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# Toward Optimal Acute Respiratory Distress Syndrome Outcomes

## Recognizing the Syndrome and Identifying Its Causes

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### KEYWORDS

- Acute respiratory distress syndrome • ARDS • ARDS risk factors
- Lung protective ventilation

### KEY POINTS

- Acute respiratory distress syndrome is a heterogeneous clinical syndrome.
- Recognition of the syndrome is essential to use appropriate lung protective ventilation and fluid conservative strategies that reduce morbidity and mortality.
- Recognizing the syndrome is just the start, because many specific causes of acute respiratory distress syndrome require specific therapy.
- Optimal outcomes require both the early recognition of acute respiratory distress syndrome and the identification of the underlying etiology.
- We discuss challenges to recognition of acute respiratory distress syndrome and some specific diseases that may present as acute respiratory distress syndrome, and suggest steps toward diagnosing such diseases.

### INTRODUCTION AND IMPORTANCE OF THE PROBLEM

Acute respiratory distress syndrome (ARDS) is an inflammatory lung injury associated with vascular leak, alveolar filling, and hypoxia,<sup>1</sup> and with vast clinical impact. In 2016, an international, multicenter prospective study found that ARDS represented 10.4% of total intensive care unit admissions and 42% of intensive care unit bed occupancy.<sup>2</sup> In the United States, ARDS was estimated to have an age-adjusted incidence of 86.2 per

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100,000 person-years, accounting for nearly 200,000 cases per year.<sup>3</sup> Despite the application of supportive standards developed through numerous clinical trials, mortality among patients with ARDS remains in the range of 33% to 45%, depending on the severity of illness.<sup>2</sup> Although such numbers do not account for the fact that patients with ARDS may die of concurrent life-threatening conditions rather than from ARDS per se, they are nevertheless staggering. Further, those who survive may experience long-lasting deficits in physical and psychiatric health.<sup>4</sup> Although a discussion of coronavirus disease 2019 (COVID-19) is beyond the scope of this article, it should be emphasized that the ~600,000 deaths in the United States attributed to COVID-19<sup>5</sup>—a disease whose major mortal complication is ARDS<sup>6</sup>—has greatly magnified the aforementioned incidence and mortality and further underscored the importance of ARDS as a clinical problem.

There are many reasons why it is imperative to define ARDS in clear terms. First, although there is no pharmacologic therapy for ARDS, numerous clinical studies have shown that application of ARDS-specific supportive care can substantially improve clinical outcomes.<sup>7–11</sup> Unfortunately, the diagnosis is often missed, with resulting failure to treat patients according to accepted standards of care.<sup>2</sup> Second, the patients studied in mechanistic and clinical trials must be sufficiently defined and/or homogenous to allow for appropriate power calculations, enrollment, and subgroup analyses that can ultimately identify biomarkers and desperately needed therapies.<sup>12</sup> Third, some patients who have a syndrome that is consistent with or resembles ARDS may benefit from particular medications or interventions—such as the withdrawal of an injurious medication, the addition of antimicrobial agents, or immunosuppression. And finally, because mortality remains high for ARDS, defining the syndrome is important for clinical prognostication. The specificity and sensitivity required to meet each of these objectives is distinct, and may be at odds. For instance, the importance of applying low tidal volume ventilation to all patients who might benefit favors inclusivity, whereas clinical trials of pharmacologic agents typically favor exclusivity.

In this article, we review the historical and current definitions of ARDS and discuss the challenges of diagnosing conditions that present as ARDS but do not fit the conceptual framework of increased lung vascular permeability induced by inflammation (such as disseminated malignancy or alveolar proteinosis), and/or those that are included in this framework, but may require specific treatment (such as pneumonia from rare pathogens or drug induced lung injury).

