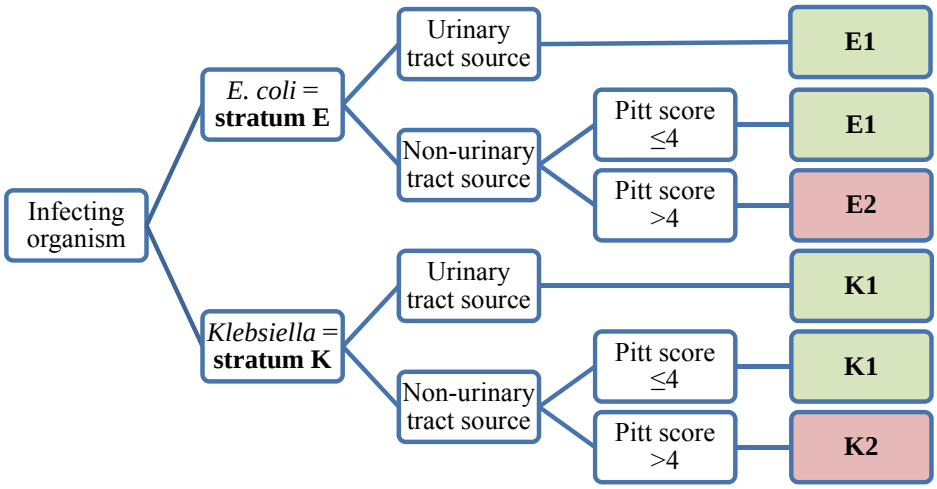
Supplementary Online Content

Harris PNA, Tambyah PA, Lye DC, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *Escherichia coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance. *JAMA*. doi:10.1001/jama.2018.12163

