Is there evidence to support a phase II trial of inhaled corticosteroids in the treatment of incipient and persistent ARDS?

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ABSTRACT

Acute respiratory distress syndrome (ARDS) is common in intensive care, with high mortality and morbidity. Preclinical studies suggest that corticosteroids reduce lung inflammation in ARDS. Early clinical trials using short courses of high-dose corticosteroids in patients at high risk of ARDS and with early ARDS showed increased mortality despite reduced lung inflammation, although more recent experience with lower doses over more prolonged periods is encouraging. After initial promise, corticosteroids now appear to lack mortality benefit in late ARDS. Systemic deleterious effects may outweigh the local benefit of corticosteroids on lung inflammation. Extensive experience has accumulated in the use of inhaled corticosteroids to treat asthma. Inhalation maximises lung effects while minimising systemic absorption. Inhaled corticosteroids have been used successfully in a variety of animal models of lung injury. There is currently sufficient evidence to support a preliminary clinical trial of inhaled corticosteroids in patients at high risk of ARDS as well as with early and/or late ARDS, using markers of inflammation as a surrogate end-point.

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Acute respiratory distress syndrome (ARDS) is a common problem in patients requiring intensive care, with incidence rates of 28 per 100 000 per year in Australia,[1] and 58.7 per 100 000 per year in the United States.[2] Mortality appears to have fallen over time,[3] but remains high, with recent estimates ranging from 34% in Australia[1] to 41% in the US.[2] The consensus definition of ARDS has three components: bilateral diffuse pulmonary infiltrate on chest radiography, $Pao_2/FIo_2 < 200$ mmHg, and no evidence of elevated left atrial pressure.[4] ARDS is a subset of acute lung injury, which is defined by the same three criteria but also includes patients with less severely compromised oxygenation (ie, $Pao_2/FIo_2 < 300$ mmHg). In addition to its high mortality, ARDS is clinically important because survivors have persisting morbidity. For example, in one study, only 49% of ARDS survivors were able to work a year later, because of persistent functional disability.[5]

ARDS is characterised by excessive and protracted inflammation. The lung inflammation observed in ARDS can be precipitated by diverse disease processes, both intrapulmonary (such as infection or aspiration) and extrapulmonary (such as shock or extensive trauma). In the early (< 7 days) stages of ARDS, an exudative inflammation is thought to predominate. In later stages (> 7 days), a fibroproliferative phase may develop. Each of these two inflammatory phases has been considered potentially amenable to the anti-inflammatory effects of corticosteroid therapy.

The cellular mechanisms regulating inflammation are increasingly understood. Central to the regulation of inflammation are two cytoplasmic transcription factors, pro-inflammatory nuclear factor- kappa B (NF-κB) and the anti-inflammatory glucocorticoid receptor alfa (GRα). These have antagonistic effects, as has been recently comprehensively reviewed in the context of lung inflammation.[6] Despite increased levels of endogenous glucocorticoids in ARDS, it appears that a state of glucocorticoid resistance develops, probably mediated by pro-inflammatory cytokines. This facilitates the relatively unopposed pro-inflammatory effects of NF-κB, and suggests the possibility that therapeutically augmenting the glucocorticoid response with exogenous corticosteroid might restore the balance.

Intravenous corticosteroids in ARDS

Preclinical studies in lung inflammation

There is extensive animal evidence that steroids reduce acute lung inflammation caused by a variety of underlying pathological processes. In rats with lung injury induced by intratracheal acid injection, intravenous prednisolone significantly reduced lung 15-hydroxyeicosatetraenoic acid (an arachidonic acid metabolite produced by activated neutrophils) and bronchoalveolar lavage (BAL) fluid cell counts.[7] In isolated rat lungs perfused with pro-inflammatory cytokines, the addition of dexamethasone to the perfusate inhibited the upregulation of pulmonary vascular and tissue endothelins.[8] In pigs given intravenous endotoxin, dexamethasone attenuated increases in BAL fluid leukotriene B4 and albumin.[9] In a similar model, treatment with methylprednisolone prevented endotoxin-induced pulmonary and

cardiovascular effects and improved survival, even if the drug was given 2 hours after endotoxin was administered.[10] In a rat caecal ligation and puncture model of sepsis, intravenous methylprednisolone given immediately after the septic insult increased survival while reducing BAL concentrations of leukotriene B4 and endothelin.[11] In rats exposed to intraperitoneal paraquat, intravenous methylprednisolone prevented changes in pulmonary collagen and elastic fibres,[12] reduced inflammatory cell counts in BAL fluid, improved oxygenation and reduced lung injury.[13] Taken together, these studies demonstrate that steroids reduce biochemical and cellular markers of inflammation and tissue damage in animals exposed to stimuli that cause lung injury, and furthermore that this is associated with improved lung function and survival.

Studies in humans

On the basis of these studies, it was hypothesised that steroids would be of benefit in humans with ARDS. Subsequently, a variety of case series and randomised trials have been reported. We systematically reviewed this literature using PubMed (search terms "corticosteroid" or "steroid" and "acute respiratory distress syndrome", limited to clinical trials, randomised controlled clinical trials and case reports published in English), and supplemented this approach using the reference lists of the resulting articles. On 23 April 2007, this search returned 175 records, 161 of which were excluded as irrelevant ($n = 122$) or case reports of two or fewer patients ($n = 39$). The available evidence, after inclusion of the secondary references, is summarised in Table 1 and Table 2.

In interpreting these reports, it is important to note some important distinctions. While some studies attempt to prevent ARDS, others aim to treat established ARDS. Among the latter, some focus on early ARDS (when the disease has been established for < 7 days), while others focus on late disease (> 7 days). Studies differ significantly in the dose of steroid given, with some studies using high doses (typically 30 mg/kg every 6 hours) and others low doses (1–2 mg/kg/day). Similarly, the duration of treatment also varies, from short courses (over a single day) to more prolonged administration (2–4 weeks or longer).

Trials in patients at risk of ARDS

The first trials of intravenous steroids in patients at risk of ARDS failed to find any benefit and, indeed, suggested possible harm. The earliest trials recruited patients with sepsis, attempting to prevent ARDS as a complication of this disease process. In the first of these trials, 304 patients with sepsis were randomised to receive 30 mg/kg methylprednisolone or placebo within 2 hours of the diagnosis of sepsis, repeated a further three times over 24 hours. Methylprednisolone was associated with a trend towards higher incidence of ARDS (32% v 25%, $P = 0.10$). In patients with established ARDS at the time of study entry, fewer in the methylprednisolone group had resolution of ARDS (31% v 61%, $P = 0.005$), and fewer survived (mortality, 52% with methylprednisolone v 22% with placebo, $P = 0.004$).[14] Most other smaller studies of methylprednisolone in patients at risk of ARDS were similarly disappointing,[15-17] with the exception of two trials which used large doses of methylprednisolone immediately before or during surgery.[18,19] In contrast, a more recent study showed a beneficial effect of a much smaller dose of intravenous steroid. Twenty-four patients with community-acquired pneumonia (but not necessarily ARDS) were randomised to a low-dose hydrocortisone infusion (10 mg/h) for 7 days, and 24 to placebo.[20] Steroid-treated patients had significantly reduced hospital mortality compared with the placebo group (0% v 30%, $P = 0.009$), as well as improved oxygenation, reduced inflammation, and less progression to septic shock.

Trials in patients with early ARDS

While trials of intravenous steroids in at-risk patients failed to prevent ARDS, it may be that steroids are effective only once lung inflammation has begun to develop, as one non-randomised study suggested.[21] The first randomised trial compared a short course of high-dose methylprednisolone (30 mg/kg body weight every 6 hours for 24 hours) to placebo in 99 patients with early ARDS due to a variety of causes (mainly sepsis and aspiration).[22] In the first 5 days after study entry, methylprednisolone had no effect on pulmonary shunting, arterial oxygenation, chest radiographic appearance, thoracic compliance, or pulmonary artery pressure. Similarly, there was no difference in 45-day mortality (60% v 63%, $P = 0.74$) or the incidence of ARDS reversal (36% v 39%, $P = 0.77$).

More recently, it has been suggested that a lower dose of steroid for a more prolonged period might be more effective. In a retrospective subgroup analysis of data obtained in a trial of low-dose steroids for the treatment of septic shock, Annane and colleagues explored the effect of 7 days of treatment with low-dose steroids in septic shock patients with or without ARDS.[23] Among the 300 subjects enrolled in the original trial, 177 had early ARDS, including 129 non-responders to the short cosyntropin stimulation test (steroids, $n = 62$; placebo, $n = 67$) and 48 responders (steroids, $n = 23$; placebo, $n = 25$). Because patients had to be enrolled within 8 hours of the onset of septic shock, they were most likely to have "early" ARDS. The steroid-treated and placebo groups were well balanced at baseline. Among non-responders with early ARDS, 28-day mortality was significantly lower in those who received steroids (53% v 75%, $P = 0.01$). There was no significant difference

Table 1. Efficacy of intravenous corticosteroids in patients at risk of acute respiratory distress syndrome (ARDS) or with early ARDS

Study	Intervention	Design	Patients	Results
Patients at risk of ARDS				
Sprung et al, 1984[17]	30 mg/kg methylprednisolone, 6 mg/kg dexamethasone, or no study treatment	Single-centre randomised controlled trial	59 patients with septic shock	Neither steroid influenced the incidence of ARDS (31% methylprednisolone v 23% dexamethsaone v 15% placebo). No difference in hospital mortality (76% v 77% v 69%)
Weigelt et al, 1985[16]	30 mg/kg methylprednisolone or placebo, repeated every 6 hours for 48 hours	Single-centre randomised controlled trial	81 patients "at risk" for ARDS, as defined by $PaO_2/FIO_2 \leq 350$	Higher incidence of ARDS with steroids (64% v 33% placebo, $P = 0.008$). Trend towards increased mortality with steroids (46% v 31% placebo)
Bone et al, 1987[14]	30 mg/kg methylprednisolone or placebo, repeated 3× over 24 hours	Multicentre randomised controlled trial	304 patients within 2 hours of a diagnosis of sepsis	Trend towards higher incidence of ARDS with steroids (32% v 25% placebo). In patients with established ARDS, increased mortality (52% v 22% placebo)
Luce et al, 1988[15]	30 mg/kg methylprednisolone or placebo, repeated 3× over 24 hours	Single-centre randomised controlled trial	75 patients with septic shock	No difference in incidence of ARDS (34% v 37% placebo) or mortality (58% v 54% placebo)
Sato et al, 2002[18]	10 mg/kg methylprednisolone or placebo, 30 mins before start of oesophageal resection	Single-centre randomised controlled trial	66 patients undergoing surgery for oesophageal carcinoma	No difference in mortality. Patients receiving steroids had less organ failure by postoperative Day 7 (33% v 61% placebo, $P = 0.02$), including less respiratory failure (non-standard ARDS definitions) (9% v 30% placebo, $P = 0.03$)
Cerfolio et al, 2003[19]	250 mg methylprednisolone or placebo immediately before pulmonary artery ligation	Single-centre randomised controlled trial	72 patients undergoing pneumonectomy	Reduced incidence of postpneumonectomy ARDS with steroids (0 v 13.5% placebo, $P = 0.049$). Steroids also reduced complication and length of stay, but the difference in mortality was not significant (2.8% v 10.8%, $P = 0.35$)
Confalonieri et al, 2005[20]	200 mg hydrocortisone loading dose, then 10 mg/h for 7 days	Multicentre randomised controlled trial	48 patients with severe community-acquired pneumonia	Steroids reduced hospital mortality (0% v 30% placebo, $P = 0.009$), improved PaO_2/FIO_2 ratio and radiograph appearance, and reduced inflammation and progression to septic shock
Patients with early ARDS				
Bernard et al, 1987[22]	30 mg/kg methylprednisolone or placebo, repeated 3× over 24 hours	Single-centre randomised controlled trial	99 patients with early ARDS, mainly due to sepsis or aspiration	No difference in mortality (60% v 63% placebo) or in resolution of ARDS (36% v 39% placebo)
Lee at al, 2005[21]	Methylprednisolone 2 mg/kg loading dose, then 2 mg/kg daily in four divided doses until resolution of clinical signs (±tapering). Median 4.5 days until tapering began, 9.5 days before cessation or changing to oral dose.	Case–control study	12 patients with early ARDS post-thoracic surgery received steroids, compared to eight historical controls who did not	Steroids reduced hospital mortality (8.3% v 87.5% control, $P = 0.001$), requirement for ICU management and mechanical ventilation
Annane et al, 2006[23]	50 mg hydrocortisone and 50 μg fludrocortisone, or placebo, daily for 7 days	Subgroup analysis of a larger multicentre randomised controlled trial	177 patients from within the 299-patient parent trial	Decreased 28-day mortality with steroids (58% v 67% placebo; adjusted hazard ratio, 0.58; $P = 0.005$); the benefit was confined to corticotropin test non-responders
Meduri et al, 2007[24]	1 mg/kg methylprednisolone or placebo daily for 14 days	Multicentre (5 hospitals) randomised controlled trial	91 patients with early ARDS	Decreased ICU mortality with steroids (20.6% v 42.9% placebo, $P = 0.03$). Improved lung injury score, reduced mechanical ventilation, reduced lung inflammation

between groups in the rates of adverse events, such as superinfection, gastrointestinal bleeding or psychiatric disorders. Interestingly, steroids did not affect mortality in cosyntropin responders or in those without ARDS.

A more recent randomised controlled trial using low-dose methylprednisolone (1 mg/kg/day for 14 days, tapering over the subsequent 14 days) in 91 patients with early ARDS[24] supports the conclusion of the subgroup analysis

Table 2. Efficacy of intravenous corticosteroids in patients with late acute respiratory distress syndrome (ARDS)

Study	Intervention	Design	Patients	Results
Ashbaugh and Maier, 1985[28]	125 mg methylprednisolone every 6 hours until clinical improvement; then tapered; total duration, 22–108 days	Case series	10 patients with ARDS for median, 8 (range, 3–21) days	Mortality 2/10 (20%)
Meduri et al, 1994[27]	200 mg methylprednisolone, followed by 2–3 mg/kg methylprednisolone daily in four divided doses until extubation, then taper over 6 weeks	Case series	25 patients with ARDS, on average 15 days of mechanical ventilation	After 7 days of steroids, significant improvement was seen in lung injury severity score, PaO_2/FIO_2 ratio, positive end-expiratory pressure requirement, and radiographic appearance. Overall mortality 6/25 (24%)
Biffl et al, 1995[25]	1–2 mg/kg every 6 hours for 7 days	Retrospective uncontrolled case series	6 patients with ARDS for > 16 days	5/6 patients survived. PaO_2/FIO_2 ratios and lung injury scores improved with steroids
Hooper and Kearl, 1996[29]	125–250 mg methyl-prednisolone every 6 hours for 3 days, then tapered over > 21 days	Case series	26 patients with ARDS for > 3 days	Mortality 5/26 (19%)
Keel et al, 1998[26]	100–250 mg methyl-prednisolone daily for 1–3 days, then tapered over the next mean 8 (range, 3–19) days	Retrospective case series with non-randomised controls	31 patients with ARDS for ⩾ 7 days, 13 of whom received steroids, starting after a mean of 15 (range, 5–44) days of mechanical ventilation	Trend towards reduced mortality with steroids (38% v 67% placebo, $P = 0.12$). Steroids improved the PaO_2/FIO_2 ratio
Meduri et al, 1998[31]	2 mg/kg methylprednisolone or placebo daily for 32 days	Multicentre (4 hospitals) randomised controlled trial	24 patients with ARDS for ⩾ 7 days, 16 of whom received steroids	Reduced hospital mortality with steroids (12% v 62% placebo, $P = 0.03$). Reduced lung injury score, improved PaO_2/FIO_2 ratio, more successfully extubated with steroids
Koontz et al, 2006[30]	200 mg methylprednisolone bolus, then 3 mg/kg per day in 4 divided doses for 6 weeks or until weaned off mechanical ventilation	Case series	9 trauma/surgical patients with ARDS for the previous 10–12 days	Mortality, 2/9 (22%)
Steinberg et al, 2006[33]	2 mg/kg methylprednisolone or placebo daily for 14 days, followed by a tapering dose	Multicentre randomised controlled trial	180 patients with ARDS for ⩾ 7 days	No difference in 60-day and 180-day mortality (29.2% v 28.6% placebo, and 31.5% v 31.9% placebo). Significantly increased mortality with steroid if enrolled ⩾ 14 days after onset of ARDS. More ventilator- and shock-free days, better oxygenation, better respiratory compliance, and fewer days of vasopressor therapy with steroids

of Annane and colleagues.[23] In this study, steroid-treated patients had significantly improved lung function (a one point reduction in lung injury score, 70% v 36%, $P = 0.002$), reduced inflammation and shorter duration of mechanical ventilation (5 v 9.5 days, $P = 0.002$) compared with controls. Intensive care unit mortality was significantly reduced (20.6% v 42.9%, $P = 0.03$), with a trend towards decreased hospital mortality with methylprednisolone (23.8% v 42.9%, $P = 0.07$). These results suggest that a lower dose of intravenous steroid given over a longer period may preserve the beneficial effect on lung inflammation, while reducing the potential for systemic side effects.

Trials in patients with late ARDS

Recognising the differences in pathology between early and late ARDS, small studies of steroids in patients with late ARDS were conducted. The results of these early studies were promising. In a case series of six patients with late ARDS (> 16 days of mechanical ventilation), methylprednisolone was used at a lower dose (1–2 mg/kg every 6 hours) than in the first trials of steroids in early ARDS.[25] After 7 days of steroid therapy, PaO_2/FIO_2 ratios and lung injury scores had improved. Five patients survived. A retrospective non-randomised study reported outcomes of 31 patients with ARDS who had been mechanically ventilated for at least 7 days, 13 of whom received high-dose

steroids.[26] There was a trend towards reduced mortality in the steroid group (38% v 67%, $P = 0.12$), along with improvement in the Pa_{O_2}/F_{IO_2} ratio.

These and other case series[27-30] led to two randomised controlled trials of intravenous steroids in late ARDS. The first of these involved 24 patients who had had severe ARDS for 7 days.[31] Sixteen patients received methylprednisolone (2 mg/kg per day) for 32 days, and eight received placebo. Four patients whose lung infection score failed to improve by at least 1 point after 10 days of treatment were blindly crossed over to the alternative treatment. After 10 days, patients receiving methylprednisolone had reduced lung injury score (1.7 v 3.0, $P < 0.001$), improved Pa_{O_2}/F_{IO_2} ratio (262 v 148, $P < 0.001$) and decreased multiple organ dysfunction syndrome (MODS) score (0.7 v 1.8, $P < 0.001$), and more had been successfully extubated (43% v 0, $P = 0.05$). Mortality in the ICU (0 v 62%, $P = 0.002$) and hospital (12% v 62%, $P = 0.03$) were significantly reduced in the steroid group. The rate of infections was similar in both groups. Patients receiving methylprednisolone had reduced serum pro-inflammatory mediators, and their plasma induced significant reductions in NF-κB binding and transcription of tumour necrosis factor (TNF)-α and interleukin (IL)-1β in normal leukocytes *in vitro*.[32]

This encouraging small trial led the ARDS Network in the US to conduct a much larger multicentre randomised double-blind placebo-controlled trial of low-dose steroids in 180 patients with ARDS of at least 7 days' duration.[33] In this study, methylprednisolone 2 mg/kg/day for 14 days (followed by a tapering dose over 2–4 days) was effective in reducing plasma IL-6 levels and neutrophil count in bronchoalveolar lavage fluid, suggesting that lung inflammation was indeed reduced. Patients who received methylprednisolone had more ventilator-free and shock-free days during the first 28 days, improved oxygenation, better respiratory-system compliance, and fewer days of vasopressor therapy. However, 60- and 180-day mortality in each group was almost identical (28.6% v 29.2%, and 31.9% v 31.5%). There were no more infectious complications in the methylprednisolone group, but there was a higher rate of neuromuscular weakness. In the subset of patients enrolled at least 14 days after the onset of ARDS, methylprednisolone was associated with significantly increased 60- and 180-day mortality. The authors suggested this may reflect less pulmonary fibrotic change in patients surviving to 14 days with ARDS, who might therefore derive less benefit from steroids while incurring all of their adverse effects.

Although this was a large and well conducted study, a number of criticisms have been raised. The study was conducted over a time period when there was a dramatic change in the intensive care approach to ventilator management of ARDS. The confounding effect of lower mortality associated with the introduction of low tidal volume ventilation and permissive hypercapnia may have obscured any mortality benefit from steroids. The study had a large number of exclusion criteria, which resulted in only 5% of otherwise eligible patients being enrolled. The methylprednisolone was tapered relatively quickly (over 2–4 days). The high need for reintubation (22% in the methylprednisolone group v 7% controls) might reflect the rebound pulmonary inflammation that has been observed when steroids are abruptly ceased.[34] The treatment group contained a disproportionate number of females, and females have previously been shown to be less responsive to steroid therapy,[26] perhaps because of a greater capacity to metabolise methylprednisolone compared with males.[35]

Possible adverse effects of intravenous steroids

The failure of the ARDS Network trial to show a benefit of steroids in late ARDS is disappointing given the results of the earlier preclinical and smaller clinical studies. In addition to the methodological concerns outlined above, it remains possible that intravenous steroids had a beneficial effect on the lung in this study that was outweighed by a detrimental systemic effect. Among the adverse systemic effects postulated for intravenous steroids are:

- increased risk of infection;
- increased risk of neuromuscular dysfunction in critical illness;[36]
- increased blood glucose level[33] and impaired glycaemic control;
- psychosis;[37] and
- gastric ulceration.[38]

Steroids are undoubtedly immunosuppressive, and while the largest trial to date did not detect increased nosocomial infection with steroids[33] there may have been insufficient power to allow this. Furthermore, blood sugar levels were higher in steroid-treated patients in this trial. In addition to these adverse systemic effects, it is of course possible that intravenous steroids have some beneficial actions in patients with ARDS. The lower incidence of shock in the steroid arm of the ARDS Network trial (5.6% v 16.5% placebo, $P = 0.03$)[33] is one example. However, this only serves to emphasise the importance of the above putative adverse effects: despite the reduced incidence of shock, mortality was unchanged.

If the failure of the ARDS Network and previous trials is indeed due to adverse systemic effects outweighing any local and systemic benefit, this raises the possibility that, if steroids could be applied locally without substantial systemic absorption, a net benefit might be observed. Steroids are applied locally to the skin, nasal mucosa, and gastrointestinal tract for conditions such as dermatitis, allergic rhinitis and inflammatory bowel disease, and inhaled steroids are used in asthma and chronic obstructive pulmonary

disease (COPD). Direct application to their site of action maximises their desired effect while minimising adverse systemic effects. Effective inhaled drug delivery systems have been developed. The delivery of steroids by the inhaled route in ARDS warrants further exploration.

Inhaled corticosteroids in ARDS

Inhaled steroids have fewer systemic effects

Extensive experience has accumulated with inhaled steroids in the management of asthma. In general, systemic effects are less frequent with inhaled as opposed to intravenous or oral steroids, primarily because of low systemic absorption via this route. At low and medium doses, there are no reported cases of adrenal suppression with inhaled steroids, although at higher doses adrenal suppression occasionally occurs.[39] In children, only 6% of a nebulised dose crossed the alveolar membrane into the systemic circulation.[40] Fractional absorption may be higher in ARDS because of increased lung permeability,[41] although this may be mitigated over time by a reduction in alveolar/epithelial permeability induced by steroids.[42] The delivery system influences systemic absorption,[43] which largely reflects the efficacy of drug deposition in the lung as absorption is greater through the lung than the gastrointestinal tract. The systemic side effects of equitherapeutic doses of the various inhaled steroids also differ: budesonide and beclomethasone have fewer systemic effects than fluticasone.[43] Ciclesonide, a more recently developed inhaled steroid, may have even fewer systemic side effects as it is 99.4% protein-bound (and therefore inactive) in the systemic circulation.[44] Ciclesonide is a pro-drug, selectively metabolised to its active form (desisobutyryl-ciclesonide) in the lung,[45] which is likely to further minimise systemic effects.

Inhaled steroids may reach their site of action more effectively

ARDS is characterised by terminal airway damage,[46] and there is some evidence that the inflammation occurring in ARDS is predominantly on the alveolar side of the interstitial space,[47] although this has not been conclusively demonstrated. It is reasonable to expect that the terminal airways and alveoli would be more accessible to inhaled rather than intravenous drugs. This effect may be even more pronounced with synthetic intravenous steroids, such as prednisone and methylprednisone, for which the capillary endothelium is a more impermeable barrier.[48] Access of intravenous steroids to the site of action may be particularly compromised in ARDS, where inflammation can cause microvascular thrombosis and occlusion in the most affected areas.[47] Studies in asthma have shown that inhaled steroids with an extra-fine particle size (around 1 μm) easily reach the distal airways,[49] where they have a greater effect on lung mechanics and symptoms than conventionally sized particles (of around 5 μm), which are preferentially deposited in larger airways.[49] New formulations of steroids[49] and modern nebulisers[50] are now capable of producing particles of this optimal size.

Countering the argument that inhaled steroids may reach their site of action more effectively than intravenous steroids is the concern that inhaled medications will be preferentially deposited in well ventilated areas of the lung. This is the most likely explanation for the improvement in ventilation/perfusion mismatch seen with the vasodilators inhaled nitric oxide and prostacyclin:[51] blood flow increases only in well ventilated alveoli. Computed tomography has demonstrated that much of the lung is atelactatic and oedematous in ARDS, with a small portion of relatively normal-appearing lung thought to be responsible for most gas exchange.[52] Penetration of inhaled medications into the oedematous portions of the lung has never been quantified. Medications with short half-lives are particularly unlikely to penetrate poorly ventilated or oedematous areas. For instance, the short half-life of inhaled prostacyclin (serum half-life, approximately 5 minutes;[53] half-life in alveolar oedema fluid, unknown) may decrease its penetration into less ventilated areas, facilitating its selective action in the open parts of the lung. The degree to which this effect is lost by using iloprost, the more stable form of prostacyclin, is not known. Steroids, on the other hand, have half-lives measured in hours rather than minutes, and may well penetrate sufficiently far into the injured lungs to be of benefit. Furthermore, oedema in ARDS is an evolving process, and exposure of well ventilated areas to inhaled steroid may protect against incipient inflammation.

Delivery systems allow safe use of inhaled steroids in ventilated patients

Whereas inhaled bronchodilators are commonly used in the ventilator circuit, there has been less experience with delivery of steroids via this route. Factors affecting aerosol penetration into the peripheral airways include initial aerosol particle size (described above), location of the nebuliser within the circuit, the presence of a spacer device,[54] carrier gas temperature and humidification, density of the inhaled gas, endotracheal tube size, and ventilator settings, such as tidal volume and inspiratory flow.[50] The mean mass aerodynamic diameter of the aerosol particles should ideally be less than 2 μm to minimise loss in the endotracheal tube,[50] while maximal deposition in the peripheral airways is achieved by particles of 1 μm.[49] Aerosols can be delivered through an endotracheal tube using a gas-driven jet nebuliser to shear

fluid into particles, a piezoelectric ultrasound crystal,[55] a metered dose inhaler, or a catheter placed through the endotracheal tube. Estimates of drug delivery to the lower respiratory tract range from 2.2%[56] to 15.3%[57] with a jet nebuliser, to 6% using a metered dose inhaler and spacer,[58] to 95% with the endotracheal catheter.[50] The relative merits of each approach are beyond the scope of this review. It is sufficient to note that delivery of steroid by this route depends on numerous factors, but, if these are held constant, a predictable drug dose of suitable particle size can be delivered.[50]

Clinical use of inhaled steroids in illnesses similar to ARDS

Inhaled beclomethasone via an endotracheal tube has been used safely in neonatal respiratory distress syndrome, with beneficial effects on oxygenation[59] and markers of pulmonary inflammation.[60] The outcome benefits in larger trials have been less encouraging, and the implementation of this therapy remains controversial.[61] Inhaled steroids have been used successfully in ventilated adult patients with COPD. Fluticasone propionate or placebo was administered via metered dose inhaler for 5 days into the ventilator circuit of 12 hypercapnic COPD patients in a randomised, placebo-controlled, crossover study.[62] By Day 6, fluticasone had significantly decreased intrinsic positive end-expiratory pressure (iPEEP) and resistance to flow compared with placebo.

A note of caution: possible increase in lung catabolism of steroids in ARDS

A possible explanation for the failure of so many trials of intravenous steroids to show benefit is the increased expression of 11β-hydroxysteroid dehydrogenase type 2 seen in the airway epithelium and other cells in lung tissue obtained at autopsy from patients who died of ARDS.[63] This enzyme metabolises steroids to their inactive forms. This would most likely have equal effects on the action of inhaled and intravenous steroids. However, the highest enzyme expression was observed in patients who had been exposed to systemic steroids at the largest doses and for the longest durations. Perhaps locally concentrated (ie, inhaled) steroid might induce the enzyme to a lesser degree. The above study included only 14 patients and has not been repeated, but it does add a note of caution to advocacy for further trials of steroids in ARDS. If steroids induce their own catabolic enzymes, this would argue for higher doses; however, almost all studies of high-dose intravenous steroids have shown a neutral, if not detrimental, effect. The inhaled route may allow higher concentrations at the required site of action without the penalty of adverse systemic effects.

Preliminary evidence for benefit of inhaled steroids in ARDS

A number of animal studies of experimental lung injury support the potential efficacy of inhaled steroids for the treatment of ARDS. Inhaled budesonide prevented increases in BAL fluid concentrations of TNF, IL-1β, IL-6 and monocyte chemotactic protein (MCP)-1 in response to intratracheal lipopolysaccharide administration in rats.[64] The formation of lung oedema was also attenuated. The effect of prophylactic treatment with aerosolised corticosteroid liposome (CSL) given 15 minutes or 2 hours before intravenous endotoxin was assessed in pigs.[65] Pretreatment with CSL at both times before endotoxin partly counteracted the late endotoxin-induced abnormalities in expiratory resistance, dynamic compliance, and mean pulmonary artery pressure. CSL administration did not affect endogenous cortisol production. In another study, pigs treated with inhaled budesonide immediately before or 30 minutes after inhalation of chlorine gas had improved clinical indices of lung injury (such as haemorrhagic oedema fluid in the ventilator tubing, Pa_{O_2}, lung compliance, and pulmonary wet–dry weight ratio).[66]

Inhaled beclomethasone was also effective in reducing acute lung injury caused by a non-pulmonary insult. Nebulised beclomethasone 50 μg/kg was administered to eight pigs at 30 and 360 minutes after intravenous infusion of live *Staphylococcus aureus*.[67] Seven control pigs did not receive nebulised steroid. Pigs in the steroid group had a smaller rise in pulmonary vascular resistance, and a lesser fall in mean arterial pressure, Pa_{O_2} and lung compliance compared with the control pigs. The wet : dry weight ratio was higher in the control group than in the steroid group. A similar series reported reduced pulmonary granulocyte accumulation when pigs with sepsis were given inhaled beclomethasone.[68]

There is only one study of inhaled steroids for the prophylaxis of ARDS in humans.[69] Sixty-three patients inhaled 880 μg fluticasone every 12 hours for 12 weeks from the start of a chemotherapeutic regimen known to cause pulmonary toxicity. Compared with 45 historical controls, delayed pulmonary toxicity syndrome was reduced from 73% to 35% ($P = 0.0003$). The severity of illness was less than in ARDS, but this at least suggests inhaled steroids may protect against a pulmonary insult.

Other inhaled medications of potential benefit in ARDS

Numerous other inhaled medications have (or had) theoretical promise as treatments for ARDS. Pulmonary surfactant has an established role in neonatal respiratory distress syndrome,[70] but the largest trial of artificial surfactant in

adults (725 patients with sepsis-induced ARDS) showed no benefit.[71] Trials continue that address the perceived methodological problems with this study, as has been recently reviewed.[72] Inhaled nitric oxide and prostacyclin improve oxygenation but have no mortality benefit.[72] N-acetylcysteine has been found to be ineffective when given intravenously (as reviewed[72]), but despite demonstration of its utility as an inhaled mucolytic,[73] its effectiveness as an inhaled antioxidant in ARDS has not been tested. Inhaled heparin may also have a beneficial effect.[74] Partial liquid ventilation with perfluorocarbon, which has anti-inflammatory properties, has been attempted in ARDS, with the hope of recruiting dependent lung regions, clearing retained secretions, redistributing blood flow to ventilated regions and reducing lung injury. Unfortunately, despite all these putative beneficial effects, partial liquid ventilation was recently found to have no benefit in a well powered clinical trial.[75]

Perhaps the most promising candidates next to steroids are inhaled β-adrenoceptor agonists, which increase the rate of alveolar epithelial fluid clearance by an effect on membrane ion transporters.[72] Inhaled β-agonists reduced resistance and peak and plateau airway pressure, and increased compliance, in eight ventilated patients with ARDS,[76] and also reduced the incidence of high-altitude pulmonary oedema,[77] presumably in part because of an effect on extravascular lung water. Intravenous salbutamol reduced lung water and plateau airway pressure in 40 patients with ARDS, with a non-significant reduction in 28-day mortality (58% v 66%, $P = 0.40$).[78]

Difficulties with studies of ARDS treatments

Despite promising animal and inflammatory cytokine surrogate end-point data, it has been difficult to demonstrate the mortality benefit of any medication in ARDS. Reasons for this include the diverse comorbidities of the patient population, the many aetiologies of ARDS (clustered around pulmonary and non-pulmonary causes), the different pathological phases of ARDS, the difficulty of classifying patients into one of these phases based on any available criteria,[79] and the fact that most ARDS patients die of multi-system organ failure rather than purely hypoxic respiratory failure.[80]

Surrogate end-points in early studies of ARDS therapy

Inflammatory mediators such as IL-1β, IL-6 and IL-8 in broncho-alveolar lavage fluid[81] and plasma[82] predict mortality in ARDS. Treatments that have had (albeit limited and inconsistent) mortality benefit have reduced the expression of these mediators.[24,32,33,83] Accepting that many therapies with promising effects on such surrogate end-points were subsequently found to be ineffective, it remains prudent from a feasibility, patient safety, and cost standpoint to first investigate the effect of any new agent or delivery route on these inflammatory mediators, before conducting a large-scale trial powered on mortality.

Conclusion: equipoise exists for a randomised controlled trial

The efficacy of inhaled steroids for the prevention and treatment of ARDS in humans has never been tested. There is a sound biological rationale for such a strategy, encouraging evidence of efficacy from animal studies, and less concern regarding safety than for steroids given intravenously. Treatment would most likely have to be continued until resolution of symptoms.[84] Further beneficial effects might be found if inhaled steroids were combined with other promising inhaled medications, especially β-agonists. Countering these hypothesised benefits is the theoretical risk of increased susceptibility to infection with inhaled steroids, although this does not appear to occur when steroids are used long-term in asthma.[85] Additionally, systemic absorption of inhaled steroids may be greater in ARDS, but whether this would be clinically significant is not known. Accordingly, we believe sufficient equipoise exists for randomised controlled trials of inhaled steroids, both in patients at high risk of ARDS, and in those with early or late ARDS. It has been difficult to demonstrate a mortality benefit for any therapy in ARDS patients, even in large trials. In contrast, markers of inflammation are consistently reduced, and levels of such markers are known to correlate with mortality. Therefore, trials of inhaled steroids in ARDS should initially be conducted as phase II studies, using serum and bronchoalveolar lavage levels of pro-inflammatory mediators as surrogates for a beneficial effect on outcome.

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