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

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Summary

Background **Colistin–carbapenem combinations are synergistic in vitro against carbapenem-resistant Gram-negative bacteria. We aimed to test whether combination therapy improves clinical outcomes for adults with infections caused by carbapenem-resistant or carbapenemase-producing Gram-negative bacteria.**

Methods **A randomised controlled superiority trial was done in six hospitals in Israel, Greece, and Italy. We included adults with bacteraemia, ventilator-associated pneumonia, hospital-acquired pneumonia, or urosepsis caused by carbapenem-non-susceptible Gram-negative bacteria. Patients were randomly assigned (1:1) centrally, by computer-generated permuted blocks stratified by centre, to intravenous colistin (9-million unit loading dose, followed by 4·5 million units twice per day) or colistin with meropenem (2-g prolonged infusion three times per day). The trial was open-label, with blinded outcome assessment. Treatment success was defined as survival, haemodynamic stability, improved or stable Sequential Organ Failure Assessment score, stable or improved ratio of partial pressure of arterial oxygen to fraction of expired oxygen for patients with pneumonia, and microbiological cure for patients with bacteraemia. The primary outcome was clinical failure, defined as not meeting all success criteria by intention-to-treat analysis, at 14 days after randomisation. This trial is registered at ClinicalTrials.gov, number NCT01732250, and is closed to accrual.**

Findings **Between Oct 1, 2013, and Dec 31, 2016, we randomly assigned 406 patients to the two treatment groups. Most patients had pneumonia or bacteraemia (355/406, 87%), and most infections were caused by *Acinetobacter baumannii* (312/406, 77%). No significant difference between colistin monotherapy (156/198, 79%) and combination therapy (152/208, 73%) was observed for clinical failure at 14 days after randomisation (risk difference –5·7%, 95% CI –13·9 to 2·4; risk ratio [RR] 0·93, 95% CI 0·83–1·03). Results were similar among patients with *A baumannii* infections (RR 0·97, 95% CI 0·87–1·09). Combination therapy increased the incidence of diarrhoea (56 [27%] *vs* 32 [16%] patients) and decreased the incidence of mild renal failure (37 [30%] of 124 *vs* 25 [20%] of 125 patients at risk of or with kidney injury).**

Interpretation **Combination therapy was not superior to monotherapy. The addition of meropenem to colistin did not improve clinical failure in severe *A baumannii* infections. The trial was unpowered to specifically address other bacteria.**

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Introduction

Carbapenem resistance among Gram-negative bacteria is increasing worldwide. These isolates are resistant to most other classes of antibiotics. A European survey[1] revealed inter-regional or endemic spread of carbapenemase-producing Enterobacteriaceae in 13 of 38 European countries in 2015, compared with six of 38 in 2013, and a similar or higher spread of *Acinetobacter baumannii*, with 12 of 27 European countries reporting more than 50% carbapenem resistance among *A baumannii* isolates.[2]

The polymyxins, colistin and polymyxin B, retain coverage against carbapenem-resistant Gram-negative bacteria in most locations worldwide.[1,2] Clinicians treating patients with carbapenem-resistant Gram-negative bacteria express little confidence in polymyxins' efficacy. The high mortality following infections caused by carbapenem-resistant Gram-negative bacteria has led to the search for optimal antimicrobial combinations to maximise bacterial killing. In vitro, polymyxin–carbapenem combinations show various degrees of synergy and increased bactericidal activity compared with polymyxins alone, especially for *A baumannii*.[3] As for many antibiotics, colistin resistance emerges with colistin monotherapy exposure, whereas colistin–doripenem combination therapy reduced and delayed resistance development in time-kill studies assessing *A baumannii*

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Research in context

Evidence before this study

We searched PubMed, the Cochrane Library, references of all included studies, and pertinent reviews for clinical studies assessing at least five patients per treatment group, regardless of study design, using the search terms "(colisti* OR polymyxin) AND (enterobacteriaceae OR klebsiella OR acinetobacter OR E. coli OR pseudomonas)". We included studies comparing intravenous polymyxin monotherapy and polymyxin–carbapenem combination therapy for adults with infections caused by carbapenem-resistant or carbapenemase-producing Gram-negative bacteria. We included all studies published until June 30, 2017, with no language or starting year restrictions. Risk of bias was assessed with the Cochrane Risk of Bias Assessment Tool for Non-Randomised Studies of Interventions. Seven studies—all observational—assessing 537 patients were identified. Adjusted results were unavailable. The pooled unadjusted odds ratio for all-cause 30-day or closest mortality with polymyxin monotherapy was 1·58 (95% CI 1·03–2·42), indicating significantly higher mortality with monotherapy than polymyxin–carbapenem combination therapy. All studies were at serious or critical risk of bias, with intervention misclassification, selection, and confounding the main affected domains. The odds ratios did not favour combination therapy in two studies scored at serious (but not critical) risk of bias (0·94, 0·42–2·09). The main reason for exclusion of eligible studies was that the specific antibiotics in combination therapies were not defined, and such studies cannot provide biological information on treatment effects.

Added value of this study

This trial was designed to compare the effectiveness of colistin monotherapy versus colistin–meropenem combination therapy among patients with severe infections caused by carbapenem-resistant Gram-negative bacteria, targeting the patient population with carbapenem-resistant Gram-negative bacterial infections treated in clinical practice, in a randomised design, with both drugs given in a pharmacokinetic-optimised dosing schedule. Most patients had ventilator-associated or hospital-acquired pneumonia, or bacteraemia and the predominant bacteria were *Acinetobacter baumannii*. The primary outcome, a composite of mortality and clinical instability at day 14 after randomisation (clinical failure), occurred with similar frequency in both study groups. All-cause 28-day mortality was 86 (43%) of 198 patients treated with colistin monotherapy and 94 (45%) of 208 patients treated with combination therapy. Clinical failure rates for patients who received monotherapy versus combination therapy were 125 (83%) of 151 versus 130 (81%) of 161 patients with *A baumannii* infections, and 23 (68%) of 34 versus 18 (46%) of 39 patients with Enterobacteriaceae infections. Mortality at 28 days was 70 (46%) of 151 patients versus 84 (52%) of 161 patients for *A baumannii* infections and 12 (35%) of 34 patients versus eight (21%) of 39 patients for Enterobacteriaceae infections. No significant difference between groups was observed in the emergence of colistin-resistant bacteria during or after therapy, and isolation of new carbapenem-resistant Gram-negative bacteria occurred among 18 (9%) of 161 patients treated with combination therapy versus ten (5%) of 151 treated with monotherapy. Adverse events requiring treatment discontinuation were rare (7/406; 2%). Diarrhoea increased and renal failure decreased with combination therapy.