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplementary Protocol Data

eFigure 1: Patient Stratification by Disease Severity at Enrollment

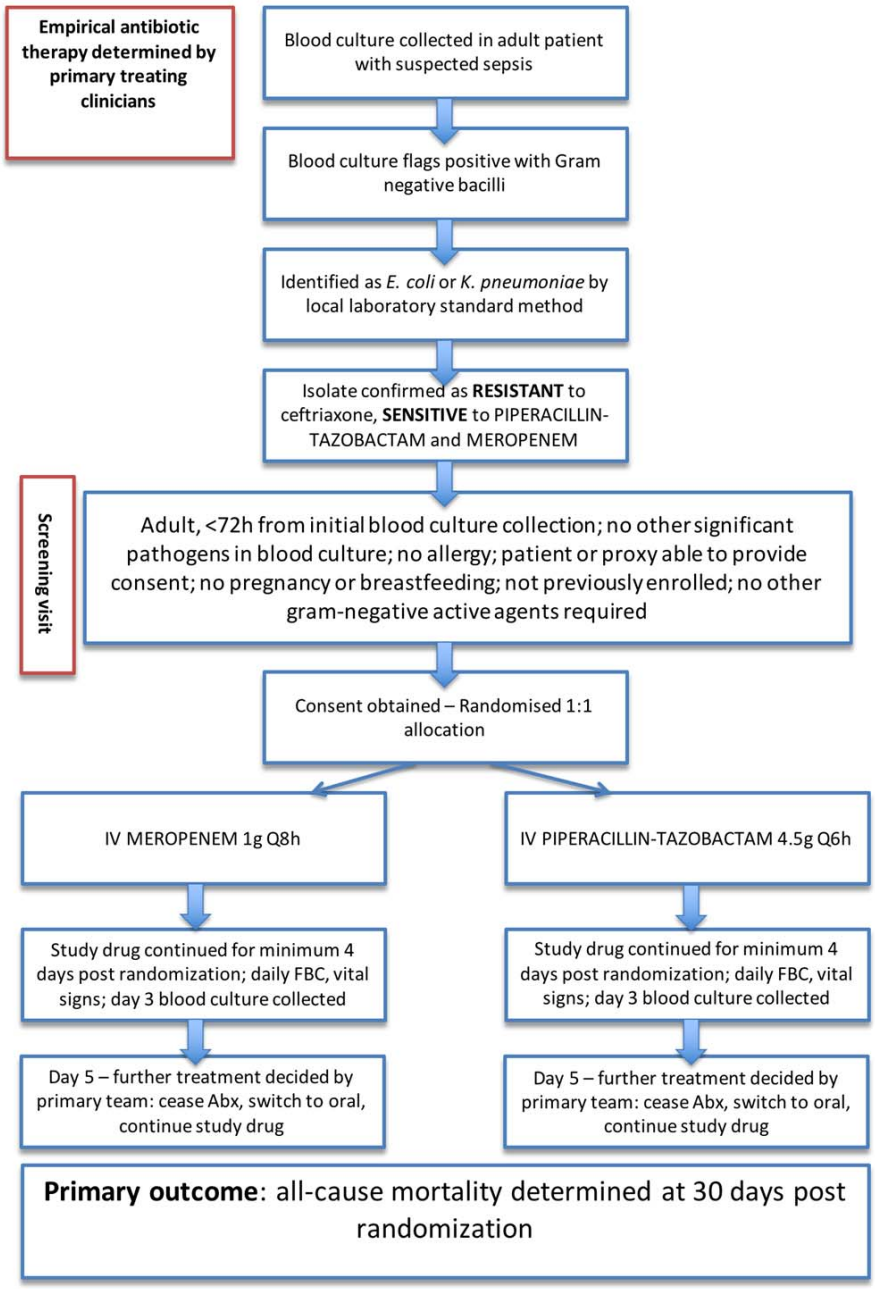


eTable 1: Baseline Clinical and Demographic Data

Categories	Variables
Demographic data	Age, gender, ethnicity, long-term residential care status, ward location
Trial characteristics	Date of screening and enrollment, inclusion criteria and consent details, date and time of randomization
Co-morbidities and risk factors	Charlson score, co-morbid conditions, date and type of any surgery within 14 days, use of cytotoxic chemotherapy, immune suppressive medication, radiotherapy, biological agents (for example, monoclonal antibody therapy), presence of intravascular devices or urinary catheters; use of 'not for resuscitation' order
Infection parameters	Bacteremia acquisition status (community, healthcare-associated or hospital-acquired infection), presumed source of infection, ICU admission, Pitt bacteremia score, Acute Physiology and Chronic Health Evaluation (APACHE) II score (if in ICU)
Antibiotic data	From 48 hours prior to blood culture collection and up to 30 days; agent/dose/route/frequency/duration recorded
Clinical observations	Daily vital signs, (highest temperature, HR, RR; lowest systolic BP), lowest arterial pCO_2 (if ventilated), white cell count, use of pressors/inotropes; recorded from day of blood culture collection up to day 5 post randomization; patient weight day 1
Microbiological data	Date and time of initial blood culture, susceptibility profile as reported by local laboratory, “clearance” blood culture result day 3 (or same species grown in blood up to day 30); any additional positive blood cultures and species identification/resistance profile; other clinical sites growing *E. coli* or *Klebsiella* spp., any multidrug-resistant gram-negative organism or *C. difficile* identified up to 30 days

HR = heart rate, RR = respiratory rate, BP = blood pressure, ICU = Intensive Care Unit

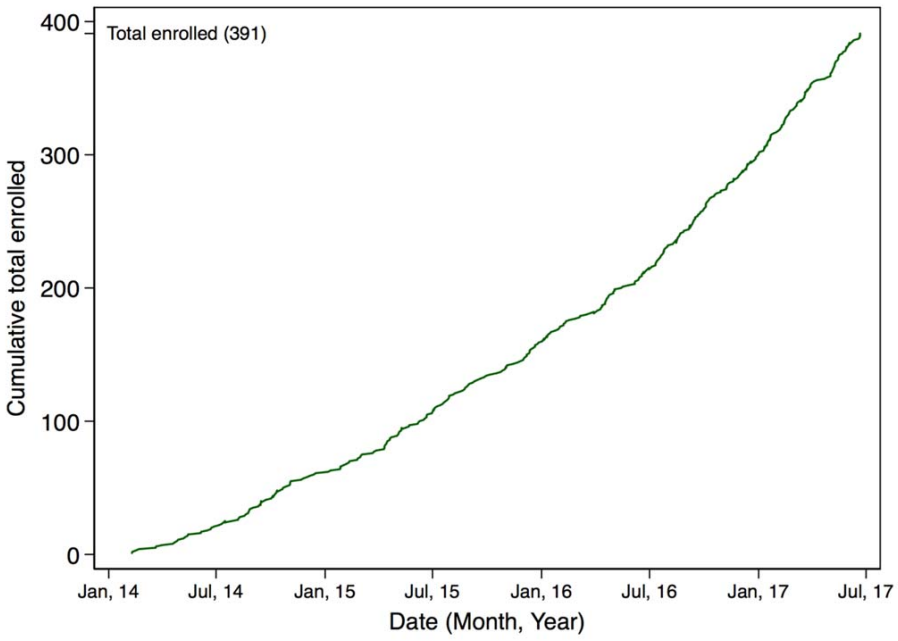
eFigure 2: Trial Workflow



Abx = antibiotics; FBC = full blood count

Recruitment Over Study Period

eFigure 3: Cumulative Enrollment



eTable 2: Screening and Enrollment by Site

Hospital		City/country	Total screened	Total enrolled
National University Hospital		Singapore	232	81
Tan Tock Seng Hospital		Singapore	659	76
Royal Brisbane & Women's Hospital		Brisbane, Australia	51	14
Princess Alexandra Hospital		Brisbane, Australia	35	8
St. Andrew's War Memorial Hospital		Brisbane, Australia	2	0
Mater Hospital		Brisbane, Australia	2	2
Royal Perth Hospital		Perth, Australia	25	2
Alfred Hospital		Melbourne, Australia	46	6
Monash Medical Centre		Melbourne, Australia	51	18
Dandenong Hospital		Melbourne, Australia	37	11
Peter MacCallum Cancer Centre		Melbourne, Australia	7	4
Geelong Hospital		Geelong, Australia	4	1
Wollongong / Shellharbour Hospitals		Wollongong, Australia	15	8
Westmead Hospital		Sydney, Australia	105	12
North Shore Hospital		Auckland, New Zealand	37	15
Middlemore Hospital		Auckland, New Zealand	46	4
Santa Maria Misericordia University		Udine, Italy	23	9
Policlinico Umberto		Rome, Italy	18	18
Sunnybrook Hospital		Toronto, Canada	23	2
Charlotte Maxeke Johannesburg		Johannesburg, S. Africa	3	0
Groote Schuur Hospital		Cape Town, S. Africa	17	11
King Abdulaziz Medical City		Riyadh, Saudi Arabia	103	22
King Fahad Specialist Hospital		Dammam, Saudi Arabia	9	4
Istanbul Medipol University		Istanbul, Turkey	50	48
American University of Beirut		Beirut, Lebanon	44	15
Townsville Hospital		Townsville, Australia	2	0
Total			1646	391

