Does antibiotic treatment duration affect the outcomes of exacerbations of asthma and COPD? A Systematic Review

Supplementary data

	<6 days trea	tment	≥7 days trea	atment		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	ed, 95% Cl	
Bennett 1988	0	20	2	21	2.9%	0.21 [0.01, 4.11]	-			
Chodosh 2000	12	312	23	302	27.4%	0.51 [0.26, 1.00]			-	
DeAbate 1999	17	195	13	193	15.3%	1.29 [0.65, 2.59]		—	+ -	
Gotfried 2001	9	174	11	175	12.8%	0.82 [0.35, 1.94]			<u> </u>	
Gotfried 2005	9	240	10	245	11.6%	0.92 [0.38, 2.22]			• <u> </u>	
Langan 1999	5	273	12	268	14.2%	0.41 [0.15, 1.15]			+	
Lorenz 1998	0	110	3	111	4.1%	0.14 [0.01, 2.76]			<u> </u>	
Masterton 2001	8	268	10	262	11.8%	0.78 [0.31, 1.95]			<u> </u>	
Total (95% CI)		1592		1577	100.0%	0.71 [0.52, 0.98]		•		
Total events	60		84							
Heterogeneity: Chi ² =	7.19, df = 7 (P	= 0.41);	l² = 3%				1 005	01	1 10	200
Test for overall effect:	Z = 2.09 (P = 0	0.04)					0.005	Favours <6 days treatment	Favours ≥7 days treatment	200

Supplementary Figure 1 – Forest plot of nausea (adverse outcome), < 6 versus ≥ 7 days antibiotic duration

	<6 days treat	tment	≥7 days trea	atment		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Chodosh 2000	15	312	18	302	13.9%	0.81 [0.41, 1.57]	•
DeAbate 1999	6	195	6	193	4.6%	0.99 [0.32, 3.02]	
Gotfried 2001	12	174	11	175	8.3%	1.10 [0.50, 2.42]	
Langan 1999	3	273	5	268	3.8%	0.59 [0.14, 2.44]	
Lorenz 1998	13	110	20	111	15.1%	0.66 [0.34, 1.25]	
Masterton 2001	13	268	7	262	5.4%	1.82 [0.74, 4.48]	
Sethi 2005	74	443	65	450	48.9%	1.16 [0.85, 1.57]	
Total (95% CI)		1775		1761	100.0%	1.03 [0.82, 1.29]	•
Total events	136		132				
Heterogeneity: Chi ² =	5.07, df = 6 (P	= 0.53);	l² = 0%			-	
Test for overall effect: Z = 0.29 (P = 0.77)							Favours <6 days treatment Favours ≥7 days treatment

Supplementary Figure 2 – Forest plot of diarrhea (adverse outcome), < 6 versus ≥ 7 days antibiotic duration

	< 6 days trea	tment	≥ 7 days treatment		F	Risk Ratio (Non-event)	Risk Ratio (Non-event)
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Chodosh 2000	127	135	138	145	19.3%	1.23 [0.46, 3.29]	
Lorenz 1998	25	35	14	17	11.6%	1.62 [0.51, 5.13]	
Sethi 2005	95	118	93	117	69.1%	0.95 [0.57, 1.58]	
Total (95% CI)		288		279	100.0%	1.08 [0.71, 1.65]	
Total events	247		245				
Heterogeneity: Chi² = 0.78, df = 2 (P = 0.68); l² = 0%							
Test for overall effect:	Z = 0.36 (P = 0	.72)			Favours <6 days treatment Favours ≥7 days treatment		

Supplementary Figure 3 – Eradication or presumed eradication of bacteria from sputum within 6 days of treatment completion, < 6 versus ≥ 7 days antibiotic duration

	< 6 days trea	tment	≥ 7 days trea	atment	R	isk Ratio (Non-event)	Risk Ratio (Non-event)
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Chodosh 2000	127	143	135	148	14.1%	1.27 [0.64, 2.55]	•
DeAbate 1999	104	138	94	123	33.9%	1.04 [0.68, 1.61]	_
Gotfried 2001	85	87	75	80	5.8%	0.37 [0.07, 1.84]	
Gotfried 2005 (1)	82	94	91	102	11.7%	1.18 [0.55, 2.55]	
Lorenz 1998	24	35	12	17	7.5%	1.07 [0.44, 2.59]	
Masterton 2001	85	112	80	101	24.4%	1.16 [0.70, 1.92]	
Roede 2007	9	11	6	8	2.6%	0.73 [0.13, 4.13]	
Total (95% CI)		620		579	100.0%	1.08 [0.83, 1.39]	+
Total events	516		493				
Heterogeneity: Chi ² =	: 2.29, df = 6 (P :	= 0.89); l ^a	²=0%			-	
Test for overall effect	Z = 0.56 (P = 0	.58)					0.1 0.2 0.5 1 2 5 10 Favours <6 days treatment Favours ≥7days treatment
							,

Footnotes (1) Eradication only

Supplementary Figure 4 - Eradication or presumed eradication of bacteria from sputum within 7-23 days of treatment completion, < 6 versus ≥ 7 days antibiotic duration

	< 6 days treatment		≥ 7 days treatment			Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl			
Chodosh 2000	274	288	266	281	27.8%	1.01 [0.97, 1.04]	— — —			
Langan 1999	141	273	149	268	0.0%	0.93 [0.79, 1.09]				
Lorenz 1998	77	108	73	109	7.5%	1.06 [0.89, 1.27]				
Masterton 2001	214	268	212	262	22.1%	0.99 [0.91, 1.07]				
Sethi 2005	414	443	417	450	42.6%	1.01 [0.97, 1.05]	_ _			
Total (95% CI)		1107		1102	100.0%	1.01 [0.98, 1.04]	+			
Total events	979		968							
Heterogeneity: Chi ² =	0.61, df = 3 (P =	: 0.89); l ^a	²= 0%			-				
Test for overall effect:					Favours ≥7 davs treatment Favours <6 davs treatment					

Supplementary Figure 5 - Forest plot of clinical success within 6 days of treatment completion, < 6 versus ≥ 7 days antibiotic duration, sensitivity analysis excluding Langan et al.



Supplementary Figure 6 - Forest plot of clinical success > 20 days after treatment completion, < 6 versus \geq 7 days antibiotic duration, sensitivity analysis excluding Langan et al.



Supplementary Figure 7 - Forest plot of overall adverse events, < 6 versus ≥ 7 days antibiotic duration, sensitivity analysis excluding Langan et al.

	<6 days treat	s treatment ≥7 days treatment			Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl			
Bennett 1988	0	20	2	21	3.3%	0.21 [0.01, 4.11]				
Chodosh 2000	12	312	23	302	31.9%	0.51 [0.26, 1.00]				
DeAbate 1999	17	195	13	193	17.8%	1.29 [0.65, 2.59]	+ =			
Gotfried 2001	9	174	11	175	15.0%	0.82 [0.35, 1.94]				
Gotfried 2005	9	240	10	245	13.5%	0.92 [0.38, 2.22]				
Langan 1999	5	273	12	268	0.0%	0.41 [0.15, 1.15]				
Lorenz 1998	0	110	3	111	4.8%	0.14 [0.01, 2.76]				
Masterton 2001	8	268	10	262	13.8%	0.78 [0.31, 1.95]				
Total (95% CI)		1319		1309	100.0%	0.76 [0.54, 1.07]	•			
Total events	55		72							
Heterogeneity: Chi ² =	5.80, df = 6 (P =	= 0.45);	I² = 0%							
Test for overall effect:	Z = 1.59 (P = 0	.11)					Favours <6 days treatment Favours ≥7 days treatment			

Supplementary Figure 8 - Forest plot of nausea (adverse event), < 6 versus ≥ 7 days antibiotic duration, sensitivity analysis excluding Langan et al.



Supplementary Figure 9 - Forest plot of diarrhea (adverse event), < 6 versus ≥ 7 days antibiotic duration, sensitivity analysis excluding Langan et al.

Supplementary	Table 1	_ (Overview	of	clinical	outcome	assessment	hv	study
Supplementary	I abic I	_		01	cinical	outcome	assessment	Uy	Study

Study	Early follow up	Medium / Late follow up	Outcomes
Bennett 1988 ²⁸	0 days after treatment completion	12 months	Absence of mucoid sputum At 12 months: number of exacerbations; time to first exacerbation
Chodosh 2000 ²⁹	0-6 days after treatment completion	7-17 days after treatment completion	Clinical success: resolution of acute signs / symptoms related to infection or sufficient improvement so that additional / alternative antibiotics were not required
DeAbate 1999 ³⁶		21-24 days after treatment completion	Clinical cure or improvement
Gotfried 2001 ³⁷		7-14 days after treatment completion Extended follow up (21-28 days after treatment completion)	Clinical cure: resolution of all signs & symptoms of acute exacerbation of chronic bronchitis which were present at study entry, without need for further antibiotics
Gotfried 2005 ²⁵		Days 10-14 after treatment completion	Clinical cure: resolution of signs / symptoms of acute exacerbation of chronic bronchitis
Langan 1999 ²⁷	1-3 days after treatment completion	21-28 days after treatment completion	Satisfactory clinical response: cure or signs / symptoms of acute exacerbation of chronic bronchitis have improved / resolved at post-

			treatment visit (day 1-3) and absent at follow up visit or incomplete resolution at follow up visit
Lorenz 1998 ³⁰	0-3 days after treatment completion	17-23 days after treatment completion	Clinical success: cure or improvement of acute bacterial exacerbation based on volume and nature of sputum and symptoms of breathlessness
Masterton 2001 ²³	1-3 days after treatment completion	7-10 days after treatmentcompletion (primary outcome)4-5 weeks after treatmentcompletion	Clinical success: resolution of all infection related signs / symptoms or return to pre- infection state or improvement with no subsequent antibacterial treatment indicated
Roede 2007 ²⁶		11 days after treatmentcompletion3 months (minus 10 days) aftertreatment completion	Cure: resolution of acute signs / symptoms of acute exacerbation of chronic bronchitis back to baseline
Sethi 2005 ²⁴	2-4 days after treatment completion	7-14 days after treatment completion (primary outcome)21-28 days after treatment completion	Clinical success: sufficient improvement or resolution of the signs and symptoms of acute exacerbation of chronic bronchitis recorded at the screening such that no additional antibacterial therapy was prescribed for the episode of acute exacerbation of chronic bronchitis