Implications of all the available evidence

Our results strongly support the avoidance of colistin–carbapenem combination therapy for carbapenem-resistant *A baumannii* infections regardless of the infection source, considering epidemiological concerns with carbapenem usage in hospitals. The gap between in-vitro and clinical studies and the discrepant results observed in observational studies and our randomised controlled trial suggest combination therapy should be assessed in randomised trials. For *Klebsiella pneumoniae*, other Enterobactericeae, and *Pseudomonas aeruginosa*, additional randomised trials are needed before combination therapy is adopted in clinical practice.

and *Pseudomonas aeruginosa*.[3] In vivo, a 2 $\log_{10}$ kill of *A baumannii* and *P aeruginosa* in a lung infection model was either unachievable or required unbound colistin concentrations-to-minimal inhibitory concentration ratios (fAUC/MIC) of 10–50.[4] Patients with good renal function infrequently reached bactericidal blood concentrations above 2 mg/L in a clinical study.[5]

These data have led to the adoption of combination therapy for the treatment of carbapenem-resistant Gram-negative bacteria, without evidence that combination is better than monotherapy.[6] The use of polymyxin–carbapenem combination therapy is frequent in clinical practice. In a survey of large hospitals (>800 beds) in nine countries in Europe and the USA, antibiotic combinations were the preferred treatment in 81% (92/114) for carbapenem-resistant *Klebsiella pneumoniae* and 59% (48/67) for *A baumannii* bacteraemia, with polymyxin–carbapenem the preferred combination in 75% and 71%.[7] Clinically, this combination is not harmless; carbapenems might favour *Clostridium difficile* infections, and carbapenem use is the strongest risk factor for carriage of and infections caused by carbapenem-resistant Gram-negative bacteria, through resistance selection or induction.[8,9]

We aimed to compare colistin monotherapy to colistin–meropenem combination therapy for the treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria in a randomised trial design. We targeted different carbapenem-resistant Gram-negative bacteria, since in-vitro and in-vivo studies show advantages to combination therapy for *A baumannii*, Enterobacteriaceae, and *P aeruginosa*, and combination

therapy is in use and evidence is necessary for the different carbapenem-resistant Gram-negative bacteria.

Methods

Study design and patients

This study was an investigator-initiated, multicentre, open-label, parallel group, randomised controlled trial. The design rationale and methods have been previously published.[10] The trial was approved by the ethics committees of the participating hospitals and informed consent was required for participation, tailored to local requirements.

Six hospitals, three in Israel, two in Greece, and one in Italy, participated in the study.[10] We included adults with severe infections caused by carbapenem-non-susceptible Gram-negative bacteria (MIC >2 mg/L) that are susceptible to colistin (MIC ≤2 mg/L for *A baumannii* and Enterobacteriaceae and ≤4 mg/L for *P aeruginosa*), according to EUCAST 2012 recommendations and criteria.[11] Infections included bacteraemia, definite ventilator-associated or hospital-acquired pneumonia, probable ventilator-associated pneumonia, and urosepsis, defined in the study protocol.[10] Causative bacteria had to be resistant to all antibiotics other than colistin, aminoglycosides, sulbactam, tetracyclines, tigecycline, and co-trimoxazole. We excluded polymicrobial infections comprising carbapenem-susceptible Gram-negative bacteria. Other exclusion criteria included previous colistin treatment for more than 96 h, previous enrolment in the trial, pregnancy, known allergy to colistin or carbapenems, and previous carbapenem-induced seizures. Patients not previously treated with a carbapenem and diagnosed with epilepsy requiring antiepileptic treatment were also excluded. No exclusion criteria relating to other underlying conditions or sepsis severity were applied, although patients for whom antibiotic treatment was deemed futile by the treating clinicians were not recruited.

Randomisation and masking

In each hospital, the local principal investigators and other researchers enrolled participants in the study. Randomisation was done by the investigators using central randomisation (registry of the patients into the trial's website that provided and documented the study group assignment). Patients were randomly assigned (1:1), either to colistin monotherapy or colistin and meropenem combination therapy, by computer-generated randomisation lists by permuted blocks stratified by centre, with block size varying randomly between four, six, and eight patients. To further decrease predictability, the first block was initiated at a random position. No masking was used after randomisation. The primary outcome was adjudicated centrally by two researchers masked to the treatment arm. The researchers analysing the data worked on a database with the study arms coded. All investigators were involved in the study planning,

