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REVIEW

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Identifying patients with ARDS: time for a different approach

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Is it important to know who has acute lung injury?

During the first 20 years after the acute respiratory distress syndrome (ARDS) was first described [1], there were virtually no large-scale randomized clinical trials of potential therapies [2]. Accordingly, arguments about who did or did not actually have lung injury were largely academic; in the absence of a specific treatment for the illness, it was hard to defend the position that identifying lung injury per se was critical to how these patients should be managed.

Recently, the situation has begun to change. Numerous trials of potential therapies for ARDS, or for predisposing conditions (like sepsis), have already been conducted [3–12]; others are in progress or are being planned. Distressingly, and despite often overwhelmingly favorable pre-clinical data, none have proved useful in reducing the mortality. By analogy with the similar lack of success in clinical trials of new interventions in sepsis, potential explanations are numerous [11, 13–17]. Certainly one especially relevant concern is that the appropriate target population has not been enrolled.

Arguments about the appropriate target population often center on prognosis [18, 19]: some patients are so severely ill that no treatment is likely to be effective. Other patients are not ill enough: for them, the prognosis is sufficiently good that any new treatment cannot be expected to have more than a marginal effect. In the latter case, it would take many hundreds, if not thousands of patients, to detect a benefit.

A corollary argument concerns underlying disease: patients with certain predisposing causes for ARDS (e.g. sepsis) have a worse prognosis than those with other causes (e.g., trauma) [20]. A similar issue exists for co-morbidities (e.g., the patient with underlying malignancy vs the patient who was previously healthy). Thus, some recent trials have tried to control for these factors by limiting enrollment to certain sub-populations with ARDS [7].

Lost in such discussions, however, is an even more basic issue: do all the patients who are enrolled into clinical trials about ARDS, even if stratified for underlying disease or comorbidity, actually have lung injury? And is the injury itself equally severe among the patients enrolled? And if not, does the severity of the injury itself affect prognosis? In other words, aside from the issues of prognosis, how do we make the diagnosis of ARDS? The argument about "who has lung injury" (or ARDS) is really an argument about who should qualify to participate in clinical trials.

Starting principles

A discussion about "what is ARDS?" or "who has ARDS?" must start with a debate about definitions, criteria, and methods to measure severity. These terms are not synonymous, although they are often confused with one another (Table 1).

For purposes of this discussion, the following is proposed: the definition of an illness (like ARDS) is simply an unambiguous description of the disease. The criteria that are used to detect the illness, on the other hand, comprise a set of threshold values for variables that, ide-

ally, follow directly from the definition. Where exactly the threshold values themselves are set may depend on several issues: for instance, the expediency or practicality of measurement; or their performance against some gold standard for identifying the illness.

Consider the following example. Hypoxemia could, and should, be one component of a definition for ARDS. Even so, the exact criteria which are used to establish hypoxemia are a legitimate matter for debate. Is an $SaO_2 < 90\%$ by finger pulse oximetry satisfactory (a "simple" criterion to determine), or must one demonstrate that the PaO_2 is < 60 mm Hg with an arterial blood gas measurement (more complex)? Must the level of oxygenation be determined on room air, or is supplemental oxygen allowed? How about mechanical ventilation? Or positive end-expiratory pressure? How do we decide?

However we decide, we must not be confused that such a debate is not about how we define ARDS; rather its a debate about the criteria we should use to make the diagnosis.

In principle, the way these criteria should be chosen are exactly the way we select other diagnostic criteria: by determining their sensitivity and specificity for identifying the problem. To do so, of course, requires a "gold standard" of some sort (Table 2). The fact that there may not be an accepted gold standard for the diagnosis of ARDS doesn't change the validity of the approach. Nor does it change our (theoretical) ability to define ARDS (i.e. to provide an unambiguous description of the syndrome). It simply ensures that the debate over criteria will involve a degree of arbitrariness that would be avoided if a gold standard did in fact exist.

Here is an appropriate point to draw another crucial distinction: the criteria we use to establish a diagnosis may not always be appropriate as markers of severity (Table 2). Whereas criteria are threshold values, which, when exceeded, establish a diagnosis, severity implies a continuum of possible values which predict outcome. Thus, we can determine the "validity" of a set of criteria by their sensitivity and specificity (or similar statistics), but we determine the validity of a severity score by how well it predicts some relevant outcome of interest (i.e. prognosis) (Table 2).