Antibiotic Therapy

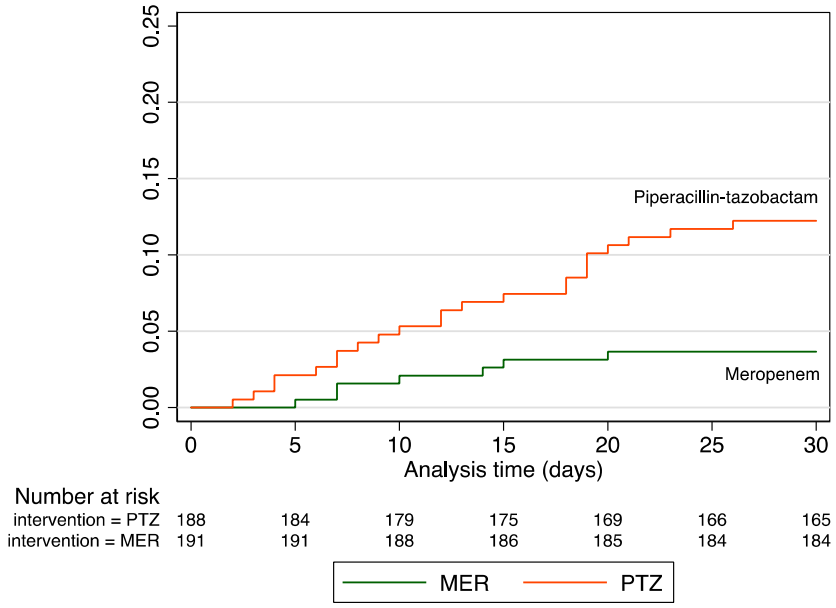
eTable 3: Details of Antibiotic Therapy

Variable	PTZ (n=188)	MER (n=191)
Total duration of study drug		
Mean days (SD)	7.3 (4.4)	7.6 (4.3)
Median days (IQR)	6 (5, 10)	6 (5, 9)
Total duration of all antibiotics		
Mean days (SD)	13.2 (6.1)	13.7 (7.6)
Median days (IQR)	13 (8,16)	13 (8, 16)
Empirical therapy		
BLBLI	39 (20.7)	50 (26.2)
Carbapenem	26 (13.8)	29 (15.2)
Other	126 (67.0)	115 (60.2)
Combination empirical therapy – no. (%)		
Yes	79 (42.0)	77 (40.3)
'Step down' therapy* – no. (%)		
Aminoglycoside	1 (0.5)	0 (0)
β-lactam/β-lactamase inhibitor	8 (4.3)	5 (2.6)
Carbapenem	38 (20.2)	39 (20.4)
Fosfomycin	2 (1.1)	1 (0.5)
Fluoroquinolone	20 (10.6)	30 (15.7)
Trimethoprim-sulfamethoxazole	7 (3.7)	13 (6.8)
Other	2 (1.1)	2 (1.0)
None	109 (58.0)	103 (53.9)
Not recorded	3 (1.6)	0 (0)
Empirical therapy congruent with randomized drug¶ - no. (%)		
Yes	39 (20.7)	29 (15.2)

*antibiotic choice once allocated trial drug ceased; ¶ includes drugs of same class; e.g. if piperacillin-tazobactam was used as empirical therapy, and the patient was randomized to piperacillin-tazobactam, this would be classified as "congruent" therapy; use of empirical ertapenem or imipenem was considered congruent with meropenem (as all are carbapenems)

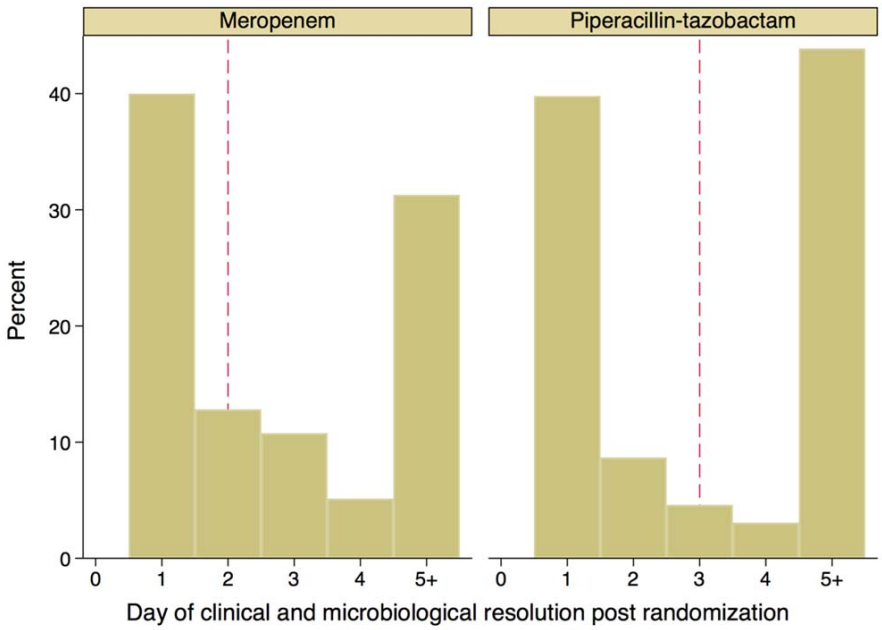
Analysis of Primary and Secondary Outcomes

eFigure 4: Kaplan-Meier Failure Estimates for Primary Outcome



Median observation time for both meropenem (MER) and piperacillin-tazobactam (PTZ) groups = 30 days; includes primary analysis population

eFigure 5: Day of Clinical and Microbiological Resolution by Treatment in the Primary Analysis Population



Red dashed line represents the median day of resolution (p=0.178, Wilcoxon rank-sum test). Note: data censored on last day of treatment protocol (i.e. non-resolution on or after day 5 designated as day 5+); day 1 is day of randomization.