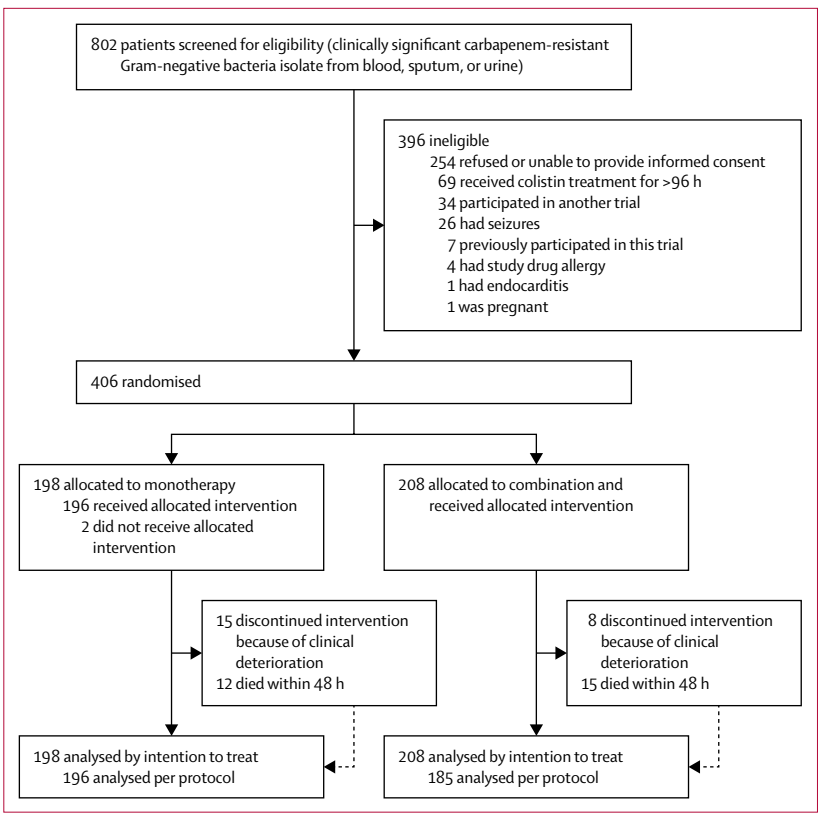

Figure 1: **Trial profile**

	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/m^2	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%)

(Table 1 continues on next page)

	Colistin (n=198)	Colistin and meropenem (n=208)
(Continued from previous page)		
Known colonisation by pathogen before infection	51 (26%)	45 (22)
Recent surgery	54 (27%)	60 (29%)
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%)
Status at randomisation		
Temperature, °C	37·8 (0·9)	37·8 (0·9)
Normal consciousness	82 (41%)	86 (41%)
Systolic blood pressure, mm Hg	110 (18)	113 (19)
Haemodynamic support	35 (18%)	47 (23%)
Mechanical ventilation (invasive)	132 (67%)	137 (66%)
Haemodialysis	12 (6%)	19 (9%)
SOFA score	5 (3–8)	6 (4–9)
Creatinine, mg/dL	0·94 (0·60–1·80)	1·00 (0·60–1·97)
Albumin, g/dL	2·3 (1·1), n=182	2·2 (1·0), n=191
White blood cells, thousands/mL^3	12·03 (9·21–17·22), n=196	12·03 (8·76–17·26)
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%)

(Table 1 continues on next page)

protocol design, running the trial, and writing the final report.

Procedures

Colistin methanesulfonate was administered as a 9-million unit (MIU) loading dose, followed by 4·5-MIU maintenance doses every 12 h, adjusted for renal function in patients with creatinine clearance of less than 50 mL/min with Garonzik and colleagues' formula.[12] Meropenem was given as a 2 g extended-infusion (3 h) every 8 h, adjusted for renal function by protocol.[10] We allowed the addition of antibiotics targeting Gram-positive or anaerobic co-infections, but did not allow the addition of other antibiotics targeting Gram-negative bacteria systemically or by inhalation. Therapeutic drug monitoring was not done for the purpose of study drug-dosing adjustment; however, samples were collected and stored for subsequent drug-concentration measurements.

Patients were included in the trial on the basis of identification and susceptibility testing of the index isolates in the local laboratories, following a structured questionnaire and approval of the methods used in each hospital (data available on request). Repeat sampling from the primary source of isolation of the carbapenem-resistant Gram-negative bacteria was done on day 7, and blood cultures were obtained every 48 h for patients with bacteraemia and persistent fever. All repeat isolates were tested for carbapenem and colistin susceptibilities locally. Other samples were obtained as clinically indicated. The follow-up is detailed in the published protocol.[10]

Outcomes

The primary outcome was clinical success 14 days after randomisation, and patients who did not meet all of the success criteria were classified as clinical failure, reported herein for consistency of the relative outcome measures. Success was defined as a composite of the patient alive, haemodynamic stability (systolic blood pressure >90 mm Hg without need for vasopressor support), improved or stable Sequential Organ Failure Assessment (SOFA) score (for baseline SOFA ≥3, we required that the score improve by at least 30%, and for baseline SOFA <3 we required that the score remain the same or decrease), stable or improved ratio of partial pressure of arterial oxygen to fraction of expired oxygen for patients with pneumonia, and microbiological cure for patients with bacteraemia (no growth in blood of index isolate on day 14 or later). Secondary outcomes included 28-day and 14-day all-cause mortality, clinical failure or treatment modification, microbiological failure defined as repeat isolation of bacteria phenotypically identical to the index isolate on or after day 7 after randomisation, duration of fever, mechanical ventilation, length of stay in the intensive care unit, and total in-hospital stay in the relevant populations of surviving patients, superinfections (defined as clinical infections caused by bacteria species different from the index isolate resistant

to carbapenems), colistin resistance development (defined as development of colistin resistance in the index or other clinical isolates), functional capacity at discharge among survivors, and adverse events. Follow-up was completed at day 28 or death.

Statistical analysis

The trial hypothesis was that combination therapy would be superior to monotherapy, reducing clinical failure from 45% with colistin monotherapy (based on previous data[10,13]) to 30% with combination therapy (15% absolute difference). A sample of 324 patients (162 per arm) was calculated to detect this reduction (uncorrected χ^2 test, type I error 0·05, power 0·8). Considering a non-evaluability rate of 10%, we originally planned to recruit 360 patients. No interim analyses were planned or done. Total mortality and safety data were reported to a safety committee and the overall percentage of patients fulfilling per-protocol criteria was reviewed yearly. In the second safety analysis, observing deaths within 48 h of randomisation and early treatment modifications, we defined a per-protocol analysis excluding early deaths and treatment modifications, and to preserve a power of 80% for this analysis set, we targeted 324 patients who could be analysed per protocol.

