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Part I

Study Summary

- **Title:** Ketoconazole and Respiratory Management in ALI/ARDS
- **Objectives:** 1) To assess the efficacies of 12 ml/kg vs 6 ml/kg ventilation strategies in reducing mortality and morbidity in patients with acute lung injury and acute respiratory distress syndrome. 2) To assess the efficacy of ketoconazole in reducing mortality and morbidity in patients with acute lung injury and acute respiratory distress syndrome.
- **Study Design:** Multi-Center, prospective, randomized, controlled clinical trial; ketoconazole to be administered in double-blind fashion.
Duration of Study
 1. Enrollment: approximately 24 months
 2. Study Duration: approximately 30 months
- **Inclusion Criteria:**
Acute Onset of:
 1. $\text{PaO}_2/\text{FiO}_2 \leq 300$ (adjusted for barometric pressure).
 2. Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph.
 3. Requirement for positive pressure ventilation via endotracheal tube.
 4. No clinical evidence of left atrial hypertension. If measured, pulmonary arterial wedge pressure ≤ 18 mmHg.
- **Exclusion Criteria:**
 1. Clinicians caring for patient not agreeable to using Volume Assist/Control ventilation for at least 12 hours.
 2. Age < 18 years.
 3. Participation in other intervention trials in ALI, ARDS, or sepsis within the past 30 days.
 4. > 36 hours since all inclusion criteria are met.

5. Neuromuscular disease that impairs ability to ventilate spontaneously, such as C₅ or higher spinal cord injury, amyotrophic lateral sclerosis, Guillain-Barre syndrome, and myasthenia gravis.
 6. Pregnancy.
 7. Increased intracranial pressure, Tricyclic antidepressant overdose (if most recent level elevated or no level), Hgb SS, Hgb SC, or other conditions where hypercapnia would be contraindicated.
 8. Severe chronic respiratory disease.
 9. Morbid obesity.
 10. Burns $\geq 30\%$ total body surface area.
 11. Malignancy or other irreversible disease or condition for which 6-month mortality is estimated $\geq 50\%$.
 12. Bone marrow transplant.
 13. Lung transplant.
 14. Not committed to full support.
 15. Treated with terfenadine, astemizole, or cisapride within the past 72 hours.
 16. Severe chronic liver disease (Child-Pugh Score of 10-15).
 17. Evidence of acute liver disease (either acute hepatitis or acute cholestasis) with significant hepatocellular or cholestatic liver injury (Appendix B).
 18. Known allergy to imidazole or its derivatives.
 19. Treated with ketoconazole or other imidazole within the past 7 days.
- **Efficacy:** The two primary efficacy variables are: 1) Percentage of patients alive with unassisted breathing at hospital discharge. Patients still alive in hospital at 180 days will be defined as survivors. 2) Number of Days of Unassisted Breathing, which is defined as the number of days after initiating unassisted breathing to day 28 after randomization, assuming a patient survives for at least 48 consecutive hours after initiating unassisted breathing. This second primary efficacy measure is related to differences in morbidity and cost attributable to differences in time to recovery from respiratory failure.

Secondary efficacy variables include: 3) Percentage of patients who achieve unassisted breathing, 4) Number of ICU-free days at 28 days after enrollment, 5) Number of Organ-failure-free days at 28 days after enrollment, 6) Number of days meeting commence-weaning criteria at 28 days after enrollment, 7) Number of days after initially achieving unassisted breathing measured at 28 days after enrollment, 8) Percentage of patients withdrawn because of elevations in liver enzymes suggesting liver toxicity from ketoconazole, 9) Incidence of barotrauma (pneumothoraces, pneumatoceles > 2 cm largest diameter, pneumomediastinum).

**KETOCONAZOLE AND RESPIRATORY MANAGEMENT IN
ALI/ARDS
Protocol for the NIH ARDS Network**

1 Background

1.1 Ketoconazole and Respiratory Management in ALI/ARDS

Acute lung injury (ALI) and adult respiratory distress syndrome¹ (ARDS) occur when an event such as sepsis or massive aspiration causes inflammation, increased pulmonary vascular permeability, and extravasation of fluid and inflammatory cells into the pulmonary interstitium and alveolar space ([58]). The inflammatory process leads to inactivation, destruction, and decreased production of surfactant ([22],[53],[62]). This causes increased surface tension at the alveolar air-fluid interface, leading to diffuse microatelectasis. Alveolar flooding and atelectasis cause hypoxemia from shunt. Management of hypoxemic respiratory failure frequently requires positive pressure ventilation. Traditional ventilator management in ALI/ARDS employs positive end-expiratory pressure (PEEP) and generous tidal volumes of ≈ 10 -15 ml/kg ([10],[13]). Despite aggressive treatments for the conditions that precipitate ARDS, many patients die without resolution of the lung injury.

Chest x-rays in ALI and ARDS are frequently interpreted as showing diffuse infiltrates. However, CT images, histologic sections, and physiologic studies indicate that the disease is patchy([18][39]). Much of the ARDS lung is atelectatic or filled with extravascular fluid and is unavailable for ventilation and gas exchange. The remaining lung is relatively normal. When conventional tidal volumes are administered to ALI/ARDS patients, the patent air spaces are distended much more than under conditions of normal ventilation. The high airway pressures typically observed in ALI/ARDS reflect these high distending forces.

¹The recent American-European Consensus Conference on ARDS ([4]) defined ALI according to the following criteria: 1) Acute onset, 2) $\text{PaO}_2/\text{FiO}_2 \leq 300$, 3) Bilateral infiltrates on frontal chest radiograph, and 4) No evidence of left atrial hypertension (pulmonary capillary wedge pressure ≤ 18 when measured). The definition of ARDS was the same except for $\text{PaO}_2/\text{FiO}_2 \leq 200$.

Substantial evidence from animal studies indicates that overdistention of normal lung tissue causes parenchymal inflammation ([74]), increased vascular permeability ([47], [48], [49]), abnormal accumulation of lung water ([78]), alveolar flooding and atelectasis ([14], [31]), radiographic infiltrates([31]), and hypoxemia from shunt ([14], [31]). These findings are very similar to those observed in ALI and ARDS. This suggests that lung injury from overdistention may exacerbate or prevent resolution of ALI and ARDS. Perhaps recovery from respiratory failure and survival from ALI and ARDS would be better using a ventilation strategy that avoided or reduced injurious stretching forces applied to the lung. Recent authoritative sources recommended avoidance of high peak airway pressures to reduce stretch-induced lung injury ([28], [66], [75]). This can be achieved by using smaller tidal volumes and/or lower levels of PEEP. Many intensivists now prescribe smaller positive pressure ventilation tidal volumes in ALI and ARDS([33]). In recent reports, survival was $\approx 80\%$ in >100 severe ARDS patients ventilated with a low tidal volume strategy ([24], [25]). Although there were no concurrent control groups in these reports, survival in comparison to historical experience with ARDS was much improved.

However, strategies that reduce lung stretch may entail adverse effects. Ventilation with lower tidal volumes may cause alveolar hypoventilation, hypercapnia, and acidosis. In the previously cited uncontrolled reports([24], [25]), the mean maximum PaCO_2 was ≈ 64 mmHg (range 38-158), which was frequently associated with acidosis (mean lowest arterial $\text{pH} \approx 7.23$, range 6.79-7.45). Respiratory acidosis may diminish cardiac contractility and systemic vascular tone ([35], [67], [71], [77]) However these effects generally occur when adrenergic responses are absent or blocked or when respiratory acidosis is more severe than occurred in the patients treated with low tidal volume ventilation ([24],[25]). In intact dogs ([64]) and humans ([54]), cardiac output and arterial pressure remained constant or increased with respiratory acidosis. This probably represented predominant sympathetic adrenergic effects. Acidosis may also contribute to dyspnea and agitation in critically ill patients. In animal models of acute lung injury, pulmonary shunt was higher when ventilation was achieved with smaller tidal volumes ([8], [23]). Thus, small tidal volume ventilation may require higher levels of PEEP and FiO_2 to maintain minimally acceptable levels of arterial oxygenation. If lower levels of PEEP are used to reduce lung stretch, higher FiO_2 's will be necessary to maintain arterial oxygenation, which could contribute to oxidant-induced

lung injury. Support strategies thus often involve trade-offs between gas exchange goals and potential toxicities associated with overdistention and high oxygen concentrations. Clinical data and guidelines to optimize these trade-offs do not exist.

1.1.1 Preliminary Results

Pilot randomized, controlled clinical trials comparing traditional vs low stretch ventilation strategies in ARDS are currently conducted in Salt Lake City, Utah and in Baltimore, Maryland. Investigators conducting these trials are members of the NIH ARDS Network, and the five hospitals contributing patients represent two of the Network Clinical Center Treatment Groups. The experience gained from these ongoing trials, as well as the cumulative experience of Network members in other studies in ARDS ([3], [7], [27], [40], [42], [42], [43], [50], [51], [60], [61], [68], [72]) and sepsis ([4], [5], [16], [21], [29], [82]) provide the basis for the proposed Network multicenter trial.