## DEFINITIONS AND THEIR LIMITATIONS

Respiratory distress syndrome, which later became known as acute respiratory distress syndrome, was first described by Ashbaugh and colleagues<sup>13</sup> in a case series of 12 patients with severe hypoxemia, decreased lung compliance, and diffuse alveolar infiltrates on chest radiography. Lacking any distinct biomarkers or signs, the syndrome continues to be defined by an overlap of nonspecific radiographic and clinical features. As agreed upon in the Berlin consensus definition, a diagnosis of ARDS requires bilateral opacities on chest imaging, developing within 7 days, incompletely explained by left heart failure, fluid overload, effusions, collapse, or nodules, and resulting in hypoxemia as defined by an arterial partial pressure of oxygen to fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) ratio of 300 mm Hg or less on a minimum positive end-expiratory pressure (PEEP) of 5 cm  $\text{H}_2\text{O}$ <sup>1</sup> (**Box 1**).

The histologic findings from 6 of 7 of Ashbaugh's patients who died were consistent with the stereotyped injury process later called diffuse alveolar damage (DAD),<sup>13,14</sup>

<b>Box 1</b>			
<b>The Berlin definition of ARDS</b>			
Timing	Within 1 wk of a known clinical insult or new/worsening respiratory symptoms		
Chest imaging <sup>a</sup>	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules		
Origin	Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present		
	Mild	Moderate	Severe
Oxygenation <sup>b</sup>	200 < PaO <sub>2</sub> :Fio <sub>2</sub> ≤ 300 with PEEP or CPAP ≥ 5 cm H <sub>2</sub> O <sup>c</sup>	100 < PaO <sub>2</sub> : ≤ 200 with PEEP ≥ 5 cm H <sub>2</sub> O	PaO <sub>2</sub> :Fio <sub>2</sub> ≤ 100 with PEEP ≥ 5 cm H <sub>2</sub> O
<sup>a</sup> Chest radiograph or computed tomography scan. <sup>b</sup> If altitude is higher than 1000 m, correction factor should be made as follows: PaO <sub>2</sub> :Fio <sub>2</sub> (barometric pressure/760). <sup>c</sup> This may be delivered noninvasively in the mild ARDS group.			

and therefore DAD has historically been considered the pathologic hallmark of ARDS. DAD is characterized by swelling and necrosis of alveolar epithelial cells with resulting hemorrhage and proteinaceous edema, followed days later by hyaline membrane formation, then by type II pneumocyte hyperplasia, fibrosis, and finally resolution.<sup>14</sup> Although the pathophysiologic processes that culminate in DAD and ARDS are incompletely understood, inflammation is almost certainly partially responsible, because the pathology most often follows on the heels of a localized tissue injury such as aspiration, pneumonia, toxic inhalation, sepsis, trauma, fat embolism, pancreatitis, or transfusion. Excellent recent reviews have summarized what is currently known of the pathophysiology that leads to DAD.<sup>5,15,16</sup>

Although ARDS and DAD have often been equated based on Ashbaugh's historical findings, ARDS remains a clinical diagnosis. And although DAD and the aforementioned risk factors remain important aspects of the conceptual framework of ARDS,<sup>1,17</sup> they are excluded from the accepted definitions. DAD is a common pattern of injury and repair that follows diverse tissue insults and is not specific to ARDS.<sup>14</sup> It may be present in patients who do not meet the clinical criteria for ARDS when sufficiently mild and can accompany other dominant histologic patterns. Similarly, the histopathology of ARDS is not limited to DAD. One large study found that, among patients who fit the Berlin criteria, only 45% had histologic evidence of DAD on autopsy, another 49% had findings of multifocal pneumonia, and the remainder was composed of a wide variety of other entities, or no definitive finding at all.<sup>18</sup> Similar findings were observed with the previous widely used American European Consensus definition of ARDS.<sup>19</sup> One interpretation of these discordant findings is that clinical and radiographic criteria are insufficiently specific to define the syndrome. Alternatively, patients with DAD could be considered a subset—or endotype—of ARDS.<sup>20</sup> In favor of the later view, the prevalence of DAD correlates positively with increased severity and duration of illness, but inversely with the application of low tidal volume ventilation.<sup>18,21</sup> All of this could be consistent with a model wherein DAD is a nonspecific pattern that reflects a combination of the initial lung injury and subsequent ventilator-induced lung injury, and upon which a number of pathologies may converge.<sup>20</sup>

