National Institute for Health and Care Excellence

Final

Cystic Fibrosis: diagnosis and management

Appendix I

Main appendix document
Forest Plots
25 October 2017

FINAL

Developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologist

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Appendix I: Forest plots

I.1 Diagnosis of cystic fibrosis

Not applicable for this review.

I.2 Information and support

Not applicable to this review.

I.3 Service delivery

I.3.1 Service configuration

I.3.1.1 Home-based care

Comparison 1.1: home *versus* hospital care for the administration of intravenous antibiotics (IV AB) in people with CF experiencing an acute pulmonary exacerbation

Figure 1: Lung function: Change in FEV₁ % predicted at 21 days follow-up (range of scores: 0-100)

	Hom	ie ca	ге	Hosp	ital ca	аге	Mean Difference			Mean D	ifference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI			IV, Fixe	d, 95% CI		
Wolter 1997	4	14	13	7	16	18	-3.00 [-13.61, 7.61]			 		_	
							•	-2	0 -1	0	Ó	10	20
									Favours ho	spital care	Favours	home of	care

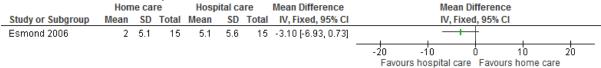
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 2: Lung function: Change in FEV₁ % predicted at 18 days follow-up (range of scores: 0-100)

	Ho	me car	е	Hosp	oital ca	are	Mean Difference			Mean Dif	ference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI			IV, Fixed	, 95% CI		
Donati 1987	6.7	15.75	31	12.3	10.8	32	-5.60 [-12.29, 1.09]			-	-		
									-				-
								-20	-10	Ó	1 1	Ö	20
								Favo	ours hosp	ital care	Favours ho	ome care	e

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 3: Lung function: Change in FEV₁ % predicted at 15 days follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 4: People starting next course of AB more than 12 weeks after completing the previous course (proxy outcome for time to next exacerbation) at 18 days follow-up



Abbreviations: AB: antibiotics; CI: confidence interval; M-H: Mantel Haenszel;

Figure 5: Nutritional status: Change in weight (kg) at 18 days follow-up

	Hon	ne car	е	Hosp	ital ca	ıre	Mean Difference		Mea	n Differer	ice	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, F	ixed, 95%	CI	
Donati 1987	0.5	8.17	37	1.6	5.6	37	-1.10 [-4.29, 2.09]			+		
								-20	-10	Ó	10	20
								Fav	ours hospital c	are Favo	urs home o	rare

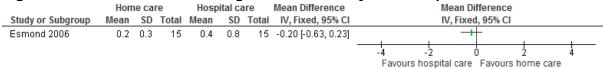
Abbreviations: CI: confidence interval; kg: kilograms; IV: inverse variance; SD: standard deviation;

Figure 6: Nutritional status: Change in weight (kg) at 10 days post-treatment follow-up

	HOII	ie cai	re	HOSP	itai ca	are	Mean Difference		wea	ın Dilleren	ce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, I	ixed, 95%	CI	
Wolter 1997	0.2	11	13	0.7	10	18	-0.50 [-8.06, 7.06]			+		
							-	-20	-10	Ó	10	20
								Favo	urs hospital (are Favo	urs home o	care

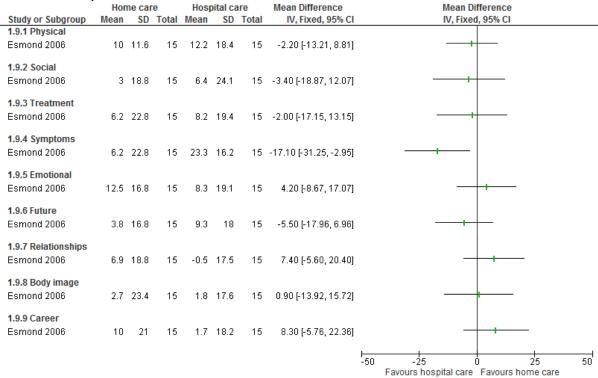
Abbreviations: CI: confidence interval; kg: kilograms; IV: inverse variance; SD: standard deviation;

Figure 7: Nutritional status: Change in BMI at 15 days follow-up



Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation;

Figure 8: Change in quality of life (CF-QOL) at 15 days follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; CF-QOL: cystic fibrosis quality of life questionnaire; IV: inverse variance; SD: standard deviation

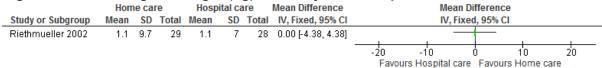
Comparison 1.2. Home *versus* hospital care for the administration of intravenous antibiotics (IV AB) in people with CF and chronic pulmonary infection with P. Aeruginosa

Figure 9: Change in FEV₁% predicted at 14 days follow-up (range of scores: 0-100)

	HOIII	e ca	e	Hospi	itai ca	ire	mean difference		wear	n billeren	ice		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fi	ixed, 95%	CI		
Riethmueller 2002	8	22	29	6	23	27	2.00 [-9.81, 13.81]						
								-20	-10	Ó	10	20	
								Favo	urs Hospital ca	are Favo	urs Home o	care	

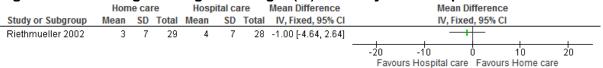
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 10: Change in weight (kg) at 14 days follow-up



Abbreviations: CI: confidence interval; kg: kilograms; SD: standard deviation; IV: inverse variance

Figure 11: Change in weight for height (%) at 14 days follow-up



Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

I.3.1.2 CF centre care

Comparison 2.1. CF centre care versus shared care

Figure 12: Lung function: Change in FEV₁ % predicted at 1 year follow-up (range of scores: 0-100)

	CF (Centr	e	Shared ca	are (UK e	quiv)	Mean Difference			Mean Di	fference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI			IV, Fixed	I, 95% CI		
van Koolwijk 2002	-2.9	4.5	41	-2.4	7	41	-0.50 [-3.05, 2.05]			-			
							•	-2	0 -1	0 ()	10	20
									Favours sh	ared care	Favours of	centre care	e

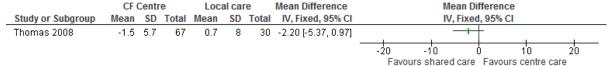
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 13: Lung function: Change from first to last FEV₁ % predicted per year at 3 years follow-up (range of scores: 0-100)

	CF (Centr	е	Loc	al ca	e	Mean Difference		Mea	an Differen	ce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV,	Fixed, 95%	CI	
Thomas 2008	-1.4	6.2	67	1	8.3	30	-2.40 [-5.72, 0.92]			++		
								-20	-10	- 	10	20
								Favo	ours shared	care Favo	urs centre d	care

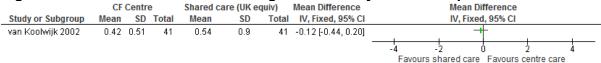
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 14: Lung function: Slope FEV₁ % predicted per year at 3 years follow-up

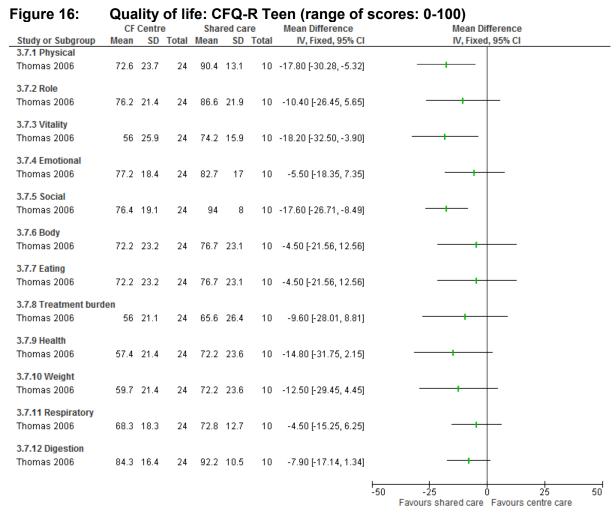


Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 15: Nutritional status: Change in BMI at 1 year follow-up



Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation



Note: Cross-sectional study

Figure 17: Quality of life: CFQ-R Child (range of scores: 0-100)

riguic ii.		_						300103. 0-100)
	CF	Centr	e	Sha	red ca	re	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.6.1 Physical								
Thomas 2006	76	21.9	46	77.2	23.1	37	-1.20 [-10.97, 8.57]	- -
3.6.4 Emotional								
Thomas 2006	76.1	14.8	46	74.8	14.9	37	1.30 [-5.13, 7.73]	+
3.6.5 Social								
Thomas 2006	70.2	15.9	46	71.9	19.4	37	-1.70 [-9.46, 6.06]	
3.6.6 Body								
Thomas 2006	78.3	24.6	46	81.1	25.4	37	-2.80 [-13.64, 8.04]	- ' -
3.6.7 Eating								
Thomas 2006	76.1	26.2	46	76.6	26.6	37	-0.50 [-11.94, 10.94]	
3.6.8 Treatment bur								
Thomas 2006	68.4	25.2	46	63.7	23.8	37	4.70 [-5.88, 15.28]	 -
3.6.11 Respiratory								
Thomas 2006	70.8	20.5	46	66.9	23.4	37	3.90 [-5.69, 13.49]	
3.6.12 Digestion								
Thomas 2006	76.1	26.9	46	72.1	29.9	37	4.00 [-8.38, 16.38]	
								-50 -25 0 25 50
								Favours shared care Favours centre care
								r avouro oriente a care il avouro contre care

Note: Cross-sectional study

Figure 18: Quality of life: CFQ-R Parent (range of scores: 0-100)

J	CF	Centr	е	Shai	red ca	re	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.8.1 Physical								
Thomas 2006	74.2	20.5	45	71.7	22.1	35	2.50 [-6.96, 11.96]	
3.8.3 Vitality								
Thomas 2006	64.3	15.4	45	65	16.5	35	-0.70 [-7.78, 6.38]	
0.0.4.5								
3.8.4 Emotional	70.4	46.0	45	75	24.4	25	4 40 (7 50 0 70)	
Thomas 2006	76.1	16.8	45	/5	21.4	35	1.10 [-7.52, 9.72]	
3.8.6 Body								
Thomas 2006	72.2	28.7	45	69.2	26.4	35	3.00 [-9.12, 15.12]	
2075-6								
3.8.7 Eating Thomas 2006	62	33.7	45	70.5	24.2	25	-7.50 [-20.22, 5.22]	
1110111a5 2000	03	33.1	40	70.5	24.3	33	-7.50 [-20.22, 5.22]	•
3.8.8 Treatment burde	en							
Thomas 2006	45.2	19.8	45	51.4	18.5	35	-6.20 [-14.63, 2.23]	
3.8.9 Health								
Thomas 2006	69.4	22.9	45	68.3	21.2	35	1.10 [-8.60, 10.80]	
111011140 2000	00.1			00.0			1.10 [0.00, 10.00]	
3.8.10 Weight								
Thomas 2006	56.3	37.5	45	57.1	33.5	35	-0.80 [-16.40, 14.80]	
3.8.11 Respiratory								
Thomas 2006	74.3	21	45	74.8	23.2	35	-0.50 [-10.33, 9.33]	
3.8.12 Digestion								
Thomas 2006	76.5	16.3	45	77.1	20	35	-0.60 [-8.76, 7.56]	-
3.8.13 School function	n							
Thomas 2006		27.7	45	65.1	22.6	35	-0.60 [-11.63, 10.43]	
							. ,	
								-50 -25 0 25 50
								Favours shared care Favours centre care

Note: Cross-sectional study

Comparison 2.2. CF centre care *versus* local care (below CF Trust recommendations)

Figure 19: Lung function: Change in FEV₁ % predicted at 1 year follow-up (range of scores: 0-100)

	CF (Centr	e	Loca	al car	е	Mean Difference			Mean Di	fference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI			IV, Fixed	I, 95% CI		
van Koolwijk 2002	-2.9	4.5	41	-5.6	7.2	23	2.70 [-0.55, 5.95]			-	-		
												+-	
								-20	-1	0 ()	10	20
									Favours I	local care	Favours	centre o	care

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 20: Lung function: Change from first to last FEV₁ % predicted per year at 3 years follow-up (range of scores: 0-100)

	CF	Centr	е	Loca	al cai	re	Mean Difference		Mea	an Differer	ice	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV,	Fixed, 95%	CI	
Thomas 2008	-1.4	6.15	67	4.3	8.6	11	-5.70 [-10.99, -0.41]					
								-20	-10	ó	10	20
								Fo	voure local (eare Favo	ure contro	care

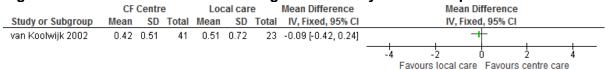
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 21: Lung function: Slope FEV₁ % predicted per year at 3 years follow-up (range of scores: 0-100)

•	CF (Centr	re	Loc	al car	e	Mean Difference		N	lean Diff	ference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight IV, Fixed, 95% CI		ľ	V, Fixed,	95% CI		
Thomas 2008	-1.5	5.7	67	1.8	4.2	11	-3.30 [-6.13, -0.47]						
								-20	-10		1	0	20
								F	avoure Inc.	al care I	Favoure co	antra care	

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 22: Nutritional status: Change in BMI at 1 year follow-up



Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation;

Comparison 2.3. CF centre care *versus* general clinic (non-CF)

Data could not be plotted.

I.3.1.3 Shared care

Comparison 3.1. Local care (below CF Trust Standards) *versus* shared care (UK equivalent)

Figure 23: Lung function: Change in FEV₁ % predicted at 1 year follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 24: Lung function: Change from first to last FEV₁% predicted per year at 3 years follow-up (range of scores: 0-100)

	Local care	below CF	Trust	Shared Ca	are (UK e	quiv)	Mean Difference		Mea	ın Differe	nce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, F	ixed, 95%	CI	
Thomas 2008	4.3	8.6	11	1	8.3	30	3.30 [-2.59, 9.19]			++	—.	
								-20	-10	- 6	10	20
								Favor	ire charadi	eare Favo	nure local e	are

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 25: Lung function: slope FEV₁ % predicted per year at 3 years follow-up

	Local care	below CF	Trust	Shared Ca	are (UK e	quiv)	Mean Difference		Mea	an Differen	ice	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, I	Fixed, 95%	CI	
Thomas 2008	1.8	4.2	11	0.7	8	30	1.10 [-2.69, 4.89]			+		
								-			-	
								-20	-10	Ö	10	20
								Favo	urs shared	care Favo	urs local ca	are

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 26: Nutritional status: Change in BMI at 1 year follow-up

	Local care	below CF	Trust	Shared Ca	are (UK e	(viup	Mean Difference		Me	an Differen	ce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV,	Fixed, 95%	CI	
van Koolwijk 2002	0.51	0.72	23	0.54	0.9	41	-0.03 [-0.43, 0.37]			+		
								-4	-2	- 6	2	4
								Favo	ure chared	care Favor	ire local ca	are.

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Comparison 3.2 Shared care (above UK standards) versus shared care (UK equivalent)

Figure 27: Lung function: Change from first to last FEV₁ % predicted per year at 3 years follow-up (range of scores: 0-100)

	Shared Ca	are (above	e UK)	Shared C	are (UK e	quiv)	Mean Difference		Mea	n Differei	ice	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, F	ixed, 95%	CI	
Thomas 2008	0.5	9.3	19	1	8.3	30	-0.50 [-5.63, 4.63]		. –	+		
							•	-20	-10	ó	10	20
								F	avours Shared	UK Favo	urs Shared a	above UK

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 28: Lung function: slope FEV₁ % per year at 3 years follow-up

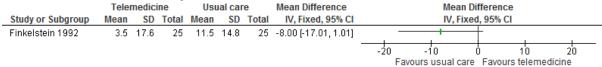
	Shared Ca	re (above	e UK)	Shared C	are (UK e	quiv)	Mean Difference			Mean Di	fference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI			IV, Fixed	1, 95% CI		
Thomas 2008	-1.4	7.5	19	0.7	8	30	-2.10 [-6.52, 2.32]			-			
							•	-20	-10		0 -	10	20
									Favours Sha	ared UK	Favours St	nared at	nove Uk

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

I.3.1.4 Telemedicine

Comparison 4.1. Home monitoring + diary recording versus usual care

Figure 29: Lung function: Change in FEV₁ % predicted at 4 years follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Comparison 4.2. Telemedicine versus usual care

Data could not be plotted.

I.3.2 Multidisciplinary teams

Not applicable, as no studies were included in this review.

I.4 Transition

Not applicable to this review.

1.5 Complications of cystic fibrosis

Not applicable to this review.

I.6 Monitoring for pulmonary disease

I.6.1 Review 1. Monitoring for pulmonary disease onset in people with CF without clinical signs or symptoms of lung disease

Comparison 1. Lung function tests versus imaging tests

No forest plots available.

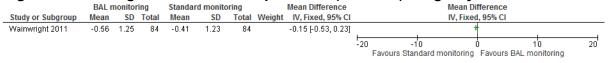
I.6.2 Review 2. Monitoring for evolving pulmonary disease in people with CF with established lung disease

Not applicable, as evidence was found for this review.

I.6.3 Review 3. Monitoring for evolving pulmonary disease in people with CF following an acute pulmonary exacerbation

Comparison 1. Monitoring using bronchoalveolar lavage (BAL) *versus* standard monitoring

Figure 30: Lung function – FEV₁% predicted (z-scores) at age 5 years



Abbreviations. BAL: bronchoalveolar lavage; CI: confidence interval; FEV_1 : forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation. Infants were recruited before age 6 months and followed until age 5 years.

Figure 31: Clearance of the organism from the cultures at age 5 years



Abbreviations: BAL: bronchoalveolar lavage; M-H: Mantel-Haenszel; CI: confidence interval. Infants were recruited before age 6 months and followed until age 5 years

Figure 32: Weight (z-scores) at age 5 years

	BAL n	nonitor	ring	Standar	d monito	ring		Mean Difference			Mean Di	fference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI			IV, Fixed	I, 95% CI		
Wainwright 2011	-0.15	0.88	80	-0.21	0.82	77		0.06 [-0.21, 0.33]				_		
									-20	-1	0	5	10	20
										avoure Stan	dard monitoring	Egyptire BAL r	nonitorina	

Abbreviations: BAL: bronchoalveolar lavage; SD: standard deviation; IV: inverse variance; CI: confidence interval. Infants were recruited before age 6 months and followed until age 5 years

Figure 33: Height (z-scores) at age 5 years

	BAL n	nonitor	ıng	Standar	d monite	oring		Mean Difference			Mean Differenc	e	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI			IV, Fixed, 95% C	1	
Wainwright 2011	-0.13	0.83	80	-0.19	0.98	77		0.06 [-0.22, 0.34]			t		
									-20	-10		10	20
										ours Standard mo	nitoring Favou	s BAL monitoring	20

Abbreviations: BAL: bronchoalveolar lavage; CI: confidence interval; IV: inverse variance; SD: standard deviation. Infants were recruited before age 6 months and followed until age 5 years

Figure 34: BMI (z-scores) at age 5 years

	BAL n	nonitor	ing	Standar	d monito	ring		Mean Difference			Mean D	ifference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI			IV, Fixe	d, 95% CI		
Wainwright 2011	0.03	0.93	80	0.01	0.83	77		0.02 [-0.26, 0.30]				†		
									-20	-1	0	Ó	10	20
										Favours Stan	dard monitoring	Favours BAL	monitoring	

Abbreviations: BAL: bronchoalveolar lavage; BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation. Infants were recruited before age 6 months and followed until age 5 years

I.7 Airway clearance techniques

Comparison 1. Manual physiotherapy versus no airway clearance techniques

No evidence was found for this comparison.

Comparison 2. Manual physiotherapy techniques versus oscillating devices

Figure 35: Change in FEV₁ % predicted after 8.8 days follow-up (range of scores: 0-100)

	Ma	nual physi	io	Oscillat	ing dev (Fl	ıtter)	Mean Difference			Mean Di	fference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI			IV, Fixed	I, 95% CI		
Homnick 1998	35.8	35.1006	22	43.7	42.8462	22	-7.90 [-31.04, 15.24]	-		+			
								-20	-10) (1	0	20
								Favor	ırs Osci	llating devi	Favours Ma	inual phy	/sio

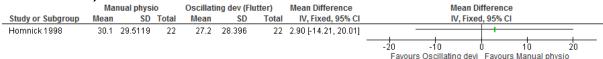
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 36: Change in FEV₁ % predicted at 1 month follow-up (range of scores: 0-100)

	Manu	al phy	sio	Oscillatin	g dev (Flu	itter)	Mean Difference		Me	ean Differen	ce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV	, Fixed, 95%	CI	
Padman 1999	6.25	5.6	6	3.66	9.6	6	2.59 [-6.30, 11.48]		_			_
								-	-			
								-20	-10	Ó	10	20
								Favoi	urs Oscillating	devi Favo	ırs Manual p	hysio

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

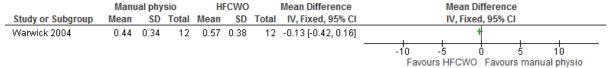
Figure 37: Change in FVC % predicted at 2 weeks follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

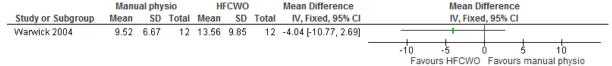
Comparison 3. Manual physiotherapy *versus* high frequency chest wall oscillation (HFCWO)

Figure 38: Wet sputum weight (g.) at 1 to 2 weeks follow-up



Abbreviations: HFCWO: High Frequency Chest Wall Oscillation; SD: standard deviation; IV: inverse variance; CI: confidence interval

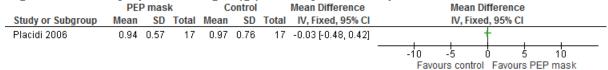
Figure 39: Dry sputum weight (g.) at 1 to 2 weeks follow-up



Abbreviations: HFCWO: High Frequency Chest Wall Oscillation; SD: standard deviation; IV: inverse variance; CI: confidence interval

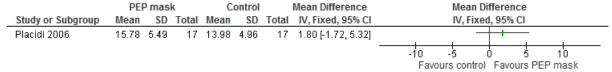
Comparison 4. Positive expiratory pressure mask (PEP) *versus* no airway clearance technique

Figure 40: Dry sputum weight (g.) at 2 days follow-up



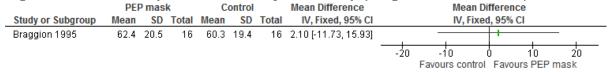
Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 41: Wet sputum weight (g.) at 2 days follow-up



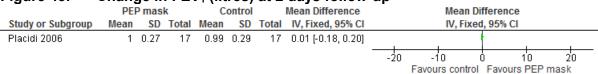
Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 42: FEV₁ % predicted at 2 days follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 43: Change in FEV₁ (litres) at 2 days follow-up



Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 44: FVC % predicted at 2 days follow-up (range of scores: 0-100)

	PE	o mas	K	C	ontrol		Mean Difference		Mean D	ifference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI		
Placidi 2006	1	0.27	17	0.99	0.29	17	0.01 [-0.18, 0.20]			1		
									10	 	 	
								-20	-10	U 1	-	
									Favours control	Favours	PEP masi	K

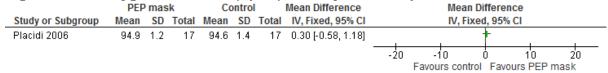
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 45: Change in FVC (litres) at 2 days follow-up

	PEI	p mas	k	C	ontrol		Mean Difference			Mean D)ifferer	ice	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI			IV, Fixe	d, 95%	CI	
Placidi 2006	2	0.62	17	1.95	0.58	17	0.05 [-0.35, 0.45]				†		
								-2	0 -1	0	Ó	10	20
									Favou	rs control	I Favo	urs PEP i	mask

Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 46: Oxygen saturation (SpO2) at 2 days follow-up



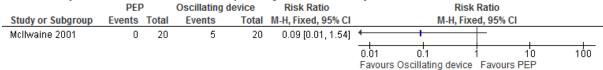
Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Comparison 5. Positive expiratory pressure mask (PEP) *versus* active cycle of breathing techniques (ACBT)

No evidence was found for this comparison.