Analysis of Primary Outcome by Predefined Subgroups

eTable 4: Risk of Mortality by Recruiting Site and Country in the Primary Analysis Population

Hospital	N	Death (PTZ) n/total (%)	Death (MER) n/total (%)	Risk difference	95% CI	RR	95% CI
National University Hospital	78	4/35 (11.4)	2/43 (4.7)	6.8	(-6.0, 22.1)	2.46	0.48, 12.63
Tan Tock Seng Hospital	75	4/36 (11.1)	1/39 (2.6)	8.5	(-3.7, 23.3)	4.33	0.51, 37.00
Royal Brisbane & Women's	14	0/7	1/7 (14.3)	-	-	-	-
Princess Alexandra Hospital	8	0/4	0/4	-	-	-	-
Mater Hospital	2	0/1	0/1	-	-	-	-
Royal Perth Hospital	2	0/2	0/0	-	-	-	-
Alfred Hospital	6	0/3	0/3	-	-	-	-
Monash Medical Centre	17	1/7 (14.3)	0/10	-	-	-	-
Dandenong Hospital	11	0/5	0/6	-	-	-	-
Peter MacCallum Cancer Centre	4	1/2 (50.0)	0/2	-	-	-	-
Geelong Hospital	1	0/1	0/0				
Wollongong Hospital	8	1/4 (25.0)	0/4	-	-	-	-
Westmead Hospital	12	1/6 (16.7)	1/6 (16.7)	0	(-50.0, 50.0)	1.00	0.08,12.56
North Shore Hospital	15	1/9 (11.1)	1/6 (16.7)	-5.6	(-52.8, 33.1)	0.67	0.51, 8.73
Middlemore Hospital	4	0/1	0/3	-	-	-	-
Santa Maria Misericordia, Udine	7	0/3	0/4	-	-	-	-
King Fahad Hospital, Dammam	3	0/2	0/1	-	-	-	-
Sunnybrook, Toronto	2	0/1	0/1	-	-	-	-
Medipol University, Istanbul	46	6/24 (25.0)	1/22 (4.6)	20.5	(-0.7, 41.6)	5.50	0.72, 42.15
American University of Beirut	15	0/8	0/7	-	-	-	-
Groote Schuur, Cape Town	11	2/5 (40.0)	0/6	-	-	-	-
King Abdulaziz MC, Riyadh	19	1/9 (16.7)	0/10	-	-	-	-
Policlinico Umberto, Rome	18	1/12 (14.3)	0/6	-	-	-	-
Country							
Singapore	153	8/71 (11.3)	3/82 (3.7)	7.6	(-0.7,17.5)	3.08	0.85, 11.17
Australia	85	4/42 (9.5)	2/43 (4.7)	4.9	(-7.4,18.2)	2.05	0.40, 10.59
New Zealand	19	1/10 (10.0)	1/9 (11.1)	-1.1	(-3.7, 33.0)	0.90	0.07, 12.38
Canada	2	0/1	0/1	-	-	-	-
South Africa	11	2/5 (40)	0/6	40	(-10.9, 78.1)	-	-
Turkey	46	6/24 (25)	1/22 (4.6)	20.5	(-0.7, 41.6)	5.50	0.72, 42.15
Italy	25	1/15	0/10	6.7	(-22.8,	-	-

		(6.7)			30.4)		
Lebanon	15	0/8	0/7	-		-	-
Saudi Arabia	22	1/11 (9.1)	0/11	9.1	(-19.0, 38.5)	-	-

MER=meropenem, PTZ=piperacillin-tazobactam; RR = risk ratio; CI = confidence interval

Multivariable Logistic Regression Model

On bivariable analysis, a UTI source was associated with a reduced risk of mortality (OR .34, 95% CI: .16-.74). A unit increase in the Charlson score was significantly associated with mortality (OR 1.35, 95% CI: 1.17-1.55), as was a Pitt score ≥4 (OR 2.96, 95% CI: 1.03-8.49). Randomization to piperacillin-tazobactam was associated with mortality in bivariable analysis (OR 3.69; 97.5% one-sided CI: 0-8.82). In the multivariable model, after adjustment for Charlson score and UTI source, the effect of randomization to piperacillin-tazobactam was largely unchanged (aOR 3.41, one-sided 97.5% CI: 0-8.38) (Table S5).

eTable 5: Adjusted Analysis of Primary Outcome in the Primary Analysis Population

Variable	Died (%) (N=30)	Survived (%) (N=348)	Bivariable analysis		
			OR	2-sided 95% CI	*P* value [c]
Age					
≤65 years	10 (6.5)	145 (93.6)	*Age <=65 as reference*		
>65 years	20 (9.0)	203 (91.0)	1.42	.64-3.14	.38
UTI Source					
Non-UTI source	19 (12.8)	129 (87.2)	*Non-UTI as reference*		
UTI source	11 (4.8)	219 (95.2)	.34	.16-0.74	.006
Illness severity [a]					
Pitt score <4	25 (7.1)	326 (92.9)	*Pitt <4 as reference*		
Pitt score ≥4	5 (18.5)	22 (81.5)	2.96	1.03-8.49	.04
Co-morbidity (median, IQR)					
Charlson score [b]	4.5 (3, 6)	2 (1, 4)	1.35	1.17-1.55	<.001
Economic region					
High income	21 (6.9)	285 (93.1)	*High income as reference*		
Middle income	9 (12.5)	63 (87.5)	1.94	.85-4.43	.12
Empirical therapy					
Inappropriate therapy	7 (5.6)	118 (94.4)	*Inappropriate therapy as reference*		
Appropriate therapy	23 (9.1)	230 (90.9)	1.69	.70-4.04	.24
Healthcare-associated infection (HAI)					
Non-HAI	8 (4.9)	156 (95.1)	*Non-HAI as reference*		
HAI	22 (10.3)	192 (89.7)	2.23	.97-5.16	.06
Infecting species					
E. coli	24 (7.3)	303 (92.7)	*E. coli as reference*		
K. pneumoniae	6 (11.8)	45 (88.2)	1.68	.65-4.34	.28
Immune compromise					
Absent	19 (6.6)	268 (93.4)	*No immune compromise as reference*		
Present	11 (12.1)	80 (87.9)	1.93	.89-4.25	.10
Diabetes mellitus					
Absent	22 (9.2)	218 (90.8)	*No diabetes as reference*		
Present	8 (5.8)	130 (94.2)	.61	.26-1.41	.25

Variable	Died (%) (N=30)	Survived (%) (N=348)	Bivariable analysis		Multivariable analysis [d]	
			OR	One-sided 97.5% CI	aOR	One-sided 97.5% CI
Meropenem	7 (3.7)	184 (96.3)	*Meropenem as reference*			
Piperacillin-tazobactam	23 (12.3)	164 (87.7)	3.69	0-8.82	3.41	0-8.38

[a] The Pitt score (range 0-14) provides a measure of in-hospital mortality risk in patients with bloodstream infections, with a score ≥4 associated with a risk of mortality of ~40%; [b] Charlson score (range 0-29) provides a 10-year mortality risk, based on weighted scores for the presence of co-morbid conditions, with a score of 4 associated with an estimated 10-year survival of ~53% and was analyzed as a continuous variable (higher scores are associated with increased risk); [c] *P* values for two-sided superiority testing used for assessment of the effect of clinical variables on the primary outcomes; [d] adjusted for Charlson score and urinary source; OR = odds ratio, aOR = adjusted odds-ratio

Serious Adverse Events

eTable 6: Details of Fatal Serious Adverse Events

Treatment	Details of SAE	Relationship to study drug	Alternative cause if not related	Date of death
PTZ	Advanced adenocarcinoma of the stomach with linitis plastica, on chemotherapy. Blood cultures post enrolment grew *Candida* sp., requiring ICU admission. CT brain showed a new large MCA territory infarct. Terminal care was initiated.	Not associated	Malignancy; other co-morbidities; new infection	March 2014
MER	Advanced metastatic cholangiocarcinoma.	Not associated	Malignancy; other co-morbidities.	May 2014
PTZ	Metastatic cholangiocarcinoma, liver collections; post enrolment blood cultures grew *Enterococcus faecium* and *Acinetobacter baumannii*. Became intermittently confused and condition deteriorated. Palliative care was initiated.	Not associated	Malignancy; other co-morbidities; new infection	Aug 2014
MER	Comorbidities including bullous pemphigoid, hydronephrosis, septic thrombophlebitis. Blood cultures day 11 post enrolment grew non-multi-resistant *Proteus mirabilis* and *Acinetobacter baumannii* susceptible only to polymyxins. Palliative care was initiated due to advanced age and co-morbid illness.	Not associated	Malignancy; other co-morbidities; new infection	Sept 2014
MER	Severe norovirus gastroenteritis, vomiting and aspiration leading to cardiac arrest.	Not associated	Other co-morbidities; new infection	Oct 2014
PTZ	Elderly, bed bound with diabetes, ischaemic heart disease, large pancreatic mass not for further investigation. Found collapsed at home post discharge in asystole / ventricular fibrillation, with evidence of GI bleeding.	Not associated	Other co-morbidities	Oct 2014

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MER	Laparotomy for repair of a duodenal perforation post-ERCP; severe sepsis, multi-organ dysfunction, acute kidney injury. Necrotic pancreatic tissue was removed, and a duodenal perforation repaired, without clinical resolution. Palliative measures were instigated.	Not associated	Other co-morbidities; new infection	Jun 2015
PTZ	Metastatic pulmonary malignancy. Died 19 days post enrolment following resolution of infection.	Not associated	Other co-morbidities	Sept 2015
PTZ	Elderly patient with liver cirrhosis, chronic renal impairment, and spontaneous bacterial peritonitis. Condition deteriorated day 14 post enrolment with persistent hypotension despite vasopressors. Palliative care was initiated	Not associated	Other co-morbidities	Sept 2015
PTZ	Died at home post discharge of known metastatic malignancy	Not associated	Malignancy	Dec 2016
PTZ	Richter's transformation from chronic lymphocytic leukemia with a poor prognosis	Not associated	Malignancy	Jan 2016
MER	Elderly patient, died at nursing home post discharge and resolution of infection	Not associated	Other co-morbidities	Jan 2016
PTZ	Elderly patient with diabetes, ischemic heart disease, atrial fibrillation and chronic kidney disease. Episodes of intractable pulmonary edema. Palliative care was initiated.	Not associated	Other co-morbidities	March 2016
PTZ	Elderly patient with multiple co-morbidities including hepatocellular carcinoma in context of hepatitis B cirrhosis.	Not associated	Malignancy; other co-morbidities	Sept 2016
PTZ	Advanced metastatic malignancy. Patient died at home during follow-up period following discharge.	Not associated	Malignancy; other co-morbidities	Sept 2016
PTZ	Following initial recovery from infection, developed septic shock and died; repeat blood culture subsequently grew *Candida albicans*.	Not associated	New infection	Nov 2016
MER	Metastatic uterine leiomyosarcoma, as primary cause of death.	Not associated	Malignancy	Nov 2016

PTZ	Advanced liver disease; died of respiratory failure associated with encephalopathy.	Not associated	Other co-morbidities	Dec 2016
PTZ	Metastatic bowel cancer. Developed perforation and acutely deteriorated.	Not associated	Malignancy	Dec 2016
PTZ	Died three days after discharge from hospital from unrelated causes	Not associated	Other co-morbidities	Jan 2017
PTZ	Patient developed ventricular fibrillation during ICU admission with cardiac and respiratory arrest.	Not associated	Other co-morbidities	Jan 2017
PTZ	Cholangiocarcinoma in a liver transplant recipient. Developed hemorrhagic shock	Not associated	Malignancy; other co-morbidities	Mar 2017
PTZ	Death due to GI bleed in context of liver failure (pre-existing) and coagulopathy	Not associated	Other co-morbidities	Mar 2017
PTZ	Elderly patient with pancreatic cancer. Their condition deteriorated following resolution of infection. The cause of death was recorded as pancreatic cancer.	Not associated	Malignancy; other co-morbidities	Feb 2017
PTZ	End stage chronic liver disease.	Not associated	Other co-morbidities	Feb 2017
MER	Retroperitoneal liposarcoma, on palliative care. Died at home following discharge.	Not associated	Malignancy; other co-morbidities	Nov 2016
PTZ	Hemorrhagic shock in the context of advanced cirrhosis	Not associated	Other co-morbidities	Apr 2017
PTZ	COPD and dementia, died of septic shock	Not associated	Other co-morbidities	May 2017
MER	Elderly patient, end stage chronic kidney disease, but had declined dialysis. Died day 17 due to progressive uremia without ongoing signs of infection.	Not associated	Other co-morbidities	May 2017
PTZ	Retroperitoneal liposarcoma, under palliative care; initial infection resolved and was discharged home, but died one day later.	Not associated	Malignancy; other co-morbidities	May 2017

eTable 7: Details of Nonfatal Serious Adverse Events

Three serious adverse events (SAEs) recorded in the MER treatment arm, were not directly attributed to the study drug. In the PTZ arm, there were five adverse events, which were possibly or definitely drug-related (Table S8). All events were reported to the relevant IRB.

Treatment	Details of SAE	Relationship to study drug	Alternative cause if not related	Outcome
PTZ	Rash requiring cessation of drug	Associated	N/A	Resolved without sequelae
PTZ	Renal dysfunction requiring cessation of drug (creatinine 254→408)	Associated	N/A	Resolved with sequelae (see fatal SAEs)
PTZ	Readmission with clinical diagnosis of colitis – no *C. difficile* testing performed	Possibly associated	Unknown	Resolved without sequelae
MER	Cerebral hemorrhage	Not associated	Cerebrovascular disease	Resolved with sequelae
MER	T9/10 infective discitis: *Pseudomonas aeruginosa* grown from operative sample	Not associated	New infection	Resolved with sequelae
MER	Renal colic, caused by renal calculi	Not associated	N/A	Resolved without sequelae
PTZ	Acute onset exertional dyspnea, fevers/chills and malaise, but negative cultures; cause unspecified	Possibly associated	Existing co-morbidities or new infection	Resolved without sequelae
PTZ	Upper limb venous thrombosis	Not associated	PICC-line associated	Resolved without sequelae

Microbiology Substudies

Whole genome sequencing methods

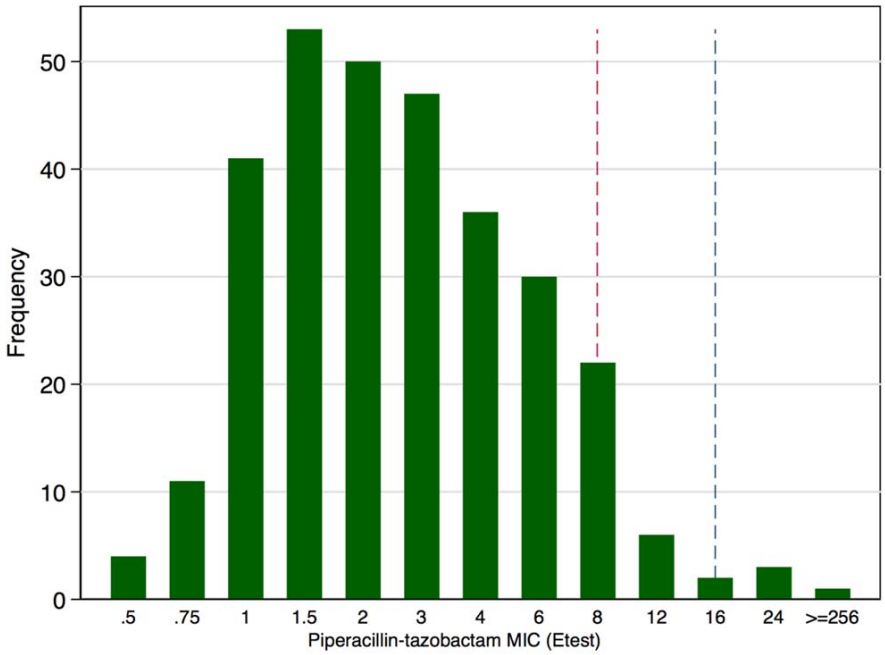
Genomic DNA was extracted using UltraClean DNA isolation kits (MoBio; Australia) and QIAmp DNA mini kits (Qiagen, Australia) and quantified by spectrophotometry (NanoDrop; ThermoFisher) and fluorometry (Qubit; ThermoFisher). Paired-end DNA libraries were prepared using Nextera kits (Illumina; Australia). Whole genome sequencing was performed at the Australian Genome Research Facility (AGRF), University of Queensland, using Illumina HiSeq (100 bp paired end) and MiSeq (300 bp paired end), as well as Illumina NextSeq (150 bp paired end) at the Forensic and Scientific Services Laboratory. MiSeq raw reads were trimmed conservatively to 150 bp and filtered using Nesoni to remove Illumina adaptor sequences, reads shorter than 80 bp and bases below Phred quality 5 (https://github.com/Victorian-Bioinformatics-Consortium/nesoni). Strains were checked for contamination using Kraken (v1.1). Genome assembly was performed using Spades (v3.9.0) and filtered for contigs demonstrating <10x coverage and <100 bp length. Antibiotic resistance genes were detected using assemblies and Abricate (v0.8) against the ResFinder and ARG-ANNOT databases (25th April 2018). Resistance genes were determined as being present only when 100% coverage of the gene sequence was present. *In silico* multi-locus sequence typing (MLST) was performed using mlst (v2.1) against finalized assemblies. Where assemblies did not match any specific ST profile, read mapping (with BWA v0.7.17) and interrogation using Artemis was used to confirm any single nucleotide polymorphisms (SNPs) present. *Klebsiella* isolates were run through Kaptive (v0.3) to determine capsule type (against the primary K-type database).

eTable 8: Susceptibility Data for Index Blood Culture Isolates (From Local Laboratory Reporting) in the Primary Analysis Population

Antibiotic	Category	*E. coli* (n=328)	*K. pneumoniae* (n=51)
Amikacin	S	224 (68.7%)	41 (80.4%)
	I	16 (4.9%)	0 (0.0%)
	R	5 (1.5%)	2 (3.9%)
	NT	81 (24.8%)	8 (15.7%)
Amoxicillin-clavulanate	S	69 (21.4%)	10 (19.6%)
	I	46 (14.2%)	9 (17.6%)
	R	85 (26.3%)	24 (47.1%)
	NT	123 (38.1%)	8 (15.7%)
Cefepime	S	38 (11.7%)	9 (17.6%)
	I	10 (3.1%)	2 (3.9%)
	R	151 (46.5%)	26 (51.0%)
	NT	126 (38.8%)	14 (27.5%)
Ceftazidime	S	8 (2.5%)	3 (5.9%)
	I	15 (4.6%)	3 (5.9%)
	R	237 (73.1%)	36 (70.6%)
	NT	64 (19.8%)	9 (17.6%)
Ceftriaxone	S*	1 (0.3%)	0 (0.0%)
	I	1 (0.3%)	2 (3.9%)
	R	325 (99.4%)	49 (96.1%)
Ciprofloxacin	S	78 (23.9%)	20 (39.2%)
	I	6 (1.8%)	7 (13.7%)
	R	202 (61.8%)	21 (41.2%)
	NT	41 (12.5%)	3 (5.9%)
Gentamicin	S	204 (62.2%)	29 (56.9%)
	I	5 (1.5%)	1 (2.0%)
	R	118 (36.0%)	21 (41.2%)
	NT	1 (0.3%)	0 (0.0%)
Meropenem	S	328 (100.0%)	51 (100.0%)
Piperacillin-tazobactam	S	328 (100.0%)	51 (100.0%)
Trimethoprim-sulphamethoxazole	S	90 (27.9%)	11 (21.6%)
	I	3 (0.9%)	1 (2.0%)
	R	149 (46.1%)	30 (58.8%)
	NT	81 (25.1%)	9 (17.6%)

S = susceptible, R = resistant, I = intermediate, NT = not tested; * single ceftriaxone-susceptible strain was ceftazidime-resistant

eFigure 6: Minimum Inhibitory Concentrations (MICs) of Piperacillin-Tazobactam (Tested at Coordinating Laboratory)



Red dashed line = European Committee for Antimicrobial Susceptibility Testing (EUCAST) breakpoint for susceptibility (≤8 mg/L); blue dashed line = Clinical and Laboratory Standards Institute (CLSI) breakpoint for susceptibility (≤16 mg/L)

eTable 9: Mortality in Patients Randomized to Piperacillin-Tazobactam According to MIC[a]

	Minimum inhibitory concentration (MIC) mg/L											
	.5	.75	1	1.5	2	3	4	6	8	12	16	24
No. deaths/ No. treated	0/2	1/6	5/15	1/26	3/20	2/24	0/12	3/10	1/11	1/3	0/1	1/2

[a]Note: not all randomized patients had isolates available for additional MIC testing

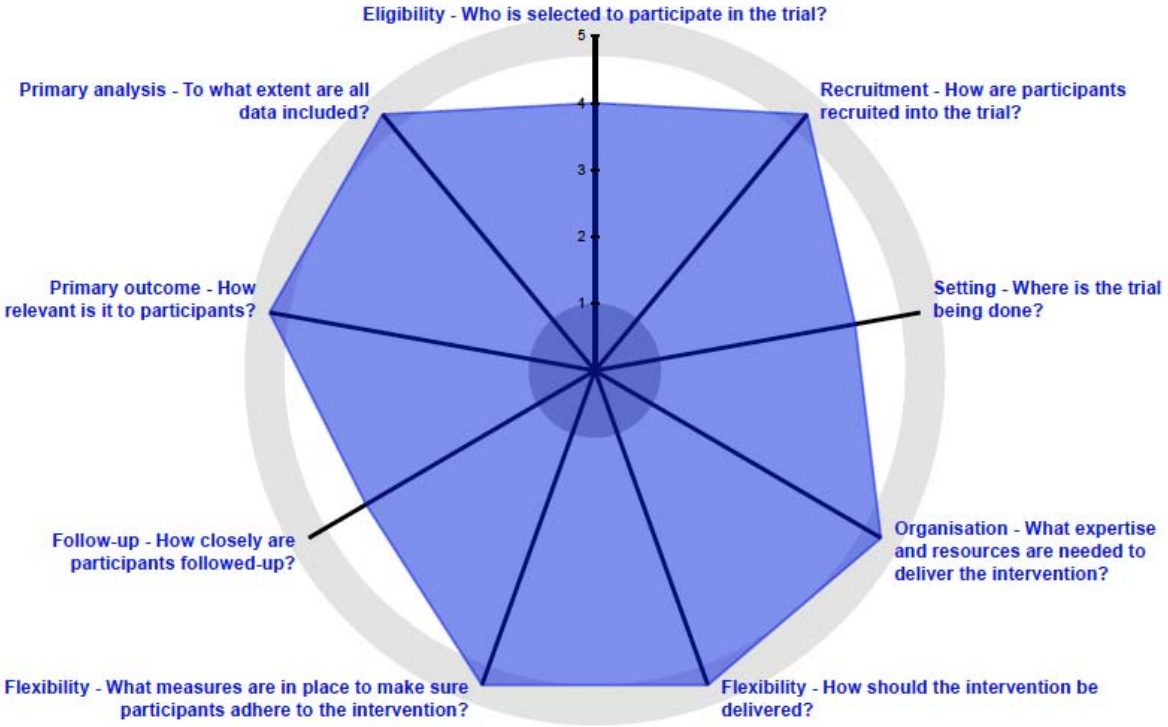
eTable 10: Other Positive Blood Cultures Postrandomization (Identified as Different Species From Index Blood Culture)

Arm	Index organism	Other positive BC (1) up to 30d	PTZ-R	MER-R	Other positive BC (2) up to 30d	PTZ-R	MER-R
MER	*E. coli*	coagulase negative staphylococci	-	-			
PTZ	*E. coli*	*Streptococcus mitis*	-	-			
PTZ	*K. pneumoniae*	*Escherichia coli*	Yes	No			
PTZ	*E. coli*	*Klebsiella* spp	Yes	Yes			
PTZ	*E. coli*	*Klebsiella* spp.	Yes	Yes			
MER	*E. coli*	coagulase negative staphylococci	-	-			
PTZ	*E. coli*	*Pseudomonas aeruginosa*	No	No			
MER	*E. coli*	Methicillin-resistant *S. aureus*	-	-			
MER	*K. pneumoniae*	*Enterococcus faecium*	-	-			
MER	*E. coli*	*Staphylococcus epidermidis*	-	-			
MER	*E. coli*	coagulase negative staphylococci	-	-			
PTZ	*E. coli*	*Candida albicans*	-	-			
PTZ	*E. coli*	*Enterococcus faecium*	-	-	*Acinetobacter baumannii*	Yes	Yes
PTZ	*E. coli*	*Candida albicans*	-	-			
PTZ	*K. pneumoniae*	Methicillin-resistant *S. aureus*	-	-			
MER	*E. coli*	*Proteus mirabilis*	No	No			

Index organism = initial species from blood culture (BC) prompting enrolment in the trial; PTZ-R = resistant to piperacillin-tazobactam; MER-R = resistant to meropenem (if gram-negative species)

PRECIS-2 Assessment for Pragmatic Trial Design

eFigure 7: PRECIS-2 Diagram



http://www.precis-2.org/Trials/Details/376

Missing Value Method Comparisons

Missing values are known to be an issue in non-inferiority trials. Three methods were compared, namely analysis of the full data set where missing values were excluded and two methods for imputation: last observation carried forward (LOCF) and multiple imputation (MI). Table S11 shows the extent of missing values.

eTable 11: No. and % Patients With Missing Values for Secondary Objectives in the Primary Analysis Population

	Secondary objectives				
	1 †	**2** †	**3**	**4**	**5**
No. missing	322	163	16	19	1
N	378	378	378	378	378
% missing	85.2	43.1	4.2	5	0.3

† note that once the peripheral blood total white cell count was <12 x10^9/L, daily blood collection could be ceased, which was the most common reason for missing clinical observation data; patients with non-resolution at day 5 were also counted as "missing" for the purposes of this comparison

Multiple Imputation (MI) was carried out using Multivariate Imputation by Chained Equations for both discrete and continuous data by fully conditional specification.[1] Computation was carried out via the 'mice' package in R 3.5.0.[2] One hundred imputations were obtained for the first four secondary objectives employing maximum and minimum daily temperature, clearance of blood cultures by day 3 and maximal heart rate measured at day 1, 3, 4 and 5 as covariates.

Secondary Objective 1: *Days to clinical microbiological resolution*.

For the purposes of this analysis, if success was not attained by day 5 then the value was deemed to be missing. This was for comparison purposes only and results in more missing values than is warranted given that resolution was attained after day 5. In the main analysis, the data are treated as a separate category of 5+ days and analysed using non-parametric methods. The t-tests yielded similar p-values for all three approaches. The mean number of days are slightly different but all estimates are close to 2 days. For the three methods, Complete Data (smaller dataset): (PTZ=2.04, MER=2.07) *P* =.95, for last value carried forward: (PTZ=1.83, MER=1.98) *P* =.39 and for MI: (PTZ=2.25, MER=2.21) *P* =.89. With a large data set we would not expect non-parametric tests to yield answers that are much different although the

MI procedure produces an average *P* value of .36 (which is smaller than the t-test). The median (IQR) statistics are Complete data: MER = 1(1.8), PTZ=2(2), *P* =.47, LOCF: 1(1), 1(2), *P* =.14 and for MI: MER = 1.7(2.3), PTZ = 1.5(2.2), *P* =.37.

Secondary Objective 2: *Clinical and microbiologic success at day 4*
All three methods yield similar results in that *P* values indicate non-significance at the .05 level. Complete data: *P* =.16, LOCF: *P* =.23 and MI: *P* =.63.

Secondary Objective 3: *Microbiological resolution at day 4*
All three methods yield similar conclusions. Complete data: *P* =.23, LOCF: *P* =.11 and MI: *P* =.51.

Secondary Objective 4: *Relapsed bloodstream infection*
All three methods are similar in that *P* values are >.05. Complete data: *P* =.11, LOCF: *P* =.17 and MI: *P* =.66.

Secondary Objective 5: *Secondary infection*
Only a single case had missing data, so imputation was not performed.

eReferences

1. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res.* 2007;16(3):219-242.
2. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software* 2011; https://www.jstatsoft.org/index.php/jss/article/view/v045i03.