In sum, ARDS is a clinical syndrome that results from a wide variety of underlying injuries and is currently defined by the Berlin criteria in deliberately inclusive terms. The current best evidence favors this inclusivity, because patients with diverse risk

factors benefit from low tidal volume ventilation and, when severe, ventilation in the prone position.<sup>22</sup> There is no evidence to suggest that patients with different histologic patterns or risk factors should be treated differently.<sup>22</sup> The current definition does not account for the substantial heterogeneity of disease, which remains a challenge to the development and application of specific diagnostics and treatments. Differences in histology, radiographic findings (dense or patchy vs diffuse ground glass), inciting injury, genetics, or biomarkers may ultimately define distinct disease entities best treated in different ways.<sup>23</sup>

## RECOGNIZING THE SYNDROME OF ACUTE RESPIRATORY DISTRESS SYNDROME

Despite the relatively simple and inclusive nature of current and past definitions,<sup>24</sup> many practical challenges to diagnosing ARDS persist (Fig. 1). For instance, establishing the duration of illness can be challenging if the patient is unable to provide a reliable history or if symptoms attributable to another diagnosis precede the progression to ARDS. Further, the degree of hypoxemia may be challenging to ascertain if arterial blood gas measurements are not easily obtained, as in resource-poor settings, or if the method of supplemental oxygen delivery does not provide PEEP. The Kigali modification, which uses the ratio of oxygen saturation to fraction of inspired oxygen ( $\text{Fio}_2$ ) has been suggested to address the former issue,<sup>25</sup> which seems pragmatic in resource-limited settings. The requirement for PEEP, which was not included in prior definitions of ARDS,<sup>17</sup> presents a progressive challenge because clinicians increasingly use high-flow nasal cannula (HFNC) for patients with acute hypoxemic respiratory failure.<sup>26</sup> This

Recognizing the Syndrome		Identifying the Cause of the Syndrome
<b>Goal:</b> Improve outcomes by implementing proper <u>supportive care</u>		<b>Goal:</b> Treat the <u>underlying conditions</u> that are causing ARDS
<ul style="list-style-type: none"> <li>• Low tidal volume ventilation</li> <li>• Careful fluid management</li> <li>• Prone positioning if severe</li> </ul>		
<b>Pitfalls in recognition</b>	<b>Tips and reminders</b>	<b>Classic Causes</b>
Lack of “classic” radiograph	<ul style="list-style-type: none"> <li>• Bilateral opacities need not be diffuse; may be very mild, patchy, or asymmetric</li> </ul>	<ul style="list-style-type: none"> <li>• Pneumonia</li> <li>• Sepsis (non pulmonary)</li> <li>• Aspiration</li> <li>• Trauma, toxin/smoke inhalations</li> <li>• Pancreatitis</li> </ul>
Use of HFNC: $\text{FIO}_2$ not predictable, PEEP absent	<ul style="list-style-type: none"> <li>• High risk for ARDS if <math>\geq 15\text{L}</math> of 100% <math>\text{O}_2</math> needed to maintain <math>\text{SpO}_2 \geq 90\% - 95\%</math></li> </ul>	<p style="text-align: center;">None likely? Atypical patient features?</p>
Unsure if cardiogenic edema	<ul style="list-style-type: none"> <li>• Dx not mutually exclusive and often coexist</li> <li>• Oxygenation and opacities rapidly improve with treatment of heart failure or volume overload</li> </ul>	<p><b>Zebra</b></p> <ul style="list-style-type: none"> <li>• Rare infections</li> <li>• Drug induced lung injury</li> <li>• Interstitial lung disease:               <ul style="list-style-type: none"> <li>• Acute eosinophilic pneumonia</li> <li>• Cryptogenic organizing pneumonia</li> <li>• NSIP</li> <li>• AE-IPF</li> </ul> </li> <li>• Alveolar hemorrhage and/or vasculitis</li> <li>• Malignancy</li> <li>• Pulmonary alveolar proteinosis</li> </ul>
Unsure if fully explained by nodules, effusion, or collapse	<ul style="list-style-type: none"> <li>• Not mutually exclusive, may coexist</li> <li>• Consider CT and/or ultrasound</li> </ul>	