The primary analysis was by intention to treat, as randomly assigned. A per-protocol analysis included patients surviving more than 48 h after randomisation and receiving the allocated treatment regimen without modification for at least 5 days or until death. Predefined subgroup analyses included a subgroup of patients who received inappropriate empirical antibiotic treatment, and a subgroup excluding patients with urosepsis and non-definite ventilator-associated pneumonia. We had planned an analysis of patients whose index pathogen's MIC to meropenem was 16 mg/L or less, but this subgroup was too small for a meaningful comparison. We added a post-hoc analysis by type of index pathogen. Dichotomous and categorical outcomes were compared with a two-sided χ^2 test and ordinal outcomes (eg, RIFLE score) with linear-by-linear association tests (presented as p for trend). For dichotomous efficacy outcomes, risk ratios (RR) with 95% CI were calculated with the Cochran's Mantel-Haenszel method for estimation of the common treatment effect, accounting for stratification by centre. Risk difference for the primary outcome by intention to treat, with 95% CI computed by use of the methods described by Deek and Higgins,[14] was similarly stratified by centre. Normally distributed continuous variables are presented with means and SD and compared with a *t* test; skewed variables are presented with medians and IQRs and compared by use of the Mann-Whitney *U* test. Survival to day 28 was compared with Kaplan-Meier analysis and log-rank test. Analyses were done with SPSS 23.

The trial was registered with ClinicalTrials.gov, number NCT01732250.

	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%)

Data are mean (SD), n (%), or median (IQR). n values indicated for outcomes assessed only for survivors, or if patient data are missing. BMI=body-mass index. SOFA=Sequential Organ Failure Assessment. *Covering treatment given in the first 48 h of infection, before reporting of final culture results. †Other antibacterials include penicillins, linezolid, cefazolin, or metronidazole. ‡Including non-steroidal anti-inflammatory drugs, aciclovir, ganciclovir or foscarnet, diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, ciclosporin, tacrolimus, amphotericin B, methotrexate, or cisplatin.

Table 1: **Patient and infection characteristics**

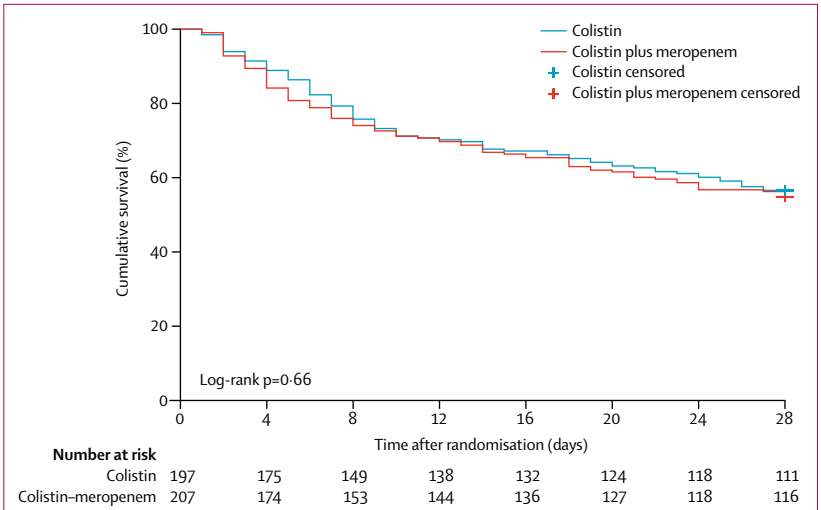

Figure 2: **Survival analysis to day 28 after randomisation**

Role of the funding source

This study was conducted as part of the EU-Commission-funded AIDA project on the preservation of old antibiotics. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Patients were enrolled between Oct 1, 2013, and Dec 31, 2016. Of the 802 patients screened for eligibility, 406 were included in the trial: 198 were randomly

	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

Data are n (%) or median (IQR). n values indicated for outcomes assessed only for survivors, or if patient data are missing. RR=risk ratio. SOFA=Sequential Organ Failure Assessment. *RRs stratified by centre, RR>1 more failures with combination therapy. RRs not assessed for continuous variables. †Composite failure at day 14 or any deviation from assigned regimen until day 10. ‡Up to 28 days.

***Table 2*: Outcomes for intention-to-treat population**

assigned to colistin monotherapy and 208 to colistin–meropenem combination therapy (figure 1). Most patients (276/406, 68%) were admitted to hospital from home, with few comorbidities (median Charlson score 2, IQR 0–3; table 1). Infections were acquired well into their stay in hospital (median time from admission to randomisation 17 days, IQR 10–27). The main pathogen was *A baumannii* (312/406, 77%), and most patients had ventilator-associated pneumonia or hospital-acquired pneumonia (182, 45%) or bacteraemia (173, 43%). Patients were moderately ill at the onset of infection (median SOFA score at randomisation 6, IQR 3–8) and 28-day mortality was 44% (180/406). About half of the patients (209/406, 51%) received appropriate empirical antibiotic treatment in the 2 days after the index culture, with no significant differences between the six centres. Appropriate empirical therapy consisted of colistin in 200 patients, and other covering antibiotics in nine patients. A carbapenem was used in 12 patients receiving colistin empirically, who were subsequently randomly assigned to colistin monotherapy (ie, ceased carbapenem therapy). Randomisation was done within a median of 3 days (IQR 2–4) from the date the culture was taken and 0 days (IQR 0–1) from the start of colistin. Baseline conditions and infection characteristics were similar between groups (table 1).

No significant difference between colistin monotherapy and combination therapy was observed for the primary outcome (ie, clinical failure at day 14), with 156 (79%) of 198 patients versus 152 (73%) of 208 patients meeting the criteria for clinical failure. The RR for failure with combination therapy was 0·93 (95% CI 0·83 to 1·03), and the risk difference was –5·73% (–13·89 to 2·43), excluding superiority, as defined in the trial protocol. By day 14, 134 (33%) of 406 patients had died; of the surviving patients, no improvement or deterioration in SOFA occurred in 167 (61%) of 272. Haemodynamic instability (no patients), persistence of bacteraemia (six patients), and respiratory failure among patients with pneumonia (one patient) had little contribution to the composite primary outcome.

