

2014

Reducing the burden of acute respiratory distress syndrome: The case for early intervention and the potential role of the emergency department

Brian M. Fuller

Washington University School of Medicine in St. Louis

Nicholas M. Mohr

University of Iowa

Richard Hotchkiss

Washington University School of Medicine in St. Louis

Marin Kollef

Washington University School of Medicine in St. Louis

Follow this and additional works at: https://digitalcommons.wustl.edu/em_pubs

Recommended Citation

This is a non-final version of an article published in final form in: Fuller, BM, Mohr, NM, Hotchkiss, RS, Kollef, MH. Reducing the burden of acute respiratory distress syndrome: The case for early intervention and the potential role of the emergency department. *Shock*. 2014; 41(5): 378-387. doi: 10.1097/SHK.000000000000142

This Article is brought to you for free and open access by the Division of Emergency Medicine/Emergency Care Research Section at Digital Commons@Becker. It has been accepted for inclusion in Peer-Reviewed Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact engeszer@wustl.edu.

**Reducing the Burden of Acute Respiratory Distress Syndrome: The Case for
Early Intervention and the Potential Role of the Emergency Department**

Brian M. Fuller, MD, MSCI

Department of Anesthesiology

Division of Critical Care

Division of Emergency Medicine

Washington University School of Medicine in St. Louis

Nicholas M. Mohr, MD

Department of Emergency Medicine

Department of Anesthesiology

Division of Critical Care

Roy J. and Lucille A. Carver College of Medicine

University of Iowa

Richard S. Hotchkiss, MD

Department of Anesthesiology

Division of Critical Care

Washington University School of Medicine in St. Louis

Marin H. Kollef, MD

Department of Medicine

Division of Pulmonary and Critical Care Medicine

Washington University School of Medicine in St. Louis

Corresponding Author:

Brian M. Fuller, MD, MSCI

660 South Euclid Avenue

Campus Box 8072

St. Louis, MO 63110

Fax: 314.3620419

Telephone: 314.7475368

Email: fullerb@wusm.wustl.edu

Sources of support:

BMF was supported by the Emergency Medicine Grant-in-Aid from the Division of Emergency Medicine, Washington University School of Medicine in St. Louis, and the Postdoctoral Mentored Training Program in Clinical Investigation. This publication was made possible, in part, by the National Center for Research Resources (NCRR) and the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through Grant UL1 TR000448. NMM declares no support. RSH was supported by National Institutes of Health (NIH) grants GM 44118 and GM 55194. MHK was supported by the Barnes Jewish Hospital Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or any of the other supporting bodies.

Conflicts of interest:

BMF, NMM, and MHK declare no conflicts of interest. RSH reports receiving grant support from MedImmune, Bristol-Myers Squibb, Agennix and Aurigene.

Running Head:

Early intervention and reducing ARDS

Abstract

The mortality for acute respiratory distress syndrome (ARDS) remains unacceptably high. Success in clinical trials has been limited, resulting in a lack of effective therapies to treat the syndrome. The projected increase in mechanically ventilated patients and global need for critical care services suggests that the clinical and research landscape in ARDS can no longer be confined to the intensive care unit (ICU). A demonstrable minority of patients present to the emergency department (ED) with ARDS, and ARDS onset typically occurs shortly after ICU admission. Furthermore, the ED is an entry point for many of the highest risk patients for ARDS development and progression. These facts, combined with prolonged lengths of stay in the ED, suggest that the ED could represent a window of opportunity for treatment and preventive strategies, as well as clinical trial enrollment. This review aims to discuss some of the potential strategies which may prevent or alter the trajectory of ARDS, with a focus on the potential role the ED could play in reducing the burden of this syndrome.

Keywords

acute respiratory distress syndrome, emergency department, prevention

Introduction

The landscape of critical care provided in the emergency department

Decades ago, delivery of critical care was envisioned to extend from the prehospital environment and into the intensive care unit (ICU). The emergency department (ED) was recognized as an important link in the care of the critically ill (1). Today, with over 100 million visits annually and increasing lengths of stay before inpatient admission, critical care is being provided in the ED more than ever (2, 3). With higher acuity in patient presentation, scarcity of available critical care beds, and impact of ED lengths of stay on critical care outcomes, the ED has become an increasingly important treatment location for the critically ill (3-9). Overcrowding is a recognized threat to patient safety, and delays in admission of critically ill patients to the ICU suggest that targeted interventions should be provided as soon as possible, regardless of patient location (4). Although time spent in the ED is a small fraction of the total inpatient stay, several series have demonstrated the early period of critical illness as being a particularly vulnerable time, where appropriate interventions have potential to change morbidity and mortality (10-12). Given these realities, the ED has proven to be an ideal setting to conduct research of early critical illness (11, 13).

This research agenda has yet to extend to mechanical ventilation and acute respiratory distress syndrome (ARDS) to any great degree however (14). Observational data suggest that the onset of ARDS is within hours to days after ICU admission (15-19). Endotracheal intubation and initiation of mechanical ventilation is common in the ED (20). Despite this, there is a lack of evidence regarding mechanical ventilation practices in the ED or the effect of ED care and mechanical ventilation on ARDS progression and outcome (12, 21). Therapeutic momentum initiated in the ED is often continued after admission (11, 12, 22). Given the influence of early interventions on outcome with other time-sensitive emergencies (e.g. sepsis and trauma), there is potential that this paradigm can be extended to ARDS prevention and treatment as well. The aim

of this review is to discuss *some* of the early interventions that can potentially prevent or alter the trajectory of ARDS, with some focus on the potential role the ED may play in the care of patients with or at risk for ARDS.

The current landscape of ARDS

ED prevalence and rate of progression after admission

ARDS affects close to 200,000 patients annually in the United States, and despite an overall improvement in mortality, remains a highly lethal condition (23, 24). Survivors of ARDS exhibit long-term morbidity across a wide range of important clinical outcomes, therefore its impact on public health is significant (23, 24). Despite extensive research, only low tidal volume ventilation has shown consistent survival benefit across syndrome severity, with prone positioning beneficial in the sickest ARDS cohort when instituted early and for prolonged periods (25-27). Prior clinical trials have focused extensively on patients in the ICU, less so in the operating room (OR), and little to none in the ED (14). Limited observational data focusing exclusively on ED patients suggests that a significant minority of patients have ARDS while in the ED, with a prevalence rate of 8.8% in mechanically ventilated patients with severe sepsis and septic shock (a high-risk cohort for the syndrome) (12). Larger observational studies of early ARDS have estimated an ED ARDS prevalence between 7 and 8.7% (21, 28).

Progression to ARDS represents a seminal event for the critically ill patient, that not only worsens pulmonary function (Figure 1), but also increases morbidity and mortality (14). At the intersection between patient risk and treatment variables, ARDS can be insidious and cryptic in onset, and often goes unrecognized by treating clinicians; this under-recognition of ARDS may contribute to the suboptimal translation of outcome-improving evidence to the bedside (Figure 2) (29-32). Risk factors for progression to ARDS have been described for decades, yet predicting ARDS at an individual patient level can be difficult. ARDS, despite a consensus definition of the

syndrome, is likely not a “yes/no” diagnosis, but rather a spectrum of inflammatory pulmonary failure. Patients progressing to ARDS have higher levels of inflammatory markers, both in bronchoalveolar lavage and serum (33). Imaging studies have shown high levels of neutrophilic inflammation in patients at risk for ARDS, but in whom the definitional criteria have not been met (NCT01486342). These data suggest that patients at high risk for ARDS have “pre-injured” lungs, and the progression to ARDS is a potentially modifiable continuum (Figure 3). A prospective, multicenter observational cohort study assessing patient conditions and risk modifiers, created a lung injury prediction score (LIPS), identifying patients at high risk (34). ED-based studies suggest an ARDS progression rate after admission of 27.5% in patients with severe sepsis and septic shock (12). Cohort studies from the ICU and one randomized controlled trial have cited an ARDS progression rate of 6.2% to 44% with a median onset of approximately 2 days (14, 33, 35). The prevalence of ARDS after ED admission, as well as the early onset, further suggests that therapeutic interventions in critically ill patients should not be constrained by the geographic location of the patient in a hospital. The time spent and treatment provided in the ED, and early ICU, could potentially alter the course of ARDS.

Therapy to alter the trajectory of ARDS

Mechanical ventilation strategies

Tidal volume

Normal mammalian tidal volume, indexed to size, is less than 7mL/kg, and was the tidal volume target used in a landmark ARDS clinical trial (25, 36). The success of that trial comparing relatively normal tidal volume to a “conventional” tidal volume showed that essentially normal tidal volume improved outcome. Despite the short- and long-term outcome benefit of low tidal volume ventilation in ARDS, adherence to this strategy in ICU patients remains poor (32). In patients without ARDS, there is no consensus on the most appropriate tidal

volume to use, and this represents an area of debate (37-40). In patients at very low risk for ARDS, especially with an exposure time to mechanical ventilation that is limited (e.g. healthy elective surgical patients), the chosen tidal volume strategy may not be *clinically* important (41). However, an increase in serum and bronchoalveolar lavage biomarkers suggests that deleterious mechanical ventilation can induce lung damage even with very time-limited ventilation (42-46). Recent data also showed that lung-protective ventilation in the OR was associated with a decrease in the composite outcome of major pulmonary complications and a trend in reduction of ARDS in elective abdominal surgical patients (47).

In contrast to most OR patients, mechanically ventilated ED patients will be admitted to the ICU and have a much longer exposure to mechanical ventilation (12). In these pre-injured lungs, conventional tidal volume may serve as another “hit”, promoting the development of ARDS after ICU admission (33). Many mechanically ventilated ED patients are exposed to high tidal volume and lung-protective ventilation is uncommon in these patients (12, 21).

