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REVIEW

Early identification of patients with or at risk of acute lung injury

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ABSTRACT

Acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS), are important critical care syndromes for which the treatment options are limited once the condition is fully established. Enormous basic and clinical research efforts have led to improvements in supportive treatment, but surprisingly little has been done on the prevention of this devastating syndrome. The development and progression of ALI/ARDS may be triggered by various intrahospital exposures including but not limited to transfusion, aspiration, mechanical ventilation, certain medications and delayed treatment of shock and infection. Early recognition of patients with or at risk of ALI/ARDS is essential for designing novel prevention and treatment strategies. Automated electronic screening tools and novel scoring systems applied at the time of hospital admission may facilitate enrolment of patients into mechanistic and outcome studies, as well as future ALI/ARDS prevention trials.

KEYWORDS

Acute lung injury, acute respiratory distress syndrome, pneumonia

INTRODUCTION

Acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS), are important critical care syndromes for which the treatment options are limited once the condition is fully established. In fact, most recent data suggest that the poor prognosis of ALI/ARDS has remained essentially the same over the past 15 years.[1] Enormous basic and clinical research efforts have led to improvements in supportive treatment,[2,3] but surprisingly little has been done on the prevention of this devastating syndrome.

Insufficient understanding of the clinical development and progression of ALI precludes the design of preventive strategies at the present time. While some studies have suggested potentially important roles of several environmental risk modifiers,[4-12] the knowledge gap persists, with limited understanding of why some patients with septic shock, trauma or pneumonia do and others do not develop ALI.

Preclinical studies support a 'two hit' model of development of ALI/ARDS whereby different exposures modify the expression of ALI/ARDS in the primed or susceptible host.[13] For example, common critical care exposures such as mechanical ventilation[14] and transfusion[15] greatly influence the development of ALI in preclinical models, and the 'two hit' experiments are considered to more accurately represent the clinical setting.[13] Preliminary clinical data suggest that ALI/ARDS is rarely present at the time of hospital admission, but develops over a period of hours to days in subsets of patients with predisposing conditions, such as pneumonia, sepsis, trauma and shock and corresponding medical and surgical interventions.[16,17]

EARLY IDENTIFICATION OF PATIENTS WITH ALI/ARDS

Electronic surveillance for ALI/ARDS

Critical care syndromes such as ALI/ARDS are not routinely coded in hospital databases and are greatly under recognised by bedside providers. Although a standardised definition has existed for more than a decade,[18] efforts required for data collection and screening have significantly limited clinical studies in this area. In a recent study, only 27% of ALI episodes were documented by bedside providers.[19] The advancement of electronic medical records (EMR) provides the opportunity for electronic screening (syndrome surveillance) of ALI/ARDS and related syndromes. Our team has developed and validated a novel syndrome surveillance

tool (ALI 'sniffer') for the recognition of patients with ALI and ARDS (*figure 1*).[19] Electronic alert is triggered by the following combination of observations: the ratio of partial pressure of oxygen to inspired oxygen concentration (PaO_2/FIO_2) <300 and chest radiograph report (free text Boolean query containing trigger words: ('bilateral' AND 'infiltrate') OR 'edema'. With an excellent negative predictive value (0.99, 95% CI 0.98 to 1.00), ALI sniffer is optimised for screening patients with a high probability of ALI/ARDS. It has been continuously running since December 2005, allowing prospective identification of ALI/ARDS cases.

Azzam *et al.*[20] have recently reported similar results. Using the American European Consensus Conference (AECC) criteria,[18] excluding current or known history of congestive heart failure, the automated screening tool had a sensitivity of 87%, specificity of 89% and accuracy of 88% in capturing patients with ALI/ARDS.

Although currently limited to a minority of institutions, electronic screening has a very promising potential application in both clinical settings and research.