**Fig. 1.** Two key steps in ARDS care: recognizing the syndrome and identifying the cause. When faced with a possible case of ARDS, clinicians should apply Berlin Criteria (see Box 1), keeping in mind some classic pitfalls that may lead to missed diagnosis, and initiate appropriate supportive care. Once ARDS has been recognized, clinicians should work to identify the underlying cause to provide targeted treatments. Although the diagnosis of the syndrome is purely clinical, the diagnosis of the underlying condition or disease may require specific imaging or diagnostic testing. AEIPF, Acute exacerbations of idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia.

practice shift has become particularly notable during the COVID-19 pandemic.<sup>27,28</sup> Higher HFNC flow rates and  $F_{iO_2}$  deliver correspondingly higher  $F_{iO_2}$  to the trachea (may approach 1.0 at 45 LPM of 100% oxygen), allowing for noninvasive support of patients with severe impairments of gas exchange and accurate assessment of  $P_{aO_2}/F_{iO_2}$ , yet are not included in the current definition of ARDS. Because definitions should be adapted to new developments in clinical medicine (as was the case with the Berlin definition in 2012), perhaps an updated definition of ARDS should include spontaneously breathing patients supported with HFNC who have bilateral chest radiographic infiltrates. Although estimates of  $F_{iO_2}$  are notoriously inaccurate at low flow rates, high flow rates allow for accurate estimates of  $F_{iO_2}$  and therefore calculation of  $P_{aO_2}/F_{iO_2}$ .<sup>26,29</sup>

Additionally, the interpretation of radiographic findings can be challenging. Plain radiographs may miss qualifying opacities that would be detected on computed tomography (CT) scan (thus, the inclusion of CT scans among imaging modalities in the Berlin definition).<sup>1</sup> Further, although many clinicians consider a diffuse distribution of opacities to be necessary for a diagnosis of ARDS, this classic pattern is not required; although opacities must be bilateral and not fully explained by effusions, lobar/lung collapse, or nodules, they may be very mild, patchy, and asymmetric.<sup>1</sup> Confluent bilateral lobar opacities, for instance, are consistent with ARDS so far as other clinical criteria are met, and examples of such are provided in the Berlin definition supplement.<sup>1</sup> Even in cases where bilateral opacities are evident, interobserver variability results in substantial underdiagnosis,<sup>2,30</sup> likely owing to misconceptions about qualifying opacities, as discussed elsewhere in this article.<sup>16</sup> Furthermore, it may be very difficult to determine that opacities are not fully explained by effusions, lobar/lung collapse, or nodules. Nearly 28% of patients with clinically diagnosed ARDS were found on autopsy to have abscess, emphysema, or no pulmonary abnormality at all,<sup>18</sup> indicating the difficulty of excluding nodules, effusions, and atelectasis.

