ClinicalEvidence

Acute respiratory distress syndrome

Search date December 2009

Sat Sharma

ABSTRACT

INTRODUCTION: Acute respiratory distress syndrome (ARDS) is characterised by a profound deterioration in systemic oxygenation or ventilation, or both, despite supportive respiratory therapy. ARDS is an acute and progressive respiratory disease of a non-cardiac cause that is associated with progressively diffuse bilateral pulmonary infiltrates, reduced pulmonary compliance, and hypoxaemia. The main causes of ARDS include direct lung injury (e.g., pneumonia, gastric acid aspiration) or indirect lung injury (e.g., sepsis, pancreatitis, massive blood transfusion, non-thoracic trauma). Sepsis and pneumonia account for about 60% of cases. Between one third and one half of people with ARDS die from the disease, but mortality depends on the underlying cause. Some survivors have long-term respiratory or cognitive problems. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of interventions in adults with acute respiratory distress syndrome? We searched: Medline, Embase, The Cochrane Library, and other important databases up to December 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 20 systematic reviews, RCTs, or observational studies that met our inclusion criteria. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: corticosteroids, low tidal-volume mechanical ventilation, nitric oxide, prone position, and protective ventilation.

QUESTIONS

INTERVENTIONS

EFFECTS OF INTERVENTIONS IN ADULTS WITH ARDS

Beneficial

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

Unlikely to be beneficial

Key points

- Acute respiratory distress syndrome (ARDS) is a syndrome of inflammation and increased permeability that is associated with clinical, radiological, and physiological abnormalities, which usually develops over 4 to 48 hours and persists for days or weeks. Pathologically, ARDS is associated with complex changes in the lungs, manifested by an early exudative phase and followed by proliferative and fibrotic phases.

  The main causes of ARDS are infections, aspiration of gastric contents, and trauma.

  Between one third and one half of people with ARDS die, but mortality depends on the underlying cause. Some survivors have long-term respiratory or cognitive problems.

  The treatment of ARDS is supportive care, including optimised mechanical ventilation, nutritional support, manipulation of fluid balance, source control and treatment of sepsis, and prevention of intervening medical complications.

- Low tidal-volume ventilation, at 6 mL/kg of predicted body weight, reduces mortality compared with high tidal-volume ventilation, but can lead to respiratory acidosis.

  Positive end expiratory pressure (PEEP) that maintains PaO_2 above 60 mmHg is considered effective in people with ARDS, but no difference in mortality has been found for high PEEP compared with lower PEEP strategies.

- People with ARDS may remain hypoxic despite mechanical ventilation. Nursing in the prone position may improve oxygenation but it has not been shown to reduce mortality, and it can increase adverse effects such as pressure ulcers.

  The prone position is contraindicated in people with spinal instability and should be used with caution in people with haemodynamic and cardiac instability, or in people who have had recent thoracic or abdominal surgery.

- We found insufficient evidence to draw reliable conclusions on the effects of corticosteroids on mortality or reversal of ARDS.

- Nitric oxide has not been shown to improve survival or duration of ventilation, or hospital stay, compared with placebo. It may modestly improve oxygenation in the short term but the improvement is not sustained.

DEFINITION

Acute respiratory distress syndrome (ARDS) is a syndrome of inflammation and increased permeability that is associated with clinical, radiological, and physiological abnormalities, which usually develops over 4 to 48 hours and persists for days or weeks. Pathologically, ARDS is associated with complex changes in the lung, manifested by an early exudative phase and followed by proliferative and fibrotic phases. ARDS, originally described by Ashbaugh et al in 1967, is a clinical syndrome that represents the severe end of the spectrum of acute lung injury (ALI). [1] In 1994, the American–European Consensus Conference on ARDS recommended the following definitions. Widespread acceptance of these definitions by clinicians and researchers has improved standardisation of clinical research. **Acute lung injury:** a syndrome of acute and persistent inflammatory disease of the lungs characterised by three clinical features: 1) bilateral pulmonary infiltrates on the chest radiograph; 2) a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) of <300; 3) absence of clinical evidence of left atrial hypertension (if measured, the pulmonary capillary wedge pressure is no more than 18 mmHg). [2] **Acute respiratory distress syndrome:** The definition of ARDS is the same as that of ALI, except that the hypoxia is severe, a PaO_2/FiO_2 ratio of 200 mmHg or less. [2] The distinction between ALI and ARDS is arbitrary, because the severity of hypoxia does not correlate reliably with the extent of the underlying pathology, and does not influence predictably clinical course or survival. ARDS is an acute disorder. Other sub-acute or chronic lung diseases, such as sarcoidosis and idiopathic pulmonary fibrosis, are excluded from the definition of ARDS. The early pathological features of ARDS are generally described as diffuse alveolar damage. Recognition of diffuse alveolar damage requires histological examination of the lung tissue, which is not necessary to make a clinical diagnosis. **Population:** For the purpose of this review, we have defined ARDS as including people with ALI and ARDS. It therefore includes adults with ALI and ARDS from any cause and with any level of severity. Neonates and children <12 years of age have been excluded.

INCIDENCE/ PREVALENCE

Between 10% and 15% of all people admitted to an intensive care unit, and up to 20% of mechanically ventilated people, meet the criteria for ARDS. [3] The incidence of ALI in the USA (17–64/100,000 person-years) seems higher than in Europe, Australia, and other developed countries (17–34/100,000 person-years). [4] One prospective, population-based cohort study (1113 people in Washington State, aged >15 years) found the crude incidence of ALI to be 78.9/100,000 person-years, and the age-adjusted incidence to be 86.2/100,000 person-years. [5] An annual national incidence of 15.5 cases per year or 5.9 cases/100,000 people per year was reported in one epidemiological study from Iceland. [6] An observational cohort reported that, in Shanghai, China, of 5320 adults admitted to intensive care units in 1 year, 108 (2%) had clinical features that met with ARDS criteria. [7]

AETIOLOGY/ RISK FACTORS

ARDS encompasses many distinct disorders that share common clinical and pathophysiological features. More than 60 causes of ARDS have been identified. Although the list of possible causes is long, most episodes of ARDS are associated with a few common causes or predisposing conditions, either individually or in combination. These include sepsis, aspiration of gastric contents, infectious pneumonia, severe trauma, surface burns, lung contusion, fat embolism syndrome, massive blood transfusion, lung and bone marrow transplantation, drugs, acute pancreatitis, near drowning, cardiopulmonary bypass, and neurogenic pulmonary oedema. [8] [9] Sepsis and pneumonia account for about 60% of cases. The incidence of ALI in a large cohort of people with subarachnoid haemorrhage has been reported to be 27% (170/620 people; 95% CI 24% to 31%). [10] One or more of these predisposing conditions are often evident at the onset of ALI. When ARDS occurs in the absence of common risk factors such as trauma, pneumonia, sepsis, or aspiration, an effort should be made to identify a specific cause for lung injury. In such cases, a systematic review of the events that immediately preceded the onset of ARDS is normally undertaken to identify the predisposing factors.

PROGNOSIS

Mortality: Survival for people with ARDS has improved remarkably in recent years, and cohort studies have found mortality to range from 34% to 58%. [4] [10] [11] [12] In an Icelandic study, hospital mortality was 40%, mean length of ICU stay was 21 days, and mean length of hospital stay was 39 days. [6] Mortality varies with the cause; however, by far the most common cause of death is multiorgan system failure rather than acute respiratory failure. In a prospective cohort study (207 people at risk of developing ARDS, of which 47 developed ARDS during the trial), only 16% of deaths were considered to have been caused by irreversible respiratory failure. Most deaths in the first 3 days of being diagnosed with ARDS could be attributed to the underlying illness or injury. Most late deaths (after 3 days, 16/22 [72.7%]) were related to the sepsis syndrome. [13] One prospective cohort study (902 mechanically ventilated people with ALI) found that an age of 70 years or younger significantly increased the proportion of people who survived at 28 days (74.6% aged up to 70 years *v* 50.3% aged at least 71 years or older; P <0.001). [14] In one observational study (2004), the overall intensive care unit mortality was 10.3%. In-hospital mortality was 68.5%, and 90-day mortality was 70.4% in people with ARDS, and accounted for 13.5% of the overall in-

tensive care unit mortality. [7] **Lung function and morbidity:** One cohort study of 16 long-term survivors of severe ARDS (lung injury score at least 2.5) found that only mild abnormalities in pulmonary function (and often none) were observed. Restrictive and obstructive ventilatory defects (each noted in 4/16 [25%] people) were observed in ARDS survivors treated with low or conventional tidal volumes. [15] One cohort study of 109 people found no significant difference between various ventilatory strategies and long-term abnormalities in pulmonary function or health-related quality of life. However, it did find an association between abnormal pulmonary function and decreased quality of life at 1-year follow-up. [16] One retrospective cohort study (41 people with ARDS) found that duration of mechanical ventilation and severity of ARDS were important determinants of persistent symptoms 1 year after recovery. [17] Better lung function was observed when no subsequent illness was acquired during the intensive care unit stay, and with rapid resolution of multiple organ failure (e.g., pneumonia during ARDS: 7/41 [17.1%] people with long-term impairment *v* 2/41 [4.9%] with no long-term impairment; significance assessment not performed). [17] Persistent disability 1 year after discharge from the intensive care unit in survivors of ARDS is secondary to extrapulmonary conditions, most importantly muscle wasting and weakness. [16] **Cognitive morbidity:** One cohort study (55 people 1 year after ARDS) found that 17/55 (30.1%) exhibited generalised cognitive decline and 43/55 (78.2%) had all, or at least one, of the following: impaired memory, attention, or concentration, and decreased mental processing speed. These deficits may be related to hypoxaemia, drug toxicity, or complications of critical illness. [18] To date, no association between different ventilatory strategies and long-term neurological outcomes has been found.