No significant difference between patients who received colistin therapy and those who received combination therapy was observed for all-cause mortality at 14 days after randomisation (64/198 [32%] *vs* 70/208 [34%]) and 28 days (86/198 [43%] *vs* 94/208 [45%]). No survival benefit was observed (log rank p=0·66, figure 2), nor were there any significant differences for all defined secondary outcomes (table 2). Among ventilated patients, time to weaning from mechanical ventilation was shorter for patients treated with combination therapy, whereas time to intensive care unit discharge among patients in the intensive care unit who survived was shorter with colistin treatment. No significant differences were observed in microbiological failure (monotherapy 62/198 [31%] *vs* combination therapy 73/208 [35%]), isolation of a new carbapenem-resistant species (10/198 [5%] *vs* 18/208 [9%]), or isolation of colistin-resistant bacteria in clinical samples (11/198 [6%] *vs* 10/208 [5%]).

Adverse events requiring treatment discontinuation were rare (seven patients; 2%), with no significant differences observed between groups (table 3). Significantly more patients treated with combination therapy than those treated with monotherapy had diarrhoea (56 [27%] *vs* 32 [16%], p=0·009). *Clostridium difficile* infection was rare, but more common with combination therapy than monotherapy. A lower incidence of renal failure at day 14 (table 3), mainly the injury and failure categories of RIFLE (p=0·001), was observed in patients treated with combination therapy than monotherapy. At baseline, more patients in the combination therapy group than the

monotherapy group had chronic kidney disease, and a similar number of patients in both groups received nephrotoxic medications during treatment (table 1).

The per-protocol population included 87% (354/406) of the patients; 27 patients (7%) died within 48 h of randomisation and 25 (6%) patients had their treatment modified in the first 5 days of treatment. Treatment modification was higher in the colistin monotherapy arm (17/198, 9%) than in the combination arm (8/208, 4%; p=0·047; table 1). Results were similar in the per-protocol population to the intention-to-treat population for clinical failure, 28-day mortality, and 14-day mortality (table 4).

Among predefined subgroup analyses, combination therapy led to less clinical failure among patients with ventilator-associated pneumonia, hospital-acquired pneumonia, or bloodstream infection (excluding patients with probable ventilator-associated pneumonia and urosepsis), although this difference was not significant (RR 0·9, 95% CI 0·8–1·004), but 14-day and 28-day mortality rates were similar (table 4). Among patients receiving inappropriate empirical antibiotic treatment, results were similar to the overall analyses. In a post-hoc subgroup analysis, compared with monotherapy, combination therapy resulted in fewer failures at 14 days after randomisation and fewer deaths at 28 days after randomisation in the subgroup of Enterobacteriaceae infections (differences not significant), with no difference in 14-day mortality. Most Enterobacteriaceae infections were bloodstream infections (56/73, 77%) caused by *K pneumoniae* (65/73, 89%). For *A baumannii*, no differences were observed between monotherapy and combination therapy for clinical failure (RR 0·97, 95% CI 0·87–1·09), or 14-day and 28-day mortality (table 4).

	Colistin (n=198)	Colistin and meropenem (n=208)	p value
Adverse event requiring treatment discontinuation	3 (2%)	4 (2%)	1·0
Creatinine on day 7, mg/dL	1·30 (0·69–2·15), n=161	1·12 (0·56–2·40), n=162	0·258
RIFLE score day 14 compared with randomisation*	n=124	n=125	0·001†
None	64 (52%)	89 (71%)	..
Risk	20 (16%)	18 (14%)	..
Injury	17 (14%)	7 (6%)	..
Failure	21 (17%)	10 (8%)	..
Loss	2 (2%)	1 (1%)	..
Creatinine on day 14, mg/dL	1·49 (0·80–2·60), n=124	1·08 (0·56–1·98), n=162	0·007
RIFLE score day 28 compared with randomisation*	n=77	n=88	0·075†
None	50 (65%)	70 (80%)	..
Injury	5 (6%)	5 (6%)	..
Failure	12 (16%)	4 (4%)	..
Loss	10 (13%)	8 (9%)	..
End-stage kidney disease	0	1 (1%)	..
Creatinine on day 28, mg/dL	1·13 (0·65–1·87), n=75	1·00 (0·60–1·84), n=82	0·544
Diarrhoea	32 (16%)	56 (27%)	0·009
Clostridium difficile infection	2 (1%)	6 (3%)	0·174
Seizures	6 (3%)	5 (2%)	0·698

Data are n (%) or median (IQR). n values indicated for outcomes assessed only for survivors or in a specific patient subgroup, or if patient data are missing. *Among patients not on haemodialysis at randomisation, alive with renal function tests available. †p for trend.

Table 3: Adverse events

Discussion

Colistin–meropenem combination therapy did not result in better outcomes compared with colistin monotherapy in a randomised controlled trial including 406 patients with severe infections caused by carbapenem-resistant Gram-negative bacteria. Most patients included in the trial had ventilator-associated pneumonia or hospital-acquired pneumonia, or bacteraemia. Clinical failure at day 14 occurred in 308 (76%) of 406 patients, with no significant difference between groups. The 28-day mortality was 44% (108/406), and similar in the two groups. No significant differences were observed between the groups for all outcomes, except for increased diarrhoea and reduced incidence of renal failure with combination therapy. The trial results relate mostly to *A baumannii*, which was the cause of infection in 77% of patients.

This study is the first randomised trial to address colistin–meropenem combination therapy for carbapenem non-susceptible Gram-negative pathogens. Observational studies showed uniformly lower mortality with combination therapy for carbapenem-resistant or carbapenemase-producing *K pneumoniae* as compared with colistin monotherapy.[15] Although initial studies, based on cohorts as small as 41 patients with *K pneumoniae* carbapenemase (KPC)-producing *K pneumoniae* bacteraemia, claimed unreserved superiority of combination therapy,[16] more recent, and larger, studies have highlighted specific patient subgroups that might benefit from combination therapy or specific antibiotic combinations. A prospective multinational study[17] of 343 patients with bacteraemia due to carbapenemase-producing Enterobacteriaceae receiving covering antibiotics, and a retrospective study[18] of 205 patients in Greece with bacteraemia due to carbapenemase-producing *K pneumoniae*, claimed superiority of combination therapy over monotherapy among patients at high risk of mortality. A multicentre Italian study[19] of 661 patients with KPC-producing *K pneumoniae* bacteraemia and non-bacteraemia infections identified combinations consisting of two in-vitro-active drugs and severe infections as factors associated with survival. Two of the cohort studies pointed to a potential advantage of colistin–meropenem combination therapy when carbapenem MIC was 8 mg/L or less.[18,19] The potential advantage of such studies is the analysis of a large cohort of uniform, rare infections (eg, KPC-producing *K pneumoniae* bacteraemia), and the inclusion of all