Clinical data suggests a causal link to tidal volume and ARDS progression in critically ill patients (15, 16, 18, 33, 48-50). In the only randomized ICU trial on this topic to date, ventilation with 6mL/kg predicted body weight (PBW) vs. 10mL/kg PBW showed a 10.9% absolute risk reduction for ARDS progression, although the trial was stopped early for safety (33, 51). A recent systematic review and meta-analysis showed a decrease in ARDS development with the use of lower tidal volume (52). Another systematic review which included only studies examining tidal volume in isolation, also showed that the majority of data suggests that higher tidal volume is associated with ARDS progression (14). These findings are physiologically consistent with randomized controlled trials (RCT) demonstrating that ventilation with lower tidal volume reduces mortality in existing ARDS (25, 53, 54). These reviews also showed that the use of low tidal volume in the OR and ICU is not harmful in patients without ARDS (14, 52). A similar safety profile should be seen in the ED, given that respiratory rate is adjusted to meet

metabolic and ventilatory demands, and positive end-expiratory pressure is used to prevent atelectasis (55).

Given the risk of progression to ARDS after emergency admission, the early progression to ARDS after admission from the ED, and a lack of ED mechanical ventilation trials, low tidal volume ventilation initiated in the ED should be studied further.

Positive end-expiratory pressure (PEEP)

Repetitive opening and closing of alveolar units at low lung volumes can contribute to injury (i.e. atelectrauma). In patients with hypoxia due to atelectasis, alveolar edema and/or volume loss, PEEP serves to restore functional residual capacity (FRC) and prevent end-expiratory volume loss (derecruitment) (56). Animal and ex-vivo lung model data has shown that PEEP can protect the lung when compared to no, or very little, PEEP (57, 58). Beyond that, the optimal level to set PEEP is less clear. In patients with established ARDS already receiving low tidal volume ventilation, higher PEEP levels were not associated with improved clinical outcomes, though a systematic review and meta-analysis suggested that patients with more severe ARDS may benefit from higher PEEP(59-62).

The majority of patients in the ED in our center are treated with a PEEP of 5 cm H₂O (12). In OR patients, higher PEEP levels are associated with a decrease in inflammatory mediators, suggesting that a potential biological signal for protection exists (44, 63). Higher levels of PEEP will improve oxygenation and lung compliance, but the use of higher PEEP in all patients to prevent lung injury cannot be recommended at this time, as it is possible that higher PEEP may overdistend ventral lung units and promote lung injury (60-62, 64). However, obesity is a known risk factor for ARDS development, as these patients have elevated pleural pressure and are therefore prone to end-expiratory alveolar collapse (12, 65). These patients may be better

suites to higher PEEP levels for ARDS prevention, as well as frequent re-positioning, and the use of prophylactic prone or semi-prone position (55, 66).

Airway pressure release ventilation (APRV)

The manner in which the lung is strained influences the development of lung injury. Repetitive, breath-by-breath tidal ventilation appears to be more damaging than static strain and deformation (67-69). Whereas conventional modes of mechanical ventilation elevate airway pressure up from a set baseline to accomplish tidal ventilation, APRV employs sustained pressure over time to maintain recruitment and mean airway pressure. In an animal model, the early application of APRV before clinical lung injury, resulted in less pulmonary inflammation and edema, with preserved gross and histological lung architecture (70, 71). The clinical application of this mode of ventilation in a single center has been associated with low incidence of ARDS in a trauma population as well but no controlled human studies have uniformly supported this practice (72). There is a theoretical concern for uncontrolled, large tidal volumes with APRV, as manifested by large volumes during the release phase. How these large volumes potentially contribute to lung injury, given the more static nature of APRV, is not fully known.

Non-invasive ventilation

The use of non-invasive ventilation is common in ED patients with dyspnea, and has been shown to reduce mortality in patients with reversible causes of respiratory failure, such as cardiogenic pulmonary edema and chronic obstructive pulmonary disease (73, 74). Data supporting its use in prevention of ARDS is less robust. Several small studies have shown a decrease in intubation rates with early application of non-invasive ventilation in immunocompromised patients (75, 76). However, given the limited data, and with a failure rate of close to 50% in lung injury patients, the use of non-invasive ventilation should be assessed on

an individual patient-level basis, with frequent reassessment of pulmonary mechanics in effort to avoid delay of appropriate and timely endotracheal intubation (77). Delayed intubation, in favor of a trial of non-invasive ventilation, has been associated with an increase incidence in adverse events, such as cardiac arrest, nosocomial pneumonia, and stress ulcers (78).

Non-ventilatory strategies

Fluid management

The Berlin definition of ARDS removed the requirement for a pulmonary artery occlusion pressure ≤ 18 mmHg to distinguish between ARDS and volume overload (79). This change was more of a reflection of the limitations of that hemodynamic parameter and the declining use of pulmonary artery catheters, rather than demoting the importance of fluid in ARDS pathophysiology. Elevated left atrial pressure and ARDS frequently coexist, suggesting that any increase in edema-promoting forces can increase edema and worsen pulmonary function (80). Edema in injured lungs is both oncotic (e.g. capillary leak) and hydrostatic in nature. This suggests (based on Starling forces) that actively lowering hydrostatic pressures (or at minimum preventing unnecessary volume administration) should be beneficial. The association between volume excess and clinical outcomes across multiple patients cohorts (e.g. sepsis, mechanical ventilation, elective surgery, and acute kidney injury) is being increasingly recognized (81-88).

With respect to ARDS, many clinical scenarios that predispose to the syndrome can be associated with extensive fluid requirements during resuscitation (e.g. septic shock and trauma). While it seems paradoxical that aggressive fluid resuscitation could decrease ARDS, this highlights the importance of *timing* in fluid administration. In patients with severe sepsis and septic shock, early “aggressive” fluid administration was associated with a decrease in the need for mechanical ventilation, as well as decreased inflammatory biomarkers, suggesting that early reversal of global tissue hypoxia promotes pulmonary integrity at an endothelial and epithelial

level (11, 89). In a cohort study of patients with lung injury and sepsis, achievement of early adequate fluid resuscitation and late conservative fluid management was associated with the greatest survival benefit (90). In a randomized trial of patients with pulmonary edema, a lower fluid balance was associated with fewer ventilator and ICU days (91). With the use of a conservative fluid strategy and diuresis, the Fluids and Catheter Treatment Trial (FACTT) increased ventilator-free days with no deleterious effect on organ perfusion in hemodynamically stable ARDS patients (92).

Observational data from both the ICU and OR suggest that fluid management is associated with progression to ARDS as well (18, 93-96). Fluid administration improves perfusion only if it increases stroke volume, and only about 50% of ICU patients are preload-responsive (97). Once early tissue hypoperfusion is corrected, a conservative fluid strategy and diuresis should be favored. At a minimum, further fluid administration should be discouraged. The general consensus for most critically ill ED patients at risk for ARDS, is that early liberal fluid administration to reverse tissue hypoperfusion should be employed when preload-responsiveness has been established. An unanswered question includes the true incidence of preload-responsiveness in critically ill ED patients at risk for ARDS.

Blood product transfusion

The use of blood products is associated with progression to ARDS in at-risk patients. As an inflammatory syndrome characterized by alveolar epithelial and vascular endothelial injury, ARDS is notable for early neutrophil sequestration in the lung (98). Transfusion of blood product is associated with transmission of leukocyte antibodies and biologically active mediators (e.g. lipids and cytokines), thought to play a role in the pathogenesis of transfusion-transfusion-associated acute lung injury (TRALI). The diagnosis of classic TRALI requires a clear temporal relationship to transfusion, with signs and symptoms occurring within 6 hours. Observational

data suggests a classic TRALI incidence of close to 10% in critically ill patients (99, 100). However, in critically ill patients, multiple studies have shown the transfusion of any amount of blood product to be associated with the progression to ARDS in at risk patients (15, 17-19, 49, 101-105). Expanding the definition of TRALI beyond six hours (i.e. delayed TRALI syndrome), shows that lung injury may occur in up to 25% of critically ill patients within 72 hours of receiving a blood transfusion (106). Recipient and transfusion risk factors, such as female donors, suggest that this incidence is modifiable, and potential targets exist for reducing TRALI (107).

There has been a general decrease in transfusion in the ICU, but transfusion patterns and influence of ED transfusion on ARDS has remained largely unexplored. Extrapolation of data from ICU patients without ARDS at the time of admission, suggests early transfusion plays a role in ARDS development (15, 17-19, 49). However, in many of these observational studies, ARDS progression was also associated with other factors (e.g. higher tidal volumes, fluid balance, etc.), highlighting the complex pathophysiologic interactions in ARDS development (14). Similar to fluid administration, transfusion may also depend on timing of administration. Early administration of PRBCs as part of a quantitative resuscitation strategy for severe sepsis was associated with a decrease in mechanical ventilation, or a trend in that direction, in the majority of published data (11, 108). However, these trials were not designed to isolate the effect of transfusion. PRBC administration in this clinical scenario is aimed at improving low central venous oxygen saturation ($S_{cv}O_2$). Observational data suggests that transfusion does not improve $S_{cv}O_2$ or organ function (109). In our opinion, given the fact that the weight of evidence does not show a benefit with PRBC transfusion, the decision to transfuse should be individualized at the patient level, as opposed to *a priori* hematocrit triggers. Transfusion should be reserved only for anemic patients with persistent evidence of tissue hypoperfusion, after a careful assessment of risk:benefit. Ongoing multicenter trials [e.g. Protocolized Care for Early Septic Shock

(ProCESS) NCT00510835] will hopefully better define the risk:benefit of potential harm associated with early transfusion versus persistent global tissue hypoxia (which transfusion *may* improve).

