Date: 2011-09-21

Question: Should treatment guided by sputum eosinophils and clinical criteria vs treatment guided by clinical criteria alone be used in adults with severe asthma?

Bibliography: Petsky HL et al. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. Cochrane Database of Systematic Reviews 2007, Issue 2. (CD005603).

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment guided by sputum eosinophils	Treatment guided by clinical criteria alone	Relative (95% CI)	Absolute		
Need for oral corticosteroids (follow-up 1 and 2 years; assessed with: (exacerbations requiring rescue courses of oral glucocorticosteroid))												
2	randomised trials	serious[1]	no serious inconsistency	serious[2,3]	serious[4]	reporting bias[5]	29 exacerbations per 79 patients[6]	91 exacerbations per 85 patients[6]	Rate ratio 0.33 (0.19 to 0.57)	72 fewer per 100 (from 46 fewer to 87 fewer)	●○○○ VERY LOW	CRITICAL
Dose of oral corticosteroids (follow-up 1 year; Better indicated by lower values)												
1	randomised trials	no serious risk of bias[7]	no serious inconsistency	serious[3,8]	very serious[9]	reporting bias[5]	34	34	-	MD 0.4 lower (2.36 lower to 1.56 higher)	●○○○ VERY LOW	CRITICAL
Symptoms[10] (follow-up 1 year; measured with: symptom scores (visual analogue scale); range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[11]	no serious inconsistency	serious[3,8]	very serious[12]	reporting bias[5]	34	34	-	MD 10.61 lower (48.14 lower to 26.92 higher)	●○○○ VERY LOW	CRITICAL
Quality of life[10] (follow-up 1 year; measured with: Asthma Quality of Life Questionnaire (AQLQ); range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	serious[11,13]	no serious inconsistency	serious[3,8]	very serious[14]	reporting bias[5]	34	34	-	MD 0.04 higher (1.08 lower to 1.16 higher)	●○○○ VERY LOW	CRITICAL
Hospitalisation (follow-up 1 to 2 years)												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[15]	reporting bias[5]	3%[16]	20%[16]	RR 0.14 (0.02 to 1.25)	17 fewer per 100 (from 20 fewer to 5 more)	●○○○ VERY LOW	CRITICAL
Absence from school/work - not measured												
0	-	-	-	-	-	–	-	-	-	-		IMPORTANT
Death - not reported												
0	-	-	-	-	-	–	-	-	-	-		IMPORTANT
Admission to the intensive care unit - not reported												
0	-	-	-	-	-	–	-	-	-	-		IMPORTANT
Need for intubation and ventilation - not reported												
0	-	-	-	-	-	–	-	-	-	-		IMPORTANT
Resource use (follow-up 1 year; measured with: cost per patient per year in US dollars; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3,8]	very serious[17]	reporting bias[5]	34	34	-	MD 314 lower (941 lower to 313 higher)	●○○○ VERY LOW	IMPORTANT
Lung function (follow-up 1.5 and 2 years; measured with: FEV1; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2,3]	very serious[18]	–	64	55	-	SMD 0.02 higher (0.34 lower to 0.38 higher)[19]	●○○○ VERY LOW	IMPORTANT

MD – mean difference, RR – relative risk, SMD – standardized mean difference

[1] All studies had unclear allocation concealment. Two studies did not report whether analyses were by intention to treat (one study excluded patients not following protocol).

[2] Studies included patients with mild to severe asthma.

[3] Studies included selected population of patients who were proved to be compliant, with no comorbidities, no history of smoking and no exacerbation within the last month.

[4] Only 164 patients.

[5] There are only 3 small studies that showed large effect on beneficial outcomes.

[6] Number of exacerbations per total number of patients in experimental or control groups in both trials.

[7] Only one study reported that important outcome. We did not downgrade for the risk of bias (selective reporting) because we already downgraded quality of evidence for other factors.

[8] Patients with moderate to severe asthma.

[9] Only 68 patients. Results do not exclude an appreciable increase or reduction in oral steroid dose.

[10] Non significant improvement when monitoring with sputum eosinophil.

[11] Results were reported only as a graph with no numerical values. Only one study reported that important outcome.

[12] Only 68 participants. Results do not exclude an appreciable improvement or appreciable deterioration of symptoms with measurement of sputum eosinophils.

[13] Measured but not reported in 1 study. Not measured in another.

[14] Only 68 participants. Results do not exclude an appreciable improvement or worsening of quality of life.

[15] Only 6 events.
[16] Risk in experimental and control groups was estimated from one study that reported any hospitalizations. In the other 2 studies there were no events.
[17] Only 68 participants. Results do not exclude an appreciable increase or reduction of cost of treatment.
[18] Only 119 patients. Results do not exclude an appreciable increase or decrease in lung function (FEV1).
[19] Two studies reported this outcome. One showed 0.8% (95% CI: -7.9 to 9.5) difference in change from baseline in the predicted value in favour of measurement of eosinophils and the other showed no difference in final scores of absolute value of FEV1 (mean difference: 0.0 L, 95% CI: -0.64 to 0.64).

Date: 2011-09-21
Question: Should treatment guided by sputum eosinophils vs treatment guided by clinical criteria alone be used in children with severe asthma?
Bibliography: Fleming L, Wilson N, Regamey N, Bush A. Use of sputum eosinophil counts to guide management in children with severe asthma. Thorax. [Published Online First 8 August 2011].

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment guided by sputum eosinophils	Treatment guided by clinical criteria alone	Relative (95% CI)	Absolute		
Need for oral corticosteroids (follow-up 1 year; assessed with: exacerbations requiring a course of OCS [at least 20 mg/day] for at least 2 days)												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/26 (30.8%)[3]	11/28 (39.3%)[3]	RR 0.78 (0.37 to 1.6)[4]	9 fewer per 100 (from 25 fewer to 24 more)	⨁⨁◯◯ LOW	CRITICAL
Dose of oral corticosteroids - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Symptoms (follow-up 1 year; measured with: symptom free days per week; Better indicated by lower values)												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[5]	none	26	28	-	mean 0.4 lower (1.2 lower to 0.4 higher)[6]	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life - not measured												
0	-	-	-	-	-	-	-	-	-	-		CRITICAL
Hospitalization (follow-up 1 year)												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/26[7]	10/28[7]	Rate ratio 1.4 (0.57 to 3.57)	14 more per 100 (from 21 fewer to 49 more)	⨁⨁◯◯ LOW	CRITICAL
Absence from school/work - not measured												
0	-	-	-	-	-	-	-	-	-	-	–	IMPORTANT
Death - not reported												
0	-	-	-	-	-	-	-	-	-	-	–	IMPORTANT
Admission to the intensive care unit - not reported												
0	-	-	-	-	-	-	-	-	-	-	–	IMPORTANT
Need for intubation and ventilation - not reported												
0	-	-	-	-	-	-	-	-	-	-	–	IMPORTANT
Resource use - not measured[8]												
0	-	-	-	-	-	-	–	-	-	-	–	IMPORTANT

RR – relative risk
[1] Authors reported that "neither the subjects and their parents nor the health professionals involved in their clinical care knew the randomisation group", however it is not clear how they acjieved blinding.
[2] Results do not exclude an appreciable benefit or appreciable harm.
[3] Based on data extracted from the graph.
[4] Rate of exacerbations requiring OCS was 1.9 vs 2.7 (rate ratio: 0.73, 95% CI: 0.42 to 1.28)
[5] Results do not exclude an appreciable benefit or no difference. Only 54 patients.
[6] Mean difference in symptom free nights was 0.5 fewer per week (95% CI: 1.1 fewer to 0.1 more)
[7] Rate of hospitalizations in experimental or control groups.
[8] See evidence profile for sputum eosinophil measurement in adults.

Date: 2011-05-10

Question: Should treatment guided by exhaled nitric oxide (NO) vs treatment guided by clinical criteria alone be used in patients with severe asthma?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment guided by exhaled NO	Treatment guided by clinical criteria alone	Relative (95% CI)	Absolute		
Need for oral corticosteroids (follow-up 1 years; assessed with: number of oral steroid courses)												
2	randomised trials	no serious risk of bias[1]	no serious inconsistency	serious[2]	very serious[3,4]	none	9/157 (5.7%)	12/148 (8.1%)	RR 0.75 (0.33 to 1.70)	20 fewer per 1000 (from 54 fewer to 57 more)	⊕○○○ VERY LOW	CRITICAL
Dose of oral corticosteroids - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Exacerbations of asthma (follow-up 1 years; assessed with: number of patients with at least one exacerbation)												
6	randomised trials	serious[5]	no serious inconsistency	serious[2]	no serious imprecision	none	160/523 (30.6%)	196/520 (37.7%)	RR 0.8 (0.68 to 0.93)	75 fewer per 1000 (from 26 fewer to 121 fewer)	⊕⊕○○ LOW	IMPORTANT
								80%		160 fewer per 1000 (from 56 fewer to 256 fewer)		
Exacerbation rate (follow-up 1 years; measured with: number of exacerbations per year; Better indicated by lower values)												
4	randomised trials	no serious risk of bias[6]	no serious inconsistency[7]	serious[2]	serious[8]	none	406	401	-	MD 0.34 lower (0.67 to 0.01 lower)	⊕⊕○○ LOW	IMPORTANT
Symptoms (follow-up 1 years; measured with: different symptom scores; Better indicated by lower values)												
5	randomised trials	serious[5]	no serious inconsistency	serious[2]	no serious imprecision	none	445	447	-	SMD 0.01 lower (0.14 lower to 0.12 higher)	⊕⊕○○ LOW	IMPORTANT
Quality of life - not measured												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Absence from school/work (follow-up 46 weeks[9]; measured with: number of days missed from school per participant; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[2]	no serious imprecision	none	276	270	-	MD 0.04 lower (0.12 lower to 0.05 higher)	⊕⊕○○ LOW	IMPORTANT
Death - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Admission to the intensive care unit (follow-up 1 years)												
1	randomised trials	serious[10]	no serious inconsistency	serious[2]	serious[11]	none	1/42 (2.4%)	0/47 (0%)	not pooled	not pooled	⊕○○○ VERY LOW	CRITICAL
Need for intubation and ventilation - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Hospitalization (follow-up 1 years)												
2	randomised trials	serious[12]	no serious inconsistency	serious[2]	very serious[3,4]	none	10/318 (3.1%)	11/317 (3.5%)	RR 0.88 (0.38 to 2.04)	4 fewer per 1000 (from 22 fewer to 36 more)	⊕○○○ VERY LOW	CRITICAL
Lung function (follow-up 1 years; measured with: percent predicted FEV1; Better indicated by higher values)												
4	randomised trials	serious[5]	no serious inconsistency	serious[2]	no serious imprecision	none	436	436	-	MD 1.97 higher (0.38 lower to 4.31 higher)	⊕⊕○○ LOW	IMPORTANT
Resource use - not measured												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL

MD – mean difference, RR – relative risk, SMD – standardized mean difference

[1] We did not downgrade for the risk of bias, however, we acknowledge a borderline judgement. Studies did not report one or more risk of bias criteria.

[2] No study explicitly included patients with severe asthma; most patients in the studies had mild to moderate asthma. It is not clear if the results would be similar in patients with severe asthma.

[3] Results do not exclude an appreciable benefit or an appreciable harm.

[4] Only 21 events.

[5] Most studies did not report methods of randomization and concealment of allocation; two studies were not blinded.

[6] We did not downgrade for the risk of bias, however, we acknowledge a borderline judgement. One study was not blinded and other studies did not report one or more risk of bias criteria.

[7] We did not downgrade for inconsistency, despite one study at higher risk of bis showed a larger effect. This, however, did not significantly affect the combined results (ifthe study was not included the pooled mean number of exacerbations per year would be 0.16 fewer (95% CI: from 0.34 fewer to 0.01 more)

[8] Results do not exclude a small benefit or no difference.

[9] Outcome was measured during the last 2 weeks of follow-up and it is not known how many days of school were missed during the whole period of observation.

[10] Study did not report several risk of bias criteria; other studies did not mention that outcome that would be expected to have been reported in such studies.
[11] Only one event among 89 patients.
[12] Only 2 studies reported that outcome that one would be expected to have been reported in such studies.

Date: 2011-09-22
Question: Should omalizumab be used in adults with severe asthma?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Omalizumab	Control	Relative (95% CI)	Absolute		
Quality of life: improvement of at least 0.5 point in AQLQ (follow-up 28 to 48 weeks; assessed with: Asthma Quality of Life Questionnaire)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none[2]	805/1206 (66.7%)	656/1173 (55.9%)	RR 1.19 (1.1 to 1.28)	11 more per 100 (from 6 more to 16 more)	●●●○ MODERATE	CRITICAL
Quality of life (follow-up 28 and 48 weeks; measured with: Asthma Quality of Life Questionnaire (AQLQ); range of scores: 1-7; Better indicated by higher values)												
2	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	631	626	-	mean ranged from 0.29 to 0.45 higher[5]	●○○○ VERY LOW	IMPORTANT
Asthma control (follow-up 32 weeks; measured with: Asthma Control Questionnaire (ACQ); Better indicated by lower values)												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	238	104	-	MD 0.87 lower (1.14 to 0.6 lower)	●●●○ MODERATE	CRITICAL
Need for systemic corticosteroids (follow-up 16 to 48 weeks)												
4	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	206/913 (22.6%)	267/915 (29.2%)	RR 0.73 (0.56 to 0.94)	8 fewer per 100 (from 2 fewer to 13 fewer)	●●●○ MODERATE	CRITICAL
Daily dose of oral corticosteroids (follow-up 32 weeks; Better indicated by lower values)												
1	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness[9]	serious[10]	none	50	45	-	MD 6 mg lower[11]	●○○○ VERY LOW	CRITICAL
Symptoms (follow-up 32 weeks; measured with: Asthma symptom score and nighttime awakenings; Better indicated by lower values)												
2	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[13]	none	368	215	-	SMD 0.27 lower (0.44 to 0.09 lower)	●●○○ LOW	CRITICAL
Symptom-free nights - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Symptom-free days - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Absence from school/work [days] - not measured												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Death (follow-up 28 to 48 weeks)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[14]	none	0/908 (0%)	2/749 (0.27%)	RR 0.23 (0.03 to 2.17)	2 fewer per 1000 (from 3 fewer to 3 more)	●●●○ MODERATE	IMPORTANT
Hospitalization (follow-up 28 weeks)												
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	serious[16]	none	13/209 (6.2%)	25/210 (11.9%)	RR 0.52 (0.27 to 0.99)	6 fewer per 100 (from 0 fewer to 9 fewer)	●●○○ LOW	CRITICAL
Admission to ICU - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Intubation and ventilation - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Emergency department visit (follow-up 28 weeks)												
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	very serious[17]	none	9/209 (4.3%)	14/210 (6.7%)	RR 0.65 (0.29 to 1.46)	2 fewer per 100 (from 5 fewer to 3 more)	●○○○ VERY LOW	IMPORTANT
Any adverse effect (follow-up 16 to 48)												
6	randomised trials	serious[7]	no serious inconsistency	serious[18]	no serious imprecision	none	828/1427 (58%)	794/1394 (57%)	RR 1.01 (0.96 to 1.07)	6 more per 1000 (from 23 fewer to 40 more)	●●○○ LOW	IMPORTANT
Serious adverse effect (follow-up 16 to 48 weeks)												
6	randomised trials	serious[7]	no serious inconsistency	no serious indirectness[19]	serious[20]	none	104/1701 (6.1%)	113/1522 (7.4%)	RR 0.84 (0.65 to 1.09)	12 fewer per 1000 (from 26 fewer to 7 more)	●●○○ LOW	CRITICAL
Discontinuation due to adverse effect (follow-up 16 to 48 weeks)												
5	randomised	serious[7]	no serious	no serious indirectness	serious[21]	none	46/1539	25/1375	RR 1.57 (0.96 to	10 more per 1000 (from 1 fewer to 28	●●○○	IMPORTANT

	trials		inconsistency				(3%)	(1.8%)	2.56)	more)	LOW	
Resource use (cost) - not measured												
0	-	-	-	-	-	none	0	-	-	-	–	CRITICAL
Rescue medication use [puffs/day] (follow-up 32 weeks; Better indicated by lower values)												
2[22]	randomised trials	serious[22,23]	no serious inconsistency	no serious indirectness	serious[24]	none	158	148	-	MD 0.78 lower (1.7 lower to 0.13 higher)[22]	●●○○ LOW	NOT IMPORTANT
Morning PEF (follow-up 32 weeks; Better indicated by higher values)												
1	randomised trials	serious[25]	no serious inconsistency	serious[26]	serious[27]	none	115	109	-	MD 9 lower (20.86 lower to 2.86 higher)	●○○○ VERY LOW	IMPORTANT
FEV1 (follow-up 32 weeks; Better indicated by higher values)												
1[28]	randomised trials	serious[29]	no serious inconsistency	serious[26]	serious[20]	none	266	121	-	MD 4.4 higher (0.54 to 8.26 higher)	●○○○ VERY LOW	IMPORTANT

MD – mean difference, RR – relative risk, SMD – standardized mean difference

[1] Some studies excluded patients after randomization, concealment of allocation and blinding were not adequately reported. There is also suspicion of publication bias based on a funnel plot.

[2] We did not downgrade for suspected publication bias since we already downgraded for risk of bias in a borderline situation where risk of publication bias is difficult to assess.

[3] Only 2 studies reported that outcome and only one reported variability.

[4] It is impossible to assess precision

[5] Mean difference between the groups in the change from baseline in one study was 0.29 points (95% CI: 0.15 to 0.43); in the other study the difference in final scores was 0.45 point, but the authors did not report variability in the results; all on a 7-point scale (AQLQ) favouring omalizumab.

[6] Study was not blinded and 15% of patients discontinued treatment prematurely.

[7] Most studies did not report concealment of allocation and in all 10-20% discontinued treatment prematurely. 2 studies measured this outcome but did not report it.

[8] Only 1 study reported that outcome, but did not provide variability in the results.

[9] All patients received oral steroids at baseline

[10] Only 90 patients.

[11] There was a mean difference of 6 mg prednisone per day in favour of omalizumab. Mean dose in omalizumab group was 69 mg and in placebo group 75 mg.

[12] Only 1 study reported that outcome. The other reported only nighttime awakenings and was not blinded.

[13] Results do not exclude a small or negligible effect.

[14] Only 2 events.

[15] Protocol changed during the study. Patients randomized before change of protocol were excluded.

[16] Only 38 events. Results do not exclude large effect or no effect.

[17] Only 23 events. Results do not exclude appreciable benefit or appreciable harm.

[18] Composite outcome with different importance of particular outcomes.

[19] Composite outcome, but importance of particular outcomes for decision making is similar.

[20] Results do not exclude appreciable benefit or no effect.

[21] Only 71 events. Results do not exclude appreciable harm or no effect.

[22] Additional 2 studies measured that outcome but did not report variability. The mean differences between groups in both studies were 0.27 and 0.6 puff/day and both favoured omalizumab.

[23] Only 2 studies reported that outcome.

[24] Results do not exclude a reduction of 2 puffs/day or no effect.

[25] Only one study provided all information about the outcome. 2 studies din not report variability and remaining studies do not report it.

[26] It is not certain how important this outcome is for patients.

[27] Only 224 events

[28] Another study reported that outcome but did not report variability.

[29] Study was open label.

Date: 2011-11-20
Question: Should omalizumab be used in children with severe asthma?
Bibliography: Busse 2011 and Lanier 2009

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Omalizumab	Control	Relative (95% CI)	Absolute		
Quality of life (follow-up 24 weeks; measured with: Pediatric Asthma Quality of Life Questionnaire (PAQLQ); range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision[3]	none	384	192	-	MD 0.04 higher[4]	⨁⨁◯◯ LOW	CRITICAL
Asthma control (follow-up 60 weeks; measured with: Childhood Asthma Control Test (C-ACT) and the Asthma Control Test (ACT); Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	serious[6]	no serious imprecision[7]	none	-	-	-	mean ranged from 0.19 to 0.78 higher[8]	⨁⨁◯◯ LOW	CRITICAL
Need for systemic corticosteroid (follow-up 60 weeks; assessed with: a minimum of 20 mg per day of prednisone, or equivalent for any 3 of 5 consecutive days)												
1	randomised trials	serious[5]	no serious inconsistency	serious[6]	no serious imprecision[9]	none	56/195 (28.7%)	81/191 (42.4%)	RR 0.68 (0.51 to 0.89)	14 fewer per 100 (from 5 fewer to 21 fewer)	⨁⨁◯◯ LOW	CRITICAL
Daily dose of oral corticosteroids - not reported												
0	-	-	-	-	-	-	-	-	-	-		CRITICAL
Symptoms (follow-up 24 weeks; measured with: nocturnal symptoms; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	serious[10]	no serious inconsistency	serious[2]	serious[11]	none	384	192	-	MD 0.35 lower (0.75 lower to 0.05 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Symptom-free days (follow-up 60 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	serious[6]	no serious imprecision	none	195	191	-	MD 3.43 higher (1.45 to 5.41 higher)[12]	⨁⨁◯◯ LOW	IMPORTANT
Absence from school [days] (follow-up 60 weeks)												
1	randomised trials	serious[5]	no serious inconsistency	serious[6]	no serious imprecision	none	not reported	not reported	-	MD 0.09 lower (0.01 to 0.18 lower)	⨁⨁◯◯ LOW	IMPORTANT
Death (follow-up 60 weeks)												
1	randomised trials	serious[5]	no serious inconsistency	serious[6]	no serious imprecision	none	0/208 (0%)	0/211 (0%)	not pooled	not pooled	⨁⨁◯◯ LOW	IMPORTANT
Hospitalization (follow-up 60 weeks)												
1	randomised trials	serious[5]	no serious inconsistency	serious[6]	serious[13]	none	3/195 (1.5%)	12/191 (6.3%)	RR 0.24 (0.07 to 0.85)	5 fewer per 100 (from 1 fewer to 6 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Admission to ICU - not reported												
0	-	-	-	-	-	-	-	-	-	-		CRITICAL
Intubation and ventilation - not reported												
0	-	-	-	-	-	-	-	-	-	-		CRITICAL
Emergency department visit - not reported												
0	-	-	-	-	-	-	-	-	-	-		IMPORTANT
Any adverse effect (follow-up 24 to 60 weeks)												
2	randomised trials	serious[5,10]	no serious inconsistency	no serious indirectness	serious[14]	none	462/616 (75%)	294/398 (73.9%)	RR 0.89 (0.7 to 1.15)	8 fewer per 100 (from 22 fewer to 11 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse effect (follow-up 24 to 60 weeks)												
2	randomised trials	serious[5,10]	no serious inconsistency	no serious indirectness	serious[15]	none	29/616 (4.7%)	43/398 (10.8%)	RR 0.47 (0.3 to 0.75)	6 fewer per 100 (from 3 fewer to 8 fewer)	⨁⨁◯◯ LOW	CRITICAL
Discontinuation due to adverse effect (follow-up 24 to 60 weeks)												
2	randomised trials	serious[5,10]	no serious inconsistency	serious[2,6]	serious[16]	none	2/629 (0.32%)	8/418 (1.9%)	RR 0.29 (0.02 to 4.55)	1 fewer per 100 (from 2 fewer to 7 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Resource use (cost) - not measured												
0	-	-	-	-	-	-	-	-	-	-		CRITICAL
Rescue medication use [puffs/day] (follow-up 24 weeks; Better indicated by lower values)												
1	randomised trials	serious[10]	no serious inconsistency	serious[2]	serious[11]	none	384	192	-	MD 0.3 lower	⨁◯◯◯	NOT IMPORTANT

										(0.75 lower to 0.15 higher)	VERY LOW	
Morning PEF - not reported												
0	-	-	-	-	-	-	-	-	-	-	–	IMPORTANT
FEV1 (follow-up 60 weeks; measured with: % predicted; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	serious[6]	no serious imprecision	none	195	191	-	MD 0.9 higher (0.82 lower to 2.62 higher)	●●○○ LOW	IMPORTANT

MD – mean difference, RR – relative risk

[1] Only one study reported that outcome and it reported neither individual group scores nor variability. Study did not measure the outcome in 16% of patients and excluded data from 2 centers from analysis.

[2] Only 64% of children had severe asthma.

[3] It was not possible to assess precision of the results due to incomplete reporting. We did not downgrade quality of evidence for imprecision because it was already very low due to very serious risk of bias and indirectness of evidence.

[4] Favoured omalizumab, but no variability or group scores were reported; result was not statistically significant

[5] Study did not blind care providers.

[6] Only 73% of children had severe asthma. Some children had no treatment at baseline -- it is possible that asthma, at least in some children, was not severe but rather not well controlled.

[7] Upper limits of confidence intervals were far from minimal important difference.

[8] Change in children aged 4 to 11 on C-ACT was 0.78 points (0.21 to 1.35) and in children older than 11 years on ACT 0.19 points (−0.42 to 0.79). C-ACT and ACT were measured on scales of 0 to 27 and 5 to 25, respectively. A score of 19 or less on either test indicates that asthma is not well controlled. The minimally important difference for ACT equals 3 points; that for Childhood ACT is not defined.

[9] We did not downgrade quality of evidence for imprecision despite only 137 events, because we already downgraded for risk of bias and indirectness in a borderline situation.

[10] Study did not measure the outcome in 16% of patients and excluded data from 2 centers from analysis.

[11] Results do not exclude appreciable benefit or no difference.

[12] This represents a difference of 6 to 23 symptom-free days per 60 weeks.

[13] Only 15 events.

[14] Results do not exclude appreciable benefit or appreciable harm.

[15] Only 72 events.

[16] Only 10 events.

Date: 2011-04-25

Question: Should methotrexate be used in patients with severe asthma?

Bibliography: 1. Davies H., Olson L., Gibson P. Methotrexate as a steroid sparing agent for asthma in adults Cochrane database of systematic reviews, 2000:CD000391. 2. Comet R., Domingo C., Larrosa M., Moron A., Rue M., Amengual M.J., Marin A. Benefits of low weekly doses of methotrexate in steroid-dependent asthmatic patients. A double-blind, randomized, placebo-controlled study Respiratory medicine, 2006;100:411-419.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate	Control	Relative (95% CI)	Absolute		
Dose of systemic corticosteroids (follow-up mean 6 months; measured with: mg/day; Better indicated by lower values)												
11	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	161	152	-	MD 3.69 mg/day lower (0.19 to 5.38 lower)	⨁⨁◯◯ LOW	CRITICAL
Symptoms - not reported												
0	-	-	-	-	-	none	-	-	-	-	–	CRITICAL
Death - not reported												
0	-	-	-	-	-	none	-	-	-	-	–	CRITICAL
Pre-bronchodilator FEV1 (follow-up mean 6 months; Better indicated by lower values)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	44	41	-	MD 0.12 higher (0.21 lower to 0.45 higher)	⨁⨁◯◯ LOW	IMPORTANT
Adverse effects (hepatic) (follow-up mean 6 months)												
9	randomised trials	serious[1]	no serious inconsistency	serious[4]	no serious imprecision	none	26/141 (18.4%)	2/134 (1.5%)	RR 6.34 (2.99 to 12.7)	8 more per 100 (from 3 more to 17 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse effects (oral ulcers and stomatitis) (follow-up mean 6 months)												
3	randomised trials	serious[1]	no serious inconsistency[5]	no serious indirectness	serious[3]	none	5/38 (13.2%)	3/38 (7.9%)	RR 1.67 (0.42 to 5.08)	53 more per 1000 (from 46 fewer to 322 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse effects (nausea) (follow-up mean 6 months)												
9	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	31/136 (22.8%)	20/136 (14.7%)	RR 1.56 (0.94 to 2.4)	8 more per 100 (from 1 fewer to 21 more)	⨁⨁◯◯ LOW	IMPORTANT
Adverse effects (vomiting) (follow-up mean 6 months)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	2/57 (3.5%)	7/57 (12.3%)	RR 0.32 (0.08 to 1.13)	8 fewer per 100 (from 11 fewer to 2 more)	⨁⨁◯◯ LOW	IMPORTANT
Adverse effects (other gastro-intestinal symptoms) (follow-up mean 6 months)												
7	randomised trials	serious[1]	no serious inconsistency	serious[4]	serious[6]	none	32/127 (25.2%)	18/120 (15%)	RR 1.82 (1.08 to 2.81)	12 more per 100 (from 1 more to 27 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Adverse effects (rash) (follow-up mean 6 months)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	5/39 (12.8%)	2/39 (5.1%)	RR 2.41 (0.55 to 7.88)	7 more per 100 (from 2 fewer to 35 more)	⨁⨁◯◯ LOW	IMPORTANT
Adverse effects (alopecia) (follow-up mean 6 months)												
10	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	7/165 (4.2%)	3/158 (1.9%)	RR 2.44 (0.66 to 8.15)[7]	3 more per 100 (from 1 fewer to 14 more)	⨁⨁◯◯ LOW	IMPORTANT
Adverse effects (pneumonia) (follow-up mean 6 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	2/32 (6.3%)	0/32 (0%)	RR 7.84 (0.47 to 130.46)	-	⨁⨁◯◯ LOW	IMPORTANT
Quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Days missed at school/work - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Hospitalization - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Admission to the ICU - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Intubation and/or mechanical ventilation - not reported												

0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Resource use (cost) - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT

MD – mean difference, RR – relative risk

[1] According to the authors of a systematic review most studies suffered from poor reporting of the methods used; 3 studies did not conceal allocation.

[2] Results do not exclude an appreciable benefit or no effect.

[3] Few patients. Results do not exclude benefit or harm.

[4] Complications were not describe in sufficient detail to allow judgements about their severity.

[5] We did not downgrade for inconsistency since we already downgraded for imprecision. Studies had to few events.

[6] Results do not exclude appreciable harm or no effect.

[7] Based on the results of 3 studies only (n = 37). In the remaining 7 studies there were no events in both groups.

Date: 2011-05-08

Question: Should macrolide antibiotics be used in patients with severe asthma?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide antibiotics	Control	Relative (95% CI)	Absolute (95% CI)		
Symptoms (follow-up 8 and 12 weeks; measured with: various symptom scores; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	28	28	-	SMD 0.1 lower (0.62 lower to 0.43 higher)	●○○○ VERY LOW	CRITICAL
Asthma control (follow-up 8 weeks; measured with: Asthma Control Questionaire (ACQ); range of scores: 1-7; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3,4]	none	22	23	-	MD 0.1 higher (0.34 lower to 0.54 higher)	●●○○ LOW	CRITICAL
Asthma control (treatment failure - inadequate control of asthma) (follow-up 16 weeks)												
1	randomised trials	serious[5]	no serious inconsistency	serious[6]	serious[3,7]	none	11/17 (64.7%)	11/19 (57.9%)	RR 1.12 (0.66 to 1.88)	7 more per 100 (from 20 fewer to 51 more)	●○○○ VERY LOW	IMPORTANT
Quality of life (follow-**up 8 weeks; assessed with: percentage of patients who improved ≥0.5 on AQLQ)**												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3,4]	none	9/22 (40.9%)	6/23 (26.1%)	RB 1.57 (0.67 to 3.38)[8,9]	15 more per 100 (from 9 fewer to 62 more)	●●○○ LOW	CRITICAL
Dose of oral corticosteroids (follow-up 8 and 52 weeks; Better indicated by lower values)												
2	randomised trials	serious[10]	no serious inconsistency[11]	no serious indirectness	serious[12]	none	35	32	-	MD 4.44 lower (2.21 to 6.67 lower)	●●○○ LOW	CRITICAL
Exacerbation requiring oral corticosteroids (follow-up 16 weeks)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[3,7]	none	1/17 (5.9%)	3/19 (15.8%)	RR 0.37 (0.04 to 3.25)	10 fewer per 100 (from 15 fewer to 36 more)	●○○○ VERY LOW	CRITICAL
Death (follow-up 12 months)												
1	randomised trials	serious[13,14]	no serious inconsistency	no serious indirectness	very serious[3,15]	none	2/30 (6.7%)[16]	1/27 (3.7%)[16]	RR 1.8 (0.17 to 18.57)	3 more per 100 (from 3 fewer to 65 more)	●○○○ VERY LOW	IMPORTANT
Hospitalizations (follow-up 12 months; assessed with: rate per patient per year)												
1	randomised trials	serious[13,15]	no serious inconsistency	no serious indirectness	serious[15]	none	30 (0.37/patient-year)	27 (0.78/patient-year)	rate ratio 0.47 (0.21 to 1.02)	41 fewer per 100 patient-years (from 2 fewer to 80 fewer)	●●○○ LOW	CRITICAL
Emergency department visits (follow-up 12 months; assessed with: rate per patient per year)												
1	randomised trials	serious[13,14]	no serious inconsistency	no serious indirectness	serious[15]	none	30 (0.37/patient-year)	27 (1.11/patient-year)	rate ratio 0.33 (0.15 to 0.68)	74 fewer per 100 patient-years (from 30 fewer to 119 fewer)	●●○○ LOW	IMPORTANT
ICU admission - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Absence from school/work - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Adverse effects (follow-up 8 to 16 weeks)												
4	randomised trials	very serious[17]	no serious inconsistency	no serious indirectness[18]	serious[17,19]	none	-	-	not pooled	not pooled	●○○○ VERY LOW	IMPORTANT
Resource use - not measured												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Lung function (FEV1) (follow-up 16 weeks; measured with: percent predicted value; Better indicated by higher values)												
1	randomised trials	serious[13]	no serious inconsistency	no serious indirectness	serious[4]	none	22	23	-	MD 5.60 higher (5.57 lower to 16.77 higher)	●●○○ LOW	IMPORTANT
Lung function (PEF) (measured with: morning pre-bronchodilator PEF; Better indicated by higher values)												
1	randomised trials	serious[13]	no serious inconsistency	no serious indirectness	very serious[3,20]	none	6	5	-	MD 52.1 higher (67.24 lower to 171.44 higher)	●○○○ VERY LOW	IMPORTANT

MD – mean difference, RR – relative risk, SMD – standardized mean difference

[1] Only 2 of the 4 studies reported this key outcome that would be expected to have been reported in such studies.

[2] Only 56 patients.

[3] Results do not exclude an appreciable benefit or an appreciable harm.

[4] Only 55 patients.

[5] Study was terminated early.
[6] Composite outcome that included patient-important outcomes and lung function.
[7] Only 36 patients.
[8] Median (IQR) AQLQ score improved from 5.5 (4.8–6.4) to 6.2 (5.4–6.6) in the clarithromycin group and did not change in placebo group (6.4 [5.2–6.7] at baseline and 6.4 [5.7–6.8] ad the end of the study).
[9] RB: relative benefit
[10] One larger study lost to follow-up 24% of participants.
[11] We did not downgrade for inconsistency, since we already downgraded for imprecision. One small study (n = 11) in children estimated a larger difference likely favouring a macrolide (mean difference: 7.7 mg/d; 95% CI: 1.3 to 14.1) and the larger study in adults estimated a smaller difference (mean difference: 4.0 mg/d; 95% CI: 3.4 to 4.7). We decided to pool the results since confidence intervals overlapped and the results were very imprecise.
[12] Only 78 patients.
[13] Only one study reported this outcome that would be expected to have been reported in all such studies.
[14] 24% lost to follow-up.
[15] Only 57 patients.
[16] Authors of the study did not consider any event to be related to study medication.
[17] Three studies inadequately reported adverse effects and one did not report them despite clearly stating that they were measured.
[18] We did not downgrade for indirectness, however, we were not able to assess the nature and importance of adverse effects due to inadequate reporting.
[19] One study reported 1 event of transiently elevated liver enzymes among 6 patients receiving troleandomycin. The other study reported 1 patients discounting treatment due to an adverse effect of study medication, however, it did not report the nature of that event.
[20] Only 11 patients.

Question: Should an antifungal agent vs no antifungal agent be used in patients with severe asthma and allergic bronchopulmonary aspergillosis?

Bibliography: 1. Shale DJ et al. Trial of ketoconazole in non-invasive pulmonary aspergillosis. Thorax; 1987. p. 26-31. 2. Stevens DA et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N Engl J Med; 2000. p. 756-762. 3. Wark PA, Gibson PG, Wilson AJ. Azoles for allergic bronchopulmonary aspergillosis associated with asthma. Cochrane Database Syst Rev 2004:CD001108. 5. Wark PA et al. Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: A randomized controlled trial. JACI; 2003. p. 952-957.

Date: 2012-07-17

Quality assessment							No of patients		Effect (95% CI)		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antifungal agent	No antifungal agent	Relative	Absolute		
Quality of life[1] (follow-up 4 months; measured with: SF-36; Better indicated by higher values)												
1	randomised trials	serious[1,2]	no serious inconsistency	serious[3]	no serious imprecision	none	22	25	-	not estimable[1]	●●○○ LOW	CRITICAL
Exacerbations requiring oral corticosteroids (follow-up 4 months; measured with: number of exacerbations per 4 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	15	14	-	MD 0.9 lower (0.22 to 1.58 lower)[5]	●●●○ MODERATE	CRITICAL
Daily dose of oral corticosteroids (follow-up 4 months; assessed with: reduction by at least 50% from baseline)												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness[7]	serious[6,8]	none	17/22 (77.3%)	14/25 (56%)	RR 1.38 (0.91 to 2.09)	21 more per 100 (from 5 fewer to 61 more)[7]	●●○○ LOW	CRITICAL
Symptoms (follow-up 12 months; measured with: percentage change from baseline; Better indicated by lower values)												
1	randomised trials	serious[9]	no serious inconsistency	serious[10]	serious[11]	none	6	4	-	MD 22.5 lower (3.92 to 41.08 lower)	●○○○ VERY LOW	CRITICAL
Adverse effects (any) (follow-up 4 months)												
2	randomised trials	no serious risk of bias	serious[12]	serious[13]	very serious[14]	none	25/34 (73.5%)	23/31 (74.2%)	RR 1.05 (0.86 to 1.28)	4 more per 100 (from 10 fewer to 21 more)	●○○○ VERY LOW	CRITICAL
Adverse effects (serious) (follow-up 4 months)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[14]	none	3/49 (6.1%)[15]	6/45 (13.3%)[16]	RR 0.51 (0.13 to 2.04)	7 fewer per 100 (from 12 fewer to 14 more)	●●○○ LOW	CRITICAL
Control of asthma - not measured												
0	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Absence form school or work - not measured												
0	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Emergency department visits or unscheduled clinic visit for asthma - not measured												
0	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Hospital admission for asthma and/or ABPA (follow-up 4 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[17]	none	0/15 (0%)	2/14 (14.3%)	RR 0.19 (0.01 to 3.6)	12 fewer per 100 (from 14 fewer to 37 more)	●●○○ LOW	IMPORTANT
Intubation and ventilation (follow-up 4 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[18]	none	0/28 (0%)	1/27 (3.7%)	RR 0.32 (0.01 to 7.57)	3 fewer per 100 (from 4 fewer to 24 more)	●●○○ LOW	IMPORTANT
Death (follow-up 4 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[19]	none	1/28 (3.6%)	0/27 (0%)	not pooled [19]	not pooled [19]	●●○○ LOW	IMPORTANT
FEV1 (percent predicted)[20,21] (follow-up 4 months; Better indicated by higher values)												
2	randomised trials	serious[20]	no serious inconsistency	no serious indirectness	serious[22]	none	19	17	-	not pooled[20,21]	●●○○ LOW	IMPORTANT
Improvement of lung function (follow-up 4 months)												
2	randomised trials	no serious risk of bias[23]	no serious inconsistency	serious[24]	very serious[25]	none	20/39 (51.3%)	13/38 (34.2%)	RR 1.45 (0.88 to 2.4)	15 more per 100 (from 4 fewer to 48 more)	●○○○ VERY LOW	IMPORTANT
Resource use (cost, availability, etc.) - not measured												

0	-	-	-	-	-	-	-	-	-	-		IMPORTANT

MD – mean difference, RR – relative risk

[1] Authors did not report any values, but stated that there was no statistically significant difference between the groups.

[2] Selective outcome reporting.

[3] Authors did not report severity of asthma and what treatment patients already received. Study used SF-36 which is a generic questionnaire that would be likely not responsive enough to pick a small but important change in asthma-related quality of life, if it existed.

[4] Only 29 patients.

[5] There was a mean of 2-3 exacerbations per patient per 1 year at baseline.

[6] Outcome has not been measured in 8 of 55 patients (15%). In a plausible worst case scenario (i.e. event rate 3 times lower in those lost than in those treated in itraconazole group) the result would be RR: 1.15 (95% CI: 0.76 to 1.71) making the estimate very imprecise.

[7] Assuming that all patients took at lest 10 mg prednisone daily (an inclusion criterion to the study but actual doses not reported), then 50% reduction in daily dose would mean at least 5 mg less of prednisone daily.

[8] Results do not exclude appreciable benefit or no difference.

[9] Method of randomization, concealment of allocation, and whether the intention-to-treat principle was followed were not reported.

[10] Outcome was measured on scale 0 to 3 points with lower values indicating fewer symptoms. Authors reported a percentage change from baseline but did not report baseline scores.

[11] It was not possible to assess imprecision because of meaningless reporting of the magnitude of the change. However, we assumed that results would be imprecise with only 10 patients in the study.

[12] One study reported no adverse effects and another reported adverse effects in 86% of patients.

[13] Studies did not clearly report what adverse effects were observed, thus, there is uncertainty to what extent those were important for patients.

[14] Results do not exclude an appreciable benefit or an appreciable harm.

[15] In treated group those were: cardiomyopathy + death, upper respiratory infection and lumbar disc prolapse.

[16] In placebo groups those were: asthma exacerbation + intubation, fever, supraventricular tachycardia, atrial fibrillation + heart failure, exacerbations of ABPA.

[17] Only 2 events. Results do not exclude appreciable benefit or appreciable harm.

[18] Results do not exclude an appreciable benefit or an appreciable harm.

[19] Only 1 event among 55 people over 4 months of observation. The estimated risk difference does not exclude benefit or harm RD: 4 more per 100 (95% CI: from 6 fewer to 13 more).

[20] One study did not report values in the control group and the other did not report variability in the results.

[21] One study that reported men changes in both groups showed a mean improvement of 7.9% in treated group and 1.9% deterioration in control group.

[22] Only 36 patients.

[23] 13% of patients were lost to follow-up in one study. We did not downgrade quality of evidence for the risk of bias since we already downgraded it because of imprecision due to the same reason.

[24] One study defined the improvement in lung function as increase in FEV1 of at least 25%, however, it is not clear whether this was an increase in absolute values or in percentage of predicted. The other study defined the improvement in lung function as increase of at least 25% in 1 of 5 pulmonary function tests but did not specify which one and they were not reported separately (FEV1, forced vital capacity, forced expiratory flow in the midexpiratory phase, peak flow rate, and carbon monoxide diffusing capacity).

[25] The results do not exclude appreciable benefit or no difference. However, one study lost 13% of patients to follow-up. Assuming a plausible worst case scenario where improvement would be observed in all 4 patients lost in the control group and in only 1 of 3 lost in treated group the effect would be RR: 1.16, 95% CI: 0.64 to 2.11) which would not exclude neither appreciable benefit nor appreciable harm.

Question: Should an antifungal agent vs no antifungal agent be used in patients with severe asthma sensitized to fungi but no allergic bronchopulmonary aspergillosis?

Bibliography: Denning DW et al. Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitization: The fungal asthma sensitization trial (FAST) study. American Journal of Respiratory & Critical Care Medicine 2009;179:11-18

Date: 2012-07-17

Quality assessment							No of patients		Effect (95% CI)		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antifungal agent	No antifungal agent	Relative	Absolute		
Quality of life (follow-up 8 months; assessed with: Improvement of >0.5 point in Asthma Quality of Life Questionnaire (AQLQ))												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/26 (53.8%)[3]	9/28 (32.1%)[3]	RR 1.68 (0.88 to 3.19)	22 more per 100 (from 4 fewer to 70 more)	●○○○ VERY LOW	CRITICAL
Quality of life [change from baseline] (follow-up 8 months; measured with: Asthma Quality of Life Questionnaire (AQLQ); range of scores: 1-7; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26[3]	28[3]	-	MD 0.86 higher (0.15 to 1.57 higher)	●○○○ VERY LOW	CRITICAL
Daily dose of oral corticosteroids - not reported												
0	-	-	-	-	-	–	-	-	-	-	-	CRITICAL
Adverse effects (serious)[4] (follow-up 8 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	0/26 (0%)	0/28 (0%)	not pooled[4]	not pooled[4]	●○○○ VERY LOW	CRITICAL
Adverse effects (any) (follow-up 8 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness[6]	serious[2]	none	6/26 (23.1%)	2/28 (7.1%)	RR 3.23 (0.71 to 14.61)	16 more per 100 (from 2 fewer to 97 more)	●○○○ VERY LOW	IMPORTANT
Control of asthma - not measured												
0	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Exacerbation of asthma or increased dyspnea (follow-up 8 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[7]	very serious[8]	none	8/26 (30.8%)	8/28 (28.6%)	RR 1.08 (0.47 to 2.45)[9]	2 more per 100 (from 15 fewer to 41 more)	●●○○ LOW	IMPORTANT
Absence form school or work - not measured												
0	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Emergency department visits or unscheduled clinic visit for asthma - not measured												
0	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Hospitalization for asthma (follow-up 8 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[8]	none	2/26 (7.7%)	2/28 (7.1%)	RR 1.08 (0.16 to 7.1)	1 more per 100 (from 6 fewer to 44 more)	●○○○ VERY LOW	IMPORTANT
Chest infection (follow-up 8 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[10]	serious[8]	none	4/26 (15.4%)	4/28 (14.3%)	RR 1.08 (0.3 to 3.87)	1 more per 100 (from 10 fewer to 41 more)	●○○○ VERY LOW	IMPORTANT
FEV_1 (percent predicted) (follow-up 8 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency[11]	no serious indirectness	serious[5]	none	26	28	-	MD 3.79 lower (10.67 lower to 3.09 higher)	●○○○ VERY LOW	IMPORTANT
Morning PEF (follow-up 8 months; measured with: L/min (change from baseline); Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency[11]	no serious indirectness	serious[2]	none	26	28	-	MD 26.3 higher (2.63 to 49.97 higher)	●●●○ MODERATE	IMPORTANT
Resource use (cost, availability, etc.) - not measured												

0	-	-	-	-	-	-	-	-	-	-		IMPORTANT

MD – mean difference, RR – relative risk

[1] Study reported the results at 4 weeks and at 8 months, however it is not clear which numerical results refer to which period. Loss to follow-up was 7% after 4 weeks and 29% after 8 months, with most patients lost in the treated group. It is not clear which results were analyzed according to an intention-to-treat principle and which were analyzed per protocol. It is not clear why only 58 of the 73 eligible patients and of 108 planned patients were enrolled.

[2] Results do not exclude appreciable benefit or no difference.

[3] Total number of patients was assumed based on the data in the article but there is some uncertainty about how many patients were actually analyzed owing to inconsistent reporting.

[4] There were no events in both groups.

[5] Only 56 patients were enrolled.

[6] Nausea, edema, breathlessness, joint pain, muscle weakness, cushingoid symptoms.

[7] Authors did not provide the definition of exacerbation but we assumed they were important to patients.

[8] Results do not exclude an appreciable benefit or an appreciable harm.

[9] Two additional studies measured exacerbations (Curie 1990, Wark 2003) but reported only median number of exacerbations in both groups. Curie and colleagues found median 4.5 exacerbations (range 1 to 10) in treated and 5 (1 to 13) in placebo groups. Wark and colleagues found median number of 0 exacerbations in treated and 1.5 in placebo groups.

[10] It has not been reported how "chest infection" was defined.

[11] Change in FEV1 was not consistent with the change in morning PEF.

Date: 2013-06-18
Question: Should bronchial thermoplasty vs sham thermoplasty or usual care alone be used in patients with severe asthma?
Settings: tertiary care hospitals
Bibliography: Castro 2010, Cox 2007 (Thomson 2011), Pavord 2007

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bronchial thermoplasty	Sham thermoplasty or usual care alone	Relative (95% CI)	Absolute (95% CI)		
Quality of life (follow-up 12 months; measured with: Asthma Quality of Life Questionnaire (AQLQ); range of scores: 1-7 points; Better indicated by higher values)												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	254	161	–	MD 0.53 points higher (0.05 to 1.02 higher)	●○○○ VERY LOW	CRITICAL
Quality of life (improvement of >0.5 point in AQLQ) (follow-up 12 months; assessed with: patients who achieved an improvement of at least 0.5 point in AQLQ)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	150/190 (78.9%)	63/98 (64.3%)	RR 1.23 (1.04 to 1.45)	148 more per 1000 (from 26 more to 289 more)	●●○○ LOW	CRITICAL
Asthma control (follow-up 12 months; measured with: Asthma Control Questionnaire (ACQ); range of scores: 0-6; Better indicated by lower values)												
3	randomised trials	serious[1]	no serious inconsistency[4]	serious[2]	serious[3]	none	254	161	–	MD 0.18 lower (0.36 lower to 0.01 higher)	●○○○ VERY LOW	CRITICAL
Symptom-free days (follow-up 12 months; measured with: percent (%); range of scores: 0-100; Better indicated by higher values)												
2	randomised trials	serious[5]	no serious inconsistency	serious[2]	serious	none	239	144	–	MD 7.59 higher (4.72 lower to 19.9 higher)	●○○○ VERY LOW	CRITICAL
Rescue bronchodilator use (follow-up 12 months; measured with: puffs/week; Better indicated by lower values)												
3	randomised trials	serious[1]	serious[6]	serious[2]	serious[3]	none	254	161	–	MD 4.19 lower (11.51 lower to 3.13 higher)	●○○○ VERY LOW	IMPORTANT
Need for systemic corticosteroids (follow-up 12 months) [7]												
1	randomised trials	serious[8]	no serious inconsistency	serious[2]	very serious[9]	none	4/15 (26.7%)	6/17 (35.3%)	RR 0.76 (0.26 to 2.18)[10]	85 fewer per 1000 (from 261 fewer to 416 more)	●○○○ VERY LOW	CRITICAL
							–	2%[11]		5 fewer per 1000 (from 15 fewer to 24 more)		
Dose of systemic corticosteroids (follow-up 12 months; measured with: percent reduction in daily dose; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[8]	no serious inconsistency	serious[2]	serious[3]	none	15	17	–	MD 37.3 lower (7.26 to 67.34 lower)[12]	●○○○ VERY LOW	CRITICAL
Death (follow-up 12 months)												
3	randomised trials	serious[1]	no serious inconsistency	serious[2,13]	no serious imprecision[14]	none	0/260 (0%)	0/169 (0%)	See comment	0 fewer per 1000 (from 17 fewer to 17 more)	●●○○ LOW	IMPORTANT
Hospitalization (follow-up 12 months)[15]												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	40/260 (15.4%)[15]	14/169 (8.3%)[15]	RR 2.27 (1.31 to 3.94)	105 more per 1000 (from 26 more to 244 more)	●●○○ LOW	CRITICAL
Admission to the ICU (follow-up 12 months)												
2	randomised trials	serious[16]	no serious inconsistency	serious[2]	serious[8]	none	0/205 (0%)	1/115 (0.87%)	RR 0.38 (0.02 to 8.57)[17]	6 fewer per 1000 (from 29 fewer to 16 more)[18]	●○○○ VERY LOW	CRITICAL
Intubation and/or mechanical ventilation (follow-up 12 months)												
2	randomised trials	serious[16]	no serious inconsistency	serious[2]	no serious imprecision[14,19]	none	0/205 (0%)	0/115 (0%)	-	0 fewer per 1000 (from 19 fewer to 19 more)[18]	●●○○ LOW	CRITICAL
Days missed at school/work (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	190	98	-	MD 2.6 lower (2.91 to 2.29 lower)[20]	●●●○ MODERATE	IMPORTANT

Any adverse effect - not reported												
0	–	–	–	–	–	–	–	–	–	–	–	CRITICAL
Any severe adverse effect - not reported												
0	–	–	–	–	–	–	–	–	–	–	–	CRITICAL
Any respiratory adverse effect during initial treatment phase (follow-up 6 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2,21]	serious[22]	none	162/190 (85.3%)	74/98 (75.5%)	RR 1.13 (0.99 to 1.28)	98 more per 1000 (from 8 fewer to 211 more)	●●○○ LOW	CRITICAL
Any respiratory adverse effect during follow-up (follow-up from 6 weeks to 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2,21]	serious[3]	none	133/190 (70%)	78/98 (79.6%)	RR 0.88 (0.77 to 1.01)	96 fewer per 1000 (from 183 fewer to 8 more)	●●○○ LOW	CRITICAL
Rate of any respiratory adverse effects (treatment phase) (follow-up 6 weeks)												
2	randomised trials	serious[23]	no serious inconsistency	serious[2]	no serious imprecision[24]	none	543/70	163/71	Rate ratio 3.26 (2.36 to 4.5)[25]	Rate difference 5.49 per patient per 6 weeks (from 4.75 to 6.22)[25]	●●○○ LOW	CRITICAL
Rate of mild respiratory adverse effects (treatment phase) (follow-up 6 weeks)												
2	randomised trials	serious[23]	no serious inconsistency	serious[2,26]	no serious imprecision[24]	none	347/70	101/71	Rate ratio 3.36 (2.46 to 4.58)	Rate difference 3.42 per patient per 6 weeks (from 2.53 to 4.31)	●●○○ LOW	IMPORTANT
Rate of moderate respiratory adverse effects (treatment phase) (follow-up 6 weeks)												
2	randomised trials	serious[23]	no serious inconsistency	serious[2,26]	no serious imprecision[24]	none	170/70	59/71	Rate ratio 2.93 (1.99 to 4.34)	Rate difference 1.59 per patient per 6 weeks (from 1.11 to 2.06)	●●○○ LOW	CRITICAL
Rate of severe respiratory adverse effects (treatment phase) (follow-up 6 weeks)												
2	randomised trials	serious[23]	no serious inconsistency	serious[2,26]	no serious imprecision[27]	none	26/70	3/71	RR 8.98 (2.71 to 29.80)	Rate difference 0.43 per patient per 6 weeks (from -0.12 to 0.98)	●●○○ LOW	CRITICAL
Resource use (cost) - not measured												
0	–	–	–	–	–	–	–	–	–	–	–	CRITICAL
Pre-bronchodilator FEV1 (measured with: % predicted; Better indicated by higher values)												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	254	161	-	MD 0.65 higher (4.02 lower to 5.32 higher)	●●○○ LOW	IMPORTANT
Morning PEF [L/min] (follow-up 12 months; Better indicated by lower values)												
2	randomised trials	serious[28]	no serious inconsistency	serious[2]	no serious imprecision	none	239	144	-	MD 4.49 higher (18.45 lower to 27.44 higher)	●●○○ LOW	IMPORTANT

MD – mean difference, RR – relative risk

[1] Allocation concealment was unclear in 2 studies; 2 studies were unblinded; 3% to 15% of randomized patients were not included in analyses

[2] Many patients in the trials had milder asthma.

[3] Results do not exclude an appreciable benefit from bronchial thermoplasty or no effect.

[4] One small study showed a larger effect favouring thermoplasty group, but it had little influence on combined estimate.

[5] in 1 study allocation concealment was unclear, one study was unblinded and 15% of randomized patients were not included in analysis; a third study measured this outcome but did not report the results.

[6] One small study with high risk of bias showed a larger effect than the other 2 studies. If this study was excluded the pooled effect from the remaining 2 studies would be MD: -0.72 puffs/week (95% CI: -3.72 to 2.28).

[7] Another study (AIR; Thomson 2011) reported results after 3 years of follow-up of 73% patients randomized to thermoplasty and 38% patients randomized to usual care alone; during the second year of observation the rate of oral corticosteroid pulses was 33 per 100 patients per year in the thermoplasty group compared to 52 per 100 patients per year in usual care group.

[8] Only one study reported this outcome in a way would enable combining the results. One study did not report the results and another one reported only the number of patients in the experimental group stating that: "Seven (7) subjects in the thermoplasty group entered the trial with daily oral steroids as part of their maintenance asthma therapy. At the post-thermoplasty year 2 evaluation, 3 subjects had no change in their daily oral steroids usage, 1 subject had reduced their daily dosage, 2 subjects had stopped taking oral steroids altogether, and 1 subject had an increase in their dosage. Three subjects not previously on daily oral steroids initiated oral steroids usage as their maintenance asthma therapy."

[9] Very few events. Results do not exclude appreciable benefit or appreciable harm from bronchial thermoplasty.

[10] In additional study that measured this outcome "seven (7) subjects in the thermoplasty group entered the trial with daily oral steroids as part of their maintenance asthma therapy. At the post-thermoplasty year 2 evaluation, 3 subjects had no change in their daily

oral steroids usage, 1 subject had reduced their daily dosage, 2 subjects had stopped taking oral steroids altogether, and 1 subject had an increase in their dosage. Three subjects not previously on daily oral steroids initiated oral steroids usage as their maintenance asthma therapy."

[11] 2% baseline risk was assumed based on one trial in which 8 patients out of 288 in both groups needed oral steroids at baseline

[12] Mean % reduction in daily dose of oral corticosteroids in control group was 26.2%

[13] There is some uncertainty about the long-term effect.

[14] Results do not exclude an absolute difference of about 2% increase or 2% decrease in mortality. We did not downgrade for imprecision because we already downgraded for risk of bias.

[15] Another study (AIR; Thomson 2011) reported results after 3 years of follow-up of 73% patients randomized to thermoplasty and 38% patients randomized to usual care alone; during the second year of observation there were 3/43 (7%) patients requiring hospitalization in the thermoplasty group compared to 1/21 (5%) in usual care group.

[16] Two studies had unclear allocation concealment, one was not blinded. One study did not report that outcome.

[17] Based on one study with one event in control group

[18] Based on risk difference meta-analysis of both studies

[19] Results do not exclude an absolute difference of about 2% increase or 2% decrease in need for intubation and/or mechanical ventilation. We did not downgrade for imprecision because we already downgraded for risk of bias.

[20] Mean number of days missed form school/work in the control group was 3.9

[21] Study used sham procedure in control group that might have increased the number of adverse effects related to at least 3 bronchoscopies in each control patient, which would not be done in the population for whom the recommendation is intended.

[22] Results do not exclude an appreciable harm with bronchial thermoplasty or no effect.

[23] Both studies were not blinded and one excluded from analysis 15% of patients.

[24] We did not downgrade quality of evidence for imprecision since we already downgraded for the risk of bias, but there were only 141 patients.

[25] One study (AIR; Thomson 2011) reported results after 3 years of follow-up of 73% patients randomized to thermoplasty and 38% patients randomized to usual care alone; during the second year of observation there were 24/43 (56%) patients with at least 1 any respiratory adverse effect in the thermoplasty group compared to 12/21 (57%) in usual care group.

[26] There is some uncertainty what adverse effects were categorized as mild, moderate or severe.

[27] Only 29 events in 141 patients, but the results seem robust: it would require 6 additional events in the control group of each of the studies (12 additional events in total) to render the results statistically not significant.

[28] Allocation concealment was unclear in 1 study. One study was unblinded; 3% to 15% of randomized patients were not included in analyses. One study measured this outcome but did not report it.