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

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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

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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

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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).

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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 endexpiratory 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 H_2O (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 suited 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).

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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 ≤18mmHg 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

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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

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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 dysynchrony 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

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multicenter RCT of patients with early (within 48 hours), severe (P_aO_2:F_iO_2 <150) ARDS, a 48 hour infusion of cisatricurium 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 ≥ 8 (≈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

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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 while likely be some combination of ventilatory and non-ventilatory strategies, along with a multidisciplinary collaboration between emergency physicians, intensivists, nurses, and respiratory therapists.

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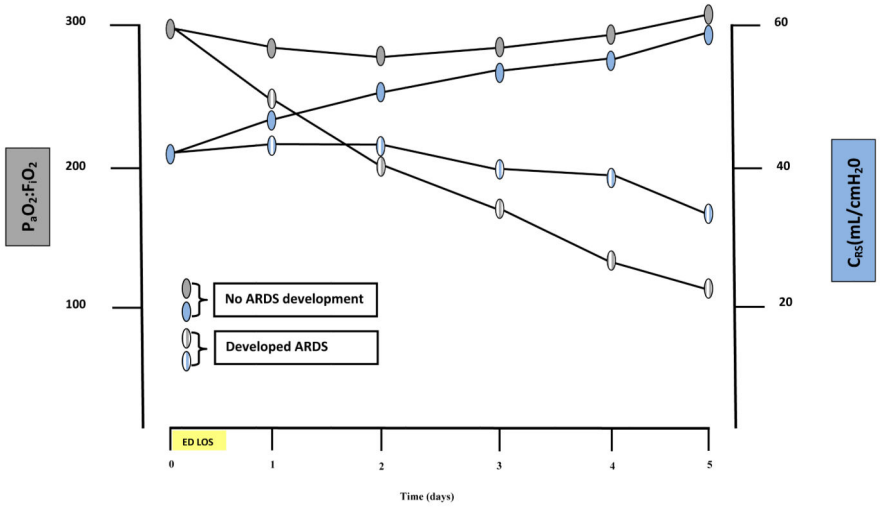

Figure 1.

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

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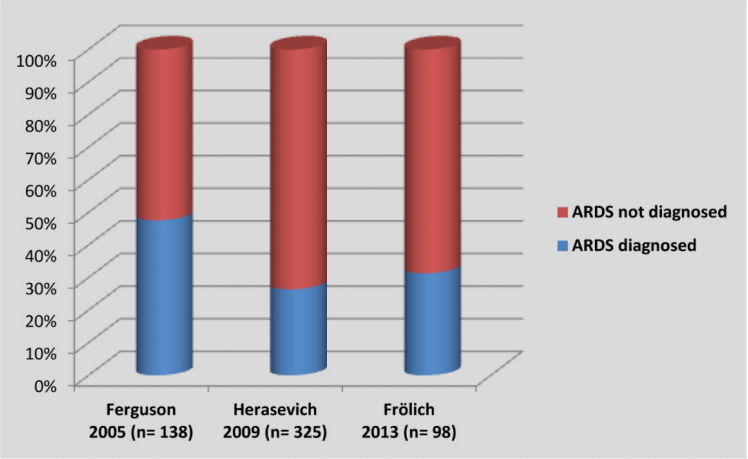

Figure 2.

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]

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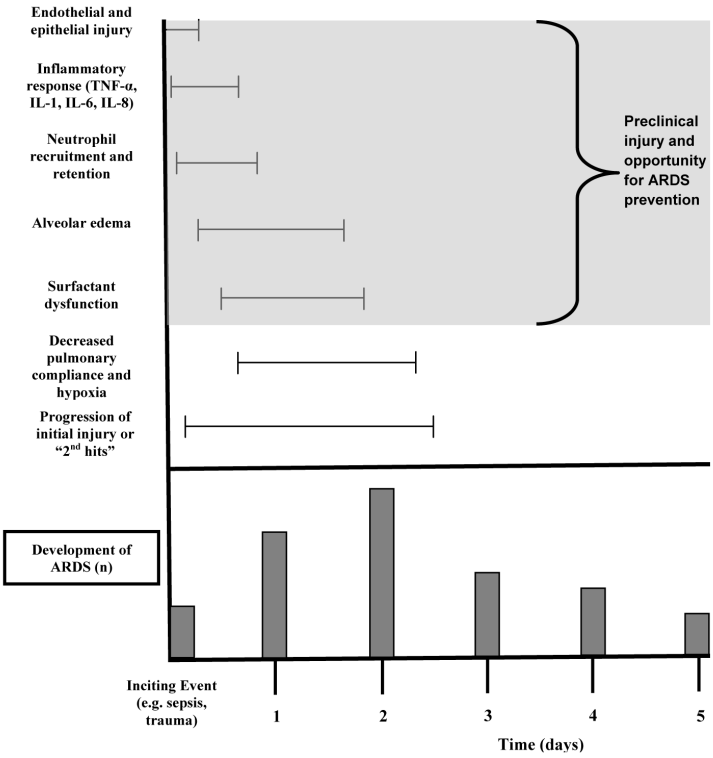

Figure 3.

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 occurs 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