Το δίλημμα με τα εισπνεόμενα αντιβιοτικά: πότε ξεκινώ θεραπεία σε VAT ή VAP;

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Πνευμονολόγος - Εντατικολόγος


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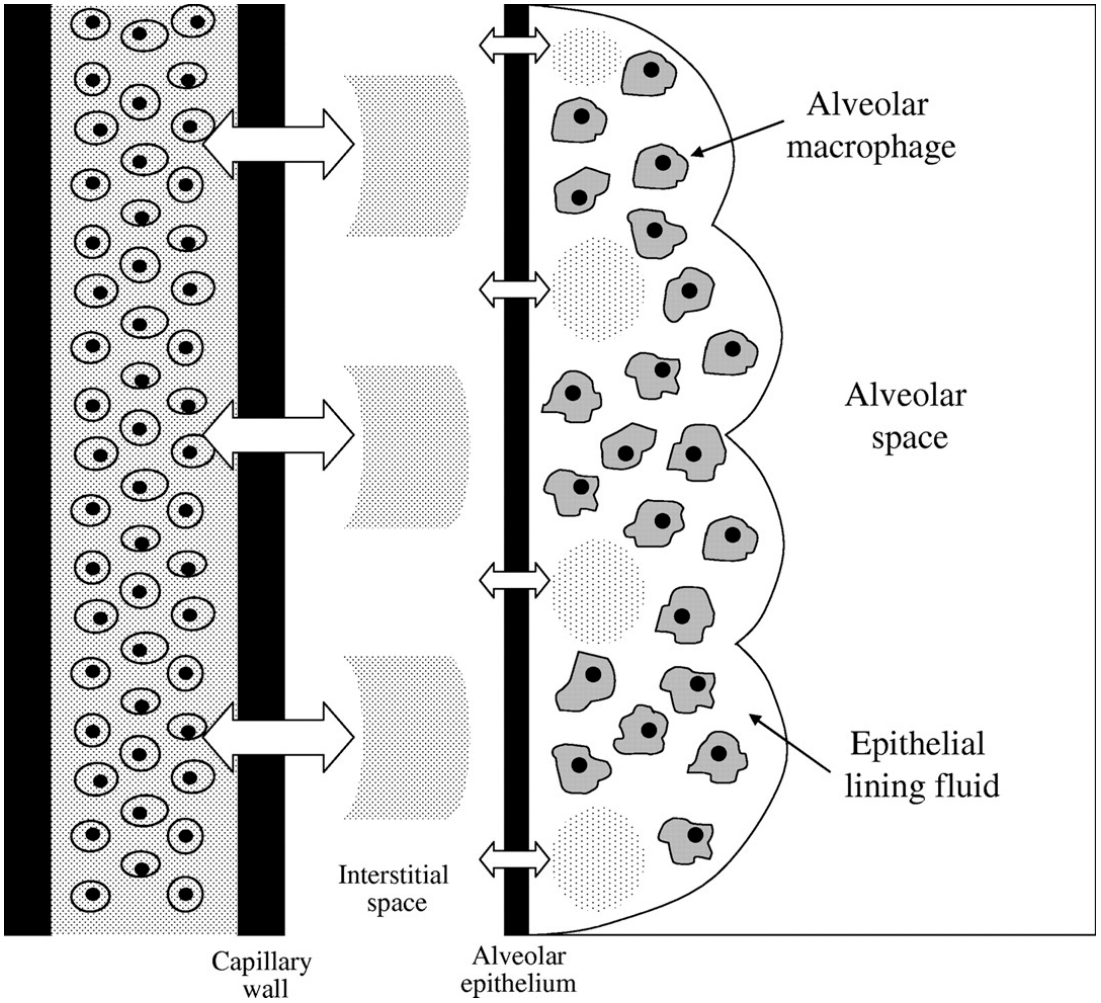
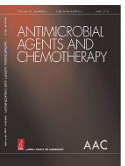
- Άνδρας 67 ετών, με ατομικό αναμνηστικό ΑΥ και Ε (από παλαιά ΚΕΚ) διασωληνώνεται στα ΤΕΠ λόγω status Ε. Μεταφέρεται στην ΜΕΘ.
- Την 3 μέρα νοσηλείας διακόπτεται η καταστολή και επιχειρείται αφύπνιση του ασθενούς. Δεν συνεργάζεται με το PS και ξανακαταστέλεται. Οι εκκρίσεις του γίνονται άθφονες και πυώδεις, η οξυγόνωση και ο αερισμός επηρεάζονται, οι δείκτες φλεγμονής ανεβαίνουν. Η ακτινογραφία επί κλίνης δείχνει ατελεκτασία ΑΚΛ.
- Αναβαθμίζεται εμπειρικά η αντιβιοτική αγωγή σε Μεροπενέμη-Κολιμυκίνη αφού πρώτα σταλούν βιολογικά δείγματα για καλλιέργεια από το κατώτερο αναπνευστικό και το αίμα.

Κλινική περίπτωση

- Την 6η μέρα ο ασθενής εξακολουθεί να παραμένει με διαταραγμένη οξυγόνωση που δεν επιτρέπει διαδικασία απογαλακτισμού, παραμένει εμπύρετος, με άφθονες πυώδεις εκκρίσεις και εμφανίζεται σκίαση στο ΑΡ πνεύμονα.
- Το εργαστήριο ενημερώνει τηλεφωνικά ότι απομονώνεται Acinetobacter Baumanii με ευαισθησία μόνο στην Κολιμυκίνη και Αμικασίνη.
- Είναι η στιγμή να προστεθούν εισπνεόμενα αντιβιοτικά στην αγωγή του;

Οι VAP και VAT αναπτύσσονται στο Epithelial Lining Fluid





Interpretation of Antibiotic Concentration Ratios Measured in Epithelial Lining Fluid. Kiem S et al. Antimicr Agents and Chemoth, Jan 2008; 24-36

Διεισδυτικότητα αντιβιοτικών στο Epithelial Lining Fluid

Table I. Plasma and epithelial lining fluid (ELF) concentrations of oral penicillins and cephalosporins

Antibacterial agent	Dosage regimen	Subjects (n)	Sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Amoxicillin/ clavulanic acid (AMO/CLA)	500 mg AMO + 250 mg CLA × 1 dose	15	1–2	AMO: 6.90 [1.2–9.8][c] CLA: 5.25 [0.7–9.95][c]	AMO: 0.89 [0–3.48][c,d] CLA: 0.96 [0–8.36][c,d]	NR NR	28
Cefuroxime axetil	500 mg × 1 dose	14	0.9–6.8[e]	3.9 ± 0.5	0.7 ± 0.2	0.15	29
	500 mg × 1 dose	4	6	1.1 ± 0.3	<LLQ	NA	30
		4	12	0.06 ± 0.12	<LLQ	NA	
		4	24	<LLQ	<LLQ	NA	
Cefpodoxime proxetil	200 mg × 1 dose[f]	6	3	1.85 ± 0.82	0.22 ± 0.13	0.108 ± 0.044	31
		6	6	1.40 ± 1.25	0.12 ± 0.14	0.0605 ± 0.0479	
Ceftibuten	400 mg × 1 dose	7	1.9 [1.38–2.67][g]	15.2 [2.4–23.2][g]	1.6 [0–2.8][g]	0.13	32
		4	6.5 [4.08–8.08][g]	14.0 [7.8–17.6][g]	1.6 [0.76–2.1][g]	0.12	
		3	13.3 [12.25–15.0][g,h]	4.1 [2.5–5.6][g,h]	1.2 [0.4–2.2][g,h]	0.38	
Cefdinir	300 mg × 1 dose	9	4	2.0 [1.4–8.0][c]	0.29 [0–.4.73][c,i]	0.15 [0–.3.26][c,i]	33
	600 mg × 1 dose	8	4	4.2 [3.05–6.4][c]	0.49 [0–.0.59][c]	0.12 [0–.0.14][c]	
Cefaclor	750 mg bid × 7 doses[j]	6	4	3.08 ± 1.7	2.71 ± 0.87	0.88	34
		6	6	0.68 ± 0.70	2.16 ± 1.70	3.2	
		6	12	0.23 ± 0.1	0.6 ± 0.3	2.6	
Cefditoren	400 mg × 1 dose	8	1.0–2.0[k]	1.78 ± 1.27	0.39 ± 0.21	0.381 ± 0.501	35
		8	2.01–3.0[k]	1.33 ± 0.95	0.34 ± 0.25	0.232 ± 0.181	
		8	3.01–4.0[k]	1.03 ± 0.51	0.30 ± 0.18	0.318 ± 0.192	

Penetration of Anti-Infective Agents into Pulmonary Epithelial Lining Fluid. Rodvold K.A et al. Clin Pharmacokinet 2011; 50: 637-664

Διεισδυτικότητα αντιβιοτικών στο Epithelial Lining Fluid

Table II. Plasma and epithelial lining fluid (ELF) concentrations of parenteral penicillins and cephalosporins

Antibacterial agent	Dosage regimen	Subjects (n)	Sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Piperacillin/ tazobactam (PIP/TAZ)	4 g PIP + 500 mg TAZ IV 0.5 h infusion q8h	10	Steady state[c]	PIP: 24.0 ± 13.8 TAZ: 2.4 ± 1.2	PIP: 13.6 ± 9.4 TAZ: 2.1 ± 1.1	PIP: 0.568 ± 0.336 TAZ: 0.913 ± 0.277	36
Cefpirome	1 g IV 0.5 h infusion × 1 dose	37	0.5–7[d]	34.5 ± 3.3[e]	7.2 ± 1.1[e,f]	0.359 ± 0.074[e,f]	37
Ceftazidime	1 g IM × 1 dose	5	1	39.89 ± 10.42	2.71 ± 0.88	NR	38
		5	2	36.04 ± 9.21	2.66 ± 0.64	NR	
		5	4	13.34 ± 4.12	1.32 ± 0.64	NR	
		5	8	6.08 ± 1.71	0.66 ± 0.36	NR	
		5	12	1.07 ± 0.45	0.12 ± 0.15	NR	
	2 g 0.5 h IV infusion × 1 dose then continuous IV infusion of 4 g/d	15	8, 12, 18[g]	39.6 ± 15.2	8.2 ± 4.8	0.206 ± 0.089	39
Cefepime	2 g IV 0.5 h infusion × 1 dose then continuous IV infusion of 4 g/d	7	8[g]	13.5 ± 3.2[h]	13.7 ± 3.0	1.01	40
		7	12[g]	13.7 ± 3.5[h]	13.5 ± 3.3	0.99	
		6	18[g]	13.3 ± 3.6[h]	14.9 ± 2.3	1.12	
Ceftobiprole	500 mg IV 2 h infusion q8h × 4 doses	6	2.5	17.68 ± 4.48	2.55 ± 0.99	0.255 ± 0.366[i]	41
		6	4	12.77 ± 2.26	2.00 ± 1.07		
		6	6	6.91 ± 4.58	4.58 ± 5.82		
		6	8	3.65 ± 1.05	1.51 ± 0.39		

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Διεισδυτικότητα αντιβιοτικών στο Epithelial Lining Fluid

Table III. Plasma and epithelial lining fluid (ELF) concentrations of carbapenems

Antibacterial agent	Dosage regimen	Subjects (n)	Sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Meropenem	1 g IV 0.5 h infusion × 1 dose	30[c]	0.5	25.96 ± 22.16	5.04 ± 3.33	0.19 ± 0.11	45
			1	14.98 ± 5.30	7.07 ± 2.87	0.51 ± 0.24	
			2	12.01 ± 3.48	3.86 ± 2.74	0.33 ± 0.20	
			4	2.51 ± 0.68	2.20 ± 2.29	1.04 ± 1.20	
			6	0.57 ± 0.27	0.59 ± 1.09	0.82 ± 1.18	
			8	0.29 ± 0.24	NR	NA	
	500 mg IV 0.5 h infusion q8h × 4 doses	4	1	10.9 ± 1.3	5.3 ± 2.5	0.49–0.80[d]	46
		4	2	5.2 ± 1.6	2.7 ± 1.8		
		4	3	2.4 ± 0.9	1.9 ± 0.9		
		4	5	0.3 ± 0.4	0.7 ± 0.4		
		4	8	0.0 ± 0.0	0.2 ± 0.1		
	1 g IV 0.5 h infusion q8h × 4 doses	4	1	19.0 ± 7.6	7.7 ± 3.1	0.32–0.53[d]	
		4	2	7.5 ± 1.3	4.0 ± 1.1		
		4	3	5.3 ± 1.5	1.7 ± 1.4		
		4	5	2.0 ± 1.3	0.8 ± 0.4		
		4	8	0.0 ± 0.0	0.03 ± 0.05		
	2 g IV 0.5 h infusion q8h × 4 doses	4	1	60.9 ± 8.0	2.9 ± 1.0	0.048	
		4	3	12.8 ± 2.7	2.8 ± 1.5	0.219	
Ertapenem	1 g IV 0.5 h infusion × 1 dose	15[e]	1	63.1 ± 16.9	4.06 ± 6.64	0.0619 ± 0.1100	47
			3	39.7 ± 15.2	2.59 ± 2.33	0.0685 ± 0.0645	
			5	27.2 ± 15.5	2.11 ± 1.80	0.0940 ± 0.1070	
	1 g IV 1 h infusion q24h	15[f]	1[g]	30.3 [27.1–37.8][h,j]	9.4 [8.0–10.7][j]	0.32 [0.28–0.46][k]	48
			12[g]	4.8 [3.9–6.4][h,j]	2.0 [1.1–2.5][j]		
			24[g]	0.8 [0.5–1.2][h,j]	0.3 [0.2–0.4][j]		
Biapenem	300 mg IV 0.5 h infusion × 1 dose	6[i]	0.5	18.1 ± 2.8	3.48 ± 1.20	0.20 ± 0.08	22
	300 mg IV 3 h infusion × 1 dose		3	6.8 ± 1.2	1.33 ± 0.26	0.20 ± 0.06	

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Διεισδυτικότητα αντιβιοτικών στο Epithelial Lining Fluid

Table X. Plasma and epithelial lining fluid (ELF) concentrations of aminoglycosides

Antibacterial agent	Dosage regimen	Subjects (n)	Sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Gentamicin	240 mg IV 30 min infusion × 1 dose	6	1	8.79 ± 0.64[c]	2.95 ± 0.37[c]	0.30 ± 0.05[c]	119
		6	2	6.37 ± 0.50[c]	4.24 ± 0.42[c]	0.85 ± 0.10[c]	
		6	4	4.70 ± 0.49[c]	3.10 ± 0.39[c]	1.14 ± 0.26[c]	
		6	6	4.70 ± 0.57[c]	2.65 ± 0.35[c]	0.74 ± 0.18[c]	
Tobramycin	150 mg IM × 1 or more doses	5	6	4.1 ± 1.5	5.3 ± 2.9	1.4 ± 0.8	120
	300 mg IM × 1 or more doses	5	6	4.3 ± 2.4	5.5 ± 2.1	1.6 ± 0.6	120
	IV doses adjusted to achieve serum C_{max} ~8 μg/mL and C_{min} <2 μg/mL while maintaining q8h dosing interval[d]	4	0.5[e]	6.90 ± 1.44	2.33 ± 0.50	0.30 ± 0.03	121
		4	2[e]	4.08 ± 1.30	1.67 ± 0.60	0.42 ± 0.16	
		4	4[e]	2.14 ± 0.85	1.62 ± 1.19	0.64 ± 0.37	
		4	8[e]	0.79 ± 0.38	0.77 ± 0.38	1.53 ± 0.76	
	7–10 mg/kg IV 30 min infusion q24h[e]	12	1	22.4 ± 5.9	2.7 ± 0.7	0.119 ± 0.019	122
	300 mg inhalation × 1 dose	12	NA	NA	90 ± 54	NA	123
Netilmicin	450 mg IV 30 min infusion × 1 dose	5	1	21.4 ± 1.19[c]	7.5 ± 1.0[c]	NR	124
		5	1.5	15.3 ± 0.85[c]	9.6 ± 0.3[c]	NR	
		5	2	12.0 ± 0.71[c]	14.7 ± 2.2[c]	NR	
		5	3	8.3 ± 0.64[c]	9.3 ± 0.6[c]	NR	

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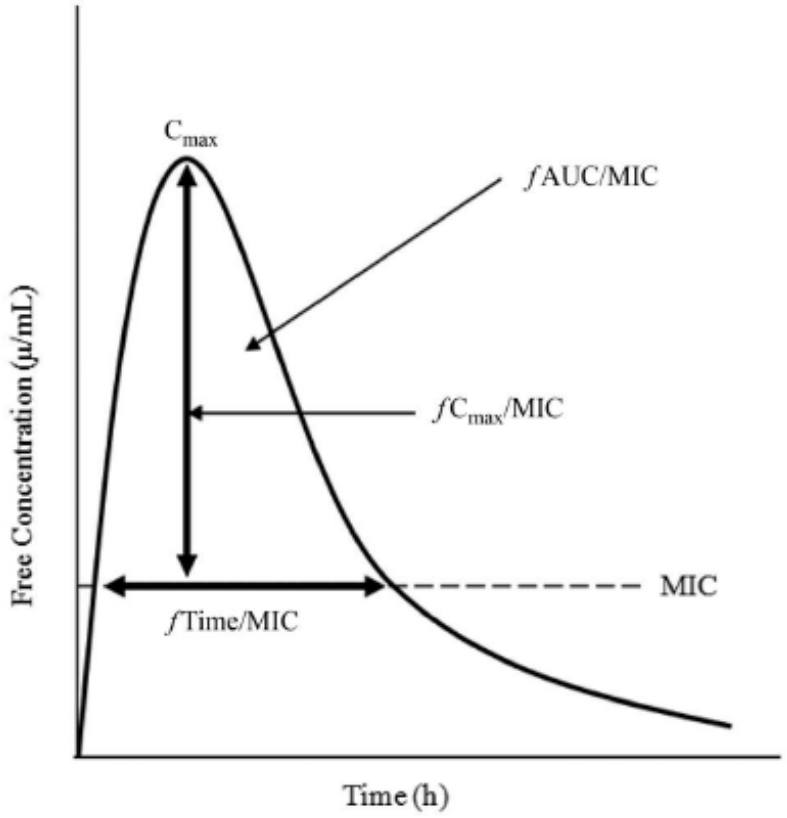
Διεισδυτικότητα αντιβιοτικών στο Epithelial Lining Fluid

Table XII. Plasma and epithelial lining fluid (ELF) concentrations of linezolid, tigecycline and iclaprim

Antibacterial agent	Dosage regimen	Subjects (n)	Sampling time (h)*	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Linezolid	600 mg PO bid × 5 doses	5	4	15.5 ± 4.9	64.3 ± 33.1	4.2 ± 1.4	135
		5	8	8.9 ± 3.2	31.4 ± 33.0	3.1 ± 2.2	
		5	12	10.2 ± 2.3	24.3 ± 13.3	2.4 ± 1.2	
		5	24	1.8 ± 0.6	7.6 ± 6.0	3.9 ± 2.3	
		5	48	0.2 ± 0.2	0.7 ± 0.8	2.3 ± 1.6	
	600 mg PO bid × 6 doses	10	5.10 ± 2.01[b]	13.40 ± 3.92	25.09 ± 14.59	8.35 ± 11.69	136
	600 mg IV 1 h infusion × 2 d	16	2[c]	17.7 ± 4.0	14.4 ± 5.6	1.05 ± 0.34	137
		16	12[c]	2.4 ± 1.2	2.6 ± 1.7	1.04 ± 0.28	
Tigecycline	100 mg IV 30 min infusion × 1 dose, then 50 mg IV 30 min infusion q12h × 7 doses	5	2[c]	0.19 ± 0.06	0.19 ± 0.15	NR	138
		5	3[c]	0.15 ± 0.05	0.12 ± 0.21	NR	
		5	4[c]	0.16 ± 0.07	0.06 ± 0.13	NR	
		5	6[c]	0.12 ± 0.06	0.37 ± 0.36	NR	
		5	12[c]	0.10 ± 0.09	0.10 ± 0.17	NR	
		5	24[c]	0.05 ± 0.01	0.00 ± 0.00	NR	
Iclaprim	1.6 mg/kg IV 1 h infusion × 1 dose	8	1.97 ± 0.08[b,c]	0.59 ± 0.18	12.61 ± 7.33	21.29 ± 11.18	139
		8	3.57 ± 0.30[b,c]	0.24 ± 0.05	6.38 ± 5.17	24.93 ± 16.53	
		8	6.50 ± 0.29[b,c]	0.14 ± 0.05	2.66 ± 2.08	20.57 ± 17.31	

Penetration of Anti-Infective Agents into Pulmonary Epithelial Lining Fluid. Rodvold K.A et al. Clin Pharmacokinet 2011; 50: 637-664

Δοσοεξαρτώμενα και χρονοεξατώμενα αντιβιοτικά



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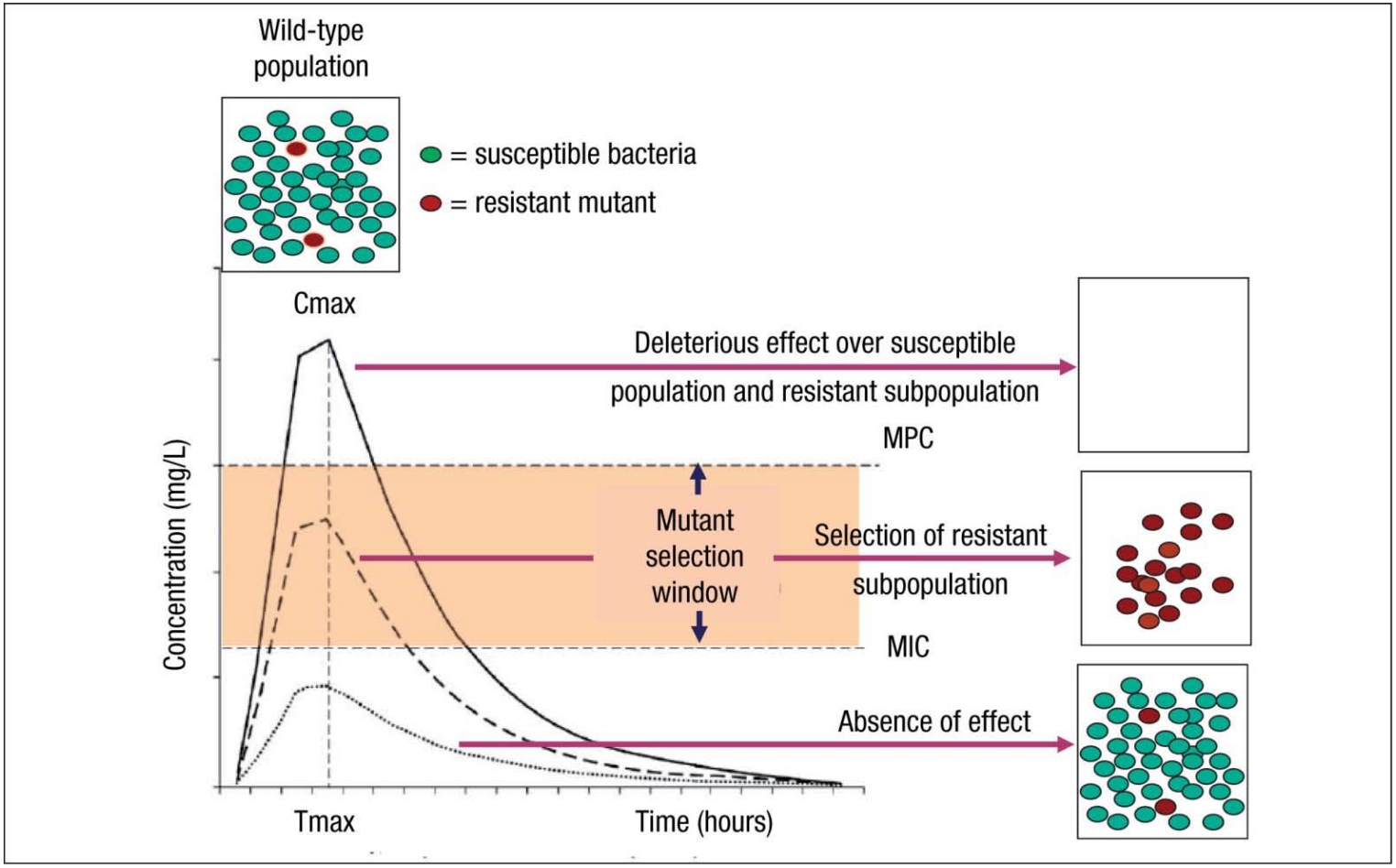
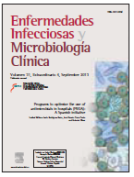




Inappropriate use of antibiotics in hospitals: the complex relationship between antibiotic use and antimicrobial resistance. Cantón R, et al. Enferm Infecc Microbiol Clin. 2013 Sep;31 Suppl 4:3-11

AUC ενδοφλέβια χορηγούμενων αντιβιωτικών στο ELF

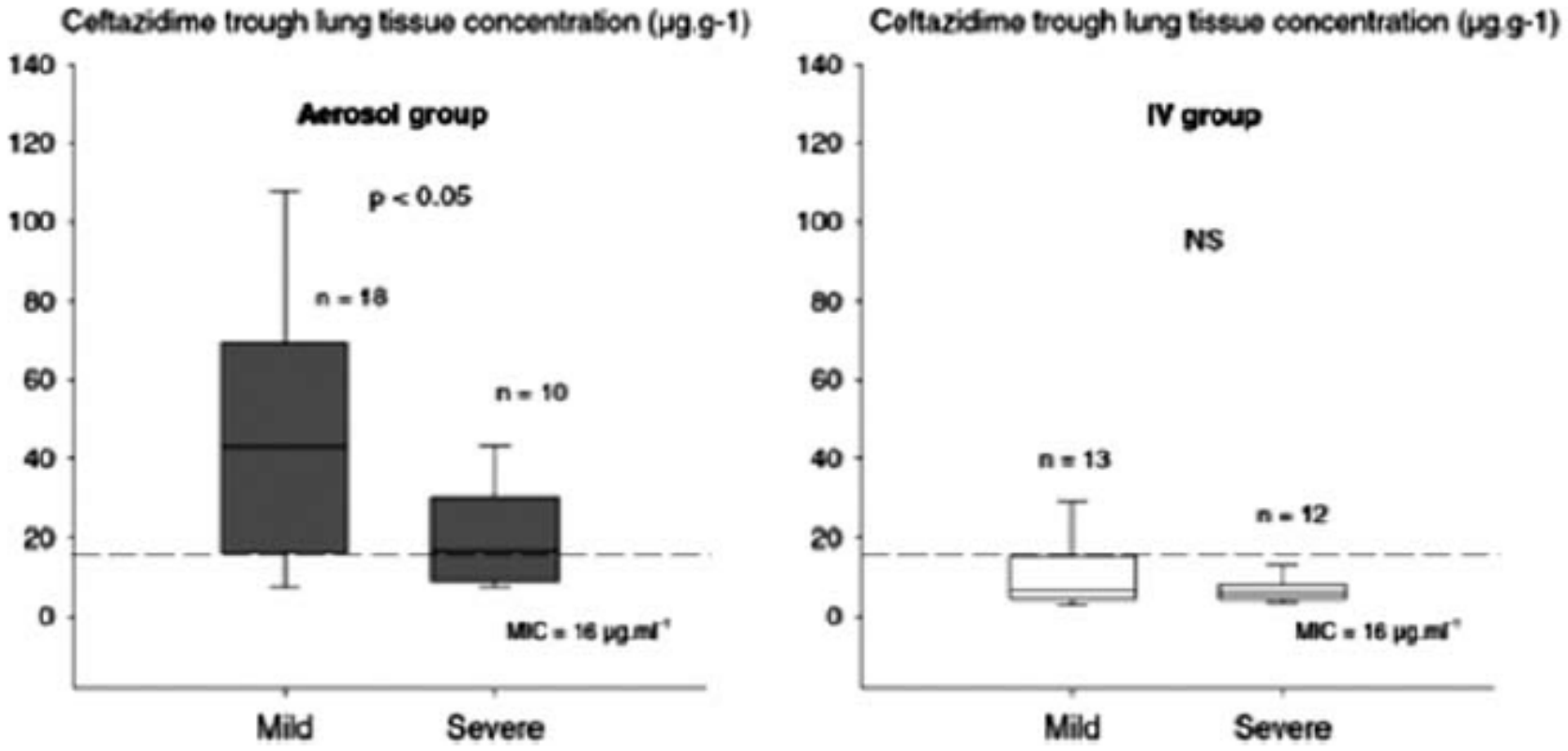
TABLE 3. Ratios of antibiotic concentrations (or AUCs) in ELF or cells compared to serum (or unbound free serum) levels[a]

Antibiotic	C_{ef}/C_s	C_{unf}/C_s	C_{ef}/C_{fs}	C_{unf}/C_{fs}	AUC_{ef}/AUC_s	AUC_{unf}/AUC_s	AUC_{ef}/AUC_{fs}	AUC_{unf}/AUC_{fs}	Reference(s)
Beta-lactams									
Amoxicillin	0.13	0.00	0.16	0.00					34
Cefdinir	0.12	0.00	0.35	0.00					32
Cefdinir	0.15	0.00	0.44	0.00					32
Meropenem					0.28	0.25	0.28	0.26	22
Meropenem					0.43	0.15	0.44	0.15	22
Macrolides									
Azithromycin	6.30–31.33	738.00–6,841.33	8.18–62.67	932.47–13,682.67	13.31	2,284.69	20.83	3,574.83	15
Azithromycin	12.63–24.40	533.75–1,010.00	19.73–48.80	833.98–2,020.00	21.29	748.46	34.95	1,228.54	88
Azithromycin	2.53–57.78	415.73–9,806.45	3.28–115.56	539.91–19,612.90	24.10	3,234.81	34.01	4,564.69	77
Azithromycin	4.60–20.43	1,756.49–5,242.86	5.60–26.53	2,142.06–6,808.91	5.59	1,828.54	8.87	3,320.07	87
Clarithromycin	5.17	94.12	25.83	470.58					53, 86
Clarithromycin	12.38–20.00	141.94–432.17	61.89–100.00	709.68–2,160.87	15.42	191.18	77.11	955.88	86, 88
Clarithromycin	13.32–60.75	98.73–721.40	66.59–303.75	493.65–3,607.00	30.27	248.47	151.36	1,242.34	21, 86
Clarithromycin	10.34–25.29	444.94–2,131.58	51.70–126.43	2224.68–10657.89	15.33	626.31	76.65	3,131.54	80, 86
Clarithromycin	39.60	181.00	198.00	905.00					19, 86
Clarithromycin	4.13–38.97	169.33–657.69	20.65–194.87	846.67–3,288.46	8.34	217.55	41.71	1,087.73	44
Telithromycin	4.83–14.91	42.98–418.18	16.08–49.70	143.27–1,393.94	6.44	124.92	21.48	416.42	72
Telithromycin	5.38–6.65	36.39–154.60	17.94–22.16	121.29–515.33					57
Telithromycin	8.01–14.22	37.27–2,019.63	26.68–47.39	124.23–6,732.08	9.23	338.47	30.76	1128.24	60
Telithromycin	2.27–6.27	48.94–240.27	7.57–20.91	163.15–800.91	3.15	84.18	10.49	280.62	78
Cethromycin	7.50–20.00	67.50–317.50	75.00–200.00	675.00–3,175.00	12.64	178.27	126.39	1782.71	27
Cethromycin	7.11–10.00	90.40–670.00	71.05–100.00	904.00–6,700.00	7.87	207.43	78.74	2,074.34	27
Fluoroquinolones									
Ciprofloxacin	0.00–0.89	12.36–28.75	0.00–1.27	17.66–41.07	0.82	15.62	1.174	22.31	45
Ciprofloxacin	0.90	2.32	1.29	3.31					91
Ciprofloxacin	1.85	7.7	2.64	11.00					97
Ciprofloxacin	2.13	11.84	3.04	16.91					9
Clinafloxacin	1.77	10.20	1.86	10.73					51
Garenoxacin	0.92–1.65	10.58–18.27	3.67–6.59	42.33–73.09	1.34	13.89	5.38	55.57	3
Gatifloxacin	1.51–1.75	17.51–36.67	1.89–2.19	21.89–45.84	1.77	24.94	2.21	31.17	52
Grepafloxacin	10.49–14.88	99.96–268.65	15.35–29.76	199.92–537.30	12.03	175.75	24.05	351.50	33
Levofloxacin	1.49–3.00	5.38–6.14	2.29–4.61	8.27–9.45	2.08	5.90	3.20	9.07	15
Levofloxacin	1.17–2.10	11.95–23.00	1.80–3.24	18.39–35.38	1.94	15.71	2.99	24.16	45
Levofloxacin	0.86–2.26	8.77–8.94	1.32–3.48	13.50–13.75	1.90	8.83	2.92	13.59	45
Levofloxacin	0.80–3.00	4.00–9.60	1.23–4.62	6.15–14.77	2.15	7.23	3.30	11.13	5
Levofloxacin	1.53–2.58	11.23–17.70	2.36–3.97	17.27–27.23	1.75	12.82	2.69	19.72	87
Levofloxacin	1.72–2.06	12.47–22.22	2.64–3.17	19.19–34.18	1.59	14.44	2.45	22.22	87
Levofloxacin					2.69	4.90	4.14	7.54	28
Lomefloxacin	1.86	20.47	2.07	22.74					9
Moxifloxacin	5.18–7.00	17.61–70.39	9.58–12.96	32.61–130.36	5.18	13.59	9.59	25.16	93
Moxifloxacin	3.61–7.32	14.76–55.77	6.54–13.56	27.33–103.28	4.92	27.33	9.11	50.61	15
Pefloxacin	13.10–13.44	13.78–18.69	17.46–17.91	18.37–24.92					79
Rufloxacin	5.08–11.67	9.97–27.17	12.71–29.17	24.93–67.92	7.66	21.55	19.14	53.88	99
Sparfloxacin	8.17–17.00	42.63–126.33	13.61–28.33	71.04–210.56	12.60	61.24	21.00	102.07	100
Sparfloxacin	12.50	44.75	20.83	74.58					100
Sparfloxacin	19.27–65.71	29.18–71.63	32.12–109.52	48.64–119.39	31.93	40.71	53.22	67.85	91
Temafloxacin	3.13	5.7	4.22	7.70					97
Temafloxacin	3.06	8.81	4.14	11.91					8
Trovafloxacin	2.16–5.53	13.32–22.55	16.62–42.54	102.46–173.46	3.65	17.55	28.09	135.01	4
Trovafloxacin	5.85	24.10	45.00	185.38					4
Others									
Pyrazinamide	13.60–24.76	0.49–1.09	27.20–49.51	0.98–2.17					20
Ethionamide	6.57–10.33	0.33–0.71	9.39–14.76	0.48–1.02					30
Linezolid	2.38–4.22	0.11–0.17	3.45–6.12	0.16–0.24	3.29	0.15	4.77	0.22	26
Linezolid	8.35	0.71	12.10	1.03					54
Itraconazole	0.14–0.56	2.33–5.44	14.29–55.56	233.33–544.44	0.22	2.94	21.51	293.60	25
Tigecycline					1.32	77.46	5.27	309.83	23
Rifampin	0.17–0.31	0.71–1.50	0.83–1.56	3.54–7.50					18
Rifampin	0.34	16.26	1.70	81.30					103
Ethambutol	0.92–1.13	19.17–48.24	1.22–1.51	25.56–64.31					26
Isoniazid fast acetylator	1.74–5.88	1.48–13.42	1.74–5.88	1.48–13.42					29
Isoniazid slow acetylator	1.37–5.69	0.74–4.40	1.37–5.69	0.74–4.40					29
Rifapentine	0.14–0.24	0.18–0.38	6.14–10.60	7.67–16.35	0.21	0.26	9.28	11.12	31

[a] C_s, serum concentration; C_{fs}, free serum concentration; AUC_s, area under the concentration-time curve in serum.

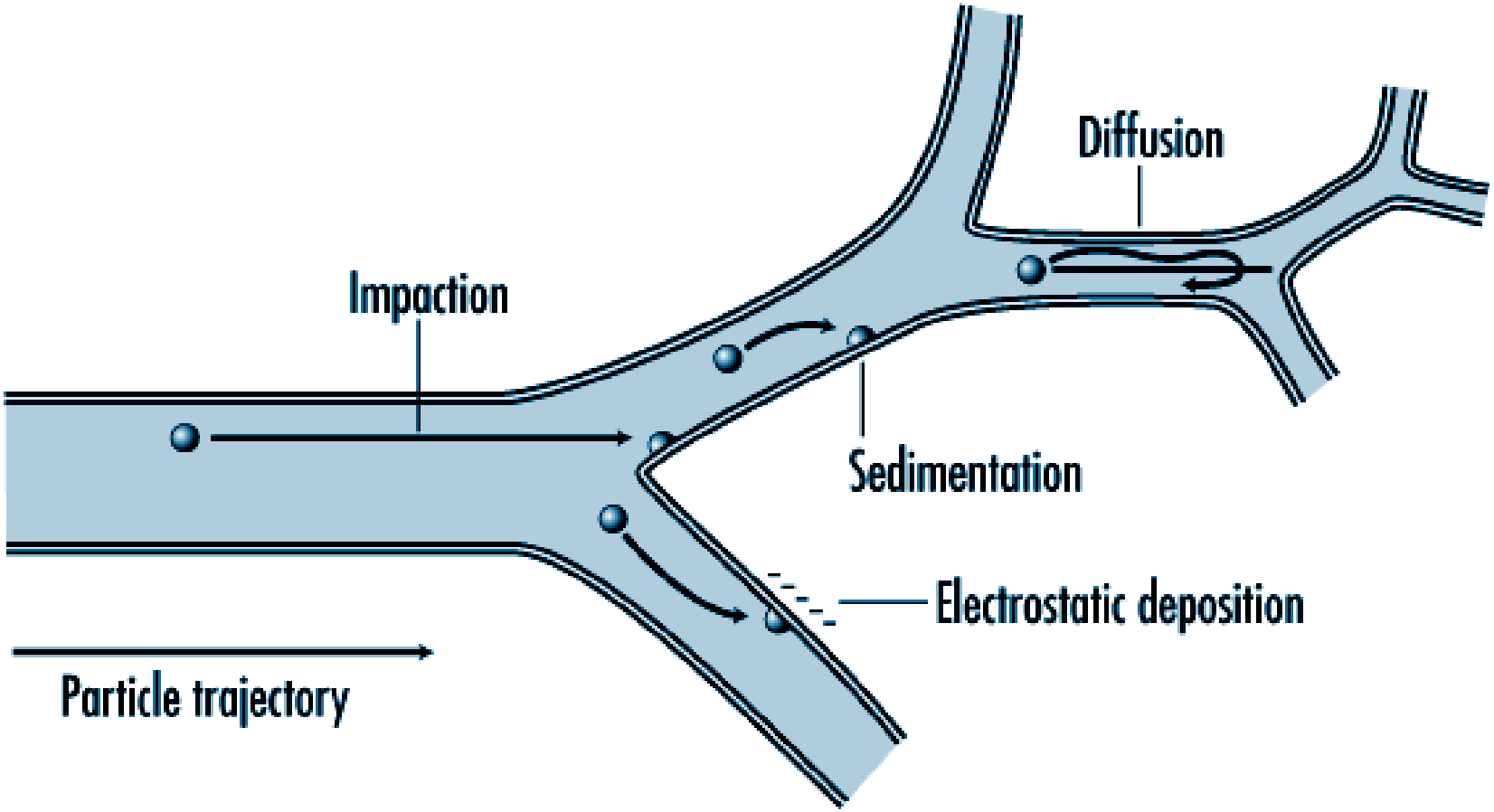
Interpretation of Antibiotic Concentration Ratios Measured in Epithelial Lining Fluid. Kiem S et al. Antimicr Agents and Chemoth, Jan 2008; 24-36

Συγκέντρωση στον πνεύμονα εισπεόμενης vs. ενδοφλέβιας χορηγούμενης Κεφταζιδίμης σε μοντέλο χοίρου

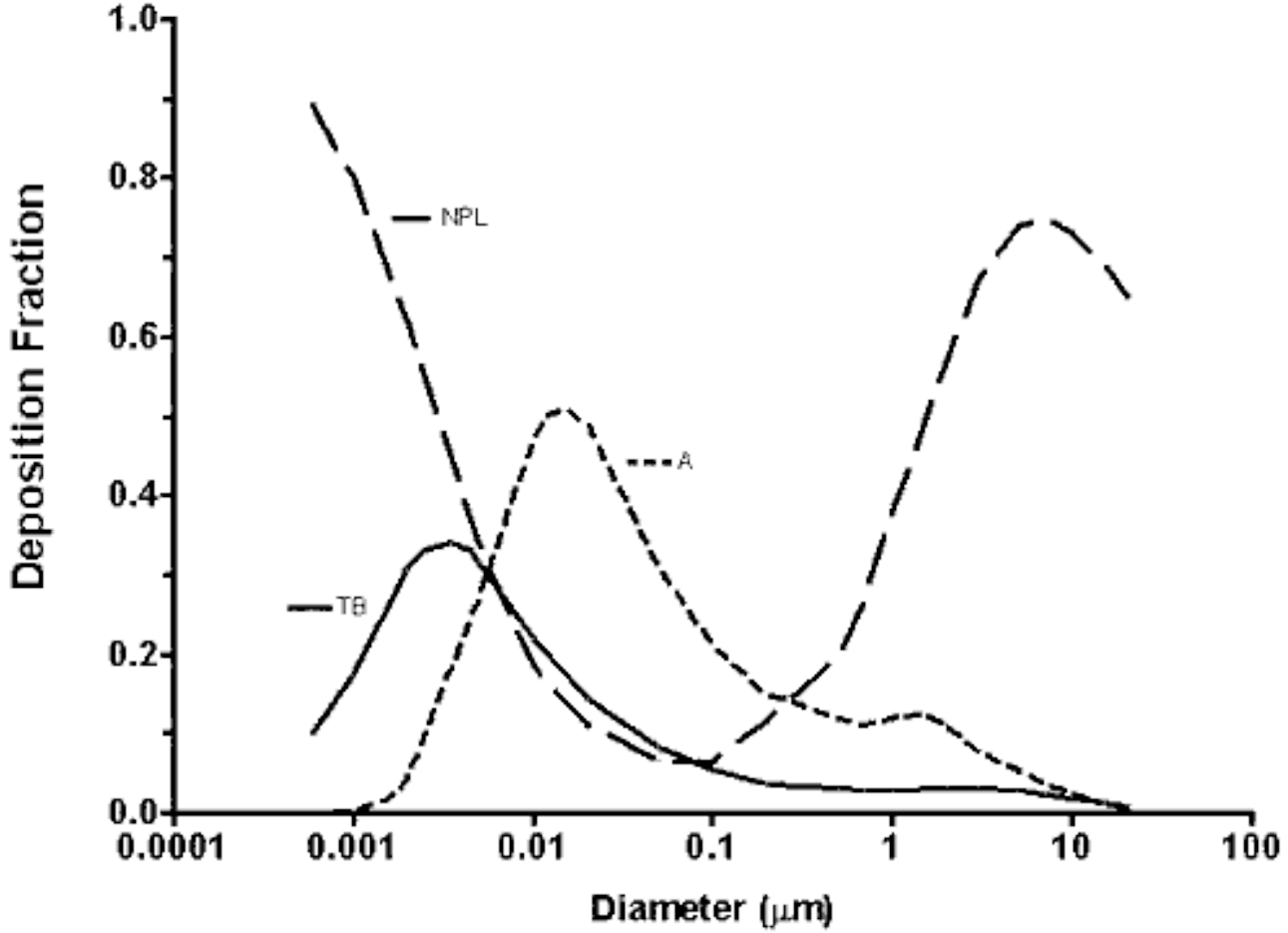


Rouby JJ, et al. Aerosolized antibiotics for Ventilator-associated Pneumonia. Anesthesiology 2012

Τρόποι εναπόθεσης σωματιδίων στους πνεύμονες

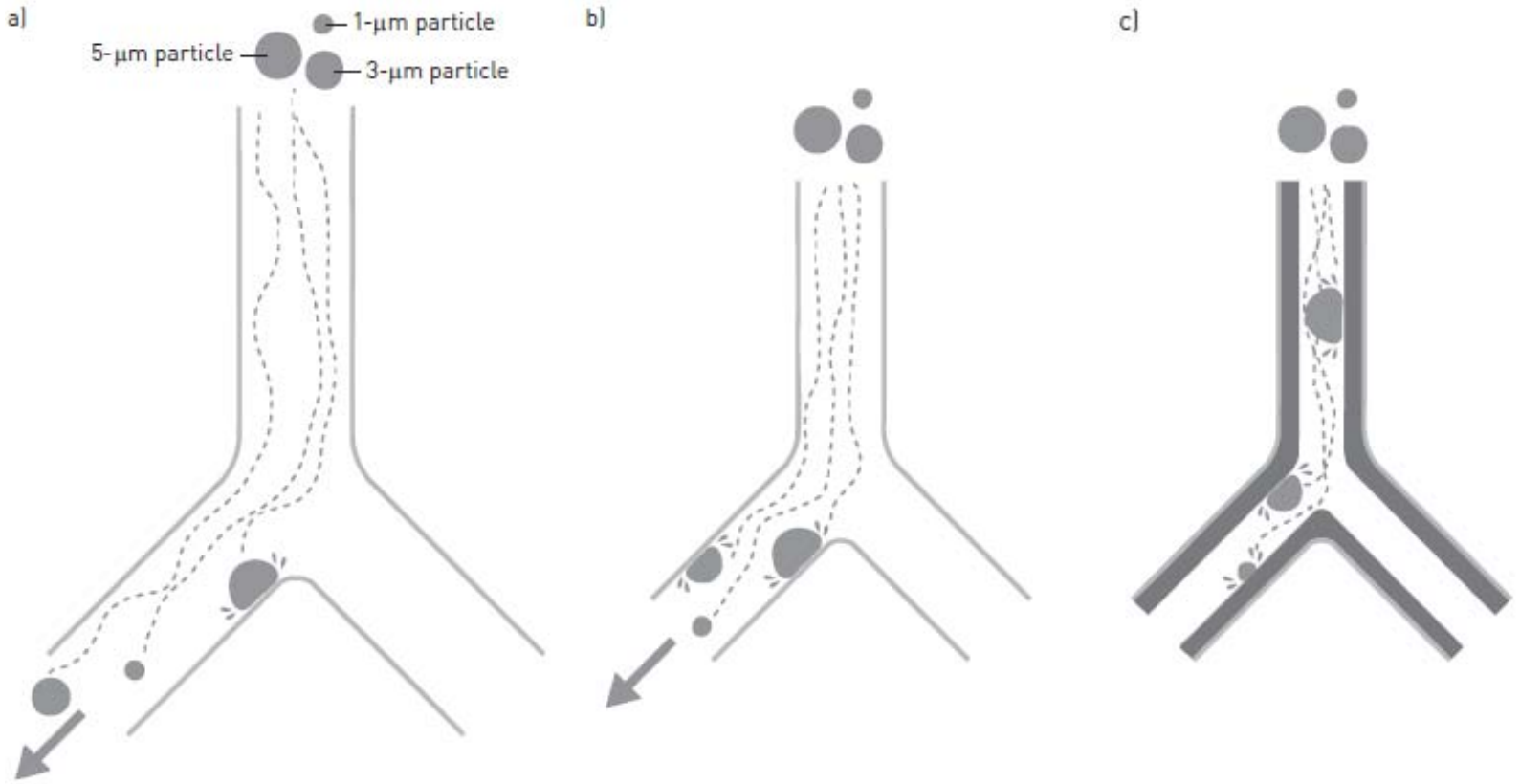


Το σημείο εναπόθεσης σχετίζεται με την διάμετρο των σωματιδίων



A = Alveolar; TB=Tracheobronchial; NPL= Nasal, Pharyngeal, Laryngeal

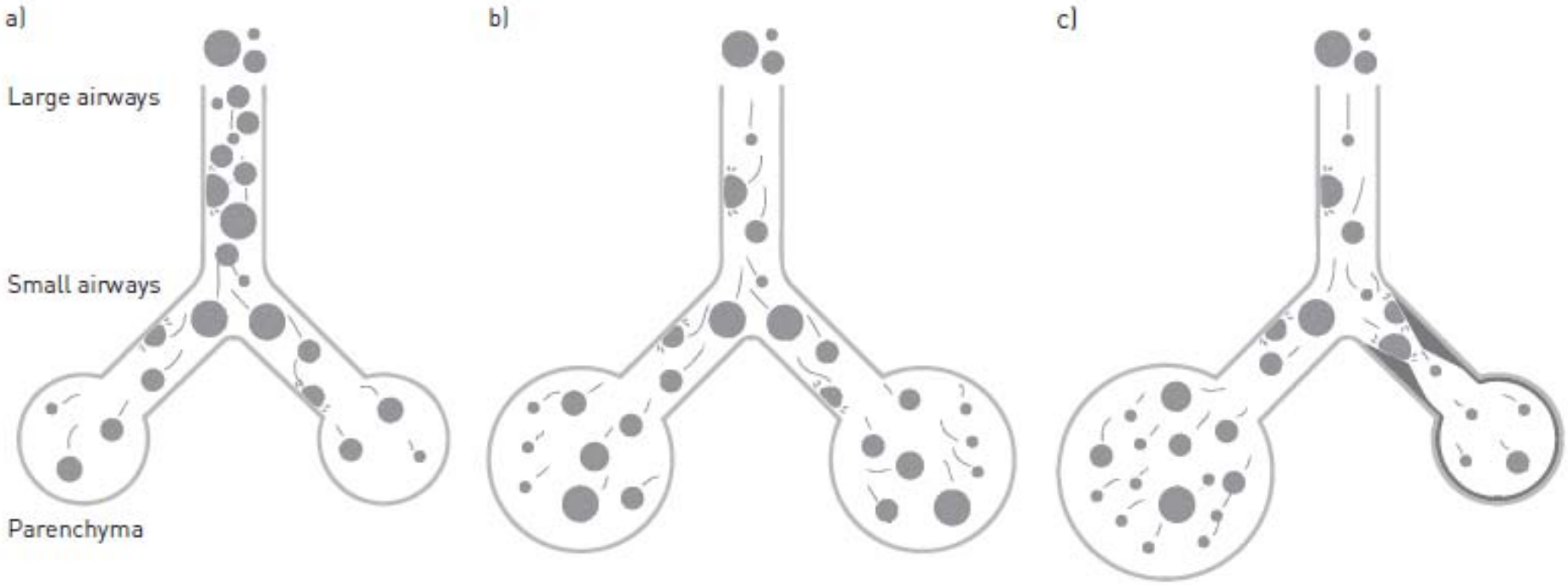
Η βαρύτητα της νόσου επηρεάζει το σημείο εναπόθεσης των σωματιδίων



EUROPEAN RESPIRATORY journal

Tiddens HAWM, et al. Inhaled antibiotics: Dry or wet? Eur Respir J 2014

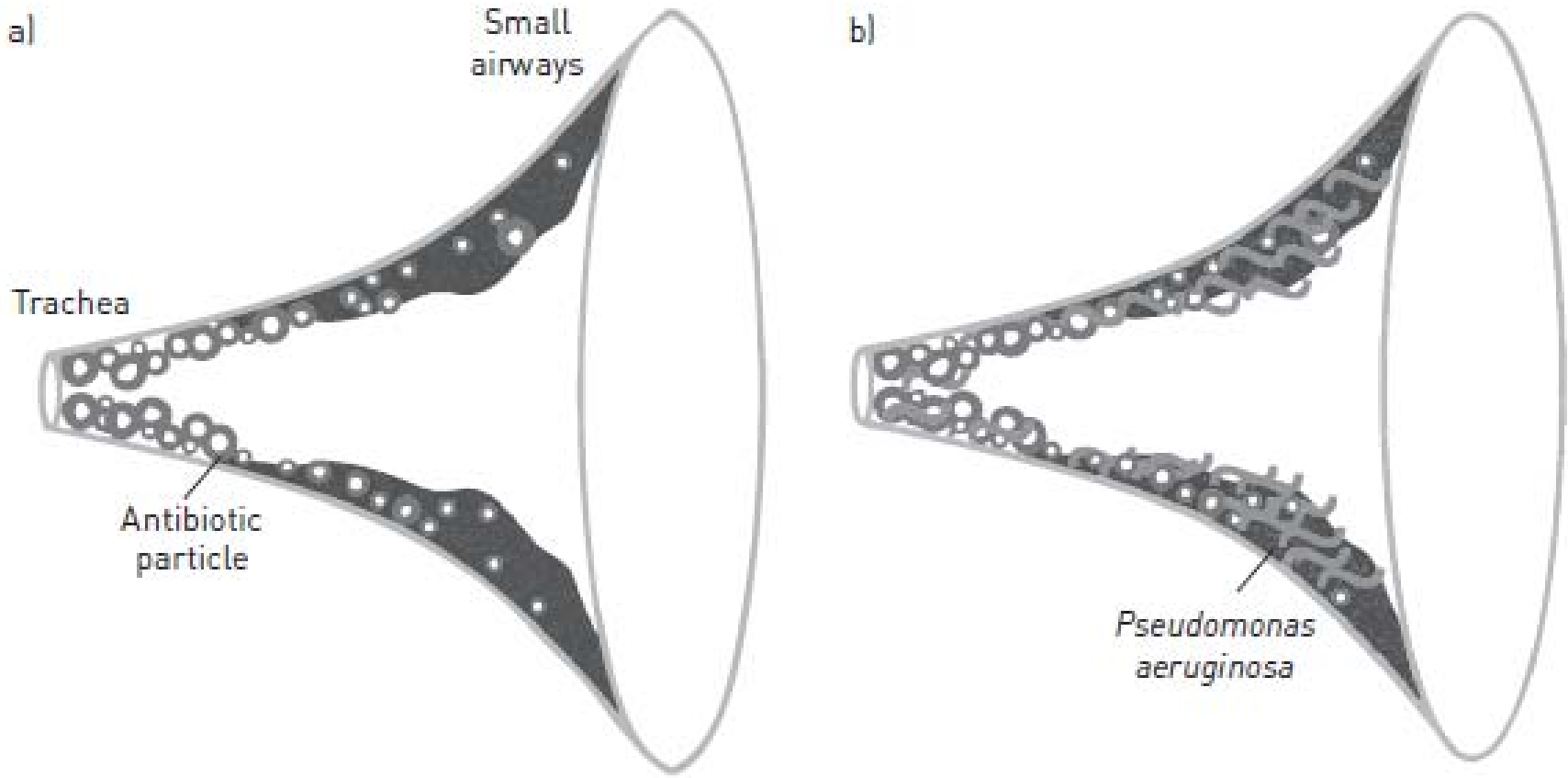
Η βαρύτητα της νόσου επηρεάζει το σημείο εναπόθεσης των σωματιδίων



EUROPEAN RESPIRATORY journal

Tiddens HAWM, et al. Inhaled antibiotics: Dry or wet? Eur Respir J 2014

Το μεγαλύτερο ποσοστό των σωματιδιων καταλήγει στους μεγάλους αεραγωγούς



EUROPEAN RESPIRATORY journal

Tiddens HAWM, et al. Inhaled antibiotics: Dry or wet? Eur Respir J 2014

American Thoracic Society Documents

Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA WAS APPROVED BY THE ATS BOARD OF DIRECTORS, DECEMBER 2004 AND THE IDSA GUIDELINE COMMITTEE, OCTOBER 2004

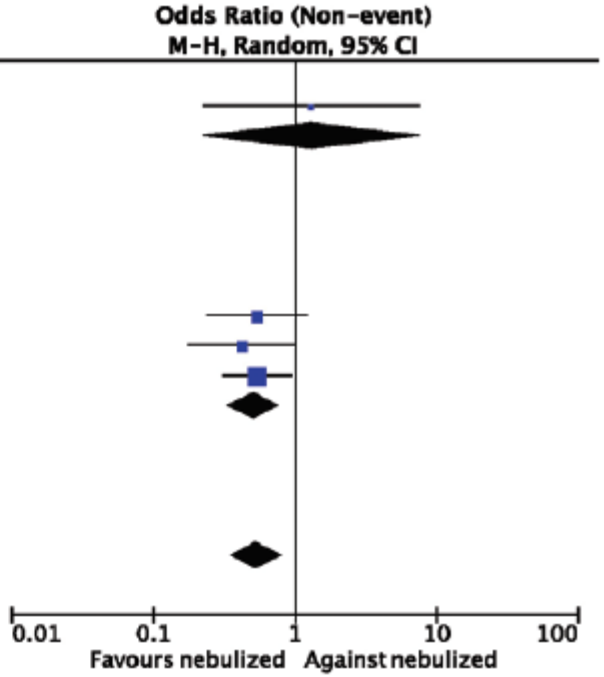
The committee believed that further investigation into the use of aerosolized antibiotics is warranted.

Study and Year	Country	Characteristics	No. of Patients	Infection	Device	Administration Strategy
Randomized controlled trials						
Palmer *et al.* 2008[34]	USA	Phase III study, double-blinded, placebo-controlled, single center	43	VAT, mixed susceptibility	Jet nebulizer	
Palmer and Smaldone 2014[35]	USA	Phase III study, double-blinded, placebo-controlled, single center	47	VAT, mixed susceptibility	Jet nebulizer	
Niederman *et al.* 2012[36]	USA, France, Spain	Phase II study, double-blinded, placebo-controlled, parallel group, multicentric	67	VAP, resistant pathogens	Vibrating-mesh nebulizer (PDDS Clinical®, Nektar Therapeutics, USA)	Adjunctive strategy
Lu *et al.* 2011[26]	France	Phase II study, single center	46	VAP, susceptible pathogens	Vibrating-mesh nebulizer	Substitution strategy
Hallal *et al.* 2007[41]	USA	Phase III study, double-blinded, pilot study, single center	10	VAP†	Jet nebulizer	Substitution strategy*
Rattanaumpawan *et al.* 2010[42]	Thailand	Phase III study, open label, single center	102	VAP†	Jet and ultrasonic nebulizers	Adjunctive strategy*
Observational trials						
Ghannam *et al.* 2009[40]	USA	Matched case–control study, retrospective, single center	32	VAP, resistant pathogens	Jet nebulizer	Substitution strategy
Kofteridis *et al.* 2010[37]	Greece	Matched case–control study (ratio 1:1), retrospective, single center	86	VAP, resistant pathogens	Vibrating-mesh nebulizer (information obtained after contacting the author)	Adjunctive strategy
Doshi *et al.* 2013[38]	USA	Cohort analysis, retrospective, multicentric	95	VAP, resistant pathogens	Jet nebulizer (in two centers), vibrating-mesh nebulizer (in one center)	Adjunctive strategy
Tumbarello *et al.* 2013[39]	Italy	Matched case–control study (ratio 1:1), retrospective, single center	208	VAP, resistant pathogens	Jet and ultrasonic nebulizers indistinctively	Adjunctive strategy
Arnold *et al.* 2012[43]	USA	Cohort study, retrospective, single center	90	VAP†	Not defined but they specified using a nebulizer generating optimal droplet sizes (1–5 μm)	Adjunctive strategy*

Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults: A Systematic Review and Meta-analysis. Solé-Lleonart C, et al. Anesthesiology. 2017 May;126(5):890-908

Κλινική βελτίωση σε MDR - VAT

Study or Subgroup	Nebulized therapy Events	Total	Intravenous therapy Events	Total	Weight	Odds Ratio (Non-event) M-H, Random, 95% CI
1.1.2 RCT						
Niederman 2012	27	32	14	16	5.2%	1.30 [0.22, 7.55]
Subtotal (95% CI)		**32**		**16**	**5.2%**	**1.30 [0.22, 7.55]**
Total events	27		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
1.1.3 Observational Studies						
Doshi 2013	24	44	20	51	24.0%	0.54 [0.24, 1.22]
Kofteridis 2010	23	43	14	43	21.0%	0.42 [0.17, 1.01]
Tumbarello 2013	72	104	57	104	49.8%	0.54 [0.31, 0.95]
Subtotal (95% CI)		**191**		**198**	**94.8%**	**0.51 [0.34, 0.77]**
Total events	119		91			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.24$, df = 2 (P = 0.89); $I^2 = 0\%$						
Test for overall effect: Z = 3.21 (P = 0.001)						
Total (95% CI)		**223**		**214**	**100.0%**	**0.53 [0.36, 0.80]**
Total events	146		105			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.26$, df = 3 (P = 0.74); $I^2 = 0\%$						
Test for overall effect: Z = 3.06 (P = 0.002)						
Test for subgroup differences: $Chi^2 = 1.02$, df = 1 (P = 0.31), $I^2 = 2.2\%$						

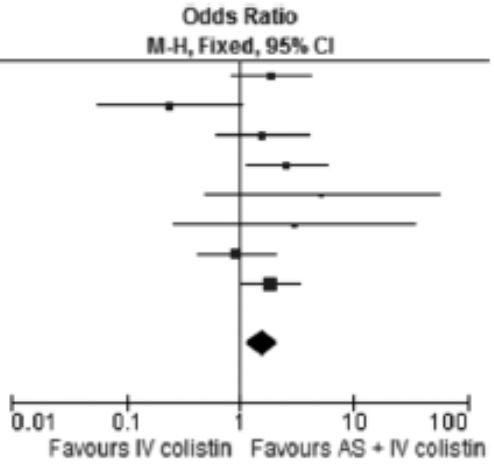


Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults: A Systematic Review and Meta-analysis. Solé-Lleonart C, et al. Anesthesiology. 2017 May;126(5):890-908

Κλινική ανταπόκριση και Θνησιμότητα - VAP

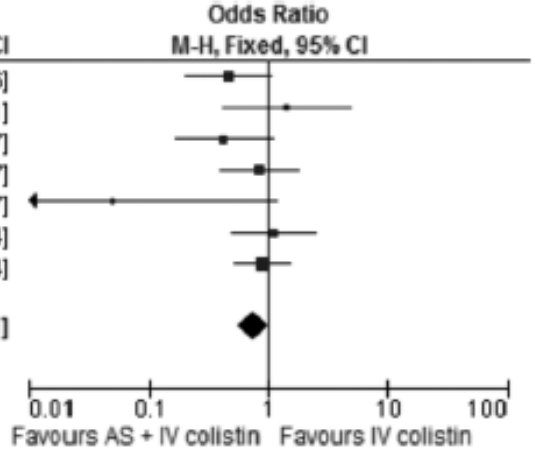
Study or Subgroup	Adjunctive AS colistin Events	Total	IV colistin Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Doshi 2013	24	44	20	51	13.8%	1.86 [0.82, 4.21]
Kalin 2012	4	29	6	15	11.1%	0.24 [0.05, 1.05]
Kofteridis 2010	32	43	28	43	11.7%	1.56 [0.62, 3.94]
Korbila 2010	62	78	26	43	11.2%	2.53 [1.11, 5.76]
Naesens 2011	7	9	2	5	0.9%	5.25 [0.49, 56.80]
Pérez-Pedrero 2011	9	10	9	12	1.3%	3.00 [0.26, 34.57]
Rattanaumpawan 2010	26	51	26	49	21.2%	0.92 [0.42, 2.02]
Tumbarello 2013	72	104	57	104	28.7%	1.86 [1.05, 3.27]
Total (95% CI)		**368**		322	**100.0%**	**1.57 [1.14, 2.15]**
Total events	236		174			

Heterogeneity: $Chi^2 = 11.05$, df = 7 (P = 0.14); $I^2 = 37\%$
Test for overall effect: Z = 2.77 (P = 0.006)



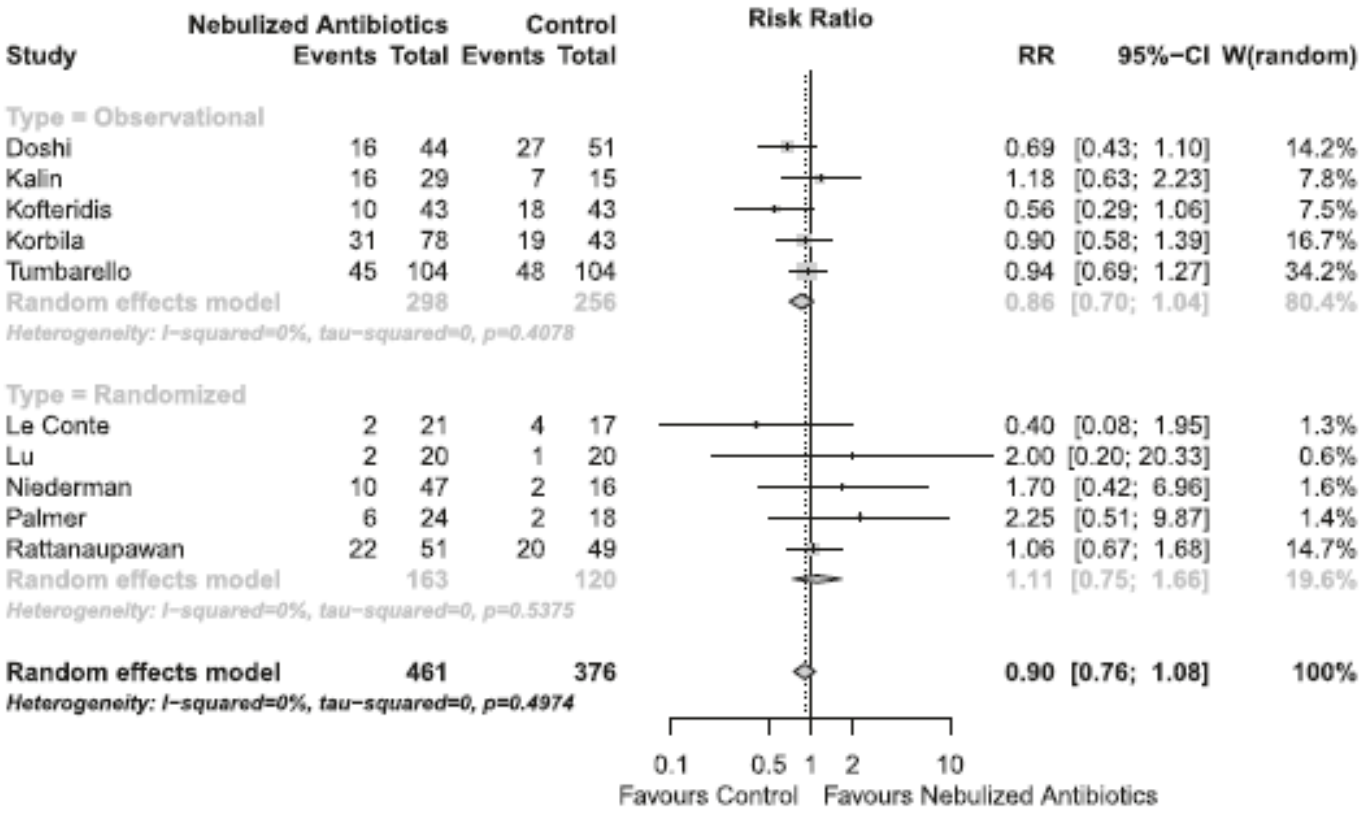
Study or Subgroup	AS + IV colistin Events	Total	IV colistin Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Doshi 2013	15	44	27	51	17.8%	0.46 [0.20, 1.06]
Kalin 2012	16	29	7	15	4.5%	1.41 [0.40, 4.91]
Kofteridis 2010	10	43	18	43	14.9%	0.42 [0.17, 1.07]
Korbila 2010	31	78	19	43	16.0%	0.83 [0.39, 1.77]
Naesens 2011	3	9	5	5	4.8%	0.05 [0.00, 1.17]
Rattanaumpawan 2010	22	51	20	49	12.5%	1.10 [0.50, 2.44]
Tumbarello 2013	45	104	48	104	29.4%	0.89 [0.51, 1.54]
Total (95% CI)		**358**		**310**	**100.0%**	**0.74 [0.54, 1.01]**
Total events	142		144			

Heterogeneity: $Chi^2 = 7.98$, df = 6 (P = 0.24); $I^2 = 25\%$
Test for overall effect: Z = 1.88 (P = 0.06)



Valachis A, et al. The role of aerosolized Colistin in the treatment of Ventilator-Associated Pneumonia: A Systemic Review and Metaanalysis. Critical Care Medicine 2015

Θνησιμότητα και VAP



Forest plot for mortality. *P* for overall effect = 0.252. CI, confidence interval; RR, relative risk.

Critical Care

Zampieri FG, et al. Nebulized antibiotics for ventilator-associated pneumonia: a systematic review and meta-analysis. Crit Care. 2015 Apr 7;19:150.

Θνησιμότητα και VAP

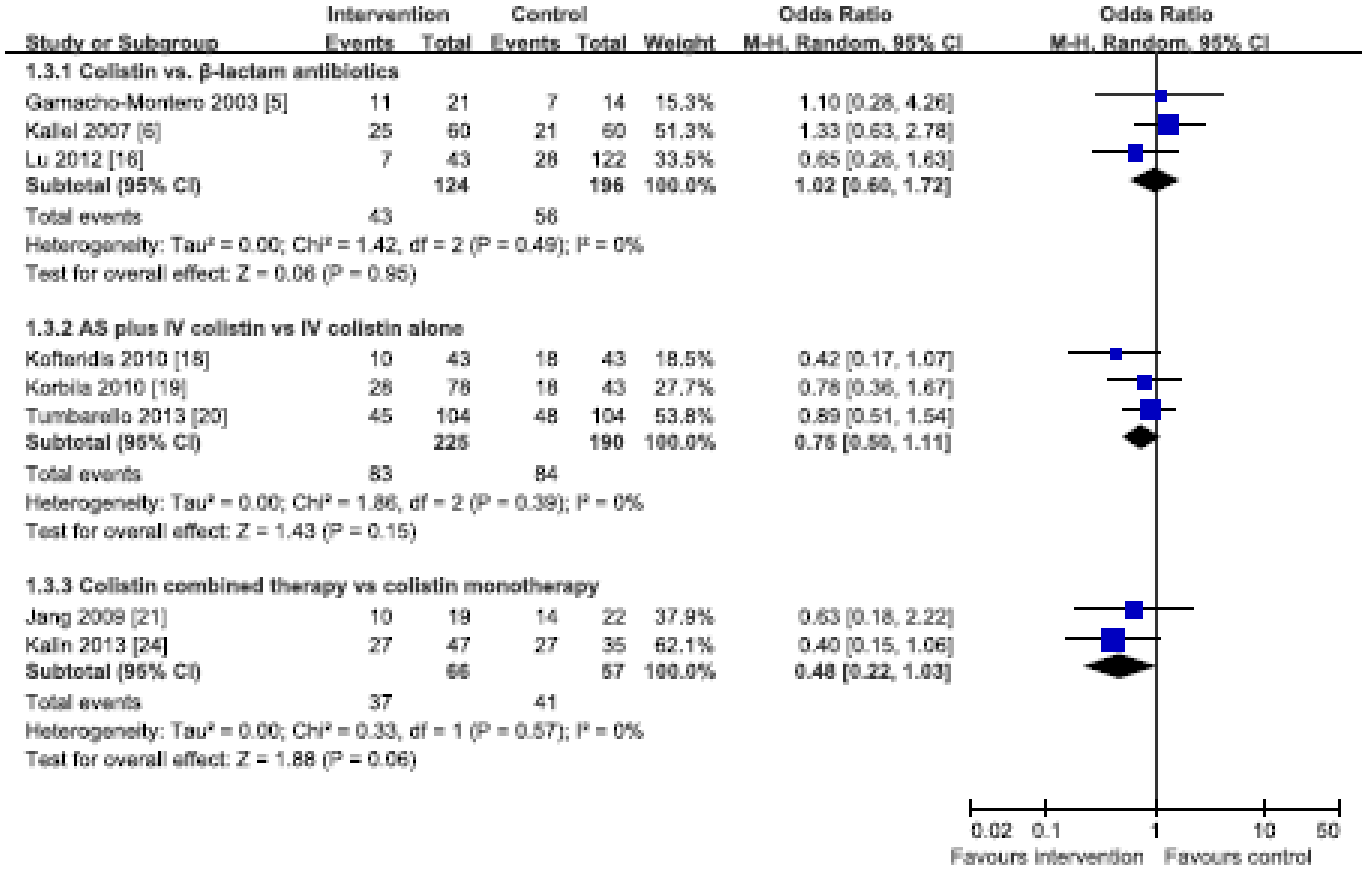
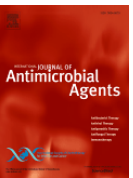
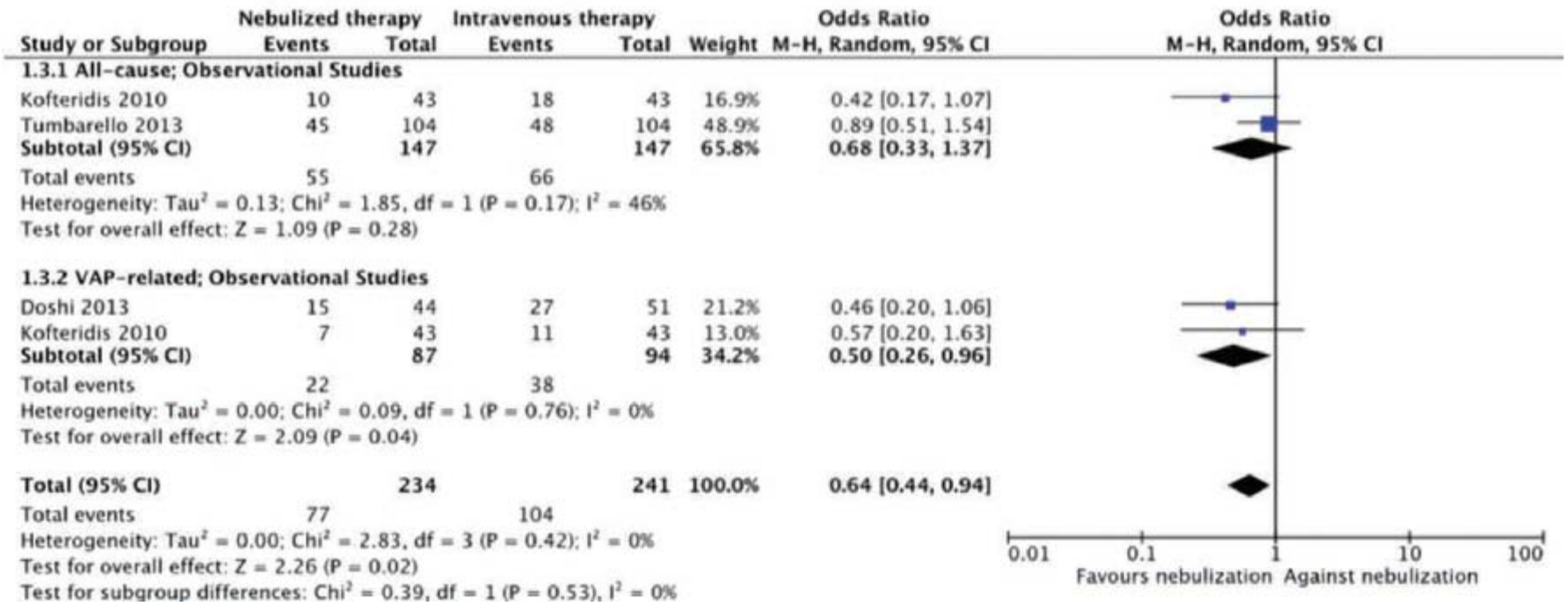


Fig. 4. Forest plot depicting intensive care unit mortality. AS, aerosolised; IV, intravenous.



Gu WJ, et al. Colistin for the treatment of ventilator-associated pneumonia caused by multidrug-resistant Gram-negative bacteria: a systematic review and meta-analysis. Int J Antimicrob Agents. 2014; 44(6):477-85

Θνησιμότητα σε MDR - VAP



Study or Subgroup	Nebulized therapy Events	Total	Intravenous therapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.3.1 All-cause; Observational Studies						
Kofteridis 2010	10	43	18	43	16.9%	0.42 [0.17, 1.07]
Tumbarello 2013	45	104	48	104	48.9%	0.89 [0.51, 1.54]
Subtotal (95% CI)		**147**		**147**	**65.8%**	**0.68 [0.33, 1.37]**
Total events	55		66			
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 1.85$, df = 1 (P = 0.17); $I^2 = 46\%$						
Test for overall effect: Z = 1.09 (P = 0.28)						
1.3.2 VAP-related; Observational Studies						
Doshi 2013	15	44	27	51	21.2%	0.46 [0.20, 1.06]
Kofteridis 2010	7	43	11	43	13.0%	0.57 [0.20, 1.63]
Subtotal (95% CI)		**87**		**94**	**34.2%**	**0.50 [0.26, 0.96]**
Total events	22		38			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0\%$						
Test for overall effect: Z = 2.09 (P = 0.04)						
Total (95% CI)		**234**		**241**	**100.0%**	**0.64 [0.44, 0.94]**
Total events	77		104			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.83$, df = 3 (P = 0.42); $I^2 = 0\%$						
Test for overall effect: Z = 2.26 (P = 0.02)						
Test for subgroup differences: $Chi^2 = 0.39$, df = 1 (P = 0.53), $I^2 = 0\%$						

Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults: A Systematic Review and Meta-analysis. Solé-Lleonart C, et al. Anesthesiology. 2017 May;126(5):890-908

Νεφροτοξικότητα

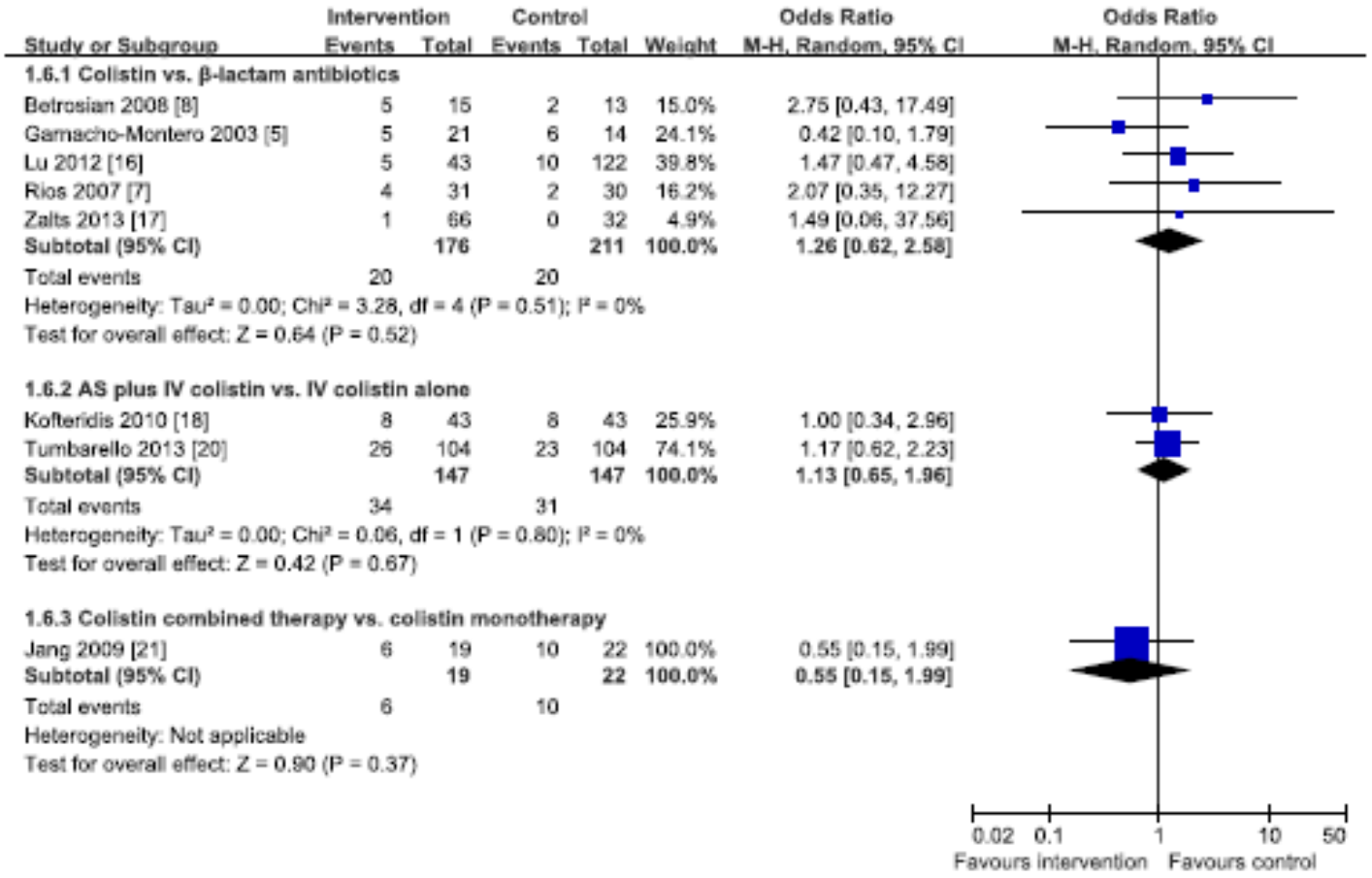
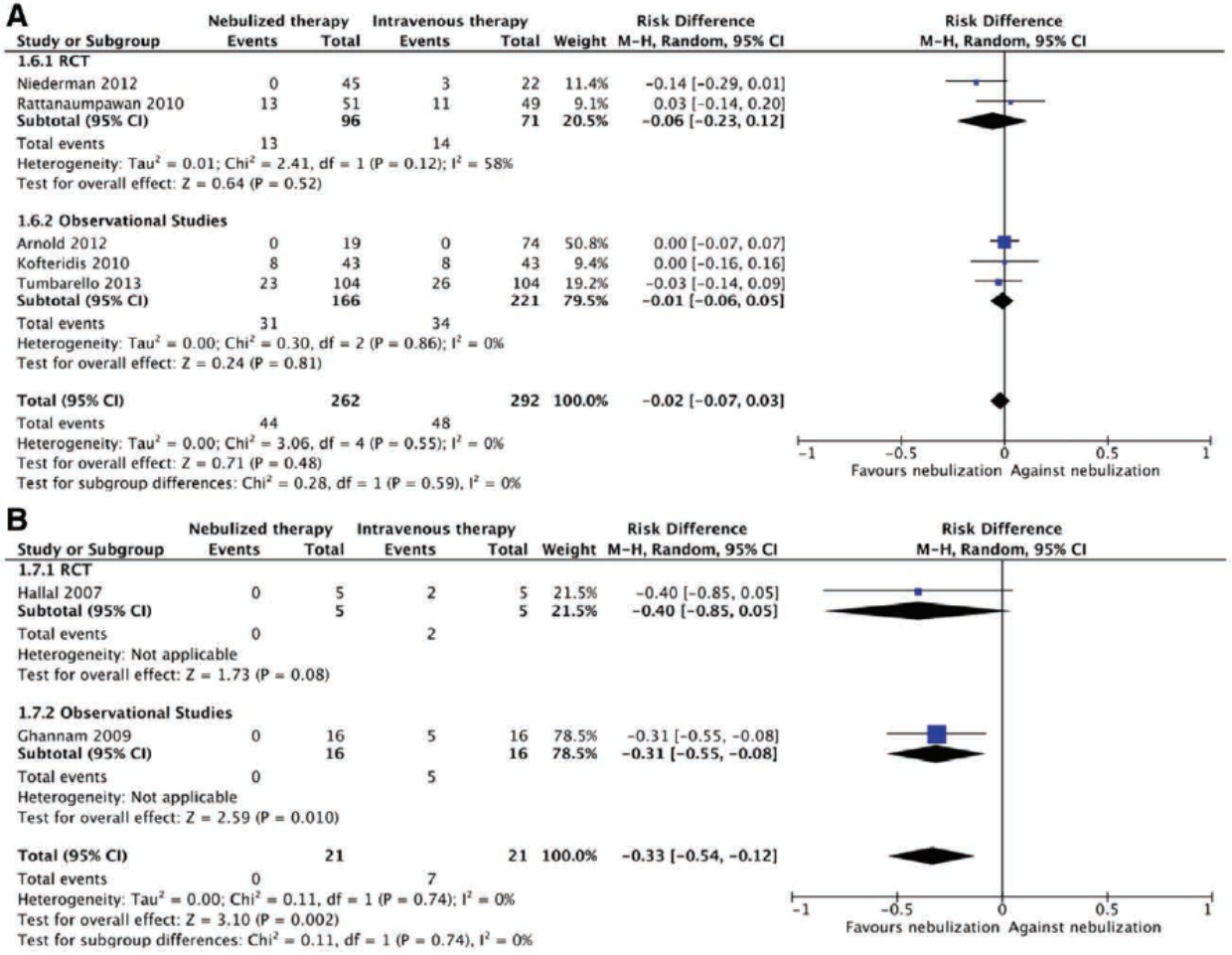


Fig. 7. Forest plot depicting nephrotoxicity. AS, aerosolised; IV, intravenous.

Gu WJ, et al. Colistin for the treatment of ventilator-associated pneumonia caused by multidrug-resistant Gram-negative bacteria: a systematic review and meta-analysis. Int J Antimicrob Agents. 2014; 44(6):477-85

Νεφροτοξικότητα



Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults: A Systematic Review and Meta-analysis. Solé-Lleonart C, et al. Anesthesiology. 2017 May;126(5):890-908

International Journal of Antimicrobial Agents 44 (2014) 477–485

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Colistin for the treatment of ventilator-associated pneumonia caused by multidrug-resistant Gram-negative bacteria: A systematic review and meta-analysis

Wan-Jie Gu[a], Fei Wang[b], Lu Tang[b], Jan Bakker[c], Jing-Chen Liu[a,*]

Based on the current evidence, colistin appears as effective and safe as β-lactam antibiotics for the treatment of MDR GNB VAP. AS colistin may be a beneficial adjunct to IV colistin in the management of MDR GNB VAP. Colistin combined therapy does not appear to provide better outcomes compared with colistin monotherapy. However, as these findings largely relied on data from observational studies, selection bias seems unavoidable, and therefore RCTs are needed to further confirm the role of colistin in the treatment of MDR GNB VAP.

Gu WJ, et al. Colistin for the treatment of ventilator-associated pneumonia caused by multidrug-resistant Gram-negative bacteria: a systematic review and meta-analysis. Int J Antimicrob Agents. 2014; 44(6):477-85

Zampieri *et al. Critical Care* (2015) 19:150
DOI 10.1186/s13054-015-0868-y

CRITICAL CARE

RESEARCH Open Access

Nebulized antibiotics for ventilator-associated pneumonia: a systematic review and meta-analysis

Fernando G Zampieri[1,2,3*†], Antonio P Nassar Jr[1,2,4†], Dimitri Gusmao-Flores[1,5,6], Leandro U Taniguchi[2,7], Antoni Torres[8] and Otavio T Ranzani[1,8,9,10]

Nebulized antibiotics might be useful for the treatment of VAP; however, the available evidence is of low quality and is highly heterogeneous. The apparent benefit in the clinical cure rate observed in traditional meta-analyses does not persist after TSA. Further high-quality trials in this subject are therefore warranted.

Zampieri FG, et al. Nebulized antibiotics for ventilator-associated pneumonia: a systematic review and meta-analysis. Crit Care. 2015 Apr 7;19:150.

RESEARCH ARTICLE Open Access

The use of inhaled antibiotic therapy in the treatment of ventilator-associated pneumonia and tracheobronchitis: a systematic review

Christopher J. Russell[1,2*], Mark S. Shiroishi[3], Elizabeth Siantz[6], Brian W. Wu[4] and Cecilia M. Patino[5]

This systematic review found insufficient evidence for the use of inhaled antibiotic therapy as primary or adjuvant treatment of VAP or VAT. Given the variations in study protocols, antibiotics studied and vague definition of clinical cure as an outcome measure, additional, adequately powered randomized-controlled trials with strict definitions of outcome assessments and use of previously validated nebulizer delivery methods for antibiotic administration are needed to assess the efficacy of inhaled antibiotic therapy for VAP and VAT.

BMC Pulmonary Medicine

The use of inhaled antibiotic therapy in the treatment of ventilator-associated pneumonia and tracheobronchitis: a systematic review. Russell CJ, et al. BMC Pulm Med. 2016 8;16:40.

Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults

A Systematic Review and Meta-analysis

Candela Solé-Lleonart, M.D., Jean-Jacques Rouby, M.D., Ph.D., Stijn Blot, R.N., Ph.D., Garyfallia Poulakou, M.D., Jean Chastre, M.D., Lucy B. Palmer, M.D., Matteo Bassetti, M.D., Ph.D., Charles-Edouard Luyt, M.D., Ph.D., Jose M. Pereira, M.D., Jordi Riera, M.D., Ph.D., Tim Felton, M.D., Jayesh Dhanani, F.C.I.C.M., M.D., Tobias Welte, M.D., Jose M. Garcia-Alamino, B.Sc., Jason A. Roberts, Ph.D., Jordi Rello, M.D., Ph.D.

In conclusion, our study shows that very limited evidence exists on the use of nebulized antibiotics in mechanically ventilated patients. Improvement in clinical resolution does not translate to improvements in other significant outcomes, which should be enclosed in further studies as predetermined outcomes.

Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults: A Systematic Review and Meta-analysis. Solé-Lleonart C, et al. Anesthesiology. 2017 May;126(5):890-908

Clinical Infectious Diseases

IDSA GUIDELINE

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

Andre C. Kalil,[1,a] Mark L. Metersky,[2,a] Michael Klompas,[3,4] John Muscedere,[5] Daniel A. Sweeney,[6] Lucy B. Palmer,[7] Lena M. Napolitano,[8] Naomi P. O'Grady,[9] John G. Bartlett,[10] Jordi Carratalà,[11] Ali A. El Solh,[12] Santiago Ewig,[13] Paul D. Fey,[14] Thomas M. File Jr,[15] Marcos I. Restrepo,[16] Jason A. Roberts,[17,18] Grant W. Waterer,[19] Peggy Cruse,[20] Shandra L. Knight,[20] and Jan L. Brozek[21]

ROLE OF INHALED ANTIBIOTIC THERAPY

XIV. Should Patients With VAP Due to Gram-Negative Bacilli Be Treated With a Combination of Inhaled and Systemic Antibiotics, or Systemic Antibiotics Alone?

Recommendation

1. For patients with VAP due to gram-negative bacilli that are susceptible to only aminoglycosides or polymyxins (colistin or polymyxin B), we suggest both inhaled and systemic antibiotics, rather than systemic antibiotics alone *(weak recommendation, very low-quality evidence).*

   Values and Preferences: This recommendation places a high value on achieving clinical cure and survival; it places a lower value on burden and cost.

   Remarks: It is reasonable to consider adjunctive inhaled antibiotic therapy as a treatment of last resort for patients who are not responding to intravenous antibiotics alone, whether the infecting organism is or is not MDR.

International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia

Antoni Torres[1,16], Michael S. Niederman[2,16], Jean Chastre[3], Santiago Ewig[4], Patricia Fernandez-Vandellos[5], Hakan Hanberger[6], Marin Kollef[7], Gianluigi Li Bassi[1], Carlos M. Luna[8], Ignacio Martin-Loeches[9], J. Artur Paiva[10], Robert C. Read[11], David Rigau[12], Jean François Timsit[13], Tobias Welte[14] and Richard Wunderink[15]

Guidelines

Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases

J. Rello [1, *, 15], C. Solé-Lleonart [2, *, 15], J.-J. Rouby [3], J. Chastre [4], S. Blot [5], G. Poulakou [6], C.-E. Luyt [3], J. Riera [7], L.B. Palmer [8], J.M. Pereira [9, 10], T. Felton [11], J. Dhanani [12], M. Bassetti [13], T. Welte [14], J.A. Roberts [12]

Recommendation

We suggest avoiding the use of nebulized antibiotics such as colistin or aminoglycosides, added to conventional IV antibiotic therapy already including IV colistin or aminoglycosides for the treatment of VAP caused by resistant pathogens as standard clinical practice.

Recommendation

We suggest avoiding the use of nebulized antibiotics such as colistin or aminoglycosides instead of their IV administration for the treatment of VAP caused by resistant pathogens as standard clinical practice.

CMI CLINICAL MICROBIOLOGY AND INFECTION ESCMID

Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases. Rello J, et al. Clin Microbiol Infect. 2017;23(9):629-639.

Guidelines

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Recommendation

We recommend avoiding the use of nebulized antibiotics such as colistin or aminoglycosides, added to conventional IV antibiotic therapy already including IV colistin or aminoglycosides for the treatment of VAP caused by antibiotic-susceptible pathogens in clinical practice.

Recommendation

We suggest avoiding the use of nebulized antibiotics such as colistin or aminoglycosides instead of their IV administration for the treatment of VAP caused by antibiotic-susceptible pathogens in clinical practice.

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Recommendation

We suggest avoiding the use of nebulized antibiotics added to conventional IV antibiotic therapy for the treatment of patients with VAT in clinical practice.

Recommendation

We recommend avoiding the use of nebulized antibiotics as a single therapy, instead of conventional IV antibiotic therapy, for the treatment of patients with VAT in clinical practice.

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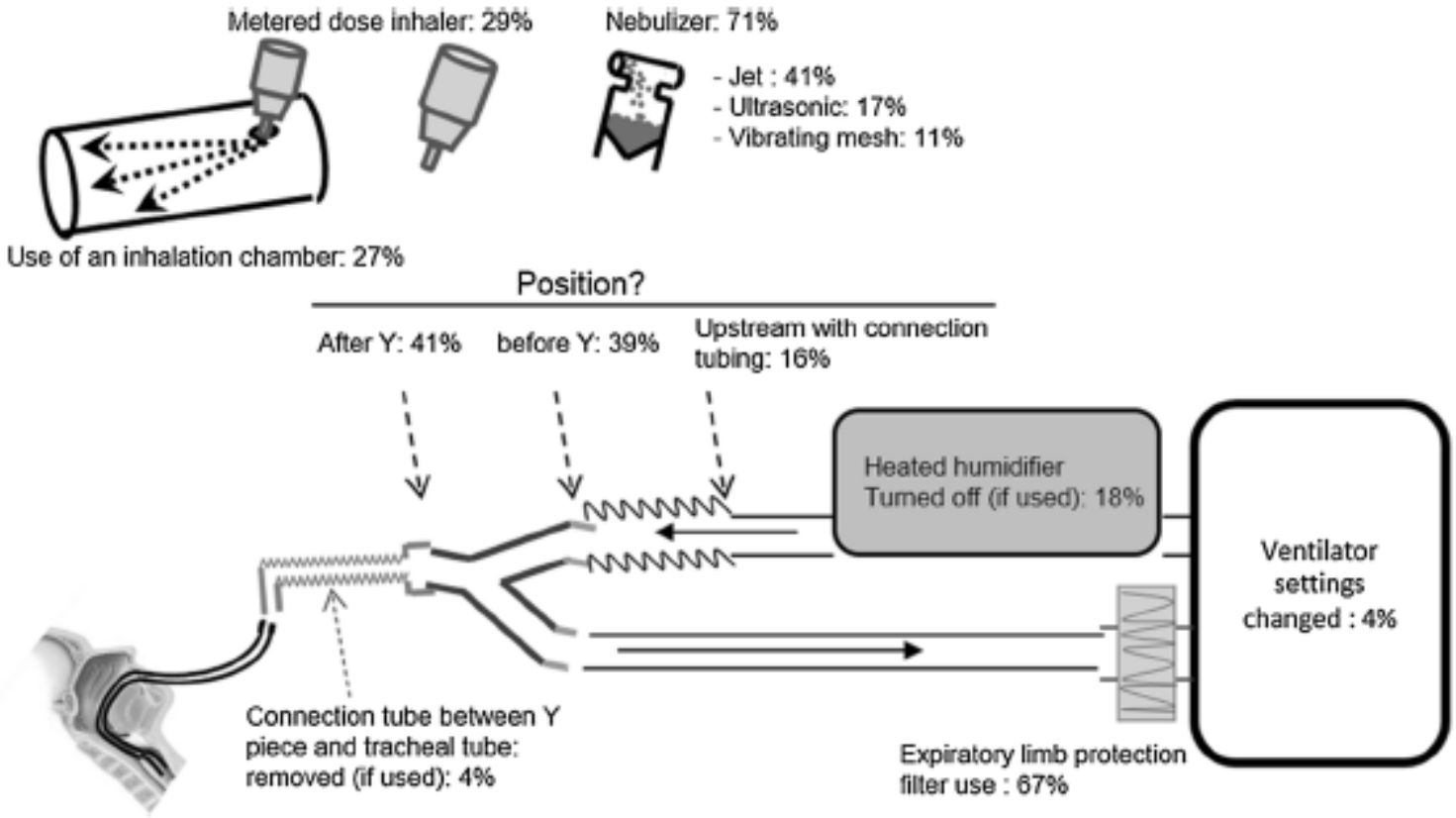
Συνήθεις τρόποι χορήγησης Νεφελώματος



Ehrmann et al. Aerosol therapy in intensive and intermediate care units: prospective observation of 2808 critically ill paients. Intensive Care Med 2016

Ρυθμίσεις για Χορήγηση Νεφελώματος

Aerosol generator	Advantages	Drawbacks
Jet nebulizer	• Low cost. • Low dimension at bedside. • Single use. • Breath synchronized.	• Percentage of drug delivery into lungs (approximately 15% of initial dose). • Highly variable delivery, depending on gas source. • Interference of gas flow with flow delivered by ventilator. • Nonhomogeneous droplet diameter. • Long duration of nebulization.
Ultrasonic nebulizer	• Efficient delivery of drug into lungs (30–40% of initial dose). • Almost no interference in circuit (low flow containing aerosol particles does not interfere with flow delivered by ventilator). • High speed of drug delivery. • Easy to use.	• Nonhomogeneous droplet diameter (depending on amplitude and frequency of vibration). • Increase in antibiotic's temperature. • High cost. • Hygiene concerns (need to sterilize after use) • Large dimension at bedside.
Vibrating-mesh nebulizer	• Efficient delivery of drug into lungs (40–60% of initial dose). • Homogeneous droplet diameter. • No temperature increase of delivered drug. • Good synchrony with ventilator. • Low residual drug volume lost. • Easy to use. • Low dimension at bedside. • Single use.	• High cost. • Not suitable for concentrated and viscous solutions.

CMI CLINICAL MICROBIOLOGY AND INFECTION ESCMID

Key considerations on nebulization of antimicrobial agents to mechanically ventilated patients.
Rello J, et al. Clin Microbiol Infect. 2017;23(9):640-646

Ρυθμίσεις για Χορήγηση Νεφελώματος

Characteristic	Description
Ventilator mode	• Volume-controlled mode. • Constant inspiratory flow.
Ideal ventilator parameters	• Tidal volume 8 mL/kg. • Respiratory frequency 12–15 breaths per minute. • Inspiratory to expiratory (I:E) ratio ≤50%. • End-inspiratory pause of 20% of duty cycle. • Positive end expiratory pressure 5–10 cm H_2O.
Important considerations	• Avoid sharp angles and rough inner surfaces in ventilator's circuit. • Avoid asynchronies and triggering. • Increase level of sedation if necessary. • Remove heat and moisture exchanger during procedure (and replace immediately afterwards). • Stop heat humidifiers during nebulization. • Change expiratory filter after each nebulization (expired particles are collected there and can cause obstruction).

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Ρυθμίσεις για Χορήγηση Νεφελώματος

Strategy related to ventilator circuits	• Place filter on expiratory limb (before flow meter). • Change expiratory filter after each nebulization. • Suspend heat and humidification except for patients with thick secretions that tend to occlude system and in patients with bronchial spasticity. • Minimize disconnection of circuit, particularly in patients with severe hypoxemia.
Strategy related to monitoring	• Monitor peak airway pressure during nebulization; increase of this parameter may be related to obstruction of expiratory filter (change it immediately!) or to bronchospasm. • If bronchospasm is mild, withdraw nebulization and administer local bronchodilators before following nebulization. • If bronchospasm is severe, consider another nebulized antibiotic or change route of administration. • If bronchoconstriction persists, consider another nebulized antibiotic or change route of administration. • Check renal function (serum creatinine levels), particularly when nebulizing aminoglycosides and in patients with previous renal dysfunction.
Oxygenation during nebulization process	• Ensure correct level of sedation; low doses of propofol avoid asynchronies with ventilator (midazolam instead of propofol can be used in haemodynamically unstable patients). • If sedation is increased to ensure patient's coordination with ventilator, it should be withdrawn at end of nebulization.
Avoid	• Recruitment manoeuvers before nebulization in haemodynamically unstable patients and if manoeuver may compromise oxygenation. • Tidal volumes of 8 ml/kg in patients with severe ARDS. • Increase of auto-PEEP in patients with high airway resistances (asthma, COPD patients) by maintaining enough expiratory time.
Other	• Nebulize colistin immediately after reconstitution of prodrug colistimethate sulfate to avoid excessive conversion to biologically active colistin, which can cause airway or alveolar injury.

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Ποιά είναι αυτήν τη στιγμή η θέση των εισπνεόμενων αντιβιοτικών;

At, present, the use of aerosolized antibiotics for VAT and VAP should only be considered for infections attributed to XDR or PDR pathogens resistant to all β-lactam and carbapenem antibiotics, due to the absence of adequate intravenous therapy and lung penetration with agents such as colistin, tigecycline and the aminoglycosides. However, the delivery of aerosolized antibiotics should be carried out in a manner that ensures proper technique is employed for optimal lung penetration of the antibiotic

CMI CLINICAL MICROBIOLOGY AND INFECTION ESCMID

Recommendations for aerosolized antibiotics in ventilator-associated pneumonia and ventilator-associated tracheobronchitis: too little and too late? Kollef MH, Micek ST. Clin Microbiol Infect. 2017;23(9):593-595


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την προσοχή σας