High-resolution monitoring of ALI/ARDS development

A standardised ALI assessment method based on the AECC definition[21] facilitated diagnosis of ALI/ARDS for clinical research and quality improvement projects in our institution.[22] The absence of left atrial hypertension as a primary explanation for pulmonary oedema is excluded by integrated clinical evaluation based on the combination of echocardiographic findings (E/E' <15), brain natriuretic peptide levels (BNP <250 pg/ml in the absence of renal failure), venous filling pressures (PAOP ≤18 cm H_2O or CVP <15 cm H_2O in the absence of pulmonary hypertension) and the response to therapy (brisk response to diuretics and positive pressure ventilation favours hydrostatic oedema). This process yielded good inter-observer agreement for differentiation between ALI and hydrostatic oedema (kappa values from 0.65 to 0.83).[22,23]

Since most clinical studies to date have been limited by a low temporal resolution ('today the patient does not have ALI and tomorrow he/she does'), it has been very difficult to distinguish between the cause and effect role of specific risk factors (effect-cause bias). High-resolution monitoring of hospitalised patients allows us to pinpoint the beginning of respiratory worsening based on the sustained changes in respiratory rate and the ratio of arterial oxygen saturation over inspired oxygen concentration (SpO_2/FIO_2) without being dependent on bedside providers ordering arterial blood gas (ABG) analysis. Rice *et al.*[24] recently validated SpO_2/FIO_2 thresholds against the gold standard of ABG. SpO_2/FIO_2 <315 corresponds to ALI (PaO_2/FIO_2 <300) and SpO_2/FIO_2 <235 corresponds to ARDS (PaO_2/FIO_2 <200). Hence, early identification of ALI/ARDS could be done without arterial blood gas confirmation which could cause delay in diagnosis and treatment as well as enrolment in clinical trials. In *figure 2* the black arrow points to a sustained decrease in oxygen saturation followed by an increase in oxygen supplementation at 1 AM suggesting the onset of respiratory worsening. The chest radiograph and blood gas analysis performed five hours later (6 AM) confirmed ALI, but only exposures occurring before 1 AM were considered in the analysis. This conservative approach minimises the effect-cause bias in this type of association study. Our group has used this approach to identify exposures of interest related to transfusions,[6] antibiotic management[25] and goal-directed resuscitation.[25]

IDENTIFICATION OF PATIENTS AT RISK OF DEVELOPING ALI AND ARDS

One of the principal barriers towards better understanding of clinical pathogenesis of ALI/ARDS and the design of effective ALI/ARDS preventive strategies is the fact that previous clinical studies focused exclusively on patients admitted to the ICU. While multiple studies around the world reported

Figure 1. *Electronic surveillance for acute lung injury (ALI 'sniffer')*

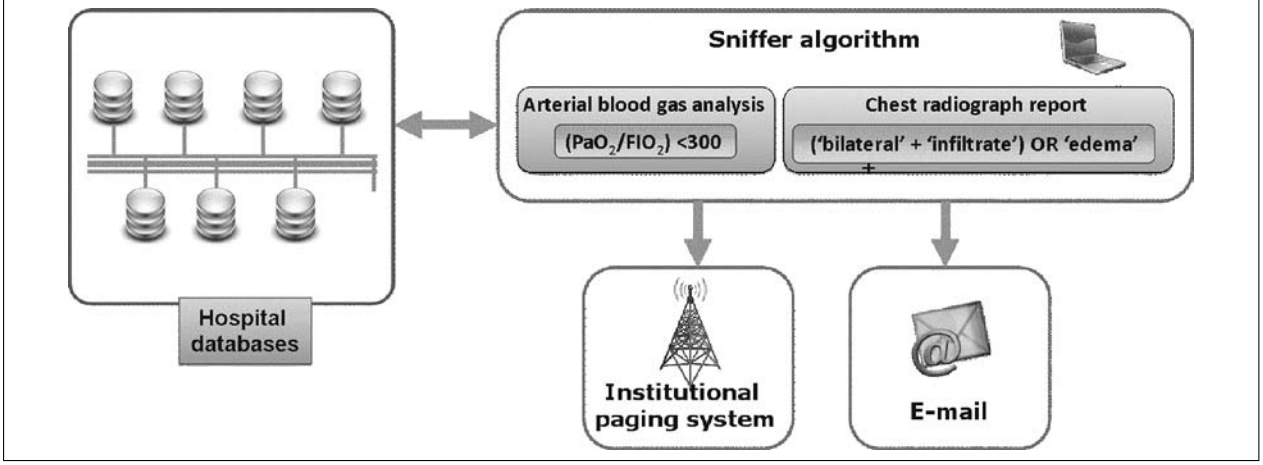

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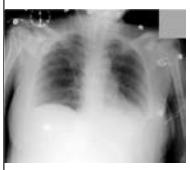
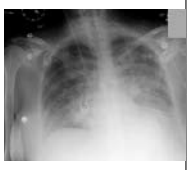
Figure 2. *High-resolution monitoring of acute lung injury development*



	20.00	21.00	22.00	23.00	00.00	01.00	02.00	03.00	04.00
Physiological parametres									
Real-time variables									
Heart rate	82	88	86	87	88	105	125	127	114
NIBP systolic	108	106	108	112	116	115	154	91	81
NIBP diastolic	58	52	52	56	58	75	81	48	39
Fresh-frozen plasma (ml)		226		245	269				
Medication infusions									
Vasopressin (unit/min)									
Crystalloid in									
0.9 NaCl (ml/h)	100	100	100	100	100	100	100	100	100
0.9 NaCl - fluid bolus (ml)								<	500
Ventilator settings									
Real-time variables									
Oxygen device #1	CFM					↓	CFM		CFM
Oxygen %/LMP #1	5.00						50%		50%
SpO_2	99	100	97	98	97	88	91	95	92



The black arrow points to a sustained decrease in oxygen saturation followed by an increase in oxygen supplementation at 01.00 AM suggesting the onset of respiratory worsening. The chest radiograph and blood gas analysis performed five hours later (06.00) confirmed ALI.

the risk factors for ALI/ARDS,[26-29] only a few prospectively followed patients with predisposing conditions to document the probability of developing ALI/ARDS. Landmark studies by Pepe *et al.*,[30] Fowler *et al.*[31] and Hudson *et al.*[32] were conducted in the early 1980s and 1990s, before the current definitions of ALI and ARDS, sepsis and pneumonia were established. Recent cohort studies used specific definitions but were still restricted to patients admitted to the ICU.[5,12,33-35,10,11,36]

The proportion of patients with risk factors who develop ALI/ARDS drops drastically when assessed at the time of hospital admission.[17] In a recent study by Ferguson *et al.*[17] only 7% of hospitalised patients with sepsis, 2% with pancreatitis, 10% with pneumonia and 15% with witnessed aspiration developed ALI.[17] Many patients with predisposing conditions never develop ALI/ARDS and are never admitted to the ICU[17] making the enrolment of non-selected patients into ALI/ARDS prevention studies neither practical nor efficient without a method to select high-risk patients.

To facilitate enrolment of patients into mechanistic and outcome studies as well as future ALI/ARDS prevention trials, our group has recently developed an ALI/ARDS prediction model,[37] (the Lung Injury Prediction Score: LIPS) which incorporates demographic, environmental and clinical characteristics at the time of, and before hospital admission. LIPS takes into consideration not only different incidences of ALI/ARDS depending on underlying risk factors (from 2% risk in patients with uncomplicated pancreatitis[17] up to 40% in those with septic shock[38]) but also the presence of significant risk modifiers (smoking,[39] alcohol,[10,40] diabetes mellitus,[11] chemotherapy,[38] hypoalbuminaemia,[41] and respiratory rate[5]). If prospectively validated and refined in relevant patient populations, this model could serve to define the patients at high risk of ALI/ARDS in whom future mechanistic studies and ALI/ARDS prevention trials will be conducted. By determining not only patients at high risk but also the attributable burden of ALI/ARDS in contemporary cohorts of patients at risk, the findings are expected to facilitate the prioritisation of preventive strategies and future clinical trials.

Another recent study[42] reported that patients who require high oxygen supplementation when in the emergency room (O_2 >2 l/min) are more likely to progress into ALI. In addition, the authors defined a clinical diagnosis of early ALI in patients who present at hospital admission with bilateral opacities on chest radiograph not exclusively due to left atrial hypertension and who initially required oxygen supplementation of >2 l/min (73% sensitive and 79% specific for progression to ALI with respiratory failure).

CONCLUSION

ALI/ARDS is rarely present at the time of hospital admission. Subsequent ('second hit') hospital exposures have modified the development and expression of the syndrome in patients with predisposing conditions. Therefore, ALI/ARDS may be viewed as a potentially preventable healthcare-acquired complication analogous to venous thromboembolism, stress ulcer bleeding or nosocomial infections. Preliminary studies suggest that early treatment of shock and infection[38] and avoidance of ventilator and transfusion-related lung injury[43] may reduce the incidence of hospital-acquired ALI/ARDS.[43] Electronic surveillance and novel scoring systems for early identification of patients with or at risk of ALI/ARDS will facilitate future mechanistic studies and ALI/ARDS prevention trials.

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