	Colistin	Colistin and meropenem	Risk ratio (95% CI) for outcome with combination	p value
Per protocol population*				
n	169	185	..	..
Clinical failure	129 (76%)	131 (71%)	0·92 (0·82–1·05)	0·220
28-day mortality	69 (41%)	75 (41%)	0·97 (0·76–1·25)	0·840
14-day mortality	48 (28%)	53 (29%)	1·00 (0·72–1·39)	0·992
Inappropriate empirical antibiotic treatment†				
n	92	105	..	..
Clinical failure	74 (80%)	76 (72%)	0·91 (0·78–1·07)	0·254
28-day mortality	40 (43%)	44 (42%)	0·98 (0·71–1·36)	0·910
14-day mortality	34 (37%)	28 (27%)	0·74 (0·49–1·13)	0·166
Bloodstream infection, ventilator-associated pneumonia, or hospital-acquired pneumonia				
n	173	182	..	..
Clinical failure	141 (82%)	133 (73%)	0·9 (0·8–1·004)	0·059
28-day mortality	77 (45%)	81 (45%)	0·99 (0·79–1·25)	0·931
14-day mortality	55 (328%)	60 (33%)	1·04 (0·78–1·38)	0·804
Main pathogen				
n	198	208	..	..
Clinical failure				
Acinetobacter baumannii	125 (83%), n=151	130 (81%), n=161	0·97 (0·87–1·09)	0·643
Enterobacteriaceae‡	23 (68%), n=34	18 (46%), n=39	0·78 (0·54–1·13)	0·185
Pseudomonas or others§	8 (62%), n=13	4 (50%), n=8	0·81 (0·36–1·84)	0·673
28-day mortality				
A baumannii	70 (46%), n=151	84 (52%), n=161	1·11 (0·87–1·41)	0·404
Enterobacteriaceae	12 (35%), n=34	8 (21%), n=39	0·62 (0·29–1·36)	0·235
Pseudomonas or others	4 (31), n=13	2 (25%), n=8	0·81 (0·19–3·47)	1·0
14-day mortality				
A baumannii	54 (36%), n=151	62 (39%), n=161	1·11 (0·82–1·52)	0·495
Enterobacteriaceae	6 (18%), n=34	6 (15%), n=39	0·90 (0·32–2·51)	0·838
Pseudomonas or others	4 (31%), n=13	2 (25%), n=8	0·81 (0·19–3·47)	1·0

n values indicated for outcomes assessed in a specific patient subgroup. *Surviving 48 h and no modification in the first 5 days after randomisation. †No covering treatment until day 3 after culture taken. Appropriate empirical antibiotic treatment consisted of colistin in all but nine patients who received aminoglycosides (three patients), co-trimoxazole, tigecycline, ampicillin–sulbactam, minocycline, gentamicin plus chloramphenicol and gentamicin plus tigecycline (one patient each). ‡Includes polymicrobial infections in which at least one of the carbapenem-resistant Gram-negative bacteria were Enterobacteriaceae; 66 of 72 patients had *Klebsiella pneumoniae* infections. §Includes *Pseudomonas aeruginosa* and *A baumannii* polymicrobial infections; 19 of 21 patients had *P aeruginosa* infections. Unstratified analysis due to small numbers.

Table 4: **Subgroup analyses**

patients in need of treatment in clinical practice. The main limitation of the aforementioned studies is that treatment was selected by physicians, with the reasons underlying the use of monotherapy or combination therapy introducing confounding factors that cannot be fully addressed, even in large numbers. Treatment was not standardised in a manner allowing enough credibility in the groups assigned for analysis.[6,20] When analysing specific antibiotic treatment regimens (eg, colistin–meropenem combination therapy), the groups become very small, even in large cohort studies. With respect to multidrug-resistant *A baumannii* infections, results from the observational studies are more heterogeneous, with some observing lower mortality with combination therapy than monotherapy and others not. These data suffer similar limitations, and sample sizes that are too small to adequately examine the independent associations between therapy and mortality. A systematic review and network meta-analysis[21] showed no difference in mortality rates for different treatment regimens, including colistin monotherapy. Even the combination of covering tigecycline with colistin does not appear to improve outcomes with *A baumannii* infections.[21–23] Resistance mechanisms in *A baumannii* are complex and combined, involving intrinsic class D β-lactamases, other class A and B carbapenemases, Amp C cephalosporinase, overexpression of chromosomal *blaOXA-51*-like gene, modification of penicillin-binding proteins and porins, upregulation of the active drug efflux ATP-binding cassette system, and more.[24] *A baumannii* is more resistant to carbapenems (higher MICs) than Enterobacteriaceae,[25] which possibly explains the absence of benefit of the addition of carbapenem to colistin.

The main strength of our trial is the randomisation process to remove selection bias, and the real-life design. The study arms were similar at baseline. We included patients with carbapenem non-susceptible Gram-negative bacteria, rather than carbapenemase-producing Gram-negative bacteria, because the question of colistin monotherapy is mainly pertinent to this population. Treatment regimens in the trial were standardised targeting optimal dosing,[26–28] and the schedule and concomitant antibiotic treatment was controlled. The cohort represents the patient population treated in clinical practice, as can be seen from the baseline patient characteristics. We used treatment indications for which drugs are needed; we did not apply exclusion criteria dissociating patient populations in randomised trials of new drugs from real life. Mortality was not lower in our study (28-day mortality 108/406 [44%]) than in the observational studies reporting in-hospital or 30-day mortality rates of 39–43%.[16,17,19]

Common to the observational studies and our randomised trial is heterogeneity of the patient population. In observational studies focusing on carbapenemase-producing *K pneumoniae*, heterogeneity relates to MICs to carbapenems and colistin, sources of infection, and treatment regimens. In our trial, heterogeneity relates to the different bacteria analysed. Even within bacterial species at our current level of speciation, heterogeneity that explains a differential response to treatment might exist, as has been shown for *A baumannii*.[29] In Greece, OXA-23-producing isolates have dominated since 2011.[30] In Italy, this dominance of OXA-23-producing isolates was also true until 2011,[31] but additional carbapenem-hydrolysing class D β-lactamases might now be involved. In Israel, the main mechanisms are OXA-24, OXA-40, and OXA-58. Thus, we focused on carbapenem resistance and infection severity as the common characteristic of our trial cohort, rather than specific bacterial species.

