Prophylactic antibiotics delivered via the respiratory tract to reduce ventilator-

associated pneumonia: A systematic review, net-work meta-analysis, and Trial

Sequential Analysis of Randomized Controlled Trials

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Author	Included studies (study type)	Primary	Results	Trial sequential	Sensitivity analysis/ secondary	Subgroup analyses	Network meta-analysis of indirect	Network meta-analysis of	Adverse events
		outcome		analysis	analyses		comparisons among different	indirect comparisons between	
							medicine	nebulization and intratracheal	
								instillation	
Li et al*	Lode et al.,1988 (RCT)	Incidence	A lower risk of	Required sample size	Confirmed by separately	The reduction in the risk of VAP	Did not find any significant	Did not find any significant	Two RCTs reported
	Rathgeber et al.,1993 (RCT)	of VAP	VAP (RR 0.69,	was almost reached.	including two RCTs with a	due to intervention was more	difference in-between those	difference in the incidence of	adverse events including
	Wood et al.,2002 (RCT)		95%CI [0·53–		portion of non-intubated	pronounced in subgroups where	antibiotics in terms of VAP	VAP in-between those two	bronchospasm,
	Claridge et al.,2007 (RCT)		0.89]).		patients and two non-RCTs	aminoglycosides or nebulization	incidence.	modalities.	hypoxemia, and acute
	Karvouniaris et al.,2015						Rank probabilities assessment	Rank probabilities assessment	kidney injury, but their
	(RCT)						showed that inhaled colistin had	showed that nebulization had	incidences were not
	Kuzovlev et al.,2015 (RCT)						the highest likelihood of reducing	the highest likelihood of	significantly increased in
	Ehrmann et al.,2023 (RCT)						the risk of VAP	reducing the risk of VAP	the intervention group.
		Hospital	No significant	Required sample size		No significant difference in	NR	NR	Five RCTs did not
		mortality	difference (RR	was not reached.		hospital mortality were also found			observe any adverse
			0.88 [0.75–			in subgroup analyses based on			events, two RCTs and two
			1.03])			types of antibiotics and modalities			non-RCTs did not report
						of antibiotics administration			data on adverse events
						through the respiratory tract			
Falagas et	Lode et al.,1988 (RCT)	Incidence	Less incidence of	NR	Confirmed by including the	NR	NR	NR	In five of the included
al.,2006[8]	Rathgeber et al., 1993 (RCT)	of ICU-	ICU-acquired		three non-randomized				studies no data regarding
	Wood et al.,2002 (RCT)	acquired	pneumonia (OR		comparative trials				toxicity were reported. In
	Greenfield et al.,1973 (RCT,	pneumonia	= 0.49, 95% CI						two RCTs it was reported
	mechanically ventilated or		0.32–0.76).						that no toxicity was
	not)	Mortality	No difference	NR		NR	NR	NR	observed during the trials,
	Klatersky et al.,1974 (RCT,		(OR = 0.86, 95%						whereas in the remaining
	mechanically ventilated or		CI 0.55–1.32).						RCT the authors
	not)								characterized the
									observed toxicity
									negligible, without
									reporting any further

Table S1. Summary of previous meta-analysis.

NR	NR	NR
NR	NR	NR

	(RCT)	ICU	No significant NR		NR	NR	NR	
	Klatersky et al.,1974 (RCT,	mortality	difference (OR					
	mechanically ventilated or		0.89; 95% CI					
	not)		0.64–1.25)					
	Rouby et al.,1994 (non-							
	RCT)							
Zha et	Lode et al.,1988 (RCT)	Incidence	Lower incidence NR	Sensitivity analyses were also	NR	In the individual comparisons, no	NR	NR
al.,2023[7]	Rathgeber et al.,1993 (RCT)	of VAP	of VAP (OR 0.70;	conducted to assess the impact		statistically difference was found		
	Wood et al.,2002 (RCT)		95% CI 0.59-	of each study on the pooled RR;		between each antibiotics		
	Claridge et al.,2007 (RCT)		0.82)	the statistical results were not		administered the respiratory tract.		
	Karvouniaris et al.,2015			markedly altered after		The assessment of rank		
	(RCT)			removing any study		probabilities indicated that		
	Klatersky et al.,1974 (RCT,					aerosolized tobramycin presented		
	mechanically ventilated or					the greatest likelihood of reducing		
	not)					the incidence of VAP		
	Rouby et al.,1994 (non-	ICU	No difference NR		NR	NR	NR	
	RCT)	mortality	(OR 0.94; 95%					
			CI 0.76–1.16)					

NR

NR

*: This meta-analysis; NR, not reported; VAP, ventilator associated pneumonia; ICU, intensive care unit; OR, odds ratio; RR, relative risk; CI, confidence interval

Lower incidence NR

of VAP (OR 0.53;

95% CI 0.34-

0.84).

Incidence

of VAP

Povoa et Lode et al.,1988 (RCT)

Wood et al.,2002 (RCT)

Claridge et al.,2007 (RCT)

Karvouniaris et al.,2015

al.,2018[6]

NR

Search strategy

All languages, all dates | PubMed, Scopus, Cochrane

Generic

("ventilator associated pneumonia" OR "ventilator-associated pneumonia" OR "vap" OR "nosocomial pneumonia" OR "hospital acquired pneumonia" OR "hospital-acquired pneumonia" OR "healthcare associated pneumonia" OR "healthcare-associated pneumonia" OR "health care associated pneumonia" OR "health careassociated pneumonia" OR "health-care associated pneumonia" OR "health-care-associated pneumonia" OR "icu acquired pneumonia" OR "icu-acquired pneumonia" OR "nosocomial bronchopneumonia") AND (antibacterial* OR "anti bacterial" OR "anti bacterials" OR "anti-bacterial" OR "anti-bacterials" OR antibiotic* OR aztreonam OR azthreonam OR urobactam OR azactam OR tobramycin OR obracin OR tobracin OR brulamycin OR nebcin OR nebicin OR "nebramycin factor six" OR "nebramycin factor 6" OR colisti* OR "polymyxin e" OR colimycin OR totazina OR ceftazidime OR fortaz OR fortum OR tazidime OR amika* OR yectamid OR biklin OR biclin OR amikin OR amikin OR amukin OR gamikal OR kanbine OR oprad OR gentamicin* OR gentamycin* OR garamycin OR gentacycol OR gentavet OR genticin OR aminoglycoside* OR ciprofloxacin OR ciprinol OR amphotericin* OR fungizone OR amphocil OR caspofungin OR cancidas OR fluconazol* OR zonal OR beagyne OR diflucan OR "fluc hexal" OR flucobeta OR flucolich OR flunazul OR fungata OR lavisa OR loitin OR neofomiral OR oxifungol OR solacap OR triflucan OR posaconazole OR noxafil OR voriconazole OR vfend OR vancomycin* OR vancocin* OR diatracin OR meropenem OR merrem OR ronem OR penem OR ertapenem OR invanoz OR invanz OR imipenem OR imipemide OR "n-formimidoylthienamycin" OR "n formimidoylthienamycin" OR doripenem) AND (inhal* OR respirat* OR nebuli* OR vapor* OR vapour* OR atomi* OR aerosol* OR aeroli* OR endotracheal* OR intratracheal* OR "intra-tracheal" OR "intra tracheal" OR instillati*)

