Table 2a. Studies pertinent to the question: Does augmented immunosuppression in patients with non-minimal AR (Grade ≥2) or LB on transbronchial lung biopsy decrease the subsequent development of BOS?

Author/ Year	Study Type	Subjects	Intervention and comparator	Major results
Development of BOS				
Husain 1999 (Ref 13)	Observational (Case-control) study Single center	N = 134 Patients who had undergone lung transplantation and survived >90 days	Intervention: Inadequate immunosuppression, defined as cyclosporine, azathioprine, and prednisone, with cyclosporine levels <200 ng/mL. Control: Adequate immunosuppression, defined as cyclosporine, azathioprine, and prednisone, with cyclosporine levels ≥200 ng/mL.	The risk of developing BOS among patients with inadequate immunosuppression was increased (X^2 = 15.3, p<0.0001). In other words, the risk of developing BOS was decreased by immunosuppression.
Guilinger 1995	Case series Single Center	N = 220 Lung transplant patients undergoing bronchoscopy to assess response to treatment of acute cellular rejection or lymphocytic bronchiolitis	Intervention: Augmented immunosuppression (specific regimens were not provided). Control: None (case series).	No. patients with Grade 2 AR: 96 patients After treatment: Rejection resolved: 52 (54%) Rejection stable: 13 (14%) Rejection worse: 11 (11%) Other diagnosis: 20 (21%) No. patients with Grade 3 AR: 105 patients After treatment: Rejection improved or resolved: 50 (48%) Rejection stable: 32 (30%) Rejection worse: 1 (1%) Other diagnosis: 22 (21%) No. patients with Grade 4 AR: 12 patients After treatment: Rejection improved or resolved: 10 (83%) Rejection stable: 1 (8%) Rejection worse: N/A Other diagnosis: 1 (8%) No. patients with LB: 7 patients After treatment: LB resolved: 3 (43%) LB stable: 1 (14%) Other diagnosis: 3 (43%)

Adverse effects: All				
Emerman, 1989	Randomized trial	N = 96 Adults with COPD exacerbation	Intervention: Intravenous methylprednisolone 100 mg given once on arrival. Control: Matching intravenous placebo.	Adverse effects: Intervention: 0/52 (0.0%) Control: 0/44 (0.0%)
Albert, 1980	Randomized trial	N = 44 Adults with COPD exacerbation	Intervention: Intravenous methylprednisolone 0.5 mg/kg every six hours for a total of 72 hours. Control: Matching intravenous placebo.	Adverse effects: Intervention: 2/22 (9.1%) Control: 3/22 (13.6%) Relative: 0.64 (95% CI 0.10-4.05)
Thompson, 1996	Randomized trial	N = 27 Adults with COPD exacerbation	Intervention: Oral prednisolone 60 mg/day for 3 days, 40 mg/day for 3 days, and 20 mg/day for 3 days. Control: Vitamin B6 orally for 9 days.	Adverse effects: Intervention: 0/13 (0.0%) Control: 0/14 (0.0%)
Maltais, 2002	Randomized trial	N = 199 Adults with COPD exacerbation	Intervention: Oral prednisone 30 mg every 12 hours for 72 hours and then 40mg/day for 7 days. Control: Matching oral placebo.	Adverse effects: Intervention: 43/62 (69.4%) Control: 40/66 (60.6%) Relative: 1.46 (95% CI 0.71-3.02)
Chen, 2005	Randomized trial	N = 130 Adults with COPD exacerbation	Intervention: Oral prednisolone 30 mg/day for 10 days and then 15 mg/day for 5 days. Control: Matching oral placebo.	Adverse effects: Intervention: 2/43 (4.7%) Control: 0/43 (0.0%) Relative: 7.57 (95% CI 0.47-122.99)
Davies, 1999	Randomized trial	N = 50 Adults with COPD exacerbation	Intervention: Oral prednisolone 30 mg/day for 14 days. Control: Matching oral placebo for 14 days.	Adverse effects: Intervention: 9/29 (31.0%) Control: 2/27 (7.4%) Relative: 4.35 (95% CI 1.18-16.08)
Wood-Baker, 1997	Randomized trial	N = 38 Adults with COPD exacerbation	Intervention: a) Oral prednisolone 2.5 mg/kg daily for 72 hours, followed by oral placebo for 11 days. b) Oral prednisolone 0.6 mg/kg daily for 7 days, followed by oral prednisolone 0.3 mg/kg daily for 7 days. Control: Matched oral placebo for 14 days.	Adverse effects: Intervention: 0/18 (0.0%) Control: 0/10 (0.0%)

Niewoehner, 1999	Randomized trial	N = 272 Adults with COPD exacerbation	Intervention: a) Intravenous methyl prednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone tapered over 60 days. b) Intravenous methyl prednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone tapered over 15 days, followed by oral placebo to complete 60 days. Control: Intravenous placebo every 6 hours for 72 hours, followed by oral placebo over 60 days.	Adverse effects: Intervention: 113/160 (70.2%) Control: 51/111 (45.9%) Relative: 2.80 (95% CI 1.71-4.59)
Adverse effects: Hyperglycemia				
Maltais, 2002	Randomized trial	N = 199 Adults with COPD exacerbation	Intervention: Oral prednisone 30 mg every 12 hours for 72 hours and then 40mg/day for 7 days. Control: Matching oral placebo.	Hyperglycemia: Intervention: 7/62 (11.3%) Control: 0/66 (0.0%) Relative: 8.73 (95% CI 1.91-39.87)
Niewoehner, 1999	Randomized trial	N = 272 Adults with COPD exacerbation	Intervention: a) Intravenous methyl prednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone tapered over 60 days. b) Intravenous methyl prednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone tapered over 15 days, followed by oral placebo to complete 60 days. Control: Intravenous placebo every 6 hours for 72 hours, followed by oral placebo over 60 days.	Hyperglycemia: Intervention: 14/80 (17.5%) Control: 4/111 (3.6%) Relative: 5.05 (95% CI 1.89-13.47)
Davies, 1999	Randomized trial	N = 50 Adults with COPD exacerbation	Intervention: Oral prednisolone 30 mg/day for 14 days. Control: Matching oral placebo for 14 days.	Hyperglycemia: Intervention: 6/28 (21.4%) Control: 0/22 (0.0%) Relative: 7.31 (95% CI 1.33-40.03)
Aaron, 2003	Randomized trial	N = 147 Adults with COPD exacerbation	Intervention: Oral prednisone 40 mg/day for 10 days. Control: Matching oral placebo for 10 days.	Hyperglycemia: Intervention: 2/67 (3.0%) Control: 2/68 (2.9%) Relative: 1.02 (95% CI 0.14-7.37)
Adverse effects: Weight gain				

Aaron, 2003	Randomized trial	N = 147 Adults with COPD exacerbation	Intervention: Oral prednisone 40 mg/day for 10 days. Control: Matching oral placebo for 10 days.	Weight gain: Intervention: 9/70 (3.0%) Control: 1/70 (2.9%) Relative: 5.53 (95% CI 1.54-19.94)
Adverse effects: Psychiatric disorder				
Aaron, 2003	Randomized trial	N = 147 Adults with COPD exacerbation	Intervention: Oral prednisone 40 mg/day for 10 days. Control: Matching oral placebo for 10 days.	Psychiatric disorder: Intervention: 13/70 (18.6%) Control: 7/70 (10.0%) Relative: 2.00 (95% CI 0.78-5.15)
Niewoehner, 1999	Randomized trial	N = 272 Adults with COPD exacerbation	Intervention: a) Intravenous methyl prednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone tapered over 60 days. b) Intravenous methyl prednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone tapered over 15 days, followed by oral placebo to complete 60 days. Control: Intravenous placebo every 6 hours for 72 hours, followed by oral placebo over 60 days.	Psychiatric disorder: Intervention: 5/80 (6.3%) Control: 3/111 (2.7%) Relative: 2.41 (95% CI 0.58-10.08)
Adverse effects: Dyspepsia				
Davies, 1999	Randomized trial	N = 50 Adults with COPD exacerbation	Intervention: Oral prednisolone 30 mg/day for 14 days. Control: Matching oral placebo for 14 days.	Dyspepsia: Intervention: 3/28 (10.7%) Control: 2/22 (9.1%) Relative: 1.19 (95% CI 0.19-7.53)
Aaron, 2003	Randomized trial	N = 147 Adults with COPD exacerbation	Intervention: Oral prednisone 40 mg/day for 10 days. Control: Matching oral placebo for 10 days.	Dyspepsia: Intervention: 7/67 (10.4%) Control: 6/68 (8.8%) Relative: 1.20 (95% CI 0.39-3.76)
Adverse effects: Hypertension				
Niewoehner, 1999	Randomized trial	N = 272 Adults with COPD exacerbation	Intervention: a) Intravenous methyl prednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone tapered over 60 days. b) Intravenous methyl prednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone	Hypertension: Intervention: 6/80 (7.5%) Control: 4/111 (3.6%) Relative: 2.18 (95% CI 0.60-7.91)

			tapered over 15 days, followed by oral placebo to complete 60 days. <u>Control</u>: Intravenous placebo every 6 hours for 72 hours, followed by oral placebo over 60 days.	

Abbreviations: AR = acute rejection; BOS = bronchiolitis obliterans syndrome; LB = lymphocytic bronchiolitis; COPD = chronic obstructive pulmonary disease.

Table 2b. Evidence Table: Does augmented immunosuppression in patients with non-minimal AR (Grade ≥2) or LB on transbronchial lung biopsy decrease the subsequent development of BOS?

--Quality of Evidence Assessment--							--Summary of Findings--
No. of Studies	**Study design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality of Evidence**	
Development of BOS							
2	Observational study and case series	Serious[1]	Not serious	Serious[2]	Serious[3]	Very low (critical outcome)	In the observational study, the risk of developing BOS among patients with inadequate immunosuppression was increased (Hussain, 1999). In the case series, augmented immunosuppression improved or eliminated cellular rejection in 54% of patients with Grade A2 AR, 48% with Grade A3 AR, 83% with Grade A4 AR, and 43% with LB. Among the patients whose AR or LB neither improved nor resolved, most remained stable (Guilinger, 1995).
Adverse effects: All							
8	Randomized trials	Not serious	Not serious	Not serious[4]	Not serious	High (important outcome)	Pooled results*: Intervention: 169/399 (42.4%); Comparator: 96/337 (28.5%); Relative: RR 2.33 (95% CI 1.60-3.40).
Adverse effects: Hyperglycemia							
4	Randomized trials	Not serious	Not serious	Not serious[4]	Not serious	High (important outcome)	Pooled results*: Intervention: 29/237 (12.2%); Comparator: 6/267 (2.2%); Relative: RR 4.95 (95% CI 2.47-9.91).
Adverse effects: Weight gain							
1	Randomized trial	Not serious	Not serious	Not serious[4]	Serious[3]	Moderate (important outcome)	Pooled results*: Intervention: 9/70 (12.8%); Comparator: 1/70 (1.4%); Relative: 5.53 (95% CI 1.54-19.94).
Adverse effects: Psychiatric disorders							
2	Randomized trials	Not serious	Not serious	Not serious[4]	Serious[3]	Moderate (important outcome)	Pooled results*: Intervention: 18/150 (12.0%); Comparator: 10/181 (5.5%); Relative: 2.12 (95% CI 0.96-4.66).

Adverse effects: Dyspepsia							
2	Randomized trials	Not serious	Not serious	Not serious[4]	Serious[3]	Moderate (important outcome)	Pooled results*: Intervention: 10/95 (10.5%); Comparator: 8/90 (8.9%); Relative: 1.20 (95% CI 0.46-3.16).
Adverse effects: Hypertension							
1	Randomized trials	Not serious	Not serious	Not serious[4]	Serious[3]	Moderate (important outcome)	Pooled results*: Intervention: 6/80 (7.5%); Comparator: 4/111 (3.6%); Relative: 2.18 (95% CI 0.60-7.91).
<u>Overall quality of evidence</u> = Very low (derived from the lowest quality of evidence among the critical outcomes).							

*We did not perform our own meta-analyses, but rather, relied upon the published meta-analyses from Walters JAE, Gibson PG, Wood-Baker R, et al. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database System Rev 2009; 3:CD001288.

[1]Caregivers were not blinded and subjects were enrolled over many years, during which assessments and post-transplant management likely changed significantly. These factors collectively increase the possibility that the results may have been affected by co-interventions.

[2] Husain, et al., included all post-transplant patients rather than specifically those with non-minimal AR or LB (i.e., indirectness of the population). Guilinger, et al., measured the change in AR or LB, rather than the development of BOS (i.e., indirectness of the outcome).

[3]The estimated effect is based upon few events.

[4] Whereas the clinical question is for patients with non-minimal AR or LB, the data are from patients with acute COPD exacerbations (indirectness of the population). We have no reason to suspect that corticosteroid therapy affects these patients differently, so we did not downgrade the quality of evidence for indirectness.

Abbreviations: AR = acute rejection; BOS = bronchiolitis obliterans syndrome; LB = Lymphocytic bronchiolitis; COPD = chronic obstructive pulmonary disease.

Table 3a. Studies pertinent to the question: Does augmented immunosuppression in patients with minimal AR (Grade A1) on transbronchial lung biopsy decrease the subsequent development of BOS?

Author/ Year	Study Type	Subjects	Intervention and Comparator	Major results
Development of BOS				
Hopkins 2004 (Ref 56)	Observational (Prospective cohort) study Single center	N = 184 Heart-lung and lung transplant recipients who survived >30 days after transplantation and were found to have Grade 1A AR	Intervention (symptomatic patients with Grade A1 AR): Received oral prednisolone 1 mg/kg, tapering by 5 mg every second day thereafter. This was superimposed on their maintenance immunosuppression regimen, which consisted of cyclosporine targeting blood trough levels of 300-350 mcg/L, azathioprine 2-3 mg/kg, and oral steroids 0.25 mg/kg/day. Control (asymptomatic patients with Grade A1 AR): Continued the maintenance immunosuppression regimen only, which consisted of cyclosporine targeting blood trough levels of 300-350 mcg/L, azathioprine 2-3 mg/kg, and oral steroids 0.25 mg/kg/day.	The effect of augmented immunosupression on the development of BOS was not reported. However, augmented immunosupression was associated with reduced progression to higher grades of AR (8.3 versus 25 percent) and LB (0 versus 15.6%). Adverse effects: No serious infections, episodes of hyperglycemia or confusion, or other adverse effects of augmented immunosuppression were described.
Khalifah 2005 (Ref 57)	Observational (Retrospective cohort) study Single center	N = 228 Adult lung transplant recipients who survived >90 days after transplantation and were found to have Grade 1A AR	Intervention (symptomatic patients with Grade A1 AR): Received 5-15 mg/kg of methylprednisolone for 3 days and then a 2-3 week prednisone taper. In some cases, the maintenance immunosuppression regimen was also altered, with tacrolimus replacing cyclosporine and/or mycophenolate replacing azathioprine. Control (asymptomatic patients with Grade A1 AR): Continued the maintenance immunosuppression regimen only, which consisted of cyclosporine targeting blood trough levels of 200-350 mcg/L, azathioprine 2 mg/kg adjusted as needed for side effects, and oral prednisone 15 mg every other day.	When the patients with Grade A1 AR were stratified into those who received treatment (N=14) and those who did not receive treatment (N=34), Grade A1 AR was associated with the development of BOS among those who were not treated (p=0.01), but not among those who were treated (p=0.48). Adverse effects: No serious infections, episodes of hyperglycemia or confusion, or other adverse effects of augmented immunosuppression were described.
Adverse effects: All				
Emerman, 1989	Randomized trial	N = 96 Adults with COPD exacerbation	Intervention: Intravenous methylprednisolone 100 mg given once on arrival. Control: Matching intravenous placebo.	Adverse effects: Intervention: 0/52 (0.0%) Control: 0/44 (0.0%)

Albert, 1980	Randomized trial	N = 44 Adults with COPD exacerbation	Intervention: Intravenous methylprednisolone 0.5 mg/kg every six hours for a total of 72 hours. Control: Matching intravenous placebo.	Adverse effects: Intervention: 2/22 (9.1%) Control: 3/22 (13.6%) Relative: 0.64 (95% CI 0.10-4.05)
Thompson, 1996	Randomized trial	N = 27 Adults with COPD exacerbation	Intervention: Oral prednisolone 60 mg/day for 3 days, 40 mg/day for 3 days, and 20 mg/day for 3 days. Control: Vitamin B6 orally for 9 days.	Adverse effects: Intervention: 0/13 (0.0%) Control: 0/14 (0.0%)
Maltais, 2002	Randomized trial	N = 199 Adults with COPD exacerbation	Intervention: Oral prednisone 30 mg every 12 hours for 72 hours and then 40mg/day for 7 days. Control: Matching oral placebo.	Adverse effects: Intervention: 43/62 (69.4%) Control: 40/66 (60.6%) Relative: 1.46 (95% CI 0.71-3.02)
Chen, 2005	Randomized trial	N = 130 Adults with COPD exacerbation	Intervention: Oral prednisolone 30 mg/day for 10 days and then 15 mg/day for 5 days. Control: Matching oral placebo.	Adverse effects: Intervention: 2/43 (4.7%) Control: 0/43 (0.0%) Relative: 7.57 (95% CI 0.47-122.99)
Davies, 1999	Randomized trial	N = 50 Adults with COPD exacerbation	Intervention: Oral prednisolone 30 mg/day for 14 days. Control: Matching oral placebo for 14 days.	Adverse effects: Intervention: 9/29 (31.0%) Control: 2/27 (7.4%) Relative: 4.35 (95% CI 1.18-16.08)
Wood-Baker, 1997	Randomized trial	N = 38 Adults with COPD exacerbation	Intervention: c) Oral prednisolone 2.5 mg/kg daily for 72 hours, followed by oral placebo for 11 days. d) Oral prednisolone 0.6 mg/kg daily for 7 days, followed by oral prednisolone 0.3 mg/kg daily for 7 days. Control: Matched oral placebo for 14 days.	Adverse effects: Intervention: 0/18 (0.0%) Control: 0/10 (0.0%)
Niewoehner, 1999	Randomized trial	N = 272 Adults with COPD exacerbation	Intervention: c) Intravenous methyl prednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone tapered over 60 days. d) Intravenous methyl prednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone tapered over 15 days, followed by oral placebo to complete 60 days.	Adverse effects: Intervention: 113/160 (70.2%) Control: 51/111 (45.9%) Relative: 2.80 (95% CI 1.71-4.59)

			Control: Intravenous placebo every 6 hours for 72 hours, followed by oral placebo over 60 days.	
Adverse effects: Hyperglycemia				
Maltais, 2002	Randomized trial	N = 199 Adults with COPD exacerbation	Intervention: Oral prednisone 30 mg every 12 hours for 72 hours and then 40mg/day for 7 days. Control: Matching oral placebo.	Hyperglycemia: Intervention: 7/62 (11.3%) Control: 0/66 (0.0%) Relative: 8.73 (95% CI 1.91-39.87)
Niewoehner, 1999	Randomized trial	N = 272 Adults with COPD exacerbation	Intervention: c) Intravenous methyl prednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone tapered over 60 days. d) Intravenous methyl prednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone tapered over 15 days, followed by oral placebo to complete 60 days. Control: Intravenous placebo every 6 hours for 72 hours, followed by oral placebo over 60 days.	Hyperglycemia: Intervention: 14/80 (17.5%) Control: 4/111 (3.6%) Relative: 5.05 (95% CI 1.89-13.47)
Davies, 1999	Randomized trial	N = 50 Adults with COPD exacerbation	Intervention: Oral prednisolone 30 mg/day for 14 days. Control: Matching oral placebo for 14 days.	Hyperglycemia: Intervention: 6/28 (21.4%) Control: 0/22 (0.0%) Relative: 7.31 (95% CI 1.33-40.03)
Aaron, 2003	Randomized trial	N = 147 Adults with COPD exacerbation	Intervention: Oral prednisone 40 mg/day for 10 days. Control: Matching oral placebo for 10 days.	Hyperglycemia: Intervention: 2/67 (3.0%) Control: 2/68 (2.9%) Relative: 1.02 (95% CI 0.14-7.37)
Adverse effects: Weight gain				
Aaron, 2003	Randomized trial	N = 147 Adults with COPD exacerbation	Intervention: Oral prednisone 40 mg/day for 10 days. Control: Matching oral placebo for 10 days.	Weight gain: Intervention: 9/70 (3.0%) Control: 1/70 (2.9%) Relative: 5.53 (95% CI 1.54-19.94)
Adverse effect: Psychiatric disorder				
Aaron, 2003	Randomized trial	N = 147 Adults with	Intervention: Oral prednisone 40 mg/day for 10 days.	Psychiatric disorder: Intervention: 13/70 (18.6%)

		COPD exacerbation	Control: Matching oral placebo for 10 days.	Control: 7/70 (10.0%) Relative: 2.00 (95% CI 0.78-5.15)
Niewoehner, 1999	Randomized trial	N = 272 Adults with COPD exacerbation	Intervention: c) Intravenous methyl prednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone tapered over 60 days. d) Intravenous methyl prednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone tapered over 15 days, followed by oral placebo to complete 60 days. Control: Intravenous placebo every 6 hours for 72 hours, followed by oral placebo over 60 days.	Psychiatric disorder: Intervention: 5/80 (6.3%) Control: 3/111 (2.7%) Relative: 2.41 (95% CI 0.58-10.08)
Adverse effect: Dyspepsia				
Davies, 1999	Randomized trial	N = 50 Adults with COPD exacerbation	Intervention: Oral prednisolone 30 mg/day for 14 days. Control: Matching oral placebo for 14 days.	Dyspepsia: Intervention: 3/28 (10.7%) Control: 2/22 (9.1%) Relative: 1.19 (95% CI 0.19-7.53)
Aaron, 2003	Randomized trial	N = 147 Adults with COPD exacerbation	Intervention: Oral prednisone 40 mg/day for 10 days. Control: Matching oral placebo for 10 days.	Dyspepsia: Intervention: 7/67 (10.4%) Control: 6/68 (8.8%) Relative: 1.20 (95% CI 0.39-3.76)
Adverse effect: **Hypertension**				
Niewoehner, 1999	Randomized trial	N = 272 Adults with COPD exacerbation	Intervention: c) Intravenous methyl prednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone tapered over 60 days. d) Intravenous methylprednisolone 125 mg every 6 hours for 72 hours, followed by oral prednisolone tapered over 15 days, followed by oral placebo to complete 60 days. Control: Intravenous placebo every 6 hours for 72 hours, followed by oral placebo over 60 days.	Hypertension: Intervention: 6/80 (7.5%) Control: 4/111 (3.6%) Relative: 2.18 (95% CI 0.60-7.91)

Abbreviations: AR = acute rejection; BOS = bronchiolitis obliterans syndrome; LB = Lymphocytic bronchiolitis; COPD = chronic obstructive pulmonary disease.

Table 3b. Evidence table: Does augmented immunosuppression in patients with minimal AR (Grade A1) on transbronchial lung biopsy decrease the subsequent development of BOS?