Finally, the exclusion of cardiogenic pulmonary edema is likely the single most difficult challenge to the diagnosis of ARDS, because differentiating cardiogenic edema from ARDS is rarely possible with chest radiograph alone.<sup>31</sup> Compounding this challenge is that the 2 conditions may coexist.<sup>10</sup> Cardiogenic pulmonary edema refers to the accumulation of fluid within the pulmonary interstitial and/or alveolar spaces as a result of elevated left atrial pressures and that develops through elevated hydrostatic pressure gradients rather than alveolar or vascular barrier disruption.<sup>32</sup> Although the left ventricular dysfunction (either systolic or diastolic) is most often to blame, cardiogenic pulmonary edema can also result from valvular disease, severe systemic hypertension (hypertensive emergency), or systemic volume overload such as in renal or liver disease and over-resuscitation with intravenous fluids. In addition to clinical history, an examination consistent with cardiac dysfunction (gallops, murmurs, displaced point of maximal impulse) or elevated right-sided pressures (elevated jugular venous pressure, peripheral edema), and related radiographic (pulmonary venous congestion, cardiomegaly, pleural effusions), laboratory (elevated B-type natriuretic peptide/N-terminal pro-BNP [BN/NT-proBNP] or troponin) or echographic features (diastolic or systolic dysfunction, valvular disease, a plethoric inferior vena cava), or occasionally right heart catheterization can be used to support the diagnosis of cardiogenic pulmonary edema. When these diagnostic clues are not definitive, a successful trial of diuresis, when not contraindicated owing to competing organ interests, may seal the diagnosis. Reexpansion pulmonary edema, an infrequent iatrogenic complication of thoracotomy or thoracentesis, or negative pressure pulmonary edema<sup>33</sup> are both likely examples of hydrostatic pulmonary edema<sup>34</sup> that may occur in the absence of systemic fluid

overload, but are less likely to be confused with ARDS given the specific clinical context in which it occurs.

It is important to note that, although the probability of cardiogenic pulmonary edema is greatly increased if the patient has a history of any cardiac disease or has advanced renal or liver disease, such conditions may also correlate with risk factors for ARDS (such as aspiration or sepsis), and their presence does not exclude a diagnosis of ARDS. In the autopsy study discussed elsewhere in this article, 8% of patients with cardiogenic pulmonary edema also had DAD,<sup>18</sup> whereas a substantial portion of patients with ARDS may have concurrent cardiogenic edema. Conversely, in the FACTT trial, 29% of patients with ARDS also had an elevated pulmonary arterial wedge pressure of greater than 18 mm Hg.<sup>10</sup> Therefore, only when the clinical criteria are resolved by diuresis alone can concurrent ARDS be ruled out.

### **RECOGNIZING ACUTE RESPIRATORY DISTRESS SYNDROME IS JUST THE START: DIAGNOSING THE CAUSE OF ACUTE RESPIRATORY DISTRESS SYNDROME**

Although there is no proven pharmacologic therapy for ARDS per se, a number of conditions that present as ARDS by the Berlin criteria do have specific therapies that should be used alongside ARDS-appropriate supportive care. Such conditions have often been called mimics, but may be better understood as specific pulmonary diagnoses that can cause or present as ARDS. These are in addition to classic extrapulmonary insults (sepsis, trauma, fat embolism, acute pancreatitis), which may also require disorder-specific treatments. Although the number of pulmonary insults leading to hypoxemia and bilateral alveolar infiltrates are too many to exhaustively list in any review, we will briefly summarize some of the entities that frequently meet all Berlin criteria, and may demand specific treatments (see [Fig. 1](#)).

#### ***Infectious Pneumonia***

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Infectious pneumonia is one of the most common pathologies presenting as ARDS, with studies showing anywhere from 27.0% to 59.4% of patients with ARDS with pre-existing or concurrent diagnosis of pneumonia, and as many of 37% to 65% of ARDS courses complicated by ventilator-associated pneumonia.<sup>35,36</sup> Current numbers are undoubtedly higher in the setting of the current COVID-19 pandemic. Given the very high co-occurrence of pneumonia and/or sepsis with ARDS, it is generally appropriate to treat all patients with ARDS with broad spectrum antibiotics while awaiting culture results. However, a diligent search for the causative organism is indicated to ensure adequate antimicrobial coverage. Typical bacterial organisms, atypical bacterial, viral, fungal, or parasitic infections should all be considered as potential etiologies of ARDS.<sup>5</sup> Patient risk factors such as age, comorbid pulmonary disease, HIV status, other severe immunocompromise, or geographic travel or origins may contribute to diagnostic considerations.<sup>5</sup> In general, we recommend blood, respiratory, and urine cultures and respiratory viral testing by direct fluorescent antibody testing or polymerase chain reaction for all patients with possible ARDS. If all of these cultures are negative, cardiogenic pulmonary edema is unlikely, no other obvious provoking factor for ARDS is present (eg, known gastric aspiration or other etiology of sepsis), and/or the patient is failing to improve on empiric antibiotics, we recommend consideration for further testing in consultation with an infectious disease specialist. Such testing may include bacterial or fungal antigen testing of blood or urine, bronchoalveolar lavage (BAL), serologies, or sequencing/polymerase chain reaction testing depending on the patient characteristics and concurrent symptoms. Again, although a dedicated