Pharmacotherapy

No pharmacological agent designed to alter the primary pathophysiology of ARDS (i.e. beyond supportive care) has improved clinical outcome. Several agents have been tested for prevention of ARDS progression. In a propensity-matched observational study, systemic corticosteroids did not reduce the incidence of ARDS (110). A single center study showed that prehospital antiplatelet therapy was associated with a reduced incidence of ARDS (111). Using propensity score matching, a multi-center study failed to show statistical significance with prehospital aspirin therapy, however the multivariable effect size remained fairly consistent and statistical significance was almost achieved ($p = 0.07$) (112). Similarly, propensity score matching analysis failed to show a decrease in ARDS with statin therapy, in contrast to prior published data (113, 114). Therapy with azithromycin was shown to decrease mortality and a 13.1% absolute risk reduction in incidence of ARDS ($p = 0.064$) in patients with Pneumococcal pneumonia (115). In patients with lung injury, the receipt of a macrolide has been shown to decrease mortality and mechanical ventilation days, in contrast to patients receiving a fluoroquinolone or cephalosporin (116). Given the pleiotropic effects of macrolides, prospective trials addressing the impact of these agents on ARDS prevention and treatment are warranted (117). Multiple clinical trials targeting various pathways, such as alveolar coagulation, inflammation, and alveolar fluid balance are currently in progress (<http://clinicaltrials.gov/ct2/results?term=ARDS+and+prevention&pg=1>).

High minute ventilation and respiratory drive is common in early lung injury, as alveolar edema and respiratory system compliance worsen. With the induction of paralysis and control of

the respiratory pattern, neuromuscular blockers (NMB) can mitigate lung injury (theoretically) by removing dyssynchrony and the associated over-distention and end-expiratory collapse associated with vigorous spontaneous respirations. Furthermore, a decrease in oxygen demand and subsequent cardiac output through an injured lung, should reduce venous admixture and pulmonary edema (118). A small RCT also showed that a short duration of NMB reduced pulmonary and systemic inflammation (119). A multicenter database study of mechanically ventilated severe sepsis patients found that the receipt of neuromuscular blockers was associated with a reduction in in-hospital mortality (120). In a multicenter RCT of patients with early (within 48 hours), severe ($P_aO_2:F_iO_2 < 150$) ARDS, a 48 hour infusion of cisatracurium was associated with decreased hospital mortality censored at 90 days (121). However, this benefit was restricted to the subgroup of patients with a $P_aO_2:F_iO_2 < 120$. These findings make recommending early NMB for patients *at risk* for ARDS difficult, and perhaps restricted only to a very small cohort, such as $LIPS \geq 8$ ($\approx 35\%$ chance of developing ARDS) with high ventilatory demands (34, 118).

Early treatment of infection

A delay in appropriate antimicrobial therapy increases the risk of death in patients with bacterial septic shock and increases progression rate to ARDS (17, 122). Globally, influenza is one of the most important causes of respiratory failure and ARDS, especially during seasonal outbreaks and pandemics (123). The majority of hospitalized patients with seasonal influenza present from the ED (124). Trials conducted primarily in healthy individuals in the outpatient setting have demonstrated that neuraminidase inhibitors can reduce illness duration for influenza patients treated within 48 hours of illness onset (125). Data is limited with respect to patients with more severe influenza. In patients hospitalized with influenza, oseltamivir has been shown to reduce mortality and decrease lengths of stay (126-130). A minority of patients receive this

therapy however (124). In patients with pandemic influenza A (H1N1), the most common cause of death is pneumonia and ARDS (131). Observational data suggest that treatment with neuraminidase inhibitors reduces pneumonia, illness severity, and mortality (132-134). While antiviral therapy for prevention of ARDS has not been specifically studied, early treatment with antivirals has also been associated with a decrease in mechanical ventilation days in critically ill patients (135). It is recommended that early neuraminidase therapy be initiated as early as possible to reduce complications from influenza for any patient with confirmed or suspected influenza who is hospitalized, is critically ill, or is at higher risk for complications (125).

Extracorporeal support

The use of extracorporeal membrane oxygenation (ECMO) and pumpless extracorporeal lung assist (pECLA) in respiratory failure is increasing in frequency. By allowing further limitation of tidal volume, end-inspiratory stretch, and regional overdistention, these strategies provide significant lung rest, potential for total strain prevention, and limitation of lung injury propagation. The current evidence to support ECMO in ARDS can be summarized as follows: Registry data points to a greater ECMO benefit when instituted early; prospective observational trials during the H1N1 influenza outbreak suggest that early ECMO referral to high volume centers is feasible and associated with high survival rates; a multicenter RCT showed that referral to an ECMO-capable center was associated with a 16% absolute risk reduction for death or severe disability at six months (136-141). Whether the benefit lies in the ECMO itself or the referral to highly specialized centers is unclear.

The application of extracorporeal technology to *prevent* lung injury may seem unlikely when considering that benefit in ARDS seems to be restricted to the sickest cohort of patients. However, support for prevention could be extrapolated from the benefit when applied in early ARDS, as well as technological advances which have increased ease of use and safety profile.

New pumpless devices can effectively support gas exchange and facilitate very low tidal volume ventilation (142-144). This has allowed full support without the aid of an endotracheal tube in case reports (145, 146).

Looking forward, with evidence suggesting that normal lungs can be damaged by even low stretch ventilation, the early application of pECLA, in experienced, high-volume centers, could allow lung rest without the aid of a mechanical ventilator in a select cohort of patients at risk for ARDS (147). This expansion of extracorporeal support beyond life-threatening hypoxemia to *life-threatening ventilator-associated lung injury* remains to be tested (148).

Extending ICU-level supportive care to the ED and prehospital environment

Until better genotyping and phenotyping of the individual patients comprising critical care syndromes (e.g. sepsis and ARDS) occurs, it seems unlikely that narrow mechanistic intervention trials will work (149, 150). Attempts at de-individualizing care, at the clinician level, have improved survival in sepsis (151). Similarly, the Checklist for Lung Injury Prevention (CLIP) attempts to standardize care for patients at risk for ARDS by incorporating evidence-based practices shown to benefit critically ill patients in general (152). While elucidating the contribution of individual elements (e.g. head of bed elevation and oral care with chlorhexidine) will likely be topics of academic debate, the efficacy to side effect profile, as well as common sense, dictate that standard ICU-level of care should be extended to the ED and prehospital environment when feasible.

Conclusion

The prevalence and clinical trajectory of ARDS is modifiable. The physiology of lung injury, as well as previous trial failures, dictate that research and intervention should be extended to earlier times of patient presentation. While the ED has proven to be a highly relevant location

for the treatment of time-sensitive emergencies (e.g. stroke, sepsis), this has yet to extend to mechanical ventilation and ARDS. Several knowledge gaps exist with respect to the long term effects of ED interventions on ARDS progression and should be investigated further. The optimal intervention for ARDS prevention will likely be some combination of ventilatory and non-ventilatory strategies, along with a multidisciplinary collaboration between emergency physicians, intensivists, nurses, and respiratory therapists.

Acknowledgement

We would like to acknowledge the work of the many researchers who have made contributions to the field of mechanical ventilation, ARDS, and lung injury prevention. Without these prior works, this review, and our ongoing research would not be possible.

REFERENCES

1. Safar, P: Critical care medicine: quo vadis. *Crit Care Med* 2(1):1-5, 1974.
2. McCaig, LF and Burt, CW: *National hospital ambulatory medical care survey: 1999 emergency department summary*. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, 2001.
3. Herring, A, Ginde A, Fahimi J, Alter H, Maselli J, Espinola J, Sullivan A, Camargo J, Carlos A.: Increasing critical care admissions from US emergency departments, 2001–2009*. *Critical care medicine* 41(5):1197-1204, 2013.
4. Trzeciak, S and Rivers, E: Emergency department overcrowding in the United States: an emerging threat to patient safety and public health. *Emergency medicine journal* 20(5):402-405, 2003.
5. Fromm Jr, RE, Gibbs, LR, McCallum, WG, Niziol, C, Babcock, JC, Gueler, AC and Levine, RL: Critical care in the emergency department: a time-based study. *Critical care medicine* 21(7):970-976, 1993.
6. Lambe, S, Washington, DL, Fink, A, Herbst, K, Liu, H, Fosse, JS and Asch, SM: Trends in the use and capacity of California's emergency departments, 1990-1999. *Annals of emergency medicine* 39(4):389-396, 2002.
7. McConnell, KJ, Richards, CF, Daya, M, Bernell, SL, Weathers, CC and Lowe, RA: Effect of increased ICU capacity on emergency department length of stay and ambulance diversion. *Annals of emergency medicine* 45(5):471, 2005.
8. Nelson, M, Waldrop, RD, Jones, J and Randall, Z: Critical care provided in an urban emergency department. *The American journal of emergency medicine* 16(1):56-59, 1998.
9. Varon, J, Fromm, RE and Levine, RL: Emergency department procedures and length of stay for critically ill medical patients. *Annals of emergency medicine* 23(3):546-549, 1994.

10. Nguyen, HB, Rivers, EP, Havstad, S, Knoblich, B, Ressler, JA, Muzzin, AM and Tomlanovich, MC: Critical care in the emergency department a physiologic assessment and outcome evaluation. *Academic Emergency Medicine* 7(12):1354-1361, 2000.
11. Rivers, E, Nguyen, B, Havstad, S, Ressler, J, Muzzin, A, Knoblich, B, Peterson, E and Tomlanovich, M: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine* 345(19):1368-1377, 2001.
12. Fuller, B, Mohr NM, Dettmer M, Cullison K, Kennedy S, Bavolek R, Rathert N, McCammon, C.: Mechanical ventilation and acute lung injury in emergency department patients with severe sepsis and septic shock: an observational study *Acad Emerg Med* 20(7):659-669, 2013.
13. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 333(1):581-1587, 1995.
14. Fuller, BM, Mohr, NM, Drewry, AM and Carpenter, CR: Lower tidal volume at initiation of mechanical ventilation may reduce progression to acute respiratory distress syndrome- a systematic review. *Critical Care* 17(1):R11, 2013.
15. Gajic, O, Dara, SI, Mendez, JL, Adesanya, AO, Festic, E, Caples, SM, Rana, R, StSauer, JL, Lymp, JF and Afessa, B: Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 32(9):1817-1824, 2004.
16. Gajic, O, Frutos-Vivar, F, Esteban, A, Hubmayr, RD and Anzueto, A: Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. *Intensive care medicine* 31(7):922-926, 2005.

17. Iscimen, R, Yilmaz, M, Cartin-Ceba, R, Hubmayr, R, Afessa, B, Gajic, O and Farmer, J: Risk factors for the development of acute lung injury in patients with septic shock: an observational cohort study. *Critical Care* 12(Suppl 2):P487, 2008.
18. Jia, X, Malhotra, A, Saeed, M, Mark, RG and Talmor, D: Risk Factors for ARDS in Patients Receiving Mechanical Ventilation for > 48 h*. *Chest* 133(4):853-861, 2008.
19. Kahn, JM, Caldwell, EC, Deem, S, Newell, DW, Heckbert, SR and Rubenfeld, GD: Acute lung injury in patients with subarachnoid hemorrhage: incidence, risk factors, and outcome. *Critical care medicine* 34(1):196, 2006.
20. Sagarin, MJ, Barton, ED, Chng, YM and Walls, RM: Airway management by US and Canadian emergency medicine residents: a multicenter analysis of more than 6,000 endotracheal intubation attempts. *Annals of emergency medicine* 46(4):328-336, 2005.
21. Hou, P, Elie-Turenne, MC, Mitani, A, Barry, JM, Kao, EY, Cohen, JE, Frenzl, G, Gajic, O, Gentile, NT.: Towards prevention of acute lung injury: frequency and outcomes of emergency department patients at-risk - a multicenter cohort study. *International Journal of Emergency Medicine* 5(1):[Epub ahead of print], 2012.
22. Fuller, B, Mohr N, Skrupky L, Mueller K, McCammon C.: Emergency department vancomycin use: dosing practices and associated outcomes. *J Emerg Med.* 44(5):910-8. , 2013.
23. Rubenfeld, GD, Caldwell, E, Peabody, E, Weaver, J, Martin, DP, Neff, M, Stern, EJ and Hudson, LD: Incidence and outcomes of acute lung injury. *New England Journal of Medicine* 353(16):1685-1693, 2005.
24. Rubenfeld, GD and Herridge, MS: Epidemiology and Outcomes of Acute Lung Injury*. *Chest* 131(2):554-562, 2007.

25. The Acute Respiratory Distress Syndrome Network: Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. *New England Journal of Medicine* 342:1301-1308, 2000.
26. Sud, S, Friedrich, JO, Taccone, P, Polli, F, Adhikari, NK, Latini, R, Pesenti, A, Guérin, C, Mancebo, J and Curley, MA: Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. *Intensive care medicine* 36(4):585-599, 2010.
27. Guérin C, RJ, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M, Hilbert G, Bengler C, Richecoeur J, Gannier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L.: Prone positioning in severe acute respiratory distress syndrome. *New England Journal of Medicine* 368:2159-68., 2013.
28. Goyal M, HD, Johnson NJ, Christie J, Mikkelsen ME, Gaieski DF.: Prevalence of acute lung injury among medical patients in the emergency department. *Acad Emerg Med* 19:1011-1018., 2012.
29. Ferguson, ND, Frutos-Vivar, F, Esteban, A, Fernández-Segoviano, P, Aramburu, JA, Nájera, L and Stewart, TE: Acute respiratory distress syndrome: Underrecognition by clinicians and diagnostic accuracy of three clinical definitions*. *Critical care medicine* 33(10):2228-2234, 2005.
30. Herasevich, V, Yilmaz, M, Khan, H, Hubmayr, RD and Gajic, O: Validation of an electronic surveillance system for acute lung injury. *Intensive care medicine* 35(6):1018-1023, 2009.
31. Fröhlich, S, Murphy, N, Doolan, A, Ryan, O and Boylan, J: Acute respiratory distress syndrome: Underrecognition by clinicians. *Journal of critical care* 28(5):663-668, 2013.

32. Needham, DM, Colantuoni, E, Mendez-Tellez, PA, Dinglas, VD, Sevransky, JE, Himmelfarb, CRD, Desai, SV, Shanholtz, C, Brower, RG and Pronovost, PJ: Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. *BMJ: British Medical Journal* 344, 2012.
33. Determann, RM, Royakkers, A, Wolthuis, EK, Vlaar, AP, Choi, G, Paulus, F, Hofstra, JJ, de Graaff, MJ, Korevaar, JC and Schultz, MJ: Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. *Critical care* 14(1):R1, 2010.
34. Gajic, O, Dabbagh, O, Park, PK, Adesanya, A, Chang, SY, Hou, P, Anderson III, H, Hoth, JJ, Mikkelsen, ME and Gentile, NT: Early Identification of Patients at Risk of Acute Lung Injury. *American journal of respiratory and critical care medicine* 183(4):462-470, 2011.
35. Mikkelsen ME, SC, Meyer NJ, Gaieski DF, Lyon S, Miltiades AN, Goyal M, Fuchs BD, Bellamy SL, Christie JD: The epidemiology of acute respiratory distress syndrome in patients presenting to the emergency department with severe sepsis. *Shock* 40(5):375-381, 2013.
36. Tenney, S, Remmers J: Comparative quantitative morphology of the mammalian lung: diffusing area. *Nature* 197:54-56., 1963.
37. Gattinoni, L: Counterpoint: Is low tidal volume mechanical ventilation preferred for all patients on ventilation? No. *Chest* 140:11-13, 2011.
38. Hubmayr, R: Point:Is Low Tidal Volume Mechanical Ventilation Preferred for All Patients on Ventilation? Yes. *CHEST* 140:9-11, 2011.
39. Mohr, N, Fuller, BM.: Low Tidal Volume Ventilation Should Be The Routine Ventilation Strategy Of Choice For All Emergency Department Patients. *Annals of emergency medicine* 60(2):215-216, 2012.

40. Wright, B, Slesinger, TL.: Low Tidal Volume Should Not Routinely be Used for Emergency Department Patients Requiring Mechanical Ventilation. *Annals of emergency medicine* 60(2):216-217., 2012.
41. Blum J, SM, Park P.: Predictors of postoperative acute lung injury in a low-incidence surgical population. *Anesthesiology*:A790, 2011.
42. Miranda, DR, Struijs, A, Koetsier, P, van Thiel, R, Schepp, R, Hop, W, Klein, J, Lachmann, B, Bogers, AJJC and Gommers, D: Open lung ventilation improves functional residual capacity after extubation in cardiac surgery*. *Critical care medicine* 33(10):2253, 2005.
43. Schilling, T, Kozian, A, Huth, C, Bühling, F, Kretzschmar, M, Welte, T and Hachenberg, T: The pulmonary immune effects of mechanical ventilation in patients undergoing thoracic surgery. *Anesthesia & Analgesia* 101(4):957, 2005.
44. Zupancich, E, Paparella, D, Turani, F, Munch, C, Rossi, A, Massaccesi, S and Ranieri, VM: Mechanical ventilation affects inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: a randomized clinical trial. *The Journal of thoracic and cardiovascular surgery* 130(2):378-383, 2005.
45. Choi, G, Wolthuis, EK, Bresser, P, Levi, M, Van Der Poll, T, Dzoljic, M, Vroom, MB and Schultz, MJ: Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents alveolar coagulation in patients without lung injury. *Anesthesiology* 105(4):689, 2006.
46. Michelet, P, D'Journo, XB, Roch, A, Doddoli, C, Marin, V, Papazian, L, Decamps, I, Bregeon, F, Thomas, P and Auffray, JP: Protective ventilation influences systemic inflammation after esophagectomy: a randomized controlled study. *Anesthesiology* 105(5):911, 2006.

47. Futier, E, Constantin, J-M, Paugam-Burtz, C, Pascal, J, Eurin, M, Neuschwander, A, Marret, E, Beaussier, M, Gutton, C and Lefrant, J-Y: A Trial of Intraoperative Low-Tidal-Volume Ventilation in Abdominal Surgery. *New England Journal of Medicine* 369(5):428-437, 2013.
48. Mascia, L, Zavala, E, Bosma, K, Pasero, D, Decaroli, D, Andrews, P, Isnardi, D, Davi, A, Arguis, MJ and Berardino, M: High tidal volume is associated with the development of acute lung injury after severe brain injury: An international observational study*. *Critical care medicine* 35(8):1815, 2007.
49. Yilmaz, M, Keegan, MT, Iscimen, R, Afessa, B, Buck, CF, Hubmayr, RD and Gajic, O: Toward the prevention of acute lung injury: Protocol-guided limitation of large tidal volume ventilation and inappropriate transfusion*. *Critical care medicine* 35(7):1660, 2007.
50. Pasero, D, Davi A, Guerriero F, Rana N, Merigo G, Mastromauro I, Viberti S, Mascia L, Rinaldi M, Ranieri M: High tidal volume as an independent risk factor for acute lung injury after cardiac surgery. *Intensive care medicine* 34(Supplement 1):0398, 2008.
51. Montori, VM, Devereaux, P, Adhikari, NK, Burns, KE, Eggert, CH, Briel, M, Lacchetti, C, Leung, TW, Darling, E and Bryant, DM: Randomized trials stopped early for benefit: a systematic review. *JAMA: the journal of the American Medical Association* 294(17):2203, 2005.
52. Neto, AS, Cardoso, SO, Manetta, JA, Pereira, VGM, Espósito, DC, Pasqualucci, MdOP, Damasceno, MCT and Schultz, MJ: Association Between Use of Lung-Protective Ventilation With Lower Tidal Volumes and Clinical Outcomes Among Patients Without Acute Respiratory Distress SyndromeA Meta-analysisProtective Ventilation and Lower Tidal Volumes. *JAMA: the journal of the American Medical Association* 308(16):1651-1659, 2012.

53. Amato, MBP, Barbas, CSV, Medeiros, DM, Magaldi, RB, Schettino, GP, Lorenzi-Filho, G, Kairalla, RA, Deheinzelin, D, Munoz, C and Oliveira, R: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *New England Journal of Medicine* 338(6):347-354, 1998.
54. Villar, J, Kacmarek, RM, Pérez-Méndez, L and Aguirre-Jaime, A: A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: A randomized, controlled trial*. *Critical care medicine* 34(5):1311-1318, 2006.
55. Kilickaya, O, Gajic, O.: Initial ventilator settings for critically ill patients. *Critical Care* 17(123), 2013.
56. Cressoni, M, Caironi, P, Polli, F, Carlesso, E, Chiumello, D, Cadringer, P, Quintel, M, Ranieri, VM, Bugedo, G and Gattinoni, L: Anatomical and functional intrapulmonary shunt in acute respiratory distress syndrome*. *Critical care medicine* 36(3):669-675, 2008.
57. Webb, H: Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. *Am Rev Respir Dis* 110(5):556-565, 1974.
58. Muscedere, J, Mullen, J, Gan, K and Slutsky, A: Tidal ventilation at low airway pressures can augment lung injury. *American journal of respiratory and critical care medicine* 149(5):1327-1334, 1994.
59. Briel, M, Meade, M, Mercat, A, Brower, RG, Talmor, D, Walter, SD, Slutsky, AS, Pullenayegum, E, Zhou, Q and Cook, D: Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome. *JAMA: the journal of the American Medical Association* 303(9):865-873, 2010.

60. Brower, R, Lanken, P, MacIntyre, N, Matthay, M, Morris, A, Ancukiewicz, M, Schoenfeld, D and Thompson, B: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *The New England journal of medicine* 351(4):327, 2004.
61. Meade, MO, Cook, DJ, Guyatt, GH, Slutsky, AS, Arabi, YM, Cooper, DJ, Davies, AR, Hand, LE, Zhou, Q and Thabane, L: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome. *JAMA: the journal of the American Medical Association* 299(6):637-645, 2008.
62. Mercat, A, Richard, J-CM, Vielle, B, Jaber, S, Osman, D, Diehl, J-L, Lefrant, J-Y, Prat, G, Richecoeur, J and Nieszkowska, A: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome. *JAMA: the journal of the American Medical Association* 299(6):646-655, 2008.
63. Miranda, DR, Gommers, D, Struijs, A, Dekker, R, Mekel, J, Feelders, R, Lachmann, B and Bogers, AJ: Ventilation according to the open lung concept attenuates pulmonary inflammatory response in cardiac surgery. *European journal of cardio-thoracic surgery* 28(6):889-895, 2005.
64. Talmor, D, Sarge, T, Malhotra, A, O'Donnell, CR, Ritz, R, Lisbon, A, Novack, V and Loring, SH: Mechanical ventilation guided by esophageal pressure in acute lung injury. *New England Journal of Medicine* 359(20):2095, 2008.
65. Gong, MN, Bajwa, EK, Thompson, BT and Christiani, DC: Body mass index is associated with the development of acute respiratory distress syndrome. *Thorax* 65(1):44-50, 2010.

66. Albert, RK: The role of ventilation-induced surfactant dysfunction and atelectasis in causing acute respiratory distress syndrome. *American journal of respiratory and critical care medicine* 185(7):702-708, 2012.
67. Tschumperlin, D, Oswari J, Margulies SS: Deformation-induced injury of alveolar epithelial cells: effect of frequency, duration, and amplitude. *American journal of respiratory and critical care medicine* 162(2):357-362, 2000.
68. Protti A, AD, Monti M, Santini A, Sparacino CC, Langer T, Votta E, Gatti S, Lombardi L, Leopardi O, Masson S, Cressoni M, Gattinoni L.: Lung stress and strain during mechanical ventilation: any difference between statics and dynamics? *Crit Care Med* 41:1046-1055., 2013.
69. Conrad, SA, Zhang, S, Arnold, TC, Scott, LK and Carden, DL: Protective effects of low respiratory frequency in experimental ventilator-associated lung injury*. *Critical care medicine* 33(4):835-840, 2005.
70. Roy S, HN, Sadowitz B, Andrews P, Ge L, Wang G, Roy P, Ghosh A, Kuhn M, Satalin J, Gatto LA, Lin X, Dean DA, Vodovotz Y, Nieman G.: Early airway pressure release ventilation prevents ARDS- a novel preventive approach to lung injury. *Shock* 39(1):28-38, 2013.
71. Roy S, EB, Sadowitz B, Gatto LA, Ghosh A, Satalin JM, Snyder KP, Ge L, Wang G, Marx W, Dean D, Andrews P, Singh A, Scalea T, Habashi N, Nieman G.: Preemptive application of airway pressure release ventilation prevents development of acute respiratory distress syndrome in a rat traumatic hemorrhagic shock model. *Shock* 40(3):210-6, 2013.
72. Shiber J, OTR, Habashi N.: APRV is associated with a low rate of ARDS in high-risk trauma patients. *Crit Care Med* 37(12):A185, 2009.

73. Collins, SP, Mielniczuk, LM, Whittingham, HA, Boseley, ME, Schramm, DR and Storrow, AB: The Use of Noninvasive Ventilation in Emergency Department Patients With Acute Cardiogenic Pulmonary Edema: A Systematic. *Annals of emergency medicine* 48(3), 2006.
74. Lightowler, JV, Wedzicha, JA, Elliott, MW and Ram, FS: Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *BMJ: British Medical Journal* 326(7382):185, 2003.
75. Squadrone, V, Massaia, M, Bruno, B, Marmont, F, Falda, M, Bagna, C, Bertone, S, Filippini, C, Slutsky, AS and Vitolo, U: Early CPAP prevents evolution of acute lung injury in patients with hematologic malignancy. *Intensive care medicine* 36(10):1666-1674, 2010.
76. Hilbert, G, Gruson, D, Vargas, F, Valentino, R, Gbikpi-Benissan, G, Dupon, M, Reiffers, J and Cardinaud, JP: Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *New England Journal of Medicine* 344(7):481-487, 2001.
77. Agarwal, R, Aggarwal, AN and Gupta, D: Role of noninvasive ventilation in acute lung injury/acute respiratory distress syndrome: a proportion meta-analysis. *Respiratory care* 55(12):1653-1660, 2010.
78. Delclaux, C, L'Her, E, Alberti, C, Mancebo, J, Abroug, F, Conti, G, Guérin, C, Schortgen, F, Lefort, Y and Antonelli, M: Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask. *JAMA: the journal of the American Medical Association* 284(18):2352-2360, 2000.
79. The ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 307(23):2526-2533., 2012.

80. Ferguson, ND, Meade, MO, Hallett, DC and Stewart, TE: High values of the pulmonary artery wedge pressure in patients with acute lung injury and acute respiratory distress syndrome. *Intensive care medicine* 28(8):1073-1077, 2002.
81. Alsous, F, Khamiees, M, DeGirolamo, A, Amoateng-Adjepong, Y and Manthous, CA: Negative Fluid Balance Predicts Survival in Patients With Septic Shock A Retrospective Pilot Study. *CHEST Journal* 117(6):1749-1754, 2000.
82. Boyd, JH, Forbes, J, Nakada, T-a, Walley, KR and Russell, JA: Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality*. *Critical care medicine* 39(2):259-265, 2011.
83. Vincent, J-L, Sakr, Y, Sprung, CL, Ranieri, VM, Reinhart, K, Gerlach, H, Moreno, R, Carlet, J, Le Gall, J-R and Payen, D: Sepsis in European intensive care units: Results of the SOAP study*. *Critical care medicine* 34(2):344-353, 2006.
84. Upadya, A, Tilluckdharry, L, Muralidharan, V, Amoateng-Adjepong, Y and Manthous, CA: Fluid balance and weaning outcomes. *Intensive care medicine* 31(12):1643-1647, 2005.
85. Brandstrup, B, Tønnesen, H, Beier-Holgersen, R, Hjortsø, E, Ørding, H, Lindorff-Larsen, K, Rasmussen, MS, Lanng, C and Wallin, L: Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Annals of surgery* 238(5):641, 2003.
86. Nisanevich, V, Felsenstein, I, Almogy, G, Weissman, C, Einav, S and Matot, I: Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology* 103(1):25-32, 2005.
87. Bouchard, J and Mehta, RL: Fluid accumulation and acute kidney injury: consequence or cause. *Current opinion in critical care* 15(6):509-513, 2009.

88. Payen, D, de Pont, A, Sakr, Y, Spies, C, Reinhart, K and Vincent, J: A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Critical Care* 12(3):R74, 2008.
89. Rivers, EP, Kruse, JA, Jacobsen, G, Shah, K, Loomba, M, Otero, R and Childs, EW: The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock*. *Critical care medicine* 35(9):2016-2024, 2007.
90. Murphy, CV, Schramm, GE, Doherty, JA, Reichley, RM, Gajic, O, Afessa, B, Micek, ST and Kollef, MH: The importance of fluid management in acute lung injury secondary to septic shock. *CHEST Journal* 136(1):102-109, 2009.
91. Mitchell, JP, Schuller, D, Calandrino, FS and Schuster, DP: Improved outcome based on fluid management in critically III patients requiring pulmonary artery catheterization. *American journal of respiratory and critical care medicine* 145(5):990-998, 1992.
92. Wiedemann, H, Wheeler, A, Bernard, G, Thompson, B, Hayden, D, DeBoisblanc, B, Connors Jr, A, Hite, R and Harabin, A: National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 354(24):2564-2575, 2006.
93. Licker, M, de Perrot, M, Spiliopoulos, A, Robert, J, Diaper, J, Chevalley, C and Tschopp, JM: Risk factors for acute lung injury after thoracic surgery for lung cancer. *Anesthesia & Analgesia* 97(6):1558, 2003.
94. Licker, M, Diaper, J, Villiger, Y, Spiliopoulos, A, Licker, V, Robert, J and Tschopp, JM: Impact of intraoperative lung-protective interventions in patients undergoing lung cancer surgery. *Critical Care* 13(2):R41, 2009.

95. Hughes, CG, Weavind, L, Banerjee, A, Mercaldo, ND, Schildcrout, JS and Pandharipande, PP: Intraoperative risk factors for acute respiratory distress syndrome in critically ill patients. *Anesthesia & Analgesia* 111(2):464-467, 2010.
96. Fernández-Pérez ER, KM, Brown DR, Hubmayr RD, Gajic O: Intraoperative tidal volume as a risk factor for respiratory failure after pneumonectomy. *Anesthesiology* 105(1):14-18, 2006.
97. Michard, F and Teboul, J-L: Predicting fluid responsiveness in ICU patientsA critical analysis of the evidence. *CHEST Journal* 121(6):2000-2008, 2002.
98. Wheeler, AP and Bernard, GR: Acute lung injury and the acute respiratory distress syndrome: a clinical review. *Lancet* 369(9572):1553-1564, 2007.
99. Gajic, O, Rana, R, Winters, JL, Yilmaz, M, Mendez, JL, Rickman, OB, O'Byrne, MM, Evenson, LK, Malinchoc, M and DeGoey, SR: Transfusion-related Acute Lung Injury in the Critically Ill Prospective Nested Case-Control Study. *American journal of respiratory and critical care medicine* 176(9):886-891, 2007.
100. Vlaar, AP, Binnekade, JM, Prins, D, van Stein, D, Hofstra, JJ, Schultz, MJ and Juffermans, NP: Risk factors and outcome of transfusion-related acute lung injury in the critically ill: A nested case-control study*. *Critical care medicine* 38(3):771-778, 2010.
101. Hébert, PC, Wells, G, Blajchman, MA, Marshall, J, Martin, C, Pagliarello, G, Tweeddale, M, Schweitzer, I and Yetisir, E: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *New England Journal of Medicine* 340(6):409-417, 1999.
102. Gong, MN, Thompson, BT, Williams, P, Pothier, L, Boyce, PD and Christiani, DC: Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion*. *Critical care medicine* 33(6):1191-1198, 2005.

103. Khan, H, Belsher, J, Yilmaz, M, Afessa, B, Winters, JL, Moore, SB, Hubmayr, RD and Gajic, O: Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. *CHEST Journal* 131(5):1308-1314, 2007.
104. Zilberberg, M, Carter, C, Lefebvre, P, Raut, M, Vekeman, F, Duh, M and Shorr, A: Red blood cell transfusions and the risk of acute respiratory distress syndrome among the critically ill: a cohort study. *Critical Care* 11(3):R63, 2007.
105. Starkey, K, Keene, D, Morrison, JJ, Doughty, H, Midwinter, MJ, Woolley, T and Jansen, JO: Impact of High Ratios of Plasma-to-Red Cell Concentrate on the Incidence of Acute Respiratory Distress Syndrome in UK Transfused Combat Casualties. *Shock* 40(1):15-20, 2013.
106. Marik, PE and Corwin, HL: Acute lung injury following blood transfusion: expanding the definition. *Critical care medicine* 36(11):3080-3084, 2008.
107. Toy, P, Gajic, O, Bacchetti, P, Looney, MR, Gropper, MA, Hubmayr, R, Lowell, CA, Norris, PJ, Murphy, EL and Weiskopf, RB: Transfusion-related acute lung injury: incidence and risk factors. *Blood* 119(7):1757-1767, 2012.
108. Rivers, EP, Coba, V and Whitmill, M: Early goal-directed therapy in severe sepsis and septic shock: a contemporary review of the literature. *Current Opinion in Anesthesiology* 21(2):128-140, 2008.
109. Fuller BM, GM, Schorr C, Gerber D, Dellinger RP, Parrillo J, Zanotti S. : Transfusion of packed red blood cells is not associated with improved central venous oxygen saturation or organ function in patients with septic shock. *J Emerg Med.* 43(4):593-8., 2012.

110. Karnatovskaia, LV, Lee, AS, Gajic, O and Festic, E: The Influence of Prehospital Systemic Corticosteroid Use on Development of Acute Respiratory Distress Syndrome and Hospital Outcomes*. *Critical care medicine* 41(7):1679-1685, 2013.
111. Erlich, JM, Talmor, DS, Cartin-Ceba, R, Gajic, O and Kor, DJ: Prehospitalization Antiplatelet Therapy Is Associated With a Reduced Incidence of Acute Lung InjuryA Population-Based Cohort Study. *CHEST Journal* 139(2):289-295, 2011.
112. Kor, DJ, Erlich, J, Gong, MN, Malinchoc, M, Carter, RE, Gajic, O and Talmor, D: Association of pre-hospitalization aspirin therapy and acute lung injury: results of a multicenter international observational study of at-risk patients. *Critical care medicine* 39(11):2393, 2011.
113. Bajwa, EK, Malhotra, CK, Thompson, BT, Christiani, DC and Gong, MN: Statin therapy as prevention against development of acute respiratory distress syndrome: An observational study*. *Critical care medicine* 40(5):1470, 2012.
114. O'Neal Jr, HR, Koyama, T, Koehler, EA, Siew, E, Curtis, BR, Fremont, RD, May, AK, Bernard, GR and Ware, LB: Prehospital Statin and Aspirin Use and the Prevalence of Severe Sepsis and ALI/ARDS. *Critical care medicine* 39(6):1343, 2011.
115. Shorr, AF, Zilberberg, MD, Kan, J, Hoffman, J, Micek, ST and Kollef, MH: Azithromycin and survival in Streptococcus pneumoniae pneumonia: a retrospective study. *BMJ open* 3(6), 2013.
116. Walkey, AJ and Wiener, RS: Macrolide Antibiotics and Survival in Patients With Acute Lung InjuryMacrolides and Acute Lung Injury. *CHEST Journal* 141(5):1153-1159, 2012.
117. Noto, MJ and Wheeler, AP: Macrolides for Acute Lung Injury. *CHEST Journal* 141(5):1131-1132, 2012.

118. Marini, JJ: Early phase of lung-protective ventilation: A place for paralytics?*. *Critical care medicine* 34(11):2851-2853, 2006.
119. Forel, J-M, Roch, A, Marin, V, Michelet, P, Demory, D, Blache, J-L, Perrin, G, Gainnier, M, Bongrand, P and Papazian, L: Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome*. *Critical care medicine* 34(11):2749-2757, 2006.
120. Steingrub, JS, Lagu, T, Rothberg, MB, Nathanson, BH, Raghunathan, K and Lindenauer, PK: Treatment With Neuromuscular Blocking Agents and the Risk of In-Hospital Mortality Among Mechanically Ventilated Patients With Severe Sepsis. *Critical care medicine*, 2013.
121. Papazian, L, Forel, J, Gacouin, A, Penot-Ragon, C, Perrin, G, Loundou, A, Jaber, S, Arnal, J, Perez, D and Seghboyan, J: ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 363(12):1107-1116, 2010.
122. Kumar, A, Roberts, D, Wood, KE, Light, B, Parrillo, JE, Sharma, S, Suppes, R, Feinstein, D, Zanotti, S and Taiberg, L: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*. *Critical care medicine* 34(6):1589-1596, 2006.
123. Lambert, LC and Fauci, AS: Influenza vaccines for the future. *New England Journal of Medicine* 363(21):2036-2044, 2010.
124. McGeer, A, Green, KA, Plevneshi, A, Shigayeva, A, Siddiqi, N, Raboud, J and Low, DE: Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clinical Infectious Diseases* 45(12):1568-1575, 2007.