We can use the same simple example to illustrate this distinction as well: if we accept hypoxemia as part of the definition of ARDS, then we might also accept a PaO_2/FiO_2 (P/F) ratio of < 200 as the criterion we use to satisfy this part of the definition. But it does not necessarily follow that a P/F ratio of < 100 indicates more severe disease than a P/F ratio of < 200 (i.e. predicts a worse outcome). Whether or not the criterion of a P/F ratio < 200 mm Hg is valid depends on how often some patients with ARDS (as determined by some other gold standard) are excluded because they didn't meet this particular criterion (sensitivity), and how often patients without ARDS are mistakenly included because they in fact met this criterion (specificity). On the other hand, whether or not a P/F ratio of < 100 indicates more severe disease than a P/F ratio of 200 depends on the relative outcome of two groups of ARDS patients, as classified by these two P/F ratios.

None of these principles are new, but it is disappointing that they have not been part of the debate over "who has ARDS".

Table 1 Distinctions between definition of, criteria for, and measurements of severity in ARDS

Definition:	a descriptive statement establishing the criteria for diagnosis
Criteria:	a set of threshold values, which when exceeded qualitatively or quantitatively establish the diagnosis
Severity of injury:	a quantitative scalar or set of scalars which, all else being equal, are predictive of recovery from lung injury

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Table 2 Use and validation of definitions, criteria, and severity indices

	Use	Gold standard
Definition/criteria	Diagnosis	Sensitivity/specificity
Severity	Prognosis	Outcome

The current state of affairs

Now consider how ARDS is currently defined, what criteria are used to satisfy the definition, and how severity is measured.

ARDS is now usually defined as a particularly severe subset of "acute lung injury" (ALI), which in turn is defined as "a syndrome of inflammation and increasing permeability that is associated with a constellation of clinical, radiologic, and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension" [21]. This is a legitimate, if still somewhat vague, definition. But from such a definition, one would expect that the key criteria used to identify patients with ARDS would include evidence of pulmonary inflammation, increased vascular permeability, and specific radiologic and physiologic derangements that are independent of left atrial pressure (Table 3).

Instead, the criteria that are generally used to identify patients with ARDS include nothing about inflammation, nothing about vascular permeability, and specifically exclude patients with left atrial hypertension (Table 3). Even so, such criteria could be accepted if they demonstrated acceptable performance in terms of sensi-

Table 3 Current criteria for ARDS (from [37])

Expected	Actual
Documented inflammation	–
Elevated PVP	–
Specific clinical, radiologic, physiologic abnormalities	Acute bilateral radiographic infiltrates P/F < 200
± LAH	Exclude LAH

PVP = pulmonary vascular permeability; *P/F* = PaO_2/FiO_2 ratio; *LAH* = left atrial hypertension
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Table 4 Shortcomings of the current algorithm to diagnose ARDS

- Excludes pulmonary edema due to lung injury *and* left atrial hypertension
- Unable to correctly classify pulmonary edema due to pulmonary venous hypertension *in absence* of left atrial hypertension
- Dependance on clinical assessment of heart failure known to be unreliable
- Fails to provide adequate measure of severity-of-injury

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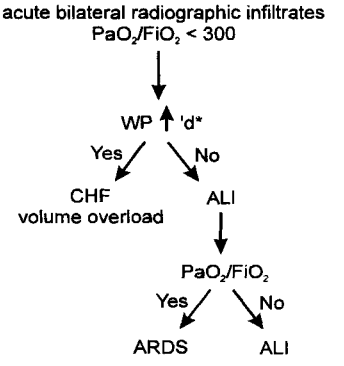

Fig. 1 Usual algorithm used for diagnosis of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) (from [21]); *WP* = wedge pressure; *CHF* = congestive heart failure; *indicates that WP can be measured directly or inferred clinically. Reproduced with permission from [48]

tivity and specificity. Simply comparing these criteria to another set of criteria [22] is not acceptable unless the sensitivity and specificity of the latter are already known. In the end, it is how well a given set of criteria perform against an accepted gold standard that determines their validity.

