Supplement

Comparable Efficacy and Better Safety of Double β-Lactam Combination Therapy versus β Lactam Plus Aminoglycoside in Gram-negatives: A Meta-analysis of Randomized, Controlled Trials

Table S1. Definition of febrile neutropenia and other infections in the included trials.

Study	Type of infection	Definition
Middleman(1972)	Febrile neutropenia	Neutropenia: neutrophils < 1000 /mm^3; Fever: Body temperature >101F (equivalent to 38.3 °C), not associated with transfusion of blood products.
Klastersky (1975)	Severe Infection	Rectal temperature > 101F (equivalent to 38.3 °C); Shaking chills; hypotension.
Schimpff (1976)	Febrile neutropenia	Neutropenia: absolute granulocyte count <1000/μL; Fever: oral temperature ≥101F (equivalent to 38.3 °C); in absence of obvious noninfective cause of fever (e.g. blood products, cytotoxic drug).
EORTC (1978)	Febrile neutropenia	Neutropenia: granulocyte <1000 cells/μL; Fever: temperature >101F (equivalent to 38.3 °C); in the absence of obvious noninfective causes of fever such as blood products or cytotoxic drugs.
Bodey (1979)	Febrile neutropenia	Neutropenia: granulocyte <1000 cells/μL; Fever: temperature ≥101F (equivalent to 38.3 °C); fever not related to transfusion of blood products or to the administration of known pyrogens, such as immunotherapeutics.
Wiston (1984)	Febrile neutropenia	Neutropenia: granulocyte count <1000/mm^3; Fever: temperature > 38 °C, not related to the administration of blood products or drugs.
Fainstein (1984)	Febrile neutropenia	Neutropenia: neutrophil count <1000/mm^3; Fever: temperature ≥ 38.5 °C; presumed or proved to have infection.
Feld (1985)	Febrile neutropenia	Neutropenic: neutrophil count <1000/mm^3; Fever: temperature > 38 °C more than 3 times during a 12 hour period, or single temperature spike of at least 39 °C, or any level of fever with rigors.
De Jongh (1986)	Febrile neutropenia	Neutropenia: granulocyte count < 1000/mm^3; Fever: temperature > 38 °C.
Rostein (1988)	Febrile neutropenia	Neutropenia: neutrophils ≤ 1000/mm^3; Fever: ≥ 38 °C at least twice during a 24-hour period, or at least 38.5 °C once.
Torres (1989)	Severe Nosocomial Pneumonia	The nosocomial pneumonia were based on the appearance of new infiltrates in the chest X-ray at least 72 h following hospital admission, bronchial purulent secretions, leukocytosis and/or presence of fever.
Kibbler (1989)	Febrile neutropenia	Neutropenia: neutrophil count < 1.0×10^9/L. Fever: temperature ≥38 °C for two consecutive hours or ≥39 °C on one occasion.
Joshi (1993)	Febrile neutropenia	Neutropenia: absolute granulocyte count < 1000/μL; Fever: temperature ≥ 38 °C.

Table S2. Definition of therapeutic response in the included trials.

