Supplement

Comparable Efficacy and Better Safety of Double $\beta\textsc{-Lactam}$ Combination Therapy versus

 β Lactam Plus Aminoglycoside in Gram-negatives: A Meta-analysis of Randomized,

Controlled Trials

Study	Type of infection	Definition
Middleman(1972)	Febrile neutropenia	Neutropenia: neutrophils < 1000 /mm³; 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 \geq 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/mm³; Fever: temperature > 38 °C.
Rostein (1988)	Febrile neutropenia	Neutropenia: neutrophils ≤ 1000/mm³; 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 S1. Definition of febrile neutropenia and other infections 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	<i>Cure</i> : 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.

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

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	<i>Improvement</i> : complete resolution of all signs and symptoms of infection occurred without any antibiotic adjustment; <i>Failure</i> : (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	<i>Clinical cure</i> : resolution of the clinical signs and symptoms; <i>Favorable evolution</i> : improvement in clinical symptoms without a complete resolution; <i>Therapeutic failure</i> : failure to eradicate the causative agent from the infection site; <i>Microbiological cure</i> : 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	<i>Response</i> : complete resolution of all signs and symptoms of infection and documentation that the infecting organism was eradicated; <i>Failure</i> : complete resolution of infection was not apparent, or only partially apparent.

		•		-					A				
Trial	DBL	BLAG		DBL			BLAG			ide doses and			g exposures
	DBL	BLAG	No.	Total	%	No.	Total	%	Daily dose mg/kg/day	AUC _{0-24h} 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	74	7.0	2.0	(2.4)
		TIC + TOB				3	53	5.7	4.5	71	7.3	3.0	(2-4)
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			5.0		
	CAR + FAM		20	170	12				8.9	141	5.9	5.9	(2-4)
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					
	AZL + CAZ	AZL + NET	2	36	5.6	9	42	21.4	7.0	102	18	4.3	(6)
Joshi 1993	CAZ + PIP	CAZ + TOB	11	95	11.6	11	89	12.4	5.0	79	8.1	3.3	(2-4)

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

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_{0-24h}: 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.

Trial	DBL	BLAG		DBL			BLAG	
mar	DDL	DLAG	No.	Total	%	No.	Total	%
Studies without mo	xalactam							
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 ca	ses 513
Studies with moxala	actam							
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 c	ases 75

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

^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.

	DBL	_	BLA	G		Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year		M-H, Random, 95% Cl
Middleman 1972	6	7	8	9	35.7%	0.96 [0.66, 1.41]	1972		-
Klastersky 1975	3	5	10	18	7.6%	1.08 [0.47, 2.47]	1975		
Schimpff 1976	3	4	1	3	1.8%	2.25 [0.41, 12.28]	1976		
EORTC 1978b	4	8	15	29	8.6%	0.97 [0.44, 2.10]	1978		-+-
Bodey 1979	5	13	2	4	3.6%	0.77 [0.23, 2.55]	1979		
Wiston 1984	1	5	7	9	1.6%	0.26 [0.04, 1.54]	1984		
Feld 1985	1	4	1	1	2.1%	0.40 [0.08, 1.90]	1985		
De Jongh 1986	4	5	3	6	6.2%	1.60 [0.64, 3.98]	1986		-
Rostein 1988	2	2	3	3	13.2%	1.00 [0.53, 1.87]	1988		_ _
Kibbler 1989a	3	4	0	2	0.8%	4.20 [0.31, 56.24]	1989		
Kibbler 1989b	1	1	3	3	6.7%	1.00 [0.41, 2.42]	1989		
Torres 1989	3	4	4	6	8.1%	1.13 [0.51, 2.50]	1989		
Joshi 1993	2	3	3	6	4.0%	1.33 [0.43, 4.13]	1993		
Total (95% CI)		65		99	100.0%	1.02 [0.81, 1.27]			♦
Total events	38		60						
Heterogeneity: Tau ² =	0.00; Ch	i ² = 7.1	9, df = 12	(P = 0.	84); I ² = 0	%		0.02	0.1 1 10 50
Test for overall effect:	Z=0.13	(P = 0.9)	30)	-				0.02	0.1 1 10 50 Favours (BLAG) Favours (DBL)

(B) Klebsiella spp.

	DBL		BLA	G		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Middleman 1972	2	5	4	10	4.0%	1.00 [0.27, 3.72]	1972	
Klastersky 1975	2	5	6	18	4.4%	1.20 [0.34, 4.22]	1975	
Schimpff 1976	1	2	5	8	3.1%	0.80 [0.18, 3.54]	1976	
EORTC 1978b	9	15	18	39	24.1%	1.30 [0.76, 2.22]	1978	
Bodey 1979	6	11	3	9	6.0%	1.64 [0.56, 4.77]	1979	
Wiston 1984	7	7	6	7	48.3%	1.15 [0.79, 1.68]	1984	
De Jongh 1986	2	3	4	5	8.3%	0.83 [0.33, 2.08]	1986	
Rostein 1988	0	0	4	4		Not estimable	1988	
Torres 1989	1	1	0	0		Not estimable	1989	
Kibbler 1989b	0	0	1	1		Not estimable	1989	
Joshi 1993	1	2	1	2	1.8%	1.00 [0.14, 7.10]	1993	
Total (95% CI)		51		103	100.0%	1.16 [0.89, 1.51]		•
Total events	31		52					
Heterogeneity: Tau ² =	0.00; Chi	² = 1.43	2, df = 7 (P = 0.9	9); I ² = 09	6		0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z=1.10(P = 0.2	(7)					0.1 0.2 0.5 1 2 5 10 Favours (BLAG) Favours (DBL)

(C) Escherichia coli

	DBL		BLA			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Middleman 1972	2	3	0	3	0.4%	5.00 [0.34, 74.52]	1972	
Klastersky 1975	10	14	16	26	15.2%	1.16 [0.74, 1.82]	1975	
Schimpff 1976	1	4	2	3	0.9%	0.38 [0.06, 2.45]	1976	
EORTC 1978b	8	18	40	57	10.4%	0.63 [0.37, 1.09]	1978	
Bodey 1979	13	16	6	7	21.0%	0.95 [0.65, 1.39]	1979	-
Wiston 1984	14	14	10	12	38.9%	1.20 [0.90, 1.59]	1984	
Feld 1985	1	3	5	9	1.1%	0.60 [0.11, 3.30]	1985	
De Jongh 1986	3	3	1	2	2.2%	1.75 [0.53, 5.76]	1986	
Rostein 1988	2	2	1	2	2.0%	1.67 [0.48, 5.76]	1988	
Torres 1989	0	0	1	4		Not estimable	1989	
Kibbler 1989a	2	2	2	3	3.7%	1.33 [0.54, 3.32]	1989	_ _
Kibbler 1989b	1	1	1	1	2.4%	1.00 [0.32, 3.10]	1989	
Joshi 1993	3	3	1	3	1.8%	2.33 [0.62, 8.72]	1993	
Total (95% CI)		83		132	100.0%	1.08 [0.90, 1.28]		•
Total events	60		86					
Heterogeneity: Tau ² =	0.00; Ch	i ² = 10.	72, df = 1	1 (P = 1	0.47); I ² =	0%		0.05 0.2 1 5 20
Test for overall effect:	Z = 0.83	(P = 0.4)	10)					0.05 0.2 1 5 20 Favours (BLAG) Favours (DBL)

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

	DBL		BLA	G		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
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: Tau ² =	0.00; Ch	² = 9.7	9, df = 12	(P = 0.	63); I ² = 0	%		0.5 0.7 1 1.5 2
Test for overall effect:	Z=1.49	(P = 0.1	3)					0.5 0.7 1 1.5 2 Favours (BLAG) Favours (DBL)

(B) Funnel plot

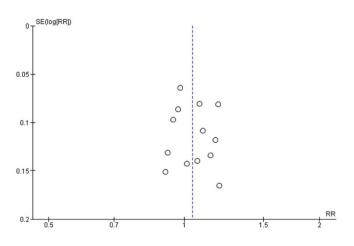


Figure S3. Sensitivity analysis for clinical response comparing double β-lactam combination with β-lactam plus aminoglycoside from eleven clinical trials in febrile neutropenia population: (A) Forest plot; (B) Funnel plot.

(A) Forest plot

	DBL		BLA	G		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
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: Tau ² =	0.00; Ch	² = 9.7	9, df = 12	(P = 0.	63); I ² = 0	%		0.5 0.7 1 1.5 2
Test for overall effect:	Z=1.49	(P = 0.1	3)					0.5 0.7 1 1.5 2 Favours [BLAG] Favours [DBL]

(B) Funnel plot

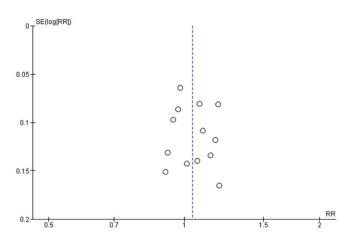


Figure S4. Clinical response between double β-lactam combination and β-lactam plus aminoglycoside from two clinical trials in non-febrile neutropenia population:
 (A) Forest plot; (B) Funnel plot.

(A) Forest plot

	DBL		BLA	G		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	
Klastersky 1975	37	62	66	124	91.5%	1.30 [0.70, 2.41]		
Torres 1989	11	13	12	16	8.5%	1.83 [0.28, 12.07]		
Total (95% CI)		75		140	100.0%	1.35 [0.75, 2.42]	•	
Total events	48		78					
Heterogeneity: Chi ² =	0.12, df=	1 (P =	0.73); l ² =	= 0%			0.01 0.1 1 10	100
Test for overall effect:	Z = 0.99	(P = 0.3	32)				0.01 0.1 1 10 Favours (BLAG) Favours (DBL)	100

(B) Funnel plot

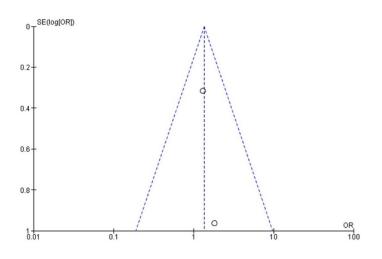


Figure S5. Forest plots for microbiological response in all bacteria (A) and microbiological

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

	DBL		BLA	G		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Klastersky 1975	25	39	45	86	14.1%	1.23 [0.90, 1.67]	1975	
Bodey 1979	72	106	27	46	17.8%	1.16 [0.88, 1.52]	1979	_ +•
Fainstein 1984	47	58	49	66	37.9%	1.09 [0.90, 1.32]	1984	
Feld 1985	16	31	15	35	5.2%	1.20 [0.72, 2.01]	1985	•
Rostein 1988	20	23	20	27	18.1%	1.17 [0.89, 1.54]	1988	
Joshi 1993	20	25	13	28	6.9%	1.72 [1.11, 2.68]	1993	
Total (95% CI)		282		288	100.0%	1.18 [1.05, 1.32]		◆
Total events	200		169					
Heterogeneity: Tau ² =	0.00; Ch	i ² = 3.6	4, df = 5 (P = 0.6	0); I ² = 09	6		0.5 0.7 1 1.5 2
Test for overall effect:	Z= 2.76	(P = 0.0)06)					Favours [BLAG] Favours [DBL]

(B) Microbiological responses in Gram-negatives

	DBL	-	BLA	G		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Klastersky 1975	19	30	36	71	32.1%	1.25 [0.87, 1.78]	1975	
Bodey 1979	40	60	15	30	25.4%	1.33 [0.89, 1.99]	1979	
Feld 1985	4	10	8	14	5.2%	0.70 [0.29, 1.69]	1985	
Rostein 1988	4	4	10	12	26.1%	1.11 [0.75, 1.65]	1988	
Joshi 1993	9	10	6	12	11.2%	1.80 [0.99, 3.29]	1993	
Total (95% CI)		114		139	100.0%	1.25 [1.02, 1.52]		◆
Total events	76		75					
Heterogeneity: Tau ² =	0.00; Ch	i ² = 3.4	0.5 0.7 1 1.5 2					
Test for overall effect:	Z= 2.14	(P = 0.0)3)					Favours [BLAG] Favours [DBL]

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

	DBL		BLA	G		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Wiston 1984	29	39	27	35	32.0%	0.96 [0.74, 1.25]	1984	
De Jongh 1986	24	37	20	35	21.2%	1.14 [0.78, 1.65]	1986	
Rostein 1988	20	23	20	27	30.2%	1.17 [0.89, 1.54]	1988	
Joshi 1993	20	25	13	28	16.6%	1.72 [1.11, 2.68]	1993	
Total (95% CI)		124		125	100.0%	1.17 [0.94, 1.44]		-
Total events	93		80					
Heterogeneity: Tau ² =								
Test for overall effect:	Z=1.42 ((P = 0.1	6)					0.5 0.7 1 1.5 2 Favours (BLAG) Favours (DBL)

(B) Microbiological responses in Gram-negatives

	DBL		BLA	G		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl		
Wiston 1984	26	32	26	32	44.2%	1.00 [0.79, 1.27]	1984			
De Jongh 1986	11	13	10	16	19.9%	1.35 [0.87, 2.11]	1986			
Rostein 1988	4	4	10	12	23.7%	1.11 [0.75, 1.65]	1988			
Joshi 1993	9	10	6	12	12.1%	1.80 [0.99, 3.29]	1993			
Total (95% CI)		59		72	100.0%	1.17 [0.93, 1.47]		◆		
Total events	50		52							
Heterogeneity: Tau ² = 0.02; Chi ² = 4.21, df = 3 (P = 0.24); i ² = 29%										
Test for overall effect:	Z=1.36	(P = 0.1		Favours [BLAG] Favours [DBL]						

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