AIMS OF INTERVENTION

Goals of treatment of people with ARDS are identification and treatment of the underlying clinical disorder and optimal supportive care. In many people with ARDS, the insult that caused lung injury, such as aspiration or multiple transfusions, cannot be treated except to prevent recurrences. Supportive care consists of appropriate ventilator management, and prevention of infections, multiorgan failure, and complications of critical care.

OUTCOMES

Mortality; length of intensive care unit and hospital stay; ventilation (duration of ventilation and ventilator-free days [defined as days alive and free from mechanical ventilation]); **adverse events** associated with mechanical ventilation (barotrauma, haemodynamic dysfunction) or with low tidal-volume ventilation (severe acidosis, central nervous system dysfunction); **quality of life/functional outcomes** (people discharged home or to an institution, or measured using validated methods such as health-related quality of life or the Medical Outcome Study 36-Item Short Form Health Survey); other **adverse events**. We have only reported clinical outcomes in the benefits section of this review. However, some RCTs also reported oxygenation as an outcome. Where they have done so, we have reported this in the comments section as background data.

METHODS

Clinical Evidence search and appraisal December 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to December 2009, Embase 1980 to December 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews, RCTs, prospective clinical trials with a control group (non-randomised), case control studies, and prospective and retrospective comparative cohort studies in any language. Studies had to contain 20 or more individuals, and for RCTs 80% or more of these had to be followed up. There was no minimum length of follow-up required to include studies. Open and blinded studies were included. Lower-quality evidence was only included in the review when RCT evidence was found to be unavailable for the outcomes of interest. Studies where the outcomes did not include any from the above list were excluded. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 17). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes

reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of interventions in adults with acute respiratory distress syndrome?**

OPTION **LOW TIDAL-VOLUME MECHANICAL VENTILATION**

Mortality

Low tidal volume compared with conventional or high tidal-volume mechanical ventilation Low tidal-volume ventilation seems to be more effective than conventional or high tidal-volume mechanical ventilation at reducing mortality at 28 days in adults with ARDS/ALI, but we don't know whether it is more effective at reducing mortality in the longer term (moderate-quality evidence).

Ventilation

Low tidal-volume compared with conventional or high tidal-volume mechanical ventilation We don't know whether low tidal-volume and conventional or high tidal-volume differ in effectiveness in reducing the duration of ventilation in adults with ARDS/ALI (moderate-quality evidence).

For GRADE evaluation of interventions for ARDS, see table, p 17 .

Benefits:

Low tidal-volume versus conventional or high tidal-volume mechanical ventilation:

We found three systematic reviews [19] [20] [21] and one observational study [22] comparing the effects of low tidal-volume mechanical ventilation versus high tidal-volume mechanical ventilation in acute respiratory distress syndrome (ARDS). The first systematic review (search date 2006) defined low tidal-volume mechanical ventilation as a tidal volume of 7 mL/kg or less, and conventional tidal-volume mechanical ventilation as a tidal volume in the range of 10 to 15 mL/kg ideal body weight. The review included six RCTs in critically ill adults with ARDS or acute lung injury (ALI). The review reported that the delivery of interventions varied among RCTs, tidal volume was calculated differently among RCTs, and plateau pressures varied between studies. The review found that, compared with conventional tidal-volume mechanical ventilation, low tidal-volume mechanical ventilation significantly reduced mortality at 28 days and also reduced mortality at the end of follow-up for each RCT, but the reduction was not statistically significant at the end of the follow-up period (critically ill people aged at least 16 years with ALI or ARDS: mortality at 28 days: 3 RCTs, 1030 people; 142/519 [27%] with low tidal volume *v* 189/511 [37%] with conventional tidal volume; RR 0.74, 95% CI 0.61 to 0.88; P = 0.0008; absolute risk difference –10%, 95% CI –4% to –15%; mortality at end-of-trial follow-up: 6 RCTs, 1297 people; 233/655 [36%] with low tidal volume *v* 274/642 [43%] with conventional tidal volume; RR 0.86, 95% CI 0.69 to 1.06 [random-effects model]; absolute risk difference –6%, 95% CI –16% to +3%). However, with regard to mortality at end-of-trial follow-up, RCTs measured this at different durations (3 RCTs measured in-hospital mortality, 1 RCT each at 28 days, 60 days, and 180 days) and the result was significant if a fixed-effects model was used (RR 0.83, 95% CI 0.72 to 0.95). It is difficult to interpret these combined results on mortality because of the differences between included trials in clinical parameters, such as different lengths of follow-up and relatively higher plateau pressures in the control arms in some of the included trials. The review conducted a subgroup analysis comparing the effects of different plateau pressures. It found that overall mortality was significantly lower with low tidal volume when a higher plateau pressure (mean pressure >31 cm H_2O) was applied in the control arm (3 RCTs, 1009 people; 163/511 [32%] with low tidal volume *v* 212/498 [43%] with conventional tidal volume; RR 0.74, 95% CI 0.63 to 0.87). It was not significantly lower when a lower plateau pressure (mean pressure 31 cm H_2O or less) was used in the control arm (3 RCTs, 288 people; 70/144 [49%] with low tidal volume *v* 62/144 [43%] with conventional tidal volume; RR 1.13, 95% CI 0.88 to 1.45). [19]

The review found no significant difference between groups in duration of mechanical ventilation (3 RCTs, 288 people; WMD –0.83 days, 95% CI –1.92 days to +0.27 days). [19]

The second systematic review (search date 2006, 5 controlled trials, 1202 people with ALI or ARDS) compared protective ventilation versus control on 28-day mortality. [20] The review found that protective ventilation significantly improved mortality at 28 days compared with control ventilation (OR 0.71, 95% CI 0.56 to 0.91; P = 0.006; absolute figures not reported). [20]

The third systematic review (search date 2006, 7 trials, 1435 people) evaluated whether low ventilation reduced mortality in ARDS. [21] The review found that low tidal-volume ventilation significantly improved mortality compared with traditional ventilation (36% with low tidal-volume ventilation *v* 43% with traditional ventilation; OR 0.75, 95% CI 0.61 to 0.93; P <0.01). [21]

The observational study (3147 people admitted to 1 of the included 198 European intensive care units) evaluated the use of higher tidal volumes than those applied in the ARDS Network (ARDSnet) study (>7.4 mL/kg of predicted body weight). [22] The review found that use of tidal volumes higher than those used by the ARDSnet study was an independent risk factor for mortality. [22]

Harms:

Low tidal-volume versus conventional or high tidal-volume mechanical ventilation:
The three reviews [19] [20] [21] and observational study [22] gave no information on adverse effects. One RCT identified by the reviews found no significant difference between lower and higher tidal volumes in barotrauma between days 1 and 28 (10% with lower tidal volumes *v* 11% with higher tidal volumes; P = 0.43). It acknowledged that pneumothorax (the most common manifestation of barotrauma) is not a sensitive or specific marker of stretch-induced injury with the tidal volumes used in the study. [23] The RCT also excluded people with elevated intracranial pressure and with sickle cell haemoglobin, because hypercapnia and acidosis could have adverse effects in these conditions. A slightly lower level of oxygenation was observed in the low tidal-volume group over the first few days; however, participants did not develop significant degrees of hypercapnia, and did not require excessive neuromuscular paralysis.

Another RCT identified by the reviews found that, compared with high tidal-volume ventilation, low tidal-volume ventilation increased the requirement for paralytic agents and dialysis for renal failure (paralytic agents: 23/60 [38%] with low tidal volume *v* 13/60 [22%] with high tidal volume; P = 0.05; dialysis for renal failure: 13/60 [22%] with low tidal volume *v* 5/60 [8%] with high tidal volume; P = 0.04). [24] The RCT also found that, compared with high tidal-volume ventilation, low tidal-volume ventilation significantly increased the proportion of people with permissive hypercapnia, as well as its severity and length of duration (permissive hypercapnia defined as an arterial carbon dioxide tension >50 mmHg: 31/62 [50%] with low tidal-volume ventilation *v* 17/60 [28%] with high tidal-volume ventilation; P = 0.009; mean $PaCO_2$: 54.4 mmHg with low tidal-volume ventilation *v* 45.7 mmHg with high tidal-volume ventilation; P = 0.002; mean length of hypercapnia: 146 hours with low tidal-volume ventilation *v* 25 hours with high tidal-volume ventilation; P = 0.017). [24]

One retrospective study (111 people) examined the effects of mechanical ventilation with a tidal volume of 6 mL/kg compared with 12-mL/kg predicted body weight on haemodynamics, vasopressor use, fluid balance, diuretics, sedation, and neuromuscular blockade within 48 hours in people with ALI/ARDS. Compared with 12-mL/kg predicted body weight, treatment with a tidal volume of 6-mL/kg predicted body weight had no adverse effects on haemodynamics. There were also no differences in the need for supportive treatments, including vasopressor drugs, intravenous fluids, or diuretic drugs. In the 12-mL/kg tidal-volume group, 44% of people received dopamine and 17% received phenylephrine (P = 0.84); whereas, in the 6-mL/kg tidal-volume group, 47% were treated with dopamine and 9% with phenylephrine (P = 0.38). In addition, there were no differences in body weight, urine output, or fluid balance. Finally, there was no difference in the need for sedation or neuromuscular blockade between the two tidal-volume protocols. On day 1, 16% of the 12-mL/kg group required neuromuscular blockade compared with 7% of the 6-mL/kg group (P = 0.22). On day 2, 13% of the 12-mL/kg group required neuromuscular blockade compared with 4% of the 6-mL/kg group (P = 0.15). [25]