Study	Type of infection	Therapeutic response
Middleman (1972)	Febrile neutropenia	*Complete response*: afebrile and all clinical and laboratory signs of infection disappeared; *Relapse*: responded to antibiotic combination but had a recurrence within one week after cessation of therapy.
Klastersky (1975)	Severe Infection	*Success*: clinical signs of infection disappeared; patient survived or else died from causes unrelated to infection; *Failed*: patient died as a result of the initial infection or superinfection; or antibiotics had to be changed because of a lack of response or sever untoward reaction related to their use.
Schimpff (1976)	Febrile neutropenia	*Improvement*: a return of temperature to normal or to the pre-infectious state with complete disappearance of all signs and symptoms of infection; *Temporary improvement*: return of temperature to normal and resolution of signs and symptoms of infection lasting at least 5 days but followed by a relapse of the same infection either while the patient was still receiving antibiotics or within 1 week after antibiotic discontinuation; *Failure*: no or poor response to antibiotic therapy; a change of antibiotics or the addition of granulocyte transfusions regardless of the patient's ultimate clinical course; *Non-evaluable*: improvement or no change without any specific relationship to antibiotics.
EORTC (1978)	Febrile neutropenia	*Improvement*: a return of temperature to normal or to the pre-infectious state with complete disappearance of all signs and symptoms of infection; *Temporary improvement*: return of temperature to normal and resolution of signs and symptoms of infection lasting at least 5 days but followed by a relapse of the same infection either while the patient was still receiving antibiotics or within 1 week after antibiotic discontinuation; *Failure*: no or poor response to antibiotic therapy; a change of antibiotics or the addition of granulocyte transfusions regardless of the patient's ultimate clinical course; *Non-evaluable*: improvement or no change without any specific relationship to antibiotics.
Bodey (1979)	Febrile neutropenia	*Cure*: disappearance of all clinical and laboratory evidence of infection at the time administration of the antibiotics was discontinued.
Wiston (1984)	Febrile neutropenia	*Improvement*: disappearance of fever with overall clinical improvement and eradication of the infecting organism; *Failure*: persistence of fever or the infecting organism without clinical improvement; *Non-evaluable*: infection considered unlikely, nonbacterial infection, or protocol violation.
Fainstein (1984)	Febrile neutropenia	*Cure*: disappearance of all clinical and laboratory evidence of infection at the time of discontinuation of administration of the antibiotics.

Feld (1985)	Febrile neutropenia	*Complete resolution*: disappearance of all signs and symptoms related to the infection, with the patient remaining afebrile for at least four days following the discontinuation of antibiotics; *Temporary improvement*: a lessening of the signs and symptoms of infection with a decrease in peak temperature of at least 1.7 °C or a return to normal with signs at the site of infection showing improvement; *Failure*: lack of improvement or death due to uncontrolled infection after four or more doses of therapy; *Indeterminate response*: evaluation of antibiotic efficacy was not possible; For purpose of analysis, only two outcome categories: responses include complete response and 'favorable' temporary improvement; failure includes all other cases that could be evaluated.
De Jongh (1986)	Febrile neutropenia	*Improvement*: complete resolution of all signs and symptoms of infection occurred without any antibiotic adjustment; *Failure*: (1) changes in antimicrobial therapy were required or clinical deterioration (including those in which a pathogen resistant to one or both drugs was isolated), or development of adverse antibiotic-related reactions; (2) patients were receiving the empiric regimen at the time of death, and the infection had not completely resolved; (3) granulocyte transfusions were administered.
Rostein (1988)	Febrile neutropenia	*Clinical response*: improvement only if resolution of all signs and symptoms of infection occurred; *Response*: temporary improvement with relapse if, after improvement with therapy, fever and infection due to an organism present at the initiation of therapy recurred within 96 hours after discontinuing the antibiotic treatment; *Failure*: (1) changes in antimicrobial therapy were required for clinical deterioration (including those in which a pathogen resistant to both drugs was isolated); or (2) there was no resolution of fever and/or the signs and symptoms of infection (when no occult fungal infection was believed to be present); *Bacteriologic response*: eradication of the offending pathogen; *Bacteriologic failure*: persistence of offending pathogen.
Torres (1989)	Severe Nosocomial Pneumonia	*Clinical cure*: resolution of the clinical signs and symptoms; *Favorable evolution*: improvement in clinical symptoms without a complete resolution; *Therapeutic failure*: failure to eradicate the causative agent from the infection site; *Microbiological cure*: complete eradication of the causative microorganism.
Kibbler (1989)	Febrile neutropenia	*Clinical response*: resolution of, or improvement in, clinical signs and symptoms before a change in therapy; *Microbiological response*: eradication of the infecting pathogen during therapy and failure to isolate it following discontinuation of antibiotics.
Joshi (1993)	Febrile neutropenia	*Response*: complete resolution of all signs and symptoms of infection and documentation that the infecting organism was eradicated; *Failure*: complete resolution of infection was not apparent, or only partially apparent.

Table S3. Renal toxicity for DBL and BLAG group as well as the exposures at studied doses.