The criteria now usually used to identify patients with ARDS (as listed in Table 3) lead, logically, to a diagnostic algorithm commonly employed both clinically and in research (Figure 1), although this incorporates several potentially important problems (Table 4). For one, the algorithm must be somewhat insensitive for it excludes patients with bona fide lung injury simply because they have, at the time of evaluation, elevated left atrial pressure (as reflected by the pulmonary arterial occlusion pressure). Likewise, it can be expected to be non-specific as well, classifying patients as having lung injury when they have pulmonary edema with a low wedge pressure, even if, in fact, they have pulmonary venous hypertension from other causes (say, from the release of mediators like thromboxane) [23].

The fact that heart failure or volume overload can be evaluated (Figure 1) purely on clinical grounds (instead of objective ones) is also problematic, since it has been shown several times that physicians are notoriously poor at being able to estimate cardiac filling pressures in complicated, critically ill patients [24–27]. Finally, the algorithm in Figure 1 limits the classification of pulmonary edema to a simple dichotomy: one either has lung injury or one has a hydrostatic form of pulmonary edema; not both.

In essence, the diagnosis of ARDS, according to this algorithm, is made by inference: when pulmonary edema occurs in the setting of normal hydrostatic pressures (estimated either clinically or from the pulmonary artery occlusion pressure), it is labeled "ARDS". Conversely, if the occlusion pressure is elevated, the primary mechanism for pulmonary edema is assumed to be due to increased pulmonary hydrostatic pressures, and the diagnosis of ARDS is excluded.

Recent studies suggest that such a simple dichotomy may be wrong more often than previously believed [28]. Thus, many studies [29, 30] have documented that the injured lung is exquisitively sensitive to what otherwise appear to be trivial differences in capillary pressure [31, 32]. Since the prevalence of pulmonary venous hypertension in ARDS is unknown, it is impossible to say just how often hydrostatic stress contributes to the pulmonary edema of ARDS.

A potentially related problem is the recently appreciated phenomenon of "capillary stress failure" [33], in which markedly elevated pulmonary capillary pressures, even if quite transient, can cause breaks in the capillary endothelium that result in extravasation of plasma and even red cells. The prevalence of this phenomenon in clinical disease is also unknown; at least theoretically, however, it may be relevant to the development of "secondary" lung injury associated with mechanical ventilation [33].

In essence, then, it is certainly possible, and indeed probable, that lung injury can be accompanied by pulmonary venous hypertension, and for pulmonary venous hypertension (if severe enough) to contribute to lung injury. If so, it is also possible that the pulmonary edema associated with ARDS comprises the entire spectrum of physiologic abnormality, from instances in which injury is solely responsible for the development of pulmonary edema (perhaps, for example, with aspiration) to instances in which injury is largely if not solely the result of severe pulmonary capillary hypertension (perhaps, for example, with high altitude pulmonary edema), and everything in-between (for example, with sepsis). In such a scenario, a simple dichotomy doesn't work. To fully characterize the pathogenesis of pulmonary edema, the relative contribution of BOTH hydrostatic pressure and injury should be quantified.

The reliance of the diagnostic algorithm in Figure 1 on oxygenation is equally problematic. Clearly, the defect in oxygenation is not a function of lung injury alone but involves multiple other factors, such as differences in regional pulmonary perfusion [34], bronchoconstriction, atelectasis, and previous lung disease. As a result, differences in oxygenation neither help identify the cause of pulmonary edema, nor help predict its outcome [35, 36].

An alternative

Everyone agrees that injury is central to the pathogenesis of ARDS. Since "damage" is synonymous with "injury", it makes sense that the definition of ARDS should link structural changes with functional abnormalities. Accordingly, an alternative to the definition currently employed to define ARDS [37] is to consider ARDS a specific form of lung injury (not simply the most severe form of any lung injury) – one in which the structural changes are characterized pathologically as diffuse alveolar damage [38, 39], and the functional abnormalities are principally the result of a breakdown in the pulmonary endothelial barrier, leading first to proteinaceous alveolar edema, and then, as a consequence, to altered respiratory system mechanics and hypoxemia (Table 5).

Acute lung injury (ALI) of the type associated with ARDS can be defined as the combination of bilateral pulmonary edema and increased pulmonary vascular permeability. Only when it is known or can be reasonably assumed that the accompanying pathology is diffuse alveolar damage should lung injury be labeled ARDS per se. Thus, ALI is a less specific entity than ARDS. If pathologies other than diffuse alveolar damage can be associated with both alveolar edema and increased vascular permeability, these should not be called ARDS but acute lung injury due to some other cause.