A secondary analysis of one RCT (61 people with ALI) compared the doses and duration of sedatives and opioid analgesics in people receiving low versus traditional tidal volumes. In 33 people randomised to the lower tidal-volume arm (6 mL/kg of predicted body weight) and 28 people randomised to the higher tidal-volume arm (12 mL/kg of predicted body weight), there were no significant differences in the percentage of study days people received sedatives, opioids, or neuromuscular blockade. People received neuromuscular blockade an average of 5% of study days in the lower tidal-volume group compared with 13% of study days in the higher tidal-volume group (difference –8%, 95% CI –20% to +3%; P = 0.16). Furthermore, there were no significant differences in the proportion of people receiving benzodiazepines, propofol, haloperidol, and opioids on days 1, 2, 3, and 7 of mechanical ventilation. There were no differences in the doses of benzodiazepines and opioids on those days. Sedatives were used (including benzodiazepines and propofol) an average of 81% of study days in the lower tidal-volume group and 92% of study days in the higher tidal-volume group (difference –11%, 95% CI –24% to +3%; P = 0.13). Likewise, opioid analgesia was used an average of 85% of study days in the lower tidal-volume group compared with 83% of study days in the higher tidal-volume group (difference +2%, 95% CI –14% to +18%; P = 0.85). [26]

Comment:

ARDS is associated with some lung regions marked by decreased respiratory system compliance caused by atelectasis, alveolar flooding, and increased surface tension at air–fluid interfaces. Other lung regions will have normal compliance and aeration, and several other regions are intermediate where alveolar collapse and flooding can be reversed. Traditional approaches to mechanical ventilation have involved the use of tidal volumes of 10 to 15 mL/kg body weight. [27] These high tidal volumes of 10 to 15 mL/kg result in elevated airway pressures and overdistention of the normal and less-affected lung regions, which exacerbate or perpetuate the lung injury. Ventilation

with small tidal volumes and limited airway pressures can reduce ventilator-associated lung injury from overdistention. In a person with ALI/ARDS requiring mechanical ventilation, the goal must be to provide adequate oxygenation without engendering morbidity from oxygen toxicity, haemodynamic compromise, barotrauma, and alveolar overdistention. Large tidal volumes are also known to cause stretch-induced lung injury and release of inflammatory mediators, and to perpetuate the cycle of inflammation and injury in people with ALI and ARDS. [28] [29] Unfortunately, despite published evidence supporting ventilation with low tidal volumes, such ventilatory strategy remains underutilised. One observational cohort study (88 people with ARDS) found that 39% had ventilation with tidal volumes of 7.5 mL/kg predicted body weight or less on day 2, 49% on day 4, and 56% on day 7. In contrast, 49% of people had ventilation with tidal volumes of more than 8.5 mL/kg predicted body weight on day 2 of ARDS, 30% on day 4, and 24% on day 7. The use of low tidal volumes was significantly associated with clinical parameters indicative of worse disease severity compared with other tidal volumes, including low values for arterial oxygen tension (PaO_2; P = 0.01), ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2; P = 0.08), and static compliance of the respiratory system (P = 0.006). [30]

ARDS due to Influenza A - pH1N1:

In March of 2009, a novel H1N1 strain of swine origin emerged in Mexico that quickly spread to the USA and Canada, and then to the rest of the world, triggering the first pandemic of this century. Although characterised by relatively mild clinical outcomes in the vast majority, for reasons not yet understood, the infection in a small segment of population (in particular aboriginals, pregnant women, obese individuals, and adults <50 years of age) led to severe respiratory illness (SRI), necessitating hospitalisation and mechanical ventilation. A case series of the first 18 people hospitalised in Mexico City documented the clinical findings of severe illness or death associated with pH1N1. [31] The patients, most of them previously healthy, had an influenza-like illness that progressed during a period of 5 to 7 days, had pneumonia, and had findings during the first day of hospital admission that fulfilled the criteria of ALI or ARDS. Seven people died, all from multiorgan system failure. Mortality among people requiring mechanical ventilation was 58%, and although four patients had nosocomial pneumonia, in most of the patients, lung damage was most likely due to the primary effect of infection with influenza virus. Possible mechanisms of damage include direct injury to the respiratory epithelium with a secondary cytokine storm.

Treatment of pH1N1-associated ARDS is similar to other causes of ARDS, oxygenation can be supported in most of these people using increased inspired oxygen concentrations (FiO_2) or higher levels of positive end expiratory pressure (PEEP). Occasionally, however, as increasing reports from institutions around the world indicate, some of these patients are developing "critical hypoxaemia", whereby arterial oxygen tensions cannot be maintained at adequate levels with basic techniques, and alternative strategies become necessary. Several "salvage" ventilatory techniques can be used in people with critical hypoxaemia. [32] These strategies should only be considered when there is impaired oxygenation and concurrent evidence of clinical instability or untoward effects of hypoxaemia (e.g., myocardial ischaemia, multiorgan dysfunction).

Salvage therapies that have been employed include: *inhaled pulmonary vasodilators* (administration of nitric oxide or prostacycline by the inhalational route); *recruitment manoeuvres* (increased transpulmonary pressure is applied to the airways for short periods using one of several different techniques in an effort to decrease atelectasis, improve gas exchange, and limit ventilator-induced lung injury); *alternative modes of mechanical ventilation* (consideration can be given to using less commonly used modes of mechanical ventilation including pressure control–inverse ratio ventilation [PC-IRV], airway pressure release ventilation [APRV], and high-frequency oscillatory or jet ventilation [HFOV and HFJV]); *neuromuscular blocking agents* (people can be paralysed in an effort to eliminate muscle activity, patient–ventilator dysynchrony, or patient-triggered breaths that could be contributing to increased oxygen demand or inadequate ventilation); *extracorporeal membrane oxygenation* (more commonly used in neonatology and paediatrics, this strategy utilises a technique similar to that used in cardiopulmonary bypass surgery and handles gas exchange in an extracorporeal manner). However, we have not performed a systematic search on any of these techniques and so cannot comment on how effective, or not, any of these procedures may be.

Clinical guide:

There is strong evidence of benefit of mechanical ventilation utilising a low tidal volume. The ARDS Network trial recommended mechanical ventilation at 6 mL/kg ideal body weight in those with ALI/ARDS. [23] The response to low tidal-volume ventilation should be assessed initially on the basis of plateau airway pressure. The goal should be to maintain a plateau airway pressure of 30 cm of water or less; if this target is exceeded, the tidal volume should be further reduced to a minimum of 4 mL/kg of predicted body weight. A common consequence of a low tidal-volume ventilatory strategy is development of hypercapnia and respiratory acidosis that is tolerated (permissive hypercapnia). The initial respiratory rate should be set in the range of 18 to 22 breaths a minute. This higher rate is intended to maintain minute ventilation high enough to avoid marked hypercapnia.

As long as adequate oxygenation is achieved, hypercapnia is an acceptable adverse effect of controlled ventilation. The current guidelines suggest maintaining a partial pressure of carbon dioxide of less than 80 mmHg and a pH of more than 7.20. Contraindications to permissive hypercapnia include predisposition to increased cranial pressure (intracerebral bleeding, brain tumour, fulminant hepatic failure) and haemodynamic instability.

OPTION POSITIVE END EXPIRATORY PRESSURE (PEEP)

Mortality
High PEEP compared with low PEEP We don't know whether high PEEP is more effective than low PEEP at reducing mortality in people with ARDS/ALI (very low-quality evidence).

Length of stay
High PEEP compared with low PEEP We don't know whether high PEEP is more effective than low PEEP at increasing ICU-free days in people with ARDS/ALI (low-quality evidence).

Ventilation
High PEEP compared with low PEEP We don't know whether high PEEP is more effective than low PEEP at increasing ventilator-free days in people with ARDS/ALI (low-quality evidence)

Note
There is consensus that PEEP is effective in people with ARDS.

For GRADE evaluation of interventions for ARDS, see table, p 17 .

Benefits:

High PEEP versus low PEEP:
We found two systematic reviews that studied the effects of high PEEP on survival in people with ARDS. [33] [34] Both reviews examined funnel plots and noted the possibility of publication bias. The first systematic review (search date 2008; 5 RCTs; 2447 people) compared the effects of high versus low PEEP in people with ARDS/ALI. [33] Three included RCTs examined the effects of high versus low PEEP in people receiving low tidal volumes, while two included RCTs compared low tidal volume plus high PEEP versus conventional tidal volume plus low PEEP. Mortality rates from these two RCTs were adjusted before pooling by the review to account for the mortality reduction expected from the use of low tidal volume using various statistical assumptions. The protocols used in the high-PEEP group varied among RCTs, and the review also noted that disease severity varied among RCTs (predicted mortality in RCTs ranged from 37% to 72%). The review found that high PEEP significantly reduced hospital mortality compared with low PEEP (5 RCTs; 408/1215 [34%] with high *v* 464/1232 [38%] with low; RR 0.89, 95% CI 0.80 to 0.99; P = 0.03). [33] The review found lower 28-day mortality with high PEEP, but differences between groups did not reach significance (3 RCTs; 253/889 [28%] with high *v* 296/914 [32%] with low; RR 0.88, 95% CI 0.76 to 1.01; P = 0.06). The clinical heterogeneities make proper interpretation of the results difficult. The review reported that differences in PEEP protocols were not associated with differences in mortality. A logistic analysis suggested that the beneficial effect of high PEEP was greater in people with higher ICU severity scores (results presented graphically). The review found no significant difference between high and low PEEP in ventilator-free days, ICU-free days, or organ failure-free days (ventilator-free days: 4 RCTs, 2394 people; WMD +1.5 days, 95% CI –0.72 days to +3.74 days; ICU-free days: 2 RCTs, 1532 people; WMD +0.04 days, 95% CI –1.03 days to +1.10 days; organ failure-free days: 2 RCTs, 1317 people; WMD +2.01 days, 95% CI –1.91 days to +5.93 days). [33]

The second systematic review (search date 2008; 6 RCTs, 2484 people from 102 intensive care units and 9 countries) compared the effect of different levels of PEEP in groups receiving comparable tidal volumes. [34] It included five RCTs included in the first review and one additional RCT. The review reported that three RCTs accounted for >85% of total weighting in the meta-analyses. Five RCTs reported in-hospital mortality and one RCT reported 28-day mortality. Overall, the review found that high PEEP significantly reduced mortality compared with low PEEP (6 RCTs, results presented graphically; RR 0.87, 95% CI 0.78 to 0.96; P = 0.07; absolute numbers not reported). However, these data included three RCTs that had also used lower tidal volumes in higher-PEEP groups in keeping with a protective ventilatory strategy. The review did a further analysis of the three large RCTs that had similar tidal volumes in each arm to determine the effect of PEEP alone, as the effect of tidal volume could be an important confounding factor. In this analysis, the review found no significant difference between groups in in-hospital mortality, although mortality was lower with high PEEP (3 RCTs, results presented graphically; RR 0.90, CI 0.81 to 1.01; P = 0.077; absolute numbers not reported). [34]

Harms:

High PEEP versus low PEEP:
The first review found no significant difference between high and low PEEP in barotrauma (113/1215 [9.3%] with high *v* 110/1232 [8.9%] with low; OR 1.19, 95% CI 0.89 to 1.58). [33] The second review

found no significant difference in barotrauma between groups (5 RCTs, results presented graphically; RR 0.95, 95% CI 0.62 to 1.45; P = 0.81). [34] An analysis restricted to three larger RCTs excluding two smaller studies with wide confidence intervals also found no significant difference between groups, although visual inspection of the forest plot indicated a possible trend towards increased risk with high PEEP (3 RCTs, results presented graphically; RR 1.17, 95% CI 0.90 to 1.52; P = 0.25).

Comment:

PEEP allows lungs to remain partially open during exhalation so that the next breath is not starting from total collapse in a non-compliant lung. There is consensus that PEEP is effective in people with ARDS. Ideal PEEP will help achieve adequate oxygenation and reduce the requirement for high fractions of inspiratory oxygen without causing any of the harmful effects of PEEP. However, the level of PEEP needed to confer maximum benefit with minimum complications has only recently been studied. In the ARDS Network trial, [35] higher PEEP produced better oxygenation and lung compliance, but no benefit to survival, time on ventilator, or non-pulmonary organ dysfunction. Although sufficient PEEP is essential in ventilation management of people with ARDS, this level varies from person to person. One included RCT found that a ventilatory strategy based on PEEP above the lower inflection point of the pressure volume curve of the respiratory system (Pflex) set on day 1 with a low tidal volume has resulted in a beneficial impact on outcome in patients with severe and persistent ARDS. [36] The evidence is emerging that the PEEP level sufficient to keep lungs above the lower inflection point of the pressure volume curve of the respiratory system (Pflex), that is, open lung strategy, is beneficial.

Clinical guide:

Management guidelines for mechanical ventilation in sepsis-induced ARDS/ALI have been formulated under the auspices of the Surviving Sepsis Campaign, an international effort to increase awareness and improve outcome in severe sepsis. [37] A minimum amount of PEEP should be set to prevent lung collapse at end expiration, and may be guided by FiO_2 requirement or measurement of thoracopulmonary compliance. The ARDS Network trial found no survival advantage in using higher PEEP levels independently of the tidal-volume strategy. [35] High levels of PEEP may also lead to overdistention, barotrauma, decreased venous return, and impaired oxygen delivery. After institution of low tidal-volume mechanical ventilation (6 mL/kg), PEEP should be gradually increased to lower FiO_2 to <60% to maintain PaO_2 >60 mmHg. There is no evidence that high levels of PEEP (>10 cm H_2O) can be routinely recommended. However, severely hypoxaemic people may require a higher PEEP to recruit atelectatic alveolar units in order to decrease intrapulmonary shunt. Titrating PEEP to maximise lung compliance (which is monitored) and ensuring that lungs are being ventilated well above the lower inflection point (Pflex) could be tried in people whose survival is threatened because of hypoxaemia. [38]

OPTION PRONE POSITION

Mortality

Prone position compared with supine position We don't know whether prone position is more effective than supine position in reducing mortality in all people with ARDS/ALI on mechanical ventilation. Subgroup analysis in some reviews suggested that prone positioning may be more effective than supine position in reducing mortality in people with the most severe disease; however, evidence was weak and not supported by a subsequent RCT (very low-quality evidence).

Length of stay

Prone position compared with supine position We don't know whether prone position is more effective than supine position in reducing length of stay on ICU in people with ARDS/ALI on mechanical ventilation (very low-quality evidence).

Ventilation

Prone position compared with supine position We don't know whether prone position is more effective than supine position in reducing duration of ventilation or increasing ventilator-free days in people with ARDS/ALI on mechanical ventilation (very low-quality evidence).

Adverse effects

Prone position compared with supine position Prone position may increase the proportion of people with pressure sores compared with supine position in people with ARDS/ALI on mechanical ventilation (very low-quality evidence).

Note

Prone positioning may improve oxygenation in some people with ARDS. Spinal instability is an absolute contraindication to prone positioning. Relative contraindications include haemodynamic and cardiac instability, and recent thoracic or abdominal surgery. Prone position may be associated with an increase in the occurrence of some adverse effects.

For GRADE evaluation of interventions for ARDS, see table, p 17 .

Benefits:

Prone position versus supine position:

We found three systematic reviews which pooled data, each of which had different inclusion criteria and performed slightly different analysis. [39] [40] [41] We found two subsequent RCTs. [42] [43]

The first review (search date 2007; 4 RCTs) compared prone position versus supine in adults receiving mechanical ventilation with ARDS/ALI. [39] Jadad score was 3 in three RCTs and 2 in the remaining RCT (Jadad score range 0–5). In three RCTs ventilation guidelines were not specified, and in one RCT application of nitric oxide was allowed. The review found no significant difference between prone and supine position in mortality on the ICU (4 RCTs; 245/662 [37%] with prone *v* 230/609 [38%] with supine; OR 0.97, 95% CI 0.77 to 1.22; P = 0.79). In a post hoc subgroup analysis of the most severely ill people, the review found that ICU mortality was significantly lower with ventilation in the prone position compared with the supine position (2 RCTs; 32/105 [30%] with prone *v* 41/83 [49%] with supine; OR 0.34, 95% CI 0.18 to 0.66; P = 0.01). The review noted that this result must be viewed with caution as it included only two RCTs and the definition of severe disease differed between the two included RCTs. The review found no significant difference between prone and supine position in duration of mechanical ventilation or length of stay on ICU (2 RCTs; duration of mechanical ventilation: WMD –1.14 days, 95% CI –2.86 days to +0.59 days; absolute numbers not reported; length of stay on ICU: 20.5 days with prone *v* 19.1 days with supine; P = 0.7).

The second systematic review (search date 2006) included the four RCTs identified by the first review, and one additional RCT. [40] The RCTs compared prone position versus supine position in adult patients on ventilation, and the prone position had to be used for a minimum of 6 hours. The review found no significant difference between groups in mortality while on the ICU, at 28–30 days, or at 90 days (ICU mortality: 3 RCTs, 466 people; OR 0.79, 95% CI 0.45 to 1.39; P = 0.41; mortality at 28–30 days: 3 RCTs, 1231 people; OR 0.95, 95% CI 0.71 to 1.28; P = 0.76; 90-day mortality: 1271 people; OR 0.99, 95% CI 0.77 to 1.27; P = 0.92). However, in a post hoc subgroup analysis in the most severely ill people, the review found that the prone position significantly improved mortality compared with the supine position (Simplified Acute Physiology Score [SAPS] II >50: 2 RCTs; 24/69 [35%] with prone *v* 25/44 [57%] with supine; OR 0.29, 95% CI 0.12 to 0.70; P = 0.006). The second review used different criteria for the most severely ill and extracted different figures than the first review in this post hoc subgroup analysis, but reached similar conclusions to the first review. It noted that one RCT in the analysis reported mortality at 10 days and another at ICU separation, and there were insufficient data to confirm similarity of the subgroups at baseline. The review found no significant difference between groups in the duration of mechanical ventilation (2 RCTs, 833 people; WMD –0.42 days, 95% CI –1.56 days to +0.72 days). [40] The review noted that two older studies used higher tidal volumes than was current practice, and that three RCTs applied prone position for short periods ranging from 7 to 11 hours/day and for up to 10 days, while another RCT used a single 12-hour period of prone ventilation.

The third systematic review (search date 2008; 13 RCTs, 1559 people) reported on the effects of mechanical ventilation in the prone position on mortality, oxygenation, duration of ventilation, and adverse effects in people with acute hypoxaemic respiratory failure (defined as the ratio of partial pressure of oxygen to inspired fraction of oxygen of 300 mmHg or less) including ARDS/ALI (see comment). [41] The review included RCTs in adults and children but did not report results separately (absolute numbers of children not reported). It included two quasi-randomised RCTs (alternate allocation), and also included additional information from the authors of the RCTs. In total, it included the five RCTs identified by the previous reviews and eight additional RCTs. In hypoxaemic people, it found no significant difference between prone and supine position in mortality (10 RCTs, 1486 people; RR 0.96, 95% CI 0.84 to 1.09). The review found no significant difference between groups in duration of ventilation or in ventilator-free days (duration of ventilation: 6 RCTs, 992 people; WMD –0.9 days, 95% CI –1.9 days to +0.1 days; ventilation-free days: WMD 3.7 days, 95% CI –1.8 days to +9.3 days). [41]

The first subsequent unblinded multicentre RCT assessed the possible outcome benefits of prone positioning (20 hours/day) compared with supine position in people with moderate and severe hypoxaemia who were affected by ARDS. [42] It included 342 adults with ARDS receiving mechanical ventilation using a lung protective strategy who were prospectively stratified into subgroups with moderate hypoxaemia (PaO_2:FiO_2 ratio between 100 and 200 mmHg; 192 people [94 prone, 98 supine]) and severe hypoxaemia (PaO_2:FiO_2 ratio <100 mmHg; 150 people [74 prone, 76 supine]). In the overall study population, the RCT found no significant difference between groups in ICU mortality or mortality at 28 days or 6 months (342 people; ICU mortality: RR 0.94, 95% CI 0.79 to 1.12; 28-day mortality: RR 0.97, 95% CI 0.84 to 1.13; 6-month mortality: RR 0.90, 95% CI 0.73 to 1.11). In the subgroup of people with moderate hypoxaemia, the RCT found no significant difference between groups in mortality (192 people: ICU mortality: RR 1.00, 95% CI 0.83 to 1.22; 28-day mortality: RR 1.0, 95% CI 0.89 to 1.22; 6-month mortality: RR 0.98, 95% CI 0.76 to 1.25). In the

subgroup of people with severe hypoxaemia, the RCT found no significant difference between groups in mortality (150 people: ICU mortality: RR 0.83, 95% CI 0.60 to 1.15; 28-day mortality: RR 0.87, 95% CI 0.66 to 1.14; 6-month mortality: RR 0.78, 95% CI 0.53 to 1.14). In the overall group, the RCT found no significant difference between groups in duration of mechanical ventilation (342 people in total; in 28-day survivors: median 25 days with prone *v* 19 days with supine; P = 0.12; in 28-day non-survivors: median 8 days with prone *v* 9 days with supine; P = 0.92) or ICU median length of stay (342 people: 17.5 days with prone *v* 16 days with supine; P = 0.17). [42]

The second subsequent RCT examined the effect on survival of prone positioning as an early and continuous treatment in people with ARDS already treated with protective ventilation. [43] The RCT included 40 mechanically ventilated patients with early and refractory ARDS despite protective ventilation in the supine position. The trial was prematurely stopped owing to a low recruitment rate (power calculation required 250 people). The RCT found no significant difference between groups in 60-day mortality or between groups in length of mechanical ventilation or ICU length of stay (60-day mortality: 8/21 [38%] with prone *v* 10/19 [53%] with supine; P = 0.3; length of mechanical ventilation: 11.9 days with prone *v* 15.7 days with supine; P = 0.5; ICU length of stay: 14.7 days with prone *v* 17.5 days with supine; P = 0.05), but may have been too small to identify clinically important differences between groups. [43]

Harms:

Prone position versus supine position:

The first systematic review found no significant difference between prone and supine position in ventilator-associated pneumonia or pneumothorax (ventilator-associated pneumonia: 3 RCTs; 112/510 [22%] with prone *v* 117/457 [26%] with supine; OR 0.81, 95% CI 0.60 to 1.10; pneumothorax: 2 RCTs; OR 0.80, 95% CI 0.47 to 1.34; absolute numbers not reported). [39] It found that the prone position significantly increased the proportion of people with pressure sores (3 RCTs; 282/586 [48%] with prone *v* 211/549 [38%] with supine; OR 1.49, 95% CI 1.17 to 1.89). It found a higher rate of complications related to the endotracheal tube with the prone position, but differences between groups did not reach significance (4 RCTs; 103/662 [15%] with prone *v* 76/609 [12%] with supine; OR 1.30, 95% CI 0.94 to 1.80). [39]

The second review found no significant difference between groups in the occurrence of ventilator-associated pneumonia (3 RCTs, 967 people; OR 0.78, 95% CI 0.40 to 1.51). [40]

The third review found that ventilation in the prone position significantly reduced ventilator-associated pneumonia (6 RCTs, 1026 people; RR 0.81, 95% CI 0.66 to 0.99). [41] It found that the prone position significantly increased the risk of pressure ulcers (6 RCTs; 89/252 [35%] with prone *v* 64/249 [26%] with supine; RR 1.36, 95% CI 1.07 to 1.71; P = 0.01).

The first subsequent RCT found that, in the overall group over the 28-day study period, prone positioning significantly increased the proportion of people with at least one episode of: need for sedation/muscle relaxants; airway obstruction; transient desaturation; vomiting; hypotension, arrhythmias, and increased vasopressors; loss of venous access; and displacement of endotracheal tube (need for sedation/muscle relaxants: 80% with prone *v* 56% with supine; P <0.001; airway obstruction: 51% with prone *v* 34% with supine; P = 0.02; transient desaturation: 64% with prone *v* 51% with supine; P = 0.01; vomiting: 29% with prone *v* 13% with supine; P <0.01; hypotension, arrhythmias, and increased vasopressors: 72% with prone *v* 55% with supine; P <0.01; loss of venous access: 16% with prone *v* 4% with supine; P <0.001; displacement of endotracheal tube: 11% with prone *v* 5% with supine; P = 0.03). [42]

The second subsequent RCT found no significant differences between groups in pneumothorax (P = 0.5), unplanned extubation (P = 1.0), or ventilator-associated pneumonia (P = 0.6), but may have been too small to identify clinically important differences between groups. [43]

Adverse effects are uncommon but potentially serious during prone positioning in people with ARDS.

We found one further systematic review (search date 1998, 297 people, 14 prospective cohort studies, 3 RCTs), which compared prone positioning with usual care in the supine position and reported on harms. [44] The total number of prone cycles (from supine to prone and back again) in the review was 746. It found that prone positioning was associated with haemodynamic instability, inadvertent extubation, desaturation, endotracheal tube obstruction, dislodgement of a central venous catheter, and dislodgement of a femoral haemodialysis catheter (haemodynamic instability: 8 events, 1.1% per prone cycle; inadvertent extubation: 3 events, 0.4% per prone cycle; desaturation: 2 events, 0.3% per prone cycle; endotracheal tube obstruction: 1 event, 0.1% per prone cycle; dislodgement of central venous catheter: 1 event, 0.1% per prone cycle; dislodgement of femoral haemodialysis catheter: 1 event, 0.1% per prone cycle). Significance assessments were not performed for any of these comparisons. [44]

Comment: The prone position is contraindicated in people with spinal instability, and should be used with caution in people with haemodynamic and cardiac instability, or who have had recent thoracic or abdominal surgery.

Oxygenation:
The second systematic review found significant and persistent improvement in the PaO_2/FiO_2 ratio with prone positioning compared with the supine position in the early (12 hours to 2 days), intermediate (4 days), and late (10 days) period (early: 4 RCTs, 866 people; WMD 51.50, 95% CI 6.95 to 96.05; P = 0.02; intermediate: 3 RCTs, 754 people; WMD 43.87, 95% CI 13.86 to 73.88; P = 0.004; late: 4 RCTs, 833 people; WMD 24.83, 95% CI 15.30 to 34.48; P = 00001). [40]

The third systematic review found that the ratio of partial pressure of oxygen to inspired fraction of oxygen measured at the end of proning manoeuvre was significantly higher (23–34%) at 1 to 3 days among people in the prone position than among those who remained supine (day 1: 8 RCTs, 633 people; ratio of means 1.34, 95% CI 1.23 to 1.45; P <0.001; day 2: 4 RCTs, 379 people; ratio of means 1.30, 95% CI 1.15 to 1.46; P <0.001; day 3: 5 RCTs, 445 people; ratio of means 1.23, 95% CI 1.15 to 1.32; P <0.001). [41]

The second subsequent RCT found that PaO_2/FiO_2 tended to be higher in prone compared with supine patients after 6 hours (mean: 202 mmHg with prone *v* 165 mmHg with supine; P = 0.16) and this difference reached statistical significance on day 3 (mean: 234 mmHg with prone *v* 159 mmHg with supine; P = 0.009). [43]

We found one further controlled clinical trial (25 people with ARDS; computed tomography scan used to identify those with localised infiltrates or diffuse infiltrates), which compared the effect on oxygenation of prone position versus supine position in the presence of varying levels of additional positive end expiratory pressure (PEEP). [45] Oxygenation measurements were taken at four PEEP levels (0, 5, 10, and 15 cm H_2O), applied in a random order in both positions. It found that, compared with the supine position, the prone position significantly improved oxygenation, defined as an increased PaO_2/FiO_2 ratio (mean: 86 with supine *v* 152 with prone at zero PEEP; P = 0.002; overall results presented graphically; P <0.001). PEEP independently improved oxygenation compared with supine positioning (P <0.001). A subgroup analysis found that, although both PEEP and the prone position significantly improved oxygenation in people with diffuse infiltrates compared with baseline measures (P <0.001), only the prone position improved oxygenation in people with localised infiltrates (results presented graphically; significance assessment not performed). The controlled clinical trial gave no information on adverse effects. [45]

Clinical guide:
Prone position improves oxygenation in people with ARDS and may decrease the incidence of ventilator-associated pneumonia at the expense of more pressure sores and complications related to the endotracheal tube. However, a subgroup of the most severely ill people may benefit most from this intervention, in whom it may it also may reduce mortality.

Despite mechanical ventilation, the primary treatment used in ARDS to improve arterial oxygenation, a significant number of people remain hypoxaemic. [46] Prone position ventilation may improve oxygenation in 60% to 70% of people. Because not everyone will respond, a brief test of the prone position is recommended to assess responsiveness. The optimal duration of this treatment, and the repeat benefit of successive trials, is not currently known.

OPTION CORTICOSTEROIDS

Mortality
Corticosteroids compared with placebo We don't know whether corticosteroids are more effective than control at reducing mortality in adults with ARDS/ALI (low-quality evidence).

Length of stay
Corticosteroids compared with placebo We don't know whether corticosteroids are more effective than control at reducing length of ICU stay in people with ARDS/ALI (low-quality evidence).

Ventilation
Corticosteroids compared with placebo Corticosteroids may be more effective than control at reducing days on mechanical ventilation and increasing ventilator-free days in people with ARDS/ALI (very low-quality evidence).

For GRADE evaluation of interventions for ARDS, see table, p 17 .

Benefits:

Corticosteroids versus placebo:
We found two systematic reviews. [47] [48] Most RCTs included in both reviews used methylprednisolone.

The first systematic review (search date 2007; 4 RCTs, 341 people; 5 cohorts, 307 people) investigated corticosteroids in low to moderate dose in people with ALI or ARDS. [47] It included people aged 18 years or over, and reported both RCT and cohort studies. Studies were excluded if high-dose corticosteroid treatment was used. The review noted that treatment regimens varied considerably between studies with regard to dose used and duration of treatment (7–32 days). In an analysis of RCTs only, the review found no significant difference between groups in mortality, although rates were lower with corticosteroids (4 RCTs; 45/191 [24%] with corticosteroids *v* 53/150 [35%] with control; RR 0.51, 95% CI 0.24 to 1.09; P = 0.08). In an analysis of cohorts only, it found no significant difference between groups in mortality (68/140 [49%] with corticosteroids *v* 114/167 [68%] with control; RR 0.66, 95% CI 0.43 to 1.02; P = 0.06). Combining both RCT and cohort data, it found that corticosteroids significantly reduced mortality compared with control (9 studies, 648 people; RR 0.62, 95% CI 0.43 to 0.91; P = 0.01). However, there was significant heterogeneity among studies (test for heterogeneity P = 0.039). It also reported on morbidity outcomes, but did not report RCT and cohort data separately. It found that corticosteroids significantly reduced days on mechanical ventilation compared with control (3 RCTs [276 people], 1 cohort [31 people]: difference in means –4.84 days, 95% CI –9.28 days to –0.39 days), but found no significant difference between groups in length of ICU stay (3 RCTs [317 people], 1 cohort [31 people]: difference in means –4.12 days, 95% CI –8.86 days to +0.61 days).

The second systematic review (search date 2007) included RCTs using corticosteroids at any dose in adults with ARDS. [48] It classified RCTs into two groups: preventive corticosteroid treatment in critically ill people to inhibit the development of ARDS, and corticosteroid treatment started after the onset of ARDS. We have only reported the results for treatment in people with ARDS here, as this option does not deal with the prophylaxis of ARDS in severely ill people who might develop it.

With regard to the treatment of ARDS, the second review included three RCTs included in the first review, included one RCT excluded by the first review (because it used high-dose corticosteroids), included one additional RCT, and excluded one RCT included in the first review, which examined the effects of corticosteroids in severe community-acquired pneumonia. The review used a Bayesian random-effects model to calculate and present statistical analysis. The review found no significant difference between corticosteroids and no corticosteroids in mortality, although rates were lower with corticosteroids (5 RCTs; 127/303 [42%] with corticosteroids *v* 141/268 [53%] with placebo; OR 0.62, 95% credible intervals 0.23 to 1.26). It found that corticosteroids significantly increased the number of ventilator-free days compared with placebo (3 RCTs; mean difference 4.05 days, 95% credible interval 0.22 days to 8.71 days; absolute numbers in analysis not reported). [48]

Harms:

The first systematic review included data from both cohorts and RCTs in its analysis of adverse effects. [47] It found no significant difference between groups in infection, neuromyopathy, or all major adverse events (infection: 4 RCTs and 3 cohorts, 569 people; RR 0.89, 95% CI 0.65 to 1.23; neuromyopathy: 3 RCTs, 317 people; RR 1.22, 95% CI 0.55 to 2.72; all major adverse events: 3 RCTs and 1 cohort, 494 people; RR 0.82, 95% CI 0.5 to 1.36). [47]

The second review found no significant difference between groups in new infections or pneumonia (new infections: 5 RCTs, 671 people; OR 0.78, 95% credible interval 0.41 to 1.69; pneumonia: 4 RCTs, 472 people; OR 0.59, 95% credible interval 0.14 to 2.82). [48]

Comment:

Whether or not to use corticosteroids in ARDS has been controversial. In the early (<7 days) stages of ARDS, an exudative inflammation is thought to predominate. In later stages (>7 days), a fibroproliferative phase develops. Each of these two inflammatory phases has been considered potentially amenable to the anti-inflammatory effects of corticosteroid therapy. When given early, in high doses, to people with ALI/ARDS, corticosteroids had no impact on mortality, but increased the risk of infectious complications. [49] Despite the improvement in cardiopulmonary physiology, evidence does not support the routine use of corticosteroids for persistent ARDS. In addition, starting corticosteroid therapy more than 2 weeks after the onset of ARDS may increase the risk of death. [47] [48]

Oxygenation:
The first systematic review found that corticosteroids significantly improved oxygenation (4 RCTs and 2 cohorts, 420 people; difference in means 0.64, 95% CI 0.15 to 1.13; P = 0.01). [47]

Clinical guide:
Multiple drug treatments have been studied for people with ARDS and ALI, and their role is extremely limited. [50] Despite the vigorous inflammatory reaction in ARDS, we have found no evidence that

corticosteroids have a role in early ARDS. The late phase of ARDS is characterised by an exaggerated fibroproliferative response, leading to persistent abnormalities in gas exchange. In practice, corticosteroids are sometimes used in selected cases where, despite optimal supportive therapy, ARDS is persistent (>7 days) for late rescue treatment. If a decision is made to initiate treatment with corticosteroids people should be assessed to exclude infections at the outset, and close surveillance is required to identify subsequent infectious episodes, as people on corticosteroids may not develop a febrile response.

OPTION NITRIC OXIDE

Mortality
Nitric oxide compared with standard treatment (no nitric oxide) Nitric oxide may be no more effective than control (no nitric oxide) at reducing mortality in adults or children with ARDS/ALI (very low-quality evidence).

Length of stay
Nitric oxide compared with standard treatment (no nitric oxide) Nitric oxide may be no more effective than control (no nitric oxide) at reducing the proportion of people in intensive care or in hospital at 90 days in adults or children with ARDS/ALI (very low-quality evidence).

Ventilation
Nitric oxide compared with standard treatment (no nitric oxide) We don't know whether nitric oxide is more effective than standard treatment (no nitric oxide) at reducing the duration of ventilation or increasing ventilator-free days in adults or children with ARDS/ALI (low-quality evidence).

For GRADE evaluation of interventions for ARDS, see table, p 17 .

Benefits:

Nitric oxide versus standard treatment (no nitric oxide):
We found two systematic reviews. [51] [52]

The first systematic review (search date 2002, 5 RCTs, 535 adults and children, excluding neonates in the first month of life) was in people with acute hypoxaemic respiratory failure. [51] It compared the use of inhaled nitric oxide versus placebo. A substantial proportion (about >80%) of people in these trials had respiratory failure secondary to acute lung injury/acute respiratory distress syndrome (ALI/ARDS). It found no significant difference between inhaled nitric oxide and placebo in mortality in trials without crossover (2 RCTs; RR 0.98, 95% CI 0.66 to 1.44; absolute numbers not reported), or with crossover of treatment failures to open label (3 RCTs; RR 1.22, 95% CI 0.65 to 2.29; absolute numbers not reported). There was no significant difference in ventilator-free days, duration of hospital stay, and intensive care stay (ventilator-free days [alive and extubated at 30 days]: 80 people with nitric oxide *v* 148 people with placebo; WMD –1.37, 95% CI –3.62 to +0.88 [post hoc analysis; no further data reported]; people in intensive care at 90 days: 1/93 [1.1%] with nitric oxide *v* 1/87 [1.1%] with placebo; RR 0.94, 95% CI 0.06 to 14.73; people in hospital at 90 days: 6/93 [6%] with nitric oxide *v* 4/87 [5%] with placebo; OR 1.42, 95% CI 0.40 to 5.07). [51]

The second systematic review (search date 2006) compared inhaled nitric oxide versus placebo or usual care in adults and children with 80% or more of participants having ARDS or ALI. [52] It included 12 RCTs (1237 participants), of which nine RCTs enrolled only adults, two RCTs enrolled only children (108 children; 24 children), and one RCT enrolled some children (40 adults and children in total). Of the 12 included RCTs, five RCTs had been included in the first review, two RCTs had been excluded on methods from the first review, it included one additional RCT to the first review, and four RCTs that were published subsequent to the first review. Two included RCTs were published as abstracts only. The authors of the review also obtained additional information from 10 authors directly. The review found no significant difference between nitric oxide and control in mortality (9 RCTs, 1086 people; RR 1.10, 95% CI 0.94 to 1.30; results presented graphically). It found no significant difference between groups in duration of ventilation or in ventilator-free days (duration of ventilation: 3 RCTs, 237 people; WMD +3.6 days, 95% CI –4.0 to +11.1 days; P = 0.36; ventilator-free days: 5 RCTs, 804 people; WMD –0.6 days, 95% CI –1.8 to +0.7 days; P = 0.37). [52]

Harms:

The first review gave no information on adverse effects. [51]

The second review in a post hoc analysis reported that nitric oxide significantly increased the risk of renal dysfunction compared with control (4 RCTs, 895 people; RR 1.50, 95% CI 1.11 to 2.02; results presented graphically). [52] It reported that this result should be viewed with caution as it is based on only four RCTs, it is a post hoc analysis, and the review was unable to obtain further data on renal outcomes in eight of 12 smaller RCTs in which this outcome may or may not have been measured.

Comment:

Oxygenation:
One RCT identified by the first review found that, compared with placebo, nitric oxide improved oxygenation in the first 24 hours after administration (mean oxygenation index in the first 24 hours: 14 [120 people] with nitric oxide *v* 17 [56 people] with control; P = 0.01). [51] The second review found that, on day 1 of treatment, nitric oxide significantly increased the ratio of partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2 ratio: 9 RCTs, 553 people; 13%, 95% CI 4% to 23%) and significantly decreased the oxygenation index (3 RCTs, 296 people; 14%, 95% CI 2% to 25%). [52] Some evidence suggested that improvements in oxygenation persisted until day 4. [52]

Inhaled nitric oxide may improve oxygenation in people with ADRS. However, this beneficial effect on oxygenation in the people given nitric oxide compared with placebo remains modest and is not sustained.

Clinical guide:
Nitric oxide use has not been associated with better survival in RCTs; therefore, its use is not recommended as routine treatment, and must be considered experimental.

GLOSSARY

Atelectasis is collapse of all or part of the lung, normally secondary to shallow breathing or blockage.

Intrapulmonary shunt is perfusion of alveoli without ventilation, making the resulting hypoxaemia unresponsive to oxygen supplementation.

Plateau pressure is the pressure applied in positive pressure ventilation to the small airways and alveoli. It is thought to correlate most closely with alveolar pressure and therefore is the best predictor of alveolar overinflation.

Positive end expiratory pressure (PEEP) is a form of mechanical ventilation that aims to improve oxygenation by keeping the alveoli and small airways open throughout the respiratory cycle. Its purpose is to try to prevent the damage produced by repetitive opening and closing of the alveoli (cyclical atelectasis). Although PEEP is universally used in people with acute respiratory distress syndrome, the level needed to confer maximum benefit with minimum complications has only recently been studied.

Low tidal-volume mechanical ventilation When prescribing mechanical ventilation, tidal volume needs to be set at a predetermined level based on predicted weight. Mechanical ventilation may cause ventilator-induced lung injury, termed as macrobarotrauma or microbarotrauma. Traditionally, large tidal volumes (10–15 mL/kg) were prescribed but current evidence suggests a mortality benefit from lower tidal volumes (6 mL/kg ideal body weight).

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Oxygenation index is the mean airway pressure × (the fractional concentration of oxygen × 100)/arterial oxygen tension (PaO_2). It indicates the degree of impairment of oxygenation. Values >40 are associated with about 80% mortality with conventional treatment.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Corticosteroids Two systematic reviews added. [47] [48] Both reviews included similar RCTs and found no significant difference between corticosteroids and control in mortality. The reviews found that corticosteroids may be more effective than no corticosteroids at reducing duration of mechanical ventilation, but found no difference between groups in length of ICU stay. Categorisation unchanged (Unknown effectiveness).

Low tidal-volume mechanical ventilation One already reported systematic review updated (search date 2006) and new data added to the benefits section. [19] The overall conclusions of the review remain the same. Two further reports added to the comments section as background data. [31] [32] Categorisation unchanged (Beneficial).

Nitric oxide One systematic review added, [52] which found similar results to an already reported systematic review. It found no evidence of a mortality benefit or reduction in duration of ventilation. Categorisation unchanged (Unlikely to be beneficial).

Positive end expiratory pressure (PEEP) Two systematic reviews added comparing the effects of high PEEP versus low PEEP in people with ARDS/ALI. [33] [34] Interpretation of the results was complicated owing to possible confounding factors arising from clinical heterogeneity between the included RCTs (differences between the protocols employed and participants included with regard to disease severity). When adjusting for possible confounding factors, the reviews found no consistent difference between high PEEP and low PEEP in mortality. However, these results had to be interpreted in light of the aforementioned caveats, and results (and significance between groups) also varied by the exact analysis undertaken. Categorisation unchanged (Likely to be beneficial).

Prone position Three systematic reviews added [39] [40] [41] and two subsequent RCTs [42] [43] comparing the effects of prone versus supine position in people with ARDS/ALI on ventilation. The reviews found no evidence overall of a benefit in mortality with the prone position; however, subgroup analysis suggested that there might be a benefit in mortality in the most severely ill people. However, this was a post hoc analysis based on small numbers, and one subsequent RCT found no significant benefit in mortality in people with severe hypoxaemia. The studies found that there may be a benefit in oxygenation with prone position; however, prone position was also associated with an increase in some adverse effects (e.g., pressure ulcers). Categorisation unchanged (Trade-off between benefits and harms).

REFERENCES

1. Ashbaugh D, Bigelow D, Petty T, et al. Acute respiratory distress in adults. *Lancet* 1967;2:319–323.[PubMed]
2. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818–824.[PubMed]
3. Frutos-Vivar F, Nin N, Esteban A. Epidemiology of acute lung injury and acute respiratory distress syndrome. *Curr Opin Crit Care* 2004;10:1–6.[PubMed]
4. MacCallum NS, Evans TW. Epidemiology of acute lung injury. *Curr Opin Crit Care* 2005;11:43–49.[PubMed]
5. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of lung injury. *N Engl J Med* 2005;353:1685–1693.[PubMed]
6. Sigvaldason K, Thornormar K, Bergmann JB, et al. The incidence and mortality of ARDS in Icelandic intensive care units 1988–1997. *Laeknabladid* 2006;92:201–207. [In Icelandic][PubMed]
7. Lu Y, Song Z, Zhou X, et al. A 12-month clinical survey of incidence and outcome of acute respiratory distress syndrome in Shanghai intensive care units. *Intensive Care Med* 2004;30:2197–2203.[PubMed]
8. Hudson LD, Milberg JA, Anardi D, et al. Clinical risks for development of the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;151:293–301.[PubMed]
9. Fowler A, Hamman R, Good J, et al. Adult respiratory distress syndrome: risk with common predispositions. *Ann Intern Med* 1983;98:593–597.[PubMed]
10. Kahn JM, Caldwell EC, Deem S, et al. Acute lung injury in patients with subarachnoid hemorrhage: incidence, risk factors, and outcome. *Crit Care Med* 2006;34:196–202.[PubMed]
11. Brun-Buisson C, Minelli C, Bertolini G, et al. Epidemiology and outcome of acute lung injury in European intensive care units. Results from ALIVE study. *Intensive Care Med* 2004;30:51–61.[PubMed]
12. Milberg JA, Davis DR, Steinberg KP, et al. Improved survival of patients with acute respiratory distress syndrome: 1983–1993. *JAMA* 1995;273:306–309.[PubMed]
13. Montgomery AB, Stager MA, Carrico CJ, et al. Causes of mortality in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis* 1985;132:485–489.[PubMed]
14. Ely EW, Wheeler AP, Thompson BT, et al. Recovery rate and prognosis in older persons who develop acute lung injury and the acute respiratory distress syndrome. *Ann Intern Med* 2002;136:25–36.[PubMed]
15. Neff TA, Stocker R, Frey HR, et al. Long-term assessment of lung function in survivors of severe ARDS. *Chest* 2003;123:845–853.[PubMed]
16. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;348:683–693.[PubMed]
17. Ghio AJ, Elliott CG, Crapo RO, et al. Impairment after adult respiratory distress syndrome. An evaluation based on American Thoracic Society recommendations. *Am Rev Respir Dis* 1989;139:1158–1162.[PubMed]
18. Hopkins RO, Weaver LK, Orme JF, et al. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999;160:50–56.[PubMed]
19. Petrucci N, Iacovelli W. Lung protective ventilation strategy for the acute respiratory distress syndrome. In: The Cochrane Library, Issue 4, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2006.
20. Moran JL, Bersten AD, Solomon PJ, Meta-analysis of controlled trials of ventilator therapy in acute lung injury and acute respiratory distress syndrome: an alternative perspective. *Intensive Care Med* 2005;31:227–235. Search date 2006.[PubMed]
21. Qin ZQ, Wang C. A meta-analysis of clinical studies of low volume ventilation in acute respiratory distress syndrome. *Zhonghua Yi Xue Za Zhi* 2003;83:224–227. Search date 2006. [In Chinese][PubMed]
22. Sakr Y, Vincent JL, Reinhart K, et al. High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. *Chest* 2005;128:3098–3108. [see comment][PubMed]
23. Anon. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301–1308.[PubMed]
24. Stewart TE, Meade MO, Cook DJ, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. *N Eng J Med* 1998;338:355–361.
25. Cheng IW, Eisner MD, Thompson BT, et al. Acute, and Respiratory Distress, Syndrome Network. Acute effects of tidal volume strategy on hemodynamics, fluid balance, and sedation in acute lung injury. *Crit Care Med* 2005;33:63–70.[PubMed]
26. Kahn JM, Andersson L, Karir V, et al. Low tidal volume ventilation does not increase sedation use in patients with acute lung injury. *Crit Care Med* 2005;33:766–771.[PubMed]
27. Alex CG, Tobin MJ. Assessment of pulmonary function in critically ill patients. In: Shoemaker WC, Ayres SM, Grenvik A, et al (eds). *Textbook of critical care* 3rd ed. Philadelphia: WB Saunders, 1995:649–659.
28. Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med* 1998;157:294–323.[PubMed]
29. Slutsky AS, Tremblay LN. Multiple system organ failure. Is mechanical ventilation a contributing factor? *Am J Respir Crit Care Med* 1998;157:1721–1725.[PubMed]
30. Kalhan R, Mikkelsen M, Dedhiya P, et al. Underuse of lung protective ventilation: analysis of potential factors to explain physician behavior. *Crit Care Med* 2006;34:300–306. [see comment][PubMed]
31. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med* 2009;361:680–689.[PubMed]
32. Hemmila MR, Napolitano LM. Severe respiratory failure: advanced treatment options. *Crit Care Med* 2006;34:S278–S290.[PubMed]
33. Oba Y, Thameem DM, Zaza T. High levels of PEEP may improve survival in acute respiratory distress syndrome: a meta-analysis. *Respir Med* 2009;103:1174–1181.
34. Phoenix SI, Paravastu S, Columb M, et al. Does a higher positive end expiratory pressure decrease mortality in acute respiratory distress syndrome? A systematic review and meta-analysis. *Anesthesiology* 2009;110:1098–1105.[PubMed]
35. Brower RG, Lanken PN, MacIntyre N, et al, and the National Heart, Lung and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;351:327–336.[PubMed]
36. Villar J, Kacmarek RM, Perez-Mendez L, et al. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. *Crit Care Med* 2006;34:1311–1318.[PubMed]
37. Sevransky JE, Levy MM, Marini JJ. Mechanical ventilation in sepsis-induced acute lung injury/acute respiratory distress syndrome: an evidence-based review. *Crit Care Med* 2004;32:S548–S553.[PubMed]
38. Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002:287:345–355.[PubMed]
39. Kopterides P, Siempos II, Armaganidis A, et al. Prone positioning in hypoxemic respiratory failure: meta-analysis of randomized controlled trials. *J Crit Care* 2009;24:89–100.[PubMed]
40. Alsaghir AH, Martin CM. Effect of prone positioning in patients with acute respiratory distress syndrome: a meta-analysis. *Crit Care Med* 2008;36:603–609.[PubMed]
41. Sud S, Sud M, Friedrich JO, et al. Effect of mechanical ventilation in the prone position on clinical outcomes in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *CMAJ: Can Med Assoc J* 2008;178:1153–1161.[PubMed]
42. Taccone P, Pesenti A, Latini R, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2009;302:1977–1984.[PubMed]
43. Fernandez R, Trenchs X, Klamburg J, et al. Prone positioning in acute respiratory distress syndrome: a multicenter randomized clinical trial. *Intensive Care Med* 2008;34:1487–1491.[PubMed]
44. Curley MA. Prone positioning of patients with acute respiratory distress syndrome: a systematic review. *Am J Crit Care* 1999;8:397–405. Search date 1998.[PubMed]
45. Gainnier M, Michelet P, Thirion X, et al. Prone position and positive end-expiratory pressure in acute respiratory distress syndrome. *Crit Care Med* 2003;31:2719–2726.[PubMed]
46. Brower RG, Fessler HE. Mechanical ventilation in acute lung injury and acute respiratory distress syndrome. *Clin Chest Med* 2000;21:491–510.[PubMed]
47. Tang BM, Craig JC, Eslick GD, et al. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care Med* 2009;37:1594–1603.[PubMed]
48. Peter JV, John P, Graham PL, et al. Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. *BMJ* 2008;336:1006–1009.[PubMed]
49. Bernard GR, Luce JM, Sprung CL, et al. High-dose corticosteroids in patients with the adult respiratory distress syndrome. *N Engl J Med* 1987;317:1565–1570.[PubMed]
50. Adhikari N, Burns KE, Meade MO. Pharmacologic treatments for acute respiratory distress syndrome and acute lung injury: systematic review and meta-analysis. *Treat Respir Med* 2004;3:307–328.[PubMed]
51. Sokol J, Jacobs SE, Bohn D. Inhaled nitric oxide for acute hypoxemic respiratory failure in children and adults. In: The Cochrane Library, Issue 4, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2002.
52. Adhikari NK, Burns KE, Friedrich JO, et al. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. *BMJ* 2007;334:779.[PubMed]

Acute respiratory distress syndrome

Sat Sharma
Professor and Head
Section of Respirology
Department of Internal Medicine, University of Manitoba
Winnipeg
Canada

Competing interests: SS has declared that he has no competing interests.

Disclaimer

TABLE **GRADE evaluation of interventions for acute respiratory distress syndrome (ARDS)**

Important outcomes	**Mortality; length of stay; duration of ventilation; adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of interventions in adults with acute respiratory distress syndrome?									
At least 11 (at least 2499) [19] [20] [21] [22]	Mortality	Low tidal-volume *v* conventional or high tidal-volume mechanical ventilation	4	0	0	–1	0	Moderate	Directness point deducted for clinical heterogeneity among RCTs (plateau pressures, regimens used)
3 (288) [19]	Duration of ventilation	Low tidal-volume *v* conventional or high tidal-volume mechanical ventilation	4	0	0	–1	0	Moderate	Directness point deducted for clinical heterogeneity among RCTs (plateau pressures, regimens used)
6 (2484) [33] [34]	Mortality	High PEEP *v* low PEEP	4	–1	0	–2	0	Very low	Quality point deducted for adjustment of results using assumptions for possible confounder in one review. Directness points deducted for clinical heterogeneity among RCTs (protocols, tidal volumes, populations) and possibility of publication bias
2 (1532) [33]	Length of stay	High PEEP *v* low PEEP	4	0	0	–2	0	Low	Directness points deducted for clinical heterogeneity among RCTs (protocols, tidal volumes, populations) and possibility of publication bias
4 (2394) [33]	Ventilation	High PEEP *v* low PEEP	4	0	0	–2	0	Low	Directness points deducted for clinical heterogeneity among RCTs (protocols, tidal volumes, populations) and possibility of publication bias
At least 12 (at least 1868) [39] [40] [41] [42] [43]	Mortality	Prone position *v* supine position	4	–2	0	–2	0	Very low	Quality points deducted for post hoc subgroup analysis in 2 reviews and weak methods (ventilation guidelines not specified in 3 RCTs, co-intervention allowed, quasi-randomised trials included in 1 review). Directness points deducted for 2 RCTs using higher tidal volumes than used currently affecting generalisability, including people with hypoxaemic failure but not ARDS/ALI and variation in prone positioning regimens used
3 (at least 382) [39] [42] [43]	Length of stay	Prone position *v* supine position	4	–2	0	–2	0	Very low	Quality points deducted for incomplete reporting of results and weak methods (ventilation guidelines not specified in some RCTs, co-interventions allowed). Directness points deducted for 2 RCTs using higher tidal volumes than used currently affecting generalisability and variation in prone positioning regimens used
8 (at least 9374) [39] [40] [41] [42] [43]	Ventilation	Prone position *v* supine position	4	–1	0	–2	0	Very low	Quality point deducted for weak methods (ventilation guidelines not specified in 3 RCTs, co-intervention allowed, quasi-randomised trials included in 1 review). Directness points deducted for 2 RCTs using higher tidal volumes than used currently affecting generalisability, including people with hypoxaemic failure but not ARDS/ALI and variation in prone positioning regimens used

Important outcomes	**Mortality; length of stay; duration of ventilation; adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
At least 3 (at least 1125) [39] [41]	Adverse effects	Prone position *v* supine position	4	–1	0	–2	–1	Very low	Quality point deducted for weak methods (ventilation guidelines not specified in 3 RCTs, co-intervention allowed, quasi-randomised trials included in 1 review). Directness points deducted for 2 RCTs using higher tidal volumes than used currently affecting generalisability, including people with hypoxaemic failure but not ARDS/ALI and variation in prone positioning regimens used
9 (851) [47] [48]	Mortality	Corticosteroids *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for inclusion of observational data. Directness point deducted for clinical heterogeneity among RCTs (dose, duration of treatment).
3 (317) [47]	Length of stay	Corticosteroids *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for inclusion of observational data. Directness point deducted for clinical heterogeneity among RCTs (dose, duration of treatment).
At least 4 (at least 276) [47] [48]	Ventilation	Corticosteroids *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for inclusion of observational data and incomplete reporting of results. Directness point deducted for clinical heterogeneity among RCTs (dose, duration of treatment)
At least 9 (at least 1086) [51] [52]	Mortality	Nitric oxide *v* standard treatment (no nitric oxide)	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for inclusion of people without ARDS/ALI and inclusion of children in analysis
At least 1 (180) [51]	Length of stay	Nitric oxide *v* standard treatment (no nitric oxide)	4	–1	0	–2	0	Very low	Quality point deducted for sparse data. Directness points deducted for inclusion of people without ARDS/ALI and inclusion of children in analysis
At least 5 (at least 804) [51] [52]	Ventilation	Nitric oxide *v* standard treatment (no nitric oxide)	4	0	0	–2	0	Low	Directness points deducted for inclusion of people without ARDS/ALI and inclusion of children in analysis

Type of evidence: 4 = RCT. Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio