Additional details of study methods [posted as supplied by author]

Details of search strategy

We electronically searched for trials using OVID versions of Medline (1966 to October week 2, 2006), CINAHL (1982 to October week 2, 2006), Embase (1980 to week 42, 2006), and CENTRAL (the Cochrane Central Register of Controlled Trials, 3rd quarter 2006). The Medline search strategy (available from the authors) retrieved citations containing (1) the subject headings *endothelium-dependent relaxing factors* or *nitric oxide* or the text words *endothelium dependent relax: factor:*, *endothelium derived relax: factor:* or *nitric oxide* and (2) the subject headings *respiratory insufficiency* or *respiratory distress syndrome, adult* or *lung transplantation* or the text words *(acute adj lung adj injur:) or (shock adj lung) or ARDS* or *(acute or adult) and (respiratory adj distress)* or *lung transplant:*. Terms were modified as needed for other databases. We excluded the text word *ALI* from the search strategy after pilot testing found no additional citations using this term. Medline citations were limited to randomised controlled trials (RCTs) using a maximally sensitive strategy[w24] that was modified for other databases. We searched conference proceedings (1994-2006) published in *American Journal of Respiratory and Critical Care Medicine*, *Chest*, *Critical Care Medicine* and *Intensive Care Medicine*.

Study selection criteria

We considered subgroups (that met our selection criteria) within other RCTs for inclusion in this meta-analysis because of the *a priori* expectation of a low risk of selective subgroup reporting, given that the narrow therapeutic indications of nitric oxide would limit any subgroup analyses.

Quantitative data synthesis

In studies with two or more groups receiving different doses of nitric oxide, we combined data from all doses to determine an overall effect for the nitric oxide group, since previous investigations have not shown a consistent dose-response relationship for oxygenation variables.[w25-27]

Using the random-effects method, each trial is weighted by the inverse of the variance of its estimate of treatment effect (on the logarithmic scale except for weighted mean difference).[w28] This method adjusts each study's variance in the presence of between-study heterogeneity, and is the more conservative model for our analyses in light of clear differences in study populations, interventions, and outcome measurements.

Trials calculated ventilator-free days up to either day 28 or 30.[w29] We combined these trials because absolute and relative between-group differences in ventilator-free days should be very similar regardless of whether calculated up to day 28 or 30. For physiologic outcomes, we included measurements made within 12 hours of each time of interest.

In the ratio of means method, the ratio of the mean value in the nitric oxide group is divided by the mean value in the control group for each continuous outcome in each study. We aggregated these ratios on a natural logarithm scale, calculating the standard error of each study's estimator.[w30-w31]

When investigators presented physiologic outcomes as absolute changes from baseline,[w5 w14] we calculated the variance of the physiologic outcome by using the method of Follmann and colleagues.[w32] We assumed a moderate correlation (ρ) of 0.4 between baseline measurements and absolute changes in one trial (sensitivity analyses using correlations of 0.0 and 0.8 did not change the results),[w5] but in another trial we were forced to assume ρ=0.84 to avoid undefined values.[w14]
One trial reported the duration of ventilation but assigned patients who died a duration of ventilation of 30 days.[w5] We assumed that all patients who died prior to day 30 were ventilated and derived the mean number of ventilator-free days to 30 days. For another trial we extracted the duration of ventilation from a Kaplan-Meier curve of patients alive and off mechanical ventilation over time.[w7]

We developed several *a priori* hypotheses to explain statistically significant heterogeneity (excluding duration of ventilation and ventilator-free days): (1) greater treatment effect in trials selectively enrolling NO responders (*v* non-responders) and (2) patients with ARDS (*v* all patients with ALI), (3) greater treatment effect with high dose NO *v* low dose NO (the dose separating high from low dose was defined as the weighted mean dose across all trials, with each treatment arm of multi-dose trials counted separately), and (4) for physiologic outcomes, greater treatment effect in trials administering NO until the time point of the physiologic measurement (*v* trials in which NO was discontinued before the outcome measurement).

References to included and excluded trials [posted as supplied by author]

Included studies

w1 Day RW, Allen EM, Witte MK. A randomized, controlled study of the 1-hour and 24-hour effects of inhaled nitric oxide therapy in children with acute hypoxemic respiratory failure. *Chest* 1997; 112:1324-31.
w2 Schwebel C, Beuret P, Perdrix JP, Jospe R, Duperret S, Fogliani J, et al. Early inhaled nitric oxide inhalation in acute lung injury: results of a double-blind randomized study [abstract]. *Intensive Care Med* 1997; 23(Suppl. 1):S2.
w3 Dellinger RP, Zimmerman JL, Taylor RW, Straube RC, Hauser DL, Criner GJ, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. *Crit Care Med* 1998; 26:15-23.
w4 Michael JR, Barton RG, Saffle JR, Mone M, Markewitz BA, Hillier K, et al. Inhaled nitric oxide versus conventional therapy: effect on oxygenation in ARDS. *Am J Respir Crit Care Med* 1998; 157(5 Pt. 1):1372-80.

w5 Troncy E, Collet JP, Shapiro S, Guimond JG, Blair L, Ducruet T, et al. Inhaled nitric oxide in acute respiratory distress syndrome: a pilot randomized controlled study. *Am J Respir Crit Care Med* 1998; 157(5 Pt. 1):1483-88.
w6 Dobyns EL, Cornfield DN, Anas NG, Fortenberry JD, Tasker RC, Lynch A, et al. Multicenter randomized controlled trial of the effects of inhaled nitric oxide therapy on gas exchange in children with acute hypoxemic respiratory failure. *J Pediatr* 1999; 134:406-12.
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w8 Payen D, Vallet B, Group d'étude du NO dans l'ARDS. Results of the French prospective multicentric randomized double-blind placebo-controlled trial on inhaled nitric oxide (NO) in ARDS [abstract]. *Intensive Care Med* 1999; 25(Suppl. 1):S166.
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w10 Gerlach H, Keh D, Semmerow A, Busch T, Lewandowski K, Pappert DM, et al. Dose-response characteristics during long-term inhalation of nitric oxide in patients with severe acute respiratory distress syndrome: a prospective, randomized, controlled study. *Am J Respir Crit Care Med* 2003; 167:1008-15.
w11 Park KJ, Lee YJ, Oh YJ, Lee KS, Sheen SS, Hwang SC. Combined effects of inhaled nitric oxide and a recruitment maneuver in patients with acute respiratory distress syndrome. *Yonsei Med J* 2003; 44:219-26.
w12 Taylor RW, Zimmerman JL, Dellinger RP, Straube RC, Criner GJ, Davis K, Jr., et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. *JAMA* 2004; 291:1603-9.
w13 Groupe d'étude sur le NO inhalé au cours de l'ARDS. Inhaled NO in ARDS: Presentation of a double blind randomized multicentric study [abstract]. *Am J Respir Crit Care Med* 1996; 153(4 Pt. 2):A590.
w14 Dobyns EL, Anas NG, Fortenberry JD, Deshpande J, Cornfield DN, Tasker RC, et al. Interactive effects of high-frequency oscillatory ventilation and inhaled nitric oxide in acute hypoxemic respiratory failure in pediatrics. *Crit Care Med* 2002; 30:2425-9.

Excluded studies

w15 Andalkar L, Spiegler P. Low-dose inhaled nitric oxide in patients with acute lung injury. *Clinical Pulmonary Medicine* 2004; 11:261-2.
w16 Hinohara H, Kadoi Y, Isa Y, Kunimoto F, Ohki S, Saito S, et al. In patients with adult respiratory distress syndrome, initial responders to inhaled nitric oxide did not show better outcome than nonresponders. *Journal of Anesthesia* 2003; 17:270-3.
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w18 Sindjelic R, Vlajkovic G, Ristic M, Divac I, Markovic D. Role of nitric oxide in treatment of acute lung injury after surgery with extracorporeal circulation. *Acta Chir Iugosl* 2003; 50:49-54.

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w21 Perrin G, Roch A, Michelet P, Reynaud-Gaubert M, Thomas P, Doddoli C, et al. Inhaled nitric oxide does not prevent pulmonary edema after lung transplantation measured by lung water content: a randomized clinical study. *Chest* 2006; 129:1024-30.
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w23 Cuthbertson BH, Galley HF, Webster NR. Effect of inhaled nitric oxide on key mediators of the inflammatory response in patients with acute lung injury. *Crit Care Med* 2000; 28:1736-41.

Search strategy references

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w29 Schoenfeld DA, Bernard GR, ARDS Network. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med* 2002; 30:1772-7.
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w32 Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol* 1992; 45:769-73.