Our trial faced several limitations. We did not measure drug concentrations in real time to direct treatment, but administered colistin in doses that are expected to result in plasma concentrations that are effective against colistin-susceptible bacteria in most patients.[5] We did not use central microbiology laboratory MIC determinations to direct treatment; these measurements and analyses are ongoing and will be reported separately. Of the isolates in which MIC was determined locally, very few had MICs of 8 mg/L or less (9/290); thus, we cannot establish the efficacy of the combination therapy in the lower MIC range. Our primary composite outcome was not previously validated, and we observed very high failure rates (302/406, 74% overall; 252/312, 81% in *A baumannii* infections). In our trial, clinical failure reflected death or a non-improving SOFA score among survivors; thus, we consider our primary outcome clinically relevant, and the high rates reflective of disease severity. We did not identify differences in the emergence of colistin resistance; however, resistance outcomes are difficult to assess in randomised trial design, requiring long-term follow-up after the implementation of a treatment policy. Our finding of a potential protective effect of combination therapy on renal function was unexpected, and should be further investigated. Without biological rationale, the effect on renal function should not constitute a reason to use combination therapy.

Future randomised trials are needed to address different antibiotic strategies and patients subgroups, mainly infections caused by carbapenem-resistant *K pneumoniae* or other Enterobacteriaceae if their incidence increases. A previous randomised trial refuted a clinical advantage to rifampicin–colistin over colistin monotherapy for *A baumannii*.[32] Another randomised trial comparing the same interventions as ours is ongoing (NCT01597973); after its completion we plan to compile results to increase the power for patients with infections caused by Enterobacteriaceae. The high failure and mortality rates in our trial, with or without carbapenems, point to the need for new antibiotics against carbapenem-resistant Gram-negative bacteria. Ceftazidime–avibactam might be an option for KPC-producing *K pneumoniae*,[33] but should be examined for this indication in a randomised trial. No new antibiotic, like colistin, provides a spectrum of coverage against all carbapenem-producing Enterobacteriaceae, regardless of mechanism, against *P aeruginosa* and *A baumannii*.[34] A major reason for patient exclusion in our trial was absence of informed consent (249/427, 58% of eligible patients excluded), with the main cause being inability to provide informed consent. Ethical procedures to mainstream recruitment to investigator-initiated clinical effectiveness trials of last-resort drugs would assist the conduct of future trials.[35,36]

We did not observe an advantage to combination therapy with regard to survival, clinical cure, microbiological cure, or development of resistance. Our results relate mostly to the dominant bacteria in our cohort, *A baumannii*. Given the potential of carbapenem usage to promote carbapenem resistance, we recommend against the routine use of carbapenems for the treatment of carbapenem-resistant *A baumannii* infections. Although our study cannot provide an answer for *K pneumoniae* and *P aeruginosa* infections, it points to the necessity of assessing combination therapy in randomised trials before adopting it into clinical use.

Contributors

MP, GLD, YC, AS, AAd, LEF, JWM, UT, and LL conceived of and designed the study. MP, GLD, YC, OZ AS, AAd, LEF, JWM, UT, and LL wrote the protocol and developed the database. MP, GLD, ED-M, DY, YDB, AS, RA, NE-R, AN, AAn, PCP, YD, IP, RZ, VD, RB, HZ, FK, IL, and TB recruited patients and did sampling. YDB, AS, AAn, IP, VZ, FK, IL, and TB collected data. MP, GLD, ED-M, YC, YDB, AS, LEF, JWM, UT, and LL analysed or interpreted data. All authors contributed to the writing or critical revision of the final manuscript.

Declaration of interests

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References

1 Albiger B, Glasner C, Struelens MJ, Grundmann H, Monnet DL, European Survey of Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) working group. Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015. *Euro Surveill* 2015; **20**.

2 ECDC. Carbapenem-resistant *Acinetobacter baumannii* in healthcare settings. European Centre for Disease Prevention and Control; 2016. http://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/8-Dec-2016-RRA-Acinetobacter%20baumannii-Europe.pdf (accessed Oct 31, 2017).

3 Zusman O, Avni T, Leibovici L, et al. Systematic review and meta-analysis of in vitro synergy of polymyxins and carbapenems. *Antimicrob Agents Chemother* 2013; **57:** 5104–11.

4 Cheah SE, Wang J, Nguyen VT, Turnidge JD, Li J, Nation RL. New pharmacokinetic/pharmacodynamic studies of systemically administered colistin against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in mouse thigh and lung infection models: smaller response in lung infection. *J Antimicrob Chemother* 2015; **70:** 3291–97.

5 Nation RL, Garonzik SM, Thamlikitkul V, et al. Dosing guidance for intravenous colistin in critically-ill patients. *Clin Infect Dis* 2017; **64:** 565–71.

6 Paul M, Carmeli Y, Durante-Mangoni E, et al. Combination therapy for carbapenem-resistant Gram-negative bacteria. *J Antimicrob Chemother* 2014; **69:** 2305–09.

7 Papst L, Beović B, Pulcini C, et al. Antibiotic treatment of infections caused by carbapenem-resistant Gram-negative bacilli: an international ESCMID cross-sectional survey among infection diseases specialists practicing in large hospitals. *Clin Microbiol Infect* 2018; published online Feb 3. DOI:10.1016/j.cmi.2018.01.015.

8 Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant *Klebsiella pneumoniae* acquisition among hospitalized adults and effect of acquisition on mortality. *Antimicrob Agents Chemother* 2008; **52:** 1028–33.

9 Muggeo A, Guillard T, Barbe C, et al. Factors associated with carriage of carbapenem-non-susceptible Enterobacteriaceae in North-Eastern France and outcomes of infected patients. *J Antimicrob Chemother* 2017; **72:** 1496–501.

10 Dickstein Y, Leibovici L, Yahav D, et al. Multicentre open-label randomised controlled trial to compare colistin alone with colistin plus meropenem for the treatment of severe infections caused by carbapenem-resistant Gram-negative infections (AIDA): a study protocol. *BMJ Open* 2016; **6:** e009956.

11 EUCAST. Breakpoint tables for interpretation of MICs and zone diameters version 2.0, valid from 2012-01-01. http://www.eucast.org/ast_of_bacteria/previous_versions_of_documents/ (accessed Feb 7, 2018).

12 Garonzik SM, Li J, Thamlikitkul V, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. *Antimicrob Agents Chemother* 2011; **55:** 3284–94.

13 Paul M, Bishara J, Levcovich A, et al. Effectiveness and safety of colistin: prospective comparative cohort study. *J Antimicrob Chemother* 2010; **65:** 1019–27.

14 Deeks JJ, Higgins JPT. Statistical algorithms in Review Manager 5.1. 2010. http://training.cochrane.org/handbook/statistical-methods-revman (accessed Jan 2, 2018).

15 Zusman O, Altunin S, Koppel F, Dishon Benattar Y, Gedik H, Paul M. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. *J Antimicrob Chemother* 2017; **72:** 29–39.

16 Qureshi ZA, Paterson DL, Potoski BA, et al. Treatment outcome of bacteremia due to KPC-producing *Klebsiella pneumoniae*: superiority of combination antimicrobial regimens. *Antimicrob Agents Chemother* 2012; **56:** 2108–13.

17 Gutierrez-Gutierrez B, Salamanca E, de Cueto M, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. *Lancet Infect Dis* 2017; **17:** 726–34.

18 Daikos GL, Tsaousi S, Tzouvelekis LS, et al. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. *Antimicrob Agents Chemother* 2014; **58:** 2322–28.

19 Tumbarello M, Trecarichi EM, De Rosa FG, et al. Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study. *J Antimicrob Chemother* 2015; **70:** 2133–43.

20 Giacobbe DR, Maraolo AE, Viscoli C. Pitfalls of defining combination therapy for carbapenem-resistant Enterobacteriaceae in observational studies. *Eur J Clin Microbiol Infect Dis* 2017; **36:** 1707–09.

21 Kengkla K, Kongpakwattana K, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy and safety of treatment options for MDR and XDR *Acinetobacter baumannii* infections: a systematic review and network meta-analysis. *J Antimicrob Chemother* 2018; **73:** 22–32.

22 Amat T, Gutierrez-Pizarraya A, Machuca I, et al. The combined use of tigecycline with high-dose colistin might not be associated with higher survival in critically ill patients with bacteraemia due to carbapenem-resistant *Acinetobacter baumannii*. *Clin Microbiol Infect* 2017; published online Sept 29. DOI:10.1016/j.cmi.2017.09.016.

23 Liang CA, Lin YC, Lu PL, Chen HC, Chang HL, Sheu CC. Antibiotic strategies and clinical outcomes in critically ill patients with pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*. *Clin Microbiol Infect* 2017; published online Nov 3. DOI:10.1016/j.cmi.2017.10.033.

24 Durante-Mangoni E, Utili R, Zarrilli R. Combination therapy in severe *Acinetobacter baumannii* infections: an update on the evidence to date. *Future Microbiol* 2014; **9:** 773–89.

25 EUCAST. Antimicrobial wild type distributions of microorganisms. Euroepean Committee on Antimicrobial Susceptibility Testing. 2017. https://mic.eucast.org/Eucast2/ (accessed Jan 2, 2018).

26 Karaiskos I, Friberg LE, Pontikis K, et al. Colistin population pharmacokinetics after application of a loading dose of 9 MU colistin methanesulfonate in critically ill patients. *Antimicrob Agents Chemother* 2015; **59:** 7240–48.

27 Plachouras D, Karvanen M, Friberg LE, et al. Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria. *Antimicrob Agents Chemother* 2009; **53:** 3430–36.

28 Nicolau DP. Pharmacokinetic and pharmacodynamic properties of meropenem. *Clin Infect Dis* 2008; **47** (suppl 1)**:** S32–40.

29 Nutman A, Glick R, Temkin E, et al. A case-control study to identify predictors of 14-day mortality following carbapenem-resistant *Acinetobacter baumannii* bacteraemia. *Clin Microbiol Infect* 2014; **20:** O1028–34.

30 Pournaras S, Dafopoulou K, Del Franco M, et al. Predominance of international clone 2 OXA-23-producing-*Acinetobacter baumannii* clinical isolates in Greece, 2015: results of a nationwide study. I*nt J Antimicrob Agents* 2017; **49:** 749–53.

31 Principe L, Piazza A, Giani T, et al. Epidemic diffusion of OXA-23-producing *Acinetobacter baumannii* isolates in Italy: results of the first cross-sectional countrywide survey. *J Clin Microbiol* 2014; **52:** 3004–10.

32 Durante-Mangoni E, Signoriello G, Andini R, et al. 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. *Clin Infect Dis* 2013; **57:** 349–58.

33 Shields RK, Nguyen MH, Chen L, et al. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia. *Antimicrob Agents Chemother* 2017; **61:** e008833–17.

34 WHO. Antibacterial agents in clinical development—an analysis of the antibacterial clinical development pipeline, including tuberculosis. World Health Organization. 2017. http://www.who.int/entity/medicines/areas/rational_use/antibacterial_agents_clinical_development/en/index.html (accessed Jan 2, 2018).

35 Faden RR, Beauchamp TL, Kass NE. Informed consent, comparative effectiveness, and learning health care. *N Engl J Med* 2014; **370:** 766–68.

36 Huttner A, Leibovici L, Theuretzbacher U, Huttner B, Paul M. Closing the evidence gap in infectious disease: point-of-care randomization and informed consent. *Clin Microbiol Infect* 2017; **23:** 73–77.