125. Fiore, M, Fry, A, Shay, D, Gubareva, L, Bresee, JS and Uyeki, TM: Antiviral agents for the treatment and chemoprophylaxis of influenza. *Centers for Disease Control and Prevention*, 2011.
126. Lee, N, Chan, P, Choi, KW, Lui, G, Wong, B, Cockram, CS, Hui, D, Lai, R, Tang, JW and Sung, J: Factors associated with early hospital discharge of adult influenza patients. *Antiviral therapy* 12(4):501, 2007.
127. Johnston, SL, Ferrero, F, Garcia, ML and Dutkowsky, R: Oral oseltamivir improves pulmonary function and reduces exacerbation frequency for influenza-infected children with asthma. *The Pediatric infectious disease journal* 24(3):225-232, 2005.
128. Hanshaoworakul, W, Simmerman, JM, Narueponjirakul, U, Sanasuttipun, W, Shinde, V, Kaewchana, S, Areechokechai, D, Levy, J and Ungchusak, K: Severe human influenza infections in Thailand: oseltamivir treatment and risk factors for fatal outcome. *PloS one* 4(6):e6051, 2009.
129. Lee, N, Choi, K, Chan, P, Hui, D, Lui, G, Wong, B, Wong, R, Sin, W, Hui, W and Ngai, K: Outcomes of adults hospitalised with severe influenza. *Thorax* 65(6):510-515, 2010.
130. Chemaly, RF, Torres, HA, Aguilera, EA, Mattiuzzi, G, Cabanillas, M, Kantarjian, H, Gonzalez, V, Safdar, A and Raad, II: Neuraminidase inhibitors improve outcome of patients with leukemia and influenza: an observational study. *Clinical Infectious Diseases* 44(7):964-967, 2007.
131. Louie, JK, Acosta, M, Winter, K, Jean, C, Gavali, S, Schechter, R, Vugia, D, Harriman, K, Matyas, B and Glaser, CA: Factors associated with death or hospitalization due to pandemic 2009 influenza A (H1N1) infection in California. *JAMA: the journal of the American Medical Association* 302(17):1896-1902, 2009.

132. Yu, H, Liao, Q, Yuan, Y, Zhou, L, Xiang, N, Huai, Y, Guo, X, Zheng, Y, van Doorn, HR and Farrar, J: Effectiveness of oseltamivir on disease progression and viral RNA shedding in patients with mild pandemic 2009 influenza A H1N1: opportunistic retrospective study of medical charts in China. *BMJ: British Medical Journal* 341, 2010.
133. Farias, JA, Fernández, A, Monteverde, E, Vidal, N, Arias, P, Montes, MJ, Rodríguez, G, Allasia, M, Ratto, ME and Jaén, R: Critically ill infants and children with influenza A (H1N1) in pediatric intensive care units in Argentina. *Intensive care medicine* 36(6):1015-1022, 2010.
134. Domínguez-Cherit, G, Lapinsky, SE, Macias, AE, Pinto, R, Espinosa-Perez, L, de la Torre, A, Poblano-Morales, M, Baltazar-Torres, JA, Bautista, E and Martinez, A: Critically ill patients with 2009 influenza A (H1N1) in Mexico. *JAMA: the journal of the American Medical Association* 302(17):1880-1887, 2009.
135. Rodríguez, A, Díaz, E, Martín-Loeches, I, Sandiumenge, A, Canadell, L, Díaz, JJ, Figueira, JC, Marques, A, Álvarez-Lerma, F and Vallés, J: Impact of early oseltamivir treatment on outcome in critically ill patients with 2009 pandemic influenza A. *Journal of antimicrobial chemotherapy* 66(5):1140-1149, 2011.
136. Brogan, TV, Thiagarajan, RR, Rycus, PT, Bartlett, RH and Bratton, SL: Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multi-center database. *Intensive care medicine* 35(12):2105-2114, 2009.
137. Noah, MA, Peek, GJ, Finney, SJ, Griffiths, MJ, Harrison, DA, Grieve, R, Sadique, MZ, Sekhon, JS, McAuley, DF and Firmin, RK: Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A (H1N1). *JAMA: the journal of the American Medical Association* 306(15):1659-1668, 2011.

138. Roch, A, Lepaul-Ercole, R, Grisoli, D, Bessereau, J, Brissy, O, Castanier, M, Dizier, S, Forel, J-M, Guervilly, C and Gariboldi, V: Extracorporeal membrane oxygenation for severe influenza A (H1N1) acute respiratory distress syndrome: a prospective observational comparative study. *Intensive care medicine* 36(11):1899-1905, 2010.
139. Davies, A, Jones, D, Bailey, M, Beca, J, Bellomo, R, Blackwell, N, Forrest, P, Gattas, D, Granger, E and Herkes, R: Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. *JAMA: the journal of the American Medical Association* 302(17):1888-1895, 2009.
140. Patroniti, N, Zangrillo, A, Pappalardo, F, Peris, A, Cianchi, G, Braschi, A, Iotti, GA, Arcadipane, A, Panarello, G and Ranieri, VM: The Italian ECMO network experience during the 2009 influenza A (H1N1) pandemic: preparation for severe respiratory emergency outbreaks. *Intensive care medicine* 37(9):1447-1457, 2011.
141. Peek, GJ, Mugford, M, Tiruvoipati, R, Wilson, A, Allen, E, Thalanany, MM, Hibbert, CL, Truesdale, A, Clemens, F and Cooper, N: Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet (London, England)* 374(9698):1351-1363, 2009.
142. Terragni, PP, Del Sorbo, L, Mascia, L, Urbino, R, Martin, EL, Birocco, A, Faggiano, C, Quintel, M, Gattinoni, L and Ranieri, VM: Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. *Anesthesiology* 111(4):826-835, 2009.
143. Kopp R, BR, Wardeh M, Rossaint R, Kuhlen R, Henzler D: Pumpless arterio-venous extracorporeal lung assist compared with veno-venous extracorporeal membrane

- oxygenation during experimental lung injury. *British Journal of Anaesthesia* 108(5):745-52, 2012.
144. Zimmermann, M, Bein, T, Arlt, M, Philipp, A, Rupperecht, L, Mueller, T, Lubnow, M, Graf, BM and Schlitt, HJ: Pumpless extracorporeal interventional lung assist in patients with acute respiratory distress syndrome: a prospective pilot study. *Crit Care* 13(1):R10, 2009.
145. Bein, T, Wittmann, S, Philipp, A, Nerlich, M, Kuehnel, T and Schlitt, HJ: Successful extubation of an “unweanable” patient with severe ankylosing spondylitis (Bechterew's disease) using a pumpless extracorporeal lung assist. *Intensive care medicine* 34(12):2313-2314, 2008.
146. Taylor, K and Holtby, H: Emergency interventional lung assist for pulmonary hypertension. *Anesthesia & Analgesia* 109(2):382-385, 2009.
147. Wolthuis, EK, Vlaar, A, Choi, G, Roelofs, J, Juffermans, NP and Schultz, MJ: Mechanical ventilation using non-injurious ventilation settings causes lung injury in the absence of pre-existing lung injury in healthy mice. *Crit Care* 13(1):R1, 2009.
148. Marini, JJ: Mechanical ventilation: past lessons and the near future. *Critical Care* 17(Suppl 1):S1, 2013.
149. Mondrinos, MJ, Kennedy, PA, Lyons, M, Deutschman, CS and Kilpatrick, LE: Protein kinase C and acute respiratory distress syndrome. *Shock* 39(6):467-479, 2013.
150. Cardinal-Fernández, P, Ferruelo, A, El-Assar, M, Santiago, C, Gómez-Gallego, F, Martín-Pellicer, A, Frutos-Vivar, F, Peñuelas, O, Nin, N and Esteban, A: Genetic predisposition to acute respiratory distress syndrome in patients with severe sepsis. *Shock* 39(3):255-260, 2013.
151. Dellinger, RP, Levy, MM, Rhodes, A, Annane, D, Gerlach, H, Opal, SM, Sevransky, JE, Sprung, CL, Douglas, IS and Jaeschke, R: Surviving sepsis campaign:

international guidelines for management of severe sepsis and septic shock, 2012.
Intensive care medicine 39(2):165-228, 2013.

152. Kor, DJ, Talmor, DS, Banner-Goodspeed, VM, Carter, RE, Hinds, R, Park, PK, Gajic, O and Gong, MN: Lung Injury Prevention with Aspirin (LIPS-A): a protocol for a multicentre randomised clinical trial in medical patients at high risk of acute lung injury.
BMJ open 2(5), 2012.

Figure Legends

Figure 1. Observational data suggests that acute respiratory distress syndrome (ARDS) onset ranges from 5 hours to 3.7 days, with a median onset of 2 days. Increasing acuity and prolonged emergency department (ED) lengths of stay (LOS) for the critically ill suggests that the time spent in the ED may represent a window of opportunity (“golden hours”) to initiate ARDS prevention strategies.

Solid circles indicate patients not progressing to ARDS and dashed circles indicate the development of ARDS.

$P_aO_2:F_iO_2$ - partial pressure of arterial oxygen: fraction of inspired oxygen; C_{RS} - respiratory system compliance; ED- emergency department; LOS- length of stay

Figure 2. Observational data, including patients dying with acute respiratory distress syndrome (ARDS) and receiving post-mortem examinations, reveal that clinical recognition and diagnosis of ARDS is missed in a significant percentage of patients. [30-32]

Figure 3. Simplified schematic of the pathogenesis of acute respiratory distress syndrome (ARDS) with respect to time. After an inciting event, capillary endothelial and alveolar epithelial injury can occur in minutes to hours. Activated immune cells (e.g. monocytes and macrophages) contribute to a cytokine-mediated inflammatory response. This serves to recruit neutrophils, which play a critical role in ARDS initiation and propagation, through the injured endothelium. Protein-rich pulmonary edema and subsequent surfactant loss lead to alveolar collapse, hypoxia, and reduced lung compliance [133,134]. If the primary injury is robust enough, or if modifiable secondary injuries occur (e.g. high tidal volume, transfusion, delayed sepsis treatment), ARDS develops, with a typical median onset of two days. Many of these pathogenic mechanisms for ARDS initiation occur prior to clinical evidence of the syndrome, and this window of pre-clinical injury forms the basis for ARDS preventive measures.

TNF: tumor necrosis factor; IL: interleukin; ARDS: acute respiratory distress syndrome

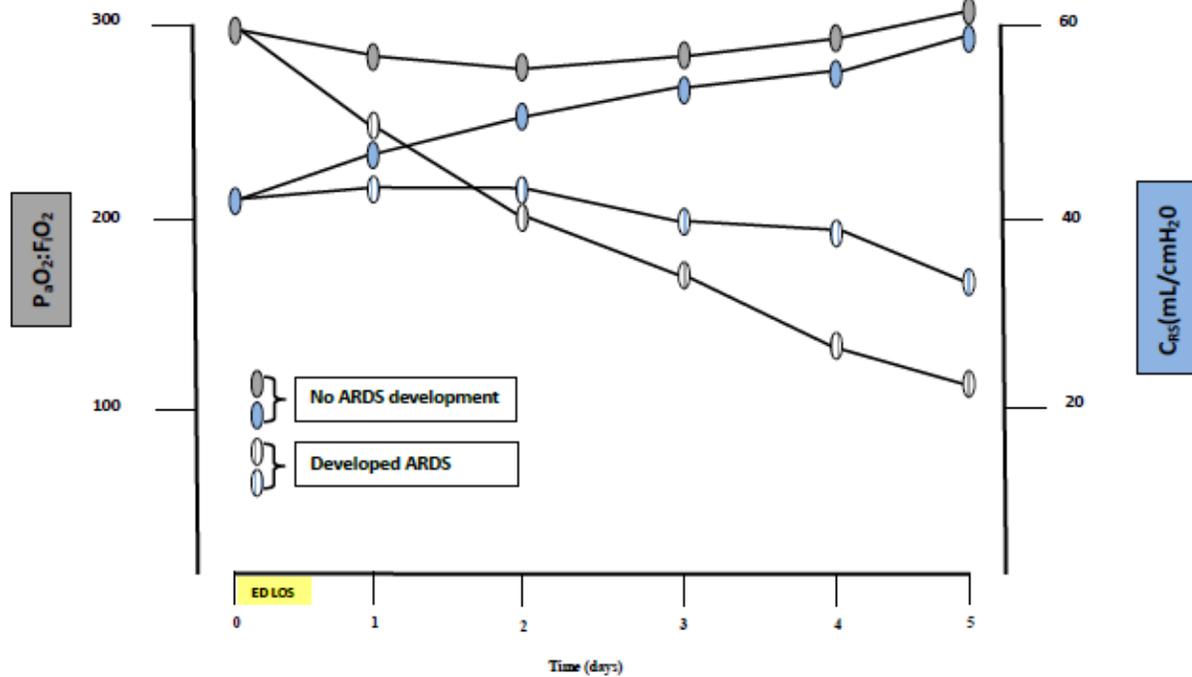


Figure 1. Observational data suggests that acute respiratory distress syndrome (ARDS) onset ranges from 5 hours to 3.7 days, with a median onset of 2 days. Increasing acuity and prolonged emergency department (ED) lengths of stay (LOS) for the critically ill suggests that the time spent in the ED may represent a window of opportunity ("golden hours") to initiate ARDS prevention strategies. Solid circles indicate patients not progressing to ARDS and dashed circles indicate the development of ARDS. $P_aO_2:F_iO_2$ - partial pressure of arterial oxygen: fraction of inspired oxygen; C_{RS} - respiratory system compliance; ED- emergency department; LOS- length of stay

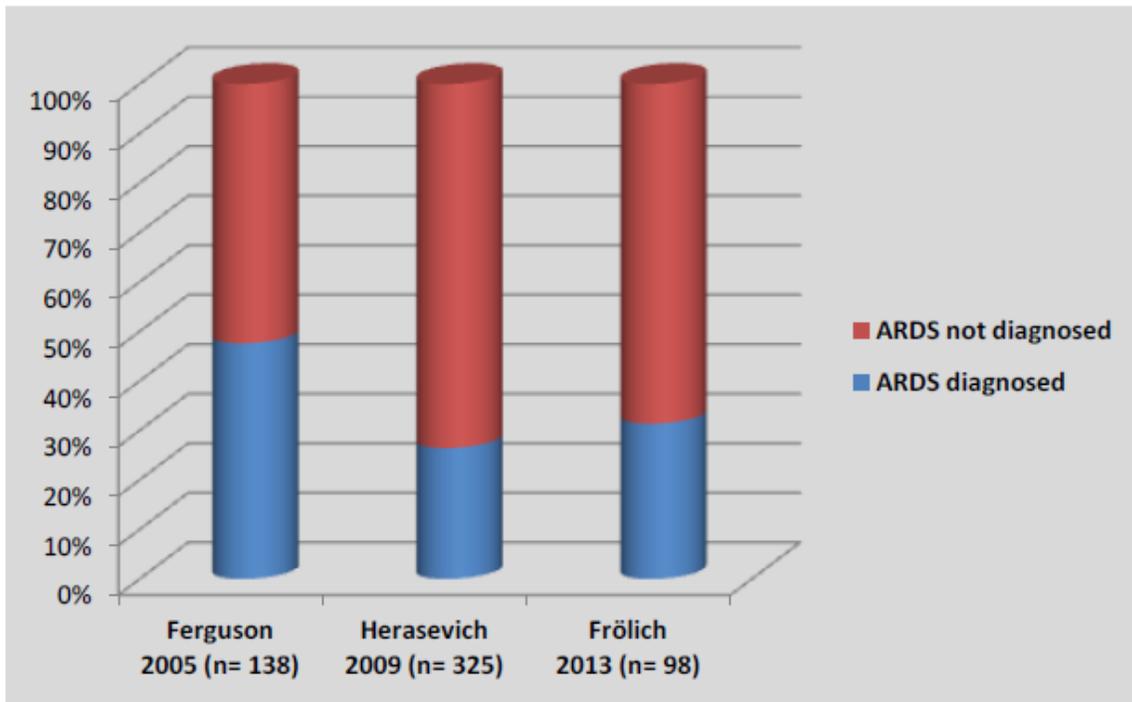


Figure 2. Observational data, including patients dying with acute respiratory distress syndrome (ARDS) and receiving post-mortem examinations, reveal that clinical recognition and diagnosis of ARDS is missed in a significant percentage of patients. [30-32]

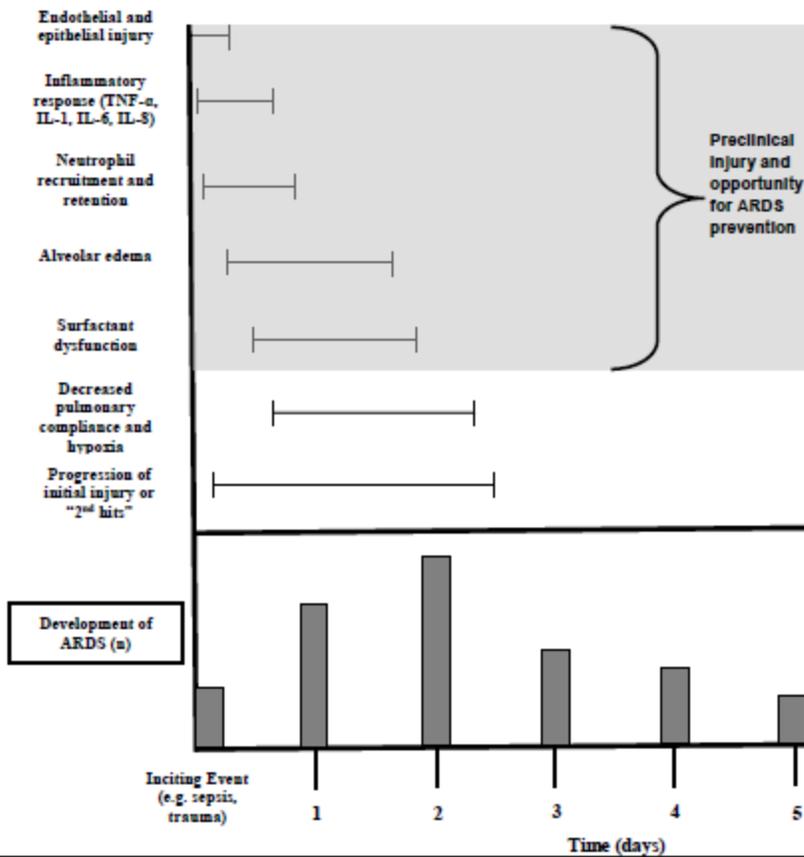


Figure 3. Simplified schematic of the pathogenesis of acute respiratory distress syndrome (ARDS) with respect to time. After an inciting event, capillary endothelial and alveolar epithelial injury can occur in minutes to hours. Activated immune cells (e.g. monocytes and macrophages) contribute to a cytokine-mediated inflammatory response. This serves to recruit neutrophils, which play a critical role in ARDS initiation and propagation, through the injured endothelium. Protein-rich pulmonary edema and subsequent surfactant loss lead to alveolar collapse, hypoxia, and reduced lung compliance [133,134]. If the primary injury is robust enough, or if modifiable secondary injuries occur (e.g. high tidal volume, transfusion, delayed sepsis treatment), ARDS develops, with a typical median onset of two days. Many of these pathogenic mechanisms for ARDS initiation occur prior to clinical evidence of the syndrome, and this window of pre-clinical injury forms the basis for ARDS preventive measures.
 TNF: tumor necrosis factor; IL: interleukin; ARDS: acute respiratory distress syndrome