In both ongoing pilot trials, ARDS is defined as: $\text{PaO}_2/\text{FiO}_2 \leq 200$, diffuse infiltrates on frontal chest radiograph, and no evidence of heart failure/fluid overload. Patients are excluded from both trials for pregnancy, conditions that would contraindicate hypercapnia (such as intracranial hypertension), and comorbid conditions where survival would be very unlikely (such as metastatic cancer unresponsive to treatment).

Baltimore

From May, 1994 through June 16, 1995, 37 patients were enrolled in 8 intensive care units at four hospitals in Baltimore. In this trial, patients must be enrolled within 24 hours of when the last inclusion criterion is met, resulting in either traditional or low stretch ventilation at relatively early phases of ARDS. All patients receive volume-cycled ventilation in either the Assist/Control or Synchronized IMV modes. Ventilator rate is adjusted up to a maximum of 30/min in both groups to achieve arterial $\text{PCO}_2 = 30\text{-}45$, if possible. Patients assigned to traditional ventilation receive initial tidal volume = 10-12 ml/kg ideal body weight (IBW). This is adjusted only if necessary to maintain end-inspiratory alveolar (plateau) pressure ≤ 50 cmH₂O. Patients assigned to low stretch ventilation receive initial tidal volume = 8 ml/kg IBW. This is subsequently reduced by 0.5

Figure 1: Plateau Pressure vs Time

ml/kg until the plateau pressure ≤ 30 . In both traditional and low stretch groups, inspiratory flow rate and pattern are adjusted to maintain I:E ratio $\leq 1:1$. In both groups, oxygenation goals are the same: $55 \leq \text{PaO}_2 \leq 75$ or $86\% \leq \text{SpO}_2 \leq 95\%$. Moreover, oxygenation is maintained in the target ranges using the same sequence of PEEP/FiO₂ combinations (e.g. 7.5/.50, 10/.50, 10/.60,.....). In both groups, bicarbonate may be administered if arterial pH < 7.30 and is required if pH < 7.20 .

The following data were available after the first 34 patients completed the protocol (either death or unassisted ventilation for 48 hours). Fifteen patients were randomized to receive the traditional treatment; 19 received the low stretch treatment. Since the incidence of death or extubation became substantial after 5 days, physiologic variables were analyzed for only this initial period. The mean plateau pressures were maintained below the target of 30 cmH₂O in the low stretch group (Figure 1). In the traditional treatment group, plateau pressures were highly variable, with mean plateau pressures ≈ 33 cm H₂O.

For many traditional treatment patients, it was necessary to reduce tidal volumes at entry to achieve the protocol tidal volume of 10-12 ml/kg IBW. On average, the "traditional" tidal volume of 10-12 ml/kg IBW was a

Figure 2: PaCO₂ vs Time

conservative estimate of those in common use. In many low-stretch patients, there was little-no hypercapnia in the first 5 days after tidal volume reduction (Figure 2); only 3 of the 19 patients experienced elevations in PaCO₂ to > 60 mmHg during the initial 5 days. Effects on acid-base balance were also relatively mild (Figure 3).

The relatively small separation in mean plateau pressures (Figure 1) between groups was partially due to the conservative tidal volumes in many "traditional" patients and the relatively mild initial tidal volume reductions in the low stretch patients. In the proposed protocol, patients assigned to the traditional treatment group will receive initial tidal volume = 12 ml/kg IBW, which will be more representative of "traditional" treatment. Patients assigned to the low stretch treatment will receive initial tidal volume = 6 ml/kg IBW, which will result in lower plateau pressures.

The process of weaning patients from mechanical ventilation is not controlled in this trial. Decisions regarding commencement of weaning and weaning technique are made by the clinicians caring for individual patients. Most survivors were weaned with either progressive reductions in Pressure Support or SIMV frequency, or some combination of Pressure

Figure 3: Arterial pH vs Time

Support and SIMV.

Salt Lake City

The trial in Salt Lake City is conducted with computerized point-of-care systems that provide decision support tools and data acquisition. Many patients are referred to the LDS Hospital from the surrounding communities and region. Most patients are enrolled within several days of the onset of ARDS, but patients may be enrolled up to 21 days after the entry criteria are met. Therefore, this trial includes some patients in the late as well as early phases of ARDS. Between May, 1994 and May, 1995, 38 patients were enrolled in this trial.

All patients receive volume cycled ventilation in the Assist/Control mode. Ventilator rate, I:E ratio, inspiratory flow pattern, and oxygenation are managed according to the same rules in both groups. Low stretch patients receive initial tidal volume = 6 ml/kg. This is adjusted to 5 and then 4 ml/kg if necessary to maintain plateau pressure ≤ 35 cmH₂O. High stretch patients receive initial tidal volume = 10 ml/kg, which is increased up to 15 ml/kg if necessary to achieve plateau pressure ≥ 45 cmH₂O. This protocol achieves greater separation of plateau pressures between

Figure 4: Frequency of Plateau Pressures by Treatment Group

treatment groups (figure 4).

Weaning is rigorously controlled in this trial to prevent potential systematic differences in weaning approaches between groups. Weaning by daily CPAP trials commences when $PEEP \leq 12$ cmH₂O and $FiO_2 \leq 0.5$. Each trial may continue to sustained unassisted ventilation unless respiratory rate, tidal volume, or oxygenation deteriorate to certain specific thresholds. The proposed Network protocol will also rigorously control weaning. Many of the same rules that govern commencement and continuation of weaning are incorporated in the proposed trial. This will help to minimize between-group variability in ventilator days due to inadvertent systematic biases in weaning approaches.

1.2 Ketoconazole or Placebo

ARDS is now thought to be a consequence of an over-aggressive inflammatory response and many components of the pathophysiology are consistent through multiple studies. Several classic events during acute pulmonary injury appear to lead to ARDS. Early pulmonary hypertension, seen in animal models, is thought to be due to activation and release of

vasoactive mediators. This effect can be alleviated with specific thromboxane synthetase inhibitors. Histologically, a common component is marked diffuse microvascular thrombosis. There is also enhanced neutrophil adherence within the micro-circulation. These neutrophils emigrate across the interstitial space into the intra-alveolar space where they, secondary to activation upon adherence, release proteases and reactive oxygen intermediates.

The tissue-fixed macrophage is thought to be a central component of the host inflammatory response underlying acute lung injury. The macrophage can contribute to the pathophysiology listed above as a major producer of thromboxane, leukotrienes (in particular, LTB_4), and procoagulant activity (PCA).

Ketoconazole is a synthetic imidazole derivative approved for use as an antifungal agent, and it has been widely used for this purpose. Interestingly, ketoconazole is also a potent in vitro inhibitor of all three of these inflammatory pathways. It is a specific thromboxane synthetase inhibitor, an enzyme in the synthetic pathway of thromboxane A_2 ([33]). Thromboxane A_2 (TXA_2) is a potent pulmonary vasoconstrictor as well as an aggregator of platelets and neutrophils. TXA_2 and other byproducts of the prostaglandin pathway have been implicated as mediators of end-organ damage in both sepsis and in ARDS ([65], [30], [59]). Ketoconazole also inhibits 5-lipoxygenase, with a decrease in LTB_4 production, and directly inhibits upregulation of procoagulant activity. Ketoconazole significantly inhibits endotoxin-stimulated alveolar macrophage production of TXB_2 (a metabolite of TXA_2), LTB_4 and PCA ([84]).

Two studies have shown ketoconazole to be effective in reducing the incidence of ARDS in critically ill surgical patients. In high-risk patients, Slotman et al [64] showed a decrease in the incidence of ARDS from 31% to 6%, with a non-significant decrease in mortality from 42% to 31% ([64]). Yu and Tomasa [80] showed a decrease in the incidence of ARDS from 64% to 15% with a significant decrease in mortality from 39% to 15%. Both studies included surgical patients with a variety of diagnoses including, but not limited to, multiple trauma and sepsis.

Although described as a prophylactic study, the Yu and Tomasa [80] study included many patients with marked hypoxemia. They used a less conventional definition of ARDS, requiring persistence of criteria for at

least 48 hours. In the treatment (ketoconazole) arm, 21 of the 28 patients were intubated at the time of enrollment and 16 had a PaO₂/FiO₂ ratio < 300 while 7 of the 16 actually had a PaO₂/FiO₂ ratio < 200. In the placebo arm, 18 of 28 patients were intubated, 16 of the 18 had a PaO₂/FiO₂ ratio < 300 and 4 of the 16 had a PaO₂/FiO₂ ratio < 200 at the time of enrollment (Yu, personal communication). Clearly, this study included many patients with acute lung injury and was not truly a prophylaxis trial but rather an early treatment trial. Despite these definitional problems, ketoconazole still appeared efficacious. The rate of ARDS in the treatment group with a PaO₂/FiO₂ ratio < 300 mm Hg was 19% compared to 63% in the comparable placebo group.

| | Ketoconazole | Placebo |
|---|--------------|----------|
| Total number of patients | 26 | 28 |
| Intubated at entry | 21 | 18 |
| Entry PaO ₂ /FiO ₂ < 300 ₁ | 16 (76%) | 16 (89%) |
| Entry PaO ₂ /FiO ₂ = 200 – 300 ₂ | 9 (43%) | 12 (67%) |
| Entry PaO ₂ /FiO ₂ < 200 ₂ | 7 (33%) | 4 (22%) |
| Progression to ARDS ₃ | 3 (19%) | 10 (63%) |

1-Mihae Yu; personal communication

2-based only on intubated patients in each group, $n = 21, 18$

3-based only on patients with a low PaO₂/FiO₂ ratio at baseline, $n = 21, 18$

1.2.1 Pharmacology

Ketoconazole is well absorbed after oral administration although there is inter- and intra- individual variation in peak serum concentrations after the same oral dose. Absorption is generally improved by food.

Ketoconazole is a weak dibasic compound and almost insoluble in water except at a pH lower than 3. Dissolution is pH dependent and at a pH of 2-3, dissolution is rapid (more than 85% in 5 minutes). H₂-blockers and antacids reduce ketoconazole dissolution in the stomach by reducing gastric acidity. However, once dissolved, ketoconazole is well absorbed by the gut. To circumvent problems of dissolution and absorption in patients with high gastric pH, several authorities recommend dissolving ketoconazole in dilute (4 mL 0.2N) HCl, orange juice or carbonated beverages ([9] [69]), Coke Classic and Diet Coke (pH=2.5 and 3.3 respectively) seem to provide the

best results with regards to dissolution and absorption in the presence of achlorhydria. Coke Classic returned serum drug levels to 65% of control in subjects on omeprazole ([9]). After absorption, ketoconazole serum levels peak in 1-3 hours. In humans, only 1% of ketoconazole is free in plasma; 84% is bound to plasma proteins (mostly albumin), and 15% is in red blood cells. The elimination half-life appears to be dose dependent, increasing with increasing dose and after repeated dosing. With oral doses of 400 mg, the half-life appears to be 2-3 hours ([11]). The drug is eliminated as metabolites and unchanged drug in the feces (approximately 50-60%) and in the urine (approximately 10- 15%).

Renal failure does not appear to affect the bioavailability of ketoconazole and no dose adjustments are necessary. Hemodialysis does not alter ketoconazole concentrations. The influence of liver disease on ketoconazole kinetics is not well known. Mild liver dysfunction does not appear to affect these kinetics. However, in one patient with advanced liver disease, serum levels remained elevated up to 8 hours after the dose. Long-term administration of ketoconazole in this patient, however did not lead to excessive accumulation of the drug.

1.2.2 Toxicity

The most common side effects of ketoconazole are nausea and vomiting. These occur in $\approx 12\%$ of patients, are usually self-limited and may be ameliorated with divided doses. Allergic reaction occur in 4% of patients. Asymptomatic, mild elevations of hepatic enzymes occur in 5% of patients, with spontaneous reversion to normal without discontinuation of the drug. The most serious side effect of ketoconazole is drug-induced hepatitis, which occurs in less than 1% of patients receiving the drug. Fulminant hepatic failure leading to death has been very rarely reported. It is estimated that the incidence of symptomatic, potentially serious hepatic injury is very low, perhaps in the range of 1 in 15,000 exposed individuals ([34]). These serious reactions are idiosyncratic and appear to be unrelated to dose, although liver damage is unlikely to occur in the first 10 days of treatment. Monitoring of liver function tests allows early detection of this condition and discontinuation to the drug at this stage may prevent further progression of the hepatitis. Ketoconazole is not recommended for pregnant women or breast feeding mothers ([19]).

Ketoconazole binds strongly to the cytochrome P-450 system. It therefore has several potential drug-drug interactions. Warfarin, chlorthalidone, cyclosporin, terfenadine, astemizole, and cisapride effects are enhanced by the presence of ketoconazole. Coadministration of astemizole, terfenadine or cisapride had been associated with serious cardiac events (e.g. Torsades). Theophylline does not appear to be affected. Phenytoin, phenobarbital, and rifampin may increase the metabolism of ketoconazole.

2 Objectives

The proposed study is designed to compare the efficacies of two ventilation strategies in reducing mortality and morbidity in ALI and ARDS. The two different strategies incorporate different prioritizations of clinical variables. The 12 ml/kg approach to ventilation in ALI and ARDS aims to preserve acid-base balance and utilize lower FiO_2 's, even if it requires ventilating with high airway pressures that may contribute to acute lung injury. The 6 ml/kg strategy aims to reduce lung overdistention, even if it requires tolerating worse gas exchange and acid-base balance.

The specific aims of the ketoconazole protocol are to determine whether the administration of ketoconazole early after the onset of ALI or ARDS will reduce mortality and morbidity.

3 Study Design

This is a randomized, controlled multi-center 2×2 factorial study. Patients will be recruited from ICUs in approximately 24 hospitals that comprise the NIH ARDS Network. Each candidate will be evaluated for eligibility by the principal investigator of the ARDS Network Center or a designee. Following enrollment, each patient will be classified into strata according to hospital. Within each stratum, patients will be randomized to either the 12 ml/kg ventilation or 6 ml/kg ventilation treatment group and between ketoconazole and placebo. The ketoconazole arms of the study will be placebo controlled and double-blinded. The study drug will be administered for 21 days or until death or until 48 consecutive hours of unassisted breathing.

End-Points

There will be two primary efficacy measures: 1) *Percentage of patients alive with unassisted breathing at hospital discharge*. Patients still alive in hospital at 180 days will be defined as survivors. This efficacy measure is used to calculate sample size and to develop interim stopping boundaries. Since survival may be affected by many factors that are indirectly or remotely related to recovery from ARDS or ALI, the following second primary efficacy measure is designed to examine differences in time to recovery from respiratory failure. This will also reflect morbidity and cost. 2) *Number of Days of Unassisted Breathing*, which is defined as the number of days after initiating unassisted breathing to day 28 after randomization, assuming a patient survives for at least 48 consecutive hours after initiating unassisted breathing. For example, if a patient begins unassisted breathing on day 16 and survives to day 28, he/she will be assigned a value of 12. If a similar patient begins unassisted breathing on day 16 but dies on day 25, he/she will be assigned a value of 9. If a patient survives for > 48 consecutive hours of unassisted breathing but requires assisted breathing (for any reason) before day 28, he/she will be assigned only the number of days of unassisted breathing before day 28. Patients who die without initiating unassisted breathing or before 48 consecutive hours of unassisted breathing will be assigned a value of zero. Patients transferred to another hospital or other health care facility (intermediate care, nursing home etc.) while still on positive pressure ventilation will be followed to assess these primary efficacy measures.

Number of Days of Unassisted Breathing is related to "number of days of assisted ventilation", which would be a simpler measure. However, if there were a trend in one treatment group towards more rapid death on assisted ventilation, the effect of this trend on duration of assisted ventilation would be misleading. "average duration of ventilation in survivors" would avoid this potential problem. However, if there were a trend towards better survival in one treatment group even though the days of assisted ventilation were longer in the survivors, then the measure of days of assisted ventilation in survivors would be of questionable value. The second primary efficacy measure chosen for this study, *Number of Days of Unassisted Breathing*, will be favorably affected by both better survival and shorter duration of ventilation in survivors.

Secondary endpoints include:

3. Percentage of patients who achieve unassisted breathing.
4. Number of ICU-free days at 28 days after enrollment
5. Number of Organ-failure-free days at 28 days after enrollment
6. Number of days after first meeting commence-weaning criteria, measured at 28 days after enrollment.
7. Number of days after initially achieving unassisted ventilation, measured at 28 days after enrollment.
8. Percentage of patients withdrawn because of elevations in liver enzymes suggesting liver toxicity from ketoconazole.
9. Incidence of barotrauma (pneumothoraces, pneumatoceles > 2 cm largest diameter, pneumomediastinum).

4 Study Population and Enrollment

4.1 Number/Source/Screening

The trial will accrue 800 patients in two years. Patients with either ALI or ARDS will be randomized to one of four treatment arms. Patients will be recruited from intensive care units (ICU's) in approximately 24 hospitals that comprise the NIH ARDS Network. Each of the ten Centers that comprise the ARDS Network have provided documentation of at least 100 ARDS patients per year and of the potential to enroll approximately 40 patients per year in multicenter studies in ARDS and sepsis.

Study Coordinators at each site will visit each intensive care unit daily to identify potential candidates for enrollment (see inclusion criteria, section 4.2 and exclusion criteria, section 4.3). Permission to approach patients/families will be requested from attending physicians. All patients meeting the study inclusion criteria (section 4.2) 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, patient refusal, etc.).

4.2 Inclusion Criteria

Acute Onset of:

1. $\text{PaO}_2/\text{FiO}_2 \leq 300$. If altitude $> 1000\text{m}$, then $\text{PaO}_2/\text{FiO}_2 \leq 300 \times (\text{B.P.}/760)$.
2. Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph. The infiltrates may be patchy, diffuse, homogeneous, or asymmetric.
3. Requirement for positive pressure ventilation via endotracheal tube.
4. No clinical evidence of left atrial hypertension. If in place, pulmonary arterial wedge pressure ≤ 18 mmHg.

Criteria 1-3 must occur together within a 24-hour interval.

The term ‘acute onset’ is defined as follows: the hypoxia criterion (#1) and the chest radiograph criterion (#2) must be in effect for ≤ 28 days at the time of randomization.

4.3 Exclusion Criteria

1. Clinicians caring for patient not agreeable to using Assist/Control Ventilation for at least 12 Hours after patient enrollment. (This exclusion criterion is intended to avoid enrollment of patients who may begin weaning within 12 hours. It is *not* implied that other forms of ventilation or gas exchange support, such as pressure control ventilation or ECMO, are allowed in this study after 12 hours.)
2. Age < 18 years.
3. Participation in other intervention trials in ALI, ARDS, or sepsis within the past 30 days.
4. > 36 hours since all inclusion criteria are met (see “Enrollment Time Window”, Section 4.4).

5. Neuromuscular disease that impairs ability to ventilate spontaneously, such as C₅ or higher spinal cord injury, amyotrophic lateral sclerosis, Guillain-Barre syndrome, and myasthenia gravis.
6. Pregnancy.
7. Elevated intracranial pressure (Appendix A), Tricyclic antidepressant overdose (if most recent level elevated or no level), Hgb SS, Hgb SC, or conditions in which hypercapnia would be contraindicated.
8. Severe chronic respiratory disease (eg COPD, pulmonary fibrosis, morbid obesity, and other chronic diseases of the lung, chest wall or neuromuscular system. (Appendix A).
9. Morbid obesity (> 1 kg/cm body weight).
10. Burns \geq 30% total body surface area.
11. Malignancy or other irreversible disease or condition for which 6-month mortality is estimated \geq 50%.
12. Bone marrow transplant.
13. Lung transplant.
14. 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).
15. Treated with terfenadine, astemizole, or cisapride within the past 72 hours.
16. Severe chronic liver disease (Child-Pugh Score of 10-15(Appendix A)).
17. Evidence of acute liver disease (either acute hepatitis or acute cholestasis) with significant hepatocellular or cholestatic liver injury (Appendix B).
18. Known allergy to imidazole or its derivatives.
19. Treated with ketoconazole or other imidazole within the past 7 days.

4.4 Enrollment and Study Initiation Time Window

All patients must be enrolled, randomized, and initial ventilator and study drug treatments administered within 36 hours of the time the last inclusion criterion was met. The last inclusion criterion may be met at either the network hospital or a referring hospital. The 36-hour window for enrollment will begin at the time of documentation of the last inclusion criterion, regardless of location. Initial ventilator changes and study drug administration must occur within 4 hours of the time of randomization, and must be administered within 36 hours of the time that the last inclusion criterion was met.

4.5 Informed Consent

Informed consent will be obtained from each patient or surrogate.

4.6 Randomization

After procuring informed consent, the data coordinating center will be called and an assignment will be made by computer-generated randomizations to either the 12 ml/kg or 6 ml/kg group and to receive either ketoconazole or placebo. Randomization system will be based on Interactive Voice Response technology. Each research coordinator will have a unique Personal Identification Number (PIN). He or she will call the system and be asked to supply the PIN. A ventilator strategy, either 12 ml/kg or 6 ml/kg, and a patient ID number will be assigned. For the blinded ketoconazole study, the ID number will inform the pharmacy which drug to dispense, either ketoconazole or placebo, based on a list in the research pharmacy.

4.7 Minorities/Women

Gender and racial patient 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 either of the two treatment interventions in the proposed study.

5 Study Procedures

5.1 Ketoconazole and Respiratory Management in ALI/ARDS

5.1.1 Volume Cycled Ventilation

1. Ventilator mode.

12 ml/kg and 6 ml/kg Treatment Groups: Volume Cycled Assist/Control.

2. Tidal Volume and Ventilator Rate Adjustments and Arterial pH Management.

- (a) Initial Ventilator Tidal Volume and Rate.

Tidal Volume

(In the following procedures, the term "tidal volume" refers to inspired volumes, corrected for gas compression in the ventilator conduits.)

12 ml/kg group: 12 ml/kg ideal body weight (IBW).²

²Ideal weight is calculated from age, gender and height (heel to crown) according to the following equations:

6 ml/kg group: 6 ml/kg IBW. Initial tidal volumes in this group will be set at 8 ml/kg IBW. This will be reduced by 1 ml/kg IBW at intervals of ≤ 2 hours until tidal volume = 6 ml/kg IBW.

Ventilator Rate

Both groups: Initial ventilator rate will be set to match minute ventilation prior to enrollment, if possible. Maximum rate = 35/min.

(b) Adjustments to Ventilator Tidal Volume and Rate.

Goals: Ventilator rate and tidal volume will be adjusted to achieve specific goals of arterial pH and end-inspiratory alveolar (plateau) pressure, respectively.

• Arterial pH Goals

Goal for both groups: $7.30 \leq \text{pH} \leq 7.45$.

Arterial pH will be measured when clinically indicated.

Management of alkalemia and acidemia may be according to the following rules:

- Alkalemia ($\text{pH} > 7.45$): Decrease ventilator rate, if possible.
- Mild acidemia ($7.15 \leq \text{pH} < 7.30$):
 - i. Increase ventilator rate up to maximum of 35 or until $\text{pH} > 7.30$ or $\text{PaCO}_2 < 25$ mm Hg.
 - ii. If ventilator rate = 35 or $\text{PaCO}_2 < 25$, then bicarbonate infusion may be given.
- Severe acidemia ($\text{pH} < 7.15$):
 - i. Increase ventilator rate to 35.
 - ii. If ventilator rate = 35 and $\text{pH} < 7.15$ and bicarbonate has been considered or infused, then tidal volume may be increased by 1 ml/kg until $\text{pH} \geq 7.15$ (under these conditions, the plateau pressure targets described below may be exceeded).

• Plateau Pressure Goals

12 ml/kg group: ≤ 50 cm H₂O

6 ml/kg group: ≤ 30 cm H₂O

Males: $\text{IBW (kg)} = 50 + 2.3 (\text{height (inches)} - 60)$.

Females: $\text{IBW (kg)} = 45.5 + 2.3 (\text{height (inches)} - 60)$.

Plateau pressures will be measured at a minimum frequency of q4 hours. Plateau pressures will also be measured and recorded 1-5 minutes after each change in PEEP or tidal volume. For each measurement, patients will be relaxed, not coughing or moving. The pressure corresponding to the first plateau that occurs after initiating a 0.5 second pause will be recorded. The pause will be removed for at least 6 breaths. The plateau pressure measurements will be replicated 3 times with at least 6 "non-plateau" breaths between measurements and the mean of the three values will be calculated. If plateau pressures cannot be measured because of air leaks, then peak inspiratory pressure will be substituted.

Tidal volumes will be reduced (if arterial pH > 7.15, see section 2b above) by 1 ml/kg q2-3 hours if necessary to maintain plateau pressures \leq the respective target values.

The minimum tidal volume in both groups will be 4 ml/kg IBW.

Changes in the tidal volume, if indicated above, will be made within five minutes.

Tidal volumes will be increased in both groups if plateau pressure \ll targets:

- i. 12 ml/kg group: if tidal volume < 12 ml/kg and plateau pressure \leq 45 cm H₂O, then tidal volume will be increased in steps of 1 ml/kg until plateau pressure \geq 45 or tidal volume = 12 ml/kg IBW.
- ii. 6 ml/kg group: if tidal volume < 6 ml/kg and plateau pressure \leq 25 cm H₂O, then tidal volume will be increased by 1 ml/kg until plateau pressure \geq 25 or tidal volume = 6 ml/kg IBW.
- iii. If tidal volume < 8 ml/kg AND P_{plat} < 30 cm H₂O AND airway pressure remains below the PEEP level during inspiration or the ventilator delivers frequent (\geq 3/minute) double breaths because airway pressure falls below trigger threshold at the end of inspiration, then tidal volume will be increased by 1 ml/kg. If these phenomena persist at tidal volume = 8 ml/kg or at tidal volume < 8 ml/kg with P_{plat} \geq 30 cm

H₂O, then additional sedation or neuromuscular blockade should be considered.

3. Inspiratory flow and I:E ratio.

Inspiratory flow rate will be adjusted to maintain the I:E ratio = 1:1.0–1:3.0.

4. Oxygenation.

In both treatment groups, the target ranges for oxygenation will be:

$$55 \text{ mmHg} \leq \text{PaO}_2 \leq 80 \text{ mm Hg}$$

or

$$88\% \leq \text{S}_p\text{O}_2 - \text{sat} \leq 95\%$$

When both PaO₂ and S_pO₂ are available simultaneously, the PaO₂ criterion will take precedence.

Oxygenation will be maintained in the target ranges using the following PEEP/FiO₂ combinations: (see table below)

| | | | | | | | | | | | | | | | |
|------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------|
| FiO ₂ | .30 | .40 | .40 | .50 | .50 | .60 | .70 | .70 | .70 | .80 | .90 | .90 | .90 | 1.0 | 1.0 |
| PEEP | 5 | 5 | 8 | 8 | 10 | 10 | 10 | 12 | 14 | 14 | 14 | 16 | 18 | 18 | 20–24 |

Levels of PEEP in this scale represent levels set on the ventilator, not levels of total PEEP, auto-PEEP, or intrinsic PEEP.

Arterial oxygenation will be assessed by either SpO₂ or PaO₂ at a minimum frequency of q4 hours. When SpO₂ is used to assess arterial oxygenation, the following measures will be taken if possible to improve accuracy: the SpO₂ sensor will be checked to ensure optimal position, cleanliness, and consistent readings with satisfactory waveforms; no position changes or endobronchial suctioning for ≥ 10 minutes; no invasive procedures or ventilator changes for ≥ 30 minutes. SpO₂ will be observed for a minimum of 1 minute, and a representative value will be recorded on the appropriate source-document flowsheet.

If arterial oxygenation is not within the target range, then FiO₂ or PEEP will be adjusted within 30 minutes. Following these

adjustments, oxygenation will be reassessed within 15 minutes and subsequent adjustments made if necessary.

If a patient's PEEP/ FiO_2 is not compatible with the PEEP/ FiO_2 scale (e.g. immediately after enrollment or after urgent changes in FiO_2 or PEEP in response to desaturations, hypotension, etc.), either PEEP or FiO_2 (or both) will be adjusted at intervals of 5-15 minutes until the PEEP/ FiO_2 is compatible with the scale. The procedures for adjusting PEEP and FiO_2 to make them compatible with the scale are outlined in Appendix F.

In the 6 ml/kg treatment group, if $\text{PaO}_2 < 55$ mm Hg or $\text{SpO}_2 < 88\%$ and tidal volume = 4 ml/kg IBW (or the minimum tidal volume necessary for pH control, section 2 above) and plateau pressure ≥ 30 , then FiO_2 will be raised until $\text{PaO}_2 \geq 55$ or $\text{SpO}_2 \geq 88\%$ or $\text{FiO}_2 = 1.0$. If $\text{PaO}_2 < 55$ mm Hg or $\text{SpO}_2 < 88\%$ and $\text{FiO}_2 = 1.0$, PEEP will be raised by 2 cm H_2O increments to 24 cm H_2O . (In these circumstances, plateau pressure may exceed 30 cm H_2O).

In the 12 ml/kg treatment group, if $\text{PaO}_2 < 55$ mm Hg or $\text{SpO}_2 < 88\%$ and tidal volume = 4 ml/kg IBW (or the minimum tidal volume necessary for pH control, section 2 above) and plateau pressure ≥ 50 , FiO_2 will be raised in increments of 0.1 until $\text{PaO}_2 \geq 55$ or $\text{SpO}_2 \geq 88\%$ or $\text{FiO}_2 = 1.0$. If $\text{PaO}_2 < 55$ or $\text{SpO}_2 < 88\%$ and $\text{FiO}_2 = 1.0$, then PEEP will be raised by 2 cm H_2O increments to 24 cm H_2O . (In these circumstances, plateau pressure may exceed 50 cm H_2O).

Brief periods (≤ 5 minutes) of $\text{SpO}_2 < 88\%$ or $> 95\%$ may be tolerated without making changes in PEEP or FiO_2 .

$\text{FiO}_2 = 1.0$ may be used for brief intervals (≤ 10 minutes) of transient desaturation or to prevent desaturation during treatments such as tracheo-bronchial suctioning or position changes.

If $\text{FiO}_2 = 1.0$ and PEEP = 25cm H_2O and I:E = 1.0 and $\text{PaO}_2 < 55$ or $\text{SpO}_2 < 88\%$, then a PEEP increase trial *may* be performed as follows:

- (a) Increase PEEP by 2-5 cm H_2O increments to a maximum of 34 cm H_2O or until $\text{PaO}_2 \geq 55$ or $\text{SpO}_2 \geq 88\%$.
- (b) If the PEEP increase trial is not effective within four hours (PaO_2 increased by at least 5 mmHg), then PEEP will be returned to 24cm H_2O .

5. Simultaneous changes

Changes in more than one ventilator setting driven by measurements of PO₂, pH, and plateau pressure may be performed simultaneously, if necessary. Arterial blood gases will be obtained after all ventilator changes as clinically indicated.

5.1.2 Weaning

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.

- (a) ≥ 12 hours since initial protocol ventilator changes, if any.
- (b) $\text{FiO}_2 \leq .40$.
- (c) Values of both PEEP and $\text{FiO}_2 \leq$ values from previous day (comparing Reference Measurement values, section 6.3).
- (d) Not receiving neuromuscular blocking agents and without neuromuscular blockade.
- (e) 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.
- (f) Systolic arterial pressure ≥ 90 mm Hg without vasopressor support ($\leq 5 \mu\text{g}/\text{kg}/\text{min}$ dopamine or dobutamine or equivalent low dose of another vasopressor will not be considered a vasopressor).

If criteria a-f are met, weaning potential will be assessed during a CPAP trial of ≤ 5 minutes at $\text{CPAP} = 5 \text{ cm H}_2\text{O}$ and $\text{FiO}_2 = .50$. If respiratory rate remains $\leq 35/\text{min}$ during the 5-minute CPAP trial, the patient will have met the commencement of weaning criteria and will enter the Pressure Support Wean Procedure (Section 2). If respiratory rate exceeds 35/min during the 5-minute CPAP trial, the patient will resume A/C

ventilation at the most recent settings. The patient will be reassessed for weaning the following day at 0600-1000. (If failure to maintain the respiratory rate ≤ 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).

2. Initial Pressure Support (PS) Setting (for patients whose respiratory rates remain ≤ 35 /min during 5-minute CPAP trial).
 - (a) Mode = Pressure Support. Only the following PS levels may be used: 5, 10, 15, and 20 cm H₂O.
 - (b) If respiratory rate ≤ 25 during the 5-minute CPAP trial and tolerance criteria (section 3, below) are met then initiate PS = 5 cm H₂O.
If respiratory rate = 26-35 during the 5-minute CPAP trial then set initial PS = 20 cm H₂O and make adjustments in PS within 5 minutes if necessary to achieve respiratory rate = 26-35.
 - (c) PEEP = 5 cm H₂O.
 - (d) FiO₂ = .50.

3. Assessment for Tolerance.

Patients will be assessed for tolerance using the following criteria:

- (a) Total respiratory rate < 35 (≤ 5 min at respiratory rate > 35 may be tolerated).
- (b) SpO₂ $\geq 88\%$ (< 15 min at $< 88\%$ may be tolerated).
- (c) No respiratory distress (two or more of the following):
 - i. Heart rate greater than 120% of the 0600 rate (≤ 5 min at $> 120\%$ may be tolerated).
 - ii. Marked use of accessory muscles.
 - iii. Abdominal paradox.
 - iv. Diaphoresis.
 - v. Marked subjective dyspnea.

If any of goals a,b, or c are not met on initial set-up to PS, then the ventilator mode will be changed back to A/C at back-up rate = to most recent A/C settings and the patient will be reassessed the next morning.

4. Subsequent Ventilator Settings.

- (a) Reduce PS level by 5 cm H₂O q1-3 hours. PS will not be decreased below 5 cm H₂O. No decreases in PS will be made after 1900.
- (b) If PS = 10, 15 or 20 cm H₂O is not tolerated, then return to A/C (patient will remain in previously assigned 12 ml/kg or 6 ml/kg treatment group).
 - i. At 0600-1000 of the next day, return to last PS level tolerated and continue with step 4(a).
- (c) If PS level = 5 cm H₂O is not tolerated, increase PS by 5 cm H₂O to 10 cm H₂O, and maintain until the following morning.
 - i. If a patient on PS = 5 or 10 must go back to A/C for reasons other than intolerance to weaning (e.g. surgical or other invasive procedures), the weaning sequence will be re-entered with section 5.1.2.1.
- (d) If PS = 5 cm H₂O is tolerated for two or more hours (using tolerance criteria 3a-c above), assess for ability to sustain unassisted breathing (section 5 below).

5. Assess for Ability to Sustain Unassisted Breathing.

Initiate a trial of spontaneous breathing on CPAP \leq 5 cm H₂O, T-piece, or tracheostomy mask with FiO₂ \leq .50. Monitor for the following:

- (a) SpO₂ \geq 90% and/or PaO₂ \geq 60 mmHg.
- (b) Spontaneous tidal volume \geq 4 ml/kg ideal body weight.
- (c) Respiratory Rate \leq 35/min.
- (d) pH \geq 7.30 if measured.
- (e) No respiratory distress (2 or more of the following):
 - i. Heart rate $>$ 120% of the 0600 rate (\leq 5 min at $>$ 120% may be tolerated).
 - ii. Marked use of accessory muscles.
 - iii. Abdominal paradox.
 - iv. Diaphoresis.
 - v. Marked subjective dyspnea.

If criteria a-e are met for > 120 minutes, continue with unassisted breathing (step 6). If any of criteria a-d are not met during the 120 minute trial, then resume PS ventilation at 5 cm H₂O and assess for tolerance (step 3).

6. Definition of Unassisted Breathing.
 - (a) Extubated with face mask, nasal prong oxygen, or room air, OR
 - (b) T-tube breathing, OR
 - (c) Tracheostomy mask breathing, OR
 - (d) CPAP ≤ 5 without PS or IMV assistance.

5.1.3 Completion of Ventilator Procedures

Patients will be considered to have completed the study ventilator procedures if any of the following conditions occur:

1. Death.
2. Hospital discharge.
3. Alive 28 days after enrollment.

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.

5.1.4 Premature Withdrawal from Treatment

Patients will be removed from the 6 ml/kg tidal volume ventilation protocol if they develop neurologic conditions where hypercapnia would be contraindicated (Appendix A.7). They will continue to receive ketoconazole or placebo.

5.2 Ketoconazole or Placebo

5.2.1 Drug Delivery

Drug or Placebo delivery will be via enteral (gastric, duodenal or jejunal) tube. Ketoconazole requires acidity for dissolution but not absorption. Drug and placebo will be dissolved in 60 ml of Coke Classic at room temperature. The liquid should be gently stirred for 5 minutes or until the tablet is completely dissolved.

Once eligibility in the study has been established and informed consent to participate has been obtained, the study pharmacist will be notified. He or she will assign each subject to a treatment arm (either ketoconazole or placebo) dependent upon the patient ID he receives from the coordinating center. The pharmacist will be unblinded to the treatment assignments. He or she will be responsible for treatment assignment, formulations, and maintaining the list of codes revealing which treatment is being taken by each study participant. The pharmacist will dissolve the study drug in 60 ml of Coke Classic and fill two 30 ml syringes for administration and deliver the study drug to the ICU. In addition, the pharmacist will ensure that study treatments are available on a 24-hour basis, so that patients may be enrolled in the study and the study drugs begun on nights and weekends.

5.2.2 Dosage

Ketoconazole therapy will consist of 400 mg per enteral tube or p.o., q a.m. Placebo therapy will consist of a tablet in a similar volume via enteral tube or p.o., q a.m.. Each dose of study medication will be flushed through the enteral tube with 20 ml normal saline. If an enteral tube is used for suctioning, the tube must be clamped for one hour following drug administration, prior to resuming suctioning. Study drug will be administered only once per calendar date. Hence, if the initial study drug is given before the usual time for administration of once-daily medications, the next study drug dose will be given the following calendar date.

5.2.3 Duration

Study drug will be given on the day of enrollment and once daily for 21 days. Study drug administration will be discontinued prior to 21 days if a patient achieves unassisted breathing for more than 48 consecutive hours or for possible drug-induced hepatic injury (Appendix B).

5.2.4 Toxicity

Toxicity is defined as the development of possible drug-induced hepatic injury (Appendix B). Study drug will be discontinued if this occurs.

Do not co-administer terfenadine, astemizole or cisapride due to a drug-drug interaction that has been associated with serious cardiac arrhythmias. Since ketoconazole may interfere with the metabolism of cyclosporin, levels of this drug, if administered, should be monitored carefully. For a more complete description of potential toxicities and drug-drug interactions, refer to section 1.2.2 and Appendix C of this protocol.

5.2.5 Stress Ulcer Prophylaxis

If needed prophylaxis may be provided. Sucralfate or antacid, if used, should be administered 2 hrs prior to the next dose of study drug.

5.2.6 Premature Withdrawal from Treatment

Patients will be removed from treatment with ketoconazole or placebo if possible drug-induced hepatic injury develops (Appendix B), or intolerance to the drug occurs. They will continue on their assignment of ventilator strategy. Patients will be withdrawn from treatment with ketoconazole or placebo if they receive terfenadine, astemizole, or cisapride during the study. Liver function tests will be monitored as described in section 6.3.6 if drug is prematurely discontinued.

6 Data Collection

6.1 Background Assessments

1. Demographic and Admission Data.
2. Pertinent Medical History and Physical Examination.
3. Height; calculated ideal body weight (IBW).
4. Time on Ventilator prior to enrollment.
5. Type of Admission
 - (a) Scheduled surgical
 - (b) Medical
 - (c) Unscheduled surgical
6. Presence of following chronic 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 pneumonia, Kaposi's sarcoma, lymphoma, tuberculosis, or toxoplasmosis).

6.2 Baseline Assessments

The following information will be recorded during the four-hour interval that precedes initial protocol ventilator changes (if any). Parameters indicated with "*" will be measured during the four-hour interval. If more than one value is available during the four-hour interval, the last value will be recorded. For other parameters, most recent values will be recorded. If no values are available during the preceding 24 hours, then values will be measured during the four-hour interval prior to initial ventilator changes (if any).

1. * Vital Signs: heart rate (b/min), systolic and diastolic BP (mmHg), body temperature ($^{\circ}\text{C}$), total respiratory rate.
2. * Ventilator Parameters: Mode, ventilator rate, tidal volume (inspired), FiO_2 , PEEP, plateau pressure (0.5 second pause), ventilator manufacturer and model.
3. Arterial PO_2 , PCO_2 , and pH and SpO_2 .
4. Urinary output (most recent 24 hour value).
5. Serum electrolytes, BUN, creatinine and glucose.
6. Blood hematocrit/hemoglobin, WBC, and platelets.
7. Serum albumin concentration.
8. Blood for IL-6 and other cytokines and mediators. Blood will be drawn sufficient to yield 6 ml of EDTA anticoagulated plasma and divided immediately after centrifugation into 3 equal 2 ml aliquots in specified tubes and frozen at -70°C .
9. * Urine thromboxane metabolite.
10. Liver function tests: Total bilirubin, AST, ALT, Alkaline Phosphatase.
11. * Glasgow coma score
12. Frontal chest radiograph (when available):
 - (a) Radiographic Lung Injury Score ([44], # of quadrants.
 - (b) Presence/absence of barotrauma:
 - i. pneumothoraces (R/L)
 - ii. pneumomediastinum
 - iii. pneumatoceles > 2 cm minimum diameter (R/L)
 - iv. subcutaneous emphysema
13. Administration of the following medications (Y/N):
 - (a) Sedatives
 - (b) Neuromuscular blocking agents

- (c) Vasopressors (maximum number given simultaneously)
- (d) H₂ blockers
- (e) Macrolide antibiotics (erythromycin, clarithromycin, TAO, etc.)

Most recent values for the following additional parameters will be recorded only if they are available from clinically required measurements.

14. Pulmonary artery systolic, diastolic, mean and pulmonary capillary wedge pressures, central venous pressure, and cardiac index.
15. Body weight (kg).

6.3 Assessments During Enrollment

The following data will provide the basis for assessing protocol compliance and safety as well as between-group differences in several efficacy variables. Data for each of the variables will be recorded on the days shown in the Time-Events schedule (Appendix E) or until death, discharge from intensive care unit, or unassisted ventilation for 48 hours.

Reference Measurements

The following parameters will be measured and recorded between 0600 and 1000 on the days specified in the Time-Events schedule (Appendix E). The following conditions will be ensured prior to measurements: supine position for ≥ 15 minutes; no endobronchial suctioning for ≥ 10 minutes; no invasive procedures or ventilator changes for ≥ 30 minutes. SpO₂ sensors will be checked for optimal position, cleanliness, and consistent readings with satisfactory waveforms, if displayed. SpO₂ values will be observed for 1 minute and a representative value recorded. All vascular pressures will be zero-referenced to the mid-axillary line.

1. If receiving positive pressure ventilation:
 - (a) Ventilator mode
 - (b) Ventilator set inspired tidal volume (if on volume cycled mode)
 - (c) Pressure Support level (if on PS for weaning)
 - (d) Total respiratory rate

- (e) Total minute ventilation
 - (f) PEEP
 - (g) Plateau pressure (if on volume cycled mode)
 - (h) Peak inspiratory pressure (if on volume cycled mode)
2. FiO₂
 3. SpO₂ on current FiO₂
 4. Hemodynamic values
 - (a) Arterial systolic, diastolic and mean pressures
 - (b) Heart Rate (beats/min)

Values for the following variables will also be recorded for the dates shown in the Time-Events Schedule.

If the measurements are not obtained during the 4-hour reference interval, then the single value obtained closest in time to the reference interval on the respective date will be recorded.

If more than one value is obtained during the reference interval, then the earliest value during the interval will be recorded.

5. Weight (kg), using same technique for each measurement (bed-scale vs lift vs other)
6. Serum electrolytes and liver function tests (total bilirubin, AST, ALT, alkaline phosphatase). Liver function tests will be required one additional time after discontinuation of study drug on the regularly scheduled day as noted on the Schedule of Events table. The final LFT's should be at least 24 hours after the final dose.
7. Blood hemoglobin concentration
8. Arterial PO₂, PCO₂, and pH and calculated bicarbonate concentrations
9. Requirements for the following medications (Y/N):
 - (a) Sedatives and tranquilizers
 - (b) Neuromuscular blocking agents

- (c) Vasopressors (maximum number given simultaneously)
 - (d) H₂ blockers
 - (e) Macrolide antibiotics (erythromycin, clarithromycin, TAO, etc.)
 - (f) Experimental treatments: nitric oxide, fluorocarbons, surfactants, extracorporeal gas exchange (ECMO, ECCO₂R, etc.)
10. AP frontal chest radiograph
 - Presence/absence of barotrauma (as described for baseline assessments)
 - Radiographic Lung Injury Score ([44], number of quadrants)
 11. Blood for Il-6 and other cytokines and mediators (specimens will be processed as described in Section 6.3.2).
 12. Urine thromboxane metabolite.
 13. Brussels Score
 - (a) Worst PaO₂/FiO₂ ratio for the date
 - (b) Worst systolic blood pressure for the date
 - (c) Worst creatinine, bilirubin, and platelet count for the date
 - (d) Use of a vasopressor (Y/N)
 - (e) Glasgow Coma Score

6.3.1 Ventilator protocol monitoring

Ventilator parameters, pH, and SpO₂ will be recorded daily at randomly selected times to assess for accuracy of the ventilator settings relative to the protocol requirements. The following parameters will be recorded:

1. Ventilator mode
2. Tidal volume
3. Respiratory rate (set)
4. Plateau pressure

5. I:E ratio
6. FiO₂
7. PEEP
8. Corresponding pH and SpO₂, when available.

6.4 Endpoint determinations

1. Patient vital status at discharge or 180 days after enrollment.
2. Time of initiation of unassisted breathing.
3. Patient status 48 hours after initiation of unassisted breathing.
4. Date of ICU discharge.
5. Date of hospital discharge.

7 Statistical Considerations

This study is a 2×2 factorial design comparing 6 ml/kg tidal volume to 12 ml/kg tidal volume Volume Assist/Control ventilation and comparing Ketoconazole, 400 mg, to placebo. The ventilator and the ketoconazole trials will be analyzed separately and one may stop before the other.

There are two primary efficacy measures. The first is *Percentage of patients alive with unassisted breathing at hospital discharge*. Patients still alive in hospital at 180 days will be defined as survivors. For the analysis, survival of the two groups will be compared using a test based on the 180-day Kaplan Meier estimate. This efficacy measure is used to calculate sample size and to develop interim stopping boundaries. The second efficacy measure, *Number of Days of Unassisted Breathing*, is designed to examine differences in time to recovery from acute respiratory failure, which will reflect morbidity and cost (see Section 3, Study Design). *Number of Days of Unassisted Breathing* will be compared between treatments using a Wilcoxon test.

7.1 Treatment of multiple endpoints

We do not plan to use a bonferroni correction to correct for the fact that there are two efficacy measures because these measures are affected by different effects of treatment. If a treatment does not reduce mortality it may still reduce the duration of mechanical ventilation which would benefit patients financially and decrease their morbidity. This effect is measured by *Number of Days of Unassisted Breathing*. This is a better efficacy measure than the duration of ventilation for all patients or the duration of ventilation for survivors because, in either case, the duration of ventilation is potentially biased against a treatment that saves the lives of a portion of the patients by increasing the time that they must be ventilated.

7.2 Sample size and early stopping for the Ventilator Protocol

7.2.1 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 6 ml/kg tidal volume and 12 ml/kg tidal volume of 10%, from 40% to 50%.

7.2.2 Early Stopping

There will be three interim analyses and one final analysis. The analyses will occur when 200, 400, 600 and 800 patients have entered the trial. We expect that interim analyses will take place every 6 months since we expect to accrue 400 patients a year.

There are two types of clinical trials, “superiority” trials and “equivalence” trials. Most trials are “superiority” trials that are designed to show that a new treatment is better than an old one. One declares that the treatments are different if the difference between the observed mortality rates is **significantly greater than zero** at a 5% significance level. If this occurs we know with relative certainty that the new treatment is superior.

However, if there is not a significant difference we do not know with the same certainty that the treatments are equivalent. This has led to the development of “equivalence” trials. In an equivalence trial one declares that the treatments are equivalent if the difference between the observed mortality rates are **significantly less than 10%**. If this occurs we know with relative certainty that the two treatments have mortality rates that do not differ by more than 10%.

This trial will be both a superiority trial and an equivalence trial. As a superiority trial, the trial will have a 80% chance of finding a significant difference at a two sided $p = .05$ significance level if the true difference between the treatments is 10%. O’Brien-Fleming boundaries [46] will be used to stop the trial due to superiority of one treatment. There will be no early stopping for equivalence to allow an adequate sample to test for differences in *Number of Days of Unassisted Breathing* in the case where there is no mortality difference.

As an equivalence trial, the trial will have a 76% chance of finding that the treatments are equivalent(i.e. that the difference is significantly less than 10% at $p=.05$) if the true mortality rates of the two treatments are the same. O’Brien-Fleming boundaries will be used for interim stopping in both cases. There is no need for a bonferroni adjustment for the significance levels of the equivalence and superiority comparisons because the null hypotheses are mutually exclusive.

The following table gives the decision rules that would be used at each interim analysis and the final analysis under the assumption that the mean mortality rate of the two treatments is 45%. To understand the table, consider the third analysis, considered on the third row, which would occur approximately 18 months after the trial began. The number $|D|$ is the absolute value of the difference between the mortality rates on the two arms. If $|D| > 9.5\%$ then the trial would stop at the third analysis with one treatment considered superior. Note that there is a possibility that the trial will end without a conclusion of either superiority or equivalence. This would occur if the observed difference was between 4.2% and 7%, such a difference would not be significantly different from either zero or 10%.

**Stopping Rules for the Ventilator trial based on the observed
absolute value of the mortality difference $|D|$**

| Analysis | Stop: Treat-ments Differ | Continue: un-less Final | |
|----------|--------------------------|-------------------------|-----------------------|
| 1 | $ D > 28.5\%$ | $ D \leq 28.5\%$ | |
| 2 | $ D > 14\%$ | $ D \leq 14\%$ | |
| 3 | $ D > 9.5\%$ | $ D \leq 9.5\%$ | |
| Final | $ D > 7.2\%$ | $ D < 4.2\%$ | $4.2\% < D < 7.2\%$ |

7.3 Sample size and early stopping for the Ketoconazole study

The monitoring of this portion of the trial will be on the same schedule as the ventilator portion. This trial will stop if ketoconazole is effective using an O'Brien-Fleming upper boundary. It will stop for futility if the observed difference in mortality rate between placebo and ketoconazole is less than 3%. 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 one sided 5% significance level is 80% if the true difference is 10%. If there is no advantage to ketoconazole then the trial has a 64% chance of stopping after 6 months and an additional 15% chance of stopping after 1 year.

Stopping Rules for the Ketoconazole trial based on the observed mortality difference $|D|$

| Analysis | Stop: Keto-conazole supe-rior | Stop: Trial is futile | Continue: un-less Final |
|----------|-------------------------------|-----------------------|--------------------------|
| 1 | $D > 22.6\%$ | $D < 3\%$ | $3\% \leq D \leq 22.6\%$ |
| 2 | $D > 11.3\%$ | $D < 3\%$ | $3\% \leq D \leq 11.3\%$ |
| 3 | $D > 7.6\%$ | $D < 3\%$ | $3\% \leq D \leq 7.6\%$ |
| Final | $D > 5.7\%$ | | |

8 Data Collection and Site Monitoring

8.1 Data Collection

Each site will have a lap-top computer. The research nurse will be responsible for maintaining a data base using a custom designed data base application. Twice a week the research nurse will make sure that his/her computer is connected to a modem. The coordinating center computer will call the site computers during the evening and download the active database from each site. The software is designed with a series of checks to avoid missing or incorrect data.

8.2 Reporting of Adverse Events

Adverse events shall be reported as described in Appendix D.

8.3 Site Monitoring

Site visits will be performed no less than twice each year by Boston Biostatistics Research Foundation, employed by the Clinical Coordinating Center, 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

9.1 Ketoconazole and Respiratory Management in ALI/ARDS

1. Patients in the 6 ml/kg treatment group will probably experience more hypercapnia and may experience worse shunt ([23]). Therefore, they may require higher FiO_2 's to achieve the target PaO_2 , which

could lead to some increased risk of oxygen toxicity. Patients in the 12 ml/kg treatment group will have higher airway pressures, consistent with the higher levels of lung stretch and potential for barotrauma.

2. Hypercapnia and respiratory acidosis in the 6 ml/kg tidal volume group may require more sodium bicarbonate to maintain arterial pH targets. This could cause volume overload or hypernatremia. However, fluid balance and serum sodium are assessed frequently in the intensive care units. The potential adverse effects of bicarbonate infusions can be anticipated and avoided, minimized, or counteracted with diuretics and adjustments in fluid management.
3. 6 ml/kg tidal volume patients may experience more dyspnea, for which they would receive more sedation. Generous sedation (benzodiazepines and narcotics) is given to most critically ill patients because of anxiety and discomfort. Additional sedation requirements in the 6 ml/kg tidal volume group will likely be small.

9.2 Ketoconazole or Placebo

Ketoconazole has a rare but known risk of inducing an idiosyncratic acute hepatic toxicity. Monitoring of liver function tests will permit early recognition and discontinuation of treatment. Drugs with known toxic interaction will not be given. Otherwise, no significant toxicity is known after many years of clinical use, including as adjuvant therapy in liver transplant patients.

10 Human subjects

All protocols will require that all study participants or a member of a patient's family sign an informed consent. All protocols will require prior IRB approval before any subject is entered into the study. All study participants or their families will be informed about the objectives of the study and the potential risks. All laboratory specimens, evaluation forms and reports will be identified by a coded number only to maintain patient confidentiality. All records will kept in a locked/password protected

computer. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring by the FDA, National Heart, Lung and Blood Institute, ARDS Clinical Coordinating Center,

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11 Appendices

A Exclusion criteria definitions

7. Conditions where hypercapnia-induced elevations in intracranial pressure should be avoided:
 - Intracranial bleeding
 - GCS \leq 8
 - Cerebral contusion
 - Cerebral edema
 - Mass effect (midline shift on CT scan)
 - Papilledema
 - Intracranial pressure monitoring
 - Flat EEG for 48 hours
 - Fixed pupils
 - Absence of responses to deep pain
 - "Severe, terminal CNS damage"
9. Severe Chronic Respiratory Disease
 - FEV₁ less than 20 ml/kg IBW (e.g. 1.4 L for a 70 kg person), or
 - FEV₁/VC less than 50% predicted, or
 - Chronic hypercarbia (PaCO₂ greater than 45 mmHg) and/or chronic hypoxemia (PaO₂ < 55 mmHg) on FiO₂ = 0.21 or
 - Radiographic x-ray evidence of any chronic over-inflation or chronic interstitial infiltration, or
 - Hospitalization within the past six months for respiratory failure (PaCO₂ > 50 mmHg or PaO₂ < 55 mmHg or O₂-Sat < 88% on FiO₂ = .21).
 - Chronic restrictive, obstructive, neuromuscular, chest wall or pulmonary vascular disease resulting in severe exercise restriction, e.g., unable to climb stairs or perform household duties, secondary polycythemia, severe pulmonary hypertension (mean PAP > 40 mmHg), or respirator dependency.

17. Liver Failure: Child-Pugh Class C, which is defined as a total of ≥ 10 points on the following scoring table ([55]).

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 |

| Measurement | Numerical score for increasing abnormality | | |
|-----------------------------------|--|---------------|-----------------|
| | 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 |

B Assessment of Severity of Liver Disease

1. Cirrhosis/Severe Chronic Liver Failure

Child-Pugh Class C. See Appendix A.13

2. Possible Drug-induced Hepatic Injury

Development of either of the following injury patterns:

- Hepatocellular injury
AST or ALT ≥ 500 , or rise in AST or ALT $> 8 \times$ baseline (> 320 if normal at baseline)
- Cholestatic injury
alkaline phosphatase ≥ 240 U/L and a rise $> 3 \times$ baseline

3. Acute Liver Disease with Significant Hepatocellular or Cholestatic Injury (either one of the following criteria)

- Hepatocellular injury
AST or ALT ≥ 500 U/L
- Cholestatic injury
alkaline phosphatase ≥ 240 U/L

C Potential Drug-Drug Interactions Involving Ketoconazole

1. Effects Increased by Ketoconazole

Astemizole
Cisapride
Coumadin
Chlordiazepoxide
Cyclosporin
Terfenadine

2. Potentially Increases Metabolism of Ketoconazole

Phenobarbital
Phenytoin
Rifampin

D Adverse Event Reporting Procedure (optional for ventilator protocol)

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, unexpected, adverse events throughout the study period. All serious adverse events associated with study drug, 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 Data 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 Data Coordinating Center and the Institutional Review Board no later than 5 days after the investigator discovers the event.

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

2. Definition 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.

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 unexpected in ARDS or more severe or frequent than expected in ARDS.

Drug-related means that the Adverse Event follows a reasonable temporal sequence from drug administration and cannot be explained by the known characteristics of the patient's clinical state or by other therapies.

Please note that organ failures related to ARDS or the patient's underlying condition should not be reported as adverse events since they are systematically captured by the protocol.

E Schedule of Events

F Oxygenation Goals

- **Arterial oxygenation higher than the target range:**

FiO₂ or PEEP will be decreased (by .10 or 2.5, respectively), whichever is farther (number of step changes) from the target scale shown in Appendix F . If both PEEP and FiO₂ are equally distanced from the scale, then PEEP will be decreased.

- **Arterial oxygenation lower than the target range:**

FiO₂ or PEEP will be increased (by .10 or 2.5, respectively), whichever is farther from the target scale shown in Appendix .F If both PEEP and FiO₂ are equidistant from the scale, then PEEP will be increased first.

- **Arterial oxygenation within the target range:**

If a single adjustment in either FiO₂ or PEEP would correct the FiO₂/PEEP to the target scale, then FiO₂ will be adjusted.

If the FiO₂/PEEP cannot be corrected to the target scale with a single adjustment, then FiO₂ will be adjusted by .10 and PEEP will be simultaneously adjusted in the opposite direction by 2.5. E.g.: increase FiO₂ by .10 and decrease PEEP by 2.5, or decrease FiO₂ by .10 and increase PEEP by 2.5.

Oxygenation Goals

G Mathematical Description of the stopping rules

G.1 Boundaries for the Ventilator trial

The stopping rule is described in [86].

The boundaries are defined as follows. Let $x = \hat{p}_1 - \hat{p}_2$ and

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

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 $|x| > z_1 v_i$. The specific values chosen for the ventilator trial, chosen from [46] where, $I = 4$, $z_1 = 2.04206$. The trial will declare equivalence if the absolute difference in the observed mortality rates is significantly less than 20% of the combined mortality rate at a one sided 5% significance level. The power of the trial was calculated by simulating 50,000 clinical trials.

G.2 Boundaries for the ketoconazole trial

The upper boundaries of the ketoconazole trial will $x > B_1$ with $z_1 \approx 1.62$ this value will have to be adjusted at analysis time because it will depend on the combined mortality rate. The lower (futility) boundary will be 3%. The value of z_1 will somewhat lower than the boundary in [46] of 1.726. This boundary in [46] can be reduced because it is possible to cross the futility boundary under the null hypothesis and then eventually cross the upper boundary. Thus the futility boundary reduces the type I error rate below 5% if the boundary in [46] is used. The power is increased by lowering the upper boundary until the type I error rate is exactly 5%.