Evidence-based antimicrobial stewardship management in bacteraemia

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Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,[1] Robert C. Owens,[2] John E. McGowan, Jr.,[3] Dale N. Gerding,[4] Robert A. Weinstein,[5] John P. Burke,[6] W. Charles Huskins,[7] David L. Paterson,[8] Neil O. Fishman,[9] Christopher F. Carpenter,[10] P. J. Brennan,[9] Marianne Billeter,[11] and Thomas M. Hooton[12]

Clinical Infectious Diseases 2007; 44:159–77

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Tamar F. Barlam,[1,a] Sara E. Cosgrove,[2,a] Lilian M. Abbo,[3] Conan MacDougall,[4] Audrey N. Schuetz,[5] Edward J. Septimus,[6] Arjun Srinivasan,[7] Timothy H. Dellit,[8] Yngve T. Falck-Ytter,[9] Neil O. Fishman,[10] Cindy W. Hamilton,[11] Timothy C. Jenkins,[12] Pamela A. Lipsett,[13] Preeti N. Malani,[14] Larissa S. May,[15] Gregory J. Moran,[16] Melinda M. Neuhauser,[17] Jason G. Newland,[18] Christopher A. Ohl,[19] Matthew H. Samore,[20] Susan K. Seo,[21] and Kavita K. Trivedi[22]

Clinical Infectious Diseases® 2016;62(10):e51–e77

Definition IDSA SHEA PIDS

Infect Control Hosp Epidemiol 2012;33(4):322-327

- Coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal antibiotic drug regimen including dosing, duration of therapy and route of administration
- The major objectives:
  - Best clinical outcomes
  - Minimising toxicity and other adverse events
  - Limiting selective pressure on emergence of antimicrobial-resistant strains
  - Reduce excessive costs attributable to suboptimal antimicrobial use

IDSA ASP guideline 2016

- 18 recommendations:
  - Pre-authorisation, prospective audit and feedback; clinical practice guidelines, specific ID syndrome; reduce antibiotics with high risk of CDI; antibiotic time-out or stop orders; CDSS at point of prescribing; TDM aminoglycosides/vancomycin; allergy assessment and penicillin skin testing
  - Stratified antibiograms, selective or cascade reporting antibiotic susceptibility; rapid viral testing respiratory pathogens, rapid diagnostic tests on blood; serial procalcitonin in ICU; non-culture fungal markers
- This lecture:
  - Alternative dosing strategies for broad-spectrum beta-lactams to save cost; shortest effective antibiotic duration
- Not recommended: didactic education alone, antibiotic cycling
- Not mentioned: formulary restriction, antibiotic order forms
- Special populations: febrile neutropenia guideline, antifungal ASP, ASP in nursing home, neonatal ICU and terminally ill
- Measurement: measure DOT rather than DDD, antibiotic cost based on prescription or administration not purchasing, goals and size of syndrome specific interventions

Outline

- Importance of blood culture
- Prolonged infusion of beta-lactams: does optimising PK PD affect clinical outcomes?
- Duration of antibiotic for gram negative bacteraemia: Still two weeks?
- Treating ESBL bacteraemia: implications of MERINO trial
- Combination antibiotics for bacteraemia: more is better?

JOURNAL OF CLINICAL MICROBIOLOGY, Sept. 1994, p. 2103–2106
0095-1137/94/$04.00+0

Vol. 32, No. 9

Controlled Evaluation of 5 versus 10 Milliliters of Blood Cultured in Aerobic BacT/Alert Blood Culture Bottles

MELVIN P. WEINSTEIN,[1,2]* STANLEY MIRRETT,[3] MICHAEL L. WILSON,[3,4]†
LARRY G. REIMER,[5,6] AND L. BARTH RELLER[3,4,7]

TABLE 1. Comparative yields of clinically important bacteria and fungi in BacT/Alert aerobic blood culture bottles inoculated with 5 and 10 ml of blood

Microorganism	No. of isolates recovered by:			P
	Both bottles	10-ml bottle only	5-ml bottle only	
Staphylococcus aureus	142	20	24	NS[a]
Coagulase-negative staphylococci	76	25	17	NS
Streptococci[b]	55	8	2	NS
Enterococcus spp.	40	11	12	NS
Other gram-positive bacteria[c]	2	4	0	NS
Escherichia coli	64	17	4	<0.01
Other members of the family *Enterobacteriaceae*	64	32	10	<0.001
Pseudomonas aeruginosa	28	7	7	NS
Other gram-negative bacteria[d]	9	4	4	NS
Gram-positive anaerobic bacteria[e]	8	1	1	NS
Gram-negative anaerobic bacteria[f]	2	2	1	NS
Yeasts and fungi[g]	59	17	19	NS
All microorganisms	549	148	101	<0.005

TABLE 2. Comparison of speed of detection of clinically important bacteria and fungi in BacT/Alert aerobic blood culture bottles inoculated with 5 and 10 ml of blood

Microorganism	No. of isolates from:			P
	Both bottles at same time	10-ml bottle earlier	5-ml bottle earlier	
Staphylococcus aureus	41	54	47	NS[a]
Coagulase-negative staphylococci	9	48	19	<0.001
Streptococci[b]	17	30	8	<0.001
Enterococcus spp.	7	20	13	NS
Other gram-positive bacteria[c]	0	1	1	NS
Escherichia coli	19	31	14	<0.025
Other members of the family *Enterobacteriaceae*	15	33	16	<0.025
Pseudomonas aeruginosa	6	15	7	NS
Other gram-negative bacteria[d]	4	3	2	NS
Gram-positive anaerobic bacteria[e]	1	4	3	NS
Gram-negative anaerobic bacteria[f]	0	1	1	NS
Yeasts and fungi[g]	6	23	30	NS
All microorganisms	125	263	161	<0.001

Yield 2 bottles >1 bottle; 10ml >5ml

Earlier detection in 10ml vs. 5ml

JOURNAL OF CLINICAL MICROBIOLOGY, Nov. 1994, p. 2829–2831
0095-1137/94/$04.00+0

Vol. 32, No. 11

Effects of Volume and Periodicity on Blood Cultures

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TABLE 1. Culture yield by volume and periodicity

No. of bacteremic episodes tested	Initial vol cultured (ml)	No. of episodes detected	Subsequent vol cultured (ml)	No. of additional episodes detected	Interval between cultures	Yield added by extra vol cultured (%)	*P*	95% confidence interval (%)
184	20	148	20	35	Simultaneous	19	<0.0001	13–25
30	20	24	20	5	10 min to 2 h apart	17	0.0313	2–31
72	20	55	20	12	2 to 24 h apart	17	<0.0003	7–26
210	20	161	20	42	Anytime within 24 h	20	<0.0001	14–26
51	20	36	40	12	Anytime within 24 h	24	<0.0003	10–37
51	40	43	20	5	Anytime within 24 h	10	0.0313	1–18

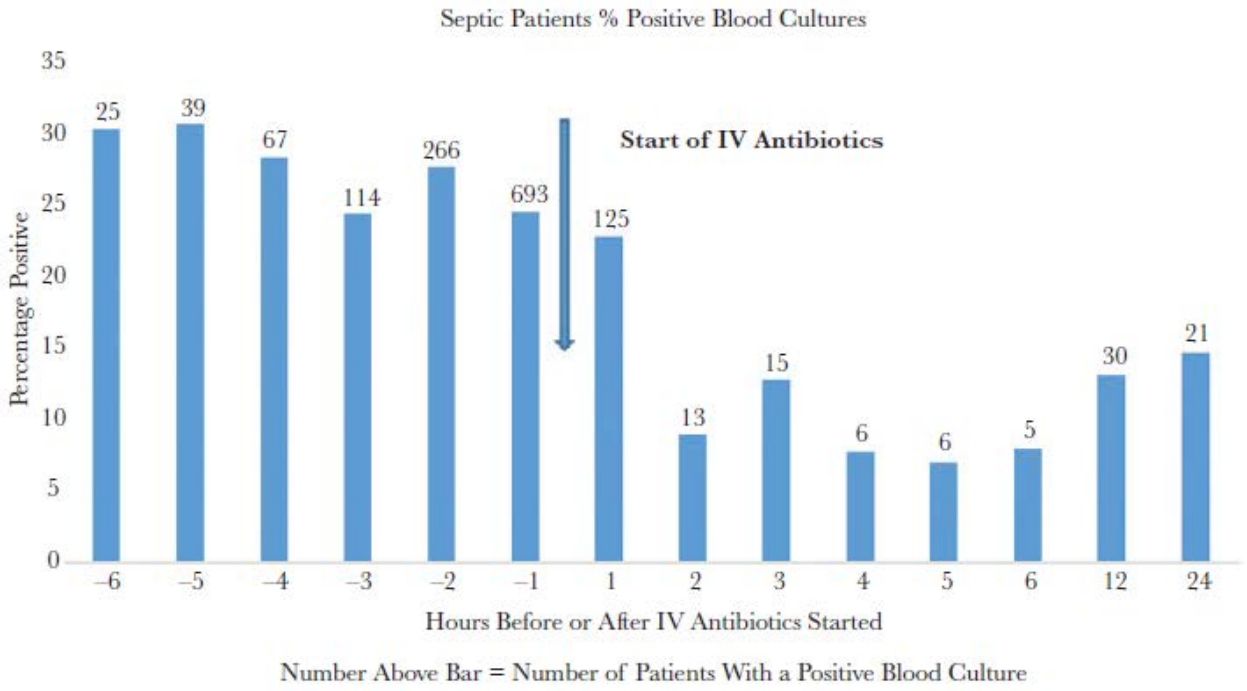
per culture and separated into 10-ml aliquots for incubation. Analysis of the results stratified by cultured volume and time interval between specimen collection accorded yield advantage to culture volume at the maximal amounts tested. No advantage was observed with any particular interval of collection. Increasing cultured volume from 20 to 40 ml increased yield by 19%. Increasing cultured volume from 40 to 60 ml increased yield by an additional 10%. The same effect was seen whether cultures were drawn simultaneously or serially within 24 h. These observations support other reports demonstrating increased yield with increased cultured blood volume. However, they demonstrate increases in yield at volumes much higher than previously considered. In conclusion, this study demonstrates that high-volume blood cultures drawn serially or simultaneously return the best yields.

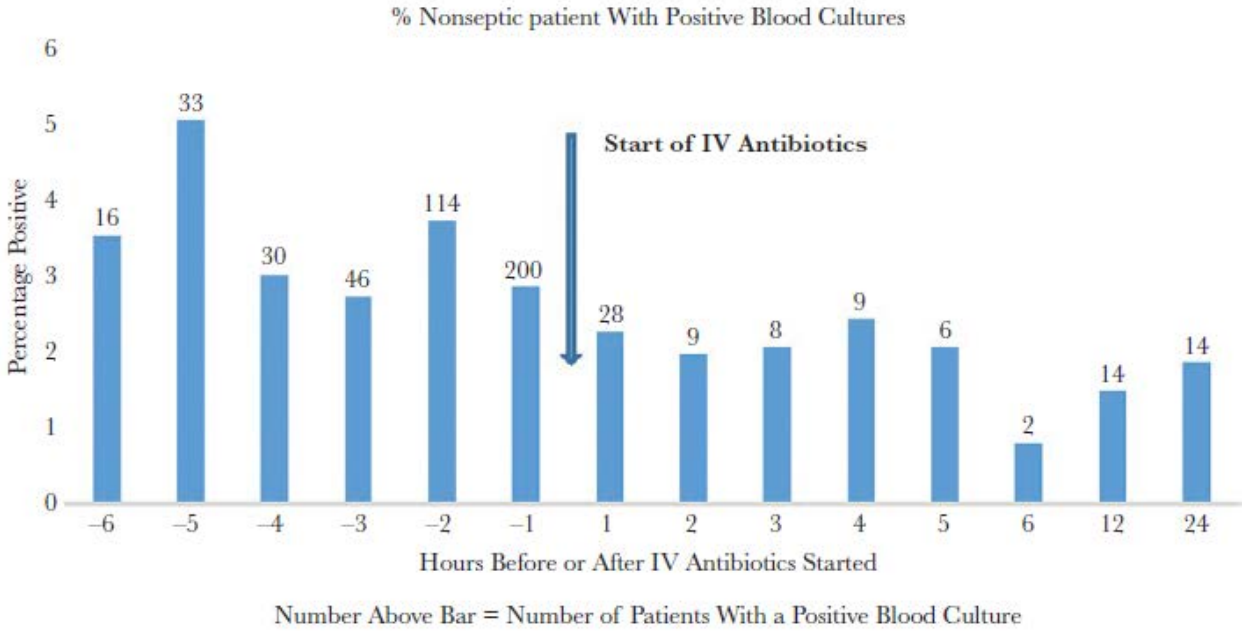
Vital to get at least 40ml, less important to get at different times

Hourly Effect of Pretreatment With IV Antibiotics on Blood Culture Positivity Rate in Emergency Department Patients

Kenneth H. Rand,[1] Stacy G. Beal,[1] Kimberly Rivera,[2] Brandon Allen,[2] Thomas Payton,[2] and Gloria P. Lipori[3]

