LATE STEROID RESCUE STUDY (LaSRS): The Efficacy of Corticosteroids as Rescue Therapy for the Late Phase of Acute Respiratory Distress Syndrome

ARDS Network

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Contents

Part I

Study Summary

The late phase of ARDS is often characterized by excessive fibroproliferation leading to gas exchange and compliance abnormalities. While corticosteroids are not effective in early ARDS, several case reports and uncontrolled case series suggest that corticosteroids may be useful in the management of late-phase ARDS. To test this hypothesis, a randomized, double-blinded trial comparing corticosteroids to placebo in severe, late-phase ARDS after 7 days is proposed. Mortality at 60 days is the primary endpoint. Secondary endpoints are ventilator-free days and organ failure-free days.

- **Title** LATE STEROID RESCUE STUDY (LaSRS): The Efficacy of Corticosteroids as Rescue Therapy for the Late Phase of Acute Respiratory Distress Syndrome
- **Objectives** To determine if the administration of corticosteroids, in the form of methylprednisolone sodium succinate, in severe, late-phase ARDS after 7 days, will reduce mortality and morbidity.
- **Study Design** Multicenter, prospective, randomized, controlled clinical trial. Methylprednisolone and placebo will be administered in a double-blind fashion.
- **Inclusion Criteria**
  1. ARDS, defined as the acute onset of:
     (a) $PaO_2/FiO_2 \leq 200$. If altitude > 1000m, use (PaO_2/FiO_2) x $(P_{bar}/760)$
     (b) Bilateral infiltrates. The infiltrates may be patchy, diffuse, homogeneous, or asymmetric, and should be consistent with pulmonary edema or the fibrotic changes of fibroproliferation. Opacities due to pleural effusions or atelectasis should not be considered.
     (c) Requirement for positive pressure ventilation via endotracheal tube.

(d) No evidence of left atrial hypertension. If measured, PAWP $\leq$ 18 mm Hg.

(e) Criteria a-d must occur together within a 24-hour interval. The first date that these criteria are met is defined as the onset of ARDS.

2. Patients will be $\geq$ 7 days and $\leq$ 28 days since onset of ARDS.
3. Since ARDS onset:
   (a) Bilateral infiltrates must have persisted.
   (b) The subject must have required continuous mechanical ventilation (defined as $<$ 24 hours of unassisted ventilation).
4. $PaO_2/FiO_2 \leq 200$ on PEEP $\geq$ 5 cm H_2O on the day of LaSRS enrollment.

- **Exclusion Criteria**

1. Clinical evidence of active, untreated infection.
   Clarifications:
   (a) A known, undrained abscess (*e.g.*, Staphylococcal lung abscess or loculated empyema or intra-abdominal abscess) or a known intravascular nidus of infection (*e.g.*, bacterial or fungal endocarditis) will be a basis for exclusion, even if it is being treated with antibiotics.
   (b) A bacterial infection being treated with a standard antibiotic regimen, with the exception of 1a above, would not be a basis for exclusion.
   (c) Disseminated fungal infection, even if being treated, is an exclusion.
   (d) Ongoing septic shock as defined by Appendix A, even if on antibiotics is a basis for exclusion. Patients may be reconsidered for enrollment after septic shock has resolved for 24 hours, as defined in Appendix A.
2. Age $<$ 13 years.
3. Participation in other IND trials within previous 30 days (Exception: A patient treated with nitric oxide in a compassionate use IND trial may be enrolled).
4. Pregnancy.
5. Burns requiring skin grafting.

6. Patients with AIDS by CDC criteria, diagnosed by either a documented AIDS defining illness or $CD_4 < 200$ (see Appendix J); prednisone therapy ≥ 300 mg (or its equivalent) cumulative dose within 21 days prior to enrollment, or > 15 mg/day (or its equivalent) within 7 days prior to enrollment; cytotoxic therapy within 3 weeks, see Appendix G.
7. Malignancy or other irreversible chronic disease or condition for which 6 month mortality is estimated $\geq 50\%$.
8. Not committed to full support (Exception: A patient will not be excluded if he/she would receive all supportive care except for attempts at resuscitation from cardiac arrest).
9. Severe chronic liver disease (Child-Pugh Class C score > 10 points, see Appendix A).
10. Transplant patients with the exception of autologous bone marrow transplants not otherwise excluded by section 4.3.6.
11. Severe chronic respiratory disease (*e.g.*, COPD, pulmonary fibrosis, morbid obesity [> 1 kg/cm body weight], and other chronic diseases of the lung, chest wall, or neuromuscular system).
12. New clinical diagnosis of nosocomial pneumonia with < 72 hours of appropriate therapy at the time of screening.
13. Extracorporeal support of gas exchange at the time of study entry (e.g., ECMO, IVOX, $ECCO_2R$).
14. Known or suspected adrenal insufficiency.
15. Vasculitis with diffuse alveolar hemorrhage.

- **Efficacy** The primary efficacy variable is the percentage of patients alive at 60 days from study entry. Patients discharged alive from the hospital on unassisted breathing before 60 days will be defined as survivors. Secondary efficacy variables include: a) Ventilator-free days at 28 days following study entry and b) Organ failure-free days at 28 days following study entry.

Part II

Study Description

LATE STEROID RESCUE STUDY (LaSRS): The Efficacy of Corticosteroids as Rescue Therapy for the Late Phase of Acute Respiratory Distress Syndrome

Protocol for the NIH ARDS Network

1 BACKGROUND

1.1 Fibroproliferation and ARDS

The acute respiratory distress syndrome (ARDS) is a pathophysiologic response of the lung to a variety of direct or indirect injurious processes. This response manifests itself clinically as severe hypoxemia and diffuse pulmonary infiltrates on chest radiograph [1]. As ARDS develops and evolves, complex changes in the lung have been divided into several stages based on pathological and clinical findings [2]. It is not clear that every case of ARDS evolves in a step-wise fashion, passing from one stage to the next leading ultimately to resolution or death. Nevertheless, therapy for ARDS might differ depending on the stage of the disease, especially if it were easy to clinically separate these stages from each other.

Histopathology of early ARDS reveals a marked acute inflammatory response with diffuse alveolar damage, influx of large numbers of neutrophils, and evidence of capillary injury. This early stage of ARDS is frequently referred to as the "exudative phase" given the outpouring of inflammatory cells and proteinaceous material into the airspaces [3],[4]. While severity of illness varies, patients may be profoundly hypoxemic during this phase of ARDS. Physiologically, hypoxemia at this time results from intrapulmonary shunting since alveoli are atelectatic or filled with exudate and hyaline membranes [5],[6]; increased deadspace is also present [6]. Thirty-three to fifty percent (33-50%) of deaths after ARDS occur within the first 3-7 days [7]. These patients who die during this early stage

of ARDS often succumb to their underlying illness and not to respiratory failure [7]. Other patients improve and are extubated. Nevertheless, given the average time on a ventilator of 10-14 days, a significant number of patients continue with persistent, severe respiratory failure at the end of one week. The fatality rate of persistent, severe ARDS in patients who survive the first week of therapy is not well-described. Some data suggest that for all ARDS patients still mechanically ventilated, it may be similar to the 40% overall fatality rate [8],[9]. This may not apply to the proposed study, however, since those data include all patients, including patients who might be improving. The fatality rate of patients not improving or deteriorating after the first week is not known.

The cause of persistent ARDS is not well understood and is likely multifactorial. After a few days of lung injury, alveolar cell, endothelial cell, and fibroblast proliferation occurs, perhaps in an attempt by the lung to heal itself. If resolution does not occur during this organizational phase (also called the proliferative phase), disordered collagen and collagen precursor deposition leads to an accumulation of extracellular matrix, alveolar and interstitial scarring, capillary obliteration, and architectural distortion [3],[4],[10]. This may occur as early as 3-7 days of lung injury [10]. Clinically, gas exchange abnormalities persist, due now to ventilation/perfusion abnormalities and increased dead-space ventilation [5]. The lungs often become very stiff. Patients respond less well to the application of positive end-expiratory pressure (PEEP). This fibrotic, or fibroproliferative, phase of ARDS carries with it a high risk of prolonged ventilatory support, and death from respiratory and multiple organ failure. Reasons for this include progressive respiratory failure or, more commonly, increased risk of nosocomial pneumonia, sepsis, multiple organ failure, and other complications of ICU care.

Collagen accumulation in ARDS results, at least in part, from increased procollagen synthesis. This has been shown in several animal models of acute lung injury [11],[12]. Immunohistologic evaluation of lung tissue from patients with ARDS has revealed an abundance of type I and type III collagen, with type III collagen predominating earlier in the disease process [10]. The N-terminal peptide of type III procollagen (procollagen III), which is cleaved from the precursor procollagen molecule during synthesis, appears to be a useful marker of collagen synthesis. A correlation between lavage fluid procollagen III concentrations and severity of illness was reported in patients with idiopathic pulmonary fibrosis [13]. Serum

procollagen III levels in patients with sarcoidosis have been shown to be increased and correlated with disease progression [14]. An association between fibrosis and elevated BAL procollagen III levels has been noted in ARDS as well [15]. The severity of fibroproliferation, as measured by BAL procollagen peptide III, appears to correlate with mortality [16]. Clark and her colleagues found that a procollagen III level $\geq$1.75 U/mL in bronchoalveolar lavage (BAL) significantly correlated with an increased risk of death. High levels of procollagen III could be found as early as 3 days after onset of ARDS, but in patients whose levels remained high by day 7, mortality was $> 60\%$. Patients with a low level of procollagen III on day 7 had a mortality of 24%. Clark speculated that analysis of lavage fluid for procollagen III might identify patients who would benefit from therapies aimed at modulating a maladaptive fibroproliferative response.

While the exact pathogenesis of fibroproliferation in ARDS is unknown, many factors have been identified [17],[18]. Several cytokines have been implicated in the pulmonary fibrotic response, including TNFα, IL-1, IL-8, PDGF, and TGF. In late ARDS, release of these mediators into the alveolar microenvironment from activated macrophages may modulate the pulmonary fibrotic response [17]. TNF can stimulate the growth of pulmonary fibroblasts and the deposition of collagen . IL-1β and IL-8 may also play a role in chronic inflammation and fibrosis. PDGF and TGF-β are pro-fibrotic cytokines that stimulate fibroblasts and the production of components of extracellular matrix.