discussion of COVID-19 is beyond the scope of this article, the proliferation of data supporting the use of steroids<sup>37</sup> and antiviral therapy<sup>38–41</sup> to treat ARDS owing to COVID-19 perfectly underscores the need to diagnose both the syndrome of ARDS and its specific cause to optimize outcomes.

### ***Chemical or Radiation Pneumonitis***

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Direct or indirect chemical injury to the lung is another common cause of ARDS. Aspiration of gastric contents can present as ARDS and follow a highly variable course, with some patients rapidly improving over 24 to 36 hours and other experiencing a protracted illness lasting days or weeks.<sup>42</sup> A variety of medications, most often anti-neoplastic therapies (cytotoxic or targeted small molecule), have been associated with pneumonitis that may be severe enough to meet Berlin criteria and can occur anytime from days to weeks after treatment.<sup>43</sup> Cessation of the inciting drug and consideration for steroids may aid in the resolution of ARDS caused by such medications.<sup>43</sup> Similarly, radiation can cause pneumonitis, often but not always localized near the targeted lesion, and usually occurring weeks after the radiation treatment.<sup>44</sup> We suggest consideration of such entities if the patient has recently received antineoplastic therapy, cardiogenic pulmonary edema is ruled out, a microbiologic workup including bronchoscopy is unrevealing, and there are no other obvious potential etiologies of ARDS.

### ***Alveolar Hemorrhage***

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Diffuse alveolar hemorrhage (DAH) may also present as ARDS. Hemorrhage can be bland (ie, not associated with vascular inflammation) or owing to capillaritis. In bland DAH, hemorrhage can result when elevated cardiac filling pressures (as in cardiogenic pulmonary edema) occur in the setting of coagulopathy or when contusion follows trauma. Alveolar hemorrhage owing to contusion should be considered when alveolar bleeding is coincident with pneumothorax, pneumatoceles, bony fractures, and cutaneous bruising. In contrast, capillaritis can be provoked by a wide range of insults including anti-neutrophil cytoplasmic antibody-associated or other small vessel vasculitides, connective tissue diseases, anti-glomerular basement membrane disease, certain drugs, and infections.<sup>45,46</sup> Hemoptysis is a classic presenting symptom of DAH, although it is absent in at least one-third of patients, and a decrease in hemoglobin may also be observed. DAH is classically diagnosed by BAL showing an increase in red blood cells in serial lavage. Although DAD and DAH may have nearly identical radiologic appearances on the chest radiograph, highly experienced radiologists can sometimes make the diagnosis of DAH based on the differential radiodensity using a CT scan. The identification of DAH does not distinguish between bland hemorrhage and capillaritis, and should be followed by an investigation into the specific cause.

### ***Inflammatory and Autoimmune Causes***

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There are a number of noninfectious entities, many of which have an inflammatory and/or autoimmune component, that can present as ARDS. Acute eosinophilic pneumonia (AEP), for example, can cause the acute onset of hypoxia and diffuse pulmonary opacities, and typically occurs either after a recent inhalation or without any clear precipitating event in previously healthy young adults. The diagnosis of AEP can be made when the differential on BAL shows more than 25% eosinophils without known causes of eosinophilic pneumonia<sup>47</sup>; this finding is in contrast with other etiologies of ARDS, in which the BAL is more typically neutrophilic. Because eosinophilic pneumonia is exquisitely and rapidly steroid responsive, AEP is a diagnosis not to be