--Quality Assessment--							--Summary of Findings--
No. of Studies	**Study design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality of Evidence**	
Development of BOS							
2	Observational studies	Serious[1]	Not serious	Serious[2]	Not serious	Very low (critical outcome)	In one observational study, intravenous steroids followed by a tapering course of oral steroids was not associated with development of BOS (p=0.48), whereas lack of treatment with systemic steroids was associated with development of BOS (p=0.01) (Khalifah, 2005). In the other observational study, a course of oral steroids reduced progression to higher grades of AR and LB (markers of risk for BOS) by 16.7% and 15.6%, respectively (Hopkins, 2004).
Adverse effects: All							
8	Randomized trials	Not serious	Not serious	Not serious[3]	Not serious	High (important outcome)	Pooled results*: Intervention: 169/399 (42.4%); Comparator: 96/337 (28.5%); Relative: RR 2.33 (95% CI 1.60-3.40).
Adverse effects: Hyperglycemia							
4	Randomized trials	Not serious	Not serious	Not serious[3]	Not serious	High (important outcome)	Pooled results*: Intervention: 29/237 (12.2%); Comparator: 6/267 (2.2%); Relative: RR 4.95 (95% CI 2.47-9.91).
Adverse effects: Weight gain							
1	Randomized trial	Not serious	Not serious	Not serious[3]	Serious[4]	Moderate (important outcome)	Pooled results*: Intervention: 9/70 (12.8%); Comparator: 1/70 (1.4%); Relative: 5.53 (95% CI 1.54-19.94).
Adverse effects: Psychiatric disorders							
2	Randomized trials	Not serious	Not serious	Not serious[3]	Serious[4]	Moderate (important outcome)	Pooled results*: Intervention: 18/150 (12.0%); Comparator: 10/181 (5.5%);

							Relative: 2.12 (95% CI 0.96-4.66).
Adverse effects: Dyspepsia							
2	Randomized trials	Not serious	Not serious	Not serious[3]	Serious[4]	Moderate (important outcome)	Pooled results*: Intervention: 10/95 (10.5%); Comparator: 8/90 (8.9%); Relative: 1.20 (95% CI 0.46-3.16).
Adverse effects: Hypertension							
1	Randomized trials	Not serious	Not serious	Not serious[3]	Serious[4]	Moderate (important outcome)	Pooled results*: Intervention: 6/80 (7.5%); Comparator: 4/111 (3.6%); Relative: 2.18 (95% CI 0.60-7.91).
Overall quality of evidence = very low (derived from the lowest quality of evidence among the critical outcomes).							

*We did not perform our own meta-analyses, but rather, relied upon the published meta-analyses from Walters JAE, Gibson PG, Wood-Baker R, et al. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database System Rev 2009; 3:CD001288.

[1] Caregivers were not blinded and subjects were enrolled over many years, during which assessments and post-transplant management likely changed significantly. In addition, the maintenance immunosuppression regimen was adjusted in some patients in one of the studies. These factors collectively increase the possibility that the results may have been affected by co-interventions.

[2] Hopkins, et al., did not measure development of BOS, but rather, progression to higher grades of AR and LB (i.e., indirectness of the outcome). Khalifah et al did not directly compare the risk of BOS among patients who were treated with the risk among patients who were not treated; rather, they looked for associations in treated and untreated patients separately via regression analysis, and then compared those results (i.e., indirectness of the comparator).

[3] Whereas the clinical question is for patients with minimal AR, the data are from patients with acute COPD exacerbations (indirectness of the population). We have no reason to suspect that corticosteroid therapy affects these patients differently, so we did not downgrade the quality of evidence for indirectness.

[4] The estimated effect is based upon few events.

Abbreviations: AR = acute rejection; BOS = bronchiolitis obliterans syndrome; LB = Lymphocytic bronchiolitis; COPD = chronic obstructive pulmonary disease.

Table 4a. Studies pertinent to the question: Should sustained treatment with high-dose corticosteroids be given to lung transplant recipients who develop BOS?

Author/ Year	Study Type	Subjects	Intervention and comparator	Major results
Lung function decline				
Ross 1997 (Ref 223)	Case series Single center	N = 10 Unilateral lung transplant recipients with lung function decline consistent with BOS	Intervention: Repeat courses of high-dose methylprednisolone (exact regimen was not specified). Comparator: None (case series).	Lung function decline progressed despite repeated courses of pulsed-dose methylprednisolone. Absolute and relative measurements were not reported.
Adverse effects: Hyperglycemia				
Walsh LJ 2001	Observational (Retrospective cohort) study Multicenter	N = 815 Patients with chronic lung disease	Intervention: Daily or frequent intermittent steroids for >6 months. In the case of the latter, the steroid dose had to be >5mg/day on average. Control: Age- and sex-matched controls who had not received systemic corticosteroids.	Participants received a median cumulative dose of 16.3 g of prednisolone (range 1.1-186 g) over a median duration of 5.5 years (range 0.5-46 years). Hyperglycemia: Intervention: 6.5% Control: 4.6% Relative: OR 1.4 (95% CI 0.8-2.5)
Adverse effects: Dyspepsia				
Walsh LJ 2001	Observational (Retrospective cohort) study Multicenter	N = 815 Patients with chronic lung disease	Intervention: Daily or frequent intermittent steroids for >6 months. In the case of the latter, the steroid dose had to be >5mg/day on average. Control: Age- and sex-matched controls who had not received systemic corticosteroids.	Participants received a median cumulative dose of 16.3 g of prednisolone (range 1.1-186 g) over a median duration of 5.5 years (range 0.5-46 years). Dyspepsia: Intervention: 22.6% Control: 7.8% Relative: OR 3.5 (95% CI 2.4-5.1)
Adverse effects: Hypertension				

Walsh LJ 2001	Observational (Retrospective cohort) study Multicenter	N = 815 Patients with chronic lung disease	Intervention: Daily or frequent intermittent steroids for >6 months. In the case of the latter, the steroid dose had to be >5mg/day on average. Control: Age- and sex-matched controls who had not received systemic corticosteroids.	Participants received a median cumulative dose of 16.3 g of prednisolone (range 1.1-186 g) over a median duration of 5.5 years (range 0.5-46 years). Hypertension: Intervention: 17.8% Control: 23.5% Relative: OR 0.7 (95% CI 0.5-1.0)
Adverse effects: Osteoporotic fractures				
Walsh LJ 2001	Observational (Retrospective cohort) study Multicenter	N = 815 Patients with chronic lung disease	Intervention: Daily or frequent intermittent steroids for >6 months. In the case of the latter, the steroid dose had to be >5mg/day on average. Control: Age- and sex-matched controls who had not received systemic corticosteroids.	Participants received a median cumulative dose of 16.3 g of prednisolone (range 1.1-186 g) over a median duration of 5.5 years (range 0.5-46 years). Fractures: Intervention: 23% Control: 14.7% Relative: OR 1.8 (95% CI 1.3-2.6) Fracture Dose-Response (p trend = 0.04): Prednisolone 5.2 g = 1.0 Prednisolone 11.7 g = OR 1.96 (95% CI 0.95-4.0) Prednisolone 23.6 g = OR 2.13 (95% CI 1.04-4.4) Prednisolone 60.6 g = OR 2.22 (95% CI 1.04-4.8)
Walsh LJ 2002	Case series Multicenter	N = 117 Patients with chronic lung disease	Intervention: Daily or frequent intermittent steroids for >6 months. In the case of the latter, the steroid dose had to be >5mg/day on average. Control: None (case series).	Fracture Absolute Dose-Response : Prednisolone 3-12 g = 48% Prednisolone 12-21 g = 54% Prednisolone 21-47 g = 64% Prednisolone >47 g = 76% Fracture Relative Dose-Response: Prednisolone 3-12 g = 1.0 Prednisolone 12-21 g = OR 1.24 (95% CI 0.43-3.58) Prednisolone 21-47 g = OR 1.94 (95% CI 0.66-5.71) Prednisolone >47 g = OR 3.38 (95% CI 1.09- 0.55) Fracture Relative Duration-Response: Prednisolone 0-4 years = 1.0 Prednisolone 4-7 years = 2.50 (95% CI 0.88-7.14)

				Prednisolone 7-15 years = OR 1.60 (95% CI 0.53-4.76) Prednisolone 15-46 years = OR 3.57 (95% CI 1.13-11.25)
Vestergaard 2007	Observational (Case control) study Multicenter	N = 561,617 Patients with chronic lung disease	Intervention: All patients with fracture in Denmark in the year 2000. Control: Individuals randomly selected from the population in Denmark who had not had a fracture in 2000.	Proportion of patients taking chronic oral steroids: Patients with fracture: 7.0% Patients without fracture: 4.8% P value: p <0.01 Relative: Adj OR 1.14 (95% CI 1.10-1.17). Fracture Relative Dose-Response: <2.5 mg/day = OR 1.02 (95% CI 0.98-1.06) 2.50-7.49 mg/day = OR 1.29 (95% CI 1.22-1.36) ≥7.50 mg/day = OR 1.79 (95% CI 1.68-1.91)
McEvoy CE 1998	Observational (Cross sectional) study Multicenter	N = 242 Patients with chronic obstructive pulmonary disease	Intervention: Patients taking chronic systemic steroids. Control: Patients who never took systemic steroids.	Fractures: Intervention: 63.3% Control: 48.7% Relative: Adj OR 2.99 (95% CI 1.38-6.49). Association of dose with fracture: Adj OR 1.35 (95% CI 0.88-2.08) Association of duration with fracture: Adj OR 1.41 (95% CI 0.9-2.23)
Tsugeno H 2002	Observational (Case control) study Single center	N = 280 Women	Intervention: Women taking chronic systemic steroids for asthma. Control: Women without asthma who don't take systemic steroids.	Participants received a mean cumulative dose of 23.5 ± 22.9 g of prednisolone over a mean duration of 10.1 ± 4.8 years. Fractures: Intervention: 65.1% Control: 23.2% p <0.0001. Relative increase in fracture risk among patients taking a cumulative dose of >10 g: OR 8.85 (95% CI 4.21-18.60).
Adverse effects: Cataracts				
Walsh LJ 2001	Observational (Retrospective cohort) study	N = 815 Patients with chronic lung disease	Intervention: Daily or frequent intermittent steroids for >6 months.	Participants received a median cumulative dose of 16.3 g of prednisolone (range 1.1-186 g) over a median duration of 5.5 years (range 0.5-46 years).

	Multicenter		Control: Age- and sex-matched controls who had not received systemic corticosteroids.	Cataract: Intervention: 18.4% Control: 8.6% Relative: OR 2.6 (95% CI 1.8-3.9) Cataract Dose-Response (p trend = 0.002): Prednisolone 5.2 g = 1.0 Prednisolone 11.7 g = OR 0.9 (95% CI 0.36-2.3) Prednisolone 23.6 g = OR 2.5 (95% CI 1.1-5.6) Prednisolone 60.6 g = OR 3.1 (95% CI 1.3-7.5)

Abbreviations: BOS = bronchiolitis obliterans syndrome.

Table 4b. Evidence table: Should sustained treatment with high-dose corticosteroids be given to lung transplant recipients who develop BOS?

--Quality Assessment--							--Summary of Findings--
No. of Studies	**Study Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality of Evidence**	
Lung function							
1	Case series	Serious[1]	Not serious	Serious[2]	Serious[3]	Very low (critical outcome)	Ten out of ten patients with lung function decline consistent with BOS exhibited progressive lung function decline despite receiving high-dose methylprednisolone.
Adverse effect: Hyperglycemia							
1	Observational study	Not serious	Not serious	Not serious[4]	Not serious	Low (important outcome)	Hyperglycemia: Intervention: 6.5% Control: 4.6% Relative: OR 1.4 (95% CI 0.8-2.5)
Adverse effect: Dyspepsia							
1	Observational study	Not serious	Not serious	Not serious[4]	Not serious	Low (important outcome)	Dyspepsia: Intervention: 22.6% Control: 7.8% Relative: OR 3.5 (95% CI 2.4-5.1)
Adverse effect: Hypertension							
1	Observational study	Not serious	Not serious	Not serious[4]	Not serious	Low (important outcome)	Hypertension: Intervention: 17.8% Control: 23.5% Relative: OR 0.7 (95% CI 0.5-1.0)
Adverse effect: Osteoporotic fracture							
5	Observational studies (N = 4) and case series (N = 1)	Not serious	Not serious	Not serious[4]	Not serious	High (important outcome)	The results were not pooled. All three studies that compared the fracture rate among patients receiving chronic systemic corticosteroids with that among patients not receiving chronic systemic corticosteroids found a statistically significant increase in fractures among those receiving chronic systemic corticosteroids. In addition, all three studies that evaluated the proportion of patients with fractures stratified according to dose found a statistically significant dose-response effect. See Table ~~5a~~4a.

							Confidence in these estimates is increased because: a) there as a dose-response effect and b) most of the patients in the study were receiving chronic low dose steroids, rather than high dose steroids. This would tend to bias the study toward a lesser effect or no effect, thereby increasing our confidence in the positive result. For these reasons, we upgraded the quality of evidence two levels, from an underlying assumption of low quality to high quality evidence.
Adverse effect: Cataracts							
1	Observational study	Not serious	Not serious	Not serious[4]	Not serious	Low (important outcome)	Cataract: Intervention: 18.4% Control: 8.6% Relative: OR 2.6 (95% CI 1.8-3.9)
<u>Overall quality of evidence</u> = very low (derived from the lowest quality of evidence among the critical outcomes).							

Abbreviations: BOS = bronchiolitis obliterans syndrome.

[1] The reporting was incomplete.

[2] Lung function is a surrogate outcome for patient-important outcomes such as dyspnea, quality of life, mortality, etc. (i.e., indirectness of the outcome). However, it is a well accepted surrogate and, therefore, we did not downgrade the quality of evidence for indirectness.

[3] There were only ten patients in the case series.

[4] The clinical question and recommendation are for transplant patients with BOS, but the data are from patients with a variety of chronic lung disease. We have no reason to suspect that long-term high dose corticosteroid therapy affects these patients differently, so we did not downgrade the quality of evidence.

Table 5a. Studies pertinent to the question: Does the replacement of cyclosporine with tacrolimus in the post-transplant immunosuppressive regimen slow the rate of lung function decline in patients who have developed criteria for BOS?

Author/ Year	Study Type	Subjects	Intervention and comparator	Major results
Lung function				
Knoop 1994 (Ref 236)	Case series Single center	N = 5 Heart-Lung Tx recipients with BOS	Intervention: Cyclosporine was changed to tacrolimus in the maintenance immunosuppression regimen. Control: None (case series).	2 of 5 patients (40%) had improvement in their FEV1, when measured three months after switching from cyclosporine to tacrolimus. Among the two respondents, the cyclosporine was changed to tacrolimus on post-op day 62 in one patient and post-op day 97 in the other patient; both patients had four episodes of "rejection" prior to the medication change.
Reichen-spurner 1995 (Ref 237)	Case series Single center	N = 2 Heart-Lung Tx recipients with histologically-confirmed obliterative bronchiolitis and lung function decline	Intervention: Cyclosporine was changed to tacrolimus in the maintenance immunosuppression regimen. Control: None (case series).	2 out of 2 patients (100%) had improvement in their FEV1, as well as other clinical improvements. The cyclosporine was changed to tacrolimus 14 months post-op in one patient and 15 months post-op in the other patient; both patients had multiple episodes of acute cellular rejection prior to the medication change.
Ross 1997 (Ref 223)	Case series Single center	N = 10 Lung Tx recipients with histologically-confirmed obliterative bronchiolitis and lung function decline refractory to	Intervention: The prednisone in the patient's maintenance immunosuppression regimen was increased to 1 mg/kg/day and then both the cyclosporine and azathioprine were discontinued. Once the cyclosporine level decreased to <200 ng/mL, tacrolimus was initiated at a dose of 0.025 to 0.050 mg/kg/day orally in two divided doses. The dose was titrated to a level of 10 to 15 ng/mL, unless the creatinine was >2.0 mg/dL, in which case a tacrolimus level of 7 to 10 ng/mL was accepted. Once the tacrolimus level was within the target range, the	Lung function declined on cyclosporine (change in FEV1 of -0.069±0.022 L/month), but then improved on tacrolimus (change in FEV1 of +0.030±0.033 L/month) (p=0.037). The change from cyclosporine + azathioprine to tacrolimus occurred 5.5 to 55 months post-transplant (mean 27.6 ± 6.7 months).

		high-dose methylprednisolone	prednisone dose was then tapered over 2 to 3 weeks to a maintenance dose of 0.1 to 0.2 mg/kg/day. Control: None (case series).	
Kesten 1997 (Ref 238)	Case series Single center	N = 12 Lung Tx recipients with BOS	Intervention: Cyclosporine was changed to tacrolimus in the maintenance immunosuppression regimen. Control: None (case series).	The median monthly rate of FEV1 decline was decreased after tacrolimus conversion (1.1 versus 5.3%; p=0.002). Subjects with a >10% improvement in FEV1: 0/12 (0%). Subjects with stabilization of the FEV1: 7/12 (58%). Subjects with >10% further decline in FEV1: 5/12 (42%).
Mentzer 1998 (Ref 239)	Case series Multicenter	N = 15 Lung Tx recipients with cyclosporine intolerance, refractory chronic rejection, or refractory acute rejection. Nine of the patients had BOS.	Intervention: Cyclosporine + azathioprine were changed to tacrolimus (0.075 to 0.15 mg/kg/day) in the maintenance immunosuppression regimen. Control: None (case series).	Among the nine patients with BOS (i.e., defined as "graft function impaired at the time of conversion"), all had persistent graft dysfunction throughout the study. Among all 15 lung transplant patients, 9 had survival of their grafts (40%) and 10 survived (67%). In addition, 12 had no episodes of rejection (80%), 2 had one episode of rejection (13%), and 1 had two episodes of rejection (7%). Patients were followed for a mean of 186±69 days after conversion from cyclosporine + azathioprine to tacrolimus.
Revell 2000 (Ref 240)	Case series Single center	N = 11 Six lung tx recipients and five heart-lung tx recipients with BOS.	Intervention: The prednisolone in the patient's maintenance immunosuppression regimen was increased to 1 mg/kg/day for one month to provide adequate immunosuppression as the cyclosporine was discontinued and tacrolimus initiated. The tacrolimus dose was titrated to a level of 13 to 18 ng/mL for the first three months and then 8 to 10 ng/mL thereafter. Once the tacrolimus level was within the target range, the prednisone dose was tapered to a maintenance dose of 0.1 mg/kg/day. Control: None (case series).	The incidence of BOS or obliterative bronchiolitis among lung and heart-lung transplant recipients in the series was 11 out of 49 patients (22%). Tacrolimus slowed the decline of lung function in BOS. During the six months prior to the conversion from cyclosporine to tacrolimus, the change in FEV1 was -70.44 ± 137.7 mL/month, whereas during the six months after the conversion, the change in FEV1 was -24.37 ± 44.9 mL/month (p=0.02). The attenuation of lung function decline persisted for ≥1 year following conversion from cyclosporine to tacrolimus.

Fieguth 2002 (Ref 241)	Case series Single center	N = 26 12 with bilateral lung tx and 14 patients with single lung tx with BOS.	Intervention: The maintenance immunosuppression regimen of mycophenolate, cyclosporine, and steroid was changed to a regimen of mycophenolate, tacrolimus, and steroid. This was achieved by leaving the mycophenolate and steroid doses unchanged, discontinuing the cyclosporine, and titrating the tacrolimus dose to a level of 10 ng/mL. Control: None (case series).	The conversion of cyclosporine to tacrolimus was associated with an improvement of lung function. The mean FEV1 at the time of conversion was 1570 mL. This increased to 1740 mL measured one month after the conversion, 2270 mL measured six months after the conversion ($p<0.05$), and 2050 mL 12 months after the conversion $p <0.05$).
Cairn 2003 (Ref 242)	Case series Single center	N = 32 Lung tx and heart-lung tx recipients with BOS	Intervention: The maintenance immunosuppression regimen of cyclosporine, azathioprine, and prednisolone was changed to a regimen of tacrolimus, azathioprine, and prednisolone. This was achieved by leaving the azathioprine and prednisolone doses unchanged, discontinuing the cyclosporine, and initiating tacrolimus at a dose of 0.1 mg/kg/day in two divided doses. The tacrolimus was titrated to a level of 7 to 12 ng/mL. Control: None (case series).	The conversion of cyclosporine to tacrolimus was associated with stabilization of lung function. The rates of decline of the FEV1 and FEF25%-75% during the 3 months prior to conversion were -0.11 liters/month and -0.13 L/sec per month, respectively. The rates of decline of the FEV1 and FEF25%-75% during the 3 months after conversion were -0.04 liters/month ($p = 0.023$) and -0.04 L/sec per month ($p = 0.022$), respectively.
Sarahrudi 2004 (Ref 243)	Case series Multicenter	N = 244 Lung tx recipients, including 134 with BOS and 110 with recurrent or progressive rejection	Intervention: Cyclosporine was changed to tacrolimus in the maintenance immunosuppression regimen. Control: None (case series).	The conversion of cyclosporine to tacrolimus was associated with stabilization of lung function in most patients with BOS. The rate of change in FEV1 among bilateral lung tx recipients averaged -3.7% of the predicted value per month prior to conversion and -0.9% of the predicted value per month following conversion ($p< 0.01$). The rate of change in FEV1 among single lung tx recipients averaged -2.5% of predicted value per month prior to conversion and -0.3% of predicted value per month following conversion ($p< 0.01$).
Borro 2007 (Ref 19)	Case series Multicenter	N = 79 Lung tx recipients with BOS	Intervention: Cyclosporine was changed to tacrolimus in the maintenance immunosuppression regimen. Control: None (case series).	Lung function decline was lessened after conversion from cyclosporine to tacrolimus. Prior to conversion from cyclosporine to tacrolimus, the mean FEV1 was 2.1 ± 0.9 L. It subsequently decreased and then stabilized following conversion from cyclosporine to tacrolimus. Following conversion, the mean FEV1 was 1.6 ±

				0.7, 1.7 ± 0.8, 1.6 ± 0.7, and 1.6 ± 0.8 L at 3, 6, 9, and 12 months. For the FEV1 measurement, the pre-conversion slope = -0.44 compared with the post-conversion slope = +0.005 ($p < 0.05$).
Adverse effect: Nephrotoxicity				
Kesten 1997 (Ref 238)	Case series Single center	N = 12 Lung Tx recipients with BOS	Intervention: Cyclosporine was changed to tacrolimus in the maintenance immunosuppression regimen. Control: None (case series).	7 out of 12 patients (58%) developed a >20% increase in their creatinine. However, the median change in the creatinine was not statistically significant ($p>0.05$)*.
Ross 1997 (Ref 223)	Case series Single center	N = 10 Lung Tx recipients with histologically-confirmed obliterative bronchiolitis and lung function decline refractory to high-dose methylprednisolone	Intervention: The prednisone in the patient's maintenance immunosuppression regimen was increased to 1 mg/kg/day and then both the cyclosporine and azathioprine were discontinued. Once the cyclosporine level decreased to <200 ng/mL, tacrolimus was initiated at a dose of 0.025 to 0.050 mg/kg/day orally in two divided doses. The dose was titrated to a level of 10 to 15 ng/mL, unless the creatinine was >2.0 mg/dL, in which case a tacrolimus level of 7 to 10 ng/mL was accepted. Once the tacrolimus level was within the target range, the prednisone dose was then tapered over 2 to 3 weeks to a maintenance dose of 0.1 to 0.2 mg/kg/day. Control: None (case series).	3 out of 10 patients (30%) developed a creatinine level >2.0 mg/dL*.
Mentzer 1998 (Ref 239)	Case series Multicenter	N = 15 Lung Tx recipients with cyclosporine intolerance, refractory chronic rejection, or refractory acute rejection. Nine of the patients had BOS.	Intervention: Cyclosporine + azathioprine were changed to tacrolimus (0.075 to 0.15 mg/kg/day) in the maintenance immunosuppression regimen. Control: None (case series).	The creatinine level increased in 26% of patients. The magnitude of the increase was from a mean of 1.42 to a mean of 1.6 mg/dL*.

Sarahrudi 2004 (Ref 243)	Case series Multicenter	N = 244 Lung tx recipients, including 134 with BOS and 110 with recurrent or progressive rejection	Intervention: Cyclosporine was changed to tacrolimus in the maintenance immunosuppression regimen. Control: None (case series).	The creatinine level increased from 1.5±0.7 mg per 100 mL to 1.7±0.9 mg per 100 mL (p=0.04) following conversion from cyclosporine to tacrolimus.
Adverse effect: Hyperglycemia				
Kesten 1997 (Ref 238)	Case series Single center	N = 12 Lung Tx recipients with BOS	Intervention: Cyclosporine was changed to tacrolimus in the maintenance immunosuppression regimen. Control: None (case series).	3 out of 12 patients (25%) developed hyperglycemia or required an increase in their insulin regimen. Median change in fasting blood glucose was +0.7 mmol/L (p=0.02)*.

*From: Baughman RP, Meyer KC, Nathanson I, Angel L, Bhorade SM, Chan KM, Culver D, Harrod CG, Hayney MS, Highland KB, et al. Monitoring of Nonsteroidal Immunosuppressive Drugs in Patients with Lung Disease and Lung Transplant Recipients: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 142:1284.

Abbreviations: BOS = Bronchiolitis Obliterans Syndrome; Tx = transplantation; and, FEV1 = forced expiratory volume in 1 second.

Table 5b. Evidence table: Does the replacement of cyclosporine with tacrolimus in the post-transplant immunosuppressive regimen slow the rate of lung function decline in patients who have developed criteria for BOS?

--Quality Assessment--							--Summary of Findings--
No. of Studies	**Study Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality of Evidence**	
Lung function							
10	Case series	Not serious	Not serious	Not serious[1]	Serious[2]	Very low (critical outcome)	The results were not pooled due to differential reporting of outcomes. However, six of the case series reported mitigation of lung function decline following conversion from cyclosporine to tacrolimus, and four of the case series reported improvement of lung function following conversion. See Table 6a.
Adverse effect: Nephrotoxicity							
4	Case series	Not serious	Not serious	Serious[3]	Serious[2]	Very low (important outcome)	Few of the case series reported potential adverse effects. However, all four of the case series that reported on the effect of converting cyclosporine to tacrolimus on renal function reported an increase in the creatinine level. Estimates varied as shown in Table 6a. However, roughly speaking, the mean creatinine level appeared to increase about 0.2 mg/dL in approximately 30% of patients.
Adverse effect: Infection							
0	-	-	-	-	-	-	-
Adverse effect: Malignancy							
0	-	-	-	-	-	-	-
Adverse effect: Hyperglycemia							
1	Case series	Not serious	Not serious	Serious[4]	Serious[2]	Very low (important outcome)	The lone case series that reported that 25% of patients developed hyperglycemia or required an increase in their insulin regimen, and the median change in fasting blood glucose was +0.7 mmol/L. See Table ~~6a~~5a.
Overall quality of evidence = very low (derived from the lowest quality of evidence among the critical outcomes).							

[1] Lung function is a surrogate outcome for patient-important outcomes such as dyspnea, quality of life, mortality, etc. (i.e., indirectness of the outcome). However, it is a well accepted surrogate and, therefore, we did not downgrade the quality of evidence for indirectness.

[2]The estimated effect is based upon few events.

[3]The creatinine level is a surrogate outcome for patient-important outcomes related to renal function. However, the committee judged it to be a reliable surrogate that did not diminish confidence in the results; thus, the evidence was not downgraded for indirectness of the outcome.

[4]The glucose level is a surrogate outcome for patient-important outcomes related to hyperglycemia. However, the committee judged it to be a reliable surrogate that did not diminish confidence in the results; thus, the evidence was not downgraded for indirectness of the outcome.

Table 6a. Studies pertinent to the question: Should azithromycin be given to patients who develop BOS?

Author/ Year	Study Type	Subjects	Intervention and comparator	Main results
Lung function				
Vos 2010 (Ref 36)	Observational (Retrospective cohort) study Single center	N = 153 Lung tx recipients with BOS	Intervention (N=107): Azithromycin 250 mg per day for five days and then 250 mg three times per week. Control (N=46): No azithromycin.	A response to azithromycin was associated with an improvement in the FEV1, but not all patients responded. 107 patients with BOS were treated with azithromycin for a mean of 3.1 ± 1.9 years. They were evaluated a mean of 6.3 ± 3.8 years after transplantation. 23 patients had BOS Stage 0p, 62 patients had BOS Stage 1, 20 patients had BOS Stage 2, and 2 patients had BOS Stage 3. After 3 to 6 months of azithromycin: --43 patients (40%) were responders (defined as FEV1 increase ≥10%). Among the responders, 33% subsequently relapsed. -- 64 patients (60%) were non-responders. Among the non-responders, 78% had continued FEV1 decline and 22% stabilized. BAL neutrophil percentage was higher in responders (29.3%, 9.3% to 69.7%) than in non-responders (11.5%, 2.9% to 43.8%) (p = 0.025). After 3-6 months of azithromycin, the BAL neutrophil percentage declined to 4.2% (1.8% to 17.6%) (p = 0.041). An initial response and earlier post-transplant initiation of azithromycin were protective against BOS progression (HR = 0.12, 95% CI 0.05 to 0.28, p<0.0001) and BOS relapse (HR=0.98, 95% CI 0.97 to 0.98, p < 0.0001).
Gerhardt 2003 (Ref 257)	Case series Single center	N = 6 Lung tx recipients with BOS	Intervention: Azithromycin 250 mg per day for five days and then 250 mg three times per week. Control: None (case series).	The addition of azithromycin was associated with improved lung function. 5 out of the 6 patients (83%) had significant improvement in FEV1 over a mean follow-up of 13.7 weeks. The mean increase in % predicted of FEV1 was 17.1% (p ≤ 0.05) and the mean absolute increase in FEV1 was 0.50 L (range -0.18 to 1.36 L).
Verleden 2004 (Ref 258)	Case series Single center	N = 8 Lung tx recipients with BOS	Intervention: Azithromycin 250 mg per day for five days and then 250 mg every other day. Control: None (case series).	The addition of azithromycin was associated with improved lung function.

				Before the addition of azithromycin, there was a decrease in the % predicted of FEV1 (-34.4%±-14.7%) relative to the best post-operative values. After the addition of azithromycin, there was an increase in the % predicted of FEV1 (+18.3%+/-14.6%) (p<0.0001). A mean absolute increase in the FEV1 of 328+/-305 mL was seen 12 weeks after azithromycin was started.
Shitrit 2005 (Ref 260)	Case series Single center	N = 11 Lung tx recipients with BOS	Intervention: Azithromycin 250 mg three times per week. Control: None (case series).	The addition of azithromycin was not associated with improved lung function, but may have slowed progression of lung function decline. Mean % predicted of FEV1 was 40 ± 9% when azithromycin was initiated, 39 ± 10% after 1 month of therapy, 39 ± 12% after 4 months, 38 ± 10% after 7 months, and 38 ± 10% after 10 months (p>0.05)
Yates 2005 (Ref 259)	Case series Single center	N = 20 Lung tx recipients with BOS	Intervention: Azithromycin 250 mg every other day. Control: None (case series).	The addition of azithromycin was associated with improved lung function. FEV1 improved following the initiation of azithromycin by a median value of 110 ml (range, -70 to 730 ml) (p = 0.002), when measured 3 months after initiation. The improvement was sustained beyond 3 months in the majority of patients. The azithromycin was started a mean of 82 months after lung transplantation. The BOS stage at the initiation of treatment was BOS 3 (N=10), BOS 2 (N=2), BOS 1 (N=6), and BOS 0-p (N=2).
Verleden 2006 (Ref 261)	Case series Single center	N = 14 Lung tx recipients with BOS	Intervention: Azithromycin 250 mg per day for five days and then 250 mg three times per week. Control: None (case series).	The addition of azithromycin was associated with improved lung function overall, although not all patients benefited. The mean FEV1 increased from 2.36±0.82 L to 2.67±0.85 L (p = 0.007), measured at the initiation of therapy and after 3 months of therapy. There were six responders to azithromycin (FEV1 increase of >10%) and eight non-responders. Univariate linear regression analysis suggested that the main differences between responders and nonresponders were the postoperative day at which the azithromycin was started (p = 0.036), the initial BAL neutrophilia (p < 0.0001), and IL-8 mRNA ratio (p = 0.0009).

Porhownik 2008 (Ref 262)	Case series Single center	N = 7 Lung tx recipients with BOS of >3 months duration	Intervention: Azithromycin 1 gm oral loading dose, then 500 mg on days 2 and 4, and then 250 mg three times per week. Control: None (case series).	The addition of azithromycin was not associated with improvement of lung function among patients who had BOS for >3 months. There was no significant difference in the rate of FEV1 decline during the six months prior to the initiation of azithromycin (p=0.32) and the rate of FEV1 increase during the 3 months (p=0.16) and 12 months (p=0.18) following the initiation of azithromycin therapy. The mean duration from lung transplantation to the onset of BOS was 22 months (range 3 to 67 months), while the mean duration from lung transplantation to the initiation of azithromycin was 67 months (range 17 to 117 months).
Gottlieb 2008 (Ref 37)	Case series Single center	N = 81 Lung tx recipients with BOS	Intervention: Azithromycin 250 mg three times per week. Control: None (case series).	The addition of azithromycin was associated with improved lung function, although not all patients benefited. Most of the patients who benefited showed improvement after three months of therapy. 24 out of 81 patients (30%) had an improved FEV1 after 6 months of azithromycin. Among the 24 responders, 22 had improvement by 3 months. In contrast, 33 patients (40%) had a worsened FEV1 during follow-up of a mean of 491±165 days. Increased neutrophils in the BAL predicted improvement at 6 months. Proton pump inhibitor therapy was also associated with a beneficial treatment response. In contrast, a rapid pre-treatment decline in the FEV1 increased the likelihood of treatment failure.
Mertens 2011 (Ref 93)	Case series Single center	N = 37 Lung tx recipients with BOS	Intervention: Azithromycin 250 mg three times per week. Control: None (case series).	The addition of azithromycin was not associated with improved lung function overall. However, some patients appeared to benefit while others had little or no benefit. At 3 months, azithromycin was associated with a non-significant increase in the % of predicted FEV1 of 6% (−5 to 16%). However: --17 patients (46%) had ≥ 10% increase in the % of predicted FEV1. --23 patients (62%) had ≥ 5% increase in the % of predicted FEV1. In a subgroup analysis comparing patients with bile salts on BAL (N=9) with patients without bile salts on BAL (N=18), patients with bile acids developed more severe BOS especially at 3 years. In addition, the % freedom from BOS ≥ 1 in patients was significantly better for those without bile salts than those with bile salts in the BAL (p = 0.04).

				Mortality in the study was 19%.
Vos 2011 (Ref 38)	Case series Single center	N = 23 Lung tx recipients with BOS	Intervention: Azithromycin 250 mg three times per week. Control: None (case series).	The addition of azithromycin was associated with improved lung function overall, although not all patients benefited. The case series included 23 patients who developed BOS during a randomized trial of azithromycin prophylaxis and, therefore, were treated with azithromycin. 18 of the patients were from the trial's placebo arm and 5 patients were from the trial's azithromycin arm. BOS developed a mean of 328.1 ± 199.9 days after transplantation. Effects of azithromycin: --Among those in the placebo group of the randomized trial, 10 out of 18 (55.6%) had improvement of their FEV1 to BOS Stage 0, 7 had no improvement, and 1 could not be assessed. --Among those in the azithromycin arm of the randomized trial 2 out 5 (40%) had improvement of their FEV1 to BOS Stage 0. These patients later admitted not taking the azithromycin during the trial. The remaining 3 patients had no improvement. --Responders generally developed BOS earlier and higher BAL neutrophilia.
Mortality				
Jain 2010 (Ref 263)	Observational (retrospective cohort) study Single center	N = 178 Lung tx recipients with BOS	Intervention (N=78): Azithromycin 250 mg per day for five days and then 500 mg three times per week for patients >70 kg or 250 mg three times per week for patients <70 kg. Control (N=95): No azithromycin.	Azithromycin treatment was associated with decreased mortality when given to patients with BOS Stage 1, but not when given to patients with BOS Stage 2. Out of the 178 lung tx recipients with BOS, 78 were treated with azithromycin (44%), 95 were not treated with azithromycin (53%), and 6 were excluded (3%). Effect of azithromycin treatment on mortality: --All patients: HR 1.08, 95% CI 0.66-1.74, p=0.78. --Patients with BOS Stage 1: HR 0.29, 95% CI 0.11-0.82, p=0.02. --Patients with BOS Stage 2: HR 1.54, 95% CI 0.91-2.61, p=0.11.
Vos 2010 (Ref 36)	Observational (Retrospective cohort) study Single center	N = 153 Lung tx recipients with BOS	Intervention (N=107): Azithromycin 250 mg per day for five days and then 250 mg three times per week. Control (N=46): No azithromycin.	A response to azithromycin was associated with improved survival, but not all patients responded. 107 patients with BOS were treated with azithromycin for a mean of 3.1 ± 1.9 years. They were evaluated a mean of 6.3 ± 3.8 years after

				transplantation. 23 patients had BOS Stage 0p, 62 patients had BOS Stage 1, 20 patients had BOS Stage 2, and 2 patients had BOS Stage 3. After 3 to 6 months of azithromycin: --43 patients (40%) responded (defined as FEV1 increase ≥10%). Among the responders, 33% subsequently relapsed. -- 64 patients (60%) did not respond. Among the non-responders, 78% had continued FEV1 decline and 22% stabilized. BAL neutrophil percentage was higher in responders (29.3%, 9.3% to 69.7%) than in non-responders (11.5%, 2.9% to 43.8%) (p = 0.025). After 3-6 months of azithromycin, the BAL neutrophil percentage declined to 4.2% (1.8% to 17.6%) (p = 0.041). An initial response and earlier post-transplant initiation of azithromycin were protective against death (HR 0.96, 95% CI 0.95 to 0.98, p < 0.0001) and retransplantation (HR 0.10, 95% CI 0.02 to 0.48], p = 0.004).
Gastrointestinal distress				
Vos 2010 (Ref 36)	Observational (Retrospective cohort) study Single center	N = 153 Lung tx recipients with BOS	Intervention (N=107): Azithromycin 250 mg per day for five days and then 250 mg three times per week. Control (N=46): No azithromycin.	Azithromycin was temporarily or permanently halted for nausea, colitis, or dyspepsia in 5 out of 107 patients (4.7%).
Vos 2011 (Ref 38)	Case series Single center	N = 83 Lung tx recipients	Intervention: Azithromycin 250 mg three times per week. Control: None (case series).	Azithromycin was halted in 3 out of 83 patients for nausea and diarrhea (3.6%). The cessation was temporary for one patient and permanent for two patients.
Yates 2005 (Ref 259)	Case series Single center	N = 20 Lung tx recipients with BOS	Intervention: Azithromycin 250 mg every other day. Control: None (case series).	Azithromycin was associated with gastrointestinal distress in 0 out of 20 patients (0%).
Fatal cardiac arrhythmias				
				No study identified by the systematic review reported on fatal cardiac arrhythmias.
Allergic reactions				

Vos 2010 (Ref 36)	Observational (Retrospective cohort) study Single center	N = 153 Lung tx recipients with BOS	Intervention (N=107): Azithromycin 250 mg per day for five days and then 250 mg three times per week. Control (N=46): No azithromycin.	Azithromycin caused an allergic reaction in 0 out of 107 patients (0%).
Gottlieb 2008 (Ref 37)	Case series Single center	N = 81 Lung tx recipients with BOS	Intervention: Azithromycin 250 mg three times per week. Control: None (case series).	Azithromycin was discontinued due to laryngeal edema in 1 out of 81 patients (1.2%).
Vos 2011 (Ref 38)	Case series Single center	N = 83 Lung tx recipients	Intervention: Azithromycin 250 mg three times per week. Control: None (case series).	Azithromycin caused an allergic reaction in 0 out of 83 patients (0%).
Yates 2005 (Ref 259)	Case series Single center	N = 20 Lung tx recipients with BOS	Intervention: Azithromycin 250 mg every other day. Control: None (case series).	Azithromycin caused an allergic reaction in 0 out of 20 patients (0%).

Abbreviations: BAL = bronchoalveolar lavage; BOS = bronchiolitis obliterans syndrome; CI = Confidence interval; FEV1 = forced expiratory volume in 1 second; HR = Hazard Ratio; and, Tx = transplant.

Table 6b. Evidence table: Should azithromycin be given to patients who develop BOS?

--Quality Assessment--							--Summary of Findings--
No. of Studies	**Study Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality of Evidence**	
Lung function							
10	Observational study x 1 and case series x 9	Not serious	Not serious	Not serious[1]	Not serious	Very low (important outcome)	All 10 studies found that some patients' lung function improved after beginning azithromycin, usually those who received it early. In addition, 7 out of the 10 studies found azithromycin was associated with improvement of mean lung function. See Table 7a above.
Mortality							
2	Observational studies	Not serious	Not serious	Not serious	Not serious	Low (critical outcome)	Two observational studies compared mortality among patients who received azithromycin for BOS with that among those who did not. Both studies reported that azithromycin was associated with decreased mortality if initiated early: Jain 2010 (ref 263): Azithromycin was associated with decreased mortality if initiated during BOS Stage 1 (HR 0.29, 95% CI 0.11-0.82, p=0.02) but not during BOS Stage 2 (HR 1.54, 95% CI 0.91-2.61, p-0.11). See table 7a above. Vos 2010 (ref 36): Earlier post-transplant initiation of azithromycin and an early response to azithromycin were protective against death (HR 0.96, 95% CI 0.95 to 0.98, p < 0.0001). See table ~~7a~~ 6a above.
Adverse effect: Gastrointestinal distress							
3	Observational study x 1 and case series x 2	Not serious	Not serious	Not serious	Serious[2]	Very low (important outcome)	Azithromycin was temporarily or permanently discontinued for nausea, diarrhea, colitis, or dyspepsia in 8 out of 210 patients (3.8%). See table 7a above.
Adverse effect: Fatal cardiac arrhythmia							
0							No study identified by the systematic review reported on fatal cardiac arrhythmias.
Adverse effect: Allergic reaction							

4	Observational study x 1 and case series x 3	Not serious	Not serious	Not serious	Serious[2]	Very low (important outcome)	Azithromycin was associated with laryngeal edema in 1 out of 288 patients (0.3%).
Overall quality of evidence = low (derived from the lowest quality of evidence among the critical outcomes).							

[1] Lung function is a surrogate outcome for patient-important outcomes such as dyspnea, quality of life, mortality, etc. (i.e., indirectness of the outcome). However, it is a well accepted surrogate and, therefore, we did not downgrade the quality of evidence for indirectness.

[2]The estimated effect is based upon few events.

Table 7a. Studies pertinent to the question: Should anti-reflux surgery (e.g., fundoplication) be performed for patients who develop BOS and have documented GER?

Author/ Year	Study Type	Subjects	Intervention and comparator	Main results
Lung function				
Davis 2003 (Ref 79)	Case series (nested within a retrospective cohort study) Single center	N = 26 Lung tx recipients with confirmed GER and BOS undergoing anti-reflux surgery	Intervention: Anti-reflux surgery, the majority of which were Nissen fundoplications. Control: None (case series).	16 out of the 26 patients (62%) had improved FEV1 following anti-reflux surgery, including 13 patients (50%) who improved to such an extent that they no longer met BOS criteria. The mean FEV1 improved from 1.87 L to 2.19 L ($p<0.0002$).
Halsey 2008 (Ref 85)	Case report Single center	N = 1 Lung tx recipient with GER and lung function decline consistent with BOS	Intervention: Anti-reflux surgery via Nissen fundoplication. Control: None (case report).	Prior to anti-reflux surgery, the mean FEV1 fell from 1.60-1.65 L/min to 1.30 L/min. Following anti-reflux surgery, the mean FEV1 returned to 1.65-1.70 L/min. The decline in FEV1 consistent with BOS occurred 7 months post-transplant.
Cantu 2004 (Ref 81)	Observational (retrospective cohort) study Single center	N = 457 Lung tx recipients	Intervention: Anti-reflux surgery, the majority of which were Nissen fundoplications. Control: No anti-reflux surgery.	Freedom from BOS at 1 year ($p=0.01$ across groups): No GER (N=47): 91% GER with early anti-reflux surgery (N=14): 100% GER with late anti-reflux surgery (N=62): 90% GER with no anti-reflux surgery (N=79): 92% Freedom from BOS at 3 years ($p=0.01$ across groups): No GER (N=47): 62% GER with early anti-reflux surgery (N=14): 100% GER with late anti-reflux surgery (N=62): 47% GER with no anti-reflux surgery (N=79): 60%

Linden 2006 (Ref 269)	Observational (retrospective cohort) study Single center	N = 45 Pre-lung tx patients with IPF	Intervention: Anti-reflux surgery, all of which were Nissen fundoplications. Control: No anti-reflux surgery.	14 patients with GER underwent anti-reflux surgery, while 31 patients did not undergo anti-reflux surgery because they were without GER. FEV1 (% predicted) (p=0.97): With anti-reflux surgery: +2% Without anti-reflux surgery: -6% Oxygen requirement (p=0.002): With anti-reflux surgery: -0.5 L/min Without anti-reflux surgery: +1.0 L/min 6-minute walk distance (feet) (p=0.66): With anti-reflux surgery: -335 feet Without anti-reflux surgery: -42 feet
Burton 2009 (Ref 274)	Case series Single center	N = 21 Lung tx recipients with confirmed GER	Intervention: Anti-reflux surgery via either a full 360-degree Nissen fundoplication (N=5) or a posterior 270-degree Toupet fundoplication (N=16). Control: None (case report).	The mean percent predicted FEV1 did not change significantly from pre-anti-reflux therapy (72.9±20.9%) to post-anti-reflux therapy (70.4±26.8%) (p=0.33). Those patients who developed BOS progressed quickly to BOS Stage 1, but did not necessarily progress to BOS Stage 2 or 3. The mean duration between lung tx and anti-reflux surgery was 768 days (range 145 to 1524 days). The mean duration of follow-up following anti-reflux surgery was 576 days (range 394 to 1508 days). 13 out of 14 patients (93%) with preoperative GER-related symptoms had improvement or resolution of GER symptoms. One patient reported no change in GER-related symptoms.
Hoppo 2011 (Ref 74)	Case series Single center	N = 24 Lung tx recipients with confirmed GER	Intervention: Anti-reflux surgery via either a Nissen fundoplication or a Dor fundoplication. Control: None (case report).	The mean percent predicted FEV1 significantly improved in 91% of lung tx recipients following anti-reflux surgery (from 81.5% [range 61.3 to 92.8%] to 92.5% [range 65.8 to 102.5%], p<0.01). Similarly, the FVC and FEF15-75% significantly improved. Among the lung tx recipients whose FEV1 was declining prior to anti-reflux therapy, 92% had reversal of the decline after the anti-reflux surgery.

				8 out of 24 patients (33%) had an episode of acute rejection prior to anti-reflux surgery, whereas only 1 out of 24 patients (4%) had an episode of acute rejection prior to anti-reflux surgery. The mean duration between lung tx and anti-reflux surgery was 31±24 months.
Hartwig 2011 (Ref 276)	Observational (retrospective cohort) study Single center	N = 297 Lung tx recipients	Intervention: Anti-reflux surgery via Nissen fundoplication or Toupet fundoplication. Control: No anti-reflux surgery.	222 out of the 297 lung tx recipients (75%) had GER. Mean percent predicted FEV1 at 1-year: a) No GER – 76% b) GER without anti-reflux surgery – 68% c) GER with anti-reflux surgery – 77% Compare a versus b: p=0.015 Compare b versus c: p=0.0005 Compare a versus c: p=0.80 Mean percent predicted FEV1 at maximum: d) No GER – 82% e) GER without anti-reflux surgery – 75% f) GER with anti-reflux surgery – 85% Compare a versus b: p=0.025 Compare b versus c: p=0.001 Compare a versus c: p=0.46 Patients with GER who underwent anti-reflux surgery had a mean percent predicted FEV1 at 1-year that was 9.5% (95% CI 3.9 to 15.0%) higher than that in patients with GER who did not undergo anti-reflux surgery. Patients with GER who underwent anti-reflux surgery had a mean percent predicted FEV1 at maximum that was 8.3% (95% CI 3.4 to 13.1%) higher than that in patients with GER who did not undergo anti-reflux surgery. The median duration between lung tx and anti-reflux surgery was 68 days. The median duration of follow-up varied among patients with GER who underwent anti-reflux therapy (37.6 months), patients with GER who did not undergo anti-reflux therapy (49.2 months), and patients without GER (39.5 months).

Robertson 2012 (Ref 278)	Case series Single center	N = 16 Lung tx recipients	Intervention: Anti-reflux surgery via Nissen fundoplication. Control: None (case report).	In the subgroup of 8 patients with declining lung function (7 patients with confirmed BOS), the rate of FEV1 decline decreased following anti-reflux surgery, from -96.7±87.3 mL/month to +9.5±26.5 mL/month (p=0.008). One patient had reversal, 2 patients stabilized, and 5 patients had a reduction in the rate of FEV1, yet ongoing decline. The mean duration of follow-up after anti-reflux surgery was 476±180 days.
Mortality				
Davis 2003 (Ref 79)	Observational (retrospective cohort) study Single center	N = 396 Lung tx recipients	Intervention: Anti-reflux surgery, the majority of which were Nissen fundoplications. Control: No anti-reflux surgery.	43 lung tx recipients underwent anti-reflux surgery for GER; the remaining 353 were lung tx recipients with or without GER who did not undergo anti-reflux surgery. Patients who underwent anti-reflux surgery had lower mortality than the total population of lung tx recipients: 1 year mortality: 5 versus 22% (p=0.013) 3 year mortality: 14 versus 31 % (p=0.013) 5 year mortality: 29 versus 52 % (p=0.013)
Cantu 2004 (Ref 81)	Observational (retrospective cohort) study Single center	N = 457 Lung tx recipients	Intervention: Anti-reflux surgery, the majority of which were Nissen fundoplications. Control: No anti-reflux surgery.	76 lung tx recipients underwent anti-reflux surgery for GER; the remaining 126 were lung tx recipients with or without GER who did not undergo anti-reflux surgery. Mortality at 1 year (p=0.03 across groups): No GER (N=47): 98% GER with early anti-reflux surgery (N=14): 100% GER with late anti-reflux surgery (N=62): 98% GER with no anti-reflux surgery (N=79): 92% Mortality at 3 years (p=0.03 across groups): No GER (N=47): 82% GER with early anti-reflux surgery (N=14): 100% GER with late anti-reflux surgery (N=62): 86% GER with no anti-reflux surgery (N=79): 76%
Adverse effects: Perioperative complications other than mortality				

Gasper 2008 (Ref 270)	Case series Single center	N = 35 Patients with end-stage lung disease, 15 were pre-lung tx and 20 were lung tx recipients	Intervention: Anti-reflux surgery, including 32 via fundoplication, two via pyloroplasty, and one via both fundoplication and pyloroplasty. Control: None (case report).	1 out of 35 patients (3%) experienced a perioperative complication – readmission for a urinary tract infection.
Burton 2009 (Ref 274)	Case series Single center	N = 21 Lung tx recipients with confirmed GER	Intervention: Anti-reflux surgery via either a full 360-degree Nissen fundoplication (N=5) or a posterior 270-degree Toupet fundoplication (N=16). Control: None (case report).	2 out of 21 patients (9%) developed a postoperative respiratory infection requiring antibiotics and physiotherapy.
Roberts on 2012 (Ref 278)	Case series Single center	N = 16 Lung tx recipients	Intervention: Anti-reflux surgery via Nissen fundoplication. Control: None (case report).	0 out of 16 patients (0%) experienced a major perioperative complication.
Fisichell a 2011 (Ref 275)	Observational (retrospective cohort) study Single center	N = 52 Patients with confirmed GER	Intervention: Lung transplant patients with GER undergoing anti-reflux surgery via Nissen fundoplication or Toupet fundoplication. Control: Non-transplant patients with GER undergoing anti-reflux surgery.	When lung tx patient with GER were compared to non-tx patients with GER, there were no differences in estimated blood loss, duration of surgery, length of hospital stay, complications, or readmission rate. Among lung tx recipients, one patient required upper endoscopy for food impaction. Among non-tx patients, one patient required upper endoscopy for food impaction and one patient developed a pulmonary embolism.
Adverse effects: Perioperative mortality				
Davis 2003 (Ref 79)	Case series (nested within a retrospective cohort study) Single center	N = 43 Lung tx recipients with confirmed GER undergoing anti-reflux surgery	Intervention: Anti-reflux surgery, the majority of which were Nissen fundoplications. Control: None (case series).	0 out of 43 patients (0%) experienced in-hospital or 30-day mortality attributable to the anti-reflux surgery.
Linden 2006 (Ref 269)	Case series (nested within a retrospective cohort study)	N = 14 Pre-lung tx patients with IPF and	Intervention: Anti-reflux surgery, all of which were Nissen fundoplications. Control: None (case series).	0 out of 14 patients (0%) experienced perioperative death attributable to the anti-reflux surgery.

	Single center	confirmed GER undergoing anti-reflux surgery		
Gasper 2008 (Ref 270)	Case series Single center	N = 35 Patients with end-stage lung disease, 15 were pre-lung tx and 20 were lung tx recipients	Intervention: Anti-reflux surgery, including 32 via fundoplication, two via pyloroplasty, and one via both fundoplication and pyloroplasty. Control: None (case report).	0 out of 35 patients (0%) experienced perioperative death attributable to the anti-reflux surgery.
Burton 2009 (Ref 274)	Case series Single center	N = 21 Lung tx recipients with confirmed GER	Intervention: Anti-reflux surgery via either a full 360-degree Nissen fundoplication (N=5) or a posterior 270-degree Toupet fundoplication (N=16). Control: None (case report).	1 out of 21 patients (5%) died postoperatively from causes attributable to the anti-reflux surgery. The patient underwent anti-reflux surgery due to rapid deterioration of FEV1 in the setting of GER; post-operatively, she developed a respiratory infection and had insufficient reserve to tolerate the infection. An additional 3 out of 21 patients died postoperatively, but these deaths were not attributable to the anti-reflux surgery.
Hoppo 2011 (Ref 74)	Case series Single center	N = 24 Lung tx recipients with confirmed GER	Intervention: Anti-reflux surgery via either a Nissen fundoplication or a Dor fundoplication. Control: None (case report).	0 out of 24 patients (0%) experienced perioperative death attributable to the anti-reflux surgery.
Robertson 2012 (Ref 278)	Case series Single center	N = 16 Lung tx recipients	Intervention: Anti-reflux surgery via Nissen fundoplication. Control: None (case report).	0 out of 16 patients (0%) experienced perioperative death attributable to the anti-reflux surgery.
Fisichella 2011 (Ref 275)	Observational (retrospective cohort) study Single center	N = 52 Patients with confirmed GER	Intervention: Lung transplant patients with GER undergoing anti-reflux surgery via Nissen fundoplication or Toupet fundoplication. Control: Non-transplant patients with GER undergoing anti-reflux surgery.	There was no in-hospital or 30-day mortality among lung tx patients (N=29) or non-tx patients (N=23) who underwent anti-reflux surgery (despite the higher surgical risk score of the lung tx recipients).
Adverse effects: Dysphagia				

Gasper 2008 (Ref 270)	Case series Single center	N = 35 Patients with end-stage lung disease, 15 were pre-lung tx and 20 were lung tx recipients	Intervention: Anti-reflux surgery, including 32 via fundoplication, two via pyloroplasty, and one via both fundoplication and pyloroplasty. Control: None (case report).	5 out of 35 patients (14%) developed post-operative dysphagia.
Burton 2009 (Ref 274)	Case series Single center	N = 17 Lung tx recipients with confirmed GER	Intervention: Anti-reflux surgery via either a full 360-degree Nissen fundoplication (N=5) or a posterior 270-degree Toupet fundoplication (N=16). Control: None (case report).	The mean dysphagia score was 5.6 (0= no dysphagia, 45= total dysphagia). The mean difficulty swallowing was 1.8 (0= no difficulty swallowing, 10= unable to swallow). 1 out of 17 patients (6%) needed to change their diet due to dysphagia, the remaining 16 patients did not.
Robertson 2012 (Ref 278)	Case series Single center	N = 16 Lung tx recipients	Intervention: Anti-reflux surgery via Nissen fundoplication. Control: None (case report).	2 out of 16 patients (12%) developed postoperative dysphagia. One was self-limited, while the other required a minor surgical revision.

Abbreviations: BOS = Bronchiolitis Obliterans Syndrome; CI = Confidence interval; FEV1 = forced expiratory volume in 1 second; GER = gastroesophageal reflux; IPF = idiopathic pulmonary fibrosis; Tx = transplant.

Table 7b. Evidence table: Should anti-reflux surgery (e.g., fundoplication) be performed for patients who develop BOS and have documented GER?

--Quality Assessment--							--Summary of Findings--
No. of Studies	**Study Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality of Evidence**	
Lung function							
8	Observational studies and case series	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Very low (important outcome)	7 out of the 8 studies found that FEV1 improved following anti-reflux surgery.
Mortality							
2	Observational studies	Serious[4]	No serious inconsistency	Serious[5]	No serious imprecision	Very low (critical outcome)	In both studies, anti-reflux surgery was associated with decreased mortality.
Adverse effect: Perioperative complications other than mortality							
4	Observational studies and case series	No serious limitations	No serious inconsistency	Serious[6]	Serious[7]	Very low (important outcome)	Case series reported perioperative complications in 3 out of 72 patients (4.2%). The observational study found that lung tx patients did not have a higher incidence of complications than non-tx patients.
Adverse effect: Perioperative mortality							
7	Observational studies and case series	No serious limitations	No serious inconsistency	Serious[6]	Serious[7]	Very low (critical outcome)	Perioperative mortality attributable to anti-reflux surgery was rare, occurring in 1 out of 205 patients (0.5%).
Adverse effect: Dysphagia							
3	Case series	No serious limitations	No serious inconsistency	Serious[6]	Serious[7]	Very low (important outcome)	Post-operative dysphagia was reported in 6 to 14% of patients.
Overall quality of evidence = very low (derived from the lowest quality of evidence among the critical outcomes).							

Abbreviations: BOS = Bronchiolitis Obliterans Syndrome; FEV1 = forced expiratory volume in 1 second; GER = gastroesophageal reflux; Tx = transplant.

[1]Three of the studies were from the same medical center and may have included many of the same patients, including the two largest studies.
[2]Only three of the studies specifically evaluated patients with BOS. The remaining five studies included lung tx recipients with or without BOS.
[3]Six of the eight studies included <200 patients and, therefore, the estimates were based upon few events.
[4]Both of the studies were from the same medical center and may have included many of the same patients.
[5]Neither of the studies specifically evaluated patients with BOS; rather, they evaluated lung tx recipients in general.
[6]None of the studies specifically evaluated patients with BOS; rather, they all evaluated lung tx recipients in general or pre-lung tx patients with end-stage lung disease.
[7]All of the studies included <100 patients and, therefore, the estimates were based upon few events.

Table 8a. Studies pertinent to the question: Should lung re-transplantation be offered to patients who develop end-stage BOS refractory to other therapies?

Author/ Year	Study Type	Subjects	Intervention and comparator	Main results
Lung function				
Novick 1996 (Ref 283)	Observational (retrospective cohort) study Multicenter	N = 160 Lung tx recipients who underwent re-transplantation	Intervention: Re-transplantation of the lung due to BOS. Control: Re-transplantation of the lung for reasons other than BOS.	Median follow-up was 780 days. Among lung tx recipients who underwent re-transplantation for any reason, the prevalence of BOS Stage 3 (severe) was 12% at 1 year, 15% at 2 years, and 33% at 3 years post re-transplantation. The FEV1 was significantly worse at 3 years among patients who underwent re-transplantation of lung due to BOS, than among patients who underwent re-transplantation due to acute graft failure or an airway complication (p=0.02). Freedom from BOS at 3 years was significantly less among patients who underwent re-transplantation of lung due to BOS (31%) than among patients who underwent re-transplantation due to an alternative indication (83%) (p=0.02).
Novick 1998 (Ref 284)	Observational (retrospective cohort) study Multicenter	N = 230 Lung tx recipients who underwent re-transplantation	Intervention: Re-transplantation of the lung due to BOS. Control: Re-transplantation of the lung for reasons other than BOS.	Reasons for re-transplantation included the following: BOS (63%), acute graft failure (23%), intractable airway complications (6%), severe acute rejection (4%), and miscellaneous reasons (4%). Among lung tx recipients who underwent re-transplantation for any reason, freedom from BOS was 81% at 1 year, 62% at 3 years, and 50% at 5 years. Among lung tx recipients who underwent re-transplantation for any reason, the prevalence of BOS Stage 3 (severe) was 12% at 1 year, 24% at 3 years, and 27% at 5 years. Patients undergoing re-transplantation due to BOS had a significant decrease in FEV1 at 2 years (p=0.04) and 3 years (p=0.01) compared with patients undergoing re-transplantation due to other indications.
Brugiere 2003 (Ref 179)	Case series Single center	N = 15 Lung tx recipients who	Intervention: Re-transplantation of the lung. Control: None (case series).	Median duration between primary lung tx and re-transplantation was 31 months (12 to 39 months). Median duration of follow-up was 49.5 months (range, 16.5 to 105 months). Five of the patients were followed for >5 years.

		underwent re-transplantation for BOS		Freedom from BOS was 90% at 1 year, 72% at 3 years, and 66% at 5 years.
Strueber 2006 (Ref 280)	Observational (retrospective cohort) study Single center	N = 54 Lung tx recipients who underwent re-transplantation for BOS	Intervention: Re-transplantation of the lung due to BOS. Control: Primary lung transplantation.	BOS incidence following re-transplantation for BOS was similar to that following primary LTX (p=0.09). In both groups, freedom from BOS was roughly 70% at 2 years and 50% at 4 years.
Aigner 2008 (Ref 281)	Case series Single center	N = 46 Lung tx or Heart-lung tx recipients who underwent lung re-transplantation	Intervention: Re-transplantation of the lung. Control: None (case series).	Reasons for re-transplantation included the following: primary graft dysfunction (50%), BOS (41%), and intractable airway problems (9%). Mean duration between primary lung tx (or heart-lung tx) and re-transplantation was 26 ± 27 days in the primary graft dysfunction group, 1069 ± 757 days in the BOS group, and 220 ± 321 days in the intractable airway problems group. Freedom from BOS after re-transplantation for BOS was 85% at 1 year, 77% at 3 years, and 77% at 5 years.
Osaki 2008 (Ref 282)	Case series Single center	N = 17 Lung tx or Heart-lung tx recipients who underwent lung re-transplantation	Intervention: Re-transplantation of the lung. Control: None (case series).	Reasons for re-transplantation included the following: BOS (71%), primary graft failure (24%), and severe dehiscence of the bronchial anastomosis (6%). Median duration between primary lung tx and re-transplantation was 269 days (range 4 to 4978 days). Freedom from BOS for all patients undergoing re-transplantation (N=17): 84 ± 20% at 1 year, 72 ± 22% at 2 years, and 48 ± 43% at 5 years. Freedom from BOS for patients undergoing re-transplantation due to BOS (N=12): 90 ± 19% at 1 year, 75 ± 21% at 2 years, and 50 ± 45% at 5 years.

				Freedom from BOS for patients undergoing re-transplantation due to acute graft failure (N=5): 67% at 1 year.
Kawut 2008 (Ref 285)	Observational (retrospective cohort) study Multicenter	N = 6,046 Primary lung tx recipients (N=5,657) Modern era re-transplantation recipients (N=205) Historical era re-transplantation recipients (N=184)	Intervention: Lung re-transplantation. Control: Primary lung tx.	Re-transplantation during the modern era was associated with a higher incidence of BOS than primary transplantation: HR 2.0, 95% CI 1.4-1.3, p<0.001). For re-transplantation during the modern era, the cumulative incidence of BOS was 22% at 2 years and 46% at 4 years. For primary transplantation, the cumulative incidence of BOS was 12% at 2 years and 30% at 4 years.
Mortality				
Novick 1996 (Ref 283)	Observational (retrospective cohort) study Multicenter	N = 160 Lung tx recipients who underwent re-transplantation	Numerous comparisons were done, including the following: Intervention: Re-transplantation of the lung due to BOS. Control: Re-transplantation of the lung for reasons other than BOS.	Median follow-up was 780 days. Among all lung tx recipients who underwent re-transplantation for any reason, survival was 45±4% at 1 year, 41±4% at 2 years, and 33±4% at 3 years. Lung tx recipients who develop BOS Stage 3 (severe) within 3 years of re-transplantation have worse survival than those who develop BOS Stage 0, Stage 1, or Stage 2 (p<0.01).
Novick 1998 (Ref 284)	Observational (retrospective cohort) study Multicenter	N = 230 Lung tx recipients who underwent re-transplantation	Numerous comparisons were done, including the following: Intervention: Re-transplantation among ambulatory non-ventilated patients. Control: Re-transplantation among non-ambulatory ventilated patients.	Reasons for re-transplantation included the following: BOS (63%), acute graft failure (23%), intractable airway complications (6%), severe acute rejection (4%), and miscellaneous reasons (4%). Among all lung tx recipients who underwent re-transplantation for any reason, survival was 47% ± 3% at 1 year, 40% ± 3% at 2 years, and 33% ± 4% at 3 years.

				Among ambulatory non-ventilated patients undergoing re-transplantation, survival was 64% ± 5% at 1 year. In comparison, among non-ambulatory ventilated recipients undergoing re-transplantation, survival was 33% ± 4% at 1 year.
Brugiere 2003 (Ref 179)	Case series Single center	N = 15 Lung tx recipients who underwent re-transplantation for BOS	Intervention: Re-transplantation of the lung due to BOS. Control: None (case series).	Median duration between primary lung tx and re-transplantation was 31 months (12 to 39 months). Median duration of follow-up was 49.5 months (range, 16.5 to 105 months). Five of the patients were followed for >5 years. Survival was 60% at 1 year, 53% at 2 years, and 45% at 5 years. Ten patients died during long-term follow-up: six from infection. The retained graft (for those who underwent contralateral re-transplantation) was the site of infection in four of the six fatal infections.
Strueber 2006 (Ref 280)	Observational (retrospective cohort) study Single center	N = 54 Lung tx recipients who underwent re-transplantation for BOS	Intervention: Re-transplantation of the lung due to BOS. Control: Re-transplantation of the lung for reasons other than BOS.	Survival for patients undergoing re-transplantation for BOS was 78% at 1 year and 62% at 2 years. In comparison, survival for patients undergoing re-transplantation for acute graft failure or airway complications was 50% at 1 year.
Aigner 2008 (Ref 281)	Case series Single center	N = 46 Lung tx or Heart-lung tx recipients who underwent lung re-transplantation for BOS	Intervention: Re-transplantation of the lung. Control: None (case series).	Reasons for re-transplantation included the following: primary graft dysfunction (50%), BOS (41%), and intractable airway problems (9%). Mean duration between primary lung tx (or heart-lung tx) and re-transplantation was 26 ± 27 days in the primary graft dysfunction group, 1069 ± 757 days in the BOS group, and 220 ± 321 days in the intractable airway problems group. Among the 19 patients who underwent lung re-transplantation due to BOS, survival was 89% at 30 days, 73% at 1 year, and 61% at 5 years. In contrast, among the 23 patients who underwent lung re-transplantation due to primary graft dysfunction, survival was 52% at 30 days, 35% at 1 year, and 29% at 5 years.

Osaki 2008 (Ref 282)	Case series Single center	N = 17 Lung tx or Heart-lung tx recipients who underwent lung re-transplantation	Intervention: Re-transplantation of the lung. Control: None (case series).	Reasons for re-transplantation included the following: BOS (71%), primary graft failure (24%), and severe dehiscence of the bronchial anastomosis (6%). Median duration between primary lung tx and re-transplantation was 269 days (range 4 to 4978 days). Survival for all patients undergoing re-transplantation (N=17): 59 ± 23% at 1 year, 59 ± 23% at 2 years, and 42 ± 25% at 5 years. Survival for patients undergoing re-transplantation due to BOS (N=12): 67 ± 26% at 1 year, 67 ± 26% at 2 years, and 44 ± 30% at 5 years. In contrast, survival for patients undergoing re-transplantation due to acute graft failure (N=5): 40% at 1 year. Survival for all patients undergoing initial lung tx (N=352): 88 ± 4% at 1 year, 80 ± 4% at 2 years, and 65 ± 5% at 5 years.
Kawut 2008 (Ref 285)	Observational (retrospective cohort) study Multicenter	N = 6,046 Primary lung tx recipients (N=5,657) Modern era re-transplantation recipients (N=205) Historical era re-transplantation recipients (N=184)	Intervention: Lung re-transplantation. Control: Primary lung tx.	During the modern era, re-transplantation was associated with the following survival: 62% (95% CI 53-70%) at 1 year, 49% (95% CI 38-58%) at 3 years, and 45% (95% CI 34-56%) at 5 years. Survival for primary transplantation was better than survival for re-transplantation during the modern era, which was better than survival for re-transplantation during the historical era ($p<0.05$ for all comparisons).
Adverse effects: Perioperative complications other than mortality				
0	-	-	-	-
Adverse effects: Perioperative mortality				

Kawut 2008 (Ref 285)	Observational (retrospective cohort) study Multicenter	N = 6,046 Primary lung tx recipients (N=5,657) Modern era re-transplantation recipients (N=205) Historical era re-transplantation recipients (N=184)	Intervention: Lung re-transplantation. Control: Primary lung tx.	Among patients who underwent re-transplantation, there were 39 deaths within 180 days. The causes of death were infection (n=13), respiratory failure (n=9), and multi-organ system failure (n=8). Patients undergoing re-transplantation during the modern era had an increased risk for death after the procedure compared with patients who underwent primary transplantation (HR 1.3, 95% CI 1.2-1.5, p=0.001). Much of the increased risk can be attributed to renal failure. Patients undergoing re-transplantation during the modern era had a lower risk for death after the procedure than patients who underwent re-transplantation during the historic era (HR 0.7, 95% CI 0.5-0.9, p=0.006). Risk factors for death included a male donor (p=0.04), early re-transplantation (<30 days after the initial tx), and mechanical ventilation at the time of re-transplantation.

Abbreviations: BOS = bronchiolitis obliterans syndrome; FEV1 = Forced expiratory volume in one second; CI = confidence interval; HR = hazard ratio; Tx = transplantation.

Table 8b. Evidence table: Should lung re-transplantation be offered to patients who develop end-stage BOS refractory to other therapies?

--Quality Assessment--							--Summary of Findings--
No. of Studies	**Study Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality of Evidence**	
Lung function							
7	Four observational studies and three case series	Serious[1]	Serious[2]	Serious[3]	Serious[4]	Very low (important outcome)	Freedom from BOS following re-transplantation surgery for BOS was 85-90% at 1 year, 70-77% at 2-3 years, and 50-77% at 4-5 years. Patients who undergo re-transplantation due to BOS had a higher risk of recurrent BOS than patients who underwent re-transplantation due to an alternative etiology. It is uncertain whether patients who underwent re-transplantation due to BOS had a similar or higher risk of recurrent BOS than primary lung tx recipients.[2]
Mortality							
7	Four observational studies and three case series	Serious[1]	No serious inconsistency	Serious[3]	Serious[4]	Very low (critical outcome)	Survival following re-transplantation for BOS was 60-78% at 1 year, 53-64% at 2 years, and 44-61% at 5 years. Survival was higher among patients who underwent re-transplantation for BOS than among patients who underwent re-transplantation for other reasons. In contrast, survival was lower among patients undergoing re-transplantation than primary lung tx.
Adverse effect: Perioperative complications other than mortality							
0	-	-	-	-	-	Very low (important outcome)	
Adverse effect: Perioperative mortality							
1	Observational study	No serious limitations	No serious inconsistency	Serious[3]	No serious imprecision	Very low (critical outcome)	Among 389 patients who underwent re-transplantation, there were 39 deaths within 180 days. The causes of

							death were infection (n=13), respiratory failure (n=9), and multi-organ system failure (n=8). Patients undergoing re-transplantation had an increased risk for death after the procedure compared with patients who underwent primary transplantation (HR 1.3, 95% CI 1.2-1.5, p=0.001).
<u>Overall quality of evidence</u> = very low (derived from the lowest quality of evidence among the critical outcomes).							

Abbreviations: BOS = bronchiolitis obliterans syndrome; CI = confidence interval; HR = hazard ratio; Tx = transplantation.

[1] Limitations: Two of the studies (accounting for 390 patients) may have included many of the same patients.
[2] Inconsistency: For the comparison of re-transplantation due to BOS versus primary lung tx, one study found no difference in the incidence of recurrent BOS, while another study that patients whose re-transplantation was due to BOS were more likely to develop recurrent BOS.
[3]Indirectness: Many of the estimates for freedom from BOS and survival derive from re-transplantation recipients in general, rather than patients who were re-transplanted for BOS.
[4]Imprecision: Three of the four estimates of freedom from BOS and survival were derived from studies that included fewer than 100 patients.