1.2 Effects of Corticosteroids

Corticosteroids generally exert an inhibitory effect on cytokine transcription, including the putative pro-fibrotic cytokines TNFα, IL-1, IL-6, and IL-8 [19]. Steroids also block cytokine effects by inhibiting some cytokine receptors and by antagonizing cytokine-mediated activation of transcription factors such as AP-1 and NFκB activation by TNFα [19],[20]. Steroids may also have a direct effect on the expression of adhesion molecules such as ICAM-1 and E-selectin [21]. Finally, in patients with late ARDS, corticosteroids have been shown to reduce high serum and BAL levels of TNF, IL-1, and IL-6 [22]. In that study, the reduction in cytokine levels paralleled improvements seen in lung injury score during corticosteroid administration.

In addition to reducing inflammation and fibrosis through inhibition of cytokines, corticosteroids may facilitate collagen breakdown. Corticosteroids accelerate fibroblast procollagen mRNA degradation and may also increase type I collagen degradation. In an experimental model of lung injury, corticosteroids were shown to prevent excessive collagen deposition [23]. Clinically, corticosteroids are used in several fibrotic diseases of the lung. Consequently, it is conceivable that corticosteroids may have a beneficial effect on the fibroproliferative stage of ARDS, leading several researchers to attempt treatment of so-called "chronic" or "late-phase" ARDS with high-dose corticosteroids.

1.3 Clinical Experience with Corticosteroids for Late-Phase ARDS

Four small case series, one case report, and one randomized controlled trial have been published reporting the efficacy of corticosteroids in treating patients with fibroproliferative-phase ARDS. In 1985, Ashbaugh and Maier reported ten cases of ARDS treated with corticosteroids [24]. Corticosteroids were initiated a mean of 12 days (range 6-22 days) after the onset of ARDS. An extensive pre-treatment evaluation was conducted to rule out infection, including open-lung biopsies which also demonstrated pulmonary fibrosis. A dose of methylprednisolone 125 mg every 6 hours was given, corresponding to 4-8 mg/kg/day. Eight of the ten patients survived. Steroids were given for a mean of 51 days (range 22-108 days). The two non-survivors died of overwhelming sepsis (Maier, personal communication).

In 1990, Hooper and Kearl also reported on ten patients with established ARDS [25]. They updated their observations to include a total of 26 patients [26]. Patients were considered eligible for corticosteroids if they had established ARDS of at least 3 days duration that had not improved for 72 hours, the event or process that caused the ARDS had to be resolved or controlled, and the patient had to be free of active infections. Steroids were started at an average of 9 days into the course of ARDS (range 3-40 days). Methylprednisolone was used in very high doses: 125 - 250 mg every 6 hours "to ensure an anti-inflammatory effect". This is the highest reported dose of methylprednisolone for established ARDS in the literature. Methylprednisolone was continued for 3 - 4 days and then

tapered every 2 - 3 days as clinically tolerated. Patients often were on Methylprednisolone for 3 to 5 weeks. The authors report significant improvement in all patients after 3 - 5 days of therapy. The overall survival rate was 81% (21/26). When patients were separated into single-organ failure pulmonary, n = 12) and multiple-organ failure, (n = (14), the survival rates were 100% and 64% respectively. Three patients died of MODS, one died of systemic candidiasis, and one died of a cardiac arrhythmia. Other complications included one wound infection, one empyema, and two GI bleeds. Routine bronchoscopy was not part of their protocol, nor were other aspects of clinical management controlled. However, after the death occurred from systemic candidiasis, all subsequent patients were treated with prophylactic fluconazole.

In 1991, Meduri and colleagues presented 8 patients with fibroproliferative ARDS who received methylprednisolone (2 mg/kg bolus followed by 2-3 mg/kg/day at 6-hour intervals) after infection was ruled out [27]. Steroids were given for a prolonged period of time and six of the eight patients survived. Also reported were improvements in oxygenation (PaO_2/FiO_2 ratio), compliance, and lung injury score. Meduri and associates expanded their observations and subsequently described 25 patients with ARDS (including the original 8) who received steroids for fibroproliferative ARDS [28]. Nineteen of these 25 patients (76%) survived.

Braude and colleagues, in 1992, described a single patient who had ARDS for 3 weeks before receiving 1 mg/kg/day (prednisolone 60 mg daily) [29]. The authors claim dramatic improvements were seen after 48 hours of therapy but they do not comment on the duration of prednisolone. The patient survived.

In 1995, Biffl and colleagues reported on 6 patients over a 5 year period of time who received corticosteroids for "refractory" ARDS [30]. These patients had no evidence of other organ failure and underwent an evaluation, including bronchoalveolar lavage, to exclude an active infection. During steroid therapy, infection surveillance was heightened including repeated BAL at 3-5 day intervals. Corticosteroids were started 16 days after onset of ARDS (range: 12 - 26 days). Weaning of steroids, based on a clinical response (increase in PaO_2/FiO_2 ratio by 50%) was initiated on days 4 - 11 in the 5 responders. A patient who had lung cancer never responded and subsequently died on the ventilator. The mean duration of steroid therapy was 21.3 ± 4.3 days (range 13 - 42 days) and the total

number of ventilator days was 43.8 ± 9.6 (range 24 - 90). Five of the six patients (83%) survived. Complications included gastric necrosis, *Staphylococcus aureus* lung abscess, two episodes of catheter-related sepsis, a fungal UTI, and an episode of prolonged neuromuscular blockade following concurrent use of atracurium and steroids. Several patients (n=4) had barotrauma prior to treatment; two pneumothoraces were reported after therapy commenced. The authors state that all responders had a dramatic response within 3 - 7 days.

Finally, a small randomized controlled clinical trial of methylprednisolone (2 mg/kg bolus foloowed by 2 mg/kg/day; n=16) versus placebo (n=8) demonstrated a reduction in hospital mortality from 62% in placebo treated patients to 12% in steroid treated patients (p=0.03)[34]. The rate of infections per day of treatment was similar in both groups.

The four case series, with a combined N = 67 (N = 10, 26, 25, 6), have a consistently high survival rate of 76%-83% (Table 1). Unfortunately, these studies are uncontrolled and, therefore, cannot detect an improvement in survival compared to any control group. The one randomized controlled trial also demonstrated a high survival rate (88%) but the control group, half of which crossed over to steroids, was relatively small making a meaningful comparison of the treatment groups difficult. In fact, the reported survival rates for steroid treated patients in these series are not very different than the survival rate of patients with ARDS still alive and on the ventilator 2 weeks from onset of ARDS [8], [9]. Finally, the dose of corticosteroids differed amongst the studies as shown in Table 2.

The lack of a large randomized controlled trial and the potential risks of corticosteroids in the ICU, including predisposition to infectious complications, preclude recommending corticosteroids as standard therapy for late ARDS. These trials are nevertheless encouraging and support the need for a large, multicenter, randomized, controlled trial to determine the efficacy and safety of this therapy.

1.4 Toxicity of Corticosteroids

The risks associated with high-dose corticosteroids in the intensive care unit are myriad and, on occasion, can be difficult to distinguish from the complicated course that many patients with ARDS experience. The most

Table 1: Characteristics of 5 Reports and 1 Controlled Trial Describing Efficacy of Corticosteroids in Refractory ARDS

Characteristics of 5 Reports and 1 Randomized Controlled Trial Describing Efficacy of Corticosteroids in Refractory ARDS				
Author/Site	Year	Number	Survival Rate	Comments
Ashbaugh (Seattle)	1985	10	80%	Two deaths due to overwhelming sepsis
Hooper (Phoenix)	1990, 96	26	81%	1 death due to systemic candidiasis; 1 wound infection; 1 empyema
Braude (London)	1992	1	100%	
Meduri (Memphis)	1991,94	25	76%	11 nosocomial pneumonias; 2 abdominal sepsis; 2 candidemias; 1 wound dehiscence
Biffl (Denver)	1995	6	83%	4 nosocomial infection; 1 gastric rupture; 1 prolonged paralysis
Meduri (Memphis)	1998	24	88% Steroid 38% Placebo	No incease in rate of infections per day of treatment

serious, and potentially life-threatening, complication is the development of a nosocomial infection. Corticosteroids are believed to impair phagocytic and bactericidal function through several mechanisms. This can leave the host vulnerable to nosocomial infection with bacteria and filamentous fungi. Dissemination of viral infections (e.g., HSV, VZV) have been reported. Other infections with parasitic agents, such as*Pneumocystis carinii* and *Toxoplasma gondii*, are distinctly unusual as a complication of short-course, high-dose corticosteroid therapy. Several studies of corticosteroids for early and late ARDS have resulted in many nosocomial infections in the treatment groups. Unfortunately, any patient with ARDS on mechanical ventilation is at high risk of developing a nosocomial infection. It becomes difficult to determine when an infection is due to corticosteroids and when it is due to the underlying critical illness. Corticosteroids can also mask infection by reducing fever and causing a leukocytosis through demargination of neutrophils. Standard clinical

Table 2: A Comparison of Corticosteroid Dosing in 5 Case Series, One Controlled Trial, and One Proposed Trial

A Comparison of Corticosteroid Dosing in 5 Case Series One Randomized Controlled Trial, and 1 Proposed Trial			
Author/Site	Daily Dose	Dosing Schedule	Taper
Ashbaugh (Seattle)	4-8 mg/kg MPSS	1-2 mg/kg q6°	yes, after day 5 for total of 21 days
Biffl (Denver)	4-8 mg/kg MPSS	1-2 mg/kg q6°	yes, based on clinical response
Braude (London)	60 mg/day prednisolone	qd	not described; received for at least 14 days
Hooper (Phoenix)	500-1000mg/day MPSS	125-250 mg q6°	yes, after 3-4 days
Meduri (Memphis)	2-3 mg/kg MPSS	0.5-0.75 mg/kg q6°	as clinically tolerated after extubation or day 14
ARDS Network	2 mg/kg MPSS x 14d	0.5mg/kg q6° x 14d	yes, after day 14, then again after day 21;
	1 mg/kg MPSS x 7d	0.5 mg/kg q12° x 7d	approx 21 days total

criteria for infection can be obscured and rendered inaccurate.

Other untoward effects of corticosteroids in the critically ill include uncontrolled hyperglycemia, wound dehiscence, muscle weakness and/or myopathy including the respiratory muscles, acute psychosis, and acute pancreatitis.

2 OBJECTIVES

The late phase of ARDS is often characterized by excessive fibroproliferation leading to gas exchange, compliance abnormalities, and prolongation of mechanical ventilation. Corticosteroids may diminish the fibroproliferative response. The proposed study is designed to compare the effect of corticosteroids with placebo in the management of late-phase ARDS. The objective is to determine if the administration of corticosteroids, in the form of methylprednisolone sodium succinate, in

severe ARDS that is either stable or worsening after 7 days will reduce mortality and morbidity.

2.1 Hypotheses

1. The administration of corticosteroids, in the form of high-dose methylprednisolone, will improve survival compared to placebo in patients with late, non-resolving ARDS (*i.e.*, of at least one week's duration).

2. The administration of corticosteroids, in the form of high-dose methylprednisolone will reduce morbidity as measured by a decreased length of time of mechanical ventilation, improved pulmonary physiology, and increased organ failure-free days.

3. The administration of corticosteroids, in the form of high-dose methylprednisolone, will not significantly increase infectious complications compared to placebo in patients with late, non-resolving ARDS (*i.e.*, of at least one week's duration).

4. High initial levels of markers of ongoing inflammation and fibroproliferation in serum and bronchoalveolar lavage fluid of patients with late, non-resolving ARDS (of at least one week's duration) will be associated a beneficial clinical response to corticosteroids, compared to low initial levels.

3 STUDY DESIGN

This is a multicenter, randomized, double-blinded trial comparing corticosteroids to placebo in the treatment of the late ($\geq$ 7 days), non-resolving phase of the acute respiratory distress syndrome (ARDS). Subjects with severe, late-phase ARDS will be enrolled between day 7 and 28 of their illness and treated for 21 days with the study drug with tapering of the drug over the subsequent 4 days. The primary endpoint is all-cause mortality at 60 days after study enrollment. Secondary endpoints are ventilator-free days at 28 days following study entry and organ failure-free days.

3.1 Endpoints

1. Primary end-point: Mortality at hospital discharge or 60 days after study enrollment.
2. Secondary end-points, in order of priority:
   (a) Ventilator-free days at 28 days following study entry.
   (b) Number of organ failure-free days at 28 days following study entry.
   (c) Reduction in markers of ongoing inflammation and fibroproliferation at 7 days following study entry.

4 STUDY POPULATION AND ENROLLMENT

4.1 Number, Source, and Screening

The trial will accrue 200 patients in six to eight years. Patients will be recruited from intensive care units (ICUs) in approximately 24 hospitals that comprise the NIH ARDS Network. Each of the ten centers that comprise the Network have provided documentation of at least 100 ARDS patients per year although actual experience has resulted in accrual of 24-37 patients/year. Study coordinators at each site will visit each ICU daily to identify potential candidates for enrollment using inclusion and exclusion criteria described in sections 4.2, and 4.3. Permission to approach patients/families will be requested from attending physicians. All patients meeting the study inclusion criteria will be entered on a screening log. The screening log will include information explaining why patients meeting the inclusion criteria are not enrolled (exclusion criteria, attending physician denial, consent unobtainable, etc.).

4.2 Inclusion Criteria

The intent of the study is to enroll patients with unresolving, severe, late-phase ARDS (at least 7 days duration). Since fibroproliferation can not be documented without a lung biopsy, oxygenation criteria will be used as a surrogate for advanced fibroproliferation.

1. ARDS, defined as the acute onset of:
   (a) $PaO_2/FiO_2 \leq 200$. If altitude > 1000m, use (PaO_2/FiO_2) x $(P_{bar}/760)$.
   (b) Bilateral infiltrates. The infiltrates may be patchy, diffuse, homogeneous, or asymmetric and should be consistent with pulmonary edema or the fibrotic changes of fibroproliferation. Opacities due to pleural effusions or atelectasis should not be considered.
   (c) Requirement for positive pressure ventilation via endotracheal tube.
   (d) No clinical evidence of left atrial hypertension. If measured, PAWP ≤ 18 mm Hg.
   (e) Criteria a-d must occur together within a 24-hour interval. The first date that these criteria are met is defined as the onset of ARDS.
2. Patients will be $\geq$7 days and $\leq$28 days since onset of ARDS.
3. Since ARDS onset:
   (a) Bilateral infiltrates must have persisted.
   (b) The subject must have required continuous mechanical ventilation (defined as < 24 hours of unassisted breathing).
4. $PaO_2/FiO_2 \leq 200$ on PEEP ≥ 5 cm H_2O on the day of LaSRS enrollment.

4.3 Exclusion Criteria (at time of enrollment)

1. Clinical evidence of active, untreated infection.
   Clarifications:
   (a) A known, undrained abscess (*e.g.*, Staphylococcal lung abscess or loculated empyema or intra-abdominal abscess) or a known intravascular nidus of infection (*e.g.*, bacterial or fungal endocarditis) will be a basis for exclusion, even if it is being treated with antibiotics.

(b) A bacterial infection being treated with a standard antibiotic regimen, **with the exception of section 4.3.1a, would not be a basis for exclusion.**

(c) Disseminated fungal infection, even if being treated, is an exclusion.

(d) Ongoing septic shock, as defined in Appendix A , even if on antibiotics, is a basis for exclusion. Patients may be reconsidered for enrollment after septic shock has resolved for 24 hours, as defined in Appendix A.

2. Age < 13 years.

3. Participation in other IND trials within previous 30 days (Exception: A patient treated with nitric oxide in a compassionate use IND trial may be enrolled). A patient enrolled in the ARDSNet ALVEOLI trial may also be enrolled.

4. Pregnancy.

5. Burns requiring skin grafting.

6. Patients with AIDS by CDC criteria, diagnosed by either a documented AIDS defining illness or $CD_4 < 200$ (see Appendix J); prednisone therapy ≥ 300 mg (or its equivalent) cumulative dose within 21 days prior to enrollment, or > 15 mg/day (or its equivalent) within 7 days prior to enrollment; cytotoxic therapy within 3 weeks (see Appendix G).

7. Malignancy or other irreversible chronic disease or condition for which 6 month mortality is estimated $\geq$50%.

8. Not committed to full support (Exception: A patient will not be excluded if he/she would receive all supportive care except for attempts at resuscitation from cardiac arrest).

9. Severe chronic liver disease (Child-Pugh Class C score > 10 points, see Appendix A).

10. Transplant patients with the exception of autologous bone marrow transplants not meeting 4.3.6.

11. Severe chronic respiratory disease (*e.g.*, COPD, pulmonary fibrosis, morbid obesity [> 1 kg/cm body weight], and other chronic diseases of the lung, chest wall, or neuromuscular system. see Appendix A).

12. New clinical diagnosis of nosocomial pneumonia with < 72 hours of appropriate therapy at the time of screening.

13. Extracorporeal support of gas exc ange at the time of study entry (e.g., ECMO, IVOX, $ECCO_2R$).

14. Known or suspected adrenal insufficiency.

15. Vasculitis with diffuse alveolar emorr age.

4.4 Screening and Qualification

1. Patients ≥ 7 and ≤ 28 days since ARDS onset with persistent bilateral infiltrates and supported with mec anical ventilation should be screened for enrollment.

2. Disqualification criteria: If a patient meets all of the following criteria during the screening period, they are permanently disqualified and no longer need to be followed.

   (a) $PaO_2/FiO_2 > 300$, AND

   (b) Cst > 0.5 mL/cm H_2O/kg IBW, AND

   (c) $V_E \leq 10$ L/min, corrected for $PaCO_2$ ($V_{Ecorr} = V_{Emeas}$ x $PaCO_2/40$), or $V_{Ecorr} \leq$ the predicted V_E (i.e. $V_E \leq 100$ mL/kg IBW/min.

4.5 Enrollment Time Window

If the patient qualifies, consent should be obtained from the patient or the patient's surrogate, the patient should be enrolled, be randomized, undergo BAL and other baseline evaluations, and receive the first dose of study drug within 12 hours. If the patient is not enrolled or fails to qualify, the patient should be re-evaluated daily. T e patient can be enrolled any time between day 7 and 28 if the patient meets qualification criteria as long as clinical deterioration is not due to a new nosocomial pneumonia.

4.6 Informed Consent

Informed consent will be obtained from each patient or surrogate prior to enrollment in the trial.

4.7 Randomization

The randomization scheme to be employed will consist of centralized, random permuted blocks to minimize inter-center variability. Once eligibility in the study has been established and informed consent to participate has been obtained, the data coordinating center will be called and an assignment will be made by computer-generated randomizations to receive either MPSS or placebo. The randomization system will be based on Interactive Voice Response technology. Each research coordinator will have a unique Personal Identification Number (PIN). He/she will call the system and be asked to supply the PIN. A patient ID number will be assigned. The research coordinator will provide this ID number to the pharmacy which will dispense either MPSS or placebo based on a predetermined list in the research pharmacy. The pharmacist will be unblinded to the treatment assignments. He or she will be responsible for treatment assignments, formulations, and maintaining the list of codes revealing which treatment is being taken by each study participant.

4.8 Minorities and Women

Gender and racial subsets were considered by the NHLBI in selecting the Network centers. The demographic profiles of the centers selected for the Network show that the aggregate patient population contains representative proportions of minorities (28%) and women. Recruitment of minorities and women will be monitored by the Network Coordinating Center. If necessary, additional recruitment efforts will be made at specific centers to ensure that the aggregate patient sample contains appropriate gender and minority subsets.

Blinded randomization will result in approximately equal numbers of patients assigned to the treatment arms within each population subset. It will be possible to make statistical comparisons within these subsets;

however, any inferences derived from these analyses will be of low power because of the relatively small number of patients within the subsets. The primary value of such analyses would be for generating additional hypotheses, which is appropriate given the current lack of evidence of gender or race-related interactions with the current intervention in the proposed study.

5 STUDY PROCEDURES

5.1 Drug Delivery

Drug or placebo will be delivered via intravenous route.

5.2 Drug Dosage

1. Corticosteroid therapy will consist of methylprednisolone sodium succinate (MPSS) diluted in 50 mL of 5% dextrose in water.
2. The dose of MPSS is a single 2 mg/kg loading dose followed by 0.5 mg/kg every six hours x 14 days, then 0.5 mg/kg every twelve hours x 7 days, then to be tapered per Section 5.3 and Appendix D.
3. Dosage will be calculated from ideal body weight (IBW, Appendix A).
4. Placebo therapy will consist of 50 mL of 5% dextrose in water.

5.3 Duration

1. Daily for 21 days.
2. Begin slow tapering if 21 days of treatment are completed and the patient has not reached 48 hours of unassisted breathing (see Appendix D).
3. Begin rapid tapering (see Appendix D) if:
   (a) The patient develops disseminated fungal infection.

(b) The patient develops septic shock

(c) The patient reaches 48 hours of unassisted breathing.

5.4 Monitoring for Infection

Infectious complications are the most serious potential adverse effects of using corticosteroids to treat late-phase ARDS. Infections w categorized as "serious infections" and "other infections". Each will be monitored for separately.

5.4.1 Routine monitoring

The follow g clinical monitoring for the development of infection while on study drug and for 7 days after discontinuation of study drug is recommended. Items 3-5 below are not required by the protocol but are guidelines for management based on the level of clinical concern.

1. Daily physical examination. Daily physical examination should consist of assessment of line sites, nose, oropharynx, chest, abdomen, skin, and wound inspection.
2. Daily review of the medical record, radiographs, and laboratory studies for evidence of infection as defined in Appendix A
3. Periodic urinalysis (UA); obtain Gram stain and culture if UA suggests pyuria or bacteriuria
4. If abdominal exam is suspicious for an intra-abdominal infectious process, consider an U/S or CT scan and/or laboratory data (LFT's, amylase).
5. If purulent sinus drainage develops, consider evaluation for sinus infection per methods described in A x A. ppendi

5.4.2 Categorization of infections

1. Infections will be categorized as "serious infections" and "other infections". Each will be monitored for separately

2. Serious infections are defined as new, life-threatening, nosocomial infections. These will include all serious infections occurring at least 48 hours after enrollment until day 28 post-enrollment or until 7 days after completion of study drug administration, whichever comes first. This will address to some degree the issue of infections being counted that were not present at time of enrollment and makes the assumptions that immunosuppression due to this dose of steroids will take at least 48 hours to develop and will not last more than 7 days after discontinuation of a short course of corticosteroids. More than one occurrence of the same type of serious infection will be recorded as long as the second episode meets the criterion for being a new infection. This latter criterion is that it must occur at least 72 hours after a prior episode has met its criteria for ending as defined for each entity in Appendix A.

3. Serious infections include all of the following (see Appendix A for definitions):

   (a) Bacteremia (due to a known pathogen with or without signs or symptoms)

   (b) Disseminated fungal infection

   (c) Nosocomial pneumonia

   (d) Peritonitis not associated with peritoneal dialysis

   (e) Septic shock

   (f) Wound infection requiring extensive debridement and/or healing by secondary intention

   (g) Meningitis

   (h) Empyema

   (i) Abdominal or other deep tissue abscess

   (j) Disseminated viral infections (e.g., VZV, HSV)

4. Other Infections include all of the following (see Appendix A for definitions):

   (a) *C. difficile* colitis

   (b) Indwelling vascular line infection

   (c) Oral or mucosal candidiasis

   (d) Peritonitis associated with peritoneal dialysis

(e) Sinus infection

(f) Skin infection including non-disseminated viral infection.

(g) Septic arthritis

(h) Urinary tract infection

(i) Other infections not listed above or as serious infections.

5.4.3 Surveillance for nosocomial infections

The patient will be assessed for the presence of any of the above infections daily by the following surveillance system.

1. Serious Infections:

   (a) Bacteremia due to known pathogen with or without signs or symptoms: The results of any clinically obtained blood cultures will be captured up to 28 days after study entry. Routine blood cultures will not be obtained at pre-specified times given the very low rate of randomly drawn positive blood cultures in the ICU. A blood culture should be sent, however, if the diagnosis of nosocomial pneumonia is being considered (see item 5.4.3.1.c below).

   (b) Disseminated fungal infection: The results of any clinically obtained blood cultures will be captured up to 28 days after study entry. Clinically indicated examination of the retinas in patients who have three or more sites of fungal colonization with one or more signs of infection (fever, elevated WBC $>$ 15,000/mm^3, sepsis-induced hypotension) without other explanation.

   (c) Nosocomial pneumonia: Review of daily chest radiographs (when available) for new localized infiltrate (not atelectasis or pleural effusion), consolidation or cavitation and daily review of temperature and WBC count (when obtained clinically). If the patient meets the criteria for suspected or possible pneumonia (appendix A), a tracheal aspirate should be sent for Gram stain and culture except if protected-specimen brushings or bronchoalveolar lavage for quantitative culture are done clinically. One set of blood cultures should also be obtained.

Chest radiographs and routine bronchoscopies are not required, even in the presence of fever and leukocytosis, since the data suggest that clinical and radiographic criteria do not correlate well with bronchoscopy results in patients with ARDS. Data are inadequate to allow consensus regarding the utility of quantitative BAL or PSB cultures to diagnose pneumonia in patients with ARDS.

(d) Septic shock: Continuous monitoring for sepsis-induced hypotension as defined above.

(e) Peritonitis (not associated with peritoneal dialysis): Daily review of progress notes and results of radiographic and laboratory studies.

(f) Wound infection requiring extensive debridement and/or healing by secondary intention: Daily review of progress notes and nursing notes and, if wound infection is documented, discussion with medical and team regarding extent of debridement or allowing wound to heal by secondary intention.

(g) Other new infections: Meningitis, empyema, abdominal or other deep tissue abscess, disseminated viral infections: Daily review of progress notes and laboratory results.

2. Other Infections:

(a) *C. difficile* colitis: Daily review of progress notes and laboratory results.

(b) Indwelling vascular line infection: Daily review of progress notes and laboratory results.

(c) Oral or mucosal candidiasis: Daily review of progress notes and laboratory results.

(d) Peritonitis associated with peritoneal dialysis: Daily review of progress notes and laboratory results.

(e) Sinus infection: Daily review of progress notes and laboratory results.

(f) Skin infection including non-disseminated viral infection: Daily review of progress notes and laboratory results.

(g) Septic arthritis: Daily review of progress notes and laboratory results.

(h) Urinary tract infection: Daily review of progress notes and laboratory results.

(i) Other infections not listed above or as serious infections: Daily review of progress notes and laboratory results.

5.4.4 New severe sepsis or septic shock

Complete evaluation, including above items 5.4.1.1-5, should be done as clinically warranted if new severe sepsis or septic shock (Appendix A) develops while on steroids.

5.4.5 Suspected or confirmed new infection

If a new infection is suspected or confirmed, antibiotics should be instituted as soon as possible and modified, if necessary, once culture and sensitivity data are available. If disseminated fungal infection is found or septic shock develops, steroids should be rapidly tapered as outlined in Appendix D.

5.5 Toxicity

The toxicity of high-dose corticosteroids in the ICU may include any or all of the following problems: 1) Development of a serious secondary infection; 2) Uncontrolled hyperglycemia; 3) Wound dehiscence; 4) Skin breakdown, decubitus ulcers; 5) Respiratory muscle weakness; 6) Acute psychosis; and 7) Acute pancreatitis with an amylase $\geq$ 3x upper limit of normal. Monitoring for these complications will be done by daily chart review. Electrolytes, blood glucose, and amylase will be reviewed daily, the WBC will be reviewed every other day, and the bilirubin, platelet count, and creatinine will be reviewed biweekly by the Site Coordinator. A physician member of the study team will meet with the site coordinator at least three times per week to review the above laboratory findings as well as the results of infection monitoring. At times, a physician member of the study team will need to review these findings daily as the patients' safety needs dictate. Treatment for each complication should occur as clinically indicated.

5.6 Stress Ulcer Prophylaxis

Corticosteroids are no longer thought to be a significant risk factor for GI ulceration or stress gastritis. Sucralfate should be the agent of choice if a prophylactic agent for GI ulceration is required.

5.7 Mechanical Ventilation

Ventilatory strategy will not be specified by protocol. Since the time the patient achieves unassisted ventilation status affects the primary endpoint, weaning strategy will be specified by protocol once a certain ventilatory level is met, to assure similar weaning methods in the study and control populations.

5.8 Weaning

5.8.1 Commencement of Weaning

Patients will be assessed for the following criteria each day between 0600 and 1000. If a patient procedure, test, or other extenuating circumstance prevents assessment for these criteria between 0600 and 1000, then the assessment and initiation of subsequent weaning procedures may be delayed for up to four hours.

1. $\geq$ 12 hours since enrollment.
2. $FiO_2 \leq 0.50$ and PEEP $\leq$ 8 cm H_2O.
3. Values of both PEEP and $FiO_2 \leq$ values from previous day (comparing Reference Measurement values, section 6.3).
4. $V_E < 15$ L/min or $V_E < 200$ mL/kg IBW/min.
5. Not receiving neuromuscular blocking agents and without neuromuscular blockade.
6. Patient exhibiting inspiratory efforts. Ventilator rate will be decreased to 50% of baseline level for up to 5 minutes to detect inspiratory efforts if no efforts are evident at baseline ventilator rate.

7. Systolic arterial pressure $\geq$ 90 mm Hg without vasopressor support ($\leq$ 5 μg/kg/min dopamine or dobutamine or equivalent low dose of another vasopressor will not be considered a vasopressor).

   If criteria 1-6 are met, weaning potential will be assessed during a CPAP trial of $\leq$ 5 minutes at CPAP = 5 cm H_2O and FiO_2 = 0.50. If respiratory rate remains $\leq$ 35/min during the 5-minute CPAP trial, the patient will have met the commencement of weaning criteria and will enter the pressure support wean procedure (Sections 2-5). If respiratory rate exceeds 35/min during the 5-minute CPAP trial, the patient will resume previous ventilator settings. The patient will be reassessed for weaning the following day at 0600-1000. (If failure to maintain the respiratory rate $\leq$ 35 during the CPAP trial is attributed primarily to anxiety, then appropriate treatment for anxiety will be given and a second 5-minute CPAP trial initiated within 4 hours).