Open Forum Infectious Diseases DOI: 10.1093/ofid/ofz179

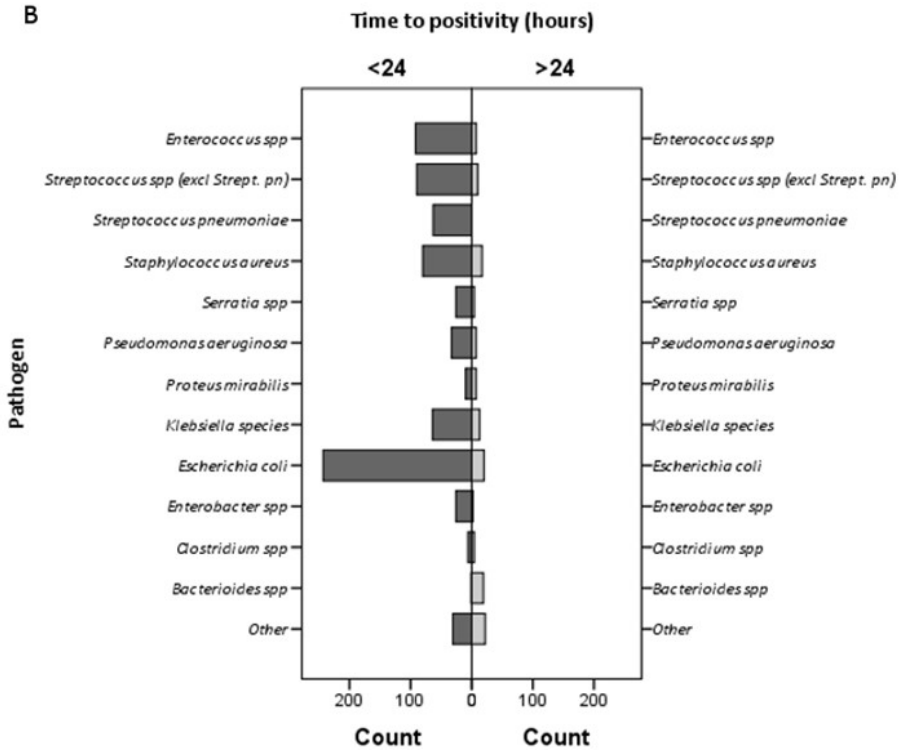


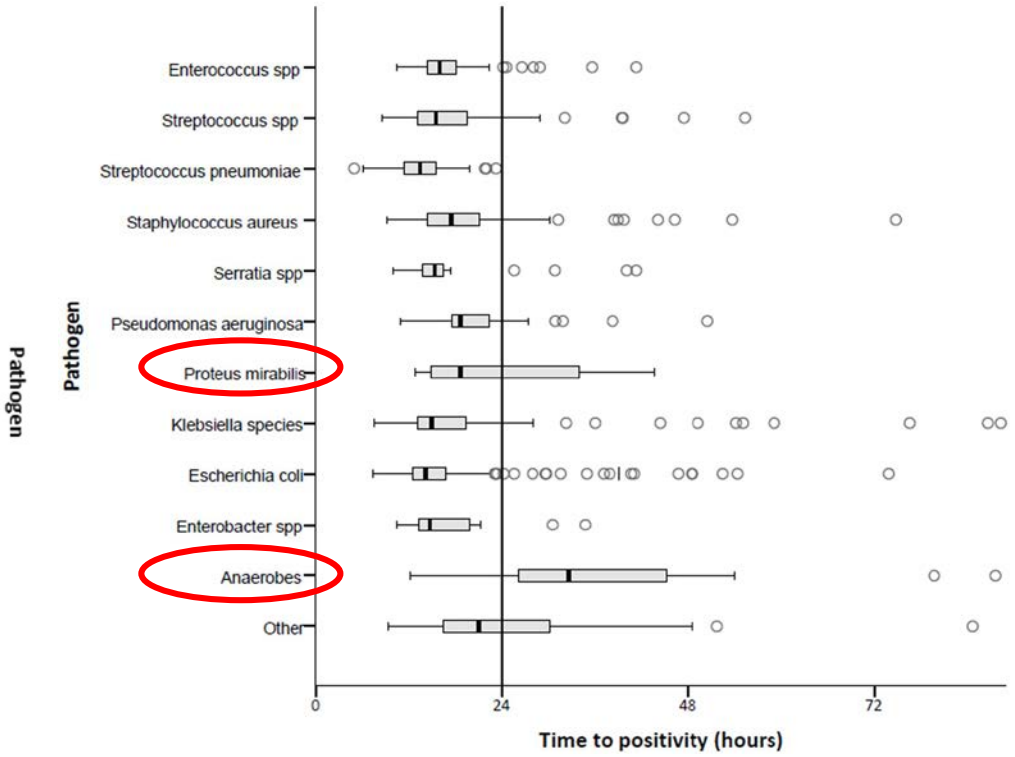


Time to positivity of blood cultures supports early re-evaluation of empiric broad-spectrum antimicrobial therapy

Merel M. C. Lambregts[1]*, Alexandra T. Bernards[2], Martha T. van der Beek[2], Leo G. Visser[1], Mark G. de Boer[1]

PLoS ONE 14(1): e0208819.





If modern blood culture systems are used in combination with adequate logistics, the probability of positivity when blood cultures are negative after 24 hours is very low. Postponing re-evaluation of the differential diagnosis, solely for the reason of pending blood culture results, is not rational at this time point. The search for alternative causes of fever can be initiated more rapidly if the probability of bacteremia is incorporated in clinical reasoning. This may lead to better timed de-escalation, iv to oral switch and earlier hospital discharge. The safety as well as the benefits of this antibiotic stewardship opportunity should be subject of future clinical trials.

Optimised pharmacodynamics

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

Jason A. Roberts[1–3]*, Carl M. J. Kirkpatrick[4], Michael S. Roberts[5], Thomas A. Robertson[5], Andrew J. Dalley[1] and Jeffrey Lipman[1,3]

Journal of Antimicrobial Chemotherapy (2009) **64**, 142–150

Table 3. CFR (%) for meropenem on day 1 of treatment for Gram-negative pathogens for various intermittent bolus, extended and continuous dosing strategies of meropenem in critically ill patients with sepsis

		Intermittent bolus dosing			Extended infusion			Continuous infusion		
Organism	MIC_{90} (mg/L)	500 mg 8 hourly	1000 mg 8 hourly	2000 mg 8 hourly	500 mg 8 hourly	1000 mg 8 hourly	2000 mg 8 hourly	1500 mg/day	3000 mg/day	6000 mg/day
E. coli	0.06	100	100	100	100	100	100	100	100	100
K. pneumoniae	0.06	100	100	100	100	100	100	100	100	100
Enterobacter sp.	0.12	100	100	100	100	100	100	100	100	100
S. marcescens	0.12	100	100	100	100	100	100	100	100	100
Citrobacter sp.	0.12	100	100	100	100	100	100	100	100	100
P. aeruginosa	8	12.5	40.6	68.8	50	68.8	96.9	43.8	100	100
Acinetobacter sp.	16	3.1	12.5	40.6	0	50	68.8	3.8	4.1	100

Extended and continuous infusion higher cumulative fractional response for gram negative bacteria with high MIC (8-16)

Pharmacokinetics-Pharmacodynamics of Antimicrobial Therapy: It's Not Just for Mice Anymore

Paul G. Ambrose,[1] Sujata M. Bhavnani,[1] Christopher M. Rubino,[1] Arnold Louie,[2] Tawanda Gumbo,[2] Alan Forrest,[1] and George L. Drusano[2]

Clinical Infectious Diseases 2007; 44:79–86

Table 2. Pharmacokinetic-pharmacodynamic (PK-PD) targets derived from animal infection models and clinical data.

Disease state, drug	Clinically-derived PK-PD target [reference(s)]	Animal infection model; organism studied	Animal-derived PK-PD target [reference(s)]
Hospital-acquired pneumonia			
Quinolones	*f*AUC_{0-24}:MIC ratio, 62–75 [11, 12]	Neutropenic mouse thigh; gram-negative bacilli	*f*AUC_{0-24}:MIC ratio, 70–90 for 90% animal survival or 2 log-unit kill [13, 14]
Community-acquired respiratory tract infections			
Quinolones	*f*AUC_{0-24}:MIC ratio, 34 [22]	Immunocompetent mouse thigh; *Streptococcus pneumoniae*	*f*AUC_{0-24}:MIC ratio, 25–34 for 90% animal survival or 2 log-unit kill [23]
β-Lactams	T>MIC, 40% of the dosing interval [14]	Immunocompetent mouse thigh; *S. pneumoniae*	T>MIC, 30–40% of the dosing interval for 90% animal survival [14]
Telithromycin	AUC_{0-24}:MIC ratio, 3.375 [20]	Neutropenic mouse thigh; *S. pneumoniae*	AUC_{0-24}:MIC ratio, 1000 for stasis [24]
Bacteremia			
Oritavancin	*f*T>MIC, 22% of the dosing interval for *Staphylococcus aureus* [25]	Neutropenic mouse thigh; *S. aureus*	*f*T>MIC, 20% of the dosing interval for a 0.5 log-unit kill [26]
Linezolid	AUC_{0-24}:MIC ratio, 85 for *S. aureus* or *Enterococcus faecium* [27]	Neutropenic mouse thigh; *S. aureus*	AUC_{0-24}:MIC ratio, 83 for stasis [33]
Complicated skin and skin structure infections			
Tigecycline	AUC_{0-24}:MIC ratio, 17.9 [28]	Neutropenic mouse thigh; *S. aureus*	AUC_{0-24}:MIC ratio, 15–20 for stasis [29]
Linezolid	AUC_{0-24}:MIC ratio, 110 [27]	Neutropenic mouse thigh; *S. aureus*	AUC_{0-24}:MIC ratio, 83 for stasis [33]

Clinical Outcomes With Extended or Continuous Versus Short-term Intravenous Infusion of Carbapenems and Piperacillin/Tazobactam: A Systematic Review and Meta-analysis

Matthew E. Falagas,[1,2,4] Giannoula S. Tansarli,[1] Kazuro Ikawa,[3] and Konstantinos Z. Vardakas[1,2]

Clinical Infectious Diseases 2013;56(2):272–82

- Carbapenems and tazocin, mainly non-randomised studies (14 studies, n=1229)
- Lower mortality among extended infusions (RR 0.59, 95%CI 0.41-0.83) and pneumonia (RR 0.50, 95%CI 0.26-0.96)

Prolonged infusion versus intermittent boluses of β-lactam antibiotics for treatment of acute infections: a meta-analysis

Jocelyn Teo, Yixin Liew, Winnie Lee, Andrea Lay-Hoon Kwa*

International Journal of Antimicrobial Agents 43 (2014) 403–411

- 29 studies, 18 RCT, 2206 patients, beta-lactams
- Prolonged infusion reduced mortality (RR 0.66, 95%CI 0.53-0.83) and higher clinical success (RR 1.12, 95%CI 1.03-1.21)
- Benefit in non-randomised studies but not randomised clinical trials

A Multicenter Randomized Trial of Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis

Joel M. Dulhunty[1,2], Jason A. Roberts[1,2,3], Joshua S. Davis[4,5], Steven A. R. Webb[6,7], Rinaldo Bellomo[8,9], Charles Gomersall[10,11], Charudatt Shirwadkar[12], Glenn M. Eastwood[8], John Myburgh[13,14], David L. Paterson[15,16], Therese Starr[1,2], Sanjoy K. Paul[17], and Jeffrey Lipman[1,2]; for the BLING II Investigators for the ANZICS Clinical Trials Group*

Am J Respir Crit Care Med Vol 192, Iss 11, pp 1298–1305, Dec 1, 2015

Table 1. Baseline Characteristics of the Intention-to-Treat Population

	Continuous (*n* = 212)	Intermittent (*n* = 220)
Age, yr	64 (54–72)	65 (53–72)
Sex, male	130 (61.3)	135 (61.4)
APACHE II score	21 (17–26)	20 (16–25)
Immunocompromise	27 (12.7)	34 (15.5)
Study drug		
Piperacillin–tazobactam	147 (69.3)	157 (71.4)
Meropenem	63 (29.7)	60 (27.3)
Ticarcillin–clavulanate	2 (0.9)	3 (1.4)
Site of infection*		
Lung	115 (54.2)	120 (54.5)
Intraabdominal	53 (25.0)	57 (25.9)
Primary bloodstream infection	17 (8.0)	18 (8.2)
Urinary tract	16 (7.5)	18 (8.2)
Skin or skin structure	13 (6.1)	18 (8.2)
Other†	22 (10.4)	12 (5.5)
Unknown	14 (6.6)	14 (6.4)
Organ dysfunction		
Cardiovascular (shock)	154 (72.6)	163 (74.1)
Respiratory	135 (63.7)	139 (63.2)
Metabolic acidosis	68 (32.1)	70 (31.8)
Renal	49 (23.1)	53 (24.1)
Hematologic	26 (12.3)	22 (10.0)

Table 3. Primary and Secondary Outcomes, Clinical Results, and Adverse Events

	Continuous (*n* = 212)	Intermittent (*n* = 220)	*P* Value
Alive ICU-free days	18 (2–24)	20 (3–24)	0.38
ICU survivors	21 (12–24)	22 (14–25)	0.12
Day-90 survival*†	156 (74.3)	158 (72.5)	0.67
ICU survival†	180 (84.9)	182 (82.7)	0.54
Hospital survival†‡	168 (79.2)	164 (74.9)	0.28
Clinical cure	111 (52.4)	109 (49.5)	0.56
Organ failure–free days	6 (0–10)	6 (0–11)	0.27
Duration of bacteremia, d§	0 (0–0)	0 (0–1)	0.24
ICU length of stay, d‖	7 (3–13)	6 (3–11)	0.042
Hospital length of stay, d‖	16 (8–32)	14 (8–27)	0.25
Adverse events	20 (9.4)	28 (12.7)	0.28
Serious adverse events	19 (9.0)	25 (11.4)	0.41

N=432, 25 ICU Australia, New Zealand and Hong Kong, tazocin 69.3-71.4%
Pneumonia 54.2-54.5%, intra-abdominal 25.0-25.9%
Similar ICU survival, 90-day survival, clinical cure, organ failure, days of bacteraemia and hospitalisation, and adverse events
Continuous infusion one day longer ICU stay

Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis

Intensive Care Med (2016) 42:1535–1545

Mohd H. Abdul-Aziz
Helmi Sulaiman
Mohd-Basri Mat-Nor
Vineya Rai
Kang K. Wong
Mohd S. Hasan
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Janattul A. Jamal
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Jeffrey Lipman
Christine E. Staatz
Jason A. Roberts

N=140, 2 ICU in Malaysia

Table 2 Primary and secondary endpoints by treatment arm in the intention-to-treat population and the subgroups of interest

Primary endpoint	Intervention ($n = 70$)	Control ($n = 70$)	Absolute difference (95 % CI)	Significance (p value)[a,b]
Clinical cure for ITT population, n (%)	39 (56)	24 (34)	22 (−0.4 to −0.1)	**0.011**
Clinical cure by antibiotic, n (%)[c]				
Piperacillin/tazobactam	22 (58)	15 (32)	26 (−0.4 to −0.1)	**0.016**
Meropenem	14 (67)	8 (38)	29 (−0.5 to 0.1)	0.064
Cefepime	3 (27)	1 (50)	23 (−0.3 to 0.7)	1.000
Clinical cure by concomitant antibiotic treatment, n (%)[d]				
Yes	14 (42)	13 (39)	3 (−0.3 to 0.2)	0.802
No	25 (68)	11 (30)	38 (−0.6 to −0.2)	**0.001**
Clinical cure by site of infection, n (%)[e]				
Lung	27 (59)	12 (33)	25 (−0.4 to −0.1)	**0.022**
Clinical cure by *A. baumannii* or *P. aeruginosa* infection, n (%)[f]				
Yes	13 (52)	6 (25)	27 (−0.5 to 0.1)	0.052
No	10 (44)	12 (38)	6 (−0.3 to 0.2)	0.655

Secondary endpoints	Intervention ($n = 70$)	Control ($n = 70$)	Absolute difference (95 % CI)	Significance (p value)[a,b]
PK/PD target attainment, n (%)[g]				
50 % $fT_{>MIC}$ on day 1	56 (98)	49 (93)	5 (−0.2 to 0.1)	0.194
100 % $fT_{>MIC}$ on day 1	55 (97)	37 (70)	27 (−0.4 to −0.1)	**<0.001**
50 % $fT_{>MIC}$ on day 3	56 (98)	49 (93)	5 (−0.2 to 0.1)	0.194
100 % $fT_{>MIC}$ on day 3	55 (97)	36 (68)	29 (−0.4 to −0.1)	**<0.001**
ICU-free days	20 (12–23)	17 (0–24)	3 (−3 to 9)	0.378
ICU survivors[h]	21 (19–23)	21 (14–24)	0 (−3 to 3)	0.824
Ventilator-free days	22 (0–24)	14 (0–24)	8 (−2 to 18)	**0.043**
ICU survivors[i]	23 (21–25)	21 (0–25)	2 (−3 to 7)	0.076
14-day survival, n (%)	56 (80)	50 (71)	9 (−0.2 to 0.1)	0.237
30-day survival, n (%)	52 (74)	44 (63)	11 (−0.3 to 0.1)	0.145
WCC normalisation days	3 (2–7)	8 (4–15)	5 (1 to 5)	**<0.001**

Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis

A Meta-analysis of Individual Patient Data from Randomized Trials

Jason A. Roberts[1,2,3,4], Mohd-Hafiz Abdul-Aziz[2,5], Joshua S. Davis[6,7], Joel M. Dulhunty[1,2,8], Menino O. Cotta[1,2,3,4], John Myburgh[9,10], Rinaldo Bellomo[11,12], and Jeffrey Lipman[1,2]

Am J Respir Crit Care Med Vol 194, Iss 6, pp 681–691, Sep 15, 2016

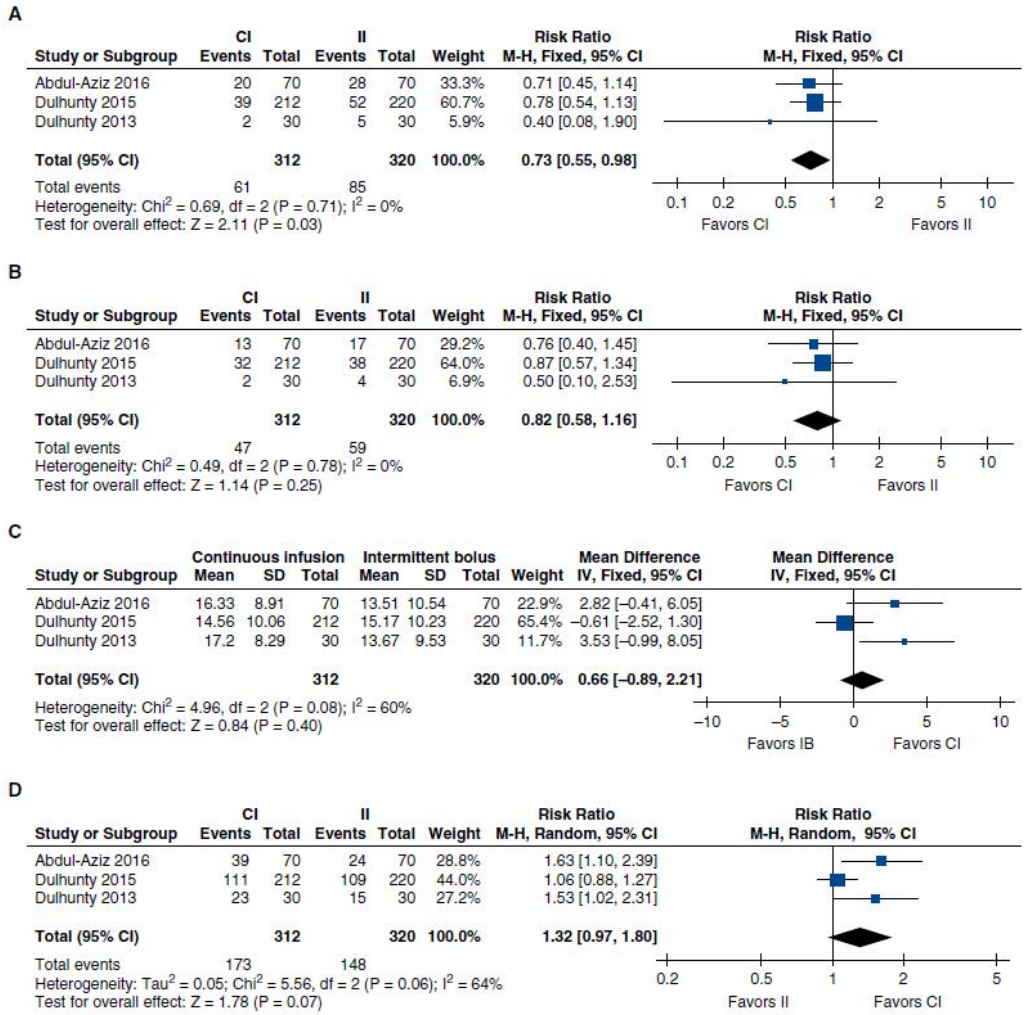

Figure 2. Differences in mortality and clinical cure, along with 95% confidence intervals (95% CIs), for continuous infusion (CI) versus intermittent infusion (II). (*A*) Hospital mortality censored at Day 30. (*B*) Intensive care unit mortality. (*C*) Intensive care unit–free days at Day 28. (*D*) Clinical cure. df = degrees of freedom; IB = intermittent bolus; IV = inverse variance; M-H = Mantel–Haenszel test.

Hospital mortality

respectively. In a multivariable model, intermittent β-lactam administration, higher Acute Physiology and Chronic Health Evaluation II score, use of renal replacement therapy, and infection by nonfermenting gram-negative bacilli were significantly associated with hospital mortality. Continuous β-lactam administration was not independently associated with clinical cure.

ICU mortality

ICU free days

Clinical cure

wardship 2016

Ongoing randomised controlled trial

- BLING III
- Jeff Lipman
- Sepsis, ICU, piperacillin-tazobactam or carbapenem
- Continuous vs intermittent infusions
- 90 day mortality
- N=7000
- 2018 → 2022
- Status: recruiting

Duration of antibiotic for gram negative bacteraemia: Still two weeks?

Comparing the Outcomes of Adults With Enterobacteriaceae Bacteremia Receiving Short-Course Versus Prolonged-Course Antibiotic Therapy in a Multicenter, Propensity Score–Matched Cohort

Darunee Chotiprasitsakul,[1] Jennifer H. Han,[2] Sara E. Cosgrove,[3] Anthony D. Harris,[4] Ebbing Lautenbach,[2] Anna T. Conley,[5] Pam Tolomeo,[2] Jacqueleen Wise,[2] and Pranita D. Tamma[6]; for the Antibacterial Resistance Leadership Group

Clinical Infectious Diseases® 2018;66(2):172–7

Table 1. Baseline Characteristics of Hospitalized Adult Patients With Enterobacteriaceae Bacteremia Receiving Short (6–10 Days) or Prolonged Courses (11–16 Days) of Antibiotic Therapy

	Whole Cohort			Propensity Score–Matched Cohort		
Characteristic	Short Course (n = 385)	Prolonged Course (n = 1384)	*P* Value	Short Course (n = 385)	Prolonged Course (n = 385)	*P* Value
Age, y, median (IQR)	60 (46–69)	58 (46–69)	.20	60 (49–69)	60 (49–70)	.73
Female sex	191 (49.6)	699 (50.5)	.76	191 (49.6)	174 (45.2)	.22
Race/ethnicity			.13			.15
White	196 (50.9)	647 (46.7)	.15	196 (50.9)	177 (46.0)	.17
Black or African American	154 (40.0)	584 (42.2)	.44	154 (40.0)	161 (41.8)	.61
Asian	11 (2.9)	62 (4.5)	.16	11 (2.9)	17 (4.4)	.25
Latino	8 (2.1)	51 (3.7)	.12	8 (2.1)	18 (4.7)	.05
Unknown or multiracial	16 (4.2)	40 (2.9)	.21	16 (4.2)	12 (3.1)	.44
Source of bacteremia						
Pneumonia	36 (9.4)	109 (7.9)	.35	36 (9.4)	33 (8.6)	.71
Skin and soft tissue	14 (3.6)	43 (3.1)	.60	14 (3.6)	17 (4.4)	.58
Urinary tract	134 (34.8)	566 (40.9)	.03	134 (34.8)	144 (37.4)	.45
Biliary	60 (15.6)	156 (11.3)	.02	60 (15.6)	65 (16.9)	.63
Gastrointestinal	87 (22.6)	261 (18.9)	.24	87 (22.6)	66 (17.1)	.12
Catheter-associated	54 (14.0)	240 (17.3)	.12	54 (14.0)	52 (13.5)	.83
Inadequate source control during antibiotic course	3 (0.8)	36 (2.6)	.48	3 (0.8)	4 (1.0)	.45
Pitt bacteremia score on day 1 of bacteremia, median (IQR)	2 (1–3)	2 (1–3)	.84	2 (1–3)	2 (1–3)	.59
Intensive care unit on day 1 of bacteremia	113 (29.4)	403 (29.1)	.93	113 (29.4)	122 (31.7)	.48
Preexisting medical conditions						
End-stage liver disease	35 (9.1)	87 (6.3)	.06	35 (9.1)	31 (8.1)	.61
ESRD requiring dialysis	18 (4.7)	59 (4.3)	.73	18 (4.7)	21 (5.5)	.62
Structural lung disease[a]	34 (8.8)	109 (7.9)	.54	34 (8.8)	24 (6.2)	.17
CHF with an ejection fraction <45%	46 (11.9)	131 (9.5)	.15	46 (11.9)	51 (13.2)	.59
Diabetes	96 (24.9)	325 (23.5)	.55	96 (24.9)	96 (24.9)	1.00
Immunocompromised[b]	127 (33.0)	523 (37.8)	.08	127 (33.0)	134 (34.8)	.59
HIV	14 (3.6)	63 (4.6)	.44	14 (3.6)	21 (5.5)	.23
Chemotherapy within 6 mo	93 (24.2)	419 (30.3)	.02	93 (24.2)	106 (27.5)	.29
Absolute neutrophil count ≤100 cells/μL	24 (6.2)	108 (7.8)	.30	24 (6.2)	22 (5.7)	.76
Immunomodulatory therapy or corticosteroids for ≥14 d	23 (6.0)	56 (4.0)	.01	23 (6.0)	16 (4.1)	.32

Comparing the Outcomes of Adults With Enterobacteriaceae Bacteremia Receiving Short-Course Versus Prolonged-Course Antibiotic Therapy in a Multicenter, Propensity Score–Matched Cohort

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Table 2. Enterobacteriaceae Isolated in the Bloodstream of Hospitalized Adult Patients Between 2008 and 2014

		Duration of Therapy in Matched Cohort	
Enterobacteriaceae	Entire Cohort (N = 1769)	6–10 d (n = 385)	11–16 d (n = 385)
Escherichia coli	841 (47.5)	177 (46.0)	184 (47.8)
Klebsiella species	557 (31.5)	137 (35.6)	114 (29.6)
Enterobacter species	200 (11.3)	36 (9.4)	54 (14.0)
Serratia species	58 (3.3)	13 (3.4)	9 (2.3)
Proteus species	81 (4.6)	13 (3.4)	14 (3.6)
Citrobacter species	32 (1.8)	9 (2.3)	10 (2.6)

Table 3. Thirty-Day All-Cause Mortality for Hospitalized Adult Patients With Enterobacteriaceae Bacteremia in a Propensity Score–Matched Cohort

Variable	Unadjusted HR (95% CI)	*P* Value	Adjusted HR[a] (95% CI)	*P* Value
Short-course therapy (6–10 d)	1.12 (.70–1.80)	.64	1.00 (.62–1.63)	.97
Urinary source	0.36 (.19–.67)	.001	0.49 (.26–.94)	.03
Pneumonia	3.06 (1.73–5.42)	<.001	1.60 (.85–3.02)	.15
Pitt bacteremia score	1.31 (1.21–1.42)	<.001	1.29 (1.17–1.43)	<.001
ICU on day 1 of bacteremia	2.38 (1.48–3.81)	<.001	0.99 (.56–1.76)	.98
End-stage liver disease	3.58 (2.05–6.06)	<.001	4.12 (2.30–7.39)	<.001
Immunocompromised status	1.03 (.63–1.70)	.89	1.40 (.83–2.36)	.21

Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial

Dafna Yahav,[1,2] Erica Franceschini,[3] Fidi Koppel,[4] Adi Turjeman,[2,5] Tanya Babich,[2,5] Roni Bitterman,[4] Ami Neuberger,[4,6] Nesrin Ghanem-Zoubi,[4] Antonella Santoro,[3] Noa Eliakim-Raz,[1,2] Barak Pertzov,[5] Tali Steinmetz,[5] Anat Stern,[4] Yaakov Dickstein,[4] Elias Maroun,[4] Hiba Zayyad,[4] Jihad Bishara,[1,2] Danny Alon,[7] Yonatan Edel,[2,8] Elad Goldberg,[9] Claudia Venturelli,[3] Cristina Mussini,[3] Leonard Leibovici,[2,5] Mical Paul[4,6]; for the Bacteremia Duration Study Group[a]

Clinical Infectious Diseases® 2018:XX(XX):1–8

Table 1. Baseline Characteristics of Included Patients

Variable	Short-duration Arm (7 d) (n = 306)	Long-duration Arm (14 d) (n = 298)
Patient characteristics		
Age, y, median (IQR)	71 (61.8–81)	71 (61–80)
Sex, female	156 (51.0)	163 (54.7)
Center		
Rambam Hospital, Israel	133 (43.5)	118 (39.6)
Beilinson Hospital, Israel	131 (42.8)	143 (48.0)
Hospital of Modena, Italy	42 (13.7)	37 (12.4)
Charlson comorbidity score, median (IQR)	2 (1–3)	2 (1–4)
Malignancy		
None	222 (72.5)	223 (74.8)
Solid	64 (20.9)	58 (19.5)
Hematological	20 (6.5)	17 (5.7)
Immunosuppression[a]		
Any	69 (22.5)	81 (27.2)
Solid organ transplantation	25 (8.2)	26 (8.7)
Stem cell transplantation	2 (0.7)	3 (1.0)
Functional capacity		
Independent	186 (61.1)	189 (63.4)
Needs assistance in ADL	53 (17.3)	44 (14.8)
Dependent in ADL	40 (13.1)	51 (17.1)
Bedridden	26 (8.5)	14 (4.7)
Devices at baseline		
Urinary device[b]	61 (19.9)	72 (24.2)
Central venous catheter	22 (7.2)	19 (6.4)
Endotracheal tube	8 (2.6)	8 (2.7)
Prosthetic valve/intracardiac implantable device	14 (4.6)	13 (4.4)
Infection characteristics		
Hospital-acquired infection	81 (26.5)	95 (31.9)

Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial

Dafna Yahav,[1,2] Erica Franceschini,[3] Fidi Koppel,[4] Adi Turjeman,[2,5] Tanya Babich,[2,5] Roni Bitterman,[4] Ami Neuberger,[4,6] Nesrin Ghanem-Zoubi,[4] Antonella Santoro,[3] Noa Eliakim-Raz,[1,2] Barak Pertzov,[5] Tali Steinmetz,[5] Anat Stern,[4] Yaakov Dickstein,[4] Elias Maroun,[4] Hiba Zayyad,[4] Jihad Bishara,[1,2] Danny Alon,[7] Yonatan Edel,[2,8] Elad Goldberg,[9] Claudia Venturelli,[3] Cristina Mussini,[3] Leonard Leibovici,[2,5] Mical Paul[4,6]; for the Bacteremia Duration Study Group[a]

Clinical Infectious Diseases® 2018;XX(XX):1–8

Presentation of infection		
SOFA score at presentation, median (IQR)	2 (1–3)	2 (1–3)
Leukocytes at presentation, cells/μL, median (IQR)	10.6 (7.4–15.4) (n = 306)	11.3 (7.8–15.2) (n = 297)
Creatinine at presentation, mg/dL, median (IQR)	1.2 (0.9–1.7) (n = 304)	1.3 (0.8–1.8) (n = 297)
Albumin at presentation, g/dL, median (IQR)	3.3 (2.7–3.8) (n = 195)	3.3 (2.9–3.8) (n = 197)
SOFA score at randomization, median (IQR)	1 (0–2)	1 (0–2)
Systolic blood pressure at randomization, mm Hg, median (IQR)	128.0 (115.0–144.3)	126.0 (110.0–140.0)
Temperature at randomization, °C, median (IQR)	36.8 (36.6–37.1) (n = 304)	36.8 (36.6–37.0) (n = 298)
Appropriate empirical therapy administered within 48 h	260 (85.0)	242 (81.2)
Bacteria type[c]		
Escherichia coli	186 (60.8)	194 (65.1)
Klebsiella spp	47 (15.3)	33 (11.1)
Other Enterobacteriaceae	40 (13.1)	43 (14.4)
Acinetobacter spp	2 (0.7)	4 (1.3)
Pseudomonas spp	28 (9.2)	20 (6.7)
Other	3 (1)	4 (1.3)
MDR gram-negative bacteremia[d]	58 (18.9)	51 (17.1)
Source of bacteremia		
Urinary tract	212 (69.3)	199 (66.8)
Primary bacteremia	23 (7.5)	28 (9.4)
Abdominal	37 (12.1)	34 (11.4)
Respiratory	14 (4.6)	10 (3.4)
Central venous catheter	15 (4.9)	23 (7.7)
Skin and soft tissue	5 (1.6)	4 (1.3)

Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial

Dafna Yahav,[1,2] Erica Franceschini,[3] Fidi Koppel,[4] Adi Turjeman,[2,5] Tanya Babich,[2,5] Roni Bitterman,[4] Ami Neuberger,[4,6] Nesrin Ghanem-Zoubi,[4] Antonella Santoro,[3] Noa Eliakim-Raz,[1,2] Barak Pertzov,[5] Tali Steinmetz,[5] Anat Stern,[4] Yaakov Dickstein,[4] Elias Maroun,[4] Hiba Zayyad,[4] Jihad Bishara,[1,2] Danny Alon,[7] Yonatan Edel,[2,8] Elad Goldberg,[9] Claudia Venturelli,[3] Cristina Mussini,[3] Leonard Leibovici,[2,5] Mical Paul[4,6]; for the Bacteremia Duration Study Group[a]

Clinical Infectious Diseases® 2018;XX(XX):1–8

Table 2. Outcomes of 7 Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-Negative Bacteremia

Outcome	Short Arm (7 d) (n = 306)	Long Arm (14 d) (n = 298)	Risk Difference (95% CI)	*P* Value
Primary outcome	140 (45.8)	144 (48.3)	−2.6 (−10.5 to 5.3)	.527
90-d all-cause mortality	36 (11.8)	32 (10.7)	1.0 (−4.0 to 6.1)	.702
Readmissions	119 (38.9)	127 (42.6)	−3.7 (−11.5 to 4.1)	.363
Extended hospitalization beyond 14 d	15 (4.9)	19 (6.4)	−1.5 (−5.1 to 2.2)	.483
Distant complications	2 (0.7)	1 (0.3)	…	1.0
Relapse of bacteremia	8 (2.6)	8 (2.7)	−0.07 (−2.6 to 2.5)	.957
Suppurative complications	16 (5.2)	10 (3.4)	1.8 (−1.4 to 5.1)	.257
14-d mortality	7 (2.3)	4 (1.3)	0.95 (−1.42 to 3.44)	.288
28-d mortality	15 (4.9)	13 (4.4)	0.54 (−2.98 to 4.06)	.753
New clinically or microbiologically documented infection	70 (22.9)	68 (22.8)	0.06 (−6.6 to 6.8)	.987
Functional capacity: needs assistance/dependent in ADL or bedridden at 30 d	150 (51.4) (n = 292)	163 (57.2) (n = 285)	−5.8 (−13.9 to 2.3)	.031
Resistance development	33 (10.8)	29 (9.7)	1.0 (−3.7 to 5.9)	.690
Time to return to baseline activity, wk (90 d)	2 (0–8.3) (n = 218)	3 (1–12) (n = 222)	…	**.010**
Total hospital days (90 d from randomization)—survivors	3 (1–9) (n = 270 alive at day 90)	3.5 (1–10) (n = 266 alive at day 90)	…	.923
Total hospital days (90 d from randomization)—all	4 (1–10)	4 (1–12)	…	.603
Duration of appropriate antibiotic therapy for bacteremia	7 (7.0–8.0)	14.0 (14.0–14.0)	…	**< .001**
Total antibiotic days from culture collection to day 90 postrandomization	10.0 (9.0–18.0) (n = 270 alive at day 90)	16.0 (15.0–22.0) (n = 266 alive at day 90)	…	**< .001**
Adverse events				
Acute kidney injury	14 (4.6)	12 (4.0)	0.5 (−2.7 to 3.8)	.842
Liver function abnormalities	16 (5.2)	20 (6.7)	−1.5 (−5.3 to 2.3)	.494
Diarrhea during hospital stay	17 (5.6)	23 (7.7)	−2.2 (−6.1 to 1.8)	.285
Diarrhea until day 90[a]	49 (16)	54 (18.1)	−2.1 (−8.1 to 3.9)	.491
Rash	2 (0.7)	4 (1.4)	…	.445
Clostridium difficile infection	3 (1.0)	1 (0.3)	…	.322

Effect of C-Reactive Protein–Guided Antibiotic Treatment Duration, 7-Day Treatment, or 14-Day Treatment on 30-Day Clinical Failure Rate in Patients With Uncomplicated Gram-Negative Bacteremia

A Randomized Clinical Trial

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JAMA. 2020;323(21):2160-2169.

Table 3. Clinical Outcomes in a Study of the Effect of C-Reactive Protein (CRP)–Guided, 7-Day, or 14-Day Antibiotic Treatment Duration on Clinical Failure in Patients With Gram-Negative Bacteremia

	Antibiotic therapy duration group, No. (%)			CRP-guided vs 14 d		7 d vs 14 d	
Outcome	CRP-guided (n = 169)	7 d (n = 169)	14 d (n = 165)	Difference, % (1-sided 97.5% CI)	*P* value[a]	Difference, % (1-sided 97.5% CI)	*P* value[a]
Primary outcome							
Clinical response through day 30				−3.1 (−∞ to 1.1)	<.001	1.1 (−∞ to 6.3)	<.001
Clinical success	160 (97.6)	155 (93.4)	154 (94.5)				
Clinical failure	4 (2.4)	11 (6.6)	9 (5.5)				
Recurrent bacteremia	0	1 (9)[a]	2 (22)				
Suppurative local complication	0	2 (18)[b]	1 (11)				
Distal complication	0	0	0				
Targeted therapy restart	2 (50)	3 (27)	2 (22)				
30-d all-cause mortality[c]	2 (50)	6 (55)	4 (44)				
Missing[d]	5 (2.9)	3 (1.8)	2 (1.2)				
Secondary outcomes							
Clinical response through day 60				−1.8 (−∞ to 3.7)	<.001	2.6 (−∞ to 8.9)	.010
Clinical success	146 (94.2)	141 (89.8)	146 (92.4)				
Clinical failure	9 (5.8)	16 (10.2)	12 (7.6)				
Recurrent bacteremia	0	1 (6)[b]	2 (17)				
Suppurative local complication	0	1 (6)[b]	1 (8)				
Distal complication	0	0	0				
Targeted therapy restart	7 (78)	9 (56)	5 (42)				
30-d all-cause mortality[c]	2 (22)	6 (38)	4 (33)				
Missing[d]	9 (5.3)	7 (4.1)	3 (1.8)				
Death after day 30	5 (3.0)	5 (3.0)	4 (2.4)				
Clinical response through day 90				−3.5 (−∞ to 2.9)	<.001	0.1 (−∞ to 7.0)	.002
Clinical success	133 (93.0)	135 (89.4)	137 (89.5)				
Clinical failure	10 (7.0)	16 (10.6)	16 (10.5)				
Recurrent bacteremia	0	1 (6)[b]	2 (13)				
Suppurative local complication	0	1 (6)[b]	1 (6)				
Distal complication	0	0	0				
Targeted therapy restart	8 (80)	9 (56)	9 (56)				
30-d all-cause mortality[c]	2 (20)	6 (38)	4 (25)				
Missing[d]	15 (8.9)	10 (5.9)	7 (4.2)				
Death after day 30	11 (6.5)	8 (4.7)	5 (3.0)				

One ongoing randomised controlled trial

- BALANCE
- Nick Daneman
- Bacteraemia in ICU
- 7 vs 14 days
- 30 day mortality
- N=3598
- 2017 → 2022
- Status: recruiting

Treatment ESBL bacteraemia: Implications of MERINO trial

Antibiotic Therapy for *Klebsiella pneumoniae* Bacteremia: Implications of Production of Extended-Spectrum β-Lactamases

David L. Paterson,[1,2] Wen-Chien Ko,[3] Anne Von Gottberg,[4] Sunita Mohapatra,[5] Jose Maria Casellas,[6] Herman Goossens,[7] Lutfiye Mulazimoglu,[8] Gordon Trenholme,[5] Keith P. Klugman,[4] Robert A. Bonomo,[9] Louis B. Rice,[9] Marilyn M. Wagener,[1] Joseph G. McCormack,[2] and Victor L. Yu[1]

Clinical Infectious Diseases 2003; 39:31–7

Table 4. Antibiotic choice and mortality associated with bacteremia due to extended-spectrum β-lactamase–producing *Klebsiella pneumoniae*.

Type of therapy	All-cause 14-day mortality
Carbapenem monotherapy	1/27 (3.7)
Imipenem	1/24
Meropenem	0/3
Quinolone monotherapy (ciprofloxacin)	4/11 (36.3)
Cephalosporin monotherapy	2/5 (40)
Cefepime	1/2
Ceftriaxone	1/2
Cefotaxime	0/1
β-Lactam/β-lactamase inhbitor combination	2/4 (50)
Piperacillin-tazobactam	2/2
Ticarcillin-clavulanate	0/2
Aminoglycoside monotherapy (amikacin)	0/2 (0)
No active antibiotics	7/11 (63.6)

Comparison Between Carbapenems and β-Lactam/β-Lactamase Inhibitors in the Treatment for Bloodstream Infections Caused by Extended-Spectrum β-Lactamase-Producing *Enterobacteriaceae*: A Systematic Review and Meta-Analysis

Maged Muhammed, Myrto Eleni Flokas, Marios Detsis, Michail Alevizakos, and Eleftherios Mylonakis

Open Forum Infectious Diseases® DOI: 10.1093/ofid/ofx099

Empiric therapy

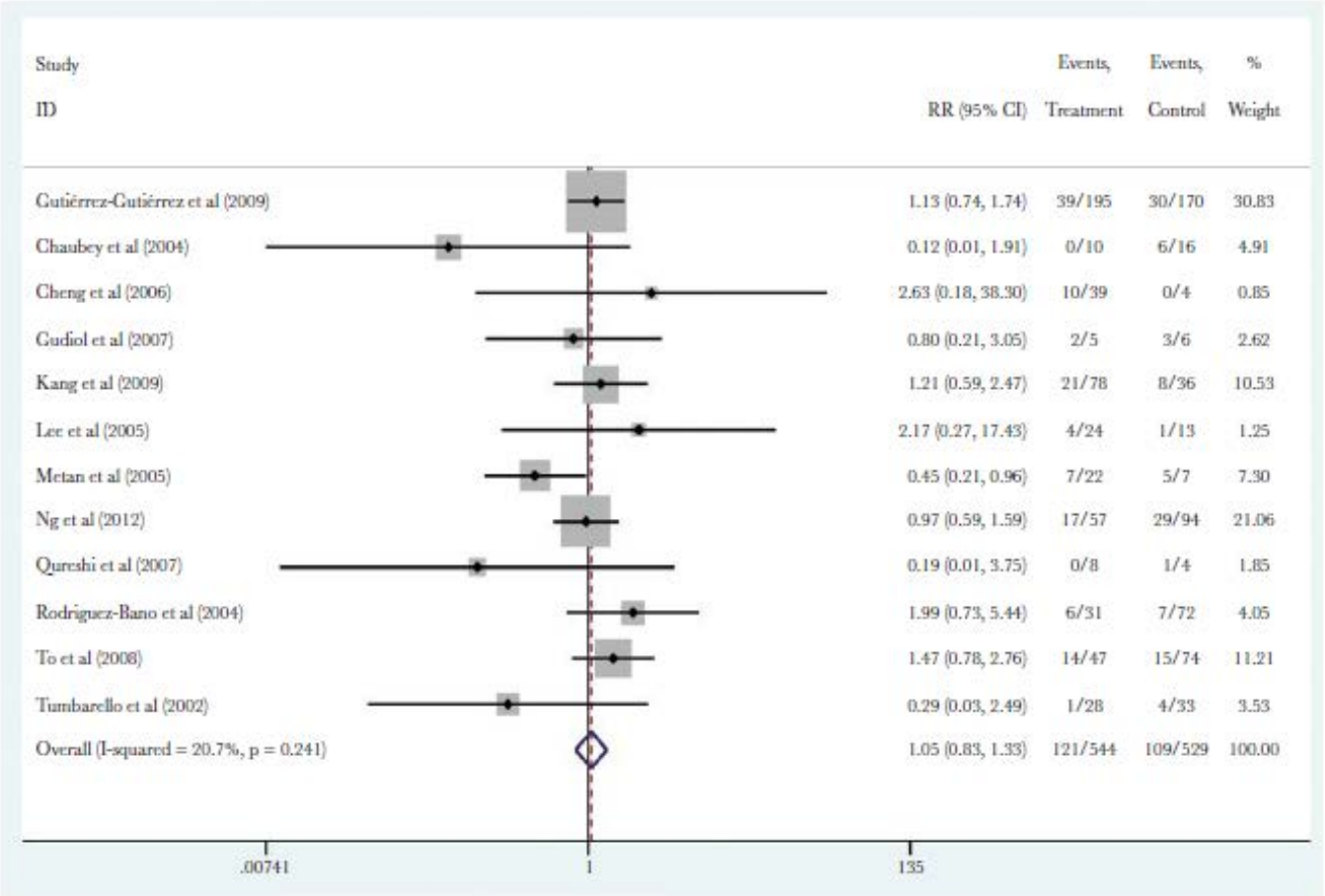

Figure 2. Forest plot of included studies. Relative risk (RR) of mortality among patients with extended-spectrum β-lactamase-producing *Enterobacteriaceae* bloodstream infections that were treated with empiric carbapenems versus empiric β-lactam/β-lactamase inhibitors. Abbreviation: CI, confidence interval.

Comparison Between Carbapenems and β-Lactam/β-Lactamase Inhibitors in the Treatment for Bloodstream Infections Caused by Extended-Spectrum β-Lactamase-Producing *Enterobacteriaceae*: A Systematic Review and Meta-Analysis

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Culture-guided therapy

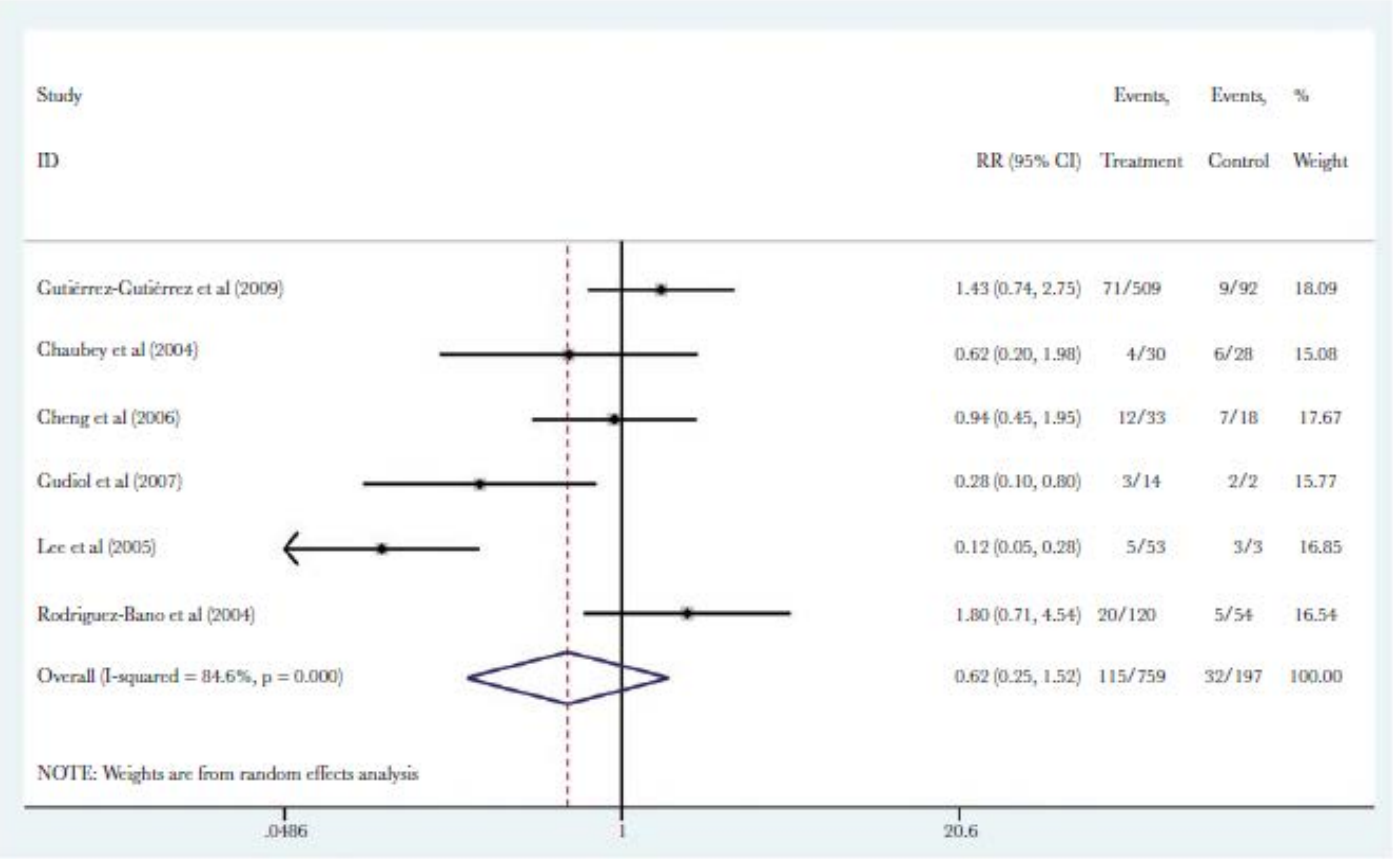

Figure 4. Forest plot of included studies. Relative risk (RR) of mortality among patients with extended-spectrum β-lactamase-producing *Enterobacteriaceae* bloodstream infections that were treated with definitive therapy with carbapenems versus definitive therapy with β-lactam/β-lactamase inhibitors. Abbreviation: CI, confidence interval.

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

A Randomized Clinical Trial

Patrick N. A. Harris, MBBS; Paul A. Tambyah, MD; David C. Lye, MBBS; Yin Mo, MBBS; Tau H. Lee, MBBS; Mesut Yilmaz, MD; Thamer H. Alenazi, MD; Yaseen Arabi, MD; Marco Falcone, MD; Matteo Bassetti, MD, PhD; Elda Righi, MD, PhD; Benjamin A. Rogers, MBBS, PhD; Souha Kanj, MD; Hasan Bhally, MBBS; Jon Iredell, MBBS, PhD; Marc Mendelson, MBBS, PhD; Tom H. Boyles, MD; David Looke, MBBS; Spiros Miyakis, MD, PhD; Genevieve Walls, MB, ChB; Mohammed Al Khamis, MD; Ahmed Zikri, PharmD; Amy Crowe, MBBS; Paul Ingram, MBBS; Nick Daneman, MD; Paul Griffin, MBBS; Eugene Athan, MBBS, MPH, PhD; Penelope Lorenc, RN; Peter Baker, PhD; Leah Roberts, BSc; Scott A. Beatson, PhD; Anton Y. Peleg, MBBS, PhD; Tiffany Harris-Brown, RN, MPH; David L. Paterson, MBBS, PhD; for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

JAMA. 2018;320(10):984-994.

Characteristic	Pipercillin-Tazobactam (n = 188)	Meropenem (n = 191)
Organism		
Escherichia coli	162 (86.2)	166 (86.9)
Klebsiella pneumoniae	26 (13.8)	25 (13.1)
Stratification[b]		
E1 (*E coli*, less severe infection)	159 (84.6)	162 (84.8)
E2 (*E coli*, more severe infection)	3 (1.6)	3 (1.6)
K1 (*K pneumoniae*, less severe infection)	23 (12.2)	25 (13.1)
K2 (*K pneumoniae*, more severe infection)	3 (1.6)	1 (0.5)
Country		
Singapore	72 (38.3)	82 (42.9)
Australia	42 (22.3)	43 (22.5)
New Zealand	10 (5.3)	9 (4.7)
Canada	1 (0.5)	1 (0.5)
South Africa	5 (2.7)	6 (3.1)
Italy	15 (8.0)	10 (5.2)
Turkey	24 (12.8)	22 (11.5)
Lebanon	8 (4.3)	7 (3.7)
Saudi Arabia	11 (5.9)	11 (5.8)
Age, median (IQR), y	70 (55-78)	69 (59-78)
Male	101 (53.7)	97 (50.8)
Acquisition		
Hospital-acquired	52 (27.7)	46 (24.1)
Health care-associated	55 (29.3)	61 (31.9)
Community-associated	81 (43.1)	84 (44.0)
Source of bacteremia		
Urinary tract	103 (54.8)	128 (67.0)
Intra-abdominal infection	34 (18.1)	28 (14.7)
Vascular catheter-related infection	3 (1.6)	3 (1.6)
Surgical site infection	8 (4.3)	4 (2.1)
Pneumonia	9 (4.8)	3 (1.6)
Mucositis/neutropenia	12 (6.4)	7 (3.7)
Musculoskeletal	1 (0.5)	0 (0)
Skin and soft tissue	4 (2.1)	1 (0.5)
Other	2 (1.1)	1 (0.5)
Unknown	12 (6.4)	16 (8.4)

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

A Randomized Clinical Trial

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JAMA. 2018;320(10):984-994.

Surgery within past 14 d	19 (10.1)	14 (7.3)
ICU admission	13 (7.0)	14 (7.5)
APACHE II Score, mean (SD)[c]	17.9 (6.1)	21.0 (6.9)
Charlson Comorbidity Index score, median (IQR)[d]	2.0 (1.0-4.0)	2.0 (1.0-4.0)
Pitt score, median (IQR)[e]	1.0 (0-2.0)	1.0 (0-2.0)
Immune compromise	51 (27.1)	40 (20.9)
Neutropenia	16 (8.5)	9 (4.7)
Central venous catheter	35 (18.6)	20 (10.5)
Urinary catheter/ nephrostomy	51 (27.1)	37 (19.4)
Moderate-severe renal dysfunction[f]	31 (16.5)	30 (15.7)
Diabetes[f]	59 (31.4)	79 (41.4)

Table 1. Baseline Characteristics of Patients in the Primary Analysis Population[a] (continued)

Characteristic	Pipercillin-Tazobactam (n = 188)	Meropenem (n = 191)
Liver disease[f]	12 (6.4)	18 (9.4)
qSOFA score ≥2[g]	86 (45.7)	77 (40.3)
Weight, mean (SD), kg	67.2 (18.1)	69.3 (19.3)
Empirical antibiotic category		
β-lactam/ β-lactamase inhibitor	38 (20.2)	49 (25.7)
Carbapenem	26 (13.8)	28 (14.7)
Other	124 (66.0)	114 (59.7)
Appropriate empirical antibiotic	126 (67.0)	127 (66.5)
Time to randomization, median (IQR), h	53.6 (44.9-65.6)	52.5 (46.0-63.7)
Time to appropriate antibiotics, median (IQR), h	5.5 (0.4-31.5)	9.6 (0.5-32.1)

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

A Randomized Clinical Trial

Patrick N. A. Harris, MBBS; Paul A. Tambyah, MD; David C. Lye, MBBS; Yin Mo, MBBS; Tau H. Lee, MBBS; Mesut Yilmaz, MD; Thamer H. Alenazi, MD; Yaseen Arabi, MD; Marco Falcone, MD; Matteo Bassetti, MD, PhD; Elda Righi, MD, PhD; Benjamin A. Rogers, MBBS, PhD; Souha Kanj, MD; Hasan Bhally, MBBS; Jon Iredell, MBBS, PhD; Marc Mendelson, MBBS, PhD; Tom H. Boyles, MD; David Looke, MBBS; Spiros Miyakis, MD, PhD; Genevieve Walls, MB, ChB; Mohammed Al Khamis, MD; Ahmed Zikri, PharmD; Amy Crowe, MBBS; Paul Ingram, MBBS; Nick Daneman, MD; Paul Griffin, MBBS; Eugene Athan, MBBS, MPH, PhD; Penelope Lorenc, RN; Peter Baker, PhD; Leah Roberts, BSc; Scott A. Beatson, PhD; Anton Y. Peleg, MBBS, PhD; Tiffany Harris-Brown, RN, MPH; David L. Paterson, MBBS, PhD; for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

JAMA. 2018;320(10):984-994.

Table 2. Primary Analysis and Subgroup Analyses

	30-d Mortality, No./Total No. (%)		Risk Difference, % (1-Sided 97.5% CI)[a]	*P* Value for Noninferiority
	Piperacillin-Tazobactam	Meropenem		
Primary analysis	23/187 (12.3)	7/191 (3.7)	8.6 (−∞ to 14.5)	.90
Per-protocol analysis	18/170 (10.6)	7/186 (3.8)	6.8 (−∞ to 12.8)	.76
Subgroup analyses[b]				*P* Value for Interaction
OECD country income				
Middle income	8/37 (21.6)	1/35 (2.9)	18.8 (−∞ to 35.0)	.31
High income	15/150 (10.0)	6/156 (3.9)	6.2 (−∞ to 12.5)	
Pitt score				
≥4	5/18 (27.8)	0/9	27.8 (−∞ to 51.3)	.99
<4	18/169 (10.7)	7/182 (3.9)	6.8 (−∞ to 12.8)	
Infecting species				
E coli	17/161 (10.6)	7/166 (4.2)	6.3 (−∞ to 12.6)	.99
K pneumoniae	6/26 (23.1)	0/25	23.1 (−∞ to 42.3)	
Infection				
HAI	18/107 (16.8)	4/107 (3.7)	13.1 (−∞ to 21.8)	.26
Non-HAI	5/80 (6.3)	3/84 (3.6)	2.7 (−∞ to 10.7)	
Appropriate empirical antibiotic therapy				
Appropriate	18/126 (14.3)	5/127 (3.9)	10.3 (−∞ to 18.0)	.70
Inappropriate	5/61 (8.2)	2/64 (3.1)	5.1 (−∞ to 15.2)	
UT vs non-UT source				
UT	7/102 (6.9)	4/128 (3.1)	3.7 (−∞ to 10.7)	.44
Non-UT	16/85 (18.8)	3/63 (4.8)	14.1 (−∞ to 24.5)	
Immune compromise[c]				
Present	10/51 (19.6)	1/40 (2.5)	17.1 (−∞ to 30.5)	.27
Absent	13/136 (9.6)	6/151 (4.0)	5.6 (−∞ to 12.2)	

Optimal Piperacillin-Tazobactam Dosing Strategies against Extended-Spectrum-β-Lactamase-Producing *Enterobacteriaceae*

Henrietta Abodakpi,[a] Kai-Tai Chang,[b] Song Gao,[a*] Ana María Sánchez-Díaz,[c] Rafael Cantón,[c] Vincent H. Tam[a,b]

February 2019 Volume 63 Issue 2 e01906-18 Antimicrobial Agents and Chemotherapy

TABLE 1 ESBL genes detected, susceptibility (MIC in μg/ml), inhibitory E_{max} parameter estimates, and model fit for clinical isolates

Bacterial species (isolate)	ESBL gene	MIC[a]		Model estimates and fit				
		CAZ	PIP-TAZ	$\log_2$ (MIC_0)	I_{max}	IC_{50}	H	r^2
K. pneumoniae (Kp3)	CTX-M-15	**64**[b]	**32/4**	9.32	6.52	2.60	1.57	0.94
K. pneumoniae (KpK91)	CTX-M-15	**64**	**32/4**	9.03	4.75	1.36	4.00	0.97
K. pneumoniae (Kp2301)	CTX-M-15	**>512**	**>512/4**	9.09	6.23	35.25	2.67	0.97
E. coli (EcF65)	SHV-12	**>512**	4/4	8.67	6.99	2.71	3.41	0.98

[a]CAZ, ceftazidime; PIP-TAZ, piperacillin-tazobactam. TAZ MIC values for all isolates were >256 μg/ml.
[b]Boldface denotes resistant phenotype according to CLSI breakpoints.

Standard dosing:
Piperacillin 4g
Tazobactam 0.5g

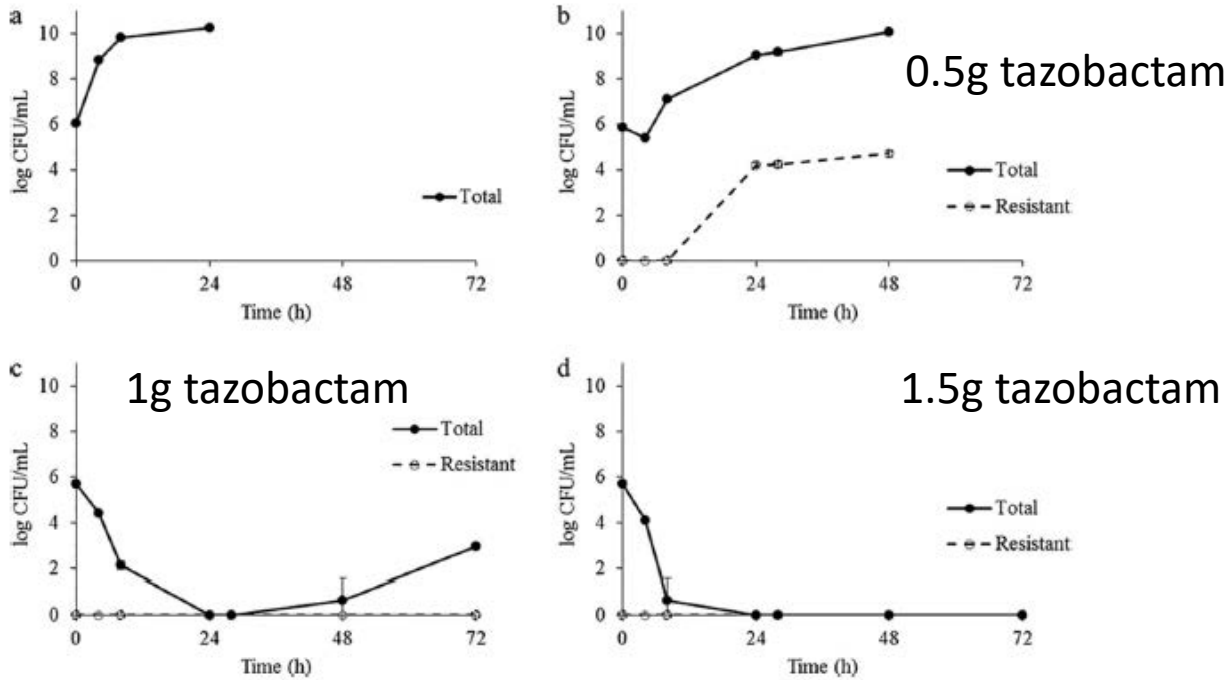


FIG 3 Killing profiles for EcF65. Shown are placebo control (a) and with killing profiles for 4 g piperacillin and 0.5 g tazobactam (%$fT>MIC_i$ = 43.8) (b), 4 g piperacillin and 1.0 g tazobactam (%$fT>MIC_i$ = 60.0) (c), and 4 g piperacillin and 1.5 g tazobactam (%$fT>MIC_i$ = 65.0) (d). Data are displayed as means ± standard deviation (SD).

OXA-1 β-lactamase and non-susceptibility to penicillin/β-lactamase inhibitor combinations among ESBL-producing *Escherichia coli*

David M. Livermore[1,2]*, Michaela Day[1], Paul Cleary[3], Katie L. Hopkins[1], Mark A. Toleman[4], David W. Wareham[5], Camilla Wiuff[6], Michel Doumith[1] and Neil Woodford[1]

J Antimicrob Chemother 2019; **74**: 326–333

Table 2. Risk of non-susceptibility to penicillin/β-lactamase inhibitor combinations in relation to the presence of secondary β-lactamases

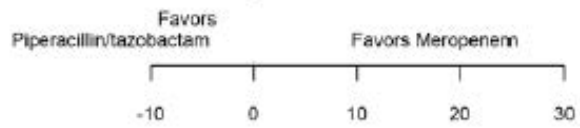
		Piperacillin/tazobactam				Amoxicillin/clavulanate			
	Secondary β-lactamase	relative risk of MIC >8 mg/L	95% lower CI	95% upper CI	*P*	relative risk of MIC >8 mg/L	95% lower CI	95% upper CI	*P*
All ESBL-producing	OXA-1[a]	6.49	3.03	13.88	<0.001	2.34	1.85	2.96	<0.001
E. coli isolates ($n = 293$)	TEM-1/191	1.32	0.81	2.14	0.257	1.00	0.82	1.22	0.992
	OXA-1 + TEM-1/191	3.49	2.22	5.48	<0.001	1.72	1.47	2.02	<0.001
		(*P* value for homogeneity = 0.33)				(*P* value for homogeneity = 0.34)			
ST131 ESBL-producing	OXA-1	12.10	3.01	48.61	<0.001	2.43	1.73	3.41	<0.001
E. coli isolates ($n = 188$)	TEM-1/191	1.58	0.92	2.71	0.094	0.96	0.77	1.21	0.741
	OXA-1 + TEM-1/191	3.41	2.06	5.66	<0.001	1.57	1.31	1.89	<0.001
		(*P* value for homogeneity = 0.47)				(*P* value for homogeneity = 0.17)			

Association between minimum inhibitory concentration, beta-lactamase genes and mortality for patients treated with piperacillin/tazobactam or meropenem from the MERINO study

A Henderson, D L Paterson ✉, M D Chatfield, P A Tambyah, D C Lye, P P De, R T P Lin, K L Chew, M Yin, T H Lee ... Show more

Clinical Infectious Diseases, ciaa1479, https://doi.org/10.1093/cid/ciaa1479

(Sub)Population	PTZ Died	PTZ Alive	MER Died	MER Alive	Between-Group Difference [95% CI]
mITT Analysis					
Primary analysis population	23	164	7	184	9 [3, 15]
Microbiologic assessable population	18	139	6	157	8 [2, 15]
Susceptible strains*					
PTZ/MER Non-susceptible Breakpoint	13	134	6	149	5 [-1, 11]
PTZ/MER Non-susceptible Breakpoint (excluding PTZ MIC = 16 mg/L)	11	116	6	119	4 [-2, 11]
Susceptible and Intermediate strains^					
PTZ/MER EUCAST Resistant Breakpoint	13	134	6	149	5 [-1, 11]
PTZ/MER CLSI Resistant Breakpoint	16	138	6	156	7 [1, 13]
Genotype					
ESBL	9	76	5	83	5 [-3, 14]
ESBL/OXA	7	39	1	52	14 [2, 28]
AmpC (Acquired)	0	15	0	13	
De-repressed AmpC	0	2	0	1	
ESBL/AmpC	1	1	0	4	
ESBL/AmpC/OXA	0	1	0	1	
OXA	0	0	0	1	
No ESBL/AmpC/OXA	1	5	0	2	



Combination antibiotics for bacteraemia: More is better?

Systematic Review and Meta-Analysis of *In Vitro* Synergy of Polymyxins and Carbapenems

Oren Zusman,[a] Tomer Avni,[a] Leonard Leibovici,[a] Amos Adler,[b] Lena Friberg,[c] Theodouli Stergiopoulou,[d] Yehuda Carmeli,[b] Mical Paul[b]

Antimicrobial Agents and Chemotherapy p. 5104–5111 October 2013 Volume 57

- 39 papers, 15 abstracts, total 54 in vitro studies
- Time-kill studies, synergy 77% *A baumannii*, 44% *K pneumoniae*, 50% *P aeruginosa*
- Doripenem highest synergy
- *A baumannii*, meropenem better synergy vs. *P aeruginosa* imipenem better
- Checkerboard and E-test studies lower synergy

Synergistic combinations of polymyxins

Justin R. Lenhard [a,b,c], Roger L. Nation [d], Brian T. Tsuji [a,b,*]

International Journal of Antimicrobial Agents 48 (2016) 607–613

7. Conclusions

The proliferation of MDR and XDR Gram-negative pathogens has forced clinicians to revisit the use of the polymyxin drug class. In a desire to improve clinical outcomes with polymyxin therapy, the medical community has investigated the use of polymyxin combinations. An abundance of recent in vitro and preclinical in vivo studies has identified various polymyxin combinations that demonstrated synergistic killing against MDR and XDR *P. aeruginosa*, *K. pneumoniae* and *A. baumannii*. However, the utility of polymyxin combinations in the clinical setting has been obscured by conflicting studies that are typically limited by small sample sizes and retrospective study designs. To address the ambiguity surrounding the use of polymyxin combinations, two large, prospective, randomised clinical trials comparing colistin alone to colistin + meropenem are currently underway in Europe and the USA (ClinicalTrials.gov IDs NCT01732250 and NCT01597973). Both trials will provide valuable insight into the potential benefits of colistin in combination with a carbapenem for MDR and XDR Gram-negative pathogens, but additional prospective trials may be needed to assess synergy between polymyxins and other agents for specific pathogens.

Systematic Review and Meta-Analysis of *In Vitro* Synergy of Polymyxins and Carbapenems

Oren Zusman,[a] Tomer Avni,[a] Leonard Leibovici,[a] Amos Adler,[b] Lena Friberg,[c] Theodouli Stergiopoulou,[d] Yehuda Carmeli,[b] Mical Paul[a]

Antimicrobial Agents and Chemotherapy p. 5104–5111 October 2013 Volume 57

TABLE 2 Pooled synergy and antagonism rates according to bacterium and carbapenem tested

Bacterium and carbapenem	Synergy		Antagonism		No. of tests	No. of bacteria	Heterogeneity	
	Rate	95% CI	Rate	95% CI			*P* value[a]	I^2 (%)
A. baumannii								
Imipenem	56	35–74	8	4–17	11	82	0.008	48
Meropenem	86	75–93	7	2–17	9	71		
Doripenem	88	70–96	9	3–24	6	33		
K. pneumoniae								
Imipenem	41	23–62	24	7–58	5	58	0.02[b]	51
Meropenem	34	13–64	9	3–23	6	39		
Doripenem	63	39–82	10	2–32	6	19		
Ertapenem	11	3–29	12	3–42	2	30		
P. aeruginosa								
Imipenem	60	18–91	21	11–38	5	39	0.013	66
Meropenem	24	15–38	2	0–16	2	54		
Doripenem	62	38–81	5	1–20	5	43		

[a] Heterogeneity *P* for subgroup comparisons.

[b] The *P* value was 0.44 when ertapenem was excluded.

Combination antibiotic treatment versus monotherapy for multidrug-resistant, extensively drug-resistant, and pandrug-resistant *Acinetobacter* infections: a systematic review

P. Poulikakos · G. S. Tansarli · M. E. Falagas

Eur J Clin Microbiol Infect Dis (2014) 33:1675–1685

- MDR, XDR and PDR A *baumannii*
- 12 studies, 1040 patients
- Mortality: monotherapy 25-100%, combination 27-57%
- Combination better than monotherapy in 3/12 studies: carbapenem/ampicillin-sulbactam, carbapenem/colistin, mixed combinations (mortality 23-31%)
- Resistance to tigecycline in 3 studies

Antibiotic Treatment of Infections Due to Carbapenem-Resistant *Enterobacteriaceae*: Systematic Evaluation of the Available Evidence

Matthew E. Falagas,[a,b,c] Panagiota Lourida,[a] Panagiotis Poulikakos,[a,b] Petros I. Rafailidis,[a] Giannoula S. Tansarli[a]

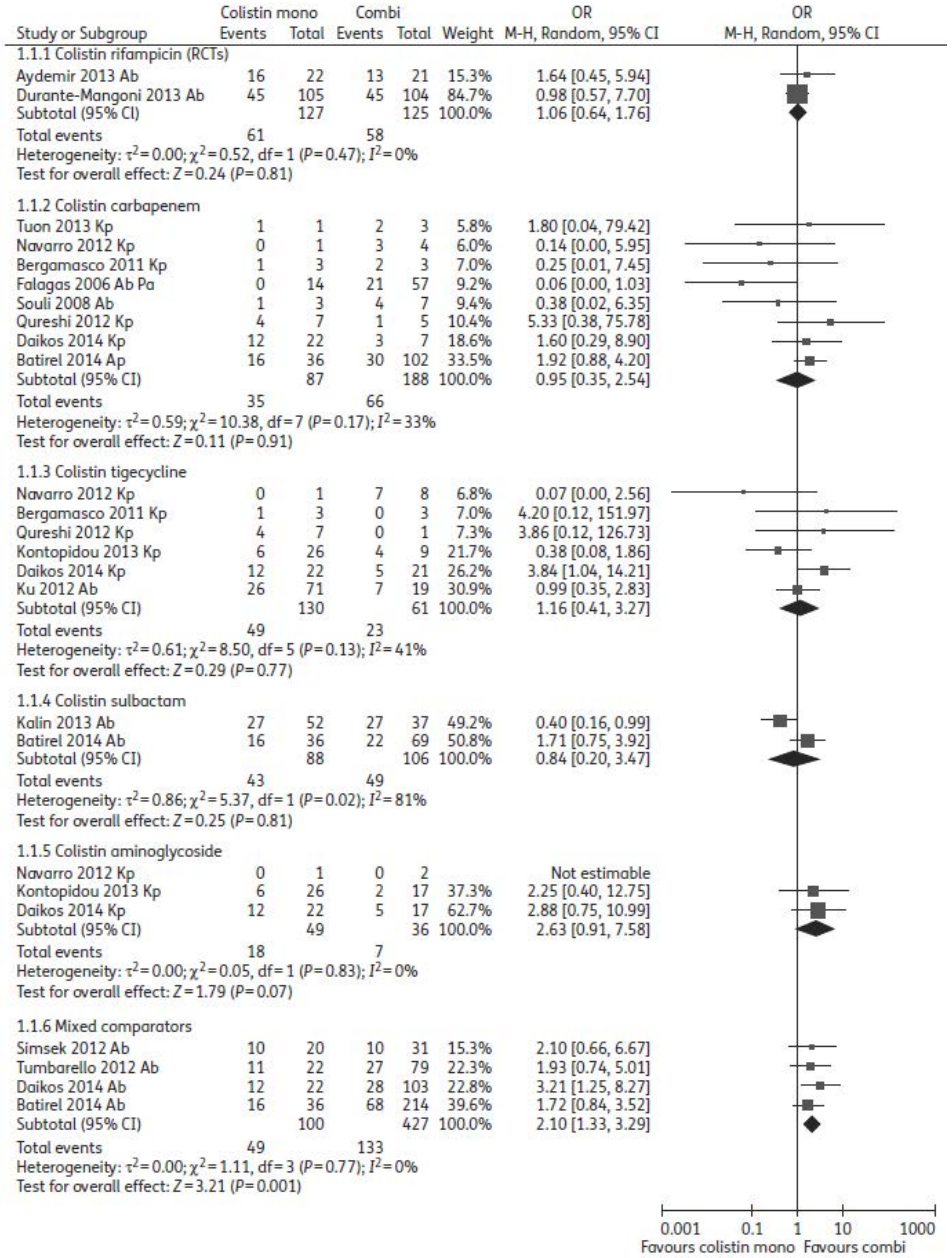
Antimicrobial Agents and Chemotherapy p. 654–663 February 2014 Volume 58

- Carbapenem-resistant *Enterobacteriaceae*
- 20 non-randomised studies, 692 patients, mainly *K pneumoniae*
- 8 studies mainly bacteraemia, 12 studies pneumonia + UTI, 10 studies critically ill
- Mortality
  - Combination: 50% tigecycline/gentamicin, 64% tigecycline/colistin, 67% carbapenem/colistin
  - Monotherapy: colistin 57%, tigecycline 80%
- 3 studies, 194 critically ill patients, lower mortality with combination

Combination therapy for carbapenem-resistant Gram-negative bacteria

Mical Paul[1]*, Yehuda Carmeli[2], Emanuele Durante-Mangoni[3], Johan W. Mouton[4], Evelina Tacconelli[5], Ursula Theuretzbacher[6], Cristina Mussini[7] and Leonard Leibovici[8,9]

J Antimicrob Chemother
doi:10.1093/jac/dku168



12 retrospective,
2 prospective, 2 RCT

No benefit
Colistin rifampicin
Colistin carbapenem
Colistin tigecycline
Colistin sulbactam
Colistin aminoglycoside
Except
mixed comparators

Combination often contained **active** antibiotic
Combination higher chance of **active empiric** therapy
Small numbers unable to adjust confounders

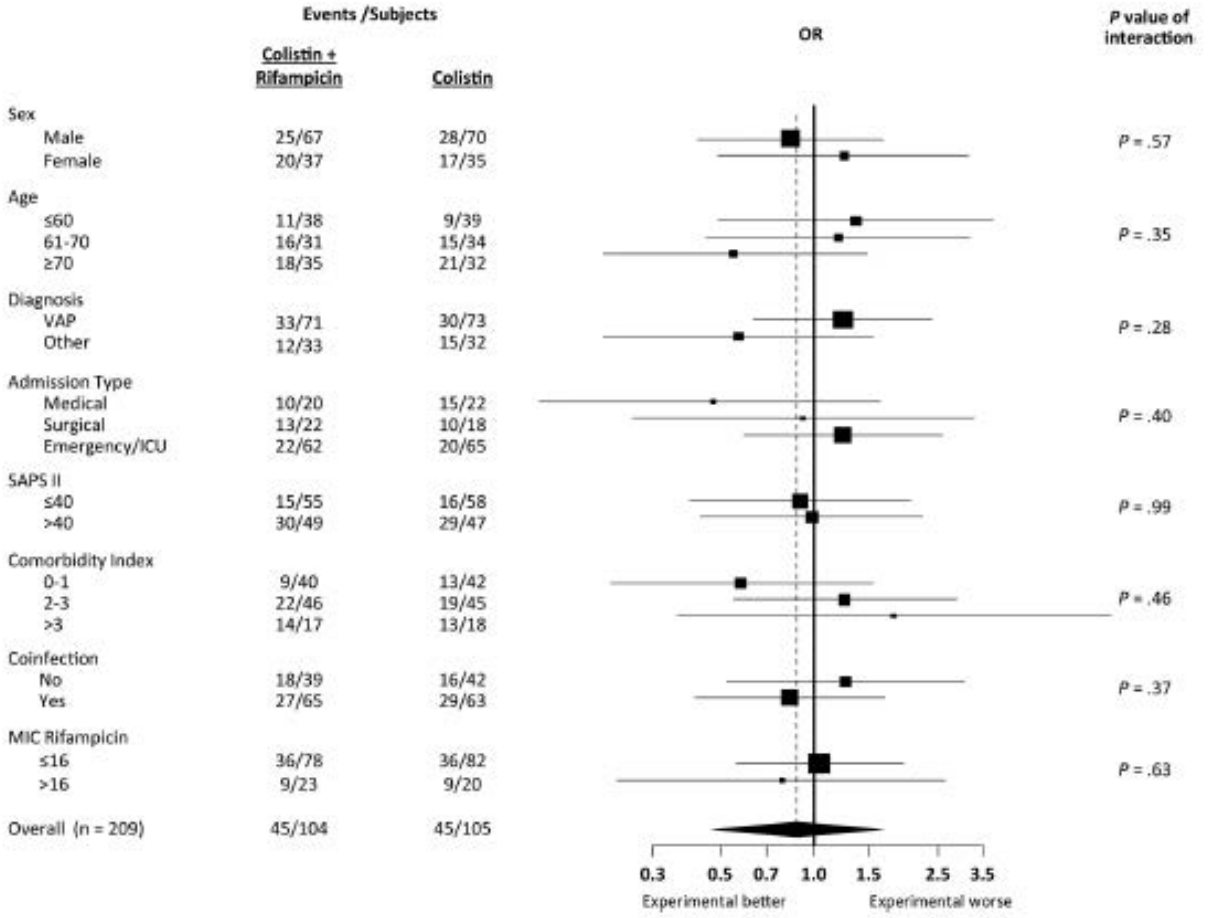
Colistin and Rifampicin Compared With Colistin Alone for the Treatment of Serious Infections Due to Extensively Drug-Resistant *Acinetobacter baumannii*: A Multicenter, Randomized Clinical Trial

Emanuele Durante-Mangoni,[1] Giuseppe Signoriello,[2] Roberto Andini,[1] Annunziata Mattei,[3] Maria De Cristoforo,[4] Patrizia Murino,[3] Matteo Bassetti,[5,a] Paolo Malacarne,[6] Nicola Petrosillo,[7] Nicola Galdieri,[3] Paola Mocavero,[3] Antonio Corcione,[3] Claudio Viscoli,[5] Raffaele Zarrilli,[8] Ciro Gallo,[2] and Riccardo Utili[1]

Clinical Infectious Diseases 2013;57(3):349–58

Table 2. Efficacy Outcomes

Outcome	Colistin + Rifampicin Arm (n = 104)	Colistin Arm (n = 105)	*P* Value
Primary outcome			
30-d mortality			
Yes	45 (43.3%)	45 (42.9%)	.95[a]
No	59 (56.7%)	60 (57.1%)	
Secondary outcomes			
Infection-related death at 30 d			
Yes	22 (21.15%)	28 (26.6%)	.29[a]
No	23 (22.1%)	17 (16.2%)	
Acinetobacter baumannii eradication			
Yes	63 (60.6%)	47 (44.8%)	.034[a]
No	38 (36.5%)	54 (51.4%)	
Median hospitalization length, d (IQR)	41 (26–61)	44 (27–59)	.96[b]
Development of colistin resistance, %	0	0	. . .



igure 2. Subgroup analysis of 30-day mortality (Forest plot). The area of each square is proportional to the size of the subgroup; horizontal lines depict 5% confidence intervals of the odds ratio estimates. Abbreviations: ICU, intensive care unit; MIC, minimum inhibitory concentration; OR, odds ratio; APS, Simplified Acute Physiology Score; VAP, ventilator-associated pneumonia.

N=209, colistin + rifampicin vs. colistin

Similar 30-day mortality and length of stay, higher microbiological eradication

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

Mical Paul, George L Daikos, Emanuele Durante-Mangoni, Dafna Yahav, Yehuda Carmeli, Yael Dishon Benattar, Anna Skiada, Roberto Andini, Noa Eliakim-Raz, Amir Nutman, Oren Zusman, Anastasia Antoniadou, Pia Clara Pafundi, Amos Adler, Yaakov Dickstein, Ioannis Pavleas, Rosa Zampino, Vered Daitch, Roni Bitterman, Hiba Zayyad, Fidi Koppel, Inbar Levi, Tanya Babich, Lena E Friberg, Johan W Mouton, Ursula Theuretzbacher, Leonard Leibovici

Lancet Infect Dis 2018; 18: 391–400

6 hospitals, Israel, Greece

	Colistin (n=198)	Colistin and meropenem (n=208)
Demographics and background		
Age, years	66 (16)	66 (18)
Women	123 (62%)	132 (63%)
Country		
Israel	134 (68%)	136 (65%)
Greece	38 (19%)	38 (18%)
Italy	26 (13%)	34 (16%)
Admitted from home	137 (69%)	139 (67%)
BMI, kg/m²	27·0 (5·6), n=194	27·7 (6·0), n=200
Charlson score	2 (0–3)	2 (0–4)
Dementia	15 (8%)	25 (12%)
Diabetes	42 (21%)	48 (23%)
Chronic kidney disease	32 (16%)	47 (23%)
Malignancy		
None	162 (82%)	172 (83%)
Solid	25 (13%)	33 (16%)
Haematological	11 (6%)	3 (1)
Congestive heart failure	41 (21%)	51 (25%)
Chronic pulmonary disease	47 (24%)	44 (21%)
Immune suppressive therapy	29 (15%)	32 (15%)

Status at infection onset (culture taken time)		
Temperature, °C	37·9 (2·3)	38·1 (1), n=207
Normal consciousness	75 (38%)	85 (41%)
Systolic blood pressure, mm Hg	109 (20), n=197	109 (22), n=207
Haemodynamic support	37 (19%)	38 (18%)
Mechanical ventilation (invasive)	131 (66%)	134 (64%)
Haemodialysis	11 (6%)	15 (7%)
SOFA score	6 (3–8)	5 (4–8)
Creatinine, mg/dL	1·00 (0·60–1·60)	0·93 (1·07–1·67)
Albumin, g/dL	2·4 (0·6), n=174	2·4 (0·7), n=183
White blood cells, thousands/mL^3	12·50 (9·30–16·66), n=197	12·30 (8·80–17·20), n=207
Arterial line	78 (39%)	73 (35%)
Central venous catheter	105 (53%)	120 (58%)
Urinary catheter	173 (87%)	181 (87%)
Nasogastric tube	141 (71%)	144 (59%)
Infection characteristics and treatment		
Acquisition of infection in the intensive care unit	77 (39%)	71 (34%)
Pathogen		
Acinetobacter baumannii	151 (76%)	161 (77%)
Enterobacteriacaeae	34 (17%)	39 (19%)
Pseudomonas/other	13 (7%)	8 (4%)
Meropenem MIC distribution	n=142	n=148
>8 mg/L	137 (97%)	144 (97%)
8 mg/L	1 (2%)	2 (1%)
>2 to <8 mg/L	4 (3%)	2 (1%)
Type of infection		
Bacteraemia	76 (38%)	97 (47%)
Ventilator-associated or hospital-acquired pneumonia	97 (49%)	85 (41%)
Probable ventilator-associated pneumonia	11 (6%)	14 (7%)
Urinary tract infection	14 (7%)	12 (6%)

	Colistin (n=198)	Colistin and meropenem (n=208)
(Continued from previous page)		
Appropriate empirical antibiotic treatment within 2 days*	106 (54%)	103 (50%)
48-h mortality	12 (6%)	15 (7%)
Modification of assigned regimen in first 5 days	17 (9%)	8 (4%)
Receipt of additional antimicrobials permitted by protocol		
Glycopeptide or daptomycin	29 (15%)	22 (11%)
Other antibacterial†	14 (7%)	11 (5%)
Antifungal	4 (2%)	5 (2%)
Total cumulative colistin for patients alive on day 14 (million units)	99·0 (72·0–135·0), n=134	106·5 (72·5–153·0), n=138
Receipt of nephrotoxic medications during treatment‡	87 (44%)	94 (45%)

	Colistin (n=198)	Colistin and meropenem (n=208)	RR (95% CI) for outcome with combination*	p value
Primary outcome				
Clinical failure at day 14	156 (79%)	152 (73%)	0·93 (0·83–1·03)	0·172
Secondary outcomes				
28-day mortality	86 (43%)	94 (45%)	1·03 (0·84–1·28)	0·781
Disposition at day 28	..	..	..	0·550
Dead	86 (43%)	94 (45%)	..	..
Alive, not discharged	60 (30%)	70 (34%)	..	..
Alive, discharged home	30 (15%)	22 (11%)	..	..
Alive, discharged to chronic care	22 (11%)	22 (11%)	..	..
14-day mortality	64 (32%)	70 (34%)	1·04 (0·79–1·37)	0·786
Failure with modification†	171 (86%)	177 (85%)	0·99 (0·91–1·07)	0·724
Microbiological failure	62 (31%)	73 (35%)	1·1 (0·84–1·44)	0·489
SOFA score day 7	5 (3–8), n=160	5 (3–8), n=162	..	0·643
SOFA score day 14	5 (3–7), n=126	4 (2–7), n=131	..	0·471
Febrile on day 3	62 (33%), n=186	71 (37%), n=194	1·11 (0·85–1·46)	0·444
Febrile on day 7	44 (27%), n=164	45 (26%), n=171	1·02 (0·71–1·45)	0·926
Time to defervescence, days	2 (0–6), n=191	2 (0–6), n=206	..	0·725
Time to weaning among ventilated patients, days	6 (0–22), n=110	4 (0–16), n=115	..	0·161
Time to intensive care unit discharge among patients discharged alive from intensive care unit, days	17 (8–28), n=52	22 (13–28), n=55	..	0·104
Time to discharge among patients discharged alive, days‡	15·0 (10·5–20·5), n=52	15·0 (11·0–20·0), n=44	..	0·635
Functional capacity independent, among 28-day survivors	12 (12%), n=101	8 (7%), n=108	0·60 (0·27–1·33)	0·209
Clinically significant superinfection by day 28	58 (29%)	56 (27%)	0·92 (0·67–1·26)	0·610
New carbapenem-resistant bacteria in clinical samples by day 28	10 (5%)	18 (9%)	1·73 (0·83–3·64)	0·146
Colistin-resistant bacteria in clinical samples by day 28	11 (6%)	10 (5%)	0·89 (0·41–1·94)	0·768

One ongoing randomised trial

Trial for the Treatment of Extensively Drug-Resistant Gram-negative Bacilli

This study is currently recruiting participants.

See Contacts and Locations

Verified May 2017 by Keith Kaye, University of Michigan

Sponsor:
University of Michigan

ClinicalTrials.gov Identifier:
NCT01597973

First Posted: May 15, 2012
Last Update Posted: May 31, 2017

USA, Israel, Taiwan, Thailand

Slow Response to Vancomycin or Vancomycin plus Rifampin in Methicillin-resistant *Staphylococcus aureus* Endocarditis

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Annals of Internal Medicine. 1991;115:674-680.

Table 1. Characteristics of Patient Groups*

Variable	All Patients (n = 42)	Group I (n = 22)†	Group II (n = 20)‡
Male sex, %	67	64	70
Median age (range), *y*	32 (23-61)	31 (23-61)	31 (26-50)
Definite endocarditis, *n*§	4	3	1
Probable endocarditis, *n*§	38	19	19
Left-sided infection, *n*	8	6	2
Right-sided infection, *n*	34	16	18
Median peak concentration of vancomycin (range), *μg/mL*	34.5 (21.3-47.0)	36.9 (30.0-47.0)	32.0 (21.3-46.0)
Median trough concentration of vancomycin (range), *μg/mL*	10.9 (6.8-17.0)	11.4 (9.0-17.0)	10.4 (6.8-16.0)
Therapeutic failures, *n*	6	4	2
Death, *n*	3	2	1

Group 2: vancomycin and rifampicin

Table 3. Median Duration of Bacteremia and Fever by Treatment Group and Infection Site*

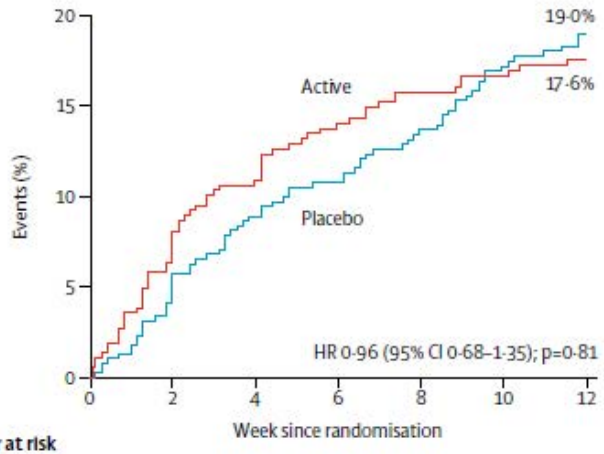
Variable	Patients	Median Duration of Bacteremia (95% CI)	Median Duration of Fever (95% CI)
	n	*d*	
All patients	42	9 (6 to 11)	7 (4 to 9)
Group I	22	7 (5 to 11)	7 (3 to 8)
Group II	20	9 (6 to 13)	7 (3 to 10)
Left-sided disease	8	9 (3 to 10)	7†
Right-sided disease	34	7 (5 to 11)	8 (3 to 10)

Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial

Lancet 2018; 391: 668–78

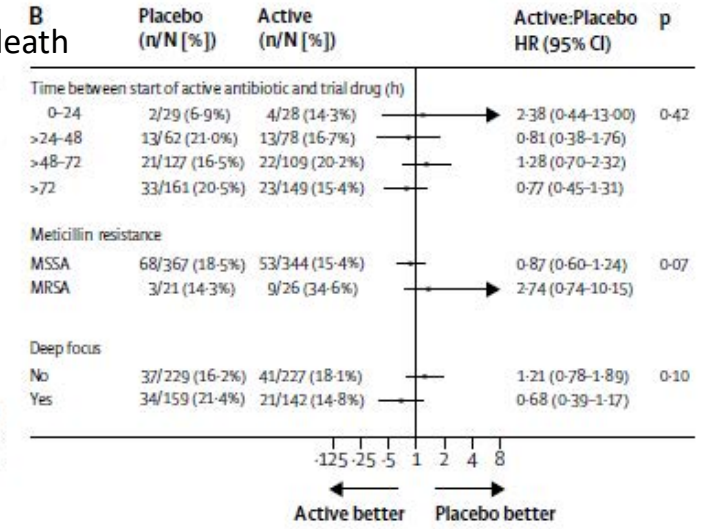
A

Bacteriological failure, recurrence or death



Number at risk (events)												
Placebo	388 (16)	364 (18)	345 (7)	335 (10)	323 (13)	305 (7)	245
Active	370 (23)	331 (15)	314 (11)	302 (7)	289 (3)	280 (3)	222

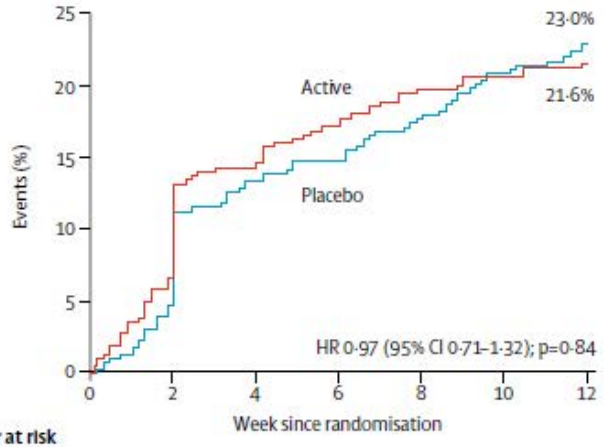
B



	Placebo (n/N [%])	Active (n/N [%])	Active:Placebo HR (95% CI)	p
Time between start of active antibiotic and trial drug (h)				
0–24	2/29 (6·9%)	4/28 (14·3%)	2·38 (0·44–13·00)	0·42
>24–48	13/62 (21·0%)	13/78 (16·7%)	0·81 (0·38–1·76)	
>48–72	21/127 (16·5%)	22/109 (20·2%)	1·28 (0·70–2·32)	
>72	33/161 (20·5%)	23/149 (15·4%)	0·77 (0·45–1·31)	
Meticillin resistance				
MSSA	68/367 (18·5%)	53/344 (15·4%)	0·87 (0·60–1·24)	0·07
MRSA	3/21 (14·3%)	9/26 (34·6%)	2·74 (0·74–10·15)	
Deep focus				
No	37/229 (16·2%)	41/227 (18·1%)	1·21 (0·78–1·89)	0·10
Yes	34/159 (21·4%)	21/142 (14·8%)	0·68 (0·39–1·17)	

C

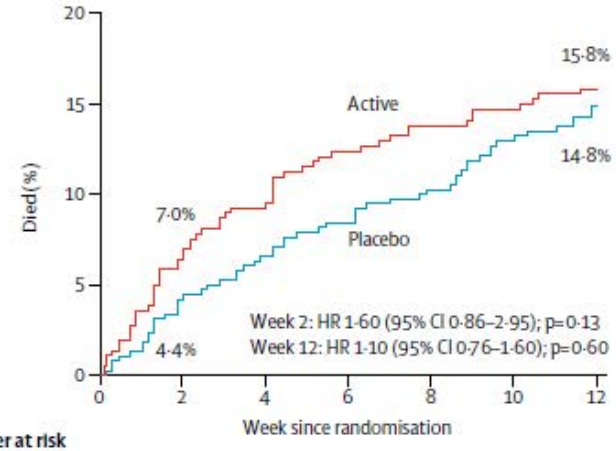
Clinical failure, recurrence or death



Number at risk (events)												
Placebo	388 (18)	362 (33)	328 (5)	320 (11)	307 (12)	290 (7)	233
Active	370 (24)	330 (27)	301 (10)	290 (9)	275 (3)	266 (3)	210

D

Mortality



Number at risk (events)												
Placebo	388 (16)	364 (9)	354 (7)	346 (7)	338 (10)	326 (7)	302
Active	370 (23)	331 (10)	320 (11)	308 (5)	301 (3)	296 (4)	273

Clinical Data on Daptomycin plus Ceftaroline versus Standard of Care Monotherapy in the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Matthew Geriak,[a] Fadi Haddad,[b] Khulood Rizvi,[c] Warren Rose,[d] Ravina Kullar,[e] Kerry LaPlante,[f] Marie Yu,[b] Logan Vasina,[a] Krista Ouellette,[a] Marcus Zervos,[c] Victor Nizet,[f] George Sakoulas[a,g]

May 2019 Volume 63 Issue 5 e02483-18 Antimicrobial Agents and Chemotherapy

TABLE 4 Study outcomes

Outcome	Values by treatment type: Combination therapy	Monotherapy	*P* value
Mortality, *n* (%)			
In hospital	0 (0)	6 (26)	0.02
30 day	0 (0)	6 (26)	0.02
90 day	0 (0)	7 (30)	0.03
Bacteremia duration, median (IQR) days	3 (1.5, 5.5)	3 (1, 5.3)	0.56
Length of stay, median (IQR) days	11 (6, 14)	12 (8, 23)	0.24

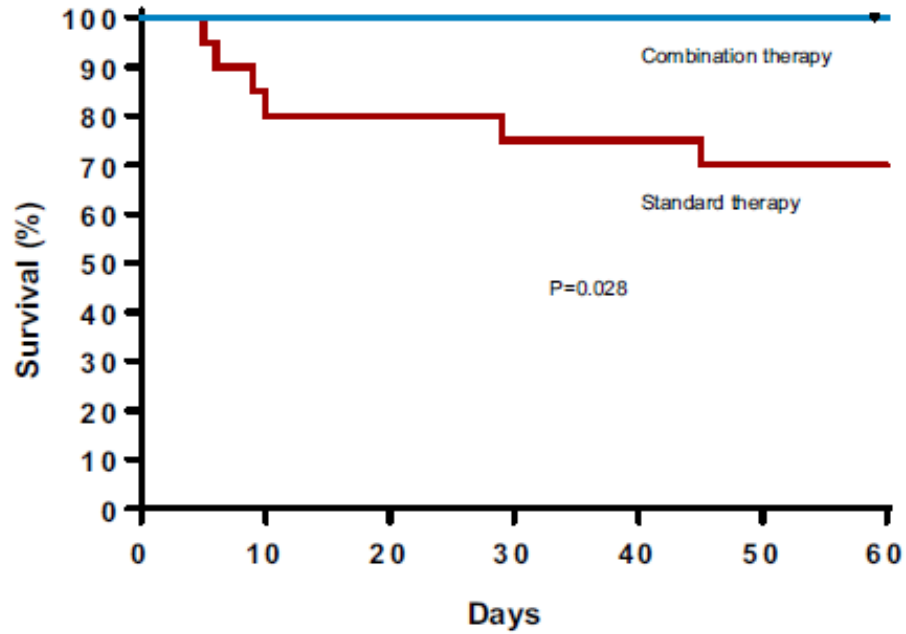


FIG 1 Survival analysis of patients receiving daptomycin plus ceftaroline compared with those receiving standard of care in a prospective randomized study. Day 0 represents the day of first positive blood culture. Significance of mortality difference at 30 days ($P = 0.048$) and 60 days ($P = 0.028$).

Effect of Vancomycin or Daptomycin With vs Without an Antistaphylococcal β-Lactam on Mortality, Bacteremia, Relapse, or Treatment Failure in Patients With MRSA Bacteremia

A Randomized Clinical Trial

Steven Y. C. Tong, MBBS, PhD; David C. Lye, MBBS; Dafna Yahav, MD; Archana Sud, MD; J. Owen Robinson, MD; Jane Nelson, BN; Sophia Archuleta, MD; Matthew A. Roberts, PhD; Alan Cass, MBBS, PhD; David L. Paterson, MBBS, PhD; Hong Foo, MBBS; Mical Paul, MD; Stephen D. Guy, MBBS; Adrian R. Tramontana, MBBS; Genevieve B. Walls, MBChB; Stephen McBride, MBChB; Narin Bak, MBBS, MPH; Niladri Ghosh, MBBS; Benjamin A. Rogers, MBBS, PhD; Anna P. Ralph, MBBS, PhD; Jane Davies, MBBS, PhD; Patricia E. Ferguson, MBBS, PhD; Ravindra Dotel, MBBS; Genevieve L. McKew, MBBS; Timothy J. Gray, MBBS(Hons); Natasha E. Holmes, MBBS(Hons), PhD; Simon Smith, MBChB; Morgyn S. Warner, MD, PhD; Shirin Kalimuddin, MBBS, MPH; Barnaby E. Young, MBBS; Naomi Runnegar, MBBS; David N. Andresen, MBBS; Nicholas A. Anagnostou, MBBS; Sandra A. Johnson, BSc, MPH; Mark D. Chatfield, MSc; Allen C. Cheng, MBBS, PhD; Vance G. Fowler Jr, MD, MHS; Benjamin P. Howden, MBBS, PhD; Niamh Meagher, MBiostat; David J. Price, PhD; Sebastiaan J. van Hal, MBChB, PhD; Matthew V. N. O'Sullivan, MBBS, PhD; Joshua S. Davis, MBBS, PhD; for the Australasian Society for Infectious Diseases Clinical Research Network

JAMA. 2020;323(6):527-537.

Table 2. Characteristics of Patients During the Trial in the Primary Analysis Population

Characteristics	Combination Therapy (n = 174)	Standard Therapy (n = 178)
Final diagnosis of infective endocarditis, No. (%)[a]	26 (15)	16 (9)
Received vancomycin, No. (%)[b]	171 (98)	178 (100)
Received daptomycin, No. (%)[b]	7 (4)	6 (3)
Trough vancomycin level, mean (SD), μg/mL		
Day 1	15.1 (8.1)	14.7 (7.3)
Day 2	17.9 (9.1)	17.2 (8.0)
Day 3	20.1 (7.6)	19.2 (7.5)
Received any nonstudy antibiotic during days 1-7, No. (%)[c]	53 (30)	48 (27)
Infectious diseases consultation, No. (%)	168 (97)	171 (96)
Presumed infected source removed, No. (%)	77/106 (73)	84/105 (80)
Time to removal of infected source, median (IQR), d[d]	0.0 (−1.0 to 2.0)	0.0 (−1.0 to 2.0)
Echocardiogram performed, No. (%)	161 (93)	168 (94)
Transthoracic	151 (87)	151 (85)
Transesophageal	61 (35)	68 (38)
Recognized infection foci at time of index blood culture, No. (%)		
Skin and soft tissue infection	40 (23)	50 (28)
Primary blood stream infection	34 (20)	35 (20)
Native osteoarticular	31 (18)	27 (15)
Intravenous line related	25 (14)	22 (12)
Pleuropulmonary infection	13 (7)	11 (6)
Device related	9 (5)	9 (5)
Infective endocarditis	9 (5)	6 (3)
Other	13 (7)	18 (10)
Any antibiotic in 72 h preceding randomization, No. (%)	170 (98)	174 (98)
Any β-lactam in 72 h preceding randomization, No. (%)	111 (64)	104 (58)
Drugs affecting kidney function in 48 h preceding randomization, No. (%)[g]	98 (56)	108 (61)
Baseline creatinine level, median (IQR), mg/dL[h]	1.13 (0.8-2.5)	1.22 (0.8-2.7)
Vancomycin MIC, No./total (%)[i,k]		
≤1 μg/mL	152/160 (95)	153/161 (95)
2 μg/mL	8/160 (5)	8/161 (5)

JAMA | Original Investigation

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Table 3. Primary and Secondary Outcomes

Outcomes	No./Total No. (%)		Risk Difference, % (95% CI)	*P* Value
	Combination Therapy	Standard Therapy		
Primary Outcome[a,b]				
Primary analysis population	59/170 (35)	68/175 (39)	−4.2 (−14.3 to 6.0)	.42
Per protocol	47/144 (33)	68/175 (39)	−6.2 (−16.7 to 4.3)	.25
Secondary Outcomes[c]				
All-cause mortality[d]				
Day 14	13/170 (8)	13/174 (7)	0.2 (−5.4 to 5.8)	.95
Day 42	25/170 (15)	19/174 (11)	3.8 (−3.3 to 10.8)	.29
Day 90	35/170 (21)	28/174 (16)	4.5 (−3.7 to 12.7)	.28
Persistent bacteremia[e]				
Day 2	50/167 (30)	61/173 (35)	−5.3 (−15.3 to 4.6)	.29
Day 5	19/166 (11)	35/172 (20)	−8.9 (−16.6 to −1.2)	.02
Microbiological relapse[a]	14/169 (8)	18/175 (10)	−2.0 (−8.1 to 4.1)	.52
Microbiological treatment failure[a]	16/170 (9)	17/175 (10)	−0.3 (−6.5 to 5.9)	.92
Acute kidney injury[f]	34/145 (23)	9/145 (6)	17.2 (9.3 to 25.2)	<.001
Duration of intravenous antibiotics, mean (SD), d	29.3 (19.5)	28.1 (17.4)		.72

Conclusions

- Adequate blood culture collection before IV antibiotic
- Antibiotic treatment of uncomplicated gram negative bacteraemia for 1 week
- Piperacillin-tazobactam not for ESBL bacteraemia
- Prolonged infusion of beta-lactam and combination antibiotic for bacteraemia should be undertaken as part of a RCT, as existing RCT's show no benefit

Thank you

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