missed. Cryptogenic organizing pneumonia can have a similar appearance to AEP, although it is more likely to present with a subacute course. In contrast, acute fibrinous organizing pneumonia, an exceedingly rare entity with an unknown cause, can present with either a subacute or acute course. It is distinguishable only pathologically through the finding of intra-alveolar fibrin balls and organizing pneumonia, and a notable absence of DAD.<sup>48</sup> In those patients who present with an acute course, there is no accepted treatment, and the disease is almost uniformly fatal. Vasculitides, although capable of producing almost any type of pulmonary infiltrate, most often produce an ARDS-like picture if presenting as DAH or AEP, and otherwise are likely to have subacute onset. Finally, although more often chronic or subacute in presentation, interstitial lung diseases in patients with connective tissue disease such as rheumatoid arthritis, Sjogren syndrome, or polymyositis/dermatomyositis can occasionally present with fulminant course and bilateral ground glass opacities, often in the pathologic patterns of nonspecific interstitial pneumonia or organizing pneumonia. Although interstitial lung disease can precede other systemic symptoms, patients with other indicators of connective tissue disease, such as rash, myositis, neuritis, renal impairment, or arthritis, should be considered for these specific diagnoses.

### ***Disseminated Malignancy***

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Although more commonly presenting with lymphangitic carcinomatosis, in which tumor cells engorge the lymphatic vessels including in the lungs, or as random nodules suggestive of hematogenous spread, aggressive and disseminated cancers can present with almost any radiographic pattern. Although more often subacute in tempo, and usually in patients with a known prior diagnosis of cancer, malignancy occasionally presents acutely and should be considered in the differential diagnosis of ARDS when a signs or history of advanced malignancy are present.

### ***Pulmonary Alveolar Proteinosis***

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Pulmonary alveolar proteinosis is a rare, pauci-inflammatory condition in which lipoproteinaceous material accumulates in the distal air spaces as a result of impaired granulocyte macrophage colony stimulating factor and/or alveolar macrophage function. In addition to congenital forms, acquired forms may result from autoantibodies that interfere with granulocyte macrophage colony stimulating factor signaling or to inhalations that cause direct macrophage toxicity, such as exposure to some dusts and metals. The onset is more often insidious than acute, but occasionally can present as ARDS, particularly in the case of superinfection (*Nocardia* being a classic opportunist in this setting, but certainly not the only possibility). The classic crazy-paving pattern of pulmonary alveolar proteinosis is neither sensitive nor specific, and BAL showing copious periodic acid-Schiff-positive material or sometimes biopsy are needed to make the diagnosis. Specific treatment depends on cause of pulmonary alveolar proteinosis, but most commonly includes whole lung lavage and/or granulocyte macrophage colony stimulating factor supplementation.

### ***Acute Exacerbation of Idiopathic Pulmonary Fibrosis***

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Acute exacerbation of idiopathic pulmonary fibrosis (AEIPF) is a form of acutely exacerbated hypoxemic respiratory failure with unclear provoking factor that occurs in a patient with preexisting IPF, and frequently presents as ARDS.<sup>49</sup> Although a sizable proportion of the available literature suggests usual risk factors for ARDS—such as infection or aspiration—there is often no definitive predisposing event. The prognosis for IPF, which is already poor, is dramatically worsened by the development of AEIPF. On occasion, AEIPF will be the patient's first presentation with IPF. Radiographic

findings consistent with usual interstitial pneumonia (reticulations, honeycombing, and traction bronchiectasis) overlaid with the typical ground glass appearance of DAD supports the diagnosis of AEIPF when other causes of ground glass opacities are unlikely or ruled out. Such patients may have stigmata of chronic hypoxemia, such as clubbing or polycythemia. Steroids are typically given in accordance with expert opinion, despite the lack of clinical trials supporting their efficacy, as well other immunosuppressants, such as rituximab.<sup>49</sup>