The criteria needed to satisfy this alternative definition are straightforward (Table 6): acute lung injury by itself could be documented as simply the presence of pulmonary edema and increased pulmonary vascular permeability. For ARDS, it would be necessary, in addition, to document that these were associated with, or could be assumed to be associated with, diffuse alveolar damage. Clinically appropriate methods to identify the presence of pulmonary edema and increased vascular permeability are available [40–45]. However, it is uncommon to specifically determine unequivocally that diffuse alveolar damage is also present, since to do so requires tissue for histological examination. In some circumstances, it may be reasonable to assume that diffuse alveolar damage is present despite no actual histologic confirmation if clinical studies provide a high degree of correlation. Acute lung injury associated with sepsis might be one such example. In others cases, the clinical correlations may not exist (for instance, in neurogenic pulmonary edema, high altitude pulmonary edema, and pulmonary edema associated with crises of pregnancy). In these circumstances, it would be more appropriate to simply say that such a patient has acute lung injury in the setting of the other specific clinical entity.

These alternative criteria give rise to an alternative, albeit more complicated diagnostic algorithm (Figure 2). Despite the increased complexity, the algorithm is still clinically appropriate and may lessen the problems noted with the algorithm of Figure 1. For one, by defining acute injury as increased vascular permeability in the presence of pulmonary edema, specificity is greatly enhanced by the demonstration of abnormal endothelial barrier function. The sensitivity of available techniques to evaluate abnormal endothelial barrier function is less certain, although studies which show instances of increased vascular permeability even in the absence of pulmonary edema would seem to suggest that these methods may have a high degree of sensitivity [42, 45].

Severity

As already noted, the variables that are used as the criteria for diagnosis may or may not be valid markers of severity (vida supra: the use of the P/F ratio). Whether a given variable is a valid measure of severity should depend upon how well it predicts outcome. But which outcome? It is probably unrealistic, and may be potentially misleading, to judge a putative marker of the severity of lung injury by how accurately it predicts mortality. The influence of comorbidities, as well as the premorbid health status of the patient, are simply too powerful to hold any single test of lung injury per se to that standard. Rather, the standard should be whether the putative marker can accurately predict recovery from lung injury.

Table 5 Proposed definitions for ALI and ARDS

ALI:	Any significant deterioration in lung function associated with characteristic pathologic abnormalities in the lungs' normal underlying structure or architecture
ARDS:	A specific form of lung injury in which structural changes (characterized pathologically as *diffuse alveolar damage*) and functional abnormalities (principally a breakdown in the pulmonary endothelial barrier) lead first to proteinaceous alveolar edema, and then (as a consequence) to altered respiratory system mechanics and hypoxemia

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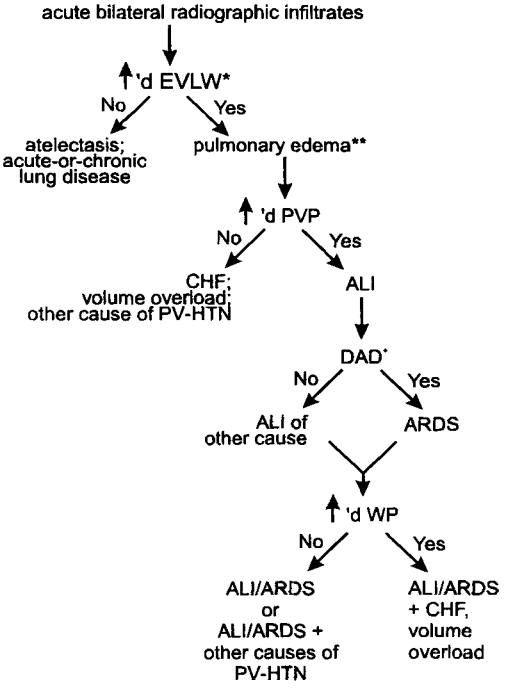

Fig. 2 Proposed algorithm to determine diagnosis of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). *EVLW* = extravascular lung water (*indicates that EVLW may be measured directly or inferred from a chest radiograph); *PVP* = a direct measure of vascular permeability (see text); *DAD* = pathologic finding of diffuse alveolar damage (+ indicates that DAD may be determined histologically, or may be assumed to be present in an appropriate clinical setting – see text); *WP* = wedge pressure; *PV-HTN* = pulmonary venous hypertension; ++ indicates that alveolar hemorrhage and cellular infiltrate may also increase EVLW and appear as radiographic infiltrates while not being causes of pulmonary *edema* per se. Reproduced with permission from [48]

If pulmonary edema is the consequence of lung injury, then resolution of pulmonary edema itself would seem to be the logical choice as an appropriate outcome variable.

The most commonly employed measure of lung injury in most current studies is the so-called "Lung Injury Score" [46], based on points assigned for abnormalities in oxygenation, the chest radiograph, lung mechanics (as assessed by quasi-static compliance measurements), and the application of positive end-expiratory pressure (PEEP). In addition to issues already discussed, however, this approach is suspect simply because the various components of the score are not independent of one another [42].

On the other hand, if lung injury is defined (functionally) as an increase in lung vascular permeability, then whether or not measurements of pulmonary vascular permeability are a good marker of severity would depend upon whether the magnitude of change in permeability could predict the resolution of pulmonary edema. The very limited information available suggests that changes in permeability may track recovery from pulmonary edema [42], but much more clinical information of this type is still needed.

Differences in approach

How these different approaches to diagnosis and prognosis affect the conduct of clinical trials in this field can be illustrated as follows. Assume one wishes to test a new treatment for acute lung injury. At present, the definition [37] and criteria for lung injury shown in Table 3 and Figure 1 are used to identify the target patient population, the Lung Injury Score and one or more global scoring systems (like APACHE or SAPS) are used to evaluate severity of illness. Either mortality or, more recently "ventilator free days", is used as the outcome variable.

The fact that so many trials of seemingly promising therapies have failed raises the concern that this approach fails to target the patient population of interest, fails to appropriately stratify the patients for severity,

Table 6 Proposed criteria for ARDS

Definitive	Practical
Diffuse (bilateral) alveolar edema (EVLW > 7 ml/kg with consistent CXR)	Radiographic infiltrates consistent with diffuse (bilateral) alveolar edema
Increased lung vascular permeability	Increased vascular permeability[a]
Diffuse alveolar damage pathologically	Appropriate clinical setting

[a] Until more complete information is available, a four- to fivefold increase over normal values; alternatively > 2 SD from the normal population mean

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and fails to evaluate a meaningful outcome variable. It seems plausible that these entry criteria are potentially both non-specific and insensitive, that the LIS doesn't adequately predict outcome of any sort, that the global scoring systems (if anything) predict mortality not recovery from lung injury per se, and that when the outcome evaluation is limited to mortality alone the potential biological effectiveness of a new therapy on lung injury itself may (unfortunately) be missed.

An alternative strategy, based on the definitions and criteria given in Tables 5 and 6 and in Figure 2 might work differently: patients for a candidate new treatment would be identified by having a compatible chest x-ray (or other quantitative measure of EVLW) and direct evidence for increased vascular permeability [47]; severity of lung injury would be defined by the magnitude of abnormality in permeability, whilst the severity of the patient's illness overall would still be measured with one of the global scoring systems. Finally, the outcome that would be used to test the effectiveness of the new drug would be resolution of pulmonary edema. In some cases, it may also be possible to accurately quantify such resolution [47]. Measures of ventilator free days or mortality would still be important to determine whether a new treatment is worth whatever costs are associated with it.

Why bother measuring lung injury?

The answer to the question "why measure lung injury" is simple and direct: at present, it is not necessary to measure lung injury to care for patients with ARDS. However, the current approach to identifying, stratifying and evaluating the outcome of patients with ALI/ARDS may be an important reason why so many clinical trials of new therapies have apparently failed. It is past time to consider alternative approaches. A direct measure of lung injury should be a criterion for entry into any clinical trial of new therapy for this condition, and the same or other measure [40] (appropriately documented to be predictive of recovery from pulmonary edema) should be used as an index of severity of injury. Although still unproven, it seems quite plausible, and is certainly testable, that a measure of vascular permeability is the best available, clinically appropriate way of verifying and quantifying lung injury at the present time.

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