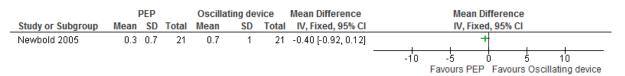
Comparison 6. Positive expiratory pressure mask (PEP) versus oscillating devices

Figure 47: Patient preference (measured as self-withdrawal due to lack of perceived effectiveness) at 1 year follow-up



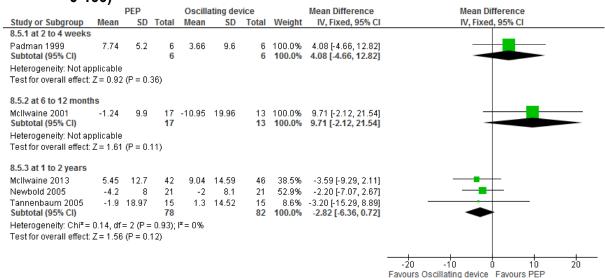
Abbreviations: PEP: positive expiratory pressure mask; M-H: Mantel-Haenszel; CI: confidence interval

Figure 48: Hospitalisations due to respiratory exacerbations (mean number per participant) at 13 months follow-up



Abbreviations: PEP: positive expiratory pressure mask; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 49: Change in FEV_1 % predicted at up to 2 years follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; df: degrees of freedom; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Figure 50: FVC % predicted at 2 to 4 weeks follow-up (range of scores: 0-100)

	F	PEP		Oscillat	ting de	vice		Mean Difference		Mear	n Diff	ference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fi	xed,	95% CI		
van Winden 1998	97	3	22	99	4	22		-2.00 [-4.09, 0.09]		-	+			
									-20	-10	_	10	20	
										scillating devi	ice	Favours PEP	20	

Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Figure 51: Change in FVC % predicted at 1 year follow-up (range of scores: 0-100)

		PEP		Oscilla	ating de	vice		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
McIlwaine 2001	0.06	7.9	17	-8.62	15.5	13	23.8%	8.68 [-0.54, 17.90]	-
McIlwaine 2013	6.39	9.39	42	11.39	15.49	46	36.7%	-5.00 [-10.30, 0.30]	
Newbold 2005	-4.7	8	21	-3	7.1	21	39.4%	-1.70 [-6.27, 2.87]	
Total (95% CI)			80			80	100.0%	-0.44 [-6.66, 5.78]	
Heterogeneity: Tau²: Test for overall effect			•	= 2 (P =	: 0.04); P	= 69%			-10 -5 0 5 10 Favours Oscillating device Favours PEP

Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Figure 52: Change in quality of life (measured with CF-QOL) at 1 year follow-up (range of scores: 0-100)

(141	ıgo oı	550	,, 00.	· · · ·	ν,			
		PEP		Oscilla	ating de	vice	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
8.9.1 CFQ: physical (domain							
McIlwaine 2013	-0.84	3.3	51	-3.04	13	56	2.20 [-1.32, 5.72]	+-
8.9.2 CFQ: treatmen	t burden							
McIlwaine 2013	-2.55	20.6	51	-3.6	18.2	56	1.05 [-6.35, 8.45]	- - - - - - - - - -
8.9.3 CFQ: respirato	ry domai	in						
McIlwaine 2013	2.98	17	51	0.19	17.1	56	2.79 [-3.68, 9.26]	
								-20 -10 0 10 20
								Favours Oscillating device Favours PEP

Abbreviations: CI: confidence interval; CF-QOL: cystic fibrosis quality of life questionnaire; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Comparison 7. Positive expiratory pressure mask (PEP) *versus* high frequency chest wall oscillation (HFCWO)

Figure 53: Sputum volume (ml.) at 1 week follow-up

	-	PEP		HF	CWC)	Mean Difference		Mean	Differen	ice	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fix	ed, 95%	CI	
Grzincich 2008	8.5	8.4	23	6.7	8.2	23	1.80 [-3.00, 6.60]			+		
								-10	-5 Favours HFCW) Eavo	5 Ure PEP	10
									FavourS HFCW	o ravo	uisfer	

Abbreviations: PEP: positive expiratory pressure mask; HFCWO: high frequency chest wall oscillation; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 54: Pulmonary exacerbations (number of patients) at 1 year follow-up

	PEF)	HFCV	VO.	Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
McIlwaine 2013	26	43	40	48	0.73 [0.55, 0.95]				
						0.05	0.2 Favours PEP	5 Favours HFCWO	20

Abbreviations: PEP: positive expiratory pressure mask; HFCWO: high frequency chest wall oscillation; M-H: Mantel-Haenszel; CI: confidence interval

Figure 55: Pulmonary exacerbations (patients requiring antibiotics) at 1 year follow-up

	PEP)	HFCV	10	Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI	
McIlwaine 2013	26	42	40	46	0.71 [0.55, 0.93]				
						0.05	0.2 1	5 Favours HFCWO	20

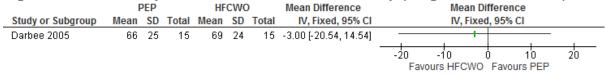
Abbreviations: PEP: positive expiratory pressure mask; HFCWO: high frequency chest wall oscillation; M-H: Mantel-Haenszel; CI: confidence interval

Figure 56: FEV₁ % predicted at 1 week follow-up (range of scores: 0-100)

		PEP		H	FCWO			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Braggion 1995	62.4	20.5	16	60.6	20.8	16	37.1%	1.80 [-12.51, 16.11]	-
Grzincich 2008	69	19	23	69	19	23	62.9%	0.00 [-10.98, 10.98]	
Total (95% CI)			39			39	100.0%	0.67 [-8.04, 9.38]	
Heterogeneity: Chi² = Test for overall effect:); I² = 09	6				-20 -10 0 10 20 Favours HFCWO Favours PEP

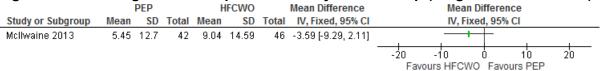
Abbreviations: CI: confidence interval; df: degrees of freedom; FEV_1 : forced expiratory volume in 1 second; HFCWO: high frequency chest wall oscillation; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Figure 57: FEV₁ % predicted at 1 to 2 weeks follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FEV_1 : forced expiratory volume in 1 second; HFCWO: high frequency chest wall oscillation; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Figure 58: Change in FEV₁ % predicted at 1 year follow-up (range of scores: 0-100)



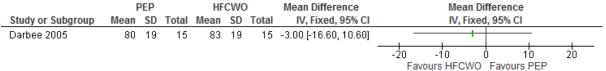
Abbreviations: CI: confidence interval; FEV_1 : forced expiratory volume in 1 second; HFCWO: high frequency chest wall oscillation; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Figure 59: FVC % predicted at 1 week follow-up (range of scores: 0-100)

		PEP		H	FCWO			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Braggion 1995	83.6	19.8	16	81.8	18.6	16	36.6%	1.80 [-11.51, 15.11]	
Grzincich 2008	91	17	23	91	18	23	63.4%	0.00 [-10.12, 10.12]	
Total (95% CI)			39			39	100.0%	0.66 [-7.40, 8.71]	
Heterogeneity: Chi² Test for overall effec		,); I² = 09	6				-20 -10 0 10 20 Favours HFCWO Favours PEP

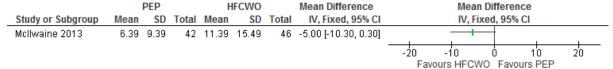
Abbreviations: CI: confidence interval; df: degrees of freedom; FVC: forced vital capacity; HFCWO: high frequency chest wall oscillation; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Figure 60: FVC % predicted at 1 to 2 weeks follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FVC: forced vital capacity; HFCWO: high frequency chest wall oscillation; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Figure 61: Change in FVC % predicted at 1 year follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FVC: forced vital capacity; HFCWO: high frequency chest wall oscillation; IV: inverse variance; PEP: positive expiratory pressure mask; SD: standard deviation

Comparison 8. Active cycle of breathing technique (ACBT) *versus* no airway clearance technique

No evidence was retrieved for this comparison.

Comparison 9. Active cycle breathing technique (ACBT) *versus* autogenic drainage (AD)

No evidence was retrieved for this comparison.

Comparison 10. Autogenic drainage (AD) versus no airway clearance technique

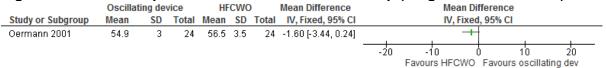
No evidence was retrieved for this comparison.

Comparison 11. Oscillating device versus no airway clearance technique

No evidence was retrieved for this comparison.

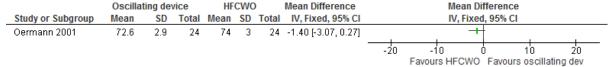
Comparison 12. Oscillating device *versus* high frequency chest wall oscillation (HFCWO)

Figure 62: FEV₁ % predicted at 2 to 4 weeks follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; HFCWO: high frequency chest wall oscillation; IV: inverse variance; SD: standard deviation

Figure 63: FVC % predicted at 2 to 4 weeks follow-up (range of scores: 0-100)



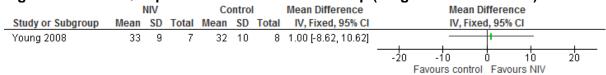
Abbreviations: CI: confidence interval; FVC: forced vital capacity; HFCWO: high frequency chest wall oscillation; IV: inverse variance; SD: standard deviation

Comparison 13. High frequency chest wall oscillation (HFCWO) *versus* no airway clearance technique

No evidence was found for this comparison.

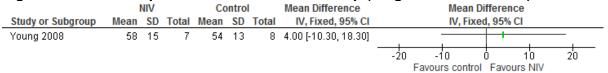
Comparison 14. Non-invasive ventilation (NIV) versus no airway clearance technique

Figure 64: FEV₁ % predicted at 6 weeks follow-up (range of scores: 0-100)



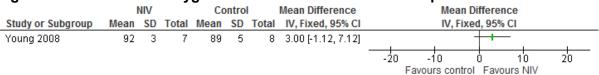
Abbreviations: CI: confidence interval; FEV_1 : forced expiratory volume in 1 second; IV: inverse variance; NIV: non-invasive ventilation; SD: standard deviation;

Figure 65: FVC % predicted at 6 weeks follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; NIV: non-invasive ventilation; SD: standard deviation

Figure 66: Nocturnal oxygen saturation at 6 weeks follow-up



Abbreviations: CI: confidence interval; IV: inverse variance; NIV: non-invasive ventilation; SD: standard deviation

Figure 67: Quality of life (CF-QOL questionnaire) at 6 weeks follow-up (range of scores: 0-100)

			,					
		NIV	-	Co	ontro	I	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
21.6.1 CF-QOL ches	t sympto	m sc	оге					
Young 2008	71	17	7	64	20	8	7.00 [-11.73, 25.73]	-
21.6.2 CF-QOL dysp	noea ind	ex so	оге					
Young 2008	1	1.8	7	-1.9	2.5	8	2.90 [0.71, 5.09]	+
							H	
							-:	50 -25 0 25 50 Favours control Favours NIV

Abbreviations: CI: confidence interval; CF-QOL: cystic fibrosis quality of life questionnaire; IV: inverse variance; NIV: non-invasive ventilation; SD: standard deviation

I.8 Mucoactive agents

I.8.1 Mannitol

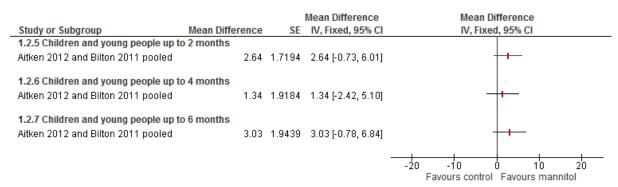
Comparison 1.1. Mannitol versus placebo

Figure 68: Lung function: change in FEV1 % predicted at 2 weeks and 2, 4 & 6 months follow-up (range of scores: 0-100)

	itiis iollow-up	Mannitol			Mean Difference	Mean Difference
Study or Subgroup	Mean Difference S	E Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.1.1 up to 2 weeks						
Jaques 2008	3.95 1.527			100.0%	3.95 [0.96, 6.94]	-
Subtotal (95% CI)		36	36	100.0%	3.95 [0.96, 6.94]	•
Heterogeneity: Not ap	•					
Test for overall effect:	Z= 2.59 (P = 0.010)					
1.1.2 up to 2 months						
Aitken 2012	3.89 1.8	1 184	121	30.0%	3.89 [0.34, 7.44]	
Bilton 2011	2.588 1.18		118	70.0%	2.59 [0.27, 4.91]	 ▼
Subtotal (95% CI)		361	239	100.0%	2.98 [1.04, 4.92]	◆
- '	0.36 , df = 1 (P = 0.55); I^2 =	0%				
Test for overall effect:	Z= 3.01 (P = 0.003)					
1.1.3 up to 4 months						
Aitken 2012	2.34 2.0	4 184	121	27.4%	2.34 [-1.66, 6.34]	+-
Bilton 2011	3.602 1.253		118	72.6%	3.60 [1.15, 6.06]	🛨
Subtotal (95% CI)		361	239	100.0%	3.26 [1.16, 5.35]	◆
	0.28, df = 1 (P = 0.60); I ² =	0%				
Test for overall effect:	Z = 3.05 (P = 0.002)					
1.1.4 up to 6 months						
Aitken 2012	4.55 2.0		121	30.4%	4.55 [0.57, 8.53]	
Bilton 2011	3.595 1.341		118	69.6%	3.60 [0.96, 6.23]	🛨
Subtotal (95% CI)		361	239	100.0%	3.89 [1.69, 6.08]	-
Heterogeneity: Chi²= Test for overall effect:	0.15 , df = 1 (P = 0.69); I^2 = $Z = 3.47$ (P = 0.0005)	0%				
						-20 -10 0 10 20
						Favours control Favours mannitol

Abbreviations: CI: confidence interval; FEV1: forced expiratory volume in 1 second; IV: inverse variance; SE: standard error

Figure 69: Lung function: change in FEV1 % predicted in children and young people at 2, 4 & 6 months follow-up (range of scores 0-100)



Abbreviations: CI: confidence interval; FEV1: forced expiratory volume in 1 second; IV: inverse variance; SE: standard error

Data was extracted from Cochrane SR Nolan 2015. Data was already pooled for Aitken 2012 and Bilton 2011 studies

Figure 70: Lung function: change in FEV1 % predicted in adults at 2, 4 & 6 months follow-up (range of scores 0-100)

			Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.3.5 Adults up to 2 months				
Aitken 2012 and Bilton 2011 pooled	3.72	1.4796	3.72 [0.82, 6.62]	
1.3.6 Adults up to 4 months				
Aitken 2012 and Bilton 2011 pooled	4.23	1.6582	4.23 [0.98, 7.48]	
1.3.7 Adults up to 6 months				
Aitken 2012 and Bilton 2011 pooled	5.74	1.7245	5.74 [2.36, 9.12]	
				-20 -10 0 10 20 Favours control Favours mannitol

Abbreviations: CI: confidence interval; FEV1: forced expiratory volume in 1 second; IV: inverse variance; SE: standard error

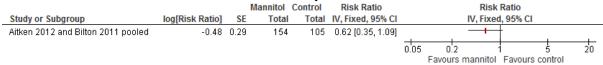
Data was extracted from Cochrane SR Nolan 2015. Data was already pooled for Aitken 2012 and Bilton 2011 studies

Figure 71: Time to first pulmonary exacerbation at 6 months follow-up

			Mannitol	Control		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Aitken 2012	-0.3011	0.2953	184	121	41.7%	0.74 [0.41, 1.32]	
Bilton 2011	-0.3857	0.25	177	118	58.3%	0.68 [0.42, 1.11]	
Total (95% CI)			361	239	100.0%	0.70 [0.48, 1.02]	•
Heterogeneity: Chi² = Test for overall effect:		3); I² = 0%	5				0.05 0.2 5 20 Favours mannitol Favours control

Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

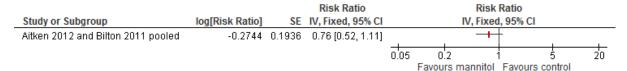
Figure 72: Number of children and young people with protocol defined exacerbations at 6 months follow-up



Abbreviations: IV: inverse variance; SE: standard error

Data was extracted from Cochrane SR Nolan 2015. Data was already pooled for Aitken 2012 and Bilton 2011 studies

Figure 73: Number of adults with protocol defined exacerbations at 6 months follow-up



Abbreviations: IV: inverse variance; SE: standard error Data was extracted from Cochrane SR Nolan 2015. Data was already pooled for Aitken 2012 and Bilton 2011 studies

Figure 74: Number of patients needing additional IV antibiotics at 6 months follow-up

.00	· · up								
	Mann	itol	Cont	rol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI	
1.4.1 Intravenous									
Aitken 2012	102	184	74	121	56.4%	0.91 [0.75, 1.10]		=	
Bilton 2011 Subtotal (95% CI)	63	177 361	60	118 239	43.6% 100.0%	0.70 [0.54, 0.91] 0.81 [0.63, 1.04]		_	
Total events	165	301	134	239	100.0%	0.01 [0.03, 1.04]		lacksquare	
Heterogeneity: Tau ² =		i² = 2.4		(P = 0.1	2); I² = 59	1%			
Test for overall effect	Z = 1.63	(P = 0.1)	10)						
							0.05	0.2 1 5	 20
								Favours mannitol Favours control	ol

Abbreviations: CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel

Figure 75: Quality of life: change in CFQ-R respiratory at 4 & 6 months follow-up (range of scores: 0-100)

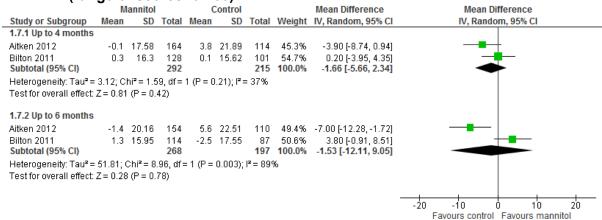


Figure 76: Quality of life: change in CFQ-R vitality at 4 & 6 months follow-up (range of scores: 0-100)

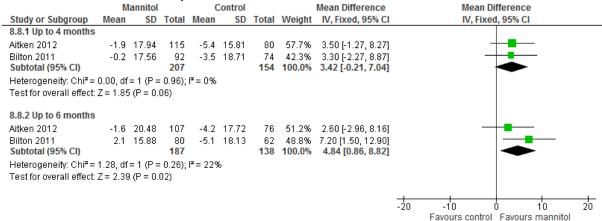


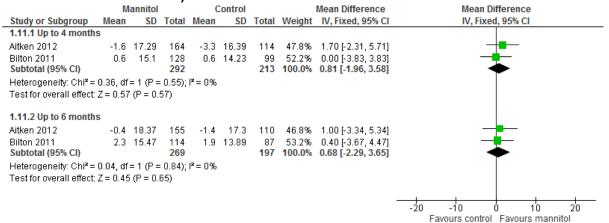
Figure 77: Quality of life: change in CFQ-R physical at 4 & 6 months follow-up (range of scores: 0-100)

(,				
	M	annitol		(Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.9.1 Up to 4 months									
Aitken 2012	-0.1	18.17	164	2.3	16.53	114	50.2%	-2.40 [-6.52, 1.72]	
Bilton 2011	-2.7	16.55	127	-1.5	15.1	100	49.8%	-1.20 [-5.33, 2.93]	
Subtotal (95% CI)			291			214	100.0%	-1.80 [-4.72, 1.11]	•
Heterogeneity: Tau ² =	0.00; C	$hi^2 = 0.1$	6, df=	1 (P = 0)	.69); l² :	= 0%			
Test for overall effect:	Z = 1.21	(P = 0.	23)						
1.9.2 Up to 6 months									
Aitken 2012	-1.7	18.85	155	1.1	18.2	110	50.6%	-2.80 [-7.31, 1.71]	
Bilton 2011	-0.5	16.22	113	-4.7	17.56	87	49.4%	4.20 [-0.55, 8.95]	
Subtotal (95% CI)			268			197	100.0%	0.66 [-6.20, 7.52]	
Heterogeneity: Tau ² =	18.91; (Chi² = 4	.38, df	= 1 (P =	0.04); P	e = 77%)		
Test for overall effect:	Z = 0.19	P = 0	85)						
									-20 -10 0 10 20
									Favours control Favours mannitol

Figure 78: Quality of life: change in CFQ-R emotion at 4 & 6 months follow-up (range of scores: 0-100)

•	·							B Diff	11 Diff
	IVI	lannitol		(Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.10.1 Up to 4 month	IS								
Aitken 2012	0.3	14.35	164	2.9	12.64	114	58.8%	-2.60 [-5.79, 0.59]	
Bilton 2011	-1.5	15.4	128	-0.1	13.94	100	41.2%	-1.40 [-5.22, 2.42]	
Subtotal (95% CI)			292			214	100.0%	-2.11 [-4.56, 0.34]	•
Heterogeneity: Chi²=	0.22, df	= 1 (P =	0.64);	$I^{2} = 0\%$					
Test for overall effect	Z = 1.68	8 (P = 0.	09)						
1.10.2 Up to 6 month	IS								
Aitken 2012	0.4	15.34	155	2.1	12.84	109	52.5%	-1.70 [-5.11, 1.71]	
Bilton 2011	-0.3	11.7	114	0.5	13.66	87	47.5%	-0.80 [-4.38, 2.78]	-
Subtotal (95% CI)			269			196	100.0%	-1.27 [-3.74, 1.20]	•
Heterogeneity: Chi²=	0.13, df	= 1 (P =	= 0.72);	$ ^2 = 0\%$					
Test for overall effect	Z = 1.01	(P = 0.	31)						
									-20 -10 0 10 20
									Favours control Favours mannitol

Figure 79: Quality of life: change in CFQ-R eating at 4 & 6 months follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation

Figure 80: Quality of life: change in CFQ-R health at 4 & 6 months follow-up (range of scores: 0-100)

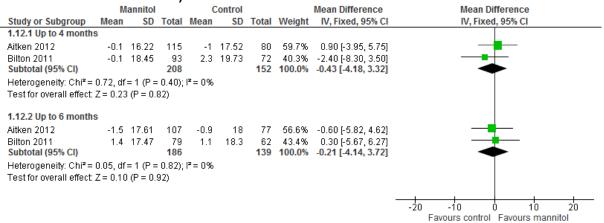


Figure 81: Quality of life: change in CFQ-R social at 4 & 6 months follow-up (range of scores: 0-100)

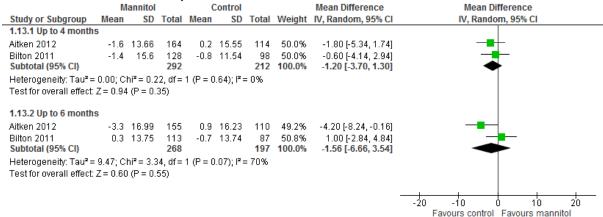


Figure 82: Quality of life: change in CFQ-R body at 4 & 6 months follow-up (range of scores: 0-100)

			/						
	M	annitol		0	Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.16.1 Up to 4 months	S								
Aitken 2012	-2	21.75	164	1.5	21.39	113	43.1%	-3.50 [-8.66, 1.66]	
Bilton 2011	-1.2	16.94	126	1.6	16.97	97	56.9%	-2.80 [-7.29, 1.69]	
Subtotal (95% CI)			290			210	100.0%	-3.10 [-6.49, 0.29]	•
Heterogeneity: Chi ² =	0.04, df	= 1 (P =	0.84);	$l^2 = 0\%$					
Test for overall effect:	Z = 1.79	P = 0.	07)						
1.16.2 Up to 6 months	S								
Aitken 2012	0.4	20.29	155	2.9	20.86	109	43.2%	-2.50 [-7.55, 2.55]	
Bilton 2011	1.6	16.26	111	1.8	15.14	86	56.8%	-0.20 [-4.60, 4.20]	
Subtotal (95% CI)			266			195	100.0%	-1.19 [-4.51, 2.13]	•
Heterogeneity: Chi ² =	0.45, df	= 1 (P =	0.50);	$I^2 = 0\%$					
Test for overall effect:	Z = 0.70	P = 0	48)						
									-20 -10 0 10 20
									Favours control Favours mannitol

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation

Figure 83: Quality of life: change in CFQ-R role at 4 & 6 months follow-up (range of scores: 0-100)

			,						
	M	annitol		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.17.1 Up to 4 month	S								
Aitken 2012	-0.9	13.93	115	-0.8	17.33	79	55.9%	-0.10 [-4.69, 4.49]	- •
Bilton 2011	0.5	18.05	92	-2.4	15.66	72	44.1%	2.90 [-2.27, 8.07]	
Subtotal (95% CI)			207			151	100.0%	1.22 [-2.21, 4.66]	*
Heterogeneity: Tau ² =	0.00; CI	$hi^2 = 0.7$	'2, df=	1 (P = 0)	.39); l² :	= 0%			
Test for overall effect:	Z = 0.70	P = 0	48)						
1.17.2 Up to 6 month	s								
Aitken 2012	-2.3	17.35	106	1.1	13.83	76	54.3%	-3.40 [-7.94, 1.14]	
Bilton 2011	-0.4	16.66	80	-1.6	15.15	62	45.7%	1.20 [-4.05, 6.45]	
Subtotal (95% CI)			186			138	100.0%	-1.30 [-5.79, 3.19]	-
Heterogeneity: Tau2=	4.32; CI	$hi^2 = 1.8$	9, df=	1 (P = 0)	.19); l ^a :	= 41%			
Test for overall effect:	Z = 0.57	P = 0	57)						
									-20 -10 0 10 20
									Favours control Favours mannitol

Figure 84: Quality of life: change in CFQ-R digestion at 4 & 6 months follow-up (range of scores: 0-100)

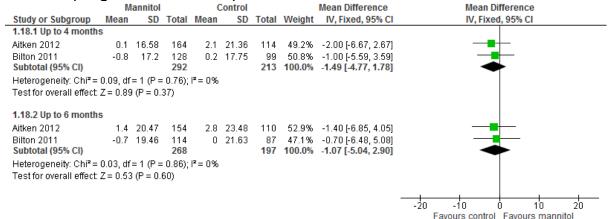
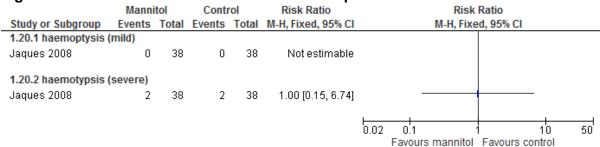


Figure 85: Quality of life: change in CFQ-R weight at 4 & 6 months follow-up (range of scores: 0-100)

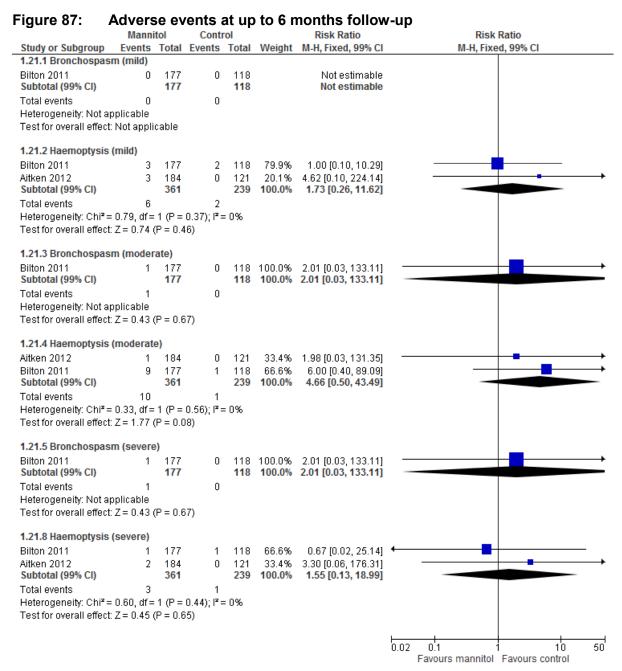
	M	annitol	•	0	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.19.1 Up to 4 months	5								
Aitken 2012	2	32.23	115	4.6	27.94	80	50.7%	-2.60 [-11.10, 5.90]	
Bilton 2011 Subtotal (95% CI)	1.4	26.11	92 207	7.3	29.53	73 153	49.3% 100.0%	-5.90 [-14.52, 2.72] - 4.23 [-10.28, 1.83]	
Heterogeneity: Chi ² =	0.29, df	= 1 (P =	0.59);	$l^2 = 0\%$					
Test for overall effect:	Z = 1.37	(P = 0.	17)						
1.19.2 Up to 6 months	S								
Aitken 2012	4.1	33.71	106	7.8	29.07	77	51.9%	-3.70 [-12.83, 5.43]	
Bilton 2011 Subtotal (95% CI)	3.7	23.72	80 186	6.5	31.85	62 139	48.1% 100.0%	-2.80 [-12.28, 6.68] - 3.27 [-9.84, 3.31]	
Heterogeneity: Chi ² =	0.02, df	= 1 (P =	0.89);	$l^2 = 0\%$					
Test for overall effect:	Z = 0.97	P = 0.	33)						
									-20 -10 0 10 20
									Favours control Favours mannitol

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation

Figure 86: Adverse events at 2 weeks follow-up

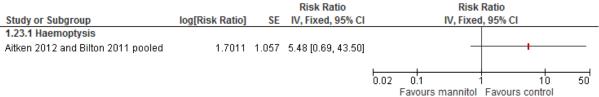


Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 88: Adverse events in children and young people at up to 6 months followup



Abbreviations: IV: inverse variance; SE: standard error Data was extracted from Cochrane SR Nolan 2015. Data was already pooled for Aitken 2012 and Bilton 2011 studies

Figure 89: Adverse events in adults at up to 6 months follow-up

			Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.24.1 Haemoptysis				
Aitken 2012 and Bilton 2011 pooled	0.6043	0.5361	1.83 [0.64, 5.23]	+
1.24.2 Bronchospasm				
Bilton 2011	1.209	1.5616	3.35 [0.16, 71.50]	
				0.02 0.1 1 10 50
				Favours mannitol Favours control

Abbreviations: IV: inverse variance; SE: standard error

Data was extracted from Cochrane SR Nolan 2015. Data was already pooled for Aitken 2012 and Bilton 2011

studies for haemoptysis

Comparison 1.2.1. Mannitol versus Dornase alfa

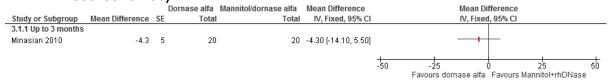
Figure 90: Lung function – FEV₁ % change from baseline up to 3 months (range of scores: 0-100)

			Mannitol	Dornase alfa	Mean Difference	Mean Difference					
Study or Subgroup	Mean Difference	SE	Total	Total	IV, Fixed, 95% CI		IV, Fix	ed, 95% CI			
2.1.1 Up to 3 months											
Minasian 2010	2.8	3.88	20	20	2.80 [-4.80, 10.40]		_	++	-		
						-20	-10	0 1	0 :	20	
						Favou	irs dornase alt	a Favours n	nannitol		

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SE: standard error

Comparison 1.2.2. Mannitol + Dornase alfa versus Dornase alfa alone

Figure 91: Lung function – FEV_1 % change from baseline up to 3 months (range of scores: 0-100)



Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SE: standard error

Comparison 1.3: Mannitol versus nebulised sodium chloride

No evidence was found for this comparison.

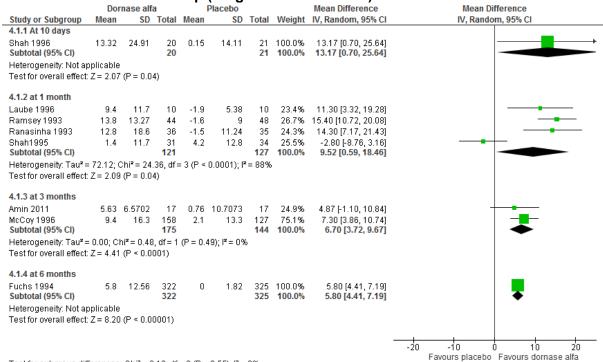
Comparison 1.4. Mannitol versus acetylcysteine

No evidence was found for this comparison.

I.8.2 Dornase alfa

Comparison 2.1. Dornase alfa versus placebo

Figure 92: Lung function: relative mean % change in FEV₁ at 10 days; and at 1, 3 & 6 months follow-up (range of scores: 0-100)

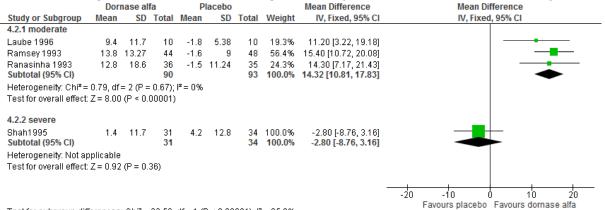


Test for subgroup differences: $Chi^2 = 2.13$, df = 3 (P = 0.55), $I^2 = 0\%$

Abbreviations: CI: confidence interval; df: degrees of freedom; FEV_1 : forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation.

Note: See sensitivity analysis

Figure 93: Lung function: relative mean % change in FEV₁ at 1 month follow-up (range of scores: 0-100) (subgroup analysis based on disease severity)



Test for subgroup differences: $Chi^2 = 23.56$, df = 1 (P < 0.00001), $I^2 = 95.8\%$

Abbreviations: CI: confidence interval; df: degrees of freedom; FEV₁: forced expiratory volume in 1 second; IV: inverse variance: SD: standard deviation

Figure 94: Lung function: mean % change in FEV₁ at 1 month follow-up (range of scores: 0-100) (subgroup analysis: participants with acute exacerbation)

	Dor	nase al	fa	Placebo			Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fix	ed, 95	% CI	
Wilmott 1996	20	19.67	43	19	42.58	37	1.00 [-13.93, 15.93]			+		-
								-20	-10	Ó	10	20
									Favours placeh	0 Fav	ours dornas	e alfa

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 95: Lung function: absolute mean % change in FEV₁ at 2 years (range of scores: 0-100)

	Dornase alfa			Placebo Mean Difference					Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI		
Quan 2001	0.04	11.43	204	-3.2	11.43	206	3.24 [1.03, 5.45]			+		
								-20	-10	0	10	20
									Favours placebo	Favours	dornase	alfa

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 96: Number of people experiencing exacerbations at 6 months & 2 years follow-up

	Dornase alfa		Place	bo	Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI				
4.5.1 at 6 months										
Fuchs 1994	71	322	89	325	0.81 [0.61, 1.06]	+				
4.5.2 at 2 years										
Quan 2001	40	236	56	234	0.71 [0.49, 1.02]					
						0.05 0.2 5 20 Favours dornase alfa Favours placebo				

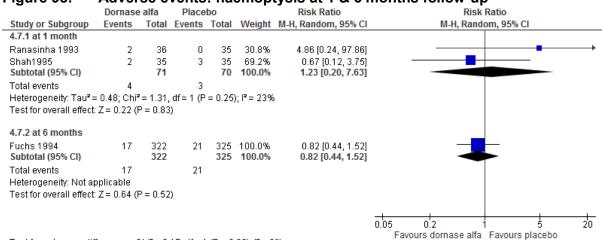
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 97: Number of days of IV antibiotics use at 1 month follow-up

	Dornase alfa		P	lacebo		Mean Difference		Mean Dr	fference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	I, 95% CI		
4.6.1 at 3 months												
McCoy 1996	25.35	19.58	158	28.31	19.94	162	-2.96 [-7.29, 1.37]		-	_		
								-20	-10 () ,	10	20
								Favours of	lornase alfa	Favours	placebo	

Abbreviations: CI: confidence interval; IV antibiotics: intravenous antibiotics; IV: inverse variance; SD: standard deviation

Figure 98: Adverse events: haemoptysis at 1 & 6 months follow-up



Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), l² = 0%

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Dornase alpha Placebo Risk Ratio Risk Ratio Weight M-H, Random, 95% CI M-H, Random, 95% CI Study or Subgroup **Events** Total Events Total 4.8.1 at 1 month Ramsev 1993 12 44 Π 48 48.3% 27.22 [1.66, 446.58] Ranasinha 1993 n 36 0 35 Not estimable Shah1995 1 35 3 35 51.7% 0.33 [0.04, 3.05] Subtotal (95% CI) 115 118 100.0% 2.79 [0.03, 278.07] Total events 13 3 Heterogeneity: $Tau^2 = 9.38$; $Chi^2 = 6.66$, df = 1 (P = 0.010); $I^2 = 85\%$ Test for overall effect: Z = 0.44 (P = 0.66) 4.8.2 at 3 months McCoy 1996 28 158 162 100.0% 2.87 [1.44, 5.71] 10 Subtotal (95% CI) 2.87 [1.44, 5.71] 158 162 100.0% Total events 28 10 Heterogeneity: Not applicable Test for overall effect: Z = 3.00 (P = 0.003) 4.8.3 at 6 months Fuchs 1994 12 322 325 100.0% 1.73 [0.69, 4.34] Subtotal (95% CI) 322 325 100.0% 1.73 [0.69, 4.34] Total events 12 Heterogeneity: Not applicable Test for overall effect: Z = 1.17 (P = 0.24) 4.8.4 at 2 years Quan 2001 26 236 100.0% 6.26 [0.39, 99.96] Subtotal (95% CI) 27 100.0% 6.26 [0.39, 99.96] 236 ٥ Total events 26 Heterogeneity: Not applicable Test for overall effect: Z = 1.30 (P = 0.19) 0.05 20 0.2 Favours dornase alfa Favours placebo

Figure 99: Adverse events: voice alteration at 1, 3, 6 months and 2 years follow-up

Test for subgroup differences: $Chi^2 = 1.19$, df = 3 (P = 0.75), $I^2 = 0\%$ Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

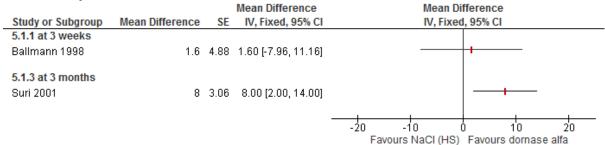
Figure 100: Quality of life (measured with CFQ-R) at 3 months (range of scores: 0-100)

•	Dornase alfa			Placebo		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
4.9.1 CFQ-R parents										
Amin 2011	-4.56	16.2702	17	0.89	12.58	17	-5.45 [-15.23, 4.33]			
4.9.2 CFQ-R 14+										
Amin 2011	-10.49	12.5	17	-5.28	17.6799	17	-5.21 [-15.50, 5.08]			
								-20 -10 0 10 20 Favours placebo Favours dornase alfa		

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

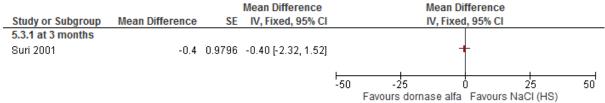
Comparison 2.2. Dornase alfa versus nebulized sodium chloride

Lung function: mean % change in FEV₁ at 3 weeks and 3 months follow-Figure 101: up



Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; NaCl (HS): sodium chloride (hypertonic saline); SE: standard error

Figure 102: Number of days of inpatient treatment at 3 months follow-up



Abbreviations: CI: confidence interval; IV: inverse variance; NaCl (HS): sodium chloride (hypertonic saline); SE: standard error

Comparison 2.3. Dornase alfa versus acetylcysteine

No evidence was found for this comparison.

I.8.3 Nebulised sodium chloride

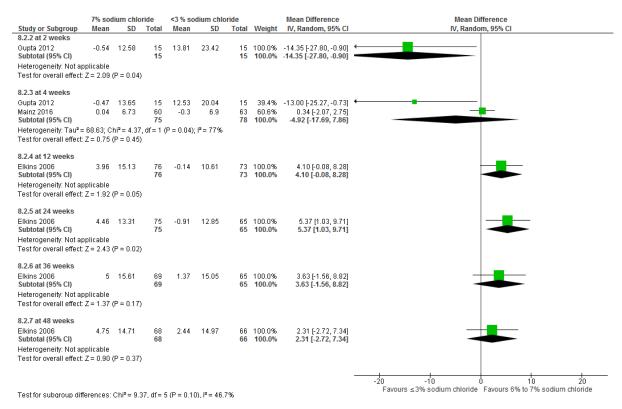
Comparison 3.1. Nebulised sodium chloride (> 3% concentration) versus placebo (0.9% to 0.12%) or low-concentration (≤ 3%)

Figure 103: Failed to regain pre-exacerbation FEV₁% predicted at hospital discharge

	7 % Soululli Cli	% Souluin Cinoriue		illoriue	RISK RAUU	RISK RAUO						
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI				
Dentice 2016	17	67	28	65	0.59 [0.36, 0.97]							
						+			-			
						0.05	0.2	1 5	20			
							7% sodium chloride	<3% sodium chloride				

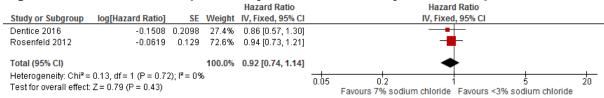
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel. Note: Length of hospital stay was 12 days for the intervention group, and 13 days for the control group. Pre-exacerbation FEV₁% predicted was measured ≈ 6 months before.

Figure 104: Lung function: % change in FEV₁ at 2, 4, 12, 24, 36 & 48 weeks follow-up (range of scores: 0-100)



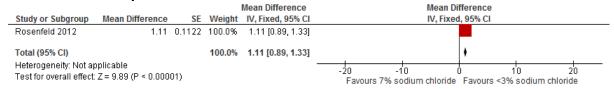
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 105: Time to next pulmonary exacerbation at 1 year follow-up



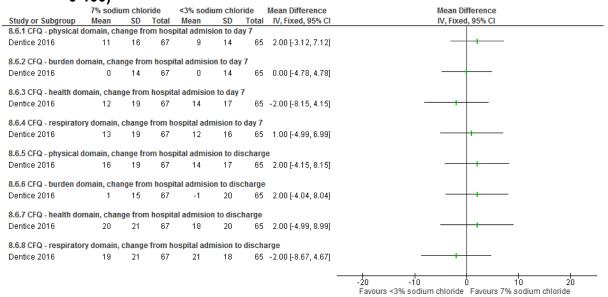
Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 106: Number of days of treatment for a pulmonary exacerbation at 48 weeks follow-up



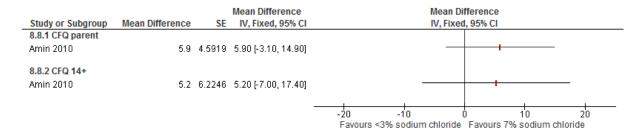
Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 107: Change in quality of life (CF-QOL) following treatment (range of scores: 0-100)



Abbreviations: CI: confidence interval; CF-QOL:: cystic fibrosis quality of life questionnaire; IV: inverse variance; SD: standard deviation

Figure 108: Change in quality of life (CFQ-R), at 4 weeks follow-up (range of scores: 0-100)



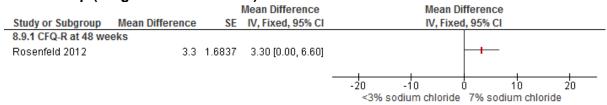
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SE: standard error

Figure 109: Change in quality of life (CFQ-R) at 48 weeks follow-up (range of scores: 0-100)

	7% soc	lium chlo	oride	<3% so	dium chlo	oride	Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI			
8.9.3 CFQ parents at	48 week	S									
Elkins 2006	0.9	11.93	34	2.03	14.48	33	-1.13 [-7.49, 5.23]				
8.9.4 CFQ 14+ at 48 w	veeks										
Elkins 2006	1.09	10.92	46	-6.68	17.09	45	7.77 [1.86, 13.68]				
								-20 -10 0 10 20			
								Favours <3% sodium chloride Favours 7% sodium chloride			

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 110: Change in quality of life: CFQ-R respiratory domain, at 48 weeks follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SE: standard error

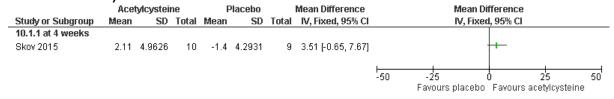
Comparison 3.2. Nebulised sodium chloride versus acetylcysteine

No evidence was found for this comparison.

I.8.4 Acetylcysteine

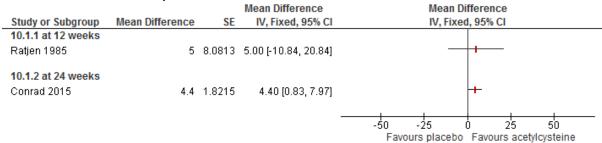
Comparison 4. Acetylcysteine versus placebo

Figure 111: Lung function: change in FEV₁ % predicted at 4 weeks (range of scores: 0-100)



Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 112: Lung function: change in FEV₁ % predicted at 12 and 24 weeks (range of scores: 0-100)



Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 113: Inflammatory markers: IL-8 at 24 weeks

			Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	IV, Fixed, 95% CI	IV, Fixed, 95% CI
10.2.1 at 24 weeks				
Conrad 2015	0.19	1.12	0.19 [-2.01, 2.39]	
				-2 -1 0 1 2
				Favours acetylcysteine Favours placebo

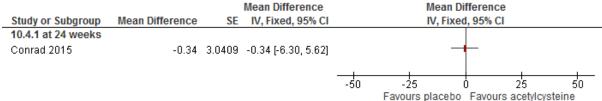
Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 114: Incidence of pulmonary exacerbations at 24 weeks

	Acetylcys	teine	Place	bo	Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fix	ed, 95% CI	
10.3.1 at 24 weeks								
Conrad 2015	15	36	17	34	0.83 [0.50, 1.39]	\dashv	+	
						0.01 0.1	1 10	100
						Favours acetylcysteine	Favours placebo	

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 115: Quality of life: QFQ-R respiratory at 24 weeks (range of scores: 0-100)

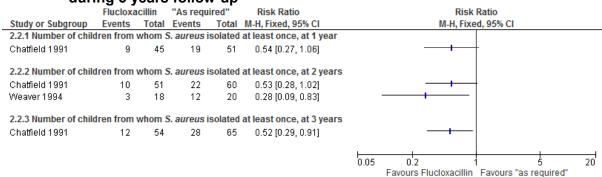


Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SE: standard error

I.9 Pulmonary infection – prophylaxis

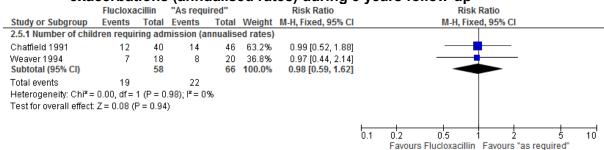
Comparison 1. Continuous oral flucloxacillin versus antibiotics as required

Figure 116: Number of children from whom *S. Aureus* was identified at least once during 3 years follow-up



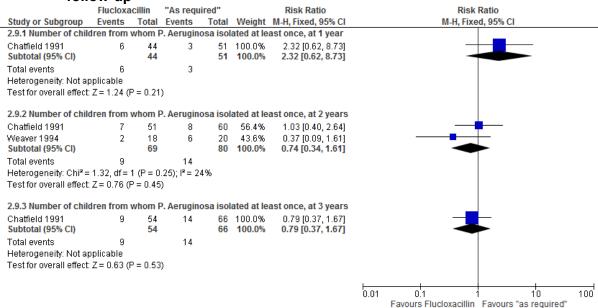
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 117: Number of children admitted to hospital due to pulmonary exacerbations (annualised rates) during 3 years follow-up



Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

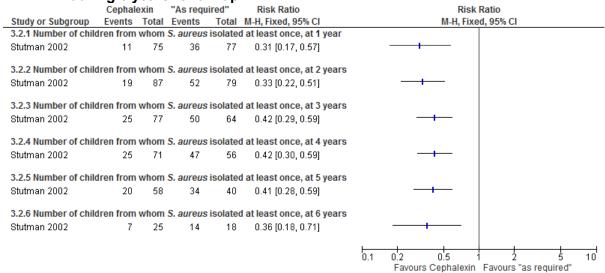
Figure 118: Number of children in whom *P. aeruginosa* was identified during 3 years follow-up



Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

Comparison 2. Continuous oral Cephalexin versus antibiotics as required

Figure 119: Number of children from whom *S. aureus* was identified at least once during 6 years follow-up



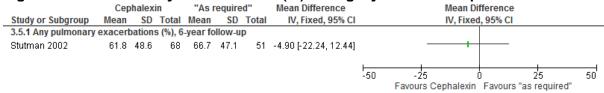
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 120: FEV₁ (litres) at 6 years follow-up

•	Cer	halex	in	"As r	equire	d"	Mean Difference		Mean D	ifference		
Study or Subgroup	Mean			Mean	•	Total				d, 95% CI		
3.3.1 FEV, at 6 years												
Stutman 2002	113.5	28.5	68	115.8	32.9	51	-2.30 [-13.59, 8.99]					
								-50	-25	Ó 2	<u>2</u> 5	50
									Favours "as required"	Favours Cep	halexin	

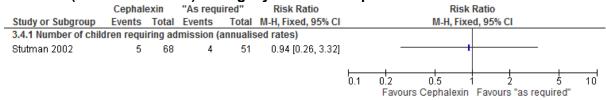
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 121: Pulmonary exacerbations (%) during 6 years follow-up



Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation;

Figure 122: Number of children admitted to hospital due to pulmonary exacerbations (annualised rates) during 6 years follow-up



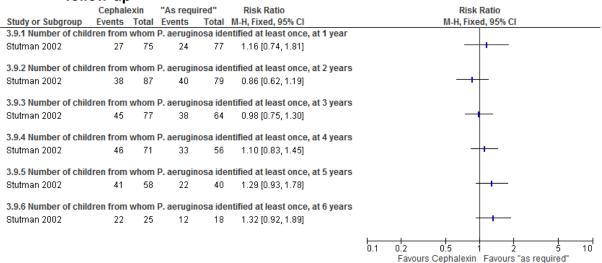
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 123: Minor adverse events during 6 years follow-up

	Cep	halex	cin	"As r	equire	ed"	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.7.1 Generalised ra	sh							
Stutman 2002	0.6	1.7	68	0.2	0.9	51	0.40 [-0.07, 0.87]	 • -
3.7.2 Nappy rash								
Stutman 2002	4	5.8	68	3.1	5.1	51	0.90 [-1.06, 2.86]	- -
3.7.3 Increased stoo	ol frequer	тсу						
Stutman 2002	4.3	6.1	68	4.1	6.9	51	0.20 [-2.18, 2.58]	
								-4 -2 0 2 4
								Favours Cephalexin Favours "as required"

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 124: Number of children in whom *P. Aeruginosa* was identified at 1 to 6 years follow-up



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

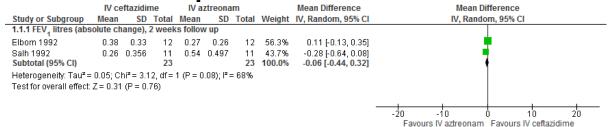
I.10 Pulmonary infection – acute

I.10.1 Pseudomonas aeruginosa

I.10.1.1 Antimicrobial treatment for pulmonary exacerbations due to P. aeruginosa

Comparison 1. Single IV antibiotic versus single IV antibiotic

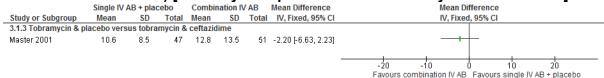
Figure 125: FEV₁ litres (absolute change) at end of 2 week course [ceftazidime *versus* aztreonam]



Abbreviations: CI: confidence interval; df: degrees of freedom; FEV_1 : forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

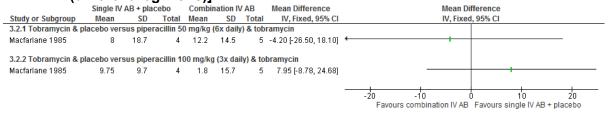
Comparison 2. Single IV antibiotic (with placebo) versus combination IV

Figure 126: FEV₁ % predicted (absolute change) at 10 days follow-up (range of scores: 0-100) [Tobramycin + placebo *versus* tobramycin + ceftazidime]



Abbreviations: CI: confidence interval; FEV_1 : forced expiratory volume in 1 second; IV: inverse variance (at the top of the plot) or intravenous (at the bottom of the plot); SD: standard deviation

Figure 127: FEV₁ % predicted (relative change) at end of 2 weeks course (range of scores: 0-100) [tobramycin + placebo *versus* tobramycin + piperacillin (different regimens)]



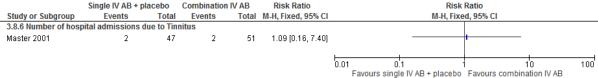
Abbreviations: AB: antibiotics; CI: confidence interval; FEV_1 : forced expiratory volume in 1 second; IV: inverse variance (at the top of the plot) or intravenous (at the bottom of the plot); SD: standard deviation

Figure 128: Adverse effects: sensitivity reaction at end of 2 weeks course [tobramycin + placebo versus tobramycin + piperacillin (all regimens)]

	Siligle IV AB + p	acebo	Combination	IV AB	RISK RAUO	RISK	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
3.7.1 Piperacillin (all I	regimens)							
Macfarlane 1985	0	8	3	10	0.17 [0.01, 2.96]		 	
						0.01 0.1	1 10	100
						Favours single IV AB + placebo	Favours combination IV AB	
	0 0	8	3	10	0.17 [0.01, 2.96]	0.01 0.1 Favours single IV AB + placebo	1 10 Favours combination IV AB	100

Abbreviations: AB: antibiotics; CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel

Figure 129: Adverse effects: number of hospital admissions due to tinnitus during 10 day course [tobramycin + placebo *versus* ceftazidime + tobramycin]



Abbreviations: AB: antibiotics; CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel;

Figure 130: Adverse effects: adverse effects (serum concentrations) during 10 day course [tobramycin + placebo *versus* ceftazidime + tobramycin]

	Single IV AB + placebo			Combin	ation IV	/ AB	Mean Difference			Mean Difference	_	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI			IV, Fixed, 95% CI		
3.9.1 Creatinine												
Master 2001	0	8	23	4	10	21	-4.00 [-9.38, 1.38]			++		
3.9.2 NAG												
Master 2001	1.5	1.1	23	3.6	3	21	-2.10 [-3.46, -0.74]			+		
								-100	-50	Ó	50	100
								Favoui	rs single IV AB +	placebo Favours	combination IV AB	

Abbreviations: AB: antibiotics; CI: confidence interval; IV: inverse variance; IV AB: intravenous antibiotics; SD: standard deviation

Comparison 3. Single IV antibiotic *versus* combination IV antibiotic for pulmonary exacerbations with PA

Figure 131: FEV₁ (relative change) at 10 to 14 days follow-up (range of scores: 0-100) [ceftazidime *versus* tobramycin & ticarcillin]

					nation I\	/ AB	Mean Difference	Mean Difference				
Study or Subgroup	Mean SD Total rsus tobramycin & tic			Mean	SD	Total	IV, Fixed, 95% CI		IV,	Fixed, 95%	CI	
4.1.1 Ceftazidime ver	rsus tobramycin & tica 13.7 23.09 17			rcillin								
Gold 1985	,			33.3	27.76	13	-19.60 [-38.26, -0.94]	← +				
								-20	-10	- 	10	20
									combination I	/ AB Favoi	irs single IV	

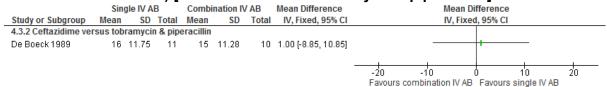
Abbreviations: AB: antibiotics; CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; IV AB: intravenous antibiotics; SD: standard deviation

Figure 132: FEV₁ ml (absolute change) at 12 days follow-up [colistin *versus* colistin + "other"]

	Sin	gle IV A					Mean Difference	Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		1	IV, Fixed	, 95% CI		
4.2.1 Colstin versus	us colistin & "other", 12 days follow up												
Conway 1997	97				330.6	35	-160.00 [-309.72, -10.28]						
								-100	-50	Ċ)	50	100
								Favou	rs combinatio	n IV AB	Favours sing	ie IV AB	

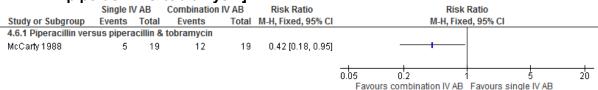
Abbreviations: AB: antibiotics; CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; IV AB: intravenous antibiotics; SD: standard deviation

Figure 133: FEV₁ % predicted (absolute change) at 14 days follow-up (range of scores: 0-100) [ceftazidime *versus* tobramycin + piperacillin]



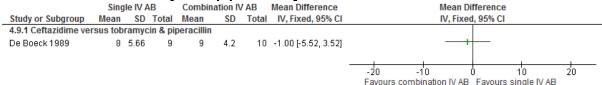
Abbreviations: AB: antibiotics; CI: confidence interval; FEV_1 : forced expiratory volume in 1 second; IV: inverse variance; IV AB: intravenous antibiotics; SD: standard deviation

Figure 134: Eradication: number of people in whom pseudomonas isolates were eradicated at end of course at 10 days follow-up [piperacillin *versus* piperacillin & tobramycin]



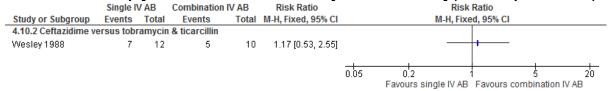
Abbreviations: AB: antibiotics; CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel;

Figure 135: Time to readmission (in months) at 24 to 26 months follow-up [ceftazidime versus tobramycin + piperacillin]



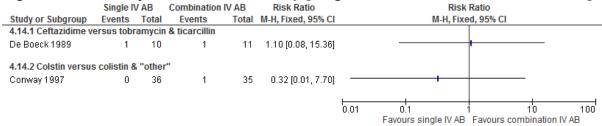
Abbreviations: AB: antibiotics; CI: confidence interval; IV: inverse variance; IV AB: intravenous antibiotics; SD: standard deviation

Figure 136: Number of admissions requiring IV antibiotics or death at 3 months follow-up [ceftazidime *versus* tobramycin & ticarcillin] (follow-up 3 months)



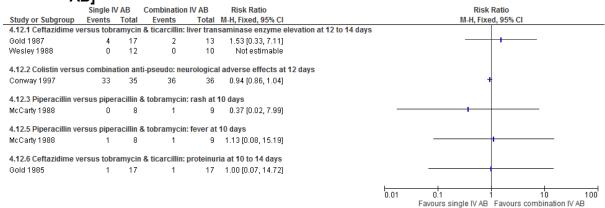
Abbreviations: AB: antibiotics; CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel

Figure 137: Mortality at 4 months follow-up [Single IV AB versus combination IV AB]



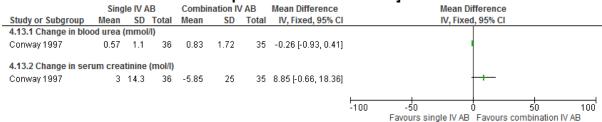
Abbreviations: AB: antibiotics; CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel;

Figure 138: Adverse events at 14 days follow-up [single IV *versus* combination IV AB]



Abbreviations: AB: antibiotics; CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel

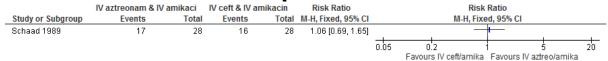
Figure 139: Adverse events: renal toxicity at 12 days follow-up [colistin *versus* combination other anti-pseudomonal antibiotic]



Abbreviations: AB: antibiotics; CI: confidence interval; IV: inverse variance; IV AB: intravenous antibiotics; SD: standard deviation

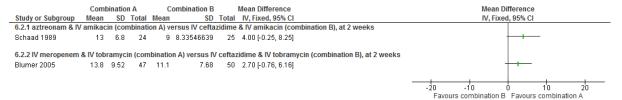
Comparison 4. Combination IV antibiotics *versus* combination IV antibiotics for pulmonary exacerbations

Figure 140: Eradication of pathogen at 2 weeks follow-up [aztreonam + amikacin versus ceftazidime + amikacin]



Abbreviations: aztreo: aztreonam; amika: amikacin; M-H: Mantel-Haenszel; Cl: confidence interval

Figure 141: FEV₁ % predicted (absolute change) at 2 weeks follow-up (range of scores: 0-100) [IV combination A vs IV combination B]



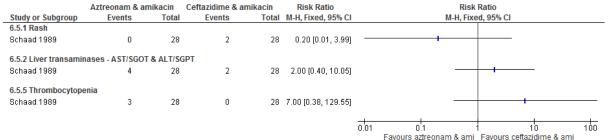
Abbreviations: amika: amikacin; ceft: ceftazidime; CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 142: FEV₁ % predicted (relative change) at 2 weeks follow-up (range of scores: 0-100) [meropenem + obramycin versus ceftazidime + tobramycin]

	Meropenem	& tobran	nycin	Ceftazidim	e & tobran	nycin	Mean Difference		Mea	n Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fi	ixed, 95% CI		
6.3.1 IV meropenem	& IV tobramyc	in versus	IV ceftaz	idime & IV t	obramycin	, at 14 d	ays					
Blumer 2005	38.8	52.3	47	29.4	35.1	50	9.40 [-8.44, 27.24]		-		+	→
								-20	-10	ò	10	20
								Favou	re coffazidima 8. f	toh Egypure r	noronono	m & toh

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation; tob: tobramycin

Figure 143: Adverse effects at 2 weeks follow-up [aztreonam + amikacin *versus* ceftazidime + amikacin



Abbreviations: ami: amikacin; CI: confidence interval; M-H: Mantel-Haenszel;

Comparison 5. Two IV antibiotics + inhaled antibiotic *versus* 2 IV without inhaled antibiotic

Figure 144: Eradication of P. aeruginosa at 15 days follow-up [IV ceftazidime + IV amikacin + inhaled amikacin versus IV ceftazidime + IV amikacin]



Abbreviations: CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel; w/o: without

Figure 145: Adverse effects: raised liver transaminases at 4 to 6 weeks follow-up [IV ceftazidime + IV amikacin + inhaled amikacin versus IV ceftazidime + IV amikacin]



Abbreviations: CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel; w/o: without

Comparison 6. IV ceftazidime + IV tobramycin versus oral ciprofloxacin

Figure 146: Eradication of P. aeruginosa at 2 weeks follow-up

	IV ceftazidime & IV tob		Oral ciprof	floxacin	Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-	H, Fixed, 959	% CI	
Richard 1997	30	48	12	49	2.55 [1.49, 4.37]				⊢ .	
						0.01	0.1	1	10	100
							Favours oral cir	oroflox Favo	urs IV ceft & IV to	ah

Abbreviations: ceft: ceftazidime; CI: confidence interval; IV: intravenous; M-H: Mantel-Haenszel; tob: tobramycin

Figure 147: Adverse effects - Treatment-related events at 2 weeks follow-up

	IV ceftazidime 8	IV tob	Oral ciprofl	oxacin	Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fix	ed, 95% CI	
15.2.1 Treatment-rel	ated events							
Richard 1997	10	53	9	55	1.15 [0.51, 2.61]	_	+	
						—	ļ	
						0.01 0.1	1 10	100
						Favours IV ceftaz & tob	Favours oral cipro	

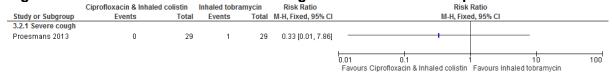
Abbreviations: ceft: ceftazidime; CI: confidence interval; cipro: ciprofloxacin; IV: intravenous; M-H: Mantel-

Haenszel; tob: tobramycin

I.10.1.2 Antimicrobial treatment for acute infection with P. aeruginosa

Comparison 7. Oral ciprofloxacin + inhaled colistin versus inhaled tobramycin

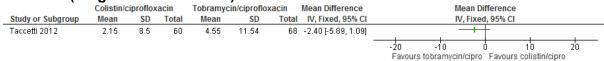
Figure 148: Adverse events: severe cough at 3 months follow-up



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

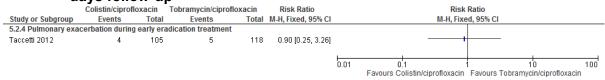
Comparison 8. Inhaled colistin + oral ciprofloxacin *versus* inhaled tobramycin + oral ciprofloxacin

Figure 149: Relative change in % predicted FEV₁ from baseline at 54 days follow-up (range of scores: 0-100)



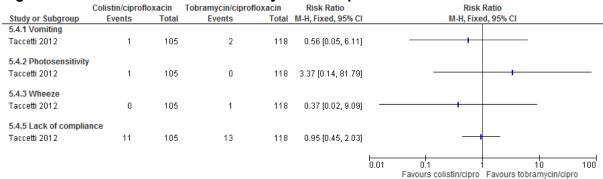
Abbreviations: CI: confidence interval; cipro: ciprofloxacin; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 150: Treatment failure - trial discontinuation due to lack of compliance at 28 days follow-up



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel;

Figure 151: Adverse effects at 28 days follow-up



Abbreviations: CI: confidence interval; cipro: ciprofloxacin; M-H: Mantel-Haenszel

I.10.2 Staphylococcus aureus

Not applicable, as no studies were identified for inclusion.

I.10.3 Burkholderia cepacia complex

Not applicable, as no studies were identified for inclusion.

I.10.4 Non-tuberculous mycobacteria

Not applicable, as no studies were identified for inclusion.

I.10.5 Non-identified pathogen

Not applicable, as no studies were identified for inclusion.

I.11 Pulmonary infection - chronic

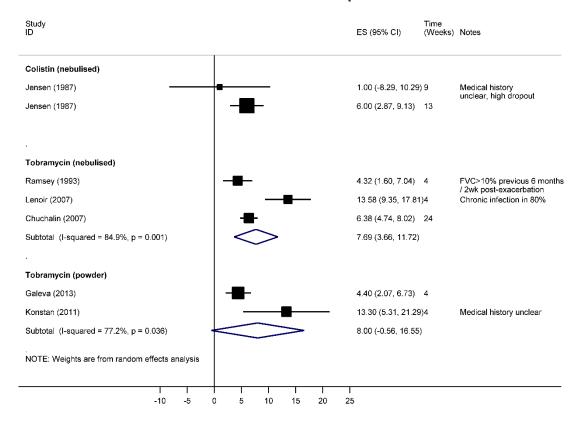
I.11.1 Pseudomonas Aeruginosa

I.11.1.1 NMA outcomes

Outcome 1: NMA FEV₁ % predicted (range of scores: 0-100)

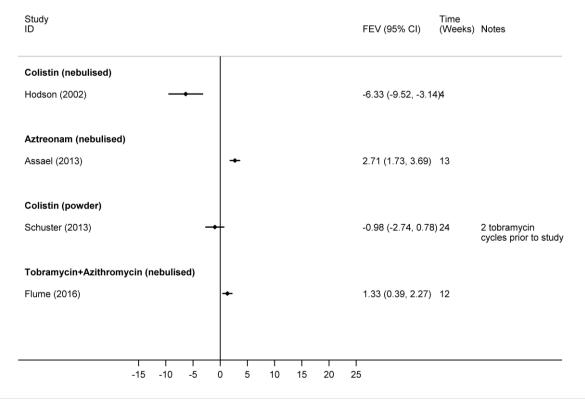
Figure 152: Forest plot showing mean differences (with their 95% CI) of study estimates for interventions *versus* placebo

Treatments versus placebo



Abbreviations: CI: confidence interval; ES: effect size

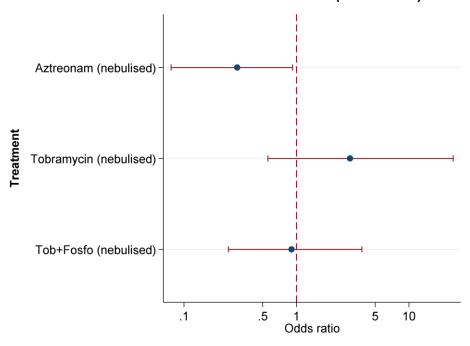
Figure 153: Forest plot showing mean differences (with their 95% CI) of study estimates for interventions *versus* tobramycin (nebulised)



Abbreviations: CI: confidence interval; FEV: forced expiratory volume

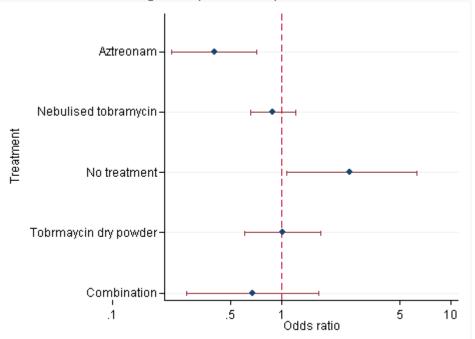
Outcome 2: NMA number of patients experiencing at last one exacerbation

Figure 154: Forest plot showing odds ratios (with their 95% CI) of NMA estimates for each intervention *versus* placebo for the number of people experiencing at least one exacerbation with short-term (4-10 weeks) treatment



Abbreviations: CI: confidence interval; Fosfo: fosfomycin; Tob: tobramycin. Note: Vertical dashed line shows line of no effect.

Figure 155: Forest plot showing odds ratios (with their 95% CI) of NMA estimates for each intervention *versus* placebo for the number of people experiencing at least one exacerbation with long-term (>10 weeks) treatment

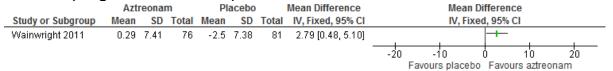


Combination: 28 days aztreonam lysine (nebulised) alternating with 28 days tobramycin (nebulised). Vertical dashed line shows the line of no effect

I.11.1.2 Non-NMA outcomes (pairwise comparisons)

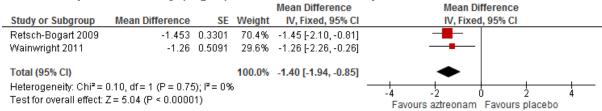
Pairwise comparison 1: Aztreonam lysine versus placebo

Figure 156: Lung function: relative change in FEV₁% predicted at 28 days follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 157: Suppression of the organism: adjusted mean change in P. aeruginosa sputum density (log10), at 4 weeks follow-up



Abbreviations: CI: confidence interval; df: degrees of freedom; IV: inverse variance; SE: standard error

Figure 158: Nutritional status: % weight change (kg), at 4 weeks follow-up

	AZ	treonam		H	^a lacebo		Mean Difference			Mean Diff	erence		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI			IV, Fixed,	95% CI		
Retsch-Bogart 2009	1.1	2.1882	80	0.1	2.1882	84	1.00 [0.33, 1.67]			-	+		
								-10	-5	 	-		10
									Favours	placebo	Favours aztr	eonam	

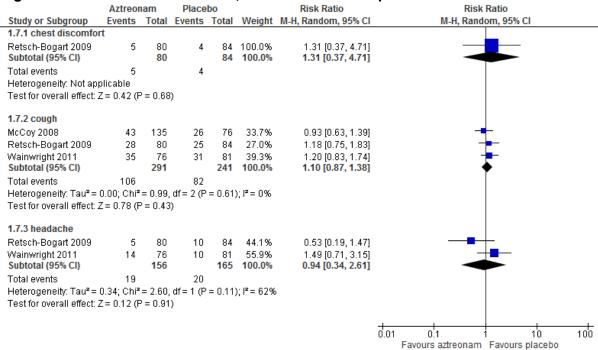
Abbreviations: CI: confidence interval; IV: inverse variance; kg: kilograms; SD: standard deviation

Figure 159: Quality of life: CFQ-R, at 4 weeks follow-up (range of scores: 0-100)

Study or Subgroup		Placebo Total Mean SD	Total Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
l .6.1 CFQ-R body imag Retsch-Bogart 2009	e 3.2 14.3703	80 1 14.3703	84 40.3%	2.20 [-2.20, 6.60]	
/ainwright 2011	3.7 10.4614	76 1.1 12.522	80 59.7%	2.60 [-1.01, 6.21]	+
ubtotal (95% CI) otorogonoity: Tau² – (. 00 · Chi≅ – 0 02 df	156 = 1 (P = 0.89); P = 0%	164 100.0%	2.44 [-0.35, 5.23]	•
est for overall effect: Z		-1 (1 - 0.03),1 - 0.0			
6.2 CFQ-R digestion					<u>_</u>
etsch-Bogart 2009 /ainwright 2011	2.2 12.4108 3.6 16.5638	80 1.9 12.4108 76 5.5 17.1	84 65.8% 81 34.2%	0.30 [-3.50, 4.10] -1.90 [-7.17, 3.37]	
ubtotal (95% CI)	3.0 10.3030	156	165 100.0%	-0.45 [-3.53, 2.63]	•
eterogeneity: Tau² = 0 est for overall effect: Z		= 1 (P = 0.51); I ² = 0%			
6.3 CFQ-R eating					
etsch-Bogart 2009	3.6 13.7172	80 -4.7 13.7172	84 49.9%	8.30 [4.10, 12.50]	_
ainwright 2011 ubtotal (95% CI)	0.5 13.0767	76 -1.2 13.5 156	81 50.1% 165 100.0%	1.70 [-2.46, 5.86] 4.99 [-1.47, 11.46]	
		ff= 1 (P = 0.03); I ^z = 79%	6		
6.4 CFQ-R emotional					
etsch-Bogart 2009	3.9 11.7576	80 -1.3 11.7576	84 49.2%	5.20 [1.60, 8.80]	
(ainwright 2011 ubtotal (95% CI)	3.3 10.4614	76 3.7 10.7331 156	80 50.8% 164 100.0%	-0.40 [-3.73, 2.93] 2.36 [-3.13, 7.84]	
	2.55; Chi² = 5.01, d	if = 1 (P = 0.03); I ² = 80%		2.00 [-0.10, 1.04]	
est for overall effect: Z	= 0.84 (P = 0.40)	•			
.6.5 CFQ-R health per	•	00 40 40 000	04 51 52	0.0014.0014.001	_
etsch-Bogart 2009 /ainwright 2011	5 16.3299 1.8 14.6969	80 -4.8 16.3299 54 -1.8 14.6969	84 51.9% 54 48.1%	9.80 [4.80, 14.80] 3.60 [-1.94, 9.14]	
ubtotal (95% CI)		134	138 100.0%	6.82 [0.75, 12.89]	
leterogeneity: Tau² = 1 est for overall effect: Z		#f = 1 (P = 0.10);	b		
.6.6 CFQ-R physical fo	_				
etsch-Bogart 2009 /ainwright 2011	2.3 18.2895 1.8 13.9485	80 -6.9 18.2895 76 -0.69 13.4164	84 46.3% 80 53.7%	9.20 [3.60, 14.80]	
ubtotal (95% CI)	1.0 13.8465	76 -0.69 13.4164 156	164 100.0%	2.49 [-1.81, 6.79] 5.60 [-0.96, 12.15]	
eterogeneity: Tau² = 1 est for overall effect: Z		ff= 1 (P = 0.06); I ^z = 71%	6		
.6.7 CFQ-R respirator	y symptoms				
Retsch-Bogart 2009	7.1 17.6363	80 -2.6 17.6363	84 49.0%	9.70 [4.30, 15.10]	<u> </u>
/ainwright 2011 ubtotal (95% CI)	3 14.8203	76 2.9 15.3 156	81 51.0% 165 100.0%	0.10 [-4.61, 4.81] 4.81 [-4.60, 14.21]	
		if = 1 (P = 0.009); I ^z = 85	%		
est for overall effect: Z					
. 6.8 CFQ-R role/scho d etsch-Bogart 2009	ol 2.1 16.3299	80 -4.2 16.3299	84 47.1%	6.30 [1.30, 11.30]	
Vainwright 2011	0.29 10.9202	53 0.29 10.3827	55 52.9%	0.00 [-4.02, 4.02]	_ -
ubtotal (95% CI)	4.40.00.2	133	139 100.0%	2.97 [-3.20, 9.13]	
est for overall effect: Z		ff= 1 (P = 0.05); F= 73%	0		
6.9 CFQ-R social fun	_				_
etsch-Bogart 2009 /ainwright 2011	-1.2 13.3906 1.9 12.1244	80 -3.6 13.3906 75 -2.6 11.6276	84 45.5% 80 54.5%	2.40 [-1.70, 6.50] 4.50 [0.76, 8.24]	T
ubtotal (95% CI)		155	164 100.0%	3.54 [0.78, 6.31]	 ◆
eterogeneity: Tau² = 0 est for overall effect: Z		= 1 (P = 0.46); I ^z = 0%			
6.10 CFQ-R treatmen	t burden				
etsch-Bogart 2009 /ainwright 2011	0.2 15.6767 1.2 13.9485	80 -3.1 15.6767 76 5.1 14.4	84 49.2% 81 50.8%	3.30 [-1.50, 8.10] -3.90 [-8.33, 0.53]	
ubtotal (95% CI)		156	165 100.0%	-0.36 [-7.42, 6.69]	
eterogeneity: Tau² = 2 est for overall effect: Z		if= 1 (P = 0.03); I ^z = 79%	6		
6.11 CFQ-R vitality					
etsch-Bogart 2009	3.6 17.9629	80 -4.4 17.9629	84 53.1%	8.00 [2.50, 13.50]	<u>-</u> -
/ainwright 2011 ubtotal (95% CI)	0.38 16.1666	54 -2.2 16.1666 134	54 46.9% 138 100.0%	2.58 [-3.52, 8.68] 5.46 [0.16, 10.76]	
		= 1 (P = 0.20); I ² = 40%		•	
.6.12 CFQ-R weight	(, 0.04)				
etsch-Bogart 2009	4.7 23.8417	80 1.4 23.8417	84 54.8%	3.30 [-4.00, 10.60]	- •
/ainwright 2011 ubtotal (95% CI)	4.3 21.1123	53 2.6 21.507 133	55 45.2% 139 100.0%	1.70 [-6.34, 9.74] 2.58 [-2.83, 7.98]	
leterogeneity: Tau² = 0		= 1 (P = 0.77); P = 0%	133 100.0%	2.30 [-2.03, 1.86]	
est for overall effect: Z	= 0.93 (P = 0.35)				
					-20 -10 0 10
					Favours placebo Favours aztreonam

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; df: degrees of freedom; IV: inverse variance; SD: standard deviation

Figure 160: Mild adverse events, at 4 weeks follow-up



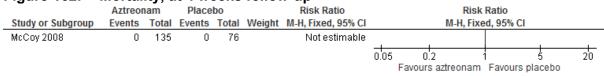
Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

Figure 161: Serious adverse events, at 4 weeks follow-up

	Aztreon	am	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.8.2 dyspnea							
Retsch-Bogart 2009 Subtotal (95% CI)	5	80 80	8	84 84	100.0% 100.0%	0.66 [0.22, 1.92] 0.66 [0.22, 1.92]	
Total events	5	00	8	04	100.070	0.00 [0.22, 1.32]	
Heterogeneity: Not app	licable						
Test for overall effect: 2	Z = 0.77 (P)	= 0.44)				
1.8.3 haematypsis							
McCoy 2008	13	135	7	76	53.4%	1.05 [0.44, 2.51]	
Retsch-Bogart 2009	5	80	8	84	46.6%	0.66 [0.22, 1.92]	
Subtotal (95% CI)		215		160	100.0%	0.86 [0.44, 1.70]	-
Total events	18		15				
Heterogeneity: Chi² = 0).43, df = 1	(P = 0)	.51); P= I	0%			
Test for overall effect: Z	Z = 0.42 (P	= 0.67)				
	,						
							0.01 0.1 1 10 10
							Favours aztreonam Favours placebo

Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

Figure 162: Mortality, at 4 weeks follow-up



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel. Not estimable as no deaths were recorded in either group.

Figure 163: Emergence of resistant organisms, at 42 weeks follow-up

	Aztreoi	nam	Place	bo	Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
1.10.1 persitent isola	ition of S. /	Aureus						
Retsch-Bogart 2009	2	74	5	81	0.44 [0.09, 2.19]			
1.10.2 persitent isola	ition of B. (Cepacia	1					
Retsch-Bogart 2009	0	74	0	81	Not estimable			
1.10.3 persitent isola	ition of S. I	Maltoph	ilia					
Retsch-Bogart 2009	2	74	0	81	5.47 [0.27, 112.04]		 	
1.10.4 persitent isola	ition of A.	Xilosida	ns					
Retsch-Bogart 2009	1	74	2	81	0.55 [0.05, 5.91]			
						t	10	
						0.002 0.1		50Ó
						Favours aztreonam	Favours placebo	

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel.

Pairwise comparison 2: Ciprofloxacin versus placebo

Figure 164: Nutritional status: weight (kg), at 6 to 12 months follow-up

	Cipro	rofloxacin Placebo				Mean Difference	Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI		
Sheldon 1993	55.7	11.4	15	51.3	11.6	16	4.40 [-3.70, 12.50]		_	+-	_	
								-20	10	1		
								-20	Favours placebo	Favours o	u z ziprofloxacii	:0 n

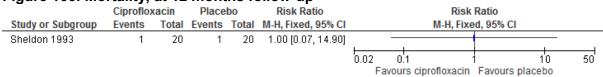
Abbreviations: CI: confidence interval; kg: kilograms; IV: inverse variance; SD: standard deviation

Figure 165: Mild adverse events, at 12 months follow-up

	Ciproflox	acin	Place	bo	Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
2.7.1 AE: gastrointes	tinal							
Sheldon 1993	2	20	0	20	5.00 [0.26, 98.00]		 	
						—		
						0.01 0.1	1 10	100
						Favours ciprofloxacin	Favours placebo	

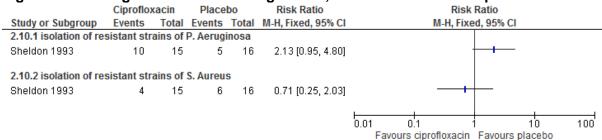
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel.

Figure 166: Mortality, at 12 months follow-up



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 167: Emergence of resistant organisms, at 12 months follow-up



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Pairwise comparison 3.1. Colistin versus placebo

Figure 168: Lung function: change in FEV₁ % predicted at 3 months follow-up (range of scores: 0-100)

	Colistin			Placebo			Mean Difference	Difference Mean D			ence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fix	ked, 95	% CI	
Jensen 1987	-11	6	18	-17	11	11	6.00 [-1.07, 13.07]					
								-20	-10	Ó	10	20
								Fa	vours placel	oo Fav	ours colist	tin

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 169: Suppression of the organism: eradication of the organism from sputum, at 3 months follow-up

	Colistin		Placebo		Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI			
Jensen 1987	0	20	0	20	Not estimable						
						0.01	0.1 Favours placebo	10 Favours colistin	100		

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel. Data cannot be plotted as there were 0 events in each group.

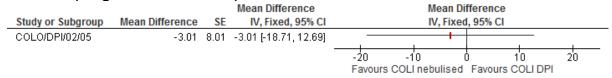
Figure 170: Emergence of resistant organisms, at 3 months follow-up

	Colist	tin	Place	bo	Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
3.9.1 superinfection	with othe	r colist	tin-resist	ant org	ganisms				
Jensen 1987	0	20	0	20	Not estimable				
3.9.2 resistance to c	olistin								
Jensen 1987	0	20	0	20	Not estimable				
3.9.3 resistance to o	ther com	monly	used ant	i-pseud	domonas txt				
Jensen 1987	0	20	0	20	Not estimable				
						<u> </u>	+		
						0.01	0.1	1 10	10
							Favours colistin	Favours placebo	

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel. Data cannot be plotted as there were 0 events in each group.

Pairwise comparison 3.2. Colistin inhalation powder (COLO DPI) *versus* colistin inhalation solution (COLI nebulised)

Figure 171: Lung function: % mean change in FEV₁% predicted at 4 weeks follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; COLI: colistin; DPI: dry powder inhalation; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SE: standard error

Figure 172: Mild adverse events, at 8 weeks follow-up

	COLL	DPI	COLI nebu	ılised	Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
4.7.2 AE: vomiting								
COLO/DPI/02/05	2	16	0	15	4.71 [0.24, 90.69]			
4.7.3 AE: productive	cough							
COLO/DPI/02/05	2	16	1	15	1.88 [0.19, 18.60]			
4.7.4 AE: chest disco	mfort							
COLO/DPI/02/05	4	16	2	15	1.88 [0.40, 8.78]		- 	
						<u> </u>		
						0.01	0.1 1 10	100
							Favours COLIDPI Favours COLI nebulise	d

Abbreviations: CI: confidence interval; COLI: colistin; DPI: dry powder inhalation; M-H: Mantel-Haenszel

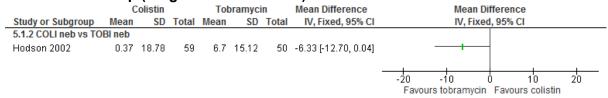
Figure 173: Serious adverse events, at 8 weeks follow-up

_	COLIT	DPI	COLI nebu	ulised	Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
4.8.1 AE: dyspnea								
COLO/DPI/02/05	3	16	4	15	0.70 [0.19, 2.63]			
						0.01 0.1	1 10	100
							Favours COLI nebul	

Abbreviations: CI: confidence interval; COLI: colistin; DPI: dry powder inhalation; M-H: Mantel-Haenszel

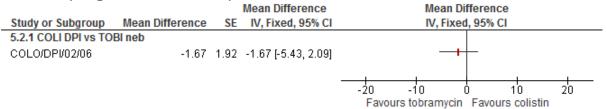
Pairwise comparison 3.3. Colistin versus tobramycin

Figure 174: Lung function: mean % change in FEV₁% predicted at 1 to 3 months follow-up (range of scores: 0-100)



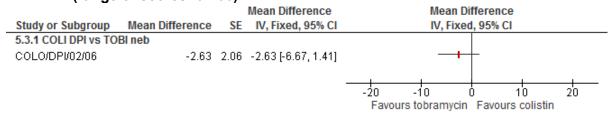
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; Neb: nebulised; SD: standard deviation

Figure 175: Lung function: mean % change in FEV₁% predicted at 4 weeks follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; Neb: nebulised; SE: standard error

Figure 176: Lung function: mean % change in FEV₁% predicted at 12 weeks follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; Neb: nebulised; SE: standard error

Figure 177: Lung function: mean % change in FEV₁% predicted at 24 weeks follow-up (range of scores: 0-100)

(14)	nge en eeen	· ·	0 100	',			
			Colistin	Tobramycin		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
5.4.1 COLI DPI vs TO)Bl neb						
COLO/DPI/02/06	-0.59	2.23	153	181	0.0%	-0.59 [-4.96, 3.78]	
Schuster2013	0.99	0.02	153	171	100.0%	0.99 [0.95, 1.03]	
Subtotal (95% CI)			306	352	100.0%	0.99 [0.95, 1.03]	\top
Heterogeneity: Chi ² =	= 0.50, df $= 1$ (P $= 0.4$	l8); l² =	: 0%				
Test for overall effect	:: Z= 49.50 (P < 0.00	001)					
Total (95% CI)			306	352	100.0%	0.99 [0.95, 1.03]	
Heterogeneity: Chi ² =	= 0.50, df = 1 (P = 0.4	l8); l² =	: 0%				
Test for overall effect	: Z = 49.50 (P < 0.00	001)					-20 -10 0 10 20
Test for subgroup dif	•						Favours tobramycin Favours colistin

Abbreviations: CI: confidence interval; df: degrees of freedom; FEV_1 : forced expiratory volume in 1 second; IV: inverse variance; Neb: nebulised; SE: standard error

Figure 178: Time to next pulmonary exacerbation: time to first additional antipseudomonal treatment (days), at 24 weeks follow-up

	Colistin						Mean Difference		Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed, 95% CI			
5.6.1 COLI DPI vs TOI	Bl neb											
COLO/DPI/02/06	55.28	43.2	183	51.79	41.9	191	3.49 [-5.14, 12.12]		+-			
								-50	-25 0 25	5 50		
									Favours tobramycin Favours colis			

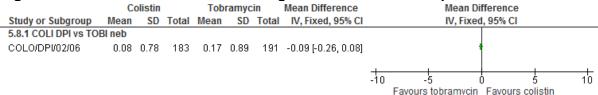
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 179: Suppression of the organism: change in sputum P. aeruginosa density Log10 CFU/ml, at 4 weeks follow-up

	Colistin		olistin Tobramycin Mean				Mean Difference		Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	ed, 95% CI		
5.7.1 TOBI neb vs CO)Ll neb											
Hodson 2002	-0.47	1.53	37	-0.79	1.35	42	0.32 [-0.32, 0.96]			+		
									1			
								-10	-5	Ó	5	10
								Fav	ours colistir	n Favours	tobran	nycin

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 180: Nutritional status: BMI change at 24 weeks follow-up



Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 181: Quality of life: CFQ-R all domains, at 24 weeks follow-up (range of scores: 0-100)

Data cannot be presented in forest plots, as SD are not reported.

Abbreviations: CFQ-R: cystic fibrosis questionnaire revised

Figure 182: Mild adverse events: change in sputum, at 4 weeks follow-up

	Colis	tin	Tobram	ycin	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI	
5.21.1 COLI neb vs T	OBI neb								_
Hodson 2002	8	62	6	53	1.14 [0.42, 3.08]			 	
						0.01	n1 ·	10	100
						0.01	Favours colistin	Favours tobr	

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 183: Mild adverse events: pharyngitis, at 4 weeks follow-up

	Colist	tin	Tobramycin		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI				
5.22.1 COLI neb vs T	OBI neb									
Hodson 2002	3	62	7	53	0.37 [0.10, 1.35]	- + 				
						0.01 0.1 1 10	100			
						Favours colistin Favours tobramyo	in			

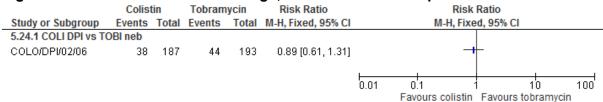
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 184: Mild adverse events: cough, at 4 weeks follow-up

	Colis	tin	Tobram	ycin	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI		
5.23.1 COLI neb vs T	OBI neb									
Hodson 2002	11	62	5	53	1.88 [0.70, 5.07]		_	 - 		
						0.01	<u> </u>	1 1	<u> </u>	100
						0.01	Favours colistin	Favours tob	ramycin	

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 185: Mild adverse events: cough, at 24 weeks follow-up



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 186: Mild adverse events: chest discomfort, at 24 weeks follow-up



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 187: Mild adverse events: vomiting, at 24 weeks follow-up

	Colist	tin	Tobramycin		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI		
5.26.1 COLI DPI vs TO	OBI neb									
COLO/DPI/02/06	6	187	8	193	0.77 [0.27, 2.19]					
						0.01	N 1	1 1	Ω	100
						0.01	Favours colistin		~	

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 188: Serious adverse events: patients with > 1 serious AE, at 4 weeks follow-

	Colist	tin	Tobramycin		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI		
5.27.1 COLI neb vs To	OBI neb									
Hodson 2002	7	62	8	53	0.75 [0.29, 1.93]		-			
						0.01	0.1	i 1	0	100
							Favours colistin	Favours tob	ramycin	

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 189: Serious adverse events: dyspnoea, at 4 weeks follow-up

_	Colis	tin	Tobram	ycin	Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI		
5.28.1 COLI neb vs T	OBI neb									
Hodson 2002	7	62	5	53	1.20 [0.40, 3.55]			 		
						<u> </u>	-			—
						0.01	0.1	1 1	Ō	100
							Favours colistin	Favours tob	ramycir	n

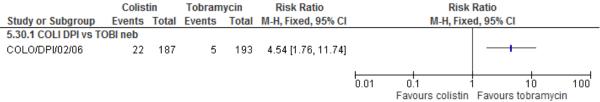
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 190: Serious adverse events: dyspnoea, at 24 weeks follow-up

	Colist	tin	Tobram	ycin	Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
5.29.1 COLI DPI vs TO	OBI neb						
COLO/DPI/02/06	49	187	52	193	0.97 [0.70, 1.36]	· •	
						0.01 0.1 1 10	100
						Favours colistin Favours tobra	

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 191: Serious adverse events: patients withdrawn, at 24 weeks follow-up



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 192: Serious adverse events: haemoptysis, at 24 weeks follow-up

	Colist	tin	Tobram	ycin	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI		
5.31.1 COLI DPI vs TO)Bl neb									
COLO/DPI/02/06	20	187	13	193	1.59 [0.81, 3.10]		-	 		
						0.01	01	1 1	<u> </u>	100
						0.01	Favours colistin	Favours tob	ramvcin	100

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

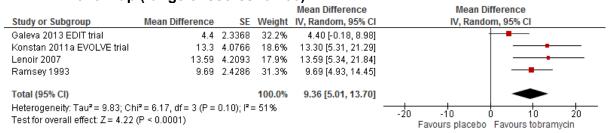
Figure 193: Emergence of resistant organisms: emergence of highly tobramycinresistant P. Aeruginosa at 4 weeks follow-up

	Colist	tin	Tobram	ycin	Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI		
5.32.1 COLI neb vs To	OBI neb									
Hodson 2002	0	62	0	53	Not estimable					
						0.01	0.1	1 1	0	100
							Favours colistin	Favours tob	ramycin	ı

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel. Data cannot be plotted, as there were 0 events in each group.

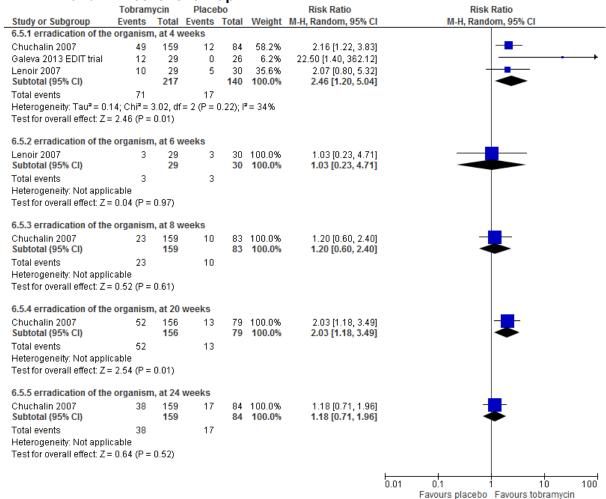
Pairwise comparison 4.1. Tobramycin versus placebo

Figure 194: Lung function: mean % change in FEV₁% predicted at 1 to 3 months follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; df: degrees of freedom; FEV_1 : forced expiratory volume in 1 second; IV: inverse variance; SE: standard error

Figure 195: Suppression of the organism: eradication of the organism at 4, 6, 12, 8, 20 and 24 weeks follow-up



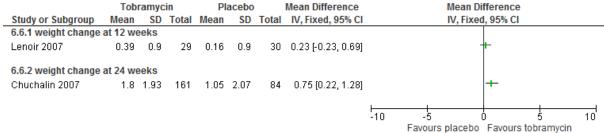
Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

Figure 196: Suppression of the organism: change in P. aeruginosa sputum density log10 CFU/G, at 4 weeks follow-up

log to Gr	⁻U/G,	aι 4	MAG	:V2 I	OHOW	-up		
	To	bramycii	n	F	Placebo		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	I IV, Fixed, 95% CI
6.6.1 change in PA sputum de	ensity log	10 CFU/	g, 4 we	eks				
Galeva 2013 EDIT trial	-1.2	1.6155	29	0	1.5297	26	-1.20 [-2.03, -0.37]	
6.6.2 change in non-mucoid P	A sputu	m densit	y log1() CFU/g,	4 weeks	;		
Konstan 2011a EVOLVE trial	-1.91	2.54	46	-0.15	0.68	49	-1.76 [-2.52, -1.00]	· · ·
6.6.3 change in mucoid PA sp	utum de	nsity log	10 CFL	J/g, 4 we	eeks			
Konstan 2011a EVOLVE trial	-2.61	2.53	46	-0.43	1.05	49	-2.18 [-2.97, -1.39]	
								-10 -5 0 5
								Favours tobramycin Favours placebo

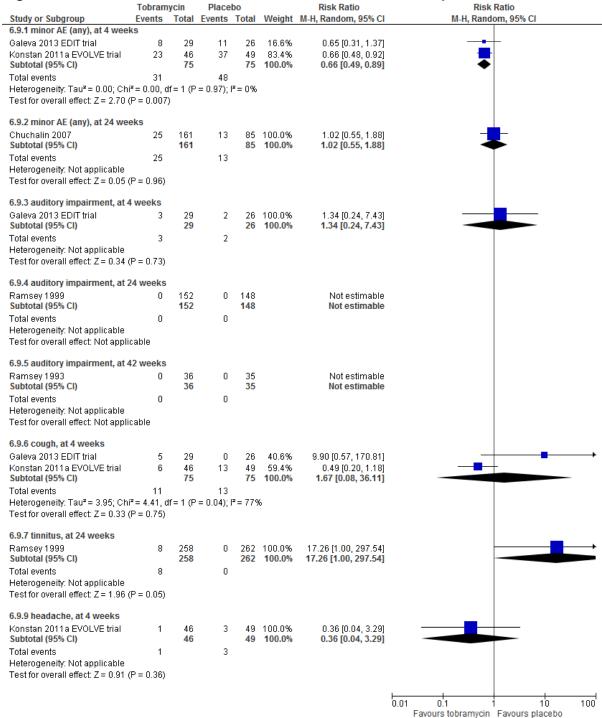
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 197: Nutrition: bodyweight change (kg), at 12 and 24 weeks follow-up



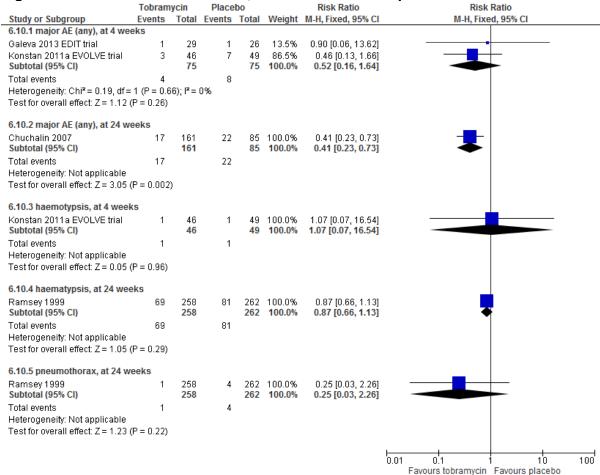
Abbreviations: CI: confidence interval; IV: inverse variance; kg: kilograms; SD: standard deviation

Figure 198: Mild adverse events, at 4, 24 and 42 weeks follow-up



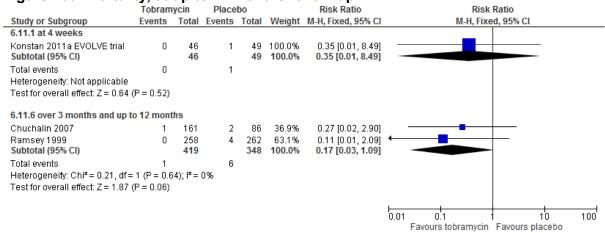
Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel





Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

Figure 200: Mortality, at up to 12 months follow-up



Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

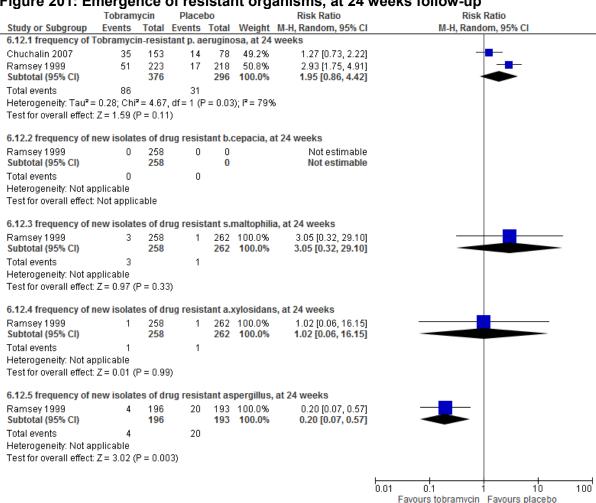
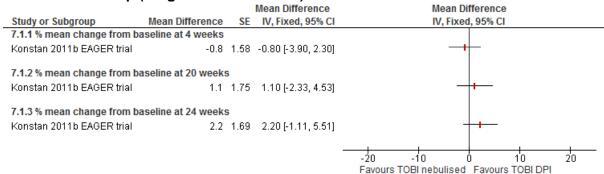


Figure 201: Emergence of resistant organisms, at 24 weeks follow-up

Abbreviations: CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel

Pairwise comparison 4.2. Tobramycin inhalation powder (TOBI DPI) versus tobramycin inhalation solution (TOBI nebulised)

Figure 202: Lung function: mean change in FEV₁% predicted at 4, 20 and 24 weeks follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; DPI: dry powder inhalation; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SE: standard error; TOBI: tobramycin

Figure 203: Suppression of the organism: mean change in P. aeruginosa sputum density log10 CFU, at 4 to 20 weeks follow-up

	TC	DBI DP	I	TOBI	nebulis	sed	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	I IV, Fixed, 95% CI
7.5.1 at 4 weeks								
Konstan 2011b EAGER trial	-1.76	1.96	308	-1.32	2.03	209	-0.44 [-0.79, -0.09]	ı +
7.5.2 at 20 weeks								
Konstan 2011b EAGER trial	-1.61	2.03	308	-0.77	1.78	209	-0.84 [-1.17, -0.51]	1 +
								-10 -5 0 5 10
								Favours TOBI DPI Favours TOBI nebulised

Abbreviations: CI: confidence interval; DPI: dry powder inhalation; FEV_1 : forced expiratory volume in 1 second; IV: inverse variance; PA: Pseudomonas aeruginosa; SD: standard deviation; TOBI: tobramycin

Figure 204: Mild adverse events, at 24 weeks follow-up

_	TOBII	DPI	TOBI neb	ulised	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
7.7.1 any mild or moderate A	E					
Konstan 2011b EAGER trial	226	308	143	209	1.07 [0.96, 1.20]	
7.7.2 AE: headache						
Konstan 2011b EAGER trial	35	308	25	209	0.95 [0.59, 1.54]	+
7.7.3 AE: productive cough						
Konstan 2011b EAGER trial	56	308	41	209	0.93 [0.64, 1.33]	+
7.7.4 AE: vomiting						
Konstan 2011b EAGER trial	19	308	12	209	1.07 [0.53, 2.17]	
						0.01 0.1 1 10 100
						Favoure TORLDPL Favoure TORLnahulicad

Abbreviations: CI: confidence interval; DPI: dry powder inhalation; M-H: Mantel-Haenszel; TOBI: tobramycin

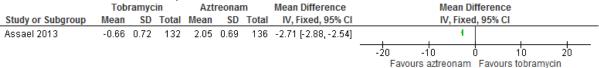
Figure 205: Serious adverse events, at 24 weeks follow-up

_	TOBII	DPI	TOBI neb	ulised	Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
7.8.3 any serious AE							
Konstan 2011b EAGER trial	84	308	61	209	0.93 [0.71, 1.24]		+
7.8.4 AE: dyspnea							
Konstan 2011b EAGER trial	48	308	26	209	1.25 [0.80, 1.95]		+-
7.8.5 AE: haemotypsis							
Konstan 2011b EAGER trial	40	308	26	209	1.04 [0.66, 1.66]		+
						-	
						0.01	0.1 1 10 100 Favours TOBI DPI Favours TOBI nebulised
							ravouis iodidri ravouis iodillebulised

Abbreviations: CI: confidence interval; DPI: dry powder inhalation; M-H: Mantel-Haenszel; TOBI: tobramycin

Pairwise comparison 4.3. Tobramycin versus Aztreonam lysine

Figure 206: Lung function: % change in FEV₁% predicted at 3 months follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation. Calculated across 3x28-day treatment courses

Figure 207: Suppression of the organism: adj mean change sputum density log10 PA CFU/G, at 20 weeks follow-up

	To	bramycir	ı	Az	treonam		Mean Difference		Mean D	ifference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI		
8.4.1 TOBI neb vs AZ	LI											
Assael 2013	-0.32	1.8713	97	-0.55	1.8713	97	0.23 [-0.30, 0.76]			+		
									1			
								-10	-5	Ó	5	10
									Favours tobramycin	Favours a	ztreonam	

Abbreviations: CI: confidence interval; CFU: colony forming unit; IV: inverse variance; PA: Pseudomonas aeruginosa; SD: standard deviation

Figure 208: Nutritional status: % adj mean weight change (kg), at 24 weeks follow-up

	To	bramyciı	1	Az	treonam		Mean Difference			Mean D)iffere	nce		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI			IV, Fixe	d, 959	% CI		
8.5.1 TOBI neb vs AZ	LI													
Assael 2013	0.06	4.9403	132	0.58	4.7814	136	-0.52 [-1.68, 0.64]			_	+			
								-10		·5	Ó	5	10	
								Fav	ours a	treonam	Fav	ours tobr	amycin	

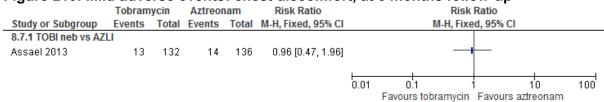
Abbreviations: CI: confidence interval; ; IV: inverse variance; kg: kilograms; SD: standard deviation

Figure 209: Quality of life: CFQ-R respiratory, adj mean change, at 20 weeks follow-up (range of scores: 0-100)

•	Tol	oramyci	in	A	ztreonam		Mean Difference		Mean Di	fference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	I, 95% CI	
8.6.1 TOBI neb vs AZ	LI										
Assael 2013	2.2	19.53	131	6.3	17.4929	131	-4.10 [-8.59, 0.39]			_	
									1	,	
								-20	-10 (10	20
								Fav	ours aztreonam	Favours tobra	mycin

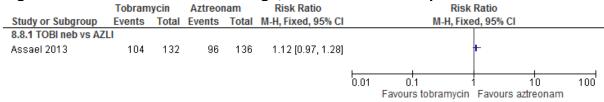
Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 210: Mild adverse events: chest discomfort, at 3 months follow-up



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 211: Mild adverse events: cough, at 3 months follow-up



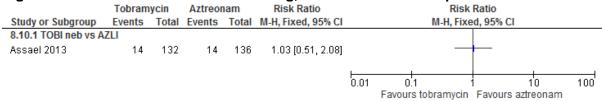
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 212: Mild adverse events: headache, at 3 months follow-up

_	Tobram	ycin	Aztreoi	nam	Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI	
8.9.1 TOBI neb vs AZ	'LI								
Assael 2013	27	132	29	136	0.96 [0.60, 1.53]		_	+	
						0.01	0.1	i 1'0	100
							Favours tobramycin	Favours aztreonam	

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 213: Mild adverse events: vomiting, at 3 months follow-up



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 214: Serious adverse events: dyspnoea, at 3 months follow-up

_	Tobram	nycin	Aztreoi	nam	Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI	
8.13.1 TOBI neb vs A	ZLI								
Assael 2013	21	132	31	136	0.70 [0.42, 1.15]		-	†	
						0.01	0.1	1 10	100
							Favours tobramycin	Favours aztreonam	

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

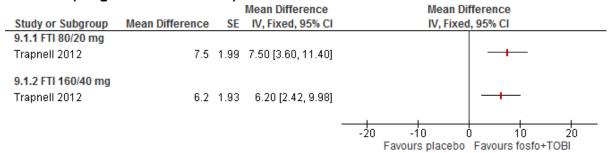
Figure 215: Serious adverse events: haemoptysis, at 3 months follow-up

	Tobram	ycin	Aztreoi	nam	Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
8.14.1 TOBI neb vs A	ZLI								
Assael 2013	21	132	31	136	0.70 [0.42, 1.15]		-+	†	
						0.01	0.1	i 1'0	100
							Favours tobramycin	Favours aztreonam	

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

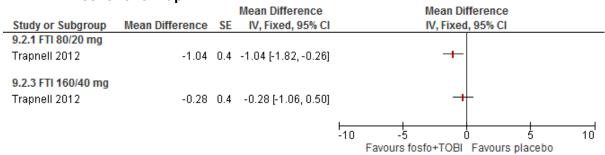
Pairwise comparison 5. Combination of fosfomycin + tobramycin versus placebo

Figure 216: Lung function: relative change in FEV₁% predicted, at 4 weeks follow-up (range of scores: 0-100)



Abbreviations: Abbreviations: CI: confidence interval; FEV_1 : forced expiratory volume in 1 second; fosfo+TOBI: fosfomycin + tobramycin; IV: inverse variance; SE: standard error

Figure 217: Suppression of the organism: sputum PA density, log 10 CFU/g at 4 weeks follow-up



Abbreviations: fosfo+TOBI: fosfomycin + tobramycin; SE: standard error; IV: inverse variance; CI: confidence interval

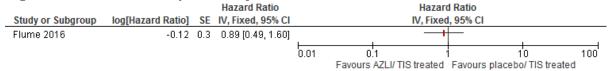
Pairwise comparison 6. Continuous alternating therapy *versus* intermittent treatment: aztreonam lysine + tobramycin or placebo + tobramycin

Figure 218: Lung function: % change in FEV₁% predicted (values at 4 ,12 and 20 weeks were averaged) (range of scores: 0-100)

	AZLI/	TIS trea	ited	placebo	/ TIS tre	ated	Mean Difference	Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV,	Fixed, 95% (CI		
Flume 2016	1.37	0.67	42	0.04	0.66	46	1.33 [1.05, 1.61]			+			
								-20	-10	- 6	10	20	
								Favours	placebo/ TIS tre	eated Favou	rs AZLI/TIS to	eated	

Abbreviations: AZLI: aztreonam lysine; CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation; TIS: tobramycin inhaled solution

Figure 219: Time to next pulmonary exacerbation



Abbreviations: AZLI: aztreonam lysine; CI: confidence interval; IV: inverse variance; SE: standard error; TIS: tobramycin inhaled solution

Figure 220: Quality of life: change in CFQ-R (scores were averaged from weeks 4, 12 and 20) (range of scores: 0-100)



Abbreviations: AZLI: aztreonam lysine; CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation; TIS: tobramycin inhaled solution

Figure 221: Adverse events at 3 months follow-up

	AZLI/ TIS ti	reated	placebo/ TIS t	reated	Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
10.6.1 cough							
Flume 2016	32	42	20	46	1.75 [1.21, 2.54]		
10.6.2 dyspnea							
Flume 2016	13	42	24	46	0.59 [0.35, 1.01]		
10.6.3 serious adver	rse events (n	ot treatr	nent related)				
Flume 2016	21	42	24	46	0.96 [0.64, 1.44]		- -
						<u> </u>	
						0.01	0.1 1 10 100
							Favours AZLI/ TIS treated Favours placebo/ TIS treated

Abbreviations: AZLI: aztreonam lysine; CI: confidence interval; M-H: Mantel-Haenszel; TIS: tobramycin inhaled solution

I.11.2 Staphylococcus Aureus

Not applicable, as no relevant studies were identified.

I.11.3 Burkholderia Cepacia Complex

Not applicable, as no relevant studies were identified.

I.11.4 Aspergillus Fumigatus

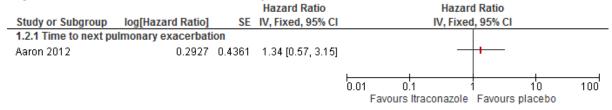
Pairwise comparison 7: Itraconazole versus placebo

Figure 222: Percentage change in FEV₁ from baseline at 24 and 48 weeks follow-up (range of scores: 0-100)

	Itraconazole Pi		Placebo		Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
1.1.1 at 24 weeks fo	llow-up									
Aaron 2012	-4.62	15.6745	18	0.32	15.6745	17	-4.94 [-15.33, 5.45]			
1.1.2 at 48 weeks fo	llow-up									
Aaron 2012	0	0	0	0	0	0	Not estimable			
								-20 -10 0 10 20 Favours placebo Favours Itraconazole		

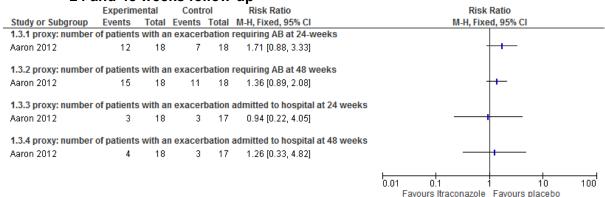
Abbreviations: CI: confidence interval; FEV_1 : forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation. Mean difference (95% CI) at 48-weeks follow-up: -3.71% (-13.26 to 20.28). Not enough data was provided for RevMan.

Figure 223: Time to next pulmonary exacerbation at 24 weeks



Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 224: Number of pulmonary exacerbations requiring AB or hospitalization, at 24 and 48 weeks follow-up



Abbreviations: AB: antibiotics; CI: confidence interval; M-H: Mantel-Haenszel. Proxy outcome.

Figure 225: Quality of life

Data could not be plotted.

Figure 226: Number of people experiencing minor adverse events at 24 weeks follow-up

	Itracona	ızole	Place	bo	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.7.1 increased dyspi	nea					
Aaron 2012	2	18	2	16	0.89 [0.14, 5.60]	
1.7.2 rash						
Aaron 2012	2	18	1	16	1.78 [0.18, 17.80]	
1.7.4 hyperglycaemia						
Aaron 2012	1	18	0	16	2.68 [0.12, 61.58]	
1.7.5 flu-like illness						
Aaron 2012	3	18	0	4.0	e ne ro ne 440 701	
Aaron 2012	3	10	U	10	6.26 [0.35, 112.70]	
1.7.6 diarrhea						
Aaron 2012	0	18	1	16	0.30 [0.01, 6.84]	
11010112012	·				0.00 [0.01, 0.01]	
1.7.7 conjunctivitis						
Aaron 2012	0	18	1	16	0.30 [0.01, 6.84]	+ + -
						0.01 0.1 1 10 100
						Favours Itraconazole Favours placebo
						rateate macerialist Tavoure placebe

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 227: Number of people experiencing major adverse events at 24 weeks follow-up

	Experim	ental	Conti	rol	Risk Ratio	Risk Ratio				
Study or Subgroup	Events Total		Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI				
1.8.1 spontaneous p	neumotho	гах								
Aaron 2012	1	18	0	17	2.84 [0.12, 65.34]		+			
1.8.3 hemoptysis										
Aaron 2012	2	18	1	16	1.78 [0.18, 17.80]		+			
						0.01 0.1	1 1	10 100		
							traconazole Favours pl			

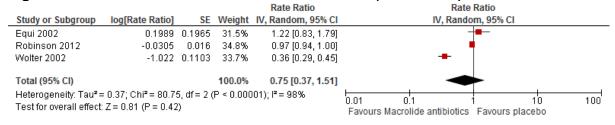
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

I.12 Immunomodulatory agents

I.12.1 NMA outcomes

Pairwise comparison from NMA. Macrolide antibiotics versus placebo

Figure 228: Rate of exacerbations after short-term (1-10 month) treatment

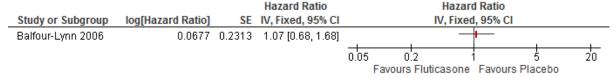


Abbreviations: CI: confidence interval; df: degrees of freedom; IV: inverse variance; SE: standard error

I.12.2 Non-NMA outcomes (pairwise comparisons)

Pairwise comparison 1. Fluticasone versus placebo

Figure 229: Time to next exacerbation at 8 months follow-up



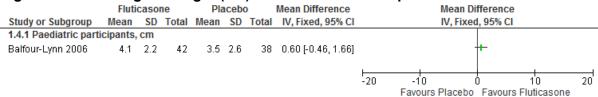
Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 230: Change in height (height standard deviation score) at 0 to 12 months follow-up

	Flu	ıticazone	•	F	Placebo		Mean Difference		Mean D	ifference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI		
1.3.1 SDS (standard devia	tion) sco	ге										
Boeck 2007(belgian trial)	-0.38	0.7359	15	-0.01	0.2711	15	-0.37 [-0.77, 0.03]		-1	1		
											+	—
								-10	-5	Ó	5	10
									Favours Placebo	Favours Flu	uticasone	a

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

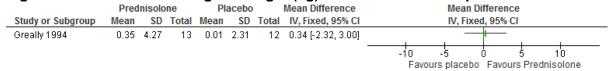
Figure 231: Change in height (cm) at 8 months follow-up



Abbreviations: CI: confidence interval; cm: centimetres; IV: inverse variance; SD: standard deviation

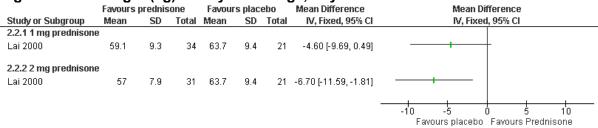
Pairwise comparison 2. Prednisone/ Prednisolone versus placebo

Figure 232: Absolute change in weight (kg) at 12 weeks follow-up



Abbreviations: Ci: confidence interval; IV: inverse variance; kg: kilograms; SD: standard deviation. Intervention: 2mg/kg Prednisolone;

Figure 233: Weight (kg) at 18 years of age, boys



Abbreviations: CI: confidence interval; IV: inverse variance; kg: kilograms; SD: standard deviation

Figure 234: Weight (kg) at 18 years of age, girls

. 9			,,	<i>,</i>			, -, g	
	Favours prednisone			Favours placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.3.1 1 mg prednison	е							
Lai 2000	49.6	10.1	20	51.9	7.2	23	-2.30 [-7.62, 3.02]	
2.3.2 2 mg prednison	е							
Lai 2000	53.6	10.1	23	51.9	7.2	23	1.70 [-3.37, 6.77]	
								
								-10 -5 0 5 10 Favours placeho Favours Prednisone

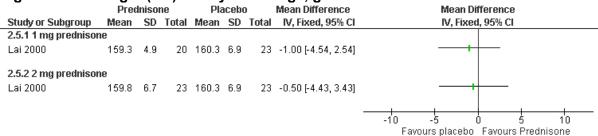
Abbreviations: CI: confidence interval; IV: inverse variance; kg: kilograms; SD: standard deviation

Figure 235: Height (cm) at 18 years of age, boys

	Prednisone			Placebo			Mean Difference	Mean Difference		
Study or Subgroup	Mean SD		Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
2.4.1 1 mg predniso	ne									
Lai 2000	170.7	7.6	34	174.6	6.8	21	-3.90 [-7.77, -0.03]	-		
2.4.2 2 mg predniso	ne									
Lai 2000	170.5	6.6	31	174.6	6.8	21	-4.10 [-7.82, -0.38]			
								-20 -10 0 10 20		
								Favours placebo Favours Prednisone		

Abbreviations: CI: confidence interval; cm: centimetres; IV: inverse variance; SD: standard deviation

Figure 236: Height (cm) at 18 years of age, girls



Abbreviations: CI: confidence interval; cm: centimetres; IV: inverse variance; SD: standard deviation

Figure 237: Adverse effects, at 3 and 4 years follow-up

•	.g	Prednis	one	Place	bo	Risk Ratio	Risk Ratio
	Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
	2.6.1 Cataracts (1 mg	predniso	one) up	to 4 yrs			
	Eigen 1995	3	95	7	95	0.43 [0.11, 1.61]	
	2.6.2 Cataracts (2mg	predniso	ne) up	to 3 year	S		
	Eigen 1995	11	95	7	95	1.57 [0.64, 3.88]	++-
	2.6.3 Diabetes mellitu	ıs (1 mg p	rednis	one) up t	o 4 yrs	i	
	Eigen 1995	3	95	1	95	3.00 [0.32, 28.33]	-
	2.6.4 Diabetes mellitu	ıs (2 mg p	rednis	one) up t	o 3 yrs	i	
	Eigen 1995	6	95	1	95	6.00 [0.74, 48.89]	+
	2.6.5 Glycosuria (1 m	g prednis	one) u	to 4 yrs			
	Eigen 1995	6	95	4	95	1.50 [0.44, 5.15]	-
	2.6.6 Glycosuria (2 m	g prednis	one) up	to 3 yrs			
	Eigen 1995	10	95	4	95	2.50 [0.81, 7.69]	+-
	2.6.7 Hyperglycaemia	(1 mg pr	edniso	ne) up to	4 yrs		
	Eigen 1995	3	95	2	95	1.50 [0.26, 8.78]	
	2.6.8 Hyperglycaemia	(2 mg pr	edniso	ne) up to	3 угѕ		
	Eigen 1995	10	95	2	95	5.00 [1.13, 22.21]	
							0.01 0.1 1 10 100
							Favours prednisone Favours placebo

Abbreviations: CI: confidence interval; : M-H: Mantel-Haenszel

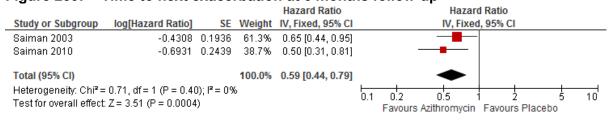
Figure 238: Mortality with 2mg/kg prednisone, at 4 year follow-up

	Prednisone		Place	bo	Risk Ratio	Risk Ratio						
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI			M-H,	Fixe	d, 95% CI		
Auberch 1985	0	21	1	24	0.38 [0.02, 8.83]							
						0.01	0	.1		i 10	100	
							Favours	Prednis	one	Eavours place	ebo	

Abbreviations: CI: confidence interval; kg: kilograms; M-H: Mantel-Haenszel; mg: milligrams

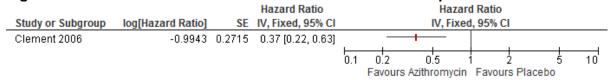
Pairwise comparison 3. Azithromycin versus placebo

Figure 239: Time to next exacerbation at 6 months follow-up



Abbreviations: CI: confidence interval; df: degrees of freedom; IV: inverse variance; SE: standard error

Figure 240: Time to next exacerbation at 12 months follow-up



Abbreviations: CI: confidence interval; IV: inverse variance; SE: standard error

Figure 241: Change in BMI z score at 12 months follow-up

	Azith	romy	cin	PI	acebo		Mean Difference		Mea	an Differe	nce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, I	Fixed, 959	6 CI	
3.22.1 at 12 months												•
Clement 2006	0.03	0.4	40	-0.12	0.44	42	0.15 [-0.03, 0.33]			+		
								-4	-2	- 	- 	
									Favours plac	ebo Favo	ours azithro	mvcin

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 242: Change in weight (kg) at 6 months follow-up

			Mean Difference		Me	an Differenc	:e	
Study or Subgroup	Mean Difference	SE	IV, Fixed, 95% CI		IV,	Fixed, 95% (CI	
Saiman 2003	0.7	0.33	0.70 [0.05, 1.35]			+		
Saiman 2010	0.58	0.22	0.58 [0.15, 1.01]			+		
				-10		 	- 5	10
					Favours place	cebo Favou	rs azithromyo	in

Abbreviations: CI: confidence interval; IV: inverse variance; kg: kilograms; SE: standard error

Figure 243: Change in quality of life (CFQ-R) at 6 months follow-up (range of scores: 0-100)

0-10	υ,							
	Azith	romy	cin	PI	acebo		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.27.1 CFQ-R physical	al domai	in						
Saiman 2003	0.8	8.9	85	-1.9	8.8	92	2.70 [0.09, 5.31]	-
3.27.2 CFQ-R psycho	social d	omain	1					
Saiman 2003	1.6	12.1	85	1.2	10.9	92	0.40 [-3.00, 3.80]	-
3.27.3 CFQ-R body in	nage do	main						
Saiman 2003	3.1	14.5	85	-0.1	7.5	92	3.20 [-0.24, 6.64]	
3.27.4 CFQ-R total so	соге							
Saiman 2003	1.7	7.5	85	0.1	7.5	92	1.60 [-0.61, 3.81]	+
								-20 -10 0 10 20
								Favours placeho Favours Azithromycin

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 244: Adverse side effects at 6 months follow-up

i iguio - 1 1 .		Joine	, 01100	to at		now ap
	Azithron	nycin	Place	bo	Risk Ratio	Risk Ratio
Study or Subgroup	Events	ents Total E		Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
3.5.20 Hearing impa	airment					
Saiman 2003	1	87	1	98	1.13 [0.07, 17.74]	
3.5.21 Tinnitus						
Saiman 2003	1	87	1	98	1.13 [0.07, 17.74]	
						<u> </u>
						0.01 0.1 1 10 100
						Favours azithromycin Favours placebo

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Pairwise comparison 4. Ibuprofen versus placebo

Figure 245: Annual rate of change in % ideal body weight at 4 years follow-up

	lbu	profe	n	PI	acebo		Mean Difference		Mean Di	fference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	I, 95% CI	
Konstan 1995	0.05	1.97	41	-0.94	1.86	43	0.99 [0.17, 1.81]			-	
								-			$\overline{}$
								-10	-5 ।	5	10
									Favours Placebo	Favours ibuprofen	

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 246: Annual rate of change in % ideal body weight by age at 4 years follow-

ωp											
_	lbu	profe	n	PI	acebo		Mean Difference	Mea	n Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, F	ixed, 95% CI		
4.2.1 Under 13 year	s at rand	omisa	tion								
Konstan 1995	-0.05	2.01	24	-1.5	2	25	1.45 [0.33, 2.57]		-		
4.2.2 13 years or old	der at ran	idomis	sation								
Konstan 1995	0.19	1.44	17	-0.15	1.44	18	0.34 [-0.61, 1.29]		+		
								-10 -5		<u> </u>	10
									ebo Favours It	buprofen	10

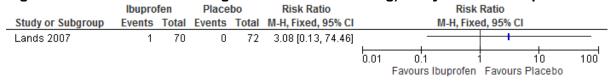
Abbreviations: CI: Confidence interval; IV: inverse variance; SD: standard deviation

Figure 247: Adverse effects: abdominal pain at 2 and 4 years follow-up

	lbupro	fen	Place	bo	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
4.3.1 up to 2 years f	ollow-up					
Lands 2007	1	70	4	72	0.26 [0.03, 2.24]	
4.3.2 up to 4 years f	ollow-up					
Konstan 1995	5	41	7	43	0.75 [0.26, 2.17]	- + -
						0.01 0.1 1 10 100
						Favours ibunrofen Favours placebo

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 248: Adverse effects: gastrointestinal bleeding) at 2 years follow-up

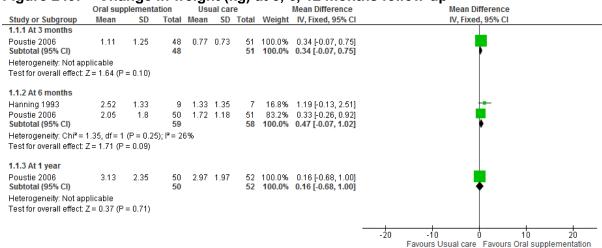


Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

I.13 Nutritional interventions

Comparison 1. Oral supplements versus usual care

Figure 249: Change in weight (kg) at 3, 6, 12 months follow-up



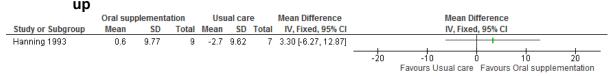
Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 250: Change in height (cm) at 3, 6, and 12 months follow-up

_	Oral sup	plement	ation	Usi	ial car	e	Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, F	ixed, 95%	CI	
1.2.1 At 3 months												
Poustie 2006	1.65	0.86	48	1.68	0.8	51	-0.03 [-0.36, 0.30]			t		
1.2.2 At 6 months												
Poustie 2006	3.09	1.03	50	3.56	2.92	51	-0.47 [-1.32, 0.38]			+		
1.2.3 At 1 year												
Poustie 2006	5.91	0.85	50	5.85	1.85	52	0.06 [-0.50, 0.62]			+		
								-20	-10	Ó	10	20
									Favoure Henalic	are Favor	ire Oral cump	lementatio

Abbreviations: CI: confidence interval; cm: centimetres; IV: inverse variance; SD: standard deviation;

Figure 251: Change in weight as % expected for age and height at 6 months follow-



Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation;

Figure 252: Change in BMI (kg/m2) at 3, 6 and 12 months follow-up

	Oral supplementation			Usi	ual car	e	Mean Difference		Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	I, 95% CI		
1.4.1 At 3 months												
Poustie 2006	0.19	0.65	48	0.05	0.41	51	0.14 [-0.08, 0.36]		•	}		
1.4.2 At 6 months												
Poustie 2006	0.39	0.87	50	0.15	0.67	51	0.24 [-0.06, 0.54]			•		
1.4.3 At 1 year												
Poustie 2006	0.32	1.03	50	0.24	0.78	52	0.08 [-0.28, 0.44]		-	+		
								-20	-10		10	20
								-20	Favours Usual care	Favours (

Abbreviations: BMI: body mass index; CI: confidence interval; kg: kilograms; IV: inverse variance; m²: square metres; SD: standard deviation

Figure 253: Change in BMI (centile) at 3, 6 and 12 months follow-up

	Oral supplementation		Usual care			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.5.1 At 3 months								
Poustie 2006	2.72	11.42	48	-0.56	8.47	51	3.28 [-0.70, 7.26]	+-
1.5.2 At 6 months								
Poustie 2006	4.46	15.5	50	-1.29	12.66	51	5.75 [0.22, 11.28]	
1.5.3 At 1 year								
Poustie 2006	0.67	18.2	50	-2.32	9.63	52	2.99 [-2.69, 8.67]	+
								-20 -10 0 10 20
								Favours Usual care Favours Oral supplementation

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 254: Change in weight (centile) at 3, 6, and 12 months follow-up

	Oral su	pplement	ation	Usi	ual car	е	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.6.1 At 3 months								
Poustie 2006	2.12	6.58	48	0.4	4.98	51	1.72 [-0.59, 4.03]	+
1.6.2 At 6 months								
Poustie 2006	2.75	9.56	50	0.63	5.6	51	2.12 [-0.94, 5.18]	+-
1.6.3 At 1 year								
Poustie 2006	0.83	10.96	50	-1	7.14	52	1.83 [-1.77, 5.43]	++-
							-	
								-20 -10 0 10 20
								Favours Usual care Favours Oral supplementatio

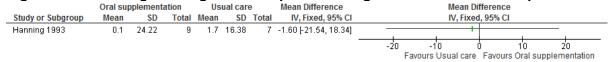
Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 255: Change in height (centile) at 3, 6 and 12 months follow-up

_	Oral sup	plement	ation	Usi	ıal caı	re	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.7.1 At 3 months								
Poustie 2006	0.57	3.69	48	1.13	3.81	51	-0.56 [-2.04, 0.92]	+
1.7.2 At 6 months								
Poustie 2006	0.24	0.27	50	1.98	9.7	51	-1.74 [-4.40, 0.92]	++
1.7.3 At 1 year								
Poustie 2006	0.53	6.94	50	1.18	5.62	52	-0.65 [-3.11, 1.81]	-+
								-20 -10 0 10 20 Favours Usual care Favours Oral supplementation

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 256: Change in height as % expected for age at 6-months follow-up



Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 257: Change in FEV₁ % predicted at 3, 6 and 12 months follow-up (range of scores: 0-100)

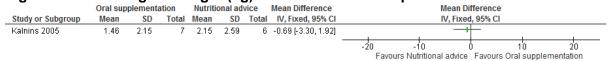
-	0.00.		,						
	Oral sup	plementa	ation	Us	ual car	е		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.10.1 At 3 months									
Poustie 2006 Subtotal (95% CI)	-2.55	12.28	31 31	5.37	12.97	38 38		-7.92 [-13.89, -1.95] - 7.92 [-13.89, -1.95]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 2.60 (F	P = 0.009							
1.10.2 At 6 months									
Hanning 1993	-9.7	14.3	9	-4.3	10.54	7	22.6%	-5.40 [-17.58, 6.78]	•
Poustie 2006 Subtotal (95% CI)	-1.78	11.51	32 41	1.61	16.45	38 45	77.4% 100.0%	-3.39 [-9.97, 3.19] - 3.84 [-9.63, 1.94]	
Heterogeneity: Chi ² =	0.08. df = 1	I/P = 0.78	$0: I^2 = 0$	%					
Test for overall effect:		•	,,,						
1.10.3 At 1 year									
Poustie 2006	-3.41	13.5	32	-1.5	14.89	38	100.0%	-1.91 [-8.57, 4.75]	
Subtotal (95% CI)			32			38	100.0%	-1.91 [-8.57, 4.75]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.56 (F	9 = 0.57)							
									-20 -10 0 10 20
									Favours Usual care Favours Oral supplementation

Test for subgroup differences: $Chi^2 = 1.87$, df = 2 (P = 0.39), $I^2 = 0\%$

Abbreviations: CI: confidence interval; df: degrees of freedom; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Comparison 1.2 Oral calorie supplementation versus nutritional advice

Figure 258: Change in weight (kg) at 3 months follow-up



Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 259: Change in weight for height (%) at 3 months follow-up

	Oral supplementation			Nutritio	onal ad	vice	Mean Difference	Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV.	Fixed, 95% (<u> </u>		
Kalnins 2005	0.71	4.5	7	1.67	3.33	6	-0.96 [-5.23, 3.31]		_				
							•	-20	-10	- -	10	20	
								Favo	urs Nutritional a	dvice Favou	rs Oral suppler	mentation	

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 260: Change in weight z score at 3 and 6 months follow-up

9				5				·
	Oral sup	plementa	ition	Nutriti	onal ad	vice	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.3.1 At 3 months								
Kalnins 2005	0.1	0.5	7	0.1	0.57	6	0.00 [-0.59, 0.59]	+
2.3.2 At 6 months								
Kalnins 2005	-0.1	0.57	7	0.2	0.66	6	-0.30 [-0.98, 0.38]	+
								-10 -5 0 5 10
								Favours Nutritional advice Favours Oral supplementation

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 261: Change in % ideal body weight at 3 and 6 months follow-up

	Oral sup	plement	ation	Nutriti	onal ad	vice	Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI			
2.4.1 At 3 months											
Kalnins 2005	-1	5.73	7	1	9.33	6	-2.00 [-10.59, 6.59]				
2.4.2 At 6 months											
Kalnins 2005	-3	5.73	7	0	9.33	6	-3.00 [-11.59, 5.59]				
								-20 -10 0 10 20			
								Favours Nutritional advice Favours Oral supplementation			

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 262: Change in height (cm) at 3 months follow-up

	Oral sup	plement	Nutritional advice N			Mean Difference	Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IN	/, Fixed, 95% (CI	
Kalnins 2005	2.17	2.54	7	2.55	2.36	6	-0.38 [-3.05, 2.29]			+		
								-20	-10	ò	10	20
								Four	uro Nutritional	advice Favor	ro Orol oupple	montation

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 263: Change in height z score at 3 and 6 months follow-up

_	Oral sup	Oral supplementation			onal ad	vice	Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI			
2.6.1 At 3 months											
Kalnins 2005	0.1	0.7	7	0.1	1.01	6	0.00 [-0.96, 0.96]				
2.6.2 At 6 months Kalnins 2005	0.1	0.66	7	0.2	1.05	6	-0.10 [-1.07, 0.87]	<u> </u>			
Naiiiiii 2005	0.1	0.00	,	0.2	1.03	٥	-0.10[1.07, 0.07]				
								-10 -5 0 5 10			
								Favours Nutritional advice Favours Oral supplementation			

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 264: Change in FEV₁ % predicted at 3 and 6 months follow-up (range of scores: 0-100)

			,							
	Oral sup	plementa	ation	Nutriti	onal ad	vice	Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
2.6.1 At 3 months										
Kalnins 2005	0.1	0.7	7	0.1	1.01	6	0.00 [-0.96, 0.96]	+		
2.6.2 At 6 months										
Kalnins 2005	0.1	0.66	7	0.2	1.05	6	-0.10 [-1.07, 0.87]	+		
								-20 -10 Ó 10 20		
								Favours Nutritional advice Favours Oral supplementation		

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

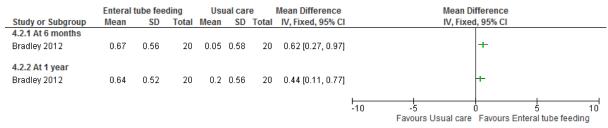
Comparison 2. Enteral tube feeding versus nutritional advice

Figure 265: Change in weight (kg) at 1, 2, and 3 years follow-up

	Enteral	tube fee	ding	Usı	ıal car	re	Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
4.1.1 At 1 year										
White 2013	7.3	3.8	15	-0.3	2.64	6	7.60 [4.74, 10.46]			
4.1.2 At 2 years										
White 2013	8.3	6.01	15	-0.8	2.57	6	9.10 [5.43, 12.77]			
4.1.3 At 3 years										
White 2013	8.9	6.26	15	-0.1	2.59	6	9.00 [5.21, 12.79]			
								-20 -10 0 10 20 Favours Usual care Favours Enteral tube feeding		
								rayours osual care rayours Efficial tube recoming		

Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 266: Change in weight z score at 6 and 12 months follow-up



Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 267: Change in height z score at 6 and 12 months follow-up

	Enteral	Enteral tube feeding			al ca	re	Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
4.3.1 At 6 months										
Bradley 2012	0.5	0.41	20	0.3	0.8	20	0.20 [-0.19, 0.59]	+		
4.3.2 At 1 year										
Bradley 2012	0.1	0.4	20	0	0.8	20	0.10 [-0.29, 0.49]	+		
								-10 -5 0 5 10		

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 268: Change in BMI z score at 6 and 12 months follow-up

	Enteral tube feeding			Usı	ıal caı	re	Mean Difference		1	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		1	V, Fixed, 95% CI		
4.4.1 At 6 months												
Bradley 2012	0.9	0.6	20	0.08	0.48	20	0.82 [0.48, 1.16]			+		
4.4.2 At 1 year												
Bradley 2012	0.78	0.55	20	0.39	0.39	20	0.39 [0.09, 0.69]			+		
								<u> </u>			<u> </u>	
								-10	-5 Favours Usu	u al care Favours	5 Enteral tube fe	10 eding

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 269: Change in BMI (kg/m²) at 1, 2 and 3 years follow-up

ga	•	. 9		/2	<i>.</i>	,	.,	Jours remem up		
	Enteral	tube fee	ding	Usi	ıal car	re	Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
4.5.1 At 1 year										
White 2013	2.7	1.18	15	-0.2	0.46	6	2.90 [2.20, 3.60]	+		
4.5.2 At 2 years										
White 2013	2.9	1.58	15	-0.3	0.44	6	3.20 [2.33, 4.07]			
4.5.3 At 3 years										
White 2013	3.3	1.74	15	0.8	0.43	6	2.50 [1.55, 3.45]			
								-10 -5 0 5 10 Favours Usual care Favours Enteral tube feeding		
								ravours osuarcare Favours Enterartupe reeding		

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; kg: kilograms; m²: square metres; SD: standard deviation

Figure 270: Change in FEV₁ % predicted at 6 months and at 1, 2, 3 years follow-up (range of scores: 0-100)

•	J			-	/			
	Enteral tube feeding		Us	ual car	е	Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
4.6.1 At 6 months, age	2-20							
Bradley 2012	-1.3	16.24	14	3.2	14.72	13	-4.50 [-16.18, 7.18]	
4.6.2 At 1 year, age 2-2	20							
Bradley 2012	-1.6	15.94	14	6.6	16.62	13	-8.20 [-20.50, 4.10]	
4.6.3 At 1 year - adults								
White 2013	5.3	14.41	15	-5.3	24.53	6	10.60 [-10.34, 31.54]	-
4.6.4 At 2 years - adult	s							
White 2013	4.2	14.65	15	-8	15.96	6	12.20 [-2.57, 26.97]	-
4.6.5 At 3 years - adult	S							
White 2013	1.2	13.95	15	-11	15.16	6	12.20 [-1.84, 26.24]	
								-20 -10 0 10 20
								-20 -10 0 10 20 Favours Usual care Favours Enteral tube feeding

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

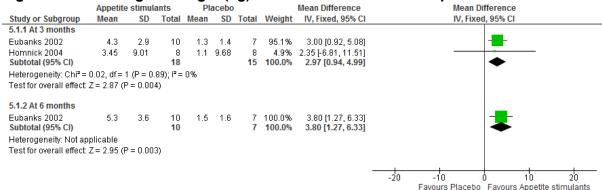
Figure 271: Change in IV treatment days at 1, 2, 3 years follow-up

_	Enteral	Enteral tube feeding		Us	ual car	е	Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI				
4.7.1 At 1 year												
White 2013	20.7	31.96	15	2.8	21.92	6	17.90 [-5.96, 41.76]	+				
4.7.2 At 2 years												
White 2013	28	54.64	15	-8	17.36	6	36.00 [5.06, 66.94]					
4.7.3 At 3 years												
White 2013	43.2	73.45	15	7	25.72	6	36.20 [-6.29, 78.69]	+				
								-100 -50 0 50 100 Favours Enteral tube feeding Favours Usual care				

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Comparison 3. Appetite stimulants versus placebo

Figure 272: Change in weight (kg) at 3 and 6 months follow-up



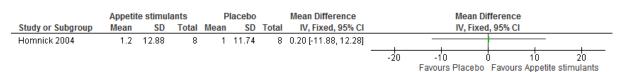
Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; CI: confidence interval; df: degrees of freedom

Figure 273: Change in weight z score at 3 and 6 months follow-up

J	_			5	-					
	Appetit	e stimul	ants	P	lacebo			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI
5.2.1 At 3 months										
Eubanks 2002	0.72	0.77	10	0.07	0.22	7	40.0%	0.65 [0.15, 1.15]		-
Homnick 2004	0.572	0.457	5	0.04	0.305	7	48.2%	0.53 [0.07, 0.99]		-
Marchand 2000 Subtotal (95% CI)	0.742	0.783	5 20	-0.05	0.783	6 20	11.8% 100.0%	0.79 [-0.14, 1.72] 0.61 [0.29, 0.93]		→
Test for overall effect: 5.2.2 At 6 months	Z= 3.75 (P = 0.00	02)							
Eubanks 2002 Subtotal (95% CI)	0.76	0.73	10 10	0.02	0.2	7 7	100.0% 100.0 %	0.74 [0.26, 1.22] 0.74 [0.26, 1.22]		.
Heterogeneity: Not ap Test for overall effect:		P = 0.00	2)							
									-10	-5 0 5

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval; df: degrees of freedom

Figure 274: Change in height (cm) at 3 months follow-up



Abbreviations: CI: confidence interval; cm: centimetres; IV: inverse variance; SD: standard deviation

Figure 275: Change in FEV₁ % predicted at 3 and 6 months follow-up (range of scores: 0-100)

	Appetit	te stimul	ants	PI	acebo		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
5.7.1 At 3 months								
Eubanks 2002	9.85	13.85	10	-3.7	17.3	7	13.55 [-1.88, 28.98]	+ + + + + + + + + + + + + + + + + + + +
5.7.2 At 6 months								
Eubanks 2002	6.47	6.64	10	0.83	12.4	7	5.64 [-4.43, 15.71]	- -
								-20 -10 0 10 20
								Favours Placebo Favours Appetite stimulants

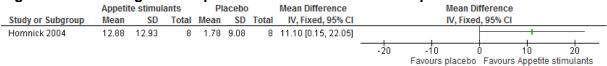
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 276: Change in BMI (kg/m²) at 3 months follow-up

	Appetite	e stimul	ants	PI	acebo		Mean Difference		Me	an Differen	ce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV,	Fixed, 95%	CI	
Homnick 2004	1.17	1.28	8	0.29	1.99	8	0.88 [-0.76, 2.52]			+		
								-20	-10	ó	10	20
									Favours place	cebo Favoi	urs Appetite	stimulants

Abbreviations: BMI: body mass index; CI: confidence interval; kg: kilograms; IV: inverse variance; m²: square metres; SD: standard deviation

Figure 277: Change in BMI percentile at 3 months follow-up



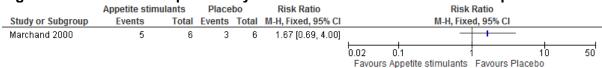
Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 278: Change in % ideal body weight at 3 months follow-up

•		•				•	•			•			
	Appetit	e stimul	ants	PI	acebo)	Mean Difference	Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV,	Fixed, 95%	CI		
Homnick 2004	6.29	4.79	8	1.15	5.28	8	5.14 [0.20, 10.08]						
								-20	-10	Ó	10	20	
									Favoure place	oho Eavo	ure Annatita	etimulante	

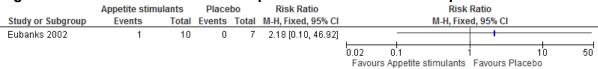
Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 279: Number of pulmonary exacerbations at 3 months follow-up



Abbreviations: M-H: Mantel-Haenszel; CI: confidence interval

Figure 280: Adverse effects: constipation at 6 months follow-up



Abbreviations: M-H: Mantel-Haenszel; CI: confidence interval

Figure 281: Adverse effects: decreased morning cortisol levels <30 nmol/L at 6 months follow-up



Abbreviations: M-H: Mantel-Haenszel; Cl: confidence interval

Comparison 4. Nutrition education versus usual care

Figure 282: Change in weight (kg) at 6 and 12 months follow-up

	Nutritio	n educa	ation	Standard treatment			Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI				
6.1.1 At 6 months												
Watson 2008	0.4	7.63	23	0.8	8.09	25	-0.40 [-4.85, 4.05]					
6.1.2 At 1 year												
Watson 2008	0.8	7.51	23	1.2	8.28	25	-0.40 [-4.87, 4.07]					
								-20 -10 0 10 20				
								-20 -10 0 10 20 Favours Standard treatment Favours Nutrition education				

Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; CI: confidence interval

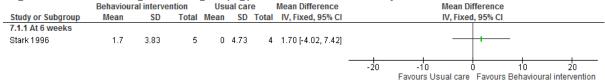
Figure 283: Change in FEV₁ % predicted at 6 and 12 months follow-up (range of scores: 0-100)

	Nutritio	on educa	ation	Standa	ird treatr	nent	Mean Difference		Mean E	ifference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI		
6.2.1 At 6 months												
Watson 2008	2.3	19.52	23	0.81	16.75	25	1.49 [-8.84, 11.82]			+		
6.2.2 At 1 year												
Watson 2008	0.2	19.16	23	-0.79	16.98	25	0.99 [-9.29, 11.27]			+		
							-	100	-10		40	20
									-10 dard treatment	Favoure	10 Nutrition od	20 lucation

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

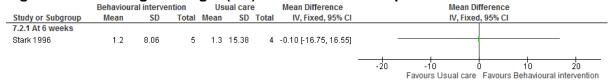
Comparison 5.1 Behavioural intervention versus usual care

Figure 284: Change in weight (kg) at 6 weeks follow-up



Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; Cl: confidence interval

Figure 285: Change in height (cm) at 6 weeks follow-up



Abbreviations: CI: confidence interval; cm: centimetres; IV: inverse variance; SD: standard deviation

Figure 286: Change in weight z score at 6 weeks follow-up

	Behaviour	al interve	ntion	Usı	ıal car	e	Mean Difference		Mean D	ifference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI		
7.3.1 At 6 weeks												
Stark 1996	0.45	0.62	5	-0.05	0.44	4	0.50 [-0.19, 1.19]			 -		
								-10	-5	<u> </u>	<u>+</u>	10
								-10	Favours Usual care	Favours Behavi	oural intervent	ion

Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

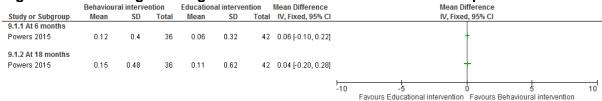
Figure 287: Change in FEV₁ % predicted at 6 weeks follow-up (range of scores: 0-100)

	Behavioura	al interve	ntion	Us	ual car	е	Mean Difference		Mean D	ifference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI		
7.5.1 At 6 weeks												
Stark 1996	-6	9.51	5	0.5	20.32	4	-6.50 [-28.09, 15.09]	←	+			
										.		+
								-20	-10	010		20
									Favours Usual care	Favours Beha	ivioural inte	rvention

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

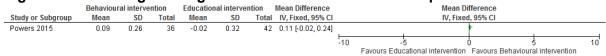
Comparison 5.2 Behavioural intervention *versus* education and attention control treatment

Figure 288: Change in weight z score at 6 and 18 months follow-up



Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 289: Change in height z score at 18 months follow-up



Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 290: Adverse effects (digestive system) at 6 months follow-up



Comparison 5.3. Behavioural management training plus educational intervention *versus* educational intervention alone

Figure 291: Change in weight (kg) at 2,12 and 24 months follow-up

_	BEH	plus E	DU	_	EDU		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
10.1.1 At 2 months								
Stark 2009	1.47	1.27	33	0.92	1.03	34	0.55 [-0.00, 1.10]	<u>†</u>
10.1.2 At 1 year								
Powers 2003	1.32	0.64	4	1.75	0.57	4	-0.43 [-1.27, 0.41]	+
10.1.3 At 2 years								
Stark 2009	6.97	3.6	28	6.45	3.67	31	0.52 [-1.34, 2.38]	+
								-20 -10 0 10 20
								Favours EDU Favours BEH plus EDU

Abbreviations: kg: kilograms; BEH plus EDU: Behavioural management training plus educational intervention; EDU: educational intervention alone; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 292: Change in BMI z score at 2 and 24 months follow-up

	BEH	plus E	DU		EDU		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
10.2.1 At 2 months								
Stark 2009	0.38	0.46	33	0.18	0.47	34	0.20 [-0.02, 0.42]	+
10.2.2 At 2 years								
Stark 2009	0.13	0.81	28	-0.22	0.5	31	0.35 [0.00, 0.70]	+
								-10 -5 0 5 10
								Favours EDU Favours BEH plus EDU

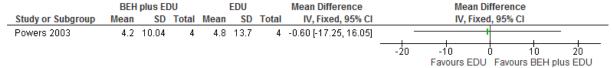
Abbreviations: BMI: body mass index; BEH plus EDU: Behavioural management training plus educational intervention; CI: confidence interval; EDU: educational intervention alone; IV: inverse variance; SD: standard deviation

Figure 293: Change in % ideal body weight at 12 months follow-up



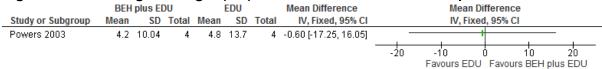
Abbreviations: BEH plus EDU: Behavioural management training plus educational intervention; EDU: educational intervention alone; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 294: Change in weight % for age at 12 months follow-up



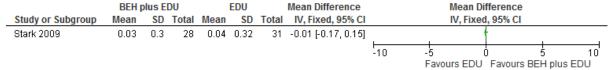
Abbreviations: BEH plus EDU: Behavioural management training plus educational intervention; EDU: educational intervention alone; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 295: Change in height (cm) at 12 and 24 months follow-up



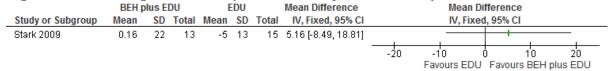
Abbreviations: BEH plus EDU: Behavioural management training plus educational intervention; CI: confidence interval; cm: centimetres; EDU: educational intervention alone; IV: inverse variance; SD: standard deviation

Figure 296: Change in height z score at 24 months follow-up



Abbreviations: BEH plus EDU: Behavioural management training plus educational intervention; CI: confidence interval; cm: centimetres; EDU: educational intervention alone; IV: inverse variance; SD: standard deviation

Figure 297: Change in FEV₁ % predicted at 2 years follow-up



Abbreviations: BEH plus EDU: Behavioural management training plus educational intervention; CI: confidence interval; EDU: educational intervention alone; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation.

Note: The study does not specify the unit of measurement for FEV₁.

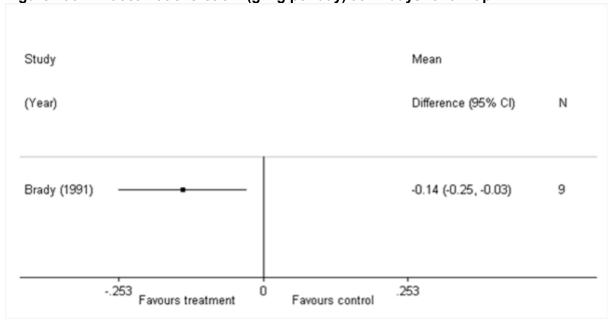
I.14 Exocrine Pancreatic insufficiency

Comparison 1. Acid suppressing agents as adjuvant therapy to PERT No forest plots available.

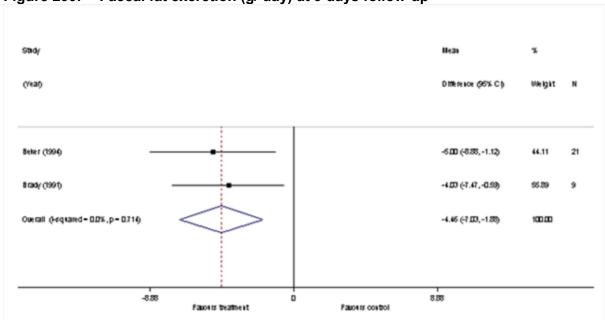
Comparison 2. High dose versus low dose PERT

Comparison 2.1. High-dose PERT versus low dose PERT in children

Figure 298: Faecal fat excretion (g/ kg per day) at 14 days follow-up

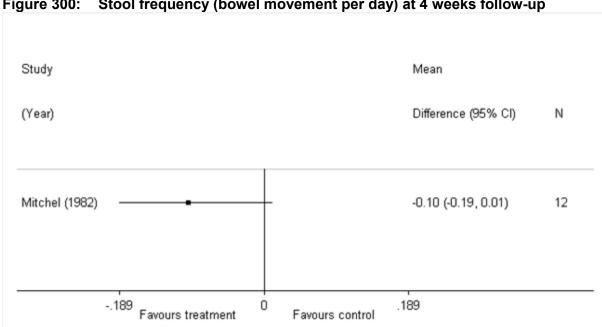


Abbreviations: g: grams; kg: kilograms; CI: confidence interval



Faecal fat excretion (g/ day) at 9 days follow-up

Abbreviations: g: grams; CI: confidence interval



Stool frequency (bowel movement per day) at 4 weeks follow-up

Abbreviations: CI: confidence interval

Comparison 2.1. High-dose PERT versus low dose PERT in children

No forest plots available.

I.15 Distal intestinal obstruction syndrome

Not applicable, as no studies were included in this review.

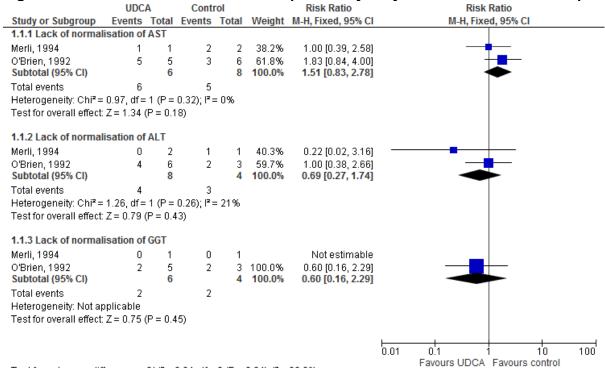
I.16 Monitoring liver disease

Not applicable to this review.

I.17 Ursodeoxycholic acid

Comparison 1. UDCA versus placebo or control

Figure 301: Lack of normalisation of hepatobiliary enzymes at 6 months follow-up



Test for subgroup differences: $Chi^2 = 2.84$, df = 2 (P = 0.24), $I^2 = 29.6\%$

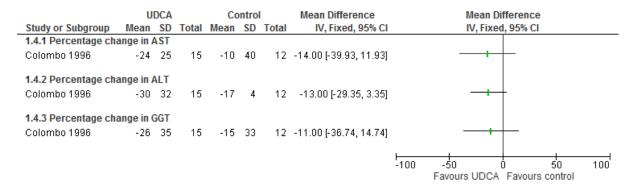
Abbreviations: UDCA: ursodeoxycholic acid; M-H: Mantel-Haenszel; CI: confidence interval; df: degrees of freedom

Figure 302: Final value of bilirubin value (umol/L) at 6 months follow-up

		UDCA			Control			Mean Difference		Mea	an Differen	ce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV,	Fixed, 95%	CI	
O'Brien, 1992	13.2	8.8182	6	9.2	3.9192	6	100.0%	4.00 [-3.72, 11.72]					
Total (95% CI)			6			6	100.0%	4.00 [-3.72, 11.72]			-		
Heterogeneity: Not ap Test for overall effect:			1)						-50	-25 Favours UI	0 OCA Favou	25 urs control	50

Abbreviations: UDCA: ursodeoxycholic acid; SD: standard deviation; IV: inverse variance; Cl: confidence interval

Figure 303: Percentage change in hepatobiliary enzymes at 12 months follow-up



Abbreviations: UDCA: ursodeoxycholic acid; SD: standard deviation; IV: inverse variance; CI: confidence interval. Colombo: Data reported as multiples of the upper limit of normal reference values.

Figure 304: No development of liver disease at 6 months follow-up

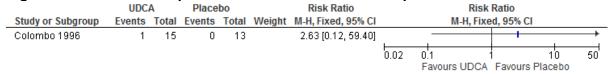
Data cannot be plotted. None of the participants developed liver disease in either treatment arm.

Figure 305: Liver failure at 12 months follow-up

	UDC	A	Place	bo		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
Colombo 1996	1	15	0	13		2.63 [0.12, 59.40]			1	
							0.02	0.1	10	50
								Favours UDCA	Favours Placebo	

Abbreviations: UDCA: ursodeoxycholic acid; M-H: Mantel-Haenszel; Cl: confidence interval

Figure 306: Liver transplantation at 12 months follow-up



Abbreviations: UDCA: ursodeoxycholic acid; M-H: Mantel-Haenszel; CI: confidence interval

I.18 Monitoring for CF related diabetes

Not applicable, as no studies were identified for this review.

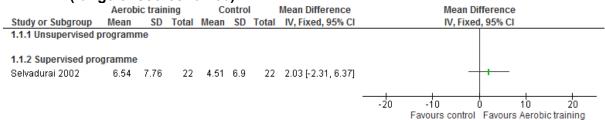
I.19 Bone mineral density

Not applicable to this review.

I.20 Exercise

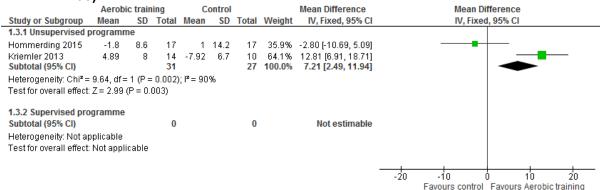
Comparison 1. Aerobic exercise training programme versus no exercise programme

Figure 307: Change in FEV₁ % predicted at hospital discharge (mean ≈ 19 days) (range of scores: 0-100)



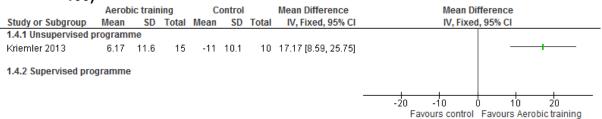
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 308: Change in FEV₁ % predicted at 3 months follow-up (range of scores: 0-100)



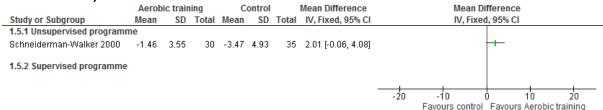
Abbreviations: CI: confidence interval; df: degrees of freedom; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 309: Change in FEV₁ % predicted at 6 months follow-up (range of scores: 0-100)



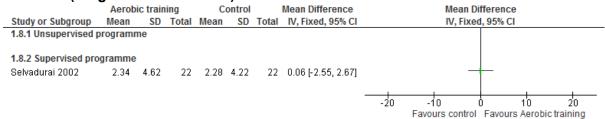
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 310: Change in FEV₁ % predicted at 3 years follow-up (range of scores: 0-100)



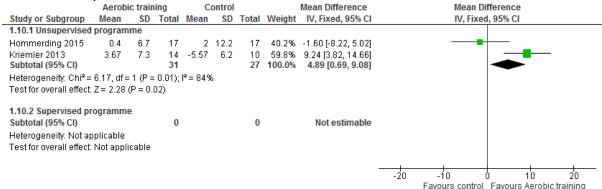
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 311: Change in FVC % predicted at hospital discharge (mean ≈ 19 days) (range of scores: 0-100)



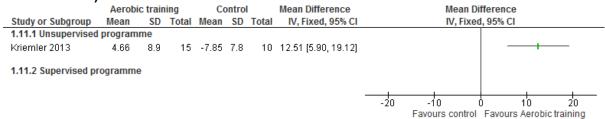
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 312: Change in FVC % predicted at 3 months follow-up (range of scores: 0-100)



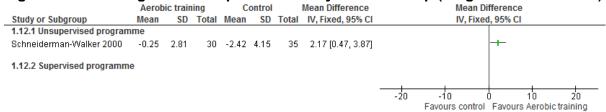
Abbreviations: CI: confidence interval; df: degrees of freedom; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation;

Figure 313: Change in FVC % predicted at 6 months follow-up (range of scores: 0-100)



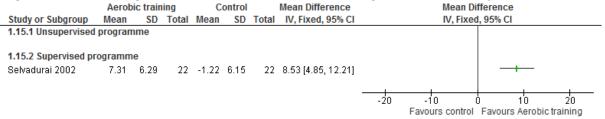
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 314: Change in FVC % predicted at 3 years follow-up (range of scores: 0-100)

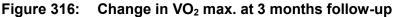


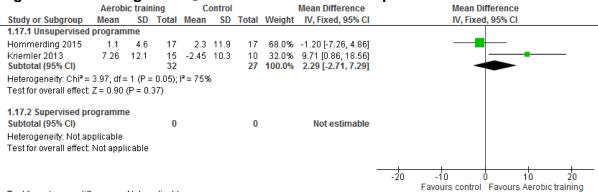
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 315: Change in VO₂ max. at hospital discharge (mean ≈ 19 days)



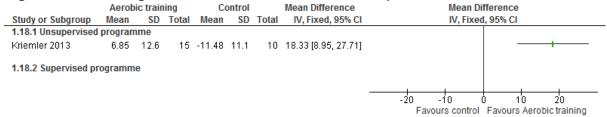
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO₂ max: maximal oxygen consumption





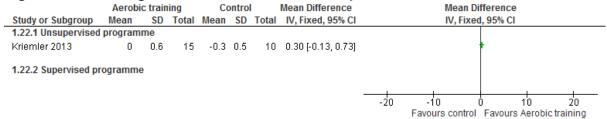
Abbreviations: CI: confidence interval; df: degrees of freedom; IV: inverse variance; SD: standard deviation; VO₂ max: maximal oxygen consumption

Figure 317: Change in VO₂ max. at 6 months follow-up



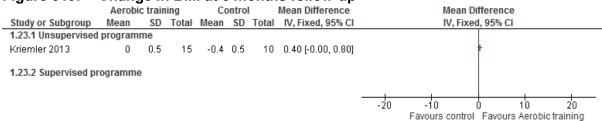
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO₂ max: maximal oxygen consumption

Figure 318: Change in BMI at 3 months follow-up



Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

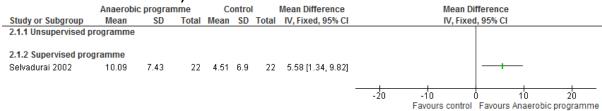
Figure 319: Change in BMI at 6 months follow-up



Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

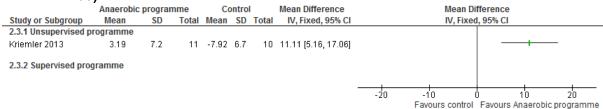
Comparison 2.1. Strength resistance/ anaerobic training programme *versus* no exercise programme

Figure 320: Change in FEV₁ % predicted at hospital discharge (mean ≈ 19 days) (range of scores: 0-100)



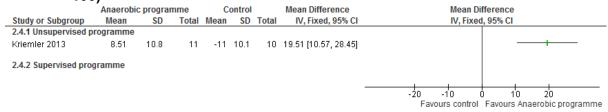
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 321: Change in FEV₁ % predicted at 3 months follow-up (range of scores: 0-100)



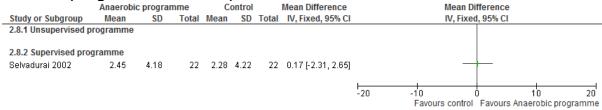
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 322: Change in FEV₁ % predicted at 6 months follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 323: Change in FVC % predicted at hospital discharge (mean ≈ 19 days) (range of scores: 0-100)



Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 324: Change in FVC % predicted at 3 months follow-up (range of scores: 0-100)

	Anaerobic	prograi	mme	Co	ontro	I	Mean Difference		Mean D	ifference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI	
2.10.1 Unsupervised	programme										
Kriemler 2013	1.8	6.6	11	-5.57	6.2	10	7.37 [1.89, 12.85]				_
2.10.2 Supervised pro	ogramme										
								-20	-10	 	20
								-20			erobic programme

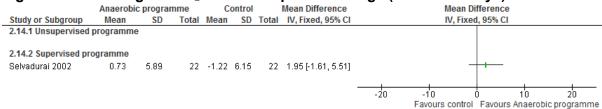
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 325: Change in FVC % predicted at 6 months follow-up (range of scores: 0-100)

	,							
	Anaerobic	ргодга	mme	C	ontro	l	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.11.1 Unsupervised	programme							
Kriemler 2013	6.2	8.3	11	-7.85	7.8	10	14.05 [7.16, 20.94]	
2.11.2 Supervised pr	ogramme							
								-20 -10 0 10 20
								Favours control Favours Anaerobic programme

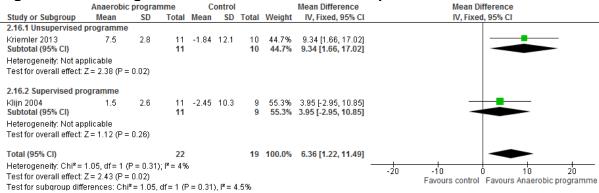
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 326: Change in VO₂ max at hospital discharge (mean ≈ 19 days)



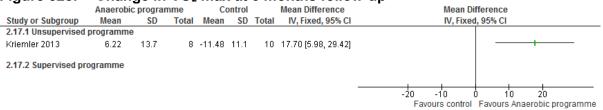
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO₂ max: maximal oxygen consumption

Figure 327: Change in VO₂ max at 3 months follow-up



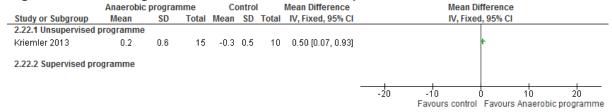
Abbreviations: CI: confidence interval; df: degrees of freedom; IV: inverse variance; SD: standard deviation; VO₂ max: maximal oxygen consumption

Figure 328: Change in VO₂ max at 6 months follow-up



Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO₂ max: maximal oxygen consumption

Figure 329: Change in BMI at 3 months follow-up



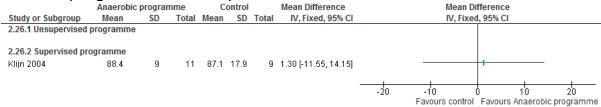
Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 330: Change in BMI at 6 months follow-up

	Anaerobio	progran	mme	Co	ntro	I	Mean Difference		Mean	Differen	ce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fix	ed, 95%	CI	
2.23.1 Unsupervised	programme											
Kriemler 2013	0.3	0.6	15	-0.4	0.5	10	0.70 [0.27, 1.13]			+		
2.23.2 Supervised pr	ogramme											
								-20	-10	<u> </u>	10	20
								20	Favours contr	ol Favou		

Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

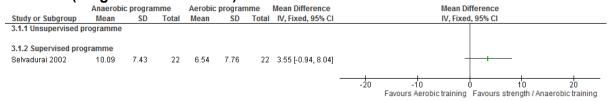
Figure 331: Change in quality of life (CFQ-R physical domain) at 3 months follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

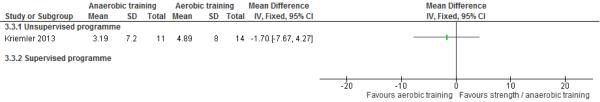
Comparison 2.2. Strength/ anaerobic training programme *versus* aerobic training programme

Figure 332: Change in FEV₁ % predicted at hospital discharge (mean ≈ 19 days) (range of scores: 0-100)



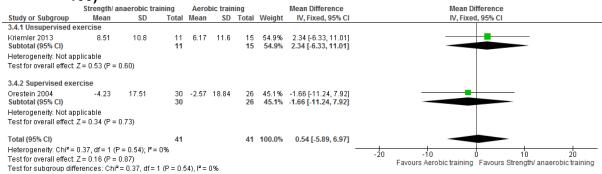
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 333: Change in FEV₁ % predicted at 3 months follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 334: Change in FEV₁ % predicted at 6 months follow-up (range of scores: 0-100)



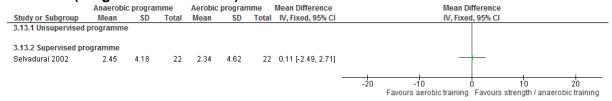
Abbreviations: CI: confidence interval; df: degrees of freedom; FEV_1 : forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 335: Change in FEV₁ % predicted at 12 months follow-up (range of scores: 0-100)

	,											
	Strength/ a	naerobic tra	aining	Aerol	oic train	ing	Mean Difference			Mean Difference	1	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI			IV, Fixed, 95% CI		
3.6.1 Unsupervised e	exercise											
3.6.2 Supervised exe	ercise											
Orestein 2004	-0.89	17.06	28	-1.19	18.13	25	0.30 [-9.21, 9.81]			-		
								-20	-10	Ó	10	20
									Favours Aerobi	ctraining Favours	Strength/ anaerob	ic training

Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 336: Change in FVC% predicted at hospital discharge (mean aprox. 19 days) (range of scores: 0-100)



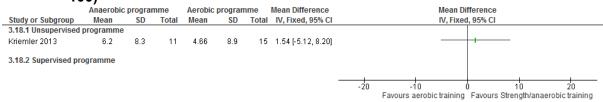
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 337: Change in FVC% predicted at 3 months follow-up (range of scores: 0-100)

	Anaerobic	progra	mme	Aerobic	progran	nme	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.15.1 Unsupervised	programme							
Kriemler 2013	1.8	6.6	11	3.67	7.3	14	-1.87 [-7.33, 3.59]	
3.15.2 Supervised pr	rogramme							
								-20 -10 0 10 20
								Favours aerobic training Favours strength / anaerobic training

Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 338: Change in FVC % predicted at 6 months follow-up (range of scores: 0-100)



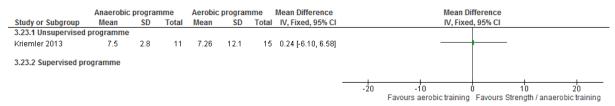
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 339: Change in VO₂ max at hospital discharge (mean ≈ 19 days)

	Anaerobi	c prograi	mme	Aerobic	progran	nme	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.21.1 Unsupervised	programme	9						
3.21.2 Supervised pr	ogramme							
Selvadurai 2002	0.73	5.89	22	7.31	6.29	22	-6.58 [-10.18, -2.98]	
								-20 -10 0 10 20
								Favours Aerobic training Favours strength/anaerobic training

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO₂ max: maximal oxygen consumption

Figure 340: Change in VO₂ max at 3 months follow-up



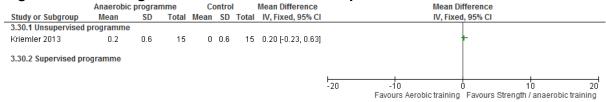
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO₂ max: maximal oxygen consumption

Figure 341: Change in VO₂ max at 6 months follow-up

_	Strength/ ar	naerobic tr	aining	Aerob	ic train	ing		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.25.1 Unsupervised e	xercise								
Kriemler 2013 Subtotal (95% CI)	6.22	13.7	11 11	6.85	12.6	15 15		-0.63 [-10.94, 9.68] - 0.63 [-10.94, 9.68]	
Heterogeneity: Not app	licable								
Test for overall effect: Z	C = 0.12 (P = 0).90)							
3.25.2 Supervised exe	rcise								
Orestein 2004 Subtotal (95% CI)	-2.16	6.05	30 30	-1.91	5.78	26 26	91.7% 91.7 %	-0.25 [-3.35, 2.85] - 0.25 [-3.35, 2.85]	-
Heterogeneity: Not app	licable								
Test for overall effect: Z	C = 0.16 (P = 0)).87)							
Total (95% CI)			41			41	100.0%	-0.28 [-3.25, 2.69]	•
Heterogeneity: Chi ² = 0	.00, df = 1 (P	= 0.94); 2=	0%						-20 -10 0 10 20
Test for overall effect: Z	C = 0.19 (P = 0)).85)							-20 -10 0 10 20 Favours Aerobic training Favours Strength/ anaerobic training
Test for subgroup differ	rences: Chi² :	= 0.00, df=	1 (P = 0.9)	$(34), ^2 = ($	0%				ravours Aerobic training Favours Strength anaerobic training

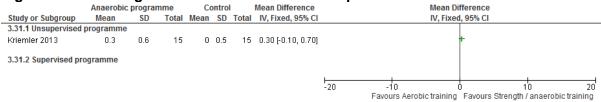
Abbreviations: CI: confidence interval; df: degrees of freedom; IV: inverse variance; SD: standard deviation; VO₂ max: maximal oxygen consumption

Figure 342: Change in BMI at 3 months follow-up



Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

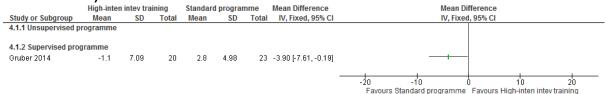
Figure 343: Change in BMI at 6 months follow-up



Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

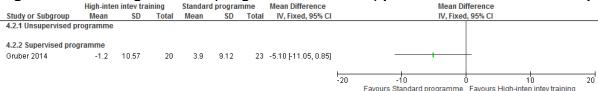
Comparison 3. High-intensity interval training *versus* standard aerobic and anaerobic exercise programme

Figure 344: Change in FEV₁ % predicted at 6 weeks follow-up (range of scores: 0-100)



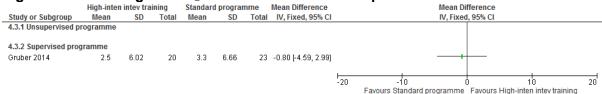
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 345: Change in VC % (range of scores: 0-100) predicted at 6 weeks follow-up



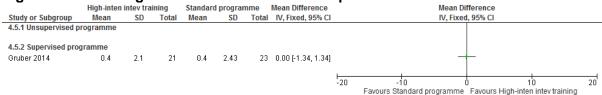
Abbreviations: VC: vital capacity; SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 346: Change in VO₂ max at 6 weeks follow-up



Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO₂ max: maximal oxygen consumption

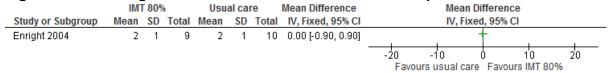
Figure 347: Change in BMI at 6 weeks follow-up



Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

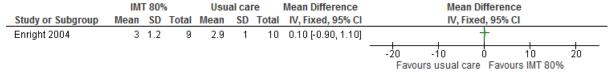
Comparison 4. Inspiratory muscle training (IMT) at 80% of maximal effort *versus* usual care

Figure 348: Change in FEV₁ litres at 2 to 6 months follow-up



Abbreviations: CI: confidence interval; FEV_1 : forced expiratory volume in 1 second; IMT 80%: inspiratory muscle training at 80% of maximal effort; IV: inverse variance; SD: standard deviation

Figure 349: Change in FVC litres at 2 to 6 months follow-up



Abbreviations: CI: confidence interval; FVC: forced vital capacity; IMT 80%: inspiratory muscle training at 80% of maximal effort; IV: inverse variance; SD: standard deviation

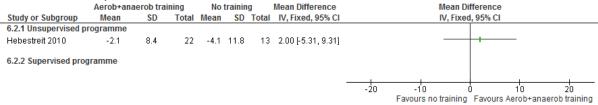
Comparison 5. Combined aerobic and anaerobic training programme *versus* no exercise programme

Figure 350: Change in FEV₁ % predicted at 3 months follow-up (range of scores: 0-100)

	Aerob+an	aerob tra	ining	No	trainin	q		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
7.1.1 Unsupervised p	programme								
Beaudoin 2016	-1.25	9.8	8	-0.5	12.81	6	16.0%	-0.75 [-13.05, 11.55]	
Rovedder 2014	-6	16.1	19	-2	7.3	22	39.1%	-4.00 [-11.86, 3.86]	
Schindel 2015 Subtotal (95% CI)	-1.8	8.6	17 44	2.7	12.8	17 45	44.9% 100.0%	-4.50 [-11.83, 2.83] - 3.71 [-8.62, 1.21]	
Heterogeneity: Chi ² = Test for overall effect: 7.1.2 Supervised pro Subtotal (95% CI)	: Z= 1.48 (P=		0			0		Not estimable	
Heterogeneity: Not ap Test for overall effect:		ble	Ü			Ū		Notestinable	
Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff	: Z = 1.48 (P =	= 0.14)				45	100.0%	-3.71 [-8.62, 1.21]	-20 -10 0 10 20 Favours no training Favours Aerob+anaerob training

Abbreviations: CI: confidence interval; df: degrees of freedom; FEV_1 : forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 351: Change in FEV₁ % predicted at 3 to 6 months follow-up (range of scores: 0-100)



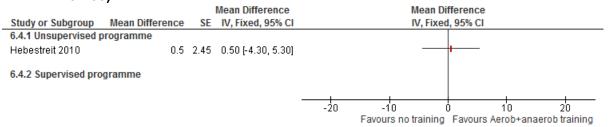
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 352: Change in FVC% predicted at 3 months follow-up (range of scores: 0-100)

	,								
	Aerob+an	aerob tra	aining	No	trainin	g		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
6.4.1 Unsupervised p	orogramme								
Beaudoin 2016	-0.38	6.34	8	-3.68	12.31	6	19.3%	3.30 [-7.49, 14.09]	
Rovedder 2014	-6.8	17.7	19	-3.5	8.3	22	29.8%	-3.30 [-11.98, 5.38]	- •
Schindel 2015	-0.41	6.8	17	1.8	12.2	17	50.9%	-2.21 [-8.85, 4.43]	
Subtotal (95% CI)			44			45	100.0%	-1.47 [-6.21, 3.27]	-
Heterogeneity: Chi ² =	0.97, df = 2	(P = 0.62)	$ I^2 = 0\% $						
Test for overall effect:	Z= 0.61 (P:	= 0.54)							
6.4.2 Supervised pro	gramme								
Subtotal (95% CI)			0			0		Not estimable	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Not applical	ble							
Total (95% CI)			44			45	100.0%	-1.47 [-6.21, 3.27]	-
Heterogeneity: Chi ² =	0.97, df = 2	(P = 0.62)	$ I^2 = 0\% $						
Test for overall effect:	Z = 0.61 (P :	= 0.54)							-20 -10 0 10 20 Favours no training Favours Aerob+anaerob training
Test for subgroup diff	ferences: No	t applicat	ole						ravours no training ravours Aerop-anaerop training

Abbreviations: CI: confidence interval; df: degrees of freedom; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 353: Change in FVC % predicted at 3 to 6 months follow-up (range of scores: 0-100)



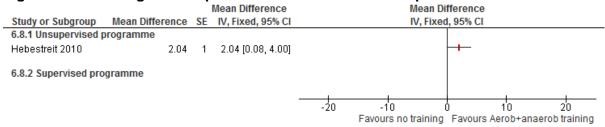
Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; SD: standard deviation

Figure 354: Change in VO₂ peak at 3 months follow-up

3					ıg	Mean Difference		Mean Difference
Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed, 95% CI
0.24	3.71	8	2.37	5.25	6	-2.13 [-7.06, 2.80]		-
ramme								
							- 1-	
							-20	-10 0 10 20 Favours no training Favours Aerob+anaerob traini
	Mean 0.24	Mean SD 0.24 3.71	Mean SD Total 0.24 3.71 8	Mean SD Total Mean 0.24 3.71 8 2.37	Mean SD Total Mean SD 0.24 3.71 8 2.37 5.25	Mean SD Total Mean SD Total 0.24 3.71 8 2.37 5.25 6	Mean SD Total Mean SD Total IV, Fixed, 95% CI 0.24 3.71 8 2.37 5.25 6 -2.13 [-7.06, 2.80]	Mean SD Total Mean SD Total IV, Fixed, 95% CI 0.24 3.71 8 2.37 5.25 6 -2.13 [-7.06, 2.80]

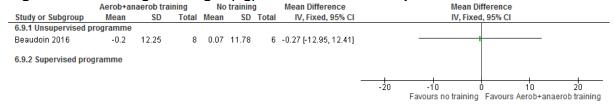
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO₂ max: maximal oxygen consumption

Figure 355: Change in VO₂ peak at 3 to 6 months follow-up



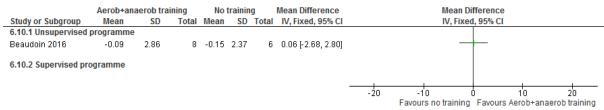
Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation; VO₂ max: maximal oxygen consumption

Figure 356: Change in weight (kg) at 3 months follow-up



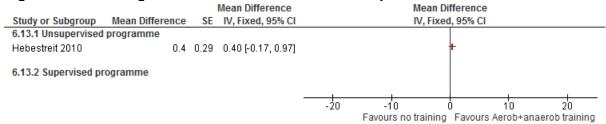
Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; Cl: confidence interval

Figure 357: Change in BMI at 3 months follow-up



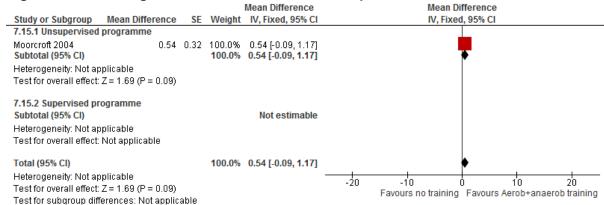
Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 358: Change in BMI at 3 to 6 months follow-up



Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 359: Change in BMI at 12 months follow-up



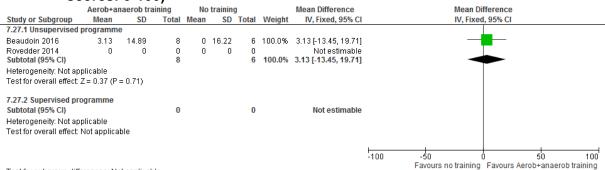
Abbreviations: BMI: body mass index; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 360: Change in quality of life – CFQ-R physical functioning at 3 months follow-up (range of scores: 0-100)

_	Aerob+anaerob training				trainin	g		Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
7.19.1 Unsupervised	programme)								<u></u>	
Beaudoin 2016	7.52	14.9	8	6.92	18.67	6	100.0%	0.60 [-17.56, 18.76]		— ——	
Rovedder 2014	0	0	0	0	0	0		Not estimable		T	
Subtotal (95% CI)			8			6	100.0%	0.60 [-17.56, 18.76]		-	
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z= 0.06 (P=	= 0.95)									
7.19.2 Supervised pr	ogramme										
Subtotal (95% CI)			0			0		Not estimable			
Heterogeneity: Not ap	plicable										
Test for overall effect	Not applicat	ole									
									-100		100
										Favours no training Favours Aerob+anaerob train	ing

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 361: Change in quality of life – CFQ-R vitality at 3 months follow-up (range of scores: 0-100)



Test for subgroup differences: Not applicable

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 362: Change in quality of life – CFQ-R emotional state at 3 months follow-up (range of scores: 0-100)

	Aerob+ana	aerob tra	ining	No	trainin	g		Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI
7.23.1 Unsupervised	programme									
Beaudoin 2016	-6.67	9.1	8	1.11	11.06	6	100.0%	-7.78 [-18.65, 3.09]		
Rovedder 2014	0	0	0	0	0	0		Not estimable		
Subtotal (95% CI)			8			6	100.0%	-7.78 [-18.65, 3.09]		•
Heterogeneity: Not ap Test for overall effect:		0.16)								
	,	0.10,								
7.23.2 Supervised pr	ogramme							N-4 6 N-		
Subtotal (95% CI)			0			0		Not estimable		
Heterogeneity: Not ap										
Test for overall effect:	Not applicab	le								
									-	
									-100	-50 0 50 1
										Favours no training Favours Aerob+anaerob train

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

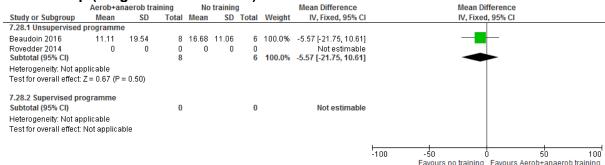
Figure 363: Change in quality of life – CFQ-R treatment burden at 3 months follow-up (range of scores: 0-100)

	Aerob+an	aerob tra	ining	No	trainin	g		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
7.26.1 Unsupervised	programme)							
Beaudoin 2016	-5.56	20.12	8	0	18.73	6	100.0%	-5.56 [-26.03, 14.91]	
Rovedder 2014 Subtotal (95% CI)	0	0	0 8	0	0	0 6	100.0%	Not estimable -5.56 [-26.03, 14.91]	
Heterogeneity: Not ap Test for overall effect:		= 0.59)							
7.26.2 Supervised pr	ogramme								
Subtotal (95% CI)			0			0		Not estimable	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Not applicat	ble							
									to to to
									-100 -50 0 50 100 Fayours no training Fayours Aerob+anaerob training

Fest for subgroup differences: Not applicable

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 364: Change in quality of life – CFQ-R health perception at 3 months follow-up (range of scores: 0-100)



Test for subgroup differences: Not applicable

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 365: Change in quality of life – CFQ-R social limitations at 3 months follow-up (range of scores: 0-100)

	Aerob+ana	erob trai	ining	No	training	g		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	I IV, Fixed, 95% CI
7.30.1 Unsupervised	programme								
Beaudoin 2016	-2.5	9.7	8	2.79	13.63	6	100.0%	-5.29 [-18.10, 7.52]	_
Rovedder 2014	0	0	0	0	0	0		Not estimable	
Subtotal (95% CI)			8			6	100.0%	-5.29 [-18.10, 7.52]	◆
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z= 0.81 (P= 0	0.42)							
7.30.2 Supervised pro	ogramme								
Subtotal (95% CI)			0			0		Not estimable)
Heterogeneity: Not ap	plicable								
Test for overall effect:	Not applicable	9							
									-100 -50 0 50 10
									Favours no training Favours Aerob+anaerob training

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 366: Change in quality of life – CFQ-R body image at 3 months follow-up (range of scores: 0-100)

` <i>I</i>	\erob+ana	erob train	ning	No	training	g		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	CI IV, Fixed, 95% CI
7.20.1 Unsupervised pro	gramme								_
Beaudoin 2016	-4.16	6.45	8	1.87	15.07	6	100.0%	-6.03 [-18.89, 6.83]	B] — — — — — — — — — — — — — — — — — — —
Rovedder 2014 Subtotal (95% CI)	0	0	0 8	0	0	0 6	100.0%	Not estimable -6.03 [-18.89, 6.83]	
Heterogeneity: Not applic	able								
Test for overall effect: Z =	0.92 (P = 0	0.36)							
7.20.2 Supervised progr	amme								
Subtotal (95% CI)			0			0		Not estimable	e
Heterogeneity: Not applic	able								
Test for overall effect: No	t applicable	9							
Total (95% CI)			8			6	100.0%	-6.03 [-18.89, 6.83]	s ₁
Heterogeneity: Not applic	able								-100 -50 0 50 100
Test for overall effect: Z=	0.92 (P = 0	0.36)							-100 -50 0 50 100 Favours no training Favours Aerob+anaerob training
Test for subgroup differe	nces: Not a	annlicable							r avours no training Pavours Action anaction training

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 367: Change in quality of life – CFQ-R role limitations at 3 months follow-up (range of scores: 0-100)

	Aerob+ana	erob tra	ining	No	trainin	g		Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI
7.31.1 Unsupervised	programme									
Beaudoin 2016	-1.04	18	8	-5.56	16.02	6	100.0%	4.52 [-13.37, 22.41]		 _
Subtotal (95% CI)			8			6	100.0%	4.52 [-13.37, 22.41]		*
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 0.50 (P = 1	0.62)								
7.31.2 Supervised pr	ogramme									
Subtotal (95% CI)			0			0		Not estimable		
Heterogeneity: Not ap	plicable									
Test for overall effect:	Not applicable	е								
									-100	-50 0 50 100
										Favours no training Favours Aerob+anaerob training

Test for subgroup differences: Not applicable

Abbreviations: CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 368: Change in quality of life – CFQ-R weight problems at 3 months follow-up

	Aerob+an	aerob tra	ining	No	training	9		Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI
7.29.1 Unsupervised p	orogramme									
Beaudoin 2016	-8.34	18.58	8	0	31.62	6	100.0%	-8.34 [-36.73, 20.05]		
Rovedder 2014	0	0	0	0	0	0		Not estimable		
Subtotal (95% CI)			8			6	100.0%	-8.34 [-36.73, 20.05]		
Heterogeneity: Not app	olicable									
Test for overall effect: 2	Z = 0.58 (P =	0.56)								
7.29.2 Supervised pro	gramme									
Subtotal (95% CI)			0			0		Not estimable		
Heterogeneity: Not app	olicable									
Test for overall effect: N	Not applicab	ole								
									-100	-50 0 50 100
										Favours no training Favours Aerob+anaerob training
Test for subgroup diffe	rences: Not	tapplicab	le							

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 369: Change in quality of life – CFQ-R respiratory symptoms at 3 months follow-up

10	11011-0	4P										
	Aerob+ai	naerob tra	ining	No	trainin	g		Mean Difference		Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI		
7.22.1 Unsupervised	programm	е										
Beaudoin 2016	0	12.84	8	4.63	10.53	6	100.0%	-4.63 [-16.88, 7.62]		-		
Rovedder 2014	0	0	0	0	0	0		Not estimable				
Subtotal (95% CI)			8			6	100.0%	-4.63 [-16.88, 7.62]		•		
Heterogeneity: Not ap Test for overall effect:		= 0.46)										
7.22.2 Supervised pr	ogramme	ŕ										
Subtotal (95% CI)	- g. a		0			0		Not estimable				
Heterogeneity: Not ap	nlicable											
Test for overall effect:	•	ble										
									400	-50 0 50		
									-100	Favours no training Favours Aerob+anaerob train		
To at fav auchavaria diff	faranaaa: Na	st annliach	da							Favours no maining Favours Aerop-arraeron hair		

Test for subgroup differences: Not applicable

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Figure 370: Change in quality of life – CFQ-R digestion symptoms at 3 months follow-up

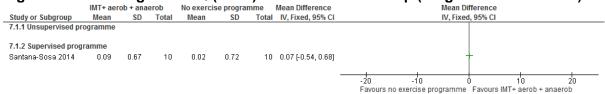
	Aerob+an	aerob tra	ining	No	trainin	g		Mean Difference		Mean	Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fix	ked, 95% CI		
7.21.1 Unsupervised	programme)											
Beaudoin 2016	5.55	7.57	8	-9.25	16.72	6	100.0%	14.80 [0.43, 29.17]					
Rovedder 2014	0	0	0	0	0	0		Not estimable			_		
Subtotal (95% CI)			8			6	100.0%	14.80 [0.43, 29.17]			~		
Heterogeneity: Not ap	plicable												
Test for overall effect:	Z = 2.02 (P =	= 0.04)											
7.21.2 Supervised pr	ogramme												
Subtotal (95% CI)			0			0		Not estimable					
Heterogeneity: Not ap	plicable												
Test for overall effect:	Not applicat	ole											
									1				
									-100	-50	0	50	100
										Favours no trainii	ng Favours Aero)b+anaerob	training

Test for subgroup differences: Not applicable

Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

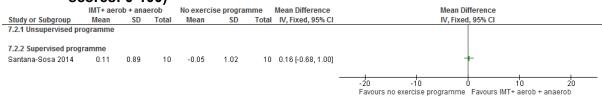
Comparison 6. Combined inspiratory muscle training (IMT), resistance and aerobic training *versus* no exercise programme

Figure 371: Change in FEV₁ (litres) at 2 months follow-up (range of scores: 0-100)



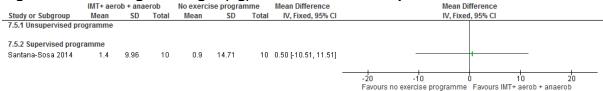
Abbreviations: CI: confidence interval; FEV₁: forced expiratory volume in 1 second; IV: inverse variance; SD: standard deviation

Figure 372: Change in forced vital capacity (litres) at 2 months follow-up (range of scores: 0-100)



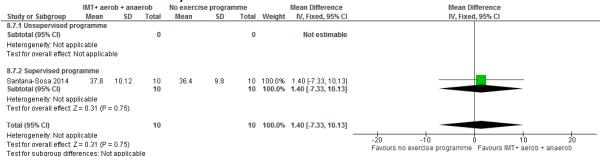
Abbreviations: SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 373: Change in weight (kg) at 2 months follow-up



Abbreviations: kg: kilograms; SD: standard deviation; IV: inverse variance; CI: confidence interval

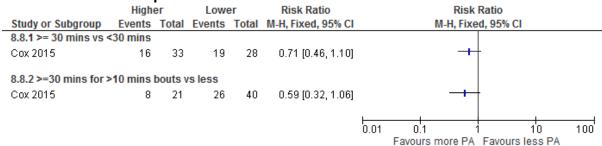
Figure 374: Change in quality of life (CFQ-R children's) at 2 months follow-up (range of scores: 0-100)



Abbreviations: CI: confidence interval; CFQ-R: cystic fibrosis questionnaire revised; IV: inverse variance; SD: standard deviation

Comparison 7. Physical activity: higher amount or longer duration *versus* lower amount or shorter duration

Figure 375: Need of hospitalization (proxy outcome for time to next exacerbation) at 12 months follow-up



Abbreviations: M-H: Mantel-Haenszel; CI: confidence interval; PA: physical activity

I.21 Psychological assessment

Not applicable to this review.

I.22 Cross-infection control

I.22.1 Outpatient care

Comparison 1. Cohort segregation by clinic times versus no cohort segregation

Figure 376: 10 year incidence of P. Aeruginosa infections at 10 years follow-up

	Conort segre	gation	No conort segre	gation	RISK RAUO		RISK	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
Hayes 2010	13	21	14	18	0.80 [0.52, 1.21]		- +		
						0.01	0.1	1 10	100
							Favours Cohort segregation	Favours No cohort segregation	

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

4-year prevalence of MRSA at 4 years follow-up

Data could not be plotted

4-year prevalence of non-mucoid PA at 4 years follow-up

Data could not be plotted

4-year prevalence of mucoid PA at 4 years follow-up

Data could not be plotted

Staff compliance at 4 years follow-up

Data could not be plotted

Comparison 2. Cohort segregation by location versus no cohort segregation

Annual incidence of new growths of PA at 9 years follow-up

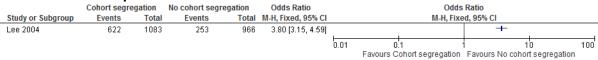
Data could not be plotted

Figure 377: Yearly prevalence of chronic P. Aeruginosa infections at 9 years follow-



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 378: Yearly prevalence of intermittent P. Aeruginosa infections at 9 years follow-up



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Comparison 3. Combination of protective equipment + individual segregation *versus* incomplete protective equipment + incomplete individual segregation

4-month prevalence of PA infections at 5 years follow-up

Data could not be plotted

4-month prevalence of MRSA infections at 5 years follow-up

Data could not be plotted

I.22.2 Inpatient care

Comparison 4. Cohort segregation by location versus no cohort segregation

Annual incidence of B. Cepacia Complex at 1 year follow-up

Data could not be plotted

Figure 379: 5-month incidence of hospital-associated colonization of P. Cepacia at 5 months follow-up

	Cohort segre	egation	No cohort seg	gregation	Odds Ratio			Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI			M-H, Fixe	ed, 95% CI	
Thomassen 1986	6	235	24	308	0.31 [0.12, 0.77]					
						0.01	0.	.1	1 10	100
							Favours C	obort segregation	Favours No cohort sen	regation

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Comparison 5. Individual segregation by location versus usual care

Patients' satisfaction

Data could not be plotted

Parents' satisfaction

Data could not be plotted

I.22.3 Combined inpatient and outpatient care

Comparison 6. Cohort segregation versus no cohort segregation

Figure 380: Monthly incidence of multiply resistant PA strain at 1 month follow-up



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 381: Annual incidence of intermittent PA at 1 year follow-up



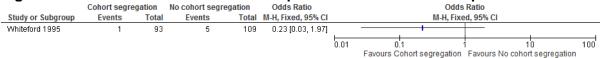
Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 382: Annual incidence of chronic PA at 1 year follow-up



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Figure 383: 6-month incidence of B. Cepacia at 6 months follow-up



Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Annual incidence of Burkholderia species infection at 1 year follow-up Data could not be plotted

Figure 384: Monthly prevalence of multiply resistant PA strain at 1 month follow-up

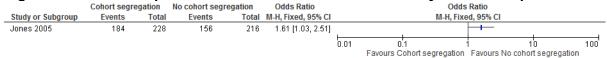


Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Prevalence of AES-1 (PA epidemic strain) at 2 years follow-up

Data could not be plotted

Figure 385: Annual prevalence of chronic PA infection at 1 year follow-up



Abbreviations: M-H: Mantel-Haenszel; CI: confidence interval

Figure 386: Annual prevalence of transmissible PA infection at 1 year follow-up

•		Cohort segregation		No cohort segregation		Odds Ratio		Odds Ratio		
Study	or Subgroup	bgroup Events Total		Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI			
Jones	2005	35	228	28	216	1.22 [0.71, 2.08]		_	1	
							0.01	0.1	1 10	100
								Favours Cohort segregation	Favours No cohort segregation	n

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel

Annual prevalence of chronic infection with transmissible PA strain at 1 year followup

Data could not be plotted

Comparison 7. Complete cohort segregation *versus* incomplete cohort segregation Annual incidence of Burkholderia species at 1 year follow-up

Data could not be plotted

Comparison 8. Individual segregation versus usual care

Patient satisfaction

Data could not be plotted

Comparison 9. Cohort segregation + individual segregation versus cohort segregation

Yearly prevalence of B. Cepacia complex infection at 1 year follow-up

Data could not be plotted

Yearly prevalence of Burkholderia species at 5 years follow-up

Data could not be plotted

Comparison 10. Cohort segregation + individual segregation + protective equipment *versus* usual care

Annual incidence of B. Cepacia complex infection at 1 year follow-up

Data could not be plotted

Comparison 11. Cohort segregation + individual segregation *versus* usual care

Patient satisfaction

Data could not be plotted