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("Pneumonia, Ventilator-Associated" [Mesh] OR "Healthcare-Associated Pneumonia" [Mesh] OR "ventilator associated pneumonia"[tiab] OR "ventilator-associated pneumonia"[tiab] OR "vap"[tiab] OR "nosocomial pneumonia"[tiab] OR "hospital acquired pneumonia"[tiab] OR "hospital-acquired pneumonia"[tiab] OR "healthcare associated pneumonia"[tiab] OR "healthcare-associated pneumonia"[tiab] OR "health care associated pneumonia"[tiab] OR "health care-associated pneumonia"[tiab] OR "health-care associated pneumonia"[tiab] OR "health-care-associated pneumonia"[tiab] OR "icu acquired pneumonia"[tiab] OR "icu-acquired pneumonia"[tiab] OR "nosocomial bronchopneumonia"[tiab]) AND ("Anti-Bacterial Agents"[Mesh] OR "Aztreonam"[Mesh] OR "Tobramycin"[Mesh] OR "Colistin"[Mesh] OR "Ceftazidime"[Mesh] OR "Amikacin"[Mesh] OR "Gentamicins" [Mesh] OR "Aminoglycosides" [Mesh] OR "Ciprofloxacin" [Mesh] OR "Amphotericin B" [Mesh] OR "Caspofungin" [Mesh] OR "Fluconazole" [Mesh] OR "posaconazole" [Supplementary Concept] OR "Voriconazole" [Mesh] OR "Vancomycin" [Mesh] OR "Meropenem" [Mesh] OR "Ertapenem" [Mesh] OR "Imipenem" [Mesh] OR "Doripenem" [Mesh] OR antibacterial* [tiab] OR "anti bacterial" [tiab] OR "anti bacterials"[tiab] OR "anti-bacterial"[tiab] OR "anti-bacterials"[tiab] OR antibiotic*[tiab] OR aztreonam[tiab] OR azthreonam[tiab] OR urobactam[tiab] OR azactam[tiab] OR tobramycin[tiab] OR obracin[tiab] OR tobracin[tiab] OR brulamycin[tiab] OR nebcin[tiab] OR nebcin[tiab] OR "nebramycin factor six"[tiab] OR "nebramycin factor 6"[tiab] OR colisti*[tiab] OR "polymyxin e"[tiab] OR colimycin[tiab] OR totazina[tiab] OR ceftazidime[tiab] OR fortaz[tiab] OR fortum[tiab] OR tazidime[tiab] OR amika*[tiab] OR yectamid[tiab] OR biklin[tiab] OR biclin[tiab] OR amikin[tiab] OR amikin[tiab] OR amukin[tiab] OR gamikal[tiab] OR kanbine[tiab] OR oprad[tiab] OR gentamicin*[tiab] OR gentamycin*[tiab] OR garamycin[tiab] OR gentacycol[tiab] OR gentacycol[tiab] OR

genticin[tiab] OR aminoglycoside*[tiab] OR ciprofloxacin[tiab] OR ciprinol[tiab] OR amphotericin*[tiab] OR fungizone[tiab] OR amphocil[tiab] OR caspofungin[tiab] OR cancidas[tiab] OR fluconazol*[tiab] OR zonal[tiab] OR beagyne[tiab] OR diflucan[tiab] OR "fluc hexal"[tiab] OR flucobeta[tiab] OR flucolich[tiab] OR flunazul[tiab] OR fungata[tiab] OR lavisa[tiab] OR loitin[tiab] OR neofomiral[tiab] OR oxifungol[tiab] OR solacap[tiab] OR triflucan[tiab] OR posaconazole[tiab] OR noxafil[tiab] OR voriconazole[tiab] OR vfend[tiab] OR vancomycin*[tiab] OR vancocin*[tiab] OR diatracin[tiab] OR meropenem[tiab] OR merrem[tiab] OR ronem[tiab] OR penem[tiab] OR ertapenem[tiab] OR invanoz[tiab] OR invanoz[tiab] OR impenem[tiab] OR doripenem[tiab] OR "n-formimidoylthienamycin"[tiab] OR "n formimidoylthienamycin"[tiab] OR doripenem[tiab]) AND ("Administration, Inhalation"[Mesh] OR "Nebulizers and Vaporizers"[Mesh] OR "Aerosols"[Mesh] OR "Instillation, Drug"[Mesh] OR inhal*[tiab] OR respirat*[tiab] OR nebuli*[tiab] OR vapor*[tiab] OR vapour*[tiab] OR "intra-tracheal*[tiab] OR instillati*[tiab] OR instillati*[tiab] OR intra-tracheal*[tiab] OR "intra-tracheal*[tiab] OR "intra-tracheal*[tia

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Author	Country	Study	Cent	ICU_type	Patient	Interventions	No.	of	Sex(F/M ^a)	Age-yr	Medicine	Mode	of	Days	of
		design	ers		s_type		Patien	Patients				administration		administration	
Rouby et	France	prospective	Unic	Surgical	Adult	Usual care	251		124/127	51±12 ^b (survivors)					
al., 1994		non-	enter	ICU						56±18 ^b (non- survivors)					
		randomized				Usual care+ topical use of	347		168/179	53±16 ^b (survivors)	Colistin,200000 U,q3h	Intratrachea	1	15 days or	until
						antibiotics				58±16 ^b (non- survivors)		instillation		extubation	
Klick et	United	prospective	Unic	R-SICU	NR	topical use of 0.9% saline	370		NR	60°	0.9% saline,q4h	Intratrachea	1	NR	
al.,1975	States	non-	enter			topical use of antibiotics	374		NR	57°	Polymyxin B, 2.5 mg/kg /day	instillation			
		randomized									in 6 divided doses,q4h				

Table S2. Summary of included non-randomized controlled trial studies in the meta-analysis.

^a F/M represents female/male.

^b The value is a mean \pm SD.

^c The value is a mean

R-SICU,Respiratory-surgical ICU;NR,not reported;q3h,every 3 hours; q4h,every 4 hours.

Table S3. Summary	v of RCT studies which	n included a portion	ı of mechanically v	ventilated patien	ts in the meta-analysis

		Country	Centers	ICU_type	Patients_ty	Group	No.	of	Sex(F/M ^d)	Age-yr	Medicine	Mode	of	Days	of
					pe		Patients					administration		administration	
Klastersky	et	Belgium	U^{a}	Neurosurgical	NR	$\mathrm{IG}^{\mathfrak{b}}$	43		14/29	51.2°	Gentamicin,80mg	Intratracheal		NR	
al.,1974				ICU		CG ^c	42		4/38	43.5°	0.9% saline	instillation, tid			
Greenfield	et	United States	U^a	R-SICU	NR	$\mathrm{IG}^{\mathfrak{b}}$	33		15/18	20-39 15% ^f	Polymyxin B, 2.5 mg/kg /day in	Intratracheal		NR	
al.1973										40-59 24% ^f	6 divided doses	instillation, q4h			
										≥60 61% ^f					
						CG^{c}	25		13/12	20-39 12% ^f					
										40-59 24% ^f					
										$\geq 60.64\%^{\mathrm{f}}$					

^aU represents unicenter.

^b IG represents intervention group.

°CG represents control group.

^d F/M represents female/male.

^e The value is a mean.

^fThis data represents the age group and proportion of patients.

R-SICU ,Respiratory-surgical ICU;NR, not reported; tid,three times a day; q4h,every four hours.





Outcome	No of	Study	No of par	ticipants		Certainty assessment			No	of patients	Effect (Random effects model)		Certainty	
	studies	design	Topical use of	Control	Risk of bias	Imprecision	Inconsistency	Indirectness	Publication	Topical use of	Control	Relative risk (95%	Absolute effect (95% CI)	•
			antibiotics						bias ^m	antibiotics		CI)		
Incidence of VAP	7	RCT	715	730	Not serious ^a	Low ^b	Moderate ^h	Low	-	151/715 (21.1%)	219/730 (30.0%)	0.69 (0.53-0.89)	-	⊕⊕⊕⊖ Moderate
Subgroup: Aminoglycosides	4	RCT	558	574	Not serious ^a	High ^c	Moderate ^h	Low	-	105/558 (18.8%)	155/574 (27.0%)	0.67 (0.47-0.97)		⊕⊕⊖⊖ Low
Subgroup: Ceftazidime	2	RCT	73	72	Not serious ^a	High ^d	Substantial ⁱ	Low	-	32/73 (43.8%)	39/72 (54.2%)	0.72 (0.35-1.49)		$\oplus \bigcirc \bigcirc \bigcirc$ Very low ⁿ
Subgroup: Colistin	1	RCT	84	84	Not serious ^a	High ^d	NA^j	Low	-	14/84 (16.7%)	25/84 (29.8%)	0.56 (0.31-1.00)		⊕⊖⊖⊖ Very low ^o
Subgroup: Intratracheal instillation	1	RCT	85	77	Not serious ^a	High^d	NA ^j	Low	-	29/85 (34.1%)	25/77 (32.5%)	1.05 (0.68-1.63)		⊕⊖⊖⊖ Very low ^o
Subgroup: Nebulization	6	RCT	630	653	Not serious ^a	Low ^e	Low ^k	Low	-	122/630 (19.4%)	194/653 (29.7%)	0.64 (0.49-0.83)		$\oplus \oplus \oplus \oplus$ High
All-cause hospital mortality	7	RCT	715	730	Not serious ^a	High ^d	Low ^k	Low	-	192/715 (26.9%)	223/730 (30.5%)	0.88 (0.75-1.03)	-	⊕⊕⊕⊖ Moderate
Subgroup: Aminoglycosides	4	RCT	558	574	Not serious ^a	High ^d	Low ^k	Low	-	153/558 (27.4%)	180/574 (31.4%)	0.83 (0.65-1.07)		⊕⊕⊕⊖ Moderate
Subgroup: Ceftazidime	2	RCT	73	72	Not serious ^a	High ^d	Low ^k	Low	-	10/73 (13.7%)	12/72 (16.7%)	0.82 (0.37-1.81)		$\oplus \oplus \bigcirc \bigcirc Low^n$
Subgroup: Colistin	1	RCT	84	84	Not serious ^a	High ^d	NA ^j	Low	-	29/84 (34.5%)	31/84 (36.9%)	0.94 (0.62-1.40)		⊕○○○ Very low ^o
Subgroup: Intratracheal instillation	1	RCT	85	77	Not serious ^a	High ^d	NA ^j	Low	-	23/85 (27.1%)	30/77 (39.0%)	0.69 (0.44-1.09)		⊕○○○ Very low ^o
Subgroup: Nebulization	6	RCT	630	653	Not serious ^a	High^d	Low ^k	Low	-	169/630 (26.8%)	193/653 (29.6%)	0.91 (0.77-1.08)		⊕⊕⊕⊖ Moderate
Incidence of VAP on day 14	2	RCT	73	72	Not serious ^a	High ^d	Substantial ⁱ	Low	-	24/73 (32.9%)	35/72 (48.6%)	0.55 (0.18-1.64)	-	$\oplus \bigcirc \bigcirc \bigcirc$ Very low ⁿ
Incidence of VAP on day 30	2	RCT	137	136	Not serious ^a	High^d	Substantial ⁱ	Low	-	40/137 (29.2%)	51/136 (37.5%)	0.77 (0.45-1.33)	-	$\oplus \bigcirc \bigcirc \bigcirc$ Very low ⁿ
VAP IDR	2	RCT	501	514	Not serious ^a	High ^e	Low ^k	Low	-	30.4/501 (6.1%)	52.6/514 (10.2%)	0.58 (0.36-0.93)	-	$\oplus \oplus \bigcirc \bigcirc$ Low ⁿ
Incidence of GNB VAP	2	RCT	501	514	Not serious ^a	Low ^e	Low ^k	Low	-	40/501 (8.0%)	82/514 (16.0%)	0.50 (0.35-0.71)	-	$\oplus \oplus \bigcirc Moderate^n$
Incidence of Staphylococcus VAP	2	RCT	137	136	Not serious ^a	$\mathrm{High}^{\mathrm{d}}$	Low ^k	Low	-	15/137 (10.9%)	14/136 (10.3%)	1.05 (0.54-2.05)	-	$\oplus \oplus \bigcirc \bigcirc$ Low ⁿ
Incidence of MDR VAP	2	RCT	137	136	Not serious ^a	$\mathrm{High}^{\mathrm{d}}$	Substantial	Low	-	21/137 (15.3%)	28/136 (20.6%)	0.71 (0.22-2.25)	-	$\oplus \bigcirc \bigcirc \bigcirc$ Very low ⁿ
Incidence of VAP after VAT	2	RCT	501	514	Not serious ^a	$\mathrm{High}^{\mathrm{d}}$	Low ^k	Low	-	29/501 (5.8%)	41/514 (8.0%)	0.85 (0.34-2.12)	-	$\oplus \oplus \bigcirc \bigcirc$ Low ⁿ
Time of VAP occurrence since	2	RCT	501	514	Not serious ^a	High ^f	Substantial ¹	Low	-	501	514	-	3.97 days longer (1.17- 6.77)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low ⁿ
randomization														
Duration of IMV	4	RCT	574	586	Not serious ^a	High ^g	Low ^k	Low	-	574	586	-	0.06 days shorter (-1.08-	⊕⊕⊕⊖ Moderate
													0.96)	
Duration of systemic antibiotics	2	RCT	437	450	Not serious ^a	High ^g	Substantial ⁱ	Low	-	437	450	-	3.45 days shorter (-8.72,	$\oplus \bigcirc \bigcirc \bigcirc$ Very low ⁿ
													1.83)	
Need for tracheostomy	2	RCT	137	136	Not serious ^a	High ^d	Moderate ^h	Low	-	77/137 (56.2%)	68/136 (50%)	1.10 (0.81-1.49)	-	$\oplus \bigcirc \bigcirc \bigcirc$ Very low ⁿ

Table S4. Grading of recommendations, assessment, development and evaluations (GRADE).

ICU length of stay	5	RCT	601	613	Not serious ^a	High ^g	Substantial ¹	Low	-	601	613	-	0.41 days shorter (-4.96-	⊕⊕⊖⊖ Low
													4.13)	
Hospital length of stay	3	RCT	554	566	Not serious ^a	High ^g	Low ^k	Low	-	554	566	-	0.74 days shorter (-3.08-	⊕⊕⊕⊖ Moderate
													1.60)	

^a. According to Figure Assessment of risk of bias for RCTs, 3 studies did not mention random sequence generation, 2 studies did not mention allocation concealment, 2 studies were open-label trials.

^b. The 95% CI of relative risk did not overlap a relative risk of 1.0 (no effect), trial sequential analysis showed that, while the required sample size of 1,449 was not quite reached, it was very close, and the cumulative Z-score did not fall within futility boundaries but crossed the O'Brian-Fleming boundaries.

^c. Although the 95% CI of relative risk did not overlap a relative risk of 1.0 (no effect). Trial sequential analysis indicated that the optimal information size was not reached.

^d. The 95% CI of relative risk overlapped a relative risk of 1.0 (no effect). Trial sequential analysis indicated that the optimal information size was not reached.

e. The 95% CI of relative risk did not overlap a relative risk of 1.0 (no effect). Trial sequential analysis supported the true positive conclusion by reaching the optimal information size.

^f. Although the 95% CI of absolute effect did not overlap a mean difference of 0.0 (no effect). Trial sequential analysis indicated that the optimal information size was not reached.

g. The 95% CI of absolute effect overlapped a mean difference of 0.0 (no effect). Trial sequential analysis indicated that the optimal information size was not reached.

 $^{\rm h}.$ I² >30% and <60%, although heterogeneity test showed p-value > 0.05.

ⁱ. I² >50% and <90%, although heterogeneity test showed p-value > 0.05.

^j. Only one study was included.

^k. $I^2 < 40\%$, heterogeneity test showed p-value > 0.05.

 1 .I² >50% and <90%, heterogeneity test showed p-value < 0.05.

^m. For each outcome, the number of trials included is less than 10, so it is difficult to assess the publication bias by the Egos test.

ⁿ. It was downgraded by one level because only two studies were included and trial sequential analysis showed that the required sample size was far from being reached.

°. It was downgraded by one level because only one study was included and the imprecision was not available.

VAP, ventilator associated pneumonia; VAP IDR, adjudicated ventilator associated pneumonia incidence density per 1,000 days of invasive mechanical ventilation; GNB, gram negative bacteria; MDR,multi-drug resistance; VAT, ventilator associated tracheitis; IMV, intensive mechanical ventilation; CI, confidence interval; ICU, intensive care unit; RCT, randomized controlled trial; NA, not applicable.

		Select	tion		Compara	bility		Outcome			
Author, year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainmen t of exposure	Outcome of interest not present at start of study	Controls for age, sex, and marital status	Controls of other factors	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Quality [#]	
Klick,1975		*	*	*			*	*	*	Poor	
Rouby, 1994	*	*	*	*	*		*	*	*	Good	

Table S5. Assessment on risk of bias for included non-RCTs using Newcastle-Ottawa Scale.

[#]The quality (good, fair, and poor) was defined based on the following criteria: Good - 3 or 4 stars in 'Selection' domain AND 1 or 2 stars in 'Comparability' domain AND 2 or 3 stars in 'Outcome' domain; Fair - 2 stars in 'Selection' domain AND 1 or 2 stars in 'Comparability' domain AND 2 or 3 stars in 'Outcome' domain; Poor - 0 or 1 star in 'Selection' domain OR 0 star in 'Comparability' domain OR 0 or 1 star in 'Outcome' domain. RCT, randomised controlled trial

Author	VAP definition
Ehrmann et al.,	1.Based on available routine clinical data, in case of new occurrence of any of
2023	the following: ①hyperleukocytosis (≥10,000 leucocytes/mm ³), ②leukopenia
	$(\leq 4,000 \text{ leukocytes/mm}^3)$, (3) fever ($\geq 38^{\circ}$ C), (4) purulent secretion, (5) new
	chest X-ray infiltrate, @significant respiratory compromise (decrease in
	PaO ₂ /FiO ₂ ratio or increase in positive end expiratory pressure), ⑦significant
	cardiovascular compromise (shock) Move to VAP suspicion work up.
	2.If not available obtain: Complete white blood, cell count, Temperature
	measurement, Semi-quantitative and qualitative secretion assessment, chest X-
	ray, blood gases, in case of : Definite or possible new chest X-ray infiltrate (or
	significant respiratory or cardiovascular compromise in patients suffering
	ARDS*) AND two among hyperleukocytosis ($\geq 10,000$ leukocytes/mm ³) or
	leukopenia (≤ 4,000 leukocytes/mm ³) OR fever (≥ 38°C) OR purulent
	secretion, Move to possible VAP work up.
	3.Obtain bacteriological lung specimen (tracheal aspirate, bronchoalveolar
	lavage or distal protected specimen), File possible VAP case report form.
	Definite VAP diagnosis will be made a posteriori by an adjudication committee
	based on possible VAP case report form comprising clinical, microbiological
	data and original chest X-rays.
Karvouniaris et	(a) the appearance of new or progressive and persistent pulmonary infiltrates on
al., 2015	chest radiography and two of the following criteria: (b) abnormal temperature
	(>380C or <360C), (c) abnormal white blood cells (WBC) count, (d) purulent
	Tracheobroncheal Aspirates (TBA) with a positive culture. Confirmation of
	diagnosis required quantitative cultures of TBA, received within two days
	before or after clinical diagnosis, that were evaluated by microscopy and
	considered positive if grew ≥100000 Colony Forming Units (CFU)/mL
Kuzovlev et al.,	standard clinical and CPIS criteria (fever, leukocytosis, characteristics of
2015	sputum, arterial oxygenation, infiltrative changes on chest X-ray, and semi-
	quantitative analysis of tracheal aspirate and Gram staining).
Wood et al.,	Clinical (criteria for the systemic inflammatory response syndrome), and
2002	microbiological (quantitative cultures from BAL yielded at least 10^5 CFU).
Rathgeber et	(a)New and persistent infiltrates on x-ray on one or more areas of the lungs, (b)
al., 1993	purulent bronchial secretions, (c) detection of pathogen in the bronchial, (d) at
	least 2 of the following: signs of respiratory failure evident by increase of FiO_2
	by at least 0.1, leukocytosis >10000/mm ³ , rectal body temperature >38°C
Claridge et al.,	Clinical (criteria for the systemic inflammatory response syndrome), and
2007	microbiological (quantitative cultures from BAL yielded > 100,000 CFU).
Lode et al.,	NR
1988	

Table S6. Summary of VAP definition from included RCTs in the meta-analysis.

NR, not reported.

Author	Age	Patient type	Invasive	Others
			mechanical	
			ventilation time	
Ehrmann et	≥18 y	Intubated patients	\geq 72h	Negative
al., 2023				pregnancy test
Karvouniari	>18 y	Intubated patients	>48 h	NR
s et al.,				
2015				
Kuzovlev et	NR	Intubated multiple trauma	NR	NR
al., 2015		patients (ISS ≥30)		
Wood et al.,	≥16 y	Intubated patients in	Expected to	NR
2002		Trauma ICU with at least 1	receive MV for >	
		risk factor for "post-	7 days	
		traumatic pneumonia"		
Rathgeber	NR	Intubated patients	\geq 4 days	NR
et al., 1993				
Claridge et	NR	Intubated patients in	NR	NR
al., 2007		Trauma ICU expected to		
		require prolonged		
		intubation with a calculated		
		probability of getting VAP		
		of \geq 0.25		
Lode et al.,	NR	Intubated patients	\geq 4 days	NR
1988				

Table S7. Summary of inclusion criteria in the 7 RCTs for the final meta-analysis.

NR: not reported; ISS: Injury Severity Score; MV: Mechanical ventilation.

Author	Suspicion or confirmed	Drug allergy	Pregnant women or	Poor prognosis	Disease status	Current treatment	Others
	pneumonia		breastfeeding women				
Ehrmann	Suspicion or confirmed	Patients known at the	Known pregnant women at	NR	Stage 2 or 3 KDIGO classification acute	Clinical indication for	Patient scheduled for
et al.,	ventilator associated	time of inclusion to	the time of inclusion and		kidney injury the day of inclusion.	systemic aminoglycoside	extubation within the next
2023	pneumonia the day of inclusion	be allergic to	breastfeeding women		Patients undergoing renal replacement	therapy the day of	24h;Patient ventilated
		aminoglycosides			therapy or for whom decision has been	inclusion: as deemed	through an endotracheal
					made to initiate renal replacement	necessary by the clinician	tube for more than four
					therapy can be included whatever the	in charge	consecutive days
					KDIGO stage;Chronic kidney failure :		(96h);Patient ventilated
					baseline estimated glomerular filtration		through a
					lower than 30 mL/min; Myasthenia		tracheostomy;Known
					gravis		guardianship or
							trusteeship at the time of
							inclusion;Patients
							previously included in this
							study
Karvounia	Grossly purulent sputum or	Allergy to colistin,	Pregnancy	NR	Severe chronic obstructive pulmonary	NR	NR
ris et al.,	pneumonia on admission, new	and colonisation			disease (COPD); infection with a strain		
2015	and persistent infiltrates on				resistant to colistin on admission		
	chest radiography within 48 h						
	from admission						
Kuzovlev	NR	NR	NR	NR	NR	NR	NR
et al.,							
2015							

Table S8. Summary of exclusion criteria in the 7 RCTs for the final meta-analysis.

Wood et	NR	Allergy to betalactam	Pregnancy	Poor prognosis	Preexistent lung disease requiring long-	Current treatment for a	NR
al., 2002					term inhalation drug therapy ;human	lower respiratory tract	
					immunodeficiency virus infection,	infection, long-term	
					cancer,or white blood cell count less	therapy with	
					than 4×10^3 /mm ³ .	corticosteroids or	
						immunosuppressive drugs	
Rathgeber	Patients diagnosed with	Known	NR	NR	NR	NR	NR
et al.,	pneumonia within the first 24	hypersensitivity to					
1993	hours of intubation	aminoglycoside					
		antibiotics					
Claridge	NR	NR	NR	Patients with	NR	NR	< 18 years old
et al.,				nonsurvivable			
2007				injuries			
				(predicted			
				survival less			
				than one week			
				based on			
				trauma/critical			
				care surgeon			
				assessment)			
Lode et	NR	NR	NR	NR	NR	NR	NR
al., 1988							

NR: not reported.





Figure S3. Sensitivity test of incidence of VAP for all RCT studies.

Study	Interv Events	ention Total	C Events	ontrol Total	Risk Ratio	RR [95%-CI]	Weight (fixed)	Weight (random)
Greenfield, 1973	2	33	4	25		0.38 [0.08; 1.91]	1.9%	2.6%
Klastersky, 1974	5	43	17	42		0.29 [0.12; 0.71]	7.2%	6.8%
Lode, 1988	29	85	25	77	5 6 6 -	1.05 [0.68; 1.63]	11.0%	15.2%
Rathgeber, 1993	5	29	17	40	<u> </u>	0.41 [0.17; 0.97]	6.0%	7.1%
Wood, 2002	6	20	13	20	<u> </u>	0.46 [0.22; 0.97]	5.5%	8.9%
Claridge, 2007	26	53	26	52	5 	0.98 [0.67; 1.44]	11.0%	16.6%
Karvouniaris, 2015	14	84	25	84		0.56 [0.31; 1.00]	10.5%	11.8%
Kuzovlev, 2015	9	27	18	27		0.50 [0.28; 0.91]	7.6%	11.5%
Ehrmann, 2023	62	417	95	430	÷	0.67 [0.50; 0.90]	39.3%	19.3%
Fixed effect model	158	791	240	797	•	0.66 [0.56; 0.79]	100.0%	
Random effects model Heterogeneity: $l^2 = 47\%$ [09	%; 75%], χ ²	= 15.09	(p = 0.06)			0.63 [0.48; 0.83]		100.0%
				Fav	0.1 0.5 1 2 10 ours intervention Favours control			

Figure S4. Sensitivity test of incidence of VAP for all RCT studies and non-RCT studies.

Study	Interv Events	ention Total	C Events	ontrol Total	Risk Ratio	RR [95%-CI]	Weight (fixed)	Weight (random)
Greenfield, 1973	2	33	4	25		0.38 [0.08; 1.91]	1.2%	1.3%
Klastersky, 1974	5	43	17	42		0.29 [0.12; 0.71]	4.5%	3.8%
Klick, 1975	18	374	30	370		0.59 [0.34; 1.05]	7.8%	8.1%
Lode, 1988	29	85	25	77	÷+-	1.05 [0.68; 1.63]	6.8%	11.4%
Rathgeber, 1993	5	29	17	40		0.41 [0.17; 0.97]	3.7%	4.0%
Rouby, 1994	97	347	100	251	÷	0.70 [0.56; 0.88]	30.2%	20.5%
Wood, 2002	6	20	13	20		0.46 [0.22; 0.97]	3.4%	5.3%
Claridge, 2007	26	53	26	52		0.98 [0.67; 1.44]	6.8%	13.1%
Karvouniaris, 2015	14	84	25	84		0.56 [0.31; 1.00]	6.5%	7.8%
Kuzovlev, 2015	9	27	18	27		0.50 [0.28; 0.91]	4.7%	7.5%
Ehrmann, 2023	62	417	95	430		0.67 [0.50; 0.90]	24.3%	17.3%
Fixed effect model	273	1512	370	1418		0.67 [0.59; 0.76]	100.0%	
Random effects model Heterogeneity: $l^2 = 35\%$ [0%	6: 68%], γ ²	. = 15.38	$\beta (p = 0.12)$			0.66 [0.55; 0.80]		100.0%
5 /		0	J -··-/		0.1 0.5 1 2 10			

Favours intervention Favours control

Figure S5. Risk of VAP incidence in RCTs reported microbiologically confirmed VAP

	Interv	ention	c	ontrol			Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR [95%-CI]	(fixed)	(random)
Wood, 2002	6	20	13	20		0.46 [0.22; 0.97]	7.4%	10.4%
Claridge, 2007	26	53	26	52		0.98 [0.67; 1.44]	14.9%	25.8%
Karvouniaris, 2015	14	84	25	84		0.56 [0.31; 1.00]	14.2%	15.3%
Kuzovlev, 2015	9	27	18	27		0.50 [0.28; 0.91]	10.2%	14.7%
Ehrmann, 2023	62	417	95	430		0.67 [0.50; 0.90]	53.2%	33.8%
Fixed effect model Random effects model	117	601	177	613		0.67 [0.55; 0.82] 0.66 [0.51: 0.87]	100.0%	
Heterogeneity: $l^2 = 33\%$ [09	%: 75%]. χ^2	= 5.96 (p = 0.20			0.00 [0.01, 0.01]		100.070
	, j, <i>1</i> 4		,		0.5 1 2			
				F				

Favours intervention Favours control



Figure S6. Trial sequential analysis of incidence of VAP in subgroups of nebulization for included RCTs



Figure S7. Trial sequential analysis of incidence of VAP in subgroups of aminoglycosides for included RCTs

Figure S8. Network meta-analysis of indirect comparisons among aminoglycosides, ceftazidime, and colistin using Bayesian methodology



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Figure S9. Network meta-analysis of indirect comparisons between nebulization and intratracheal instillation using Bayesian methodology



-	-				-			
	Interv	ention	c	Control			Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR [95%-CI]	(fixed)	(random)
Karvouniaris, 2015	11	84	26	84		0.45 [0.24; 0.84]	49.1%	46.2%
Ehrmann, 2023	19	417	27	430		0.73 [0.41; 1.28]	50.9%	53.8%
Fixed effect model	30	501	53	514		0.59 [0.39; 0.90]	100.0%	
Random effects model Heterogeneity: $I^2 = 21\%$, χ_1^2	= 1.27 (p =	= 0.26)				0.58 [0.36; 0.93]		100.0%
	0				0.0 0.5 4 0			

Figure S10. Meta analysis of the incidence density rate of VAP for included RCTs

0.2 0.5 1 2 Favours intervention Favours control

Study	Interv Events	ention Total	C Events	ontrol Total	Risk Ratio	RR [95%-CI]	Weight (fixed)	Weight (random)
2							. ,	,
Karvouniaris, 2015	9	84	21	84		0.43 [0.21; 0.88]	25.9%	24.6%
Ehrmann, 2023	31	417	61	430		0.52 [0.35; 0.79]	74.1%	75.4%
Fixed effect model	40	501	82	514		0.50 [0.35; 0.71]	100.0%	
Random effects model						0.50 [0.35; 0.71]		100.0%
Heterogeneity: $I^2 = 0\%$, χ_1^2	= 0.23 (p =	0.63)						

Figure S11. Meta analysis of the incidence of Gram-negative bacteria VAP for included RCTs

0.2 0.5 1 2 Favours intervention Favours control

Figure S12. Meta analysis of the time from randomization to the occurrence of VAP for included RCTs

Study	Total	Interve Mean	ention SD	Total	Co Mean	ontrol SD	Mean Difference	MD [95%-CI]	Weight (fixed)	Weight (random)
Karvouniaris, 2015 Ehrmann, 2023	84 417	12.22 12.66	9.53 8.95	84 430	6.53 9.88	7.62 4.16		5.69 [3.08; 8.30] 2.78 [1.84; 3.72]	11.6% 88.4%	40.9% 59.1%
Fixed effect model Random effects model Heterogeneity: / ² = 76% [09	501 %; 95%],	χ ² = 4.22	(p = 0.0	514 04)		Favou	-4 -2 0 2 4 6 8 10 rrs control Favours intervention	3.12 [2.23; 4.01] 3.97 [1.17; 6.77]	100.0% 	 100.0%

Figure S13	. Meta analysis	of incidence	of VAP on	day 14 for	included RCTs

	Interv	ention	C	ontrol			Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR [95%-CI]	(fixed)	(random)
Wood, 2002	3	20	11	20		0.27 [0.09; 0.83]	31.2%	39.6%
Claridge, 2007	21	53	24	52		0.86 [0.55; 1.34]	68.8%	60.4%
Fixed effect model	24	73	35	72	\sim	0.68 [0.45; 1.02]	100.0%	
Random effects model Heterogeneity: $l^2 = 71\%$ [0%]	6; 94%], χ ²	= 3.50 ()	p = 0.06)			0.55 [0.18; 1.64]		100.0%
					0.1 0.5 1 2 10			
				Fav	ours intervention Favours control			

Figure S14. Meta analysis of incidence of VAP on day 30 for included RCTs

	Interv	ention	c	Control						Weight	Weight
Study	Events	Total	Events	Total		Ris	k Ratio		RR [95%-CI]	(fixed)	(random)
Claridge, 2007	26	53	26	52		-	+ -	-	0.98 [0.67; 1.44]	51.2%	57.8%
Karvouniaris, 2015	14	84	25	84		1			0.56 [0.31; 1.00]	48.8%	42.2%
Fixed effect model	40	137	51	136		~	<u></u>		0.78 [0.56; 1.08]	100.0%	
Random effects model Heterogeneity: $I^2 = 60\%$ [0%	6; 91%], χ ²	= 2.49 ()	p = 0.11)		Γ				0.77 [0.45; 1.33]		100.0%
			,		0.3	0.5	1	2			
					Favou	rs interver	ntion Favo	ours cont	rol		

Figure S15. Meta analysis of incidence of VAP due to multidrug-resistant bacteria for included RCTs

Study	Interv Events	ention Total	C Events	ontrol Total	Risk Ratio	RR [95%-CI]	Weight (fixed)	Weight (random)
Claridge, 2007 Kanouniaria, 2015	15	53	12	52	<u> </u>	1.23 [0.64; 2.36]	43.1%	53.3%
Karvourlians, 2015	0	04	10	04		0.36 [0.15, 0.91]	50.9%	40.7 %
Fixed effect model Random effects model	21	137	28	136		0.74 [0.45; 1.24] 0.71 [0.22; 2.25]	100.0% 	 100.0%
Heterogeneity: I ² = 77% [1%	6; 95%], χ ²	= 4.43 (/	p = 0.04)			• • •		
					0.1 0.5 1 2 5 Fayours intervention Fayours contro	5l		

Study	Interv Events	ention Total	C Events	ontrol Total	I	Risk Ratio		RR [95%-CI]	Weight (fixed)	Weight (random)
Claridge, 2007 Karvouniaris, 2015	10 5	53 84	10 4	52 84				0.98 [0.45; 2.16] 1.25 [0.35; 4.49]	71.6% 28.4%	72.5% 27.5%
Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\chi_1^2 =$	15 = 0.10 (p =	137 0.75)	14	136 Favou	0.3 0.5 Irs interventio	1 2 on Favours co	5 ontrol	1.06 [0.54; 2.07] 1.05 [0.54; 2.05]	100.0% 	 100.0%

Figure S16. Meta analysis of incidence of VAP due to Staphylococcus species for included RCTs

	Interv	ention	C	ontrol			Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR [95%–Cl]	(fixed)	(random)
Karvouniaris, 2015	4	84	2	84		2.00 [0.38; 10.63]	5.0%	22.9%
Ehrmann, 2023	25	417	39	430		0.66 [0.41; 1.07]	95.0%	77.1%
Fixed effect model	29	501	41	514		0.73 [0.46; 1.15]	100.0%	
Random effects model Heterogeneity: $l^2 = 36\%$, χ_1^2	= 1.56 (p =	= 0.21)				0.85 [0.34; 2.12]		100.0%
					0.2 0.5 1 2 5 12			
				Favou	s intervention Favours control			







Figure S19. Trial sequential analysis of the incidence density rate of VAP for included RCTs



Figure S20. Trial sequential analysis of the time from randomization to the occurrence of VAP for included RCTs

Figure S21. Trial sequential analysis of incidence of VAP on day 14 for included RCTs



Figure S22. Trial sequential analysis of incidence of VAP on day 30 for included RCTs



Figure S23. Trial sequential analysis of incidence of VAP due to multidrug-resistant bacteria for included RCTs







Figure S25. Trial sequential analysis of incidence of VAP after ventilator-associated tracheobronchitis for included RCTs





Figure S26. Trial sequential analysis of hospital mortality for included RCTs



Figure S27. Trial sequential analysis of hospital mortality in subgroups of aminoglycosides for included RCTs

Figure S28. Trial sequential analysis of hospital mortality in subgroups of ceftazidime for included RCTs



Figure S29. Trial sequential analysis of hospital mortality in subgroups of colistin for included RCTs





Figure S30. Trial sequential analysis of hospital mortality in subgroups of intratracheal instillation for included RCTs





Figure S32. Sensitivity test of hospital mortality for all RCT studies.

Study	Interv Events	ention Total	C Events	ontrol Total	Risk Ratio	RR [95%-CI]	Weight (fixed)	Weight (random)
Greenfield, 1973	4	33	6	25		0.51 [0.16; 1.60]	2.8%	1.7%
Klastersky, 1974	23	43	16	42	{	1.40 [0.87; 2.26]	6.6%	10.2%
Lode, 1988	23	85	30	77		0.69 [0.44; 1.09]	12.9%	11.5%
Rathgeber, 1993	4	29	8	40		0.69 [0.23; 2.07]	2.8%	1.9%
Wood, 2002	3	20	6	20		0.50 [0.14; 1.73]	2.5%	1.5%
Claridge, 2007	7	53	6	52	i •	1.14 [0.41; 3.18]	2.5%	2.2%
Karvouniaris, 2015	29	84	31	84		0.94 [0.62; 1.40]	12.7%	13.9%
Kuzovlev, 2015	3	27	6	27		0.50 [0.14; 1.80]	2.5%	1.4%
Ehrmann, 2023	123	417	136	430	1	0.93 [0.76; 1.14]	54.8%	55.7%
Fixed effect model	219	791	245	797	4	0.90 [0.77; 1.05]	100.0%	
Random effects model Heterogeneity: $l^2 = 0\% [0\%]$;	; 65%], χ ₈ ² =	= 7.84 (p	= 0.45)			0.91 [0.78; 1.06]		100.0%
				_	0.1 0.5 1 2 5			

Favours intervention Favours control

Figure S33. Sensitivity test of hospital mortality for all RCT studies and non-RCT studies.

Study	Interv Events	ention Total	C Events	ontrol Total	Risk	Ratio			RR [95%-CI]	Weight (fixed)	Weight (random)
Greenfield, 1973	4	33	6	25			-		0.51 [0.16; 1.60]	2.1%	1.4%
Klastersky, 1974	23	43	16	42		- -			1.40 [0.87; 2.26]	5.0%	8.0%
Klick, 1975	45	374	45	370		-#	•		0.99 [0.67; 1.46]	13.9%	12.0%
Lode, 1988	23	85	30	77		- { 			0.69 [0.44; 1.09]	9.7%	9.0%
Rathgeber, 1993	4	29	8	40		-H-	_		0.69 [0.23; 2.07]	2.1%	1.5%
Rouby, 1994	42	347	31	251	-	_ <u>ii</u>	-		0.98 [0.63; 1.51]	11.1%	9.5%
Wood, 2002	3	20	6	20			-		0.50 [0.14; 1.73]	1.8%	1.2%
Claridge, 2007	7	53	6	52					1.14 [0.41; 3.18]	1.9%	1.7%
Karvouniaris, 2015	29	84	31	84	-	-#-			0.94 [0.62; 1.40]	9.5%	10.9%
Kuzovlev, 2015	3	27	6	27		-	_		0.50 [0.14; 1.80]	1.8%	1.1%
Ehrmann, 2023	123	417	136	430		- 1			0.93 [0.76; 1.14]	41.2%	43.6%
Fixed effect model	306	1512	321	1418					0.92 [0.80; 1.05]	100.0%	
Random effects model Heterogeneity: l^2 = 0% [0%; 60%], χ^2_{10} = 8.06 (<i>p</i> = 0.62)						4		_	0.93 [0.81; 1.06]		100.0%
					0.1 0.5	1	2	5			

Favours intervention Favours control

Study	Total	Interv Mean	ention SD	Total	C Mean	Control SD	Mean Difference	MD [95%-CI]	Weight (fixed)	Weight (random)
Wood, 2002 Claridge, 2007 Karvouniaris, 2015 Ehrmann, 2023	20 53 84 417	16.00 18.68 17.72 12.50	11.00 26.65 16.66 7.80	20 52 84 430	18.00 12.67 15.77 12.70	13.00 10.38 21.49 7.80		-2.00 [-9.46; 5.46] 6.01 [-1.70; 13.72] 1.95 [-3.86; 7.76] -0.20 [-1.25; 0.85]	1.9% 1.7% 3.0% 93.4%	1.9% 1.7% 3.0% 93.4%
Fixed effect model Random effects model Heterogeneity: $l^2 = 5\% [0\%]$	574 ; 86%], χ	2 ₃ = 3.17 (p = 0.37)	586	ı	avours	10 -5 0 5 10 15 intervention Favours control	-0.06 [-1.08; 0.96] -0.06 [-1.08; 0.96]	100.0% 	 100.0%

Figure S34. Meta analysis of duration of invasive mechanical ventilation for included RCTs

Figure S35. Meta analysis of duration of ICU length of stay for included RCTs

		Interv	ention		c	Control			Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD	Mean Difference	MD [95%-CI]	(fixed)	(random)
Wood, 2002	20	19.00	11.00	20	21.00	12.00		-2.00 [-9.13; 5.13]	5.0%	17.8%
Claridge, 2007	53	31.13	34.94	52	23.33	16.31		7.80 [-2.60; 18.20]	2.4%	11.9%
Karvouniaris, 2015	84	21.37	19.02	84	17.82	16.22	4	3.55 [-1.80; 8.90]	8.9%	22.1%
Kuzovlev, 2015	27	8.00	4.60	27	17.10	18.40		-9.10 [-16.25; -1.95]	5.0%	17.8%
Ehrmann, 2023	417	16.80	12.60	430	17.30	14.10	+	-0.50 [-2.30; 1.30]	78.7%	30.3%
Fixed effect model	601			613				-0.45 [-2.04; 1.15]	100.0%	
Random effects model								-0.41 [-4.96; 4.13]		100.0%
Heterogeneity: I ² = 61% [09	%; 85%],	$\chi_4^2 = 10.3$	7(p = 0.0	03)						
						-	-20 -10 0 10 20			
						Favou	rs intervention Favours control			

Figure S36. Meta analysis of duration of hospital length of stay for included RCTs

		Interv	ention		c	Control			Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD	Mean Difference	MD [95%-CI]	(fixed)	(random)
Claridge, 2007	53	29.76	20.30	52	29.33	16.31		0.43 [-6.61; 7.47]	11.0%	11.0%
Karvouniaris, 2015	84	21.67	13.34	84	23.88	17.97	<u>_</u>	-2.21 [-7.00; 2.58]	23.8%	23.8%
Ehrmann, 2023	417	29.70	20.80	430	30.10	22.20		-0.40 [-3.30; 2.50]	65.1%	65.1%
Fixed effect model	554			566				-0.74 [-3.08; 1.60]	100.0%	
Random effects model Heterogeneity: $I^2 = 0\% [0\%]$, 90%], χ	² ₂ = 0.52 (p = 0.77)	,				-0.74 [-3.08; 1.60]		100.0%
		-				-	10 -5 0 5 10			
						Favou	rs intervention Favours control			

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CTs
(

Study	Total	Interv Mean	ention SD	Total	C Mean	Control SD	Mean Difference	MD [95%-CI]	Weight (fixed)	Weight (random)
Wood, 2002	20	6.00	8.00	20	13.00	11.00		-7.00 [-12.96; -1.04]	7.9%	36.5%
Fixed effect model Random effects model Heterogeneity: / ² = 68% (0%	417 437 6: 93%]	$\gamma_{1}^{2} = 3.11$	(p = 0.08)	430 450	14.40	14.04		-1.85 [-3.52; -0.18] -3.45 [-8.72; 1.83]	92.1% 100.0%	 100.0%
		~1	U	-,			−15 −10 −5 0 5 Favours intervention Favours co	ntrol		

Figure S38. Meta analysis of the need for tracheostomy for included RCTs	
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	Interv	ention	c	ontrol			Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR [95%-CI]	(fixed)	(random)
Claridge, 2007	34	53	35	52		0.95 [0.72; 1.26]	51.7%	55.0%
Karvouniaris, 2015	43	84	33	84		1.30 [0.93; 1.83]	48.3%	45.0%
Fixed effect model	77	137	68	136		1.12 [0.90; 1.40]	100.0%	
Random effects model Heterogeneity: $I^2 = 49\%$, χ_1^2	= 1.97 (p =	= 0.16)				1.10 [0.81; 1.49]		100.0%
					0.5 1 2			
				Fav	ours intervention Favours control			

Figure S39. Trial sequential analysis of duration of invasive mechanical ventilation for included RCTs





Figure S40. Trial sequential analysis of duration of ICU length of stay for included RCTs



Figure S41. Trial sequential analysis of duration of hospital length of stay for included RCTs







Figure S43. Trial sequential analysis of the need for tracheostomy for included RCTs

Author	Side effects							
Ehrmann et al.,	Any serious adverse event (IG vs CG): 4% vs 3%; Respiratory tract-							
2023	disorders event: 2% vs 2%; Serious adverse effect*: 2% vs 1%; Respiratory							
	tract effect: 2% vs 1%; Acute kidney injury occurrence from randomization							
	to day 28: 4% vs 8%							
Karvouniaris et al.,	Bronchospasm (IG vs CG): 9.5% vs 3.4%							
2015								
Kuzovlev et al.,	No side effects, such as bronchospasm, coughing up blood, ototoxicity, and							
2015	nephrotoxicity, were observed.							
Wood et al., 2002	No adverse events were reported.							
Klastersky et al.,	In no case was there any suggestion of acoustic or vestibular dysfunction.							
1974								
Rathgeber et al.,	No allergic reactions, increased respiratory pressures or							
1993	bronchoconstrictions were observed.							
Greenfield et al.,	Toxicity was not detected.							
1973								
Claridge et al.,	Not mentioned.							
2007								
Lode et al., 1988	Not mentioned.							
Rouby et al., 1994	Not mentioned.							
Klick et al., 1975	Not mentioned.							

Table S9. Summary of adverse events of all RCTs and non-RCTs in the meta-analysis.

IG: intervention group; CG: control group.

*A serious adverse effect was a serious adverse event related to a trial procedure.