5.8.2 Initial Settings (only PS of 5, 10, 15, and 20 cm H_2O will be used for weaning.)

1. If the patient is on volume controlled ventilation, set initial Pressure Support (PS) at 20 cm H_2O.
2. If the patient is on PS, decrease PS for weaning to the next allowable level used for weaning (e.g., if the patient is on PS=18 and tolerates the 5 minute CPAP trial, begin weaning at PS=15).
3. If the patient is on Pressure Control (PC), set initial PS at the next allowable level used for weaning below the PC setting, not to exceed 20 cm H_2O (e.g., if patient is on PC=18 and tolerates the 5 minute CPAP trial, begin weaning at PS=15).
4. PEEP = 5 cm H_2O.
5. FiO_2 = 0.50.

5.8.3 Assessment for Tolerance

Patients will be assessed for tolerance using the following criteria:

1. Total respiratory rate < 35 (≤ 5 min at respiratory rate > 35 may be tolerated).
2. $SpO_2 \geq 88\%$ (< 15 min at $< 88\%$ may be tolerated).
3. No respiratory distress (two or more of the following):
   (a) Heart rate greater than 120% of the 0600 rate(≤ 5 minutes at $>$ 120% may be tolerated).
   (b) Marked use of accessory muscles.
   (c) Abdominal paradox.
   (d) Diaphoresis.
   (e) Marked subjective dyspnea.

   If any of goals 1,2, or 3 are not met on initial set-up to PS, then the ventilator mode will be changed back to the previous settings and the patient will be reassessed the next morning.

5.8.4 Subsequent Ventilator Settings

1. Reduce PS level by 5 cm H_2O as rapidly as tolerated at intervals not greater than 3 hours, guided by the tolerance criteria (section 5.8.3). PS will not be decreased below 5 cm H_2O. No decreases in PS will be made after 1900.
2. If PS = 5 cm H_2O is tolerated for one or more hours (using tolerance criteria 5.8.3, 1-3 above), assess for ability to sustain unassisted breathing (section 5.8.5 below).
3. If PS reduction or weaning to unassisted breathing (section 5.8.5) not tolerated, abandon weaning attempts this day. Resume pre-wean ventilator settings (clinical team resumes control of ventilator and may opt to continue PS at a level tolerated clinically by the patient and may re-attempt weaning later that same day).

5.8.5 Assess for Ability to Sustain Unassisted Breathing

Initiate a trial of spontaneous breathing on CPAP ≤ 5 cm H_2O, T-piece, or tracheostomy mask with $FiO_2 \leq 0.50$. Monitor for the following:

1. $SpO_2 \geq 90\%$ and/or $PaO_2 \geq 60$ mmHg.
2. Spontaneous tidal volume ≥ 4 ml/kg ideal body weight.
3. Respiratory Rate ≤ 35/min.
4. pH ≥ 7.30 if measured.
5. No respiratory distress (2 or more of the following):
   (a) Heart rate $> 120\%$ of the 0600 rate (≤ 5 min at $> 120\%$ may be tolerated).
   (b) Marked use of accessory muscles.
   (c) Abdominal paradox.
   (d) Diaphoresis.
   (e) Marked subjective dyspnea.

If all of criteria 1-5 are met for ≥ 60 minutes, continue with unassisted breathing (section 5.8.6). If any of criteria 1-5 are not met during the 60 minute trial, then resume PS ventilation at 5 cm H_2O and reassess for tolerance (section 5.8.3).

5.8.6 Definition of Unassisted Breathing

1. Extubated with face mask, nasal prong oxygen, or room air, OR
2. T-tube breathing, OR
3. Tracheostomy mask breathing, OR
4. CPAP ≤ 5 without PS or IMV assistance for > 120 minutes.

If a patient requires positive pressure ventilation after a period of unassisted breathing, the study ventilator procedures will resume unless the patient was discharged from the hospital or > 28 days elapsed since enrollment.

6 DATA COLLECTION

6.1 Background Assessments

1. Demographic and admission data.
2. Pertinent medical history and physical examination.
3. Height (cm) and calculated ideal body weight (IBW, kg) (Appendix A).
4. ARDS onset date and time on the ventilator since ARDS onset.
5. ARDS risk factor:
   (a) sepsis.
   (b) pneumonia.
   (c) aspiration of gastic contents.
   (d) multiple transfusion.
   (e) trauma.
   (f) other.
6. Presence of the following underlying diseases:
   (a) Metastatic cancer (proven by surgery, computed tomographic scan, or other documented method).
   (b) Hematologic malignancy (lymphoma, acute leukemia, or multiple myeloma).
   (c) AIDS with complications (PCP, Kaposi's sarcoma, lymphoma, tuberculosis, or toxoplasmosis).
7. Types of admission
   (a) Scheduled surgical.
   (b) Medical.
   (c) Unscheduled surgical.

6.2 Baseline Assessment

The following data and assessments will be collected on the day of enrollment (Day 0). If more than one value is available on the day of enrollment, the value closest to randomization will be recorded. If no values are available during the preceding 24 hours, then values will be measured during a four hour interval after randomization but before bronchoscopy.

1. Vital signs: body temperature (°C), heart rate (b/min), total respiratory rate, systolic and diastolic blood pressure (mm Hg).
2. Arterial blood gases: pH, PaO_2, $PaCO_2$, (can use the qualifying ABG if within 12 hours and ventilator settings are unchanged).
3. Ventilator parameters: mode, PEEP, FiO_2, minute ventilation (V_E; set and total), tidal volume (V_T), static thoracic compliance (Cst), and patient position (prone vs. supine).
4. Urinary output (most recent 24 hour value).
5. Serum electrolytes, BUN, creatinine, glucose, bilirubin, amylase (most recent 24 hour value, otherwise obtain).
6. Hematocrit, WBC, platelets, prothrombin time (most recent 24 hour value, otherwise obtain).
7. Serum albumin concentration (most recent 48 hour value, otherwise obtain).
8. Blood for cytokines. Supernatants will be frozen at -70°C and stored for later analysis.
9. Glasgow coma score.
10. Frontal chest radiograph (most recent value 48 hour).
    (a) radiographic lung injury score (# of quadrants).
    (b) presence of absence of barotrauma:
        i. pneumothoraces (R/L).
        ii. pneumomediastinum.
        iii. pneumatoceles > 2 cm diameter (R/L).

11. Administration of the following medications during the 24 hours preceding study initiation (yes/no):

    (a) neuromuscular blocking agents.

    (b) number of antibiotics.

    (c) vasopressors.

    (d) antipsychotics.

12. Urine or serum β-HCG (on females of reproductive potential; most recent value since hospital admission, otherwise obtain).

13. Fiberoptic bronchoscopy (see Appendix C).

    (a) Unilateral BAL.

    (b) BAL fluid analyzed for procollagen peptide III and frozen at -70°C for future cytokine analysis.

    (c) BAL fluid cell count and differential.

14. A physical examination, including the following assessments and suggested clinical responses, should be documented:

    (a) Inspection of all line sites. Consider changing and culturing lines to rule out line infection if local inflammation present (Appendix A).

    (b) Abdominal examination. Consider an U/S or CT scan if exam is suspicious for an intra-abdominal infectious process (unexplained tenderness, rebound, guarding, mass, or evidence of a paralytic ileus or bowel obstruction).

    (c) Neurological examination and muscle strength assessment.

15. In the setting of fever (T $>$ 38.5°C) or leukocytosis (WBC $\geq$15,000) not otherwise explained, the following will be done (a,b) or considered (c-f):

    (a) Review chest radiograph, if not already done per item 6.2.10.

    (b) Tracheal aspirate (sputum) Gram stain and culture, assessed for:

        - purulence.
        - presence of predominant organism.

    (c) Urinalysis, urine Gram stain and culture if UA suggests infection.

(d) Consider evaluation of sinuses for infection (see appendix A for recommended diagnostic methods).

(e) Consider pelvic examination.

(f) Consider rectal examination.

- consider U/S or CT if exam suspicious for abscess formation or perineal soft tissue infection.

16. If baseline tests indicate infection, the patient should be treated, initially empirically, then guided by sensitivities when available.

(a) If disseminated fungal infection (see Appendix A) is found, the patient should be withdrawn and corticosteroids discontinued.

(b) The patient should be withdrawn if any of the exclusion criteria (section 4.3) are met during the baseline assessment. If infection is identified during the baseline assessment and appropriate antibiotic treatment started immediately, then randomization can be carried out and study drug administered with exceptions as described under section 4.3.2c and in the case of newly diagnosed pneumonia (see Appendix A).

(c) Creatine phosphokinase (CPK)

6.3 Assessments During Enrollment

6.3.1 Daily data

The following data will be recorded on a daily basis from the time of enrollment until death, transfer to another facility, or 28 days after enrollment, whichever comes first.

1. Vital signs (daily through day 5, then weekly).
2. Ventilator parameters (mode, FiO_2, V_T, PEEP, plateau pressure, Cst, V_{Ecorr}, patient position)(daily through day 5, then weekly).
3. Any positive culture from a normally sterile site or body cavity, when clinically available [CSF, blood, pleural fluid, urine ($\geq 10^5$ cols/mL), bile, abdomen (peritoneal)].

4. Creatinine (when clinically available).
5. Bilirubin (when clinically available).
6. Platelet count (when clinically available).
7. Prothrombin time (when clinically available).
8. Concurrent medications (vasopressors, antibiotics, antifungals, antipsychotics, NMBA, and experimental medications).
9. Assessment of serious or other infections during the previous week (nosocomial pneumonia, disseminated fungal infection, sepsis, intra-abdominal infection, other)as defined in appendix A.
10. Glucose (when clinically available).
11. Creatine phosphokinase (CPK, when clincally available).
12. Chart review for myopathy, myositis, neuropathy, or unexplained weakness.

6.3.2 Weekly data

The following data will be collected weekly until death, transfer to another facility, or 28 days after enrollment, whichever comes first.

1. Amylase (required on day 7; when clinically available on days 14, 21, 28).
2. Glucose (required on day 7; when clinically available on all other days).
3. ABG (required on day 7; when clinically available on days 1-4, 7, 14, 21, 28).
4. Glasgow coma score.
5. Total 24 hour insulin dose (required on day 7, when clinically available on all other days).
6. Total calorie intake (required on day 7 only).

7. TPN (required on day 7 only).

8. Neurological examination and muscle strength testing.

6.3.3 Follow-up bronchoscopy

1. Fiberoptic bronchoscopy will be performed on day 7±1 day, to assess effects of methylprednisolone on markers of inflammation and fibroproliferation per the procedure in Appendix C.

2. A blood draw of 20mL will be performed on day 7±1 day, immediately prior to the bronchoscopy, to assess effects of methylprednisolone on markers of inflammation and fibroproliferation per the procedure in Appendix C

   (a) If the FOB is not done, the blood draw should still be done if the patient remains in the study hospital.

6.4 Endpoint Assessments

6.4.1 Vital status

1. Patient vital status at discharge or 60 days after study enrollment.

2. Date of 48 hours of unassisted breathing.

3. Date of ICU discharge.

4. Date of hospital discharge.

7 STATISTICAL CONSIDERATIONS

7.1 Sample Size and Early Stopping Rules

7.1.1 Sample size

The sample size depends on the magnitude of the difference in mortality that is considered important. The study is designed to detect a difference

between late steroid therapy and placebo of 20%, from 40% mortality to 20% mortality. The study will require a total of 200 patients.

7.1.2 Early stopping

Two interim analyses and one final analysis are planned at 60, 120, and after 200 patients.

This trial will stop if late steroid therapy is effective using an O'Brien-Fleming upper boundary. It will stop for futility if the observed difference in mortality rate between placebo and late steroid therapy is less than 3% at the second interm analysis. There will be no futility stopping at the first interim analysis. The upper O'Brien-Fleming boundary will be lowered slightly to counteract the conservatism of the 3% futility stopping boundary.

The probability of seeing a significant result at a two-sided 5% significance level is 88% if the true difference is a change in mortality from 40% to 20%. If there is no advantage to late steroid therapy then the trial has a 63% chance of stopping at the second interim analysis.

The actual stopping rules will depend on the mean mortality rate and the actual number of patients accrued at each interim analysis. The stopping rule is defined by the properties that it have a constant lower boundary of at most 3% and as close to 3% as possible (mortality of placebo minus mortality of steroids), a power of at least 80% to detect an absolute difference of 20%, an upper boundary based on an O'Brien-Fleming spending function, a maximum sample size of 200, and two-sided 5% significance level. Since the adoption of this amendment by the Steering Committee, the DSMB reviewed the first 60 patients enrolled, identified no safety concerns, and requested that the study continue to the next analysis.

7.2 Primary Data Analysis

The primary data analysis will be an intention-to-treat analysis, based on the original randomization, of mortality at 60 days after study entry.

7.3 Secondary Data Analysis

7.3.1 As treated analysis

Treatment will be compared among patients who received at least eight doses of the study drug or placebo and who have been on study for at least 48 hours.

7.3.2 Covariate analysis

Important covariates which may interact with treatment are: PaO_2/FiO_2, compliance, V_E, time of entry after onset of ARDS ($>$ 13 days), MODS score, sepsis-initiated ARDS, baseline procollagen peptide III (PCPIII $>$ median).

8 DATA COLLECTION AND SITE MONITORING

8.1 Data Collection

Each site will have a computer with ARDS Network software installed. The research coordinator will be responsible for maintaining a data base using a custom designed web-based data base application. Data will be transmitted to a central server each time the research coordinator opens the application for data entry. The software is designed with a series of checks to avoid missing or incorrect data.

8.2 Reporting of Adverse Events

Adverse events will be reported as described in Appendix E.

8.3 Site Monitoring

Site visits will be performed once each year by a research nurse from the Clinical Coordinating Center and every three years by other members of the Coordinating Center and of the Steering Committee, to ensure that all regulatory requirements for the use of investigational agents are being met and to monitor the quality of the data collected. Records of IRB approvals and patient charts will be examined on a spot check basis to evaluate the accuracy of the data entered into the database.

9 RISK ASSESSMENT

The toxicity of high-dose corticosteroids in the ICU may include any or all of the following problems: 1) Development of a serious secondary infection; 2) Uncontrolled hyperglycemia; 3) Wound dehiscence; 4) Skin breakdown, decubitus ulcers; 5) Respiratory muscle weakness (MIP $\leq$ 25 cm H_2O); 6) Acute psychosis; and 7) Acute pancreatitis with an amylase $\geq$ 3x upper limit of normal. Monitoring for these complications will occur during the course of the study. Treatment for each complication should occur as clinically indicated. Drugs with known interactions, such as those that cause prolonged neuromuscular weakness when given in conjunction with corticosteroids, will be avoided whenever clinically possible. Insulin will be used as necessary to control hyperglycemia. It is suspected that there may be increased numbers of infections in the corticosteroid-treated group. Heightened surveillance and rapid treatment of any new infections will hopefully keep morbidity to a minimum.

10 HUMAN SUBJECTS

The protocol will require the institution's prior IRB approval before any subject can be enrolled in the trial. Each patient meeting the study criteria (or their surrogate) will be approached by a member of the primary care team to inform them of the diagnosis of ARDS, and of the possibility of participating in a therapeutic trial. The research nurse or one of the site investigators will obtain informed consent prior to

randomization. In most cases, due to the seriousness of the patient's condition, consent will be sought from the next of kin. Each subject will be assigned a unique identification number. All laboratory specimens, data on the final summary forms, and all subsequent tabulated data will be recorded and stored using the study number and not the patient's name, to insure confidentiality. All computer entry and networking programs will be done with coded numbers only. All records will be kept in a locked, password protected computer. Access to the data will be restricted to those directly involved with the study. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring by the FDA, National Heart, Lung, and Blood Institute, and the ARDS Clinical Coordinating Center.

11 Appendices

A DEFINITIONS

1. IDEAL BODY WEIGHT

   Ideal body weight is calculated from gender and height (heel to crown) according to the following equations:
   Males: IBW (kg) = 50 + 2.3[height(inches) - 60]
   Females: IBW (kg) = 45.5 + 2.3[height(inches) - 60]

2. CHILD-PUGH CLASSIFICATION OF CHRONIC LIVER DISEASE[31]

   Use the table to assess severity of abnormalities in each of the five clinical variables. Add the numerical scores.

Points	Class
5-6	A
7-9	B
≥ 10	C

	Numerical score for increasing abnormality		
Measurement	1	2	3
Ascites	None	Present	Tense
Encephalopathy	None	Grade I or II	Grade III or IV
Bilirubin (mg/dl)	< 2	2-3	> 3
Albumin (g/L)	>35	28-35	<28
Prothrombin time (sec. prolonged)	1-4	4-10	> 10

3. LUNG INJURY SCORE (Murray, Matthay, Luce, & Flick. ARRD 1988; 138:720-723.)

   CXR Criteria

   0=normal
   1=alveolar consolidation in 1 quadrant
   2=alveolar consolidation in 2 quadrants
   3=aleolar consolidation in 3 quadrants
   4=alveolar consolidation in 4 quadrants

Hypoxemia (PaO_2/FiO_2 ratio)

0= $\geq$ 300
1=225-299
2=175-224
3=100-174
4= $<$ 100

Compliance (total respiratory system)

0= $\geq$ 80
1=60-79
2=40-59
3=20-39
4= $\geq$ 15

PEEP

0= $\leq$ 5
1=6-8
2=9-11
3=12-14
4= $\geq$ 15

Overall Lung Injury Score

0=no lung injury
0.1-2.5=mild-moderate lung injury
>2.5=severe lung injury(ARDS)

4. DEFINITIONS OF SERIOUS INFECTIONS

   (a) Bacteremia due to known pathogen with or without signs or symptoms

   One or more positive blood cultures of a known pathogen. For *Staphylococcus epidermidis* (coagulase-negative staphylococcus), two or more positive cultures drawn on separate occasions within 24 hours are required to define pathogenicity. Site of primary infection should be noted as confirmed, suspected or unknown.
   Note: If criteria are met for a primary site of infection and for bacteremia during the same 48 time period, then the

combination, e.g., nosocomial pneumonia/bacteremia or empyema/bacteremia, will be counted as one event of serious infection and not as two separate events, for the purposes of assessing frequency of serious infections in both groups. The primary site of infection will be recorded as the serious infection, not the bacteremia.

(b) Disseminated fungal infection

Positive blood cultures or evidence of deep tissue infection (candidal endophthalmitis; multiple small hepatic or splenic nodules with an elevated alkaline phosphatase; cutaneous embolic lesions containing fungal elements) or unexplained fever with three sites of colonization (e.g., sputum, urine, stool, superficial wound cultures).

(c) Nosocomial pneumonia

Suspected or Possible Pneumonia: patient must meet at least one criterion from two categories below (i, ii or iii).

Probable Pneumonia: patient must meet at least one criterion from all three categories below (i and ii and iii).

i. Chest radiograph shows new infiltrate corresponding in size (although not necessarily to segmental anatomical boundaries) to at least one segment or cavitation with an air-fluid level within an area of infiltrate (*i.e.*, not a simple subpleural air cyst). The qualifying radiographic abnormality must persist over at least 48 hours with no decrease in its size.

ii. New onset of or increase in fever ($T \geq 38.3°C$ or increase $\geq 1°C$ over the previous 24 hour T_{max} if T already $\geq 38.3°C$) or new hypothermia ($T \leq 36.0°C$) or increase in WBC (WBC > 10,000 and a 25% increase or an increase in band forms to > 10% of total WBC) or new decrease in WBC to < 4,000.

iii. Bacteriological confirmation of pulmonary infection (can be any of the following):

- quantitative culture of tracheal secretions with $>10^6$ cfu/mm^3.
- quantitative culture of bronchoalveolar lavage with $>10^4$ cfu/mm^3.

- quantitative culture of protected specimen brush with $>10^3$ cfu/mm^3.
- positive Gram stain with $\geq 3+$ of at least one type of bacteria.
- positive semi-quantitative sputum culture with $\geq 3+$ growth of at least one type of potentially pathogenic bacteria.
- positive blood culture for bacterial pathogen also identified in sputum or other respiratory specimens.
- positive Gram stain or culture of pleural fluid for bacterial pathogen.

Only one episode will be considered to be present during the 28 day period for the following due to difficulty in defining successful therapy during this time period.

(d) Sepsis (ACCP/SCCM Consensus Conference; Bone et al. Chest 1992; 101:1644-55)

Systemic inflammatory response syndrome (SIRS) - at least two of the following:

1. temperature $> 38°C$ or $< 36°C$.
2. heart rate > 90 beats per minute.
3. respiratory rate > 20 breaths per minute or $PaCO_2 <$ 32 mmHg.
4. white blood cell count $> 12{,}000$/cu mm < 4000/cu mm, or $> 10\%$ immature (band) forms.

Sepsis - the systemic response to infection with at least 2 of the following:

1. temperature $> 38°C$ or $< 36°C$.
2. heart rate > 90 beats per minute.
3. respiratory rate > 20 breaths per minute or $PaCO_2 <$ 32 mmHg.
4. white blood cell count $> 12{,}000$/cu mm < 4000/cu mm, or $> 10\%$ immature (band) forms.

Severe sepsis

Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may

include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.

Septic shock

Sepsis-induced hypotension (Systolic blood pressure < 90 mmHg or a reduction of ≥ 40 mmHg from baseline or vasopressor use to maintain blood pressure in the absence of other causes for hypotension) of at least 2 hours duration despite at least 500 mL fluid resuscitation along with the presence of perfusion abnormalities which may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

Sepsis-induced hypotension

Systolic blood pressure < 90 mmHg or a reduction of ≥ 40 mmHg from baseline or vasopressor use to maintain blood pressure in the absence of other causes for hypotension.

Episode ends when criteria for septic shock are no longer met for a 24 hour period.

(e) Peritonitis not associated with peritoneal dialysis

Positive Gram stain or culture of peritoneal fluid with an elevated PMN count ($>250/mm^3$) in the fluid or free peritoneal air demonstrated radiographically with bacteremia (as defined above).

Only one episode will be considered to be present during the 28 day period for the following due to difficulty in defining successful therapy during this time period.

(f) Wound infection requiring extensive debridement and/or healing by secondary intention.

Positive culture of normally sterile wound with evidence of infection locally plus debridement of tissue greater or equal in volume to 1 cm thick x 1 cm deep x 2 cm long or removal of sutures to allow wound to dehisce or unexpected wound dehiscence.

Only one episode will be considered to be present during the 28 day period for the following due to difficulty in defining successful therapy during this time period.

(g) Meningitis

Positive CSF Gram stain or culture or antigen detection for a pathogen with WBCs in CSF.

Only one episode will be considered to be present during the 28 day period for the following due to difficulty in defining successful therapy during this time period.

(h) Empyema

Grossly purulent pleural fluid or positive pleural fluid Gram stain or culture for a pathogen associated with an elevated pleural fluid WBC count.

Only one episode will be considered to be present during the 28 day period for the following due to difficulty in defining successful therapy during this time period.

(i) Abdominal or other deep tissue abscess

Unequivocal radiographic evidence or equivocal radiographic evidence confirmed by positive culture of abscess contents or documentation of a purulent fluid collection by surgical exploration.

Only one episode will be considered to be present during the 28 day period for the following due to difficulty in defining successful therapy during this time period.

(j) Disseminated viral infection

Skin rash with viral etiology of lesions confirmed by culture or cytology and characteristic lesions present over more than two adjacent dermatomes.

Only one episode will be considered to be present during the 28 day period for the following due to difficulty in defining successful therapy during this time period.

5. DEFINITIONS OF OTHER INFECTIONS

(a) *C. difficile* colitis
Diarrhea associated with the presence of *C. difficile* toxin in the stool.

(b) Indwelling vascular line infection

Central venous, peripheral venous, or peripheral arterial infection is defined as catheter-related bloodstream infection (bacteremia) or catheter colonization in the presence of local site inflamation.

Catheter-related bloodstream infection

- isolation of the same organism from the blood and one or both catheter segments ($\geq$ 15 colony-forming units), with no other identified source.

Catheter colonization

- growth of 15 or more colony-forming units of an organism on semi-quantitative culture of the tip or subcutaneous segment.

Local site inflammation

- presence of purulence alone, or erythema with one of the following: tenderness, increased warmth, induration, lymphangitis, or a palpable thrombosed vein.

(c) Oral or mucosal candidiasis

Presence of characteristic lesions on a mucosal surface (e.g., oral or vaginal mucosa) with a positive fungal stain, KOH preparation, or culture.

(d) Peritonitis associated with peritoneal dialysis

Positive Gram stain or culture of peritoneal fluid with an elevated PMN count ($> 500/mm^3$) in the fluid.

Episode ends when criteria for definition are not longer met.

(e) Sinus infection

Endoscopic observation of purulent drainage from maxillary, frontal, or sphenoid sinuses or purulent nasal drainage with moderate to abundant growth of pathogenic bacteria and a sinus CT scan demonstrating an air-fluid level or a completely opacified sinus.

(f) Skin infection including non-disseminated viral infection

Cellulitis, cutaneous abscess not requiring extensive debridement, wound infections not requiring extensive debridement or resulting in wound dehiscence.

or

Skin rash with viral etiology of lesions suggested by characteristic lesions present two or less adjacent dermatomes with or without confirmation by culture or cytology. This includes localized labial HSV infections.

(g) Septic arthritis

Clinical evidence of joint inflammation (erythema, warmth, pain, or presence of an effusion) with an elevated PMN count in joint fluid and a positive Gram stain or culture for a pathogen.

(h) Urinary tract infection

Greater than or equal to 100,000 colony forming units of a bacteria on culture of the urine associated with evidence of infection on urinalysis based on one of the following criteria: $\geq$ 2+ WBC, presence of leukocyte esterase, or presence of nitrites. The presence of perinephric or renal abscess should be classified as a serious infection under "abdominal or other deep tissue abscess".

B BRUSSELS MULTIPLE ORGAN DYSFUNCTION CLASSIFICATION

Table 3: Brussels Multiple Organ Dysfunction Classification

			Clinically Significant Organ Dysfunction		
Organs	Normal	Mild	Moderate	Severe	Extreme
Cardiovascular (systolic BP)	> 90	≤ 90 fluid responsive	≤ 90 not fluid responsive	≤ 90 pH ≤ 7.3	≤ 90 pH ≤ 7.2
Pulmonary (PaO_2/FiO_2)	> 400	400-301	300-201 acute lung injury	200-101 ARDS	≤ 100 severe ARDS
CNS (Glasgow)	15	14-13	12-10	9-6	≤ 5
Coagulation (platelets)	> 120	120-81	80-51	50-21	≤ 20
Renal (creatinine mg/dL)	< 1.5	1.5-1.9	2.0-3.4	3.5-4.9	≥ 12
Hepatic (bilirubin mg/dL)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	≥ 12

Brussels MODS Score = number of individual organ systems with clinically significant dysfunction.

C PROTOCOL FOR BRONCHOALVEOLAR LAVAGE

1. Exclusions (subjects meeting these criteria should not undergo FOB on that day but are not excluded from the trial):
   (a) $PaO_2/FiO_2 < 80$.
   (b) ETT or tracheostomy tube size < 7.0mm internal diameter.
   (c) marked cardiovascular instability.
      - acute ischemic heart disease (unstable angina, acute MI).
      - severe hypotension with a systolic BP < 90 mmHg.
      - ongoing critical cardiac dysrhythmias (SVT > 140 bpm, complex ventricular ectopy).
   (d) known elevated ICP (sustained ICP $\geq$ 20).
   (e) no longer receiving assisted ventilation.
2. Prior to Bronchoscopy:
   (a) increase FIO_2 to 1.0 5-15 mins pre-BAL.
   (b) administer β-agonist 5-15 mins pre-BAL.
   (c) sedation as clinically indicated with benzodiazepine, narcotic, or propofol.
   (d) administer 60 mg lidocaine directly into ETT 2-5 minutes pre-BAL.
   (e) consider transient paralysis with an NMBA as clinically indicated to eliminate severe coughing or 'fighting' the ventilator (both are risk factors for complications during FOB).
   (f) place bronchoscopy adapter on ETT (*e.g.* FOB Swivel Adapter; Portex; Keene, NH).
3. Respiratory therapist, or other qualified person, at bedside during the entire procedure for:
   (a) maintenance of minute ventilation (VE) during FOB.
   (b) avoidance of pressure-limited volume loss due to the presence of the bronchoscope in the airways by increasing the peak pressure limit on the ventilator during FOB.

(c) monitoring for significant increases in auto-PEEP.

(d) monitoring of pulse oximetry.

4. Continuous oximetry, cardiac monitoring,and either intermittent or continuous BP monitoring should be conducted throughout the course of bronchoscopy and the recovery period.

5. Use "narrow" bronchoscope (e.g., 4.8mm scope; 2mm channel), especially with smaller ETT's (< 8.0).

6. Lubricate scope with silicone fluid (*e.g.* Circon ACMI; division of American Hospital Supply Corp.; Stamford, CT) or similar sterile lubricant

7. Enter airway with minimal suctioning; may instill 20-40 mg lidocaine at the main carina, RUL carina, RML carina if necessary (total of 60-120 mg lidocaine) to diminish cough reflex.

8. Wedge bronchoscope in RML or lingular subsegment.

9. Lavage with five 30cc aliquots (150cc total) of sterile saline, using gentle manual suction on the syringe to return fluid.

10. After removing scope, return ventilator to pre-BAL settings and monitor patient closely on an $FIO_2 = 1.0$ for an additional 5-10 minutes, then decrease FIO_2 gradually as tolerated, using oximetry, to the pre-BAL level.

11. Fluid analysis:

    (a) record volumes of each aliquot and total BALF volume.

    (b) pour the five aliquots of bronchoalveolar lavage fluid (BALF) through moistened gauze to remove mucus and pool the aliquots.

    (c) Total cell counts are performed on the BALF in a hemacytometer.

    (d) differential cell counts are performed on cytospin preparations stained with Diff-Quik (Scientific Products Co., McGaw Park, IN).

12. Fluid storage.

(a) gently centrifuge fluid at 1600 rpm for 15 minutes and remove cell pellet.

(b) repeat centrifugation at 15,000 rpm for 10 minutes and decant the remaining supernatant.

(c) store supernatants in polypropylene tubes with caps with approximately 4 mL of fluid per tube (often have 10-25 tubes per BAL).

(d) label each tube with the subject's initials, BAL date, and study number.

(e) freeze and store fluids in a -70°C freezer.

D SCHEDULE FOR TAPERING OF METHYLPREDNISOLONE (MPSS) DOSE

1. Slow Taper
   (a) From 0.5 mg/kg every 12 hours; 1 mg/kg/day
      i. 0.5 mg/kg MPSS IV every 24 hours (0.5 mg/kg/day) x 2 days
      ii. 0.25 mg/kg MPSS IV every 24 hours (0.25 mg/kg/day) x 2 days
      iii. Discontinue MPSS
2. Rapid Taper: (clinicians may taper more rapidly or discontinue immediately if deemed necessary)
   (a) If current MPSS dose is 0.5 mg/kg every 6 hours (2 mg/kg/day):
      i. 0.5 mg/kg MPSS IV every 12 hours (1 mg/kg/day) x 1 day
      ii. 0.5 mg/kg MPSS IV every 24 hours (0.5 mg/kg/day) x 1 day
      iii. Discontinue MPSS
   (b) If current MPSS dose is 0.5 mg/kg every 12 hours (1 mg/kg/day):
      i. 0.5 mg/kg MPSS IV every 24 hours (0.5 mg/kg/day) x 1 day
      ii. 0.25 mg/kg MPSS IV every 24 hours (0.25 mg/kg/day) x 1 day
      iii. Discontinue MPSS
   (c) If current MPSS dose is 0.5 mg/kg or 0.25 mg/kg every 24 hours:
      i. Discontinue MPSS

E ADVERSE EVENT REPORTING PROCEDURE

1. Procedures for Reporting Adverse Events

   Assuring patient safety is an essential component of this protocol. Each participating investigator has primary responsibility for the safety of the individual participants under his or her care. All adverse events will be evaluated by the Principal Investigator. The Study Coordinator must view patient records for possible adverse events throughout the study period. All serious adverse events occurring within the study period must be reported in the participants' case report forms.

   The investigator will report all serious, unexpected, and drug-related adverse events to the Clinical Coordinating Center within 24 hours. The Institutional Review Board must also be informed in a timely manner. The investigator will then submit a detailed written report to the Clinical Coordinating Center and the Institutional Review Board no later than 5 days after the investigator discovers the event.

   The Clinical Coordinating Center will report serious, unexpected, and drug-related events to the FDA in accordance with FDA guidelines.

2. Definitions of Adverse Events

   A **serious** adverse event is any event that is fatal or immediately life-threatening, is permanently disabling, or severely incapacitating or requires or prolongs inpatient hospitalization. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse experiences when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

   Life-threatening means that the patient was, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include the reaction that, had it occurred

in more serious form, might have caused death. Assessment of the cause of the event has no bearing on the assessment of the event's severity.

An **unexpected** adverse event is any experience not identified by type, severity, or frequency in the current study protocol or clinical safety updates or an event that is unexpected in the course of treament for Acute Lung Injury of ARDS.

F MATHEMATICAL DESCRIPTION OF THE STOPPING RULES

The stopping rule is described in [33].

The upper boundary is defined as follows. Let $x = \hat{p}_1 - \hat{p}_2$, the difference between the mortality on placebo and the mortality on late steroids. Let

$$v_i = \sqrt{(I/i)\frac{\hat{p}_1(1-\hat{p}_1) + \hat{p}_2(1-\hat{p}_2)}{n}}$$

where I is the total number of analyses and i is the number of the present analyses and n is the number of patients in each treatment at the time of the analysis. The trial will stop and make the appropriate decision if $x > z_1 v_i$ or $x < .03$. The specific value chosen for z_1, 1.64, is less than the value in [**?**] where, $I = 4$, because some crossings of the upper boundary under the null hypothesis in [33] would occur after our futility boundary is crossed. In our study these would not lead to rejections of the null hypothesis. Thus the futility boundary reduces the type I error rate below 5% if the boundary in [33] is used. The power is increased by lowering the upper boundary until the type I error rate is exactly 5%. The value of 1.64 will need to adjusted at analysis time because it depends on the combined mortality rate.

G Equivalent Doses of Representative Corticosteroids

Compound	Relative Anti-Inflammatory Potency	Dose Equivalent to 15 mg Prednisone (mg)
Hydrocortisone	0.8 mg	75 mg
Prednisone	4 mg	15 mg
Methylprednisolone	5 mg	12 mg
Dexamethasone	25 mg	2.25 mg

$*$ Applies for oral or parenteral administration
Adapted from Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 9th ed. Hardman JG and Limbird LE, eds. New York: McGraw-Hill Health Professions Division. 1996, page 1466.

LaSRS SCHEDULE OF EVENTS AND SAFETY MONITORING TABLE

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Demographics	X																												
Vital signs	X	X	X	X	X	X		X							X							X							X
Neuro exam	X							X							X							X							X
Weight (IBW)	X																												
ß-HCG (females only)	X																												
ABG (when on vent)	X	A	A	A	A	A	+	X	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	A
Ventilator parameters	X	A	A	A	A	A	+	X	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+	+	+	+	X
Blood tests:																													
Na, K, Cl, HCO_3, BUN	X	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*							
Glucose	X	A	A	A	A	A	A	X*+	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Amylase	X	A	A	A	A	A	*	X*	*	*	*	*	*	*	A	*	*	*	*	*	*	A							A
WBC , Hct.	X		#		#			A		#		#			A		#		#			A							A
Albumin	X																												
Creatinine/CPK	X	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Bilirubin	X	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Prothrombin time	X																												
Platelets	X	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Blood (storage)	X							X																					
Glasgow coma score	X	A	A	A	A	A	A	X	A	A	A	A	A	A	X	A	A	A	A	A	A	X	A	A	A	A	A	A	X
Chest X-ray	A																												
Bronchoscopy/BAL	X							X																					
Positive cultures	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Infection monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medications (Y/N)																													
Vasopressors	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Antibiotics	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Antifungals	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Antipsychotics	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NMBA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

X = required A = when available X* = required but can be ± 72 hours (glucose and amylase)

+ = Daily review of clinically obtained ABG, ventilator parameters to be done to detect worsening pulmonary function that may indicate infection.

* = Uncontrolled hyperglycemia, electrolyte abnormalities and acute pancreatitis (amylase 3x limit of normal) are potential toxicities of study drug and review of these clinically obtained lab values will be done daily while on study drug.

= Review of white blood cell count will be performed as part of infection monitoring.

X*+ = In addition to glucose, recording of TPN use, total calories (24 hr) and total insulin use (24 hr) will be required.

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I Genetic Testing Information

Portions of the blood or BAL samples collected, processed, and stored as specified in this protocol may be used for genetic analyses in the future. Genetic analysis will involve, in part, the analysis of genomic DNA and will attempt to link genotypic information to the extensive phenotypic information measured as part of this study. A layered informed consent will be used to obtain the study subjects' consent for genetic testing. Consent for the use of these samples for genetic analysis related to the study of ARDS by the ARDS Network Investigators, consent for future studies not necessarily related to ARDS, or consent for genetic testing in both of these categories will be obtained. The level of an individual's consent for testing (e.g. none, for ARDS studies, for future studies, or all studies) will be recorded in the Case Report Forms and stored in the Clinical Coordinating Center Data Base.

Samples are stored at a central repository per ARDS Network protocol. Samples are identified by their ARDSNet Study Numbers. Approved studies for genetic testing will be sent to the CCC where samples that have the necessary level of informed consent for genetic testing will be identified. The CCC will then instruct the repository to prepare the relevant samples for shipment. The samples will have the ARDSNet Study Numbers removed and will be re-labeled with a new number. The Clinical Coordinating Center will be the only site to keep the database, relating the new sample number to the previous ARDSNet Study number, and this will be kept strictly confidential.

Upon completion of Network activities, the CCC will assign new Study Numbers for all ARDSNet Study subjects. The CCC will then instruct the repository to strip all samples of their ARDSNet identifiers and re-label them with the new study subject numbers. This will prevent investigators from using the ARDS Net Study Numbers to identify individual subjects in the future.

J HIV/AIDS CLASSIFICATION SYSTEM

	Category A	Category B	Category C
CD_4 Count/Percentage	Asymptomatic (Class I,II,III)	Symptomatic (Class IV)	Sympotomatic (Class IV)
$\geq$ 500 and/or $>$ 28%	A1	B1	C1
200-499 and/or 14-28%	A2	B2	C2
$<$ 200 and/or $<$ 14%	A3	B3	C3

Category	**LaSRS Trial**
Asymptomatic Non-AIDS (A1, A2)	Included
Symptomatic Non-AIDS (B1, B2)	Included
AIDS (A3, B3 = immunological AIDS) (C1, C2, C3 = clinical AIDS)	EXCLUDED

- Category C, AIDS Defining Illnesses
  - Candidiasis: esophageal, trachobronchial
  - Coccidioidomycosis, extrapulmonary
  - Cryptococcosis, extrapulmonary
  - Cervical cancer, invasive
  - Cryptosporidiosis, chronic intestinal ($>$ 1 month)
  - CMV retinitis, or CMV in other than liver, spleen, nodes HIV encephalopathy
  - Herpes simplex with mucocutaneous ulcer $>$ 1 month, bronchitis, pneumonia

- Histoplasmosis: disseminated, extrapulmonary
- Isosporiasis, chronic ($>$ 1 month)
- Kaposi's sarcoma
- Lymphoma: Burkitt's, immunoblastic, primary CNS
- M. avium or M. kansasii, extrapulmonary
- M. tuberculosis, pulmonary or extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent ($\geq$ 2 episodes in 1 year)
- Progressive multifocal leukoencephalopathy (PML)
- Salmonella, bacteremia, recurrent
- Toxoplasmosis, cerebral
- Wasting syndrome due to HIV

Reference: 1993 revised CDC HIV classification system and expanded AIDS surveillance definition for adolescents and adults. MMWR 41:RR-17, Dec. 18, 1992.

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