Trial	DBL	BLAG	DBL			BLAG			Aminoglycoside doses and predicted average drug exposures				
			No.	Total	%	No.	Total	%	Daily dose mg/kg/day	$AUC_{0\text{-}24h}$ mg·g/h	C_{max} mg/L	$C_{ss,avg}$ mg/L	Ref.
Middleman 1972	CAR + CEF	CAR + KAN	6	81	7.4	9	82	11.0	14.8	187	14 [c]	7.8	(1)
Klastersky 1975	TIC + CEF	CEF + TOB	1	47	2.1	10	48	20.8	4.5	71	7.3	3.0	(2-4)
		TIC + TOB				3	53	5.7					
Schimpff 1976	TIC + CEF	TIC + GEN	2	62	3.2	0	65	0.0	4.4	40	4.3	1.7	(2-4)
EORTC 1978	TIC + CEF	TIC + GEN	6	114	5.3	3	116	2.6					
	CAR + CEF	CAR + GEN	-	-	-	-	-	-	4.4	40	4.3	1.7	(2-4)
		CEF + GEN				22	135	16.3					
Bodey 1979	CAR + FAM	CAR + TOB	21	160	13	17	139	12	8.9	141	5.9	5.9	(2-4)
	CAR + FAM		20	170	12								
Wiston 1984	MOX + PIP	MOX + AMK	2	136	1.5	6	136	4.4	15	154	19	6.4	(5)
Fainstein 1984	MOX + TIC	MOX + TOB	-	-	-	6	228	2.6	8.9	141	5.9	5.9	(2-4)
Feld 1985	TIC + MOX	TIC + TOB	2	88	2.3	2	85	2.4	5.0	79	6.1	3.3	(2-4)
De Jongh 1986	MOX + PIP	MOX + AMK	2	145	1.4	12	130	9.2	14.3	147	36	6.1	(5)
Rostein 1988	CFP + PIP	MEZ + TOB	1	30	3.3	5	30	16.7	low [a]	low [a]	low [a]	low [a]	(2)
Torres 1989	CTX + ATM	CTX + AMK	0	6	0.0	3	6	50.0 [b]	14.3	147	36	6.1	(5)
Kibbler 1989	PIP + CAZ	PIP + NET	3	37	8.1	7	35	20.0	7.0	102	18	4.3	(6)
	AZL + CAZ	AZL + NET	2	36	5.6	9	42	21.4					
Joshi 1993	CAZ + PIP	CAZ + TOB	11	95	11.6	11	89	12.4	5.0	79	8.1	3.3	(2-4)

Abbreviations: EORTC = European Organization for Research on Treatment of Cancer; AZL = Azlocillin; ATM = Aztreonam; CAR = Carbenicillin; CFP = Cefoperazone; CTX = Cefotaxime; CEF = Cephalothin (Cefalotin); CAZ = Ceftazidime; FAM = Cefamandole; MEZ = Mezlocillin; MOX = Moxalactam; TIC = Ticarcillin; PIP = Piperacillin; AMK = Amikacin; GEN = Gentamicin; KAN = Kanamycin; NET = Netilmicin; TOB = Tobramycin. $AUC_{0\text{-}24h}$: Area under the plasma concentration time curve from 0 to 24 h. C_{max}: Peak concentration. $C_{ss,avg}$: Average concentration at steady-state.

[a]: Tobramycin dosing was adjusted in this study based on peak concentrations, therefore the pharmacokinetic exposure was not calculated (7).
[b]: Renal toxicity was defined differently in the this study (i.e. based on two renal biomarkers) compared to the definitions in other studies.
[c]: Peak concentration refers to intra-muscular dosing of kanamycin. Peaks after a short-term intravenous infusion would be slightly higher.

Table S4. Comparison of coagulopathy between studies with and without moxalactam (the table only shows studies which evaluated and reported coagulopathy).

Trial	DBL	BLAG	DBL			BLAG		
			No.	Total	%	No.	Total	%
Studies without moxalactam								
Klastersky 1975	TIC+CEF	CEF + TOB	2	51	3.9	0	49	0
		TIC + TOB				2	56	3.6
Schimpff 1976	TIC+CEF	TIC + GEN	1	62	1.6	0	65	0
Rostein 1988	CFP + PIP	MEZ + TOB	4	30	13.3	1	30	3.3
Joshi 1993	CAZ + PIP	CAZ + TOB	10	88	11.4	5	82	6.1
					Subtotal:	AE 25;	overall cases 513[a]	
Studies with moxalactam								
Wiston 1984	MOX + PIP	MOX + AMK	27	136	19.9	29	136	21.6
Fainstein 1984	MOX + TIC	MOX + TOB	7	61	11.5	4	28	14.3
Feld 1985	TIC + MOX	TIC + TOB	39	103	37.9	6	78	7.7
De Jongh 1986	MOX + PIP	MOX + AMK	43	98	43.9	33	112	59
					Subtotal:	AE 188;	overall cases 752	

[a] Pooled renal toxicity between groups with (25%) and without (4.9%) moxalactam, p <0.0001 (Fisher's exact test).

Figure S1. Forest plots for microbiological response by pathogens of double β-lactam compared with β-lactam plus aminoglycoside. (A) *Pseudomonas aeruginosa*; (B) *Klebsiella* spp.; (C) *Escherichia coli*.

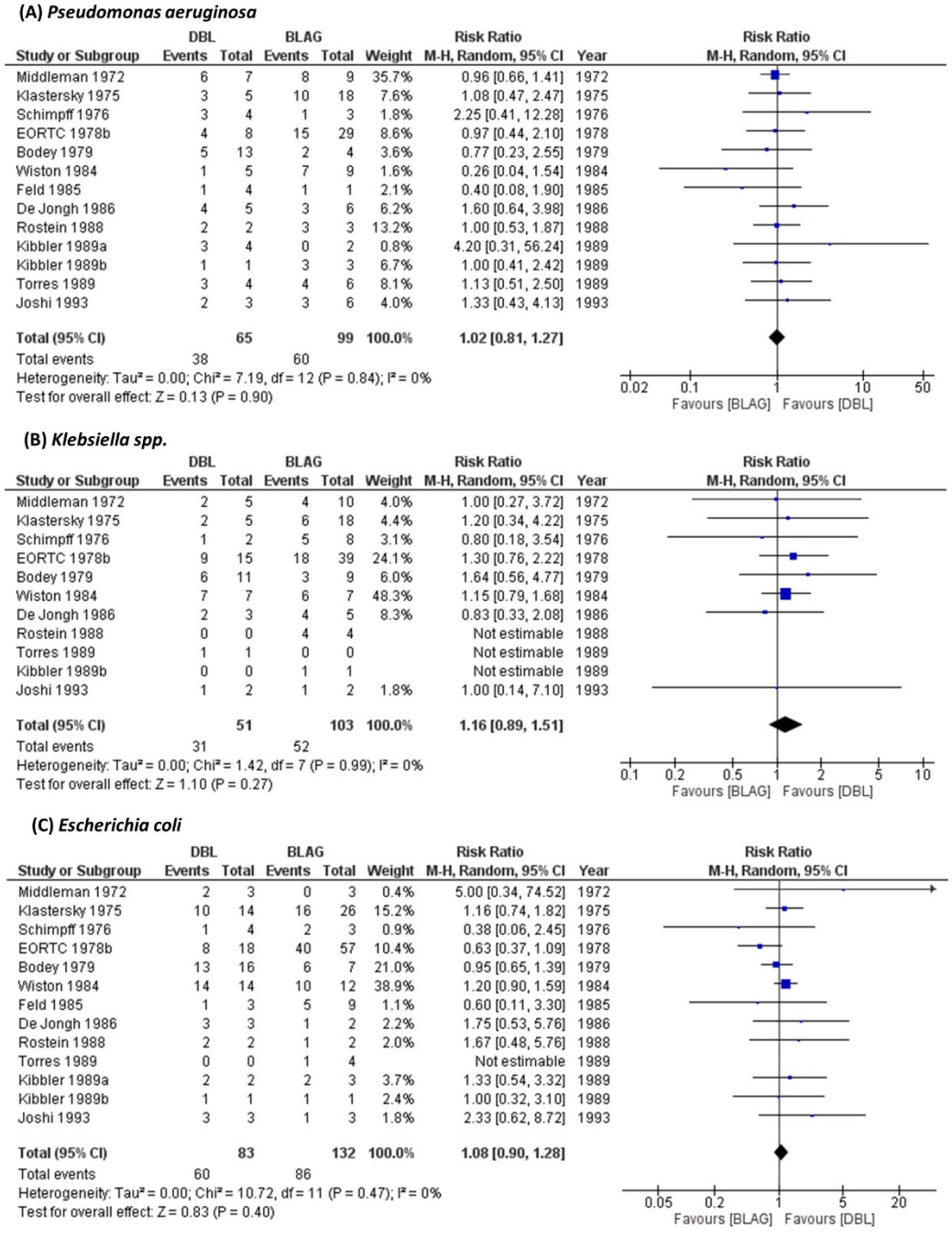
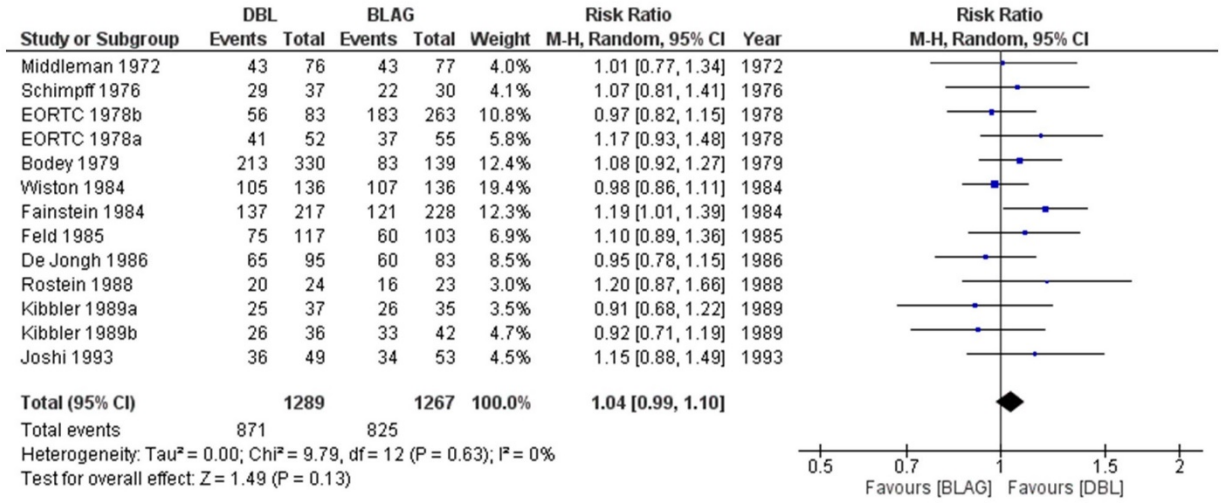


Figure S2. Sensitivity analysis for clinical response comparing double β-lactam combination with β-lactam plus aminoglycoside from eleven clinical trials in febrile neutropenia population: (A) Forest plot; (B) Funnel plot.

(A) Forest plot



Study or Subgroup	DBL Events	DBL Total	BLAG Events	BLAG Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Middleman 1972	43	76	43	77	4.0%	1.01 [0.77, 1.34]	1972
Schimpff 1976	29	37	22	30	4.1%	1.07 [0.81, 1.41]	1976
EORTC 1978b	56	83	183	263	10.8%	0.97 [0.82, 1.15]	1978
EORTC 1978a	41	52	37	55	5.8%	1.17 [0.93, 1.48]	1978
Bodey 1979	213	330	83	139	12.4%	1.08 [0.92, 1.27]	1979
Wiston 1984	105	136	107	136	19.4%	0.98 [0.86, 1.11]	1984
Fainstein 1984	137	217	121	228	12.3%	1.19 [1.01, 1.39]	1984
Feld 1985	75	117	60	103	6.9%	1.10 [0.89, 1.36]	1985
De Jongh 1986	65	95	60	83	8.5%	0.95 [0.78, 1.15]	1986
Rostein 1988	20	24	16	23	3.0%	1.20 [0.87, 1.66]	1988
Kibbler 1989a	25	37	26	35	3.5%	0.91 [0.68, 1.22]	1989
Kibbler 1989b	26	36	33	42	4.7%	0.92 [0.71, 1.19]	1989
Joshi 1993	36	49	34	53	4.5%	1.15 [0.88, 1.49]	1993
Total (95% CI)		**1289**		**1267**	**100.0%**	**1.04 [0.99, 1.10]**	
Total events	871		825				

Heterogeneity: Tau² = 0.00; Chi² = 9.79, df = 12 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.13)

(B) Funnel plot

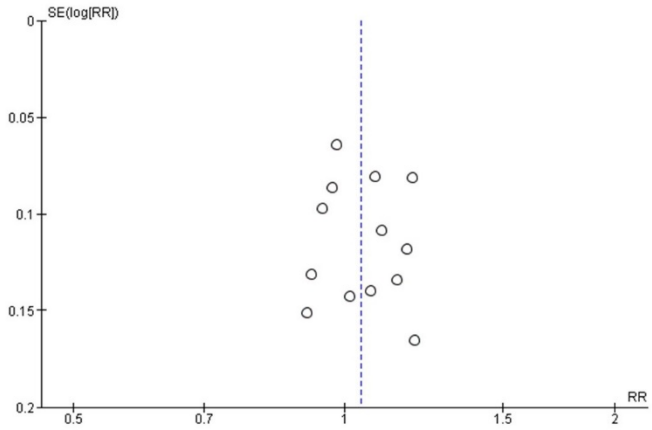


Figure S3. Sensitivity analysis for clinical response comparing double β-lactam combination with β-lactam plus aminoglycoside from eleven clinical trials in febrile neutropenia population: (A) Forest plot; (B) Funnel plot.

(A) Forest plot

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Wiston 1984	105	136	107	136	19.4%	0.98 [0.86, 1.11]	1984
Fainstein 1984	137	217	121	228	12.3%	1.19 [1.01, 1.39]	1984
Feld 1985	75	117	60	103	6.9%	1.10 [0.89, 1.36]	1985
De Jongh 1986	65	95	60	83	8.5%	0.95 [0.78, 1.15]	1986
Rostein 1988	20	24	16	23	3.0%	1.20 [0.87, 1.66]	1988
Kibbler 1989a	25	37	26	35	3.5%	0.91 [0.68, 1.22]	1989
Kibbler 1989b	26	36	33	42	4.7%	0.92 [0.71, 1.19]	1989
Joshi 1993	36	49	34	53	4.5%	1.15 [0.88, 1.49]	1993
Total (95% CI)		**1289**		**1267**	**100.0%**	**1.04 [0.99, 1.10]**	
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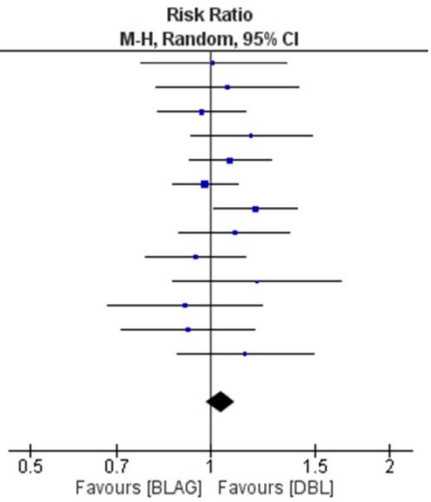
Heterogeneity: Tau² = 0.00; Chi² = 9.79, df = 12 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.13)



(B) Funnel plot

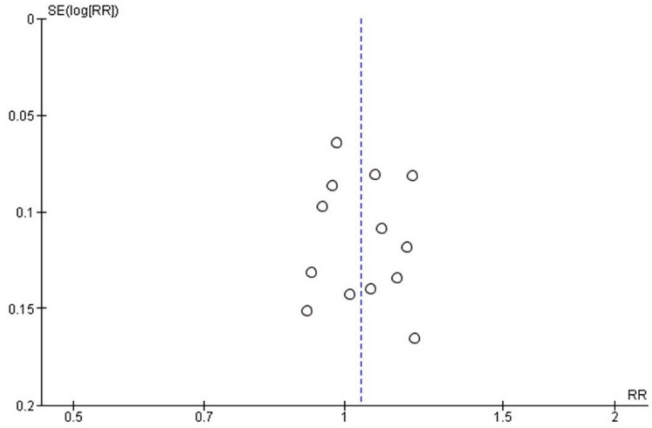
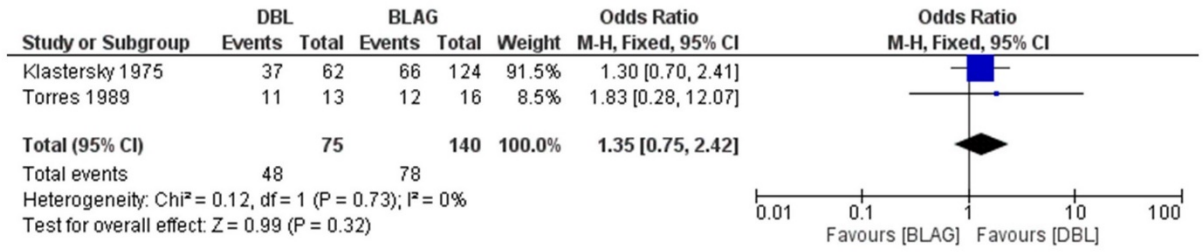


Figure S4. Clinical response between double β-lactam combination and β-lactam plus aminoglycoside from two clinical trials in non-febrile neutropenia population: (A) Forest plot; (B) Funnel plot.

(A) Forest plot



(B) Funnel plot

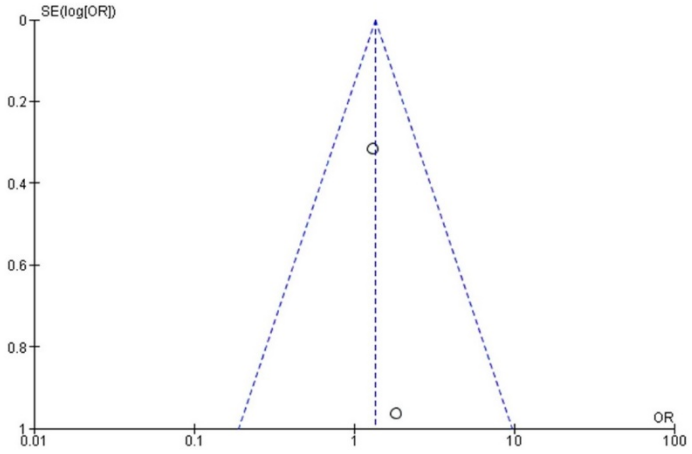
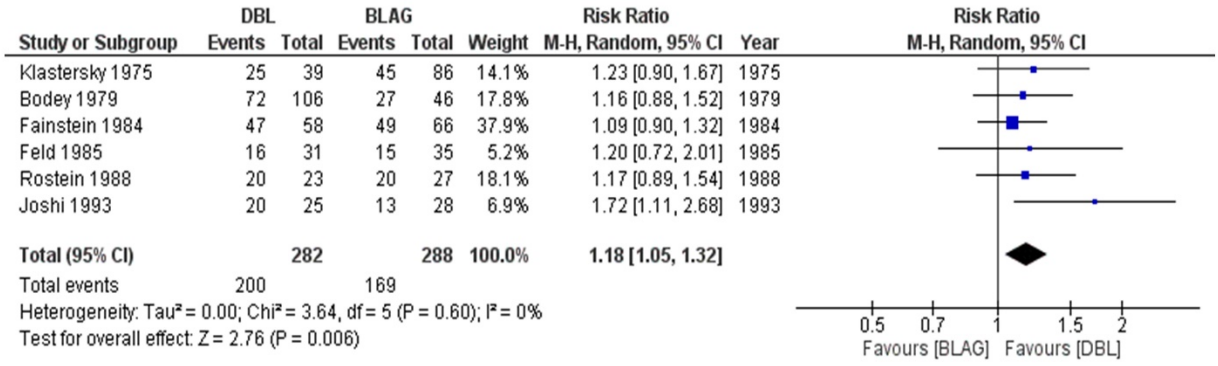


Figure S5. Forest plots for microbiological response in all bacteria (A) and microbiological response in Gram-negatives (B) for studies that included tobramycin. Please see Table S3 for the expected aminoglycoside drug exposures in these trials.

(A) Microbiological responses



(B) Microbiological responses in Gram-negatives

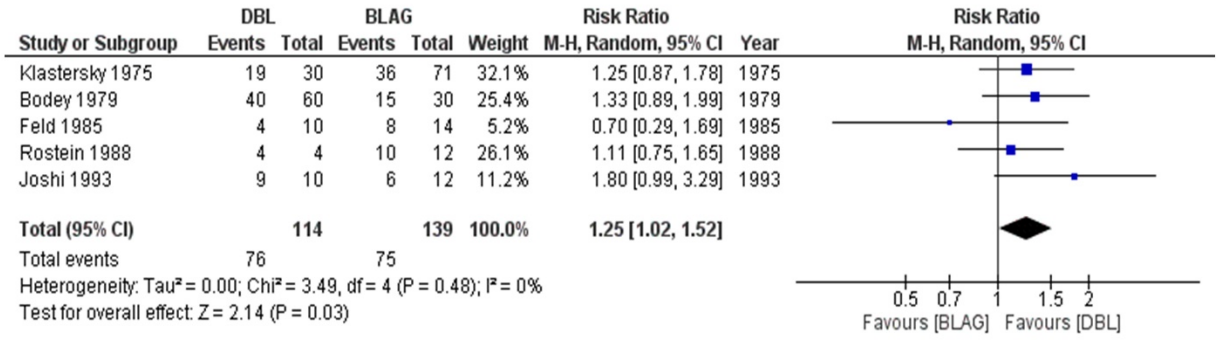
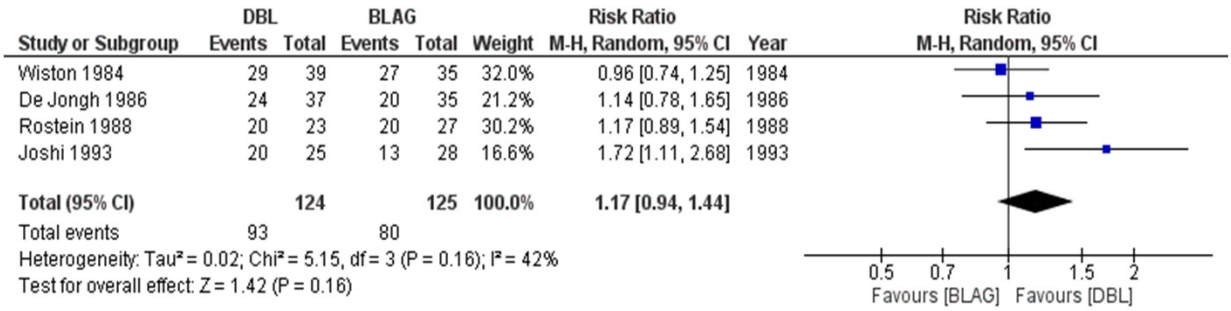
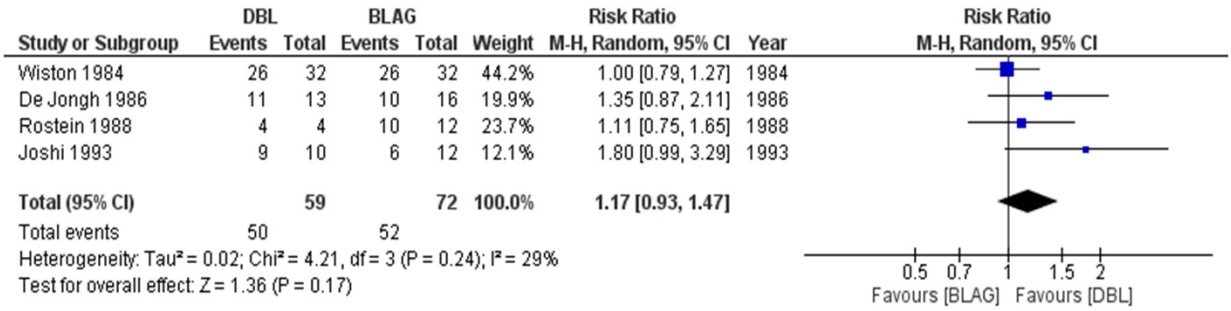


Figure S6. Forest plots for microbiological response in all bacteria (A) and microbiological response in Gram-negatives (B) for studies that included piperacillin in the DBL but not in the BLAG regimens.

(A) Microbiological responses



(B) Microbiological responses in Gram-negatives



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