### ***Other Specific, Nonclassical Causes of Acute Respiratory Distress Syndrome***

Neurogenic pulmonary edema is a form of noncardiogenic pulmonary edema that specifically occurs in patients with severe neurologic injury, and is possibly attributable to catecholamine surge.<sup>50</sup> Although the etiology of neurogenic pulmonary edema is hydrostatic in approximately one-half of patients, it is likely owing to increased vascular permeability in the other half.<sup>51</sup>

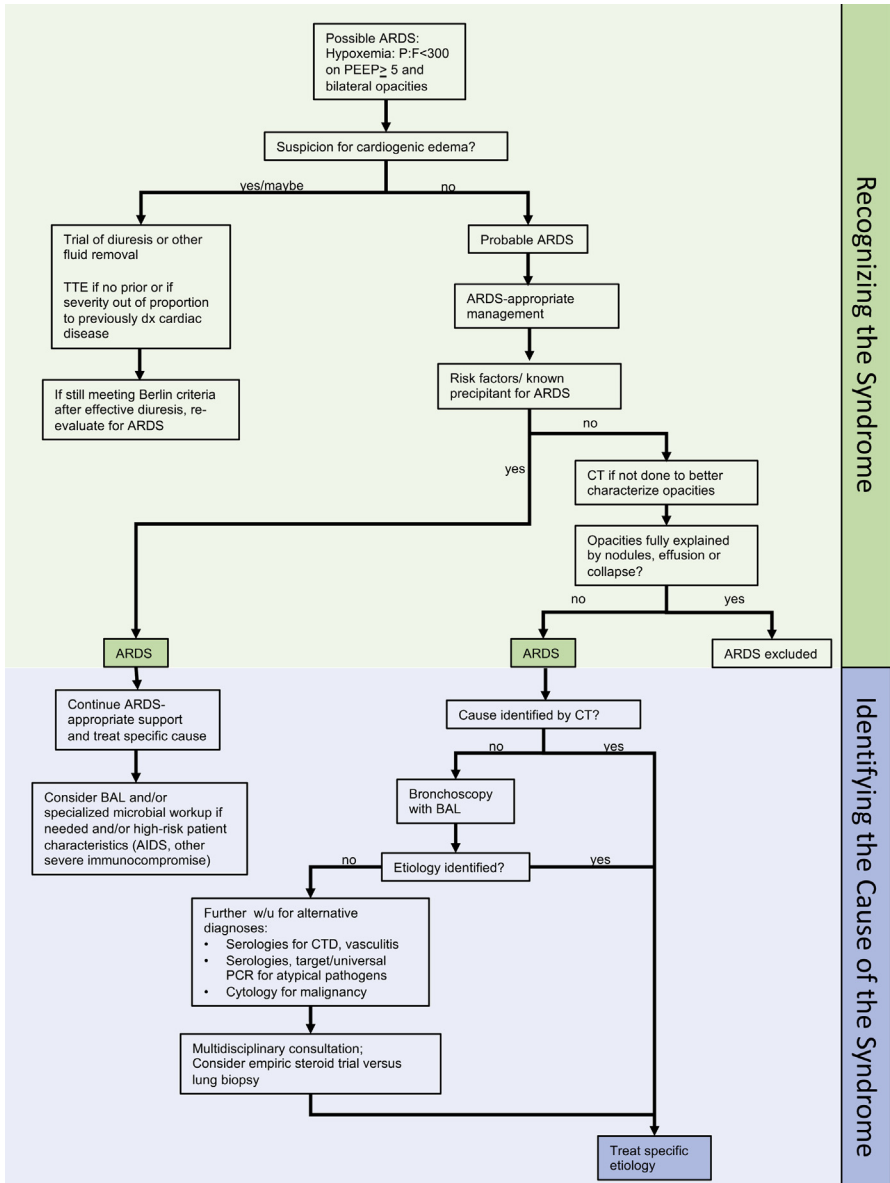
E-cigarette or vaