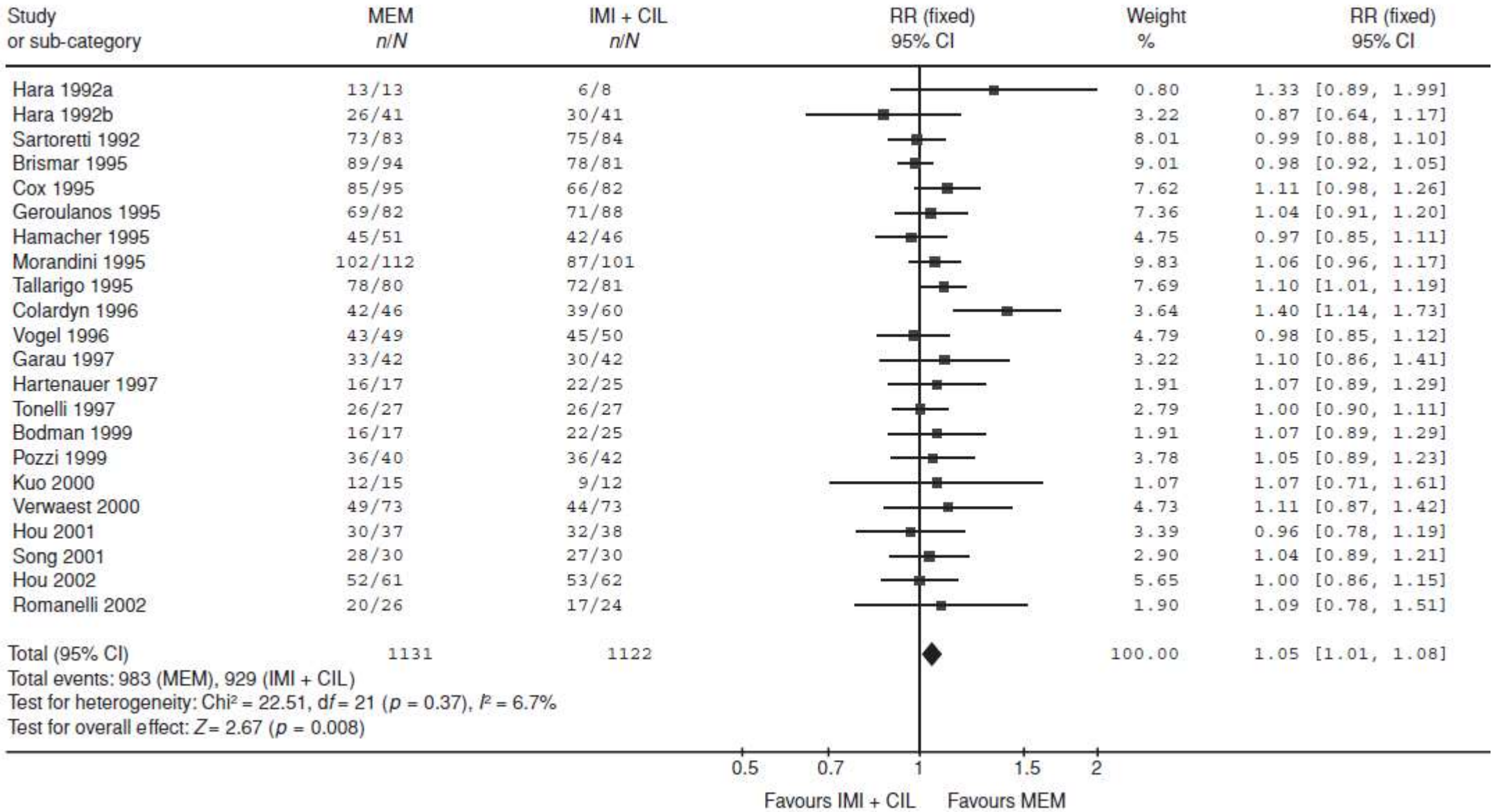
Systematic review comparing meropenem with imipenem plus cilastatin in the treatment of severe infections

Edwards et. al.

- 27 RCTs till March 2004
- Comparing effectiveness of meropenem with imipenem plus cilastatin in treatment of severe infections
- RESULTS:
- Meropenem is associated with significantly greater clinical response (Relative Risk 1.04; 95% Cl: 1.01–1.06), significantly greater bacteriologic response (RR 1.05; 95% CI: 1.01–1.08), non-significant reduction in mortality (RR 0.98; 95% CI: 0.71–1.35), and significantly lower adverse event rate (RR 0.87; 95% CI: 0.77–0.97)
- CONCLUSION:
- Meropenem compared to Imipenem plus cilastatin has significantly greater clinical and bacteriologic response with significant reduction in adverse events



META-ANALYSIS OF CLINICAL RESPONSE FOR MEROPENEM COMPARED WITH IMIPENEM PLUS CILASTATIN IN THE TREATMENT OF SEVERE INFECTIONS



META-ANALYSIS OF BACTERIOLOGIC RESPONSE FOR MEROPENEM COMPARED WITH IMIPENEM PLUS CILASTATIN IN TREATMENT OF SEVERE INFECTIONS

Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis

Zusman et.al.

- Twenty two studies with 28 comparisons
- RESULTS: 9 studies assessed tigecycline, 7 studies assessed carbapenems, 3 studies assessed rifampicin, 3 studies assessed aminoglycosides, 3 studies assessed sulbactam, 2 studies assessed vancomycin, 1 study assessed piperacillin/tazobactam and one study assessed intravenous fosfomycin.

  5 studies used polymyxin B while all others used colistin formulations
- Three were RCTs and all others were retrospective observational studies including from 7–138 patients per treatment group

Zusman et. al. J Antimicrob Chemother 2017

- RESULTS:

- Polymyxin monotherapy associated with OR 1.58 (95% CI – 1.03-2.42) for mortality compared with polymyxin/carbapenem combination therapy (seven observational studies, 537 patients) without heterogeneity

Zusman et. al. J Antimicrob Chemother 2017

- RESULTS:

- Mortality significantly higher with polymyxin monotherapy compared with combination therapy with tigecycline, aminoglycosides or fosfomycin with OR 1.57 (95% CI – 1.06-2.32) overall (10 observational studies and 1 RCT, 585 patients, no heterogeneity) and 2.09 (95% CI – 1.21 -3.6) for Klebsiella pneumonia bacteraemia (7 observational studies, 285 patients, no heterogeneity)

Zusman et. al. J Antimicrob Chemother 2017

RESULTS

- Two RCTs and one observational study assessing rifampicin/colistin combination therapy for Acinetobacter baumannii infections showed no difference in mortality compared with colistin monotherapy

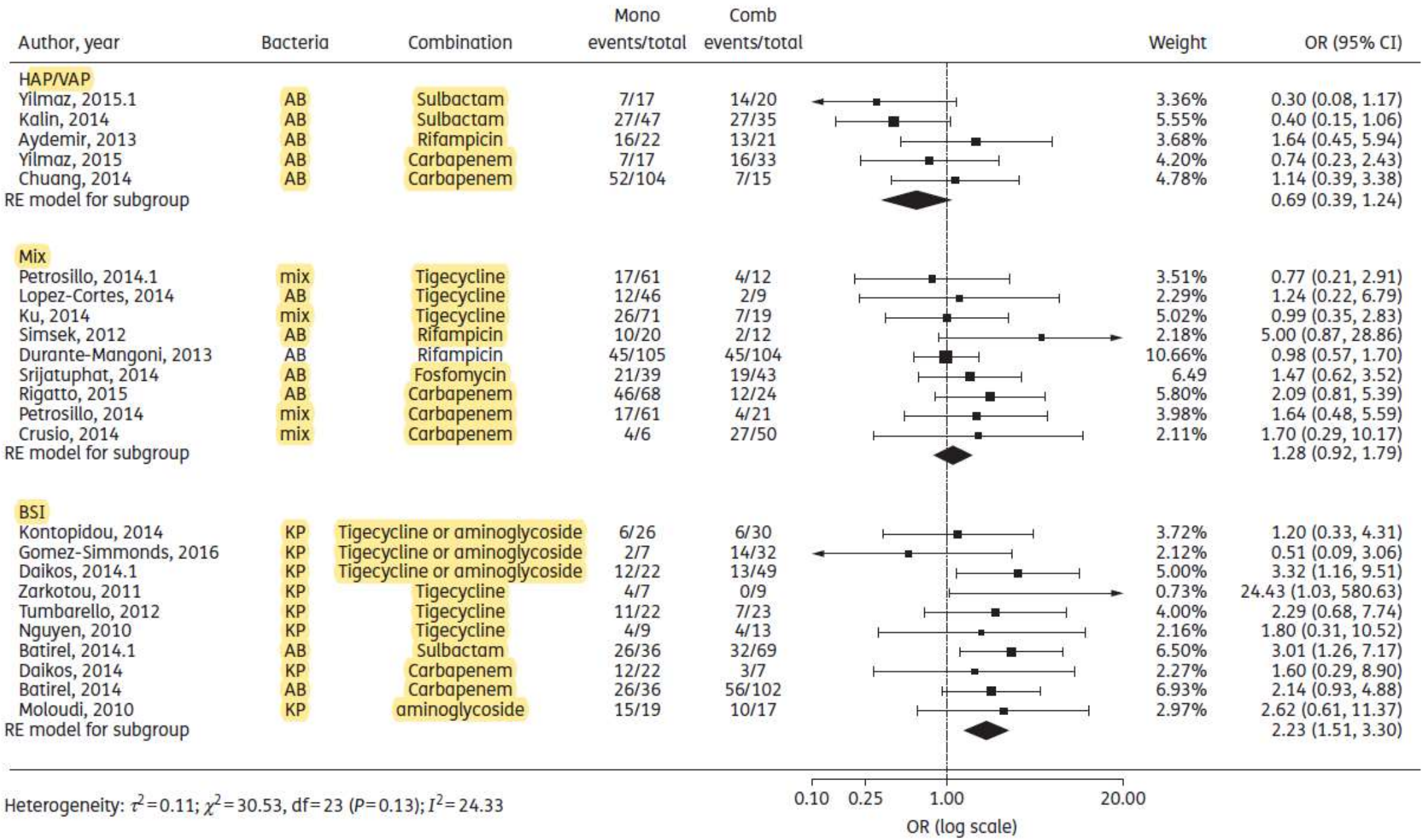
Zusman et. al. J Antimicrob Chemother 2017

CONCLUSION-

Significant association observed in observational studies between polymyxin monotherapy and mortality cannot be taken as taken as proof of combination therapy effects due to low quality of evidence

Three RCTs to date show no effect of rifampicin/colistin or fosfomycin/colistin on mortality for Acinetobacter infections

Zusman et. al. J Antimicrob Chemother 2017



POLYMYXIN MONOTHERAPY VERSUS COMBINATION THERAPY, ALL-CAUSE MORTALITY BY INFECTION TYPE

Zusman et. al. J Antimicrob Chemother 2017

RESTORE-IMI 1: A Multicenter, Randomized, Double-blind Trial Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections

Motsch et.al.

- Randomized, controlled, double blind, phase 3 trial
- Patients with HAP/VAP, complicated intraabdominal infection or complicated urinary tract infection by imipenem nonsusceptible (but colistin and imipenem/relebactam susceptible) pathogen randomized 2:1 to 5-21 days imipenem/relebactam or colistin/imipenem
- Thirty one patients received imipenem/relebactam and 16 colistin/imipenem

Endpoint	IMI/REL (n = 21)		Colistin + IMI (n = 10)		Unadjusted Difference	Adjusted Difference[a]	
	n	% (95% CI)[b]	n	% (95% CI)[a]	%	%	90% CI
Primary endpoint							
Favorable overall response[c]	15	71.4 (49.8, 86.4)	7	70.0 (39.2, 89.7)	1.4	–7.3	(–27.5, 21.4)
Hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia	7/8	87.5 (50.8, 99.9)	2/3	66.7		20.8	
Complicated intraabdominal infection	0/2[d]	0.0	0/2[e]	0.0		0.0	
Complicated urinary tract infection	8/11	72.7 (42.9, 90.8)	5/5	100.0 (51.1, 100.0)		–27.3 (–52.8, 12.8)	
Secondary endpoints							
Favorable clinical response (day 28)	15[f]	71.4 (49.8, 86.4)	4[g]	40.0 (16.7, 68.8)	31.4	26.3	(1.3, 51.5)
28-day all-cause mortality	2	9.5 (1.4, 30.1)	3	30.0 (10.3, 60.8)	–20.5	–17.3	(–46.4, 6.7)
Treatment-emergent nephrotoxicity[h]	3/29	10.3 (2.8, 27.2)	9/16	56.3 (33.2, 76.9)		–45.9 (–69.1, –18.4)	

Qualifying baseline pathogens: *Pseudomonas aeruginosa* (77%), *Klebsiella* spp. (16%), other Enterobacteriaceae (6%)

- Favorable overall response was observed in 71% imipenem/relebactam and 70% colistin+imipenem patients (90% confidence interval [CI] for difference, –27.5, 21.4)

  Day 28 favorable clinical response in 71% and 40% (90% CI, 1.3, 51.5)
- 28-day mortality in 10% and 30% (90% CI, –46.4, 6.7), respectively
- Serious adverse events (AEs) occurred in 10% of imipenem/relebactam and 31% of colistin+imipenem patients,
- Drug-related AEs in 16% and 31% (no drug related deaths), and treatment-emergent nephrotoxicity in 10% and 56% (*P* = .002), respectively

Effect and Safety of Meropenem–Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial

Wunderink et. al.

- Phase 3, randomized-controlled, multicenter, multinational, open-label, active-controlled trial
- 27 hospital sites in 8 countries (Argentina, Brazil, Colombia, Greece, Israel, Italy, United Kingdom, United States) with known prevalence of KPC-producing CRE
- Conducted from 2014 to 2017

Wunderink et. al. Infect Dis Ther. 2018

Effect and Safety of Meropenem–Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial

Wunderink et. al.

- Evaluated efficacy/safety of meropenem–vaborbactam monotherapy versus best available therapy (BAT) for CRE (mono/combination therapy with polymyxins, carbapenems, aminoglycosides, tigecycline; or ceftazidime avibactam alone)
- 47 patients with confirmed CRE infection (bacteremia, hospital acquired/ventilator-associated bacterial pneumonia, complicated intra-abdominal infection, complicated urinary tract infection/acute pyelonephritis)

Wunderink et. al. Infect Dis Ther.2018

- Within the CRE population, cure rates were 65.6% (21/32) and 33.3% (5/15) [95% CI of difference, 3.3% to 61.3%; P = 0.03)] at End of Treatment and 59.4% (19/32) and 26.7% (4/15) (95% CI of difference, 4.6% to 60.8%; P = 0.02) at 7±2 days of EOT
- Day-28 all-cause mortality was 15.6% (5/32) and 33.3% (5/15) **(95% CI of difference,(-44.7% to 9.3%)** for meropenem–vaborbactam

CONCLUSION:

Monotherapy with meropenem–vaborbactam for CRE infection was associated with increased clinical cure, decreased mortality, and reduced nephrotoxicity compared with BAT

Wunderink et. al. Infect Dis Ther.2018

- Use colistin with meropenem to treat susceptible KPC-producing Klebsiella spp. if the meropenem MIC is ≤8 mg/L and consider higher meropenem dose by continuous infusion if the MIC is >8 and ≤32 mg/L (CONDITIONAL)

Hawkey et al. J Antimicrob Chemother 2018

- Consider colistin with aminoglycosides or tigecycline in infections with strains producing KPC or other carbapenemases, which are susceptible to these but resistant to meropenem with MIC >32 mg/L (CONDITIONAL)

Hawkey et al. J Antimicrob Chemother 2018

Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution

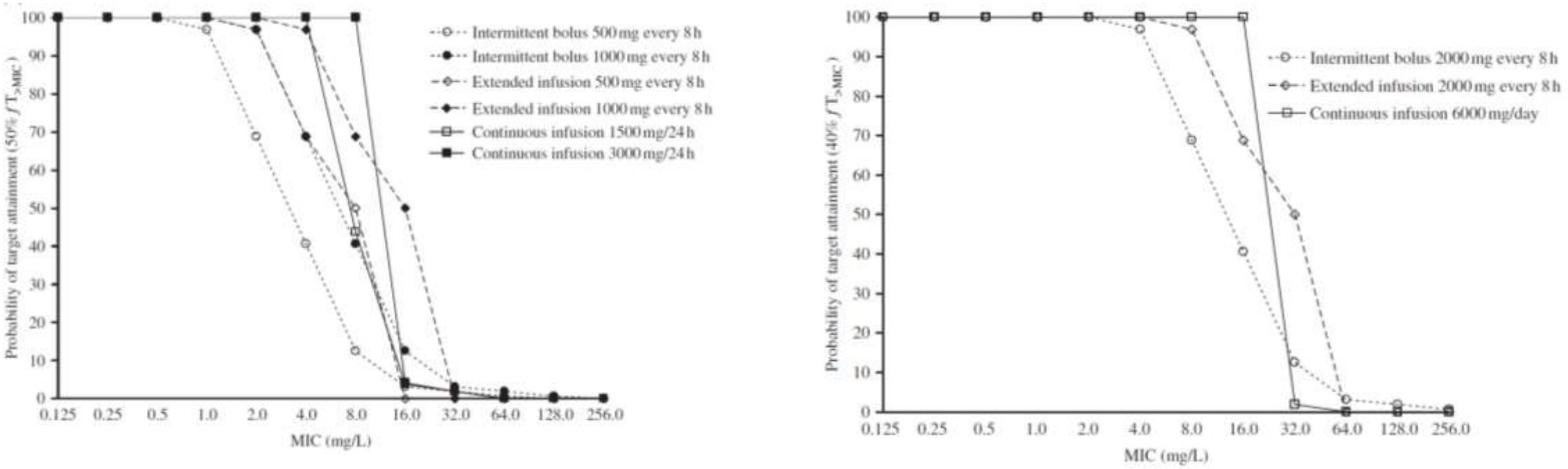
Roberts et.al.

- Randomized 10 patients with sepsis to receive meropenem by intermittent bolus administration (n=5; 1 g 8 hourly) or an equal dose administered by continuous infusion (n=5)
- Continuous infusion maintains higher median trough concentrations, in both plasma (intermittent bolus 0 versus infusion 7 mg/L) and subcutaneous tissue (0 versus 4 mg/L)
- Superior obtainment of pharmacodynamics targets was achieved using administration by extended or continuous infusion against less susceptible Pseudomonas aeruginosa and Acinetobacter species

Roberts et.al. Journal of Antimicrobial Chemotherapy (2009)

CONTINUOUS TREATMENT GROUP

Loading dose of 500 mg (in 10 mL of water-for-injection infused by central line over 3 min) followed immediately by a continuous infusion of 3000 mg of meropenem over 24 h (given as three 1000 mg infusions over 8 h in 250 mL of 0.9% NaCl)



PTA for meropenem administered by intermittent bolus (infused over 3 min), extended infusion (infused over 4 h) or continuous infusion as 1500–3000 mg per 24 h period and 6000 mg per 24 h period

Might real-time pharmacokinetic/pharmacodynamic optimisation of high-dose continuous-infusion meropenem improve clinical cure in infections caused by KPC-producing *Klebsiella pneumoniae*? Pea et. al.

- Retrospective study of 30 patients
- Data for all patients with KPC-Kp-related infections who received antimicrobial combination therapy containing high-dose continuous-infusion meropenem optimized by means of therapeutic drug monitoring (TDM) retrieved
- 53.3% had infections caused by meropenem-resistant KPC-Kp (MIC $\geq$ 16 mg/L)
- Tigecycline and colistin most frequently combined with meropenem

F. Pea et al. International Journal of Antimicrobial Agents 2017

- Clinical outcome successful in 73.3% of cases after median treatment length of 14 days
- In univariate analysis, significant correlation with successful clinical outcome found for *C*ss/MIC ratio ≥1 (OR = 10.556, 95% CI 1.612–69.122; *P* = 0.014), *C*ss/MIC ratio ≥4 (OR = 12.250, 95% CI 1.268–118.361; *P* = 0.030) and a Charlson co-morbidity index of ≥4 (OR = 0.158, 95% CI 0.025–0.999; *P* = 0.05)

CONCLUSION:

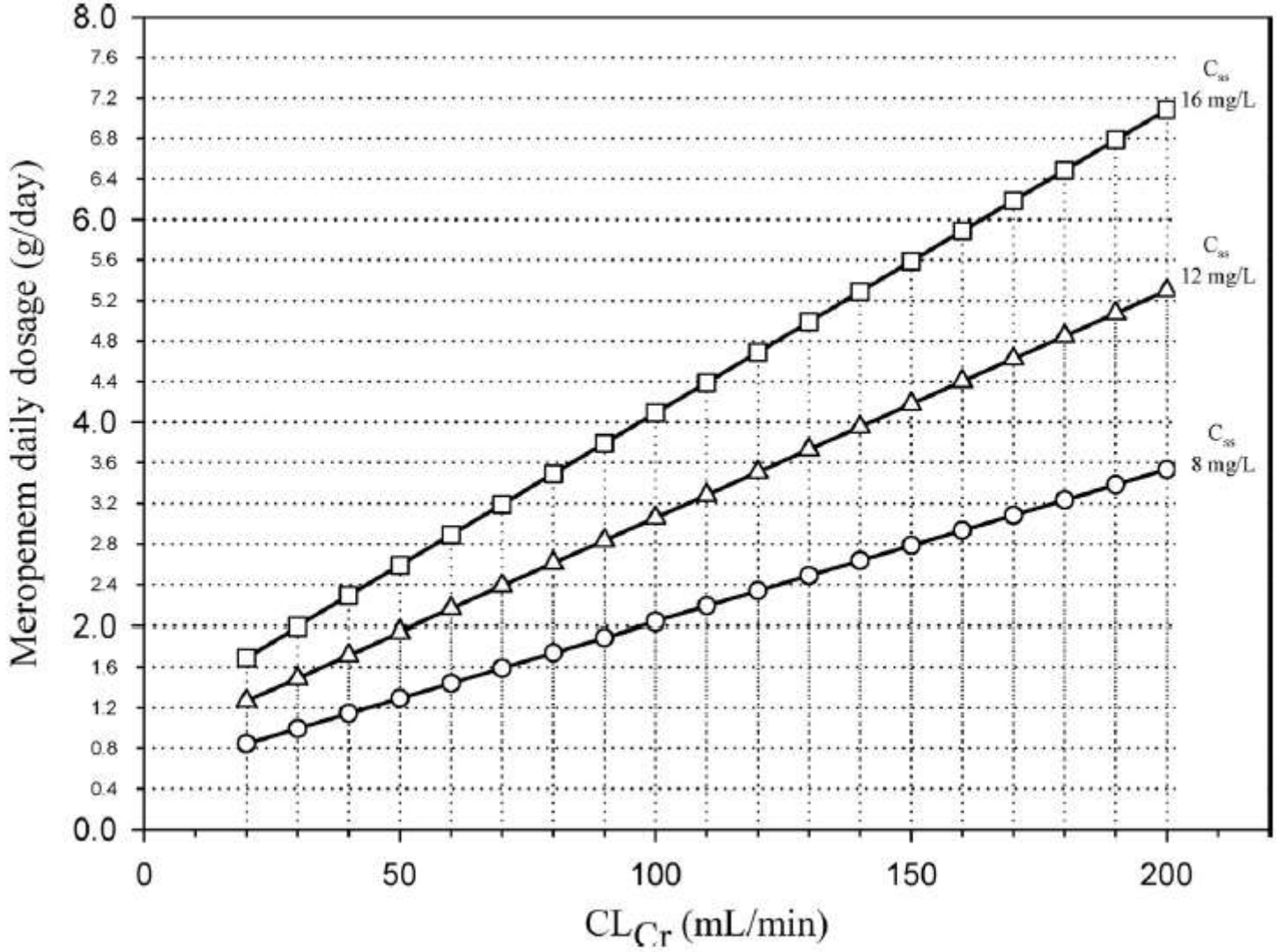
- High dose continuous-infusion meropenem optimised by means of real-time TDM represent valuable tool in improving clinical outcome when dealing with treatment of infections caused by KPC-Kp with meropenem MIC ≤ 64 mg/L

F. Pea et al. International Journal of Antimicrobial Agents 2017

Dosing Nomograms for Attaining Optimum Concentrations of Meropenem by Continuous Infusion in Critically Ill Patients with Severe Gram-Negative Infections: a Pharmacokinetics/ Pharmacodynamics-Based Approach

Pea et.al.

- Continuous infusion can maximize time-dependent activity of meropenem
- In experimental animal models, t > MIC for about 40% of the dosing interval ensure bactericidal activity
- Dosing nomograms in relation to different creatinine clearance (CLcr) estimates for use in daily clinical practice to target the steady-state concentrations (*C*ss) of meropenem during continuous infusion at 8 to 16 mg/liter (after the administration of an initial loading dose of 1 to 2 g over 30 min)
- Formula for Infusion rate (g/24 h) = [0.078CLcr (ml/min)2.85]target *C*ss(24/1,000)



NOMOGRAMS BASED ON CLcr ESTIMATES BY MEANS OF COCKCROFT AND GAULT FORMULA FOR CALCULATION OF MEROPENEM DAILY DOSAGE ADMINISTERED BY CONTINUOUS INFUSION WHICH IS NECESSARY FOR ACHIEVEMENT OF TARGET *C*ss OF 8 mg/liter (CIRCLES), 12 mg/liter (TRIANGLES), AND 16 mg/liter (SQUARES) IN CRITICALLY ILL PATIENTS

Outcome of Cephalosporin Treatment for Serious Infections Due to Apparently Susceptible Organisms Producing Extended-Spectrum β-Lactamases: Implications for the Clinical Microbiology Laboratory

Paterson et. al.

- Prospective, multinational study of Klebsiella pneumoniae bacteremia and identified 32 patients who were treated for ESBL-producing K. pneumoniae bacteremia with cephalosporins and infecting organisms were susceptible in vitro to the utilized cephalosporin
- 100% (4 of 4) patients experienced clinical failure when MICs of cephalosporin used for treatment were in intermediate range and 54% (15 of 28) experienced failure when MICs of the cephalosporin used for treatment were in susceptible range
- It is clinically important to detect ESBL production by Klebsiellae or *E. coli* even when cephalosporin MICs are in susceptible range (< 8 mg/ml) and to report ESBL-producing organisms as resistant to aztreonam and all cephalosporins (with exception of cephamycins)

Paterson et. al. J ClinMicrobiol 2001

Mortality Associated With Bacteremia Due To Colistin-Resistant Klebsiella Pneumoniae with High-Level Meropenem Resistance: Importance of Combination Therapy Without Colistin and Carbapenems

Machuca et.al.

- Prospective cohort study
- From July 2012 to February 2016
- COHORT – 104 patients with bacteremia caused by colistin resistant and high level meropenem resistant (MIC ≥ 64 mg/l) KPC producing K. pneumonia
- RESULTS: 32 (30.8%) patients received targeted monotherapy and 72 (69.2%) received targeted combination therapy; none received colistin or carbapenem

Machuca et.al. Antimicrobial Agents and Chemotherapy Aug 2017

Treatment regimen	No. dead/treated	Mortality (%)
Monotherapy		
Tigecycline	8/15	53.3
Gentamicin	4/9	44.4
Fosfomycin	2/8	25
Total for monotherapy	14/32	43.8
Combination therapy		
Tigecycline + gentamicin	3/13	23.1
Tigecycline + fosfomycin	6/16	37.5
Gentamicin + fosfomycin	3/11	27.3
Tigecycline + fosfomycin + gentamicin	6/32	18.8
Total for combination therapy	18/72	25

OUTCOME OF PATIENTS WITH BACTEREMIA DUE TO COLISTIN-RESISTANT KELBSIELLA PNEUMONIAE WITH HIGH-LEVEL MEROPENEM ACCORDING TO TREATMENT REGIMEN

Machuca et.al. Antimicrobial Agents and Chemotherapy Aug 2017

Mortality Associated With Bacteremia Due To Colistin-Resistant Klebsiella Pneumoniae with High-Level Meropenem Resistance: Importance of Combination Therapy Without Colistin and Carbapenems

Machuca et.al.

- The 30 day crude mortality rate was 30.8% (43.8% monotherapy group and 25% combination therapy)
- The 30 days mortality was independently associated with septic shock at BSI onset (HR 6.03, 95% CI, 1.65 to 21.9, p=0.006)
- Targeted combination therapy associated with lower mortality only in patients with septic shock (HR, 0.14; 95% CI, 0.03 to 0.67; p = 0.01)

Machuca et.al. Antimicrobial Agents and Chemotherapy Aug 2017

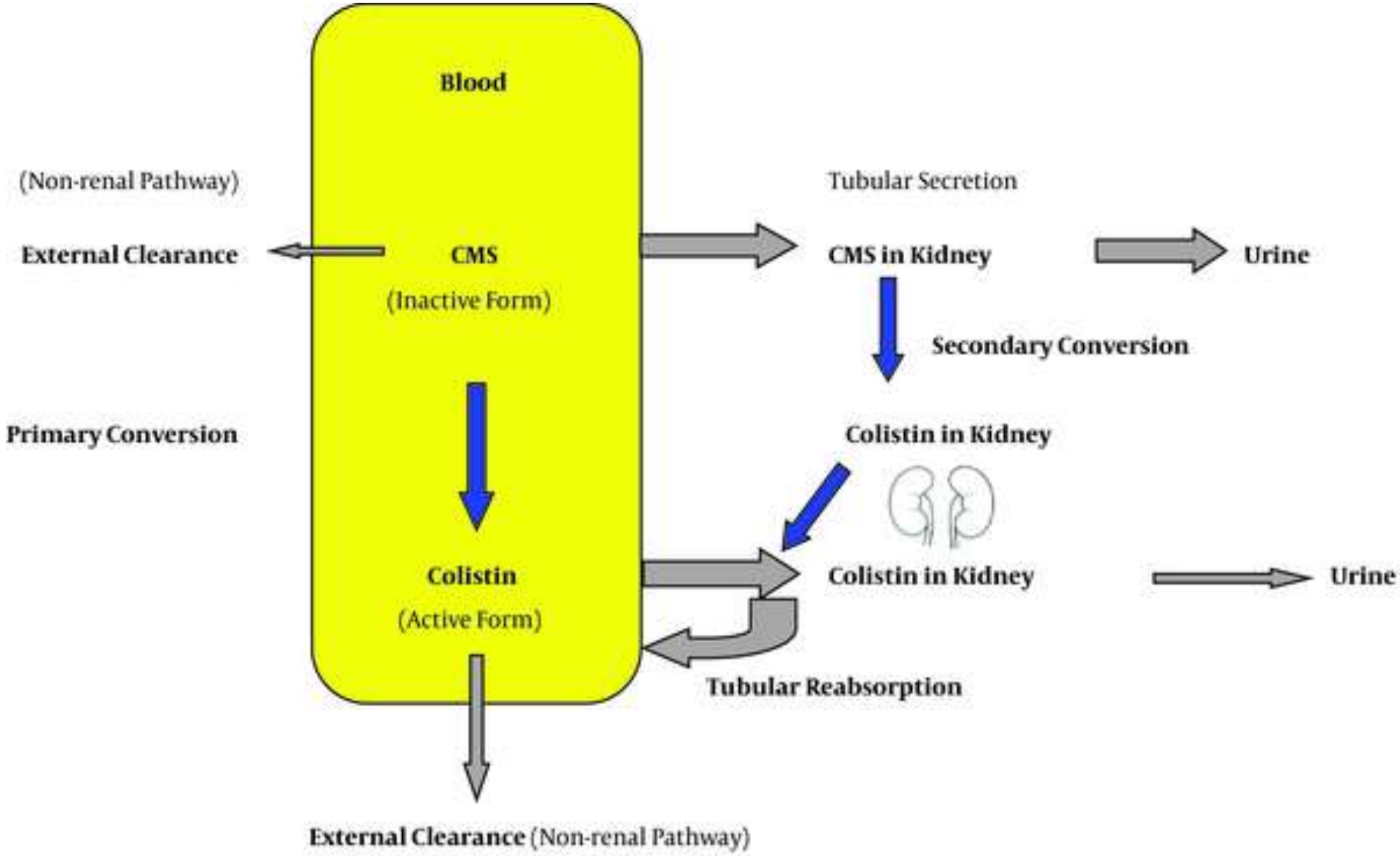
Mortality Associated With Bacteremia Due To Colistin-Resistant Klebsiella Pneumoniae with High-Level Meropenem Resistance: Importance of Combination Therapy Without Colistin and Carbapenems

Machuca et.al.

CONCLUSION:

Combination therapy is associated with reduced mortality in patients with bacteremia due to colistin resistant KPC producing K. pneumonia with high level of resistance in patients with septic shock

POLYMYXINS


Blood
(Non-renal Pathway)
External Clearance
CMS
(Inactive Form)
Primary Conversion
Colistin
(Active Form)
External Clearance (Non-renal Pathway)
Tubular Secretion
CMS in Kidney
Urine
Secondary Conversion
Colistin in Kidney
Colistin in Kidney
Urine
Tubular Reabsorption

Clinical Infectious Diseases

MAJOR ARTICLE

Dosing Guidance for Intravenous Colistin in Critically Ill Patients

Nation et.al.

- Four centre study (Greece, United States and Thailand)
- Plasma concentration-time data from 214 adult critically ill patients (creatinine clearance, 0–236 mL/min; 29 receiving renal replacement therapy)
- To balance potential antibacterial benefit against risk of nephrotoxicity algorithms are designed to achieve target attainment rates of >80% for Css,avg ≥2 and <30% for Css,avg ≥4 mg/L

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

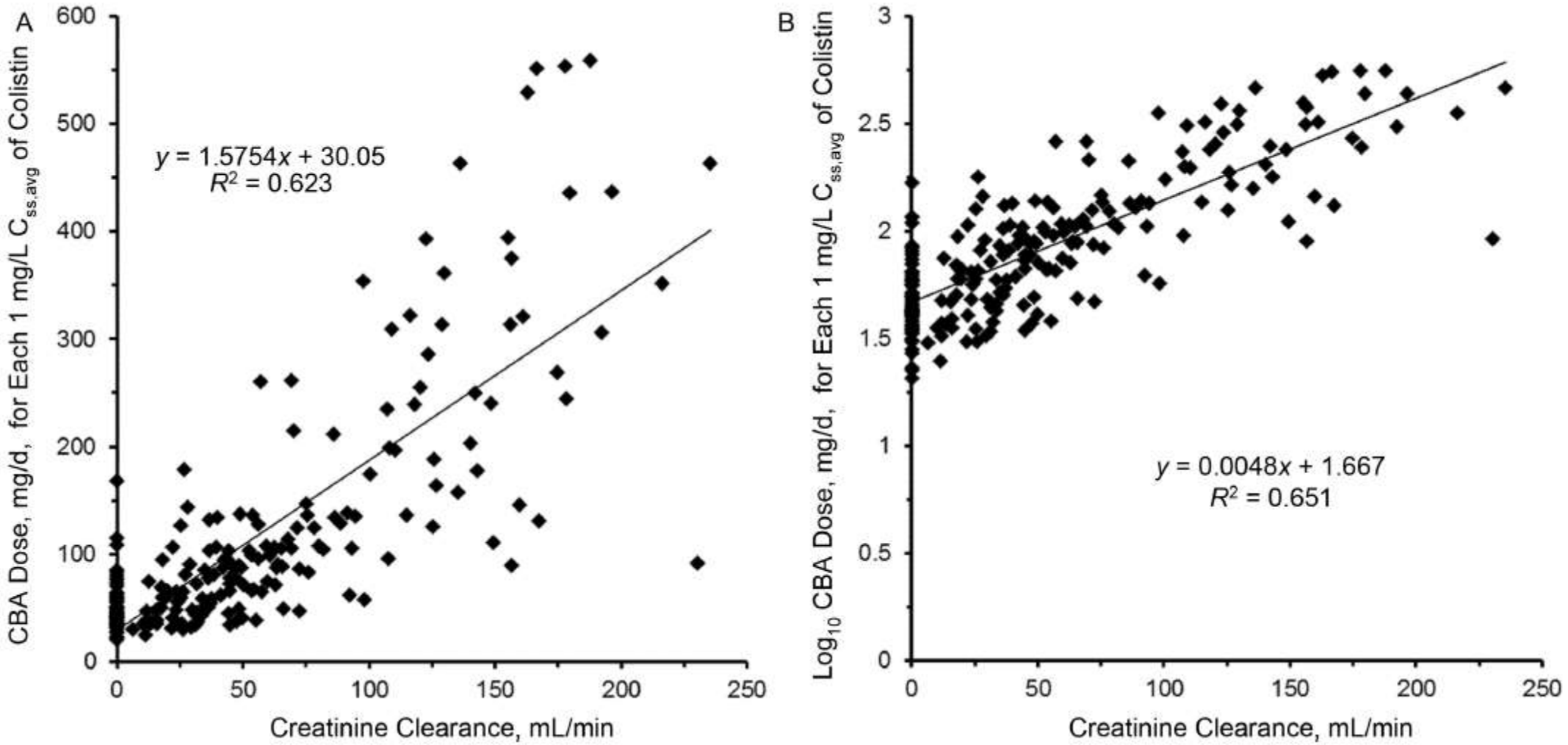
hivma hiv medicine association

OXFORD

Dosing Guidance for Intravenous Colistin in Critically Ill Patients

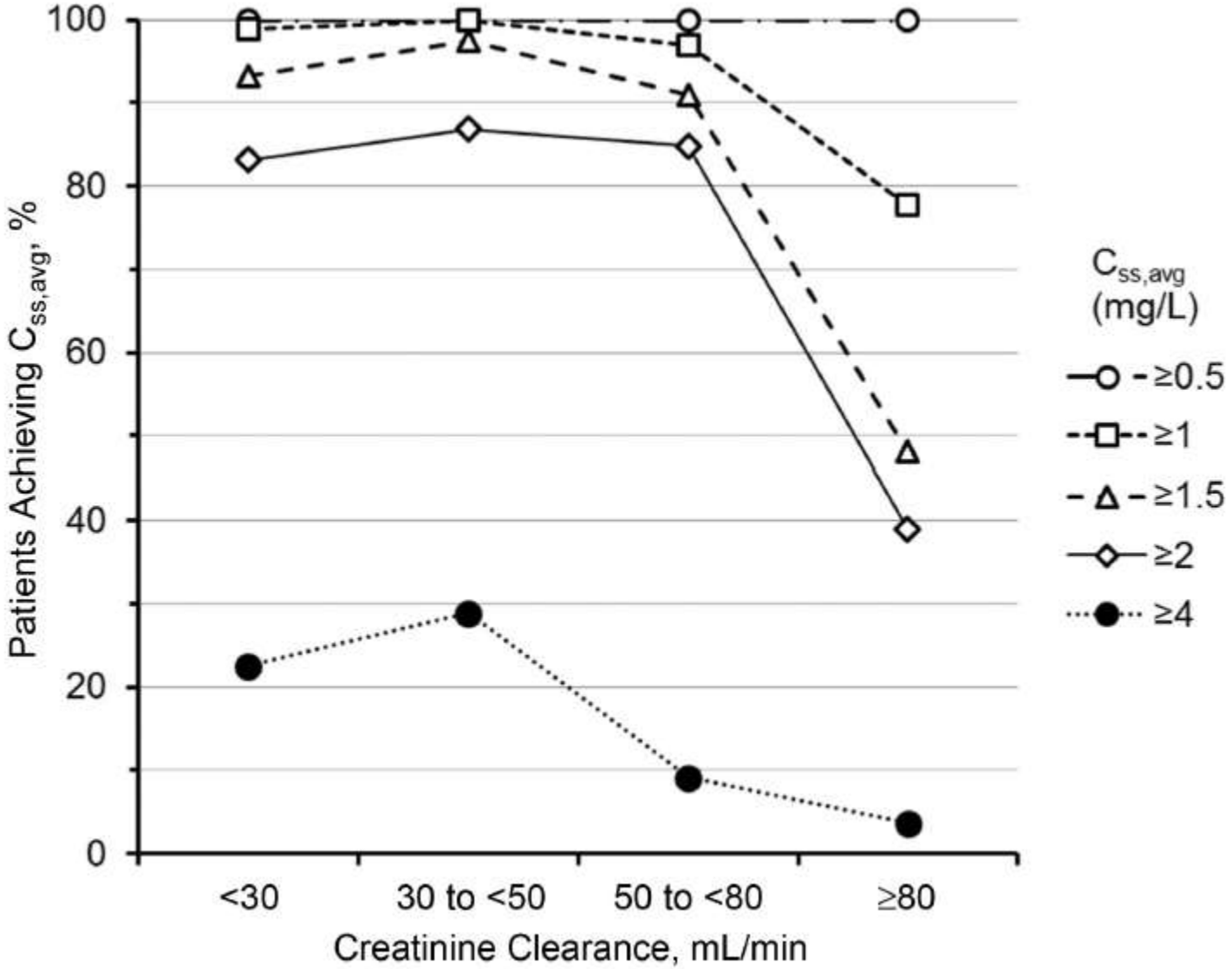
Nation et.al.

- Risk of nephrotoxicity increases as plasma colistin exposure exceeds approximately 2.5 mg/L
- Target plasma colistin Css,avg of 2 mg/L is not appropriate for infections in MIC >2 mg/L
- Insufficient for pulmonary infections even with MICs <1 mg/L unless other approaches are undertaken (eg, combination with other antibiotics, nebulization of colistimethate)



LINEAR-LINEAR AND LOG-LINEAR PLOTS OF RELATIONSHIP BETWEEN DAILY DOSE OF COLISTIN BASE ACTIVITY (CBA) NEEDED FOR EACH 1 MG/L OF AVERAGE STEADY STATE PLASMA CONCENTRATION OF COLISTIN (CSS,AVG) AND CREATININE CLEARANCE

Nation et.al. Dosing Guidance for Intravenous Colistin CID 2017



PERCENTAGE OF PATIENTS IN EACH CREATININE CLEARANCE CLUSTER ACHIEVING AVERAGE STEADY-STATE PLASMA CONCENTRATIONS OF COLISTIN (Css,AVG) OF ≥0.5, ≥1, ≥1.5, ≥2, AND ≥4 MG/L USING DAILY DOSE OF COLISTIMETHATE RELEVANT TO THE ACTUAL CREATININE CLEARANCE OF EACH PATIENT

Nation et.al. Dosing Guidance for Intravenous Colistin CID 2017

Dose	Category of Critically Ill Patient	Dosing Suggestions[a]
Loading dose	All patient categories	Equation 1: Loading dose of CBA (mg) = $C_{ss,avg}$ target (mg/L) × 2.0 × ideal body weight (kg) To achieve a $C_{ss,avg}$ of 2 mg/L in a patient with an ideal body weight of 75 kg, the loading dose would be 300 mg CBA (9 million IU), the suggested maximum loading dose. The 1st regular daily dose should be administered 12 h later.
Daily dose[b]	Not receiving RRT	Equation 2[c]: Daily dose of CBA (mg) = $C_{ss,avg}$ target (mg/L) × $10^{(0.0048 \times CrCl + 1.825)}$ See ("look-up" table) for the daily dose to target a plasma colistin $C_{ss,avg}$ of 2 mg/L, depending on the patient's creatinine clearance.
	Receiving RRT	The baseline daily dose of colistimethate for a $C_{ss,avg}$ of 2 mg/L in a patient with creatinine clearance of 0 mL/min is 130 mg/d of CBA (3.95 million IU/d) (see Table 3)[d]; the supplement to the baseline daily dose needed during receipt of RRT is 10% of the baseline dose per 1 h of RRT.
	Intermittent hemodialysis	Nondialysis day: CBA dose of 130 mg/d (3.95 million IU/d), ie, baseline dosing for a $C_{ss,avg}$ of 2 mg/L; dialysis day supplement: add 30% or 40% to baseline daily dose after a 3- or 4-h session, respectively.[e] The dialysis session should occur toward the end of a colistimethate dosing interval, and the supplement to the baseline (nondialysis) daily dose should be administered with next regular dose, after the dialysis session has ended.
	SLED	During SLED: add 10% per 1 h of SLED replacement to baseline daily dose for a $C_{ss,avg}$ of 2 mg/L[f]; for a patient receiving a 10-h nocturnal SLED session each day and receiving colistimethate every 12 h, the dose would be (baseline CBA dose of 130 mg/d for a patient with creatinine clearance of 0 mL/min + supplemental dose comprising 10% of the baseline dose per h × 10 h); ie, for this case the CBA dose would be 260 mg/d (7.9 million IU/d). It is suggested that the SLED session begin 1–2 h after the afternoon/evening dose; in such a case, it may be most convenient and safe to administer 130 mg CBA (3.95 million IU) every 12 h.
	CRRT	During CRRT: add 10% per 1 h of CRRT to the baseline daily dose for a $C_{ss,avg}$ of 2 mg/L[g]; the suggested CBA dose is 440 mg/d (~13 million IU/d).

LOADING AND DAILY DOSES OF COLISTIMETHATE FOR DESIRED TARGET COLISTIN Css,avg OF 2 mg/l

COLISTIN PK/PD

- Attainment rates of >90% desirable
- For patients with creatinine clearance ≥80 mL/min, very large increase in dose above maximum of 360 mg/d of CBA used be required to push the attainment rate from approx 40% to >80%
- Combination therapy strongly considered for patients with creatinine clearance ≥80 mL/min (especially if patient has respiratory tract infection and/or MIC of infecting organism is ≥1 mg/L)

Nation et.al. Dosing Guidance for Intravenous Colistin CID 201

Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) position statements on polymyxin B and colistin clinical breakpoints Satlin et. al.

- Steady state concentration of 2 ug/mL required for killing bacteria with colistin minimum inhibitory concentrations (MICs) of 2 ug/mL
- Less than 50% of patients with normal renal function achieve this exposure and it is associated with high risk of nephrotoxicity
- CLSI eliminated “susceptible” interpretive category for polymyxins, whereas EUCAST maintains this interpretive category

Satlin et. al. CLINICAL INFECTIOUS DISEASE NO

COLISTIN PK/PD

- Colistin plasma protein binding ~50% in humans
- For both colistin and polymyxin B, area under unbound plasma drug concentration-time curve related to MIC (*f*AUC/MIC) shown to best predict bacterial killing
- Risk of nephrotoxicity increased markedly with plasma colistin $C_{ss,average}$ ≥1.88.g/mL and ≥ 2.25g/mL in patients with and without pre-existing kidney impairment, respectively

Forrest et. al. Antimicrob Agents Chemother 2017

CLSI STAND POINT

- Together, the preclinical PK/PD, clinical PK/TD and MIC distribution data indicate that an MIC of 2 µg/mL is the only viable clinical breakpoint
- Even with optimized dosing regimens, it is not possible to safely achieve PK/PD targets that correlate with efficacy for isolates with MICs >2 µg/mL

Satlin et. al. CLINICAL INFECTIOUS DISEASE NOV

CLSI STAND POINT

- Susceptible category deemed to be inappropriate, and intermediate-only category established because this category identifies isolates “that approach usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates

Satlin et. al. CLINICAL INFECTIOUS DISEASE NOV 2020

EUCAST

- EUCAST maintains lowest possible clinical breakpoint for species which is deemed to be suitable target for the agent is ECOFF (highest MIC-value of wild type organisms)
- ECV differentiates, by MIC, isolates that are wild-type to given antimicrobial from those that are not and is informed solely by *in vitro* MIC data
- ECOFFs are 2 mg/L for most important members of Enterobacterales and Acinetobacter spp. and 4 mg/L for Pseudomonas

EUCAST STAND POINT

- EUCAST narrowed definition of I-category from “Intermediate” to “Susceptible, increased exposure” and whenever “I” is used in EUCAST terminology it implies that species or isolate is treatable provided highest acceptable exposure (dose, dosing interval, mode of administration, etc.) is used
- EUCAST “I” category unsuitable for polymyxins because EUCAST maintains that the highest possible exposure should always be used for susceptible (“S”) organisms

Satlin et. al. CLINICAL INFECTIOUS DISEASE

UPCOMING STUDIES

- Observational, Prospective Cohort Study
- COHORT: 250 participants, patients receiving IV polymyxin B for treatment of pneumonia and/or bloodstream infection
- Official Title: Optimizing Clinical Use of Polymyxin B: Teaching an Old Drug to Treat Superbugs
- Study Duration: February 2016 - May 31, 2021
- Trial ID: NCT02682355

- Primary Outcome Measures

- Polymyxin B plasma concentrations

- Secondary Outcome Measures

- Changes in serum creatinine

- Clinical response based on resolution of signs and symptoms of infection

- Microbiologic response based on eradication of pathogens from blood and respiratory cultures

A Review of Intravenous Minocycline for Treatment of Multidrug-Resistant *Acinetobacter* Infections

Ritchie et.al.

- Synergistic and bactericidal activity against MDR Acinetobacter has been noted with minocycline in combination with colistin or carbapenems
- Free drug AUC/minimum inhibitory concentration is most closely associated with the antibacterial effect
- Favorable pharmacokinetic profile of minocycline intravenous, stability to many tetracycline resistance mechanisms, suggests potential role for minocycline intravenous for treatment of some serious MDR Acinetobacter infections

Study	Description	Outcomes Evaluated	Results
Pneumonia			
Wood et al [18]	Retrospective case series VAP Critically ill trauma patients MDR *Acinetobacter baumannii* n = 4 All sensitive to tetracycline Monotherapy (n = 2) and combination therapy (n = 2) Minocycline 100 mg intravenous every 12 h Treatment duration ranged from 10 to 20 d	Success was defined as negative follow-up BAL and clinical improvement. If follow-up BAL was unavailable, then success was defined as clinical improvement and survival until hospital discharge. Failure was defined as death due to VAP complications or persistent positive BAL culture without clinical improvement.	All 4 patients achieved success. Three patients had a negative follow-up BAL. One patient did not have a follow-up BAL.
Chan et al [19]	Retrospective study VAP Trauma center Carbapenem-resistant *Acinetobacter* n = 19 Minocycline 200 mg, then 100 mg intravenous every 12 h (or 200 mg orally or per tube every 12 h) Overall average treatment duration = 13.3 d	Clinical response, defined as improvement and resolution of signs and symptoms of VAP, or microbiologic eradication from follow-up BAL or sputum culture	Clinical response to minocycline intravenous: 15/19 (78.9%) Clinical response to minocycline oral: 14/17 (82.5%) Overall clinical response to minocycline-based regimens: 29/36 (80.6%) Overall clinical response regardless of specific antibiotic therapy: 42/55 (76.4%)
Jankowski et al [20]	Retrospective case series Intensive care unit patients MDR *Acinetobacter baumannii* n = 3 Minocycline 100 mg intravenous every 12 h Treatment duration ranged from 10 to 13 d	Successful clinical outcome was defined as the absence of or partial resolution of clinical and laboratory parameters of infection. Successful microbiologic outcome was defined as documented or presumed eradication.	Successful clinical outcome: n = 2/3 Successful microbiologic outcome: n = 3/3
Bishburg et al [21]	Retrospective study Hospitalized patients *Acinetobacter baumannii* n = 2 Minocycline 100 mg intravenous every 12 h (allowed transition to minocycline oral therapy to complete the course) Treatment duration ranged from 5 to 18 d	Clinical improvement Hospital discharge	Both patients demonstrated clinical improvement and were discharged from the hospital.

Wood et.al. Intensive Care Med 2003
Chan et.al. J Intensive Care Med 2010
Jankowski et.al. Infect Dis Clin Pract 2012

OTHER MEASURES

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Targeted versus Universal Decolonization to Prevent ICU Infection

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RANDOMIZED EVALUATION OF DECOLONIZATION VERSUS UNIVERSAL CLEARANCE TO ELIMINATE MRSA (REDUCE MRSA) TRIAL

REDUCE MRSA TRIAL

- Pragmatic, cluster randomized trial
- Total 43 hospitals (including 74 ICUs and 74,256 patients)
- Hospitals were randomly assigned to one of three strategies, with all adult ICUs in given hospital assigned to same strategy

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RECRUITMENT

- Baseline period (12-month) from January 1 through December 31, 2009
- Phase-in period from January 1 through April 7, 2010
- Intervention period (18-month) from April 8, 2010, through September 30, 2011

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IN GROUP 1 (SCREENING AND ISOLATION)

- Bilateral screening of nares for MRSA performed on ICU admission
- Contact precautions implemented for patients with history of MRSA colonization or infection and for those who had any positive MRSA test

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IN GROUP 2 (TARGETED DECOLONIZATION)

- Patients known to have MRSA colonization or infection underwent 5-day decolonization regimen consisting of twice daily intranasal mupirocin and daily bathing with chlorhexidine-impregnated cloths

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IN GROUP 3 (UNIVERSAL DECOLONIZATION)

- No screening for MRSA on admission to ICU
- Contact precautions were similar to those in group 1
- All patients received twice-daily intranasal mupirocin for 5 days, plus daily bathing with chlorhexidine-impregnated cloths for entire ICU stay

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RESULTS

- In intervention period versus baseline period, modeled hazard ratios for MRSA clinical isolates were 0.92 for screening and isolation (crude rate, 3.2 vs. 3.4 isolates per 1000 days), 0.75 for targeted decolonization (3.2 vs. 4.3 isolates per 1000 days), and 0.63 for universal decolonization (2.1 vs. 3.4 isolates per 1000 days) (P = 0.01 for test of all groups being equal)

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RESULTS

- In intervention versus baseline periods, hazard ratios for bloodstream infection with any pathogen in three groups were 0.99 (crude rate, 4.1 vs. 4.2 infections per 1000 days), 0.78 (3.7 vs. 4.8 infections per 1000 days), and 0.56 (3.6 vs. 6.1 infections per 1000 days), respectively ($P<0.001$ for test of all groups being equal)

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RESULTS

- Universal decolonization resulted in significantly greater reduction in the rate of all bloodstream infections than either targeted decolonization or screening and isolation
- One bloodstream infection prevented per 99 patients who underwent decolonization
- The reductions in rates of MRSA bloodstream infection were similar to those of all bloodstream infections, but difference was not significant

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CONCLUSION

- In routine ICU practice, universal decolonization was more effective than targeted decolonization or screening and isolation in reducing rates of MRSA clinical isolates and bloodstream infection from any pathogen

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- No antibiotic prescriptions for treating the elderly with asymptomatic bacteriuria (ASB), or urinary tract infection (UTI) in the presence of a urinary catheter unless bacteraemia or renal infection is suspected
- No antibiotic prophylaxis for urinary catheter insertion or change unless previous history of symptomatic UTI associated with a change of catheter, or if there is trauma during catheter insertion, or if a urinary continence device has been inserted

- Do not use trimethoprim to treat lower UTIs as a first-line agent. Only consider use if there are no risk factors for resistance, or if confirmed in vitro susceptibility

CONCLUSION

- Antibiotics decision to be taken after consideration of respective MICs
- Need to look for alternative antibiotics other than colistin
- Routine use of nomograms for attaining appropriate blood concentration for antibiotics according to renal functions
- Regular use of prophylactic mupirocin in ICU patients
- Consideration of minocycline use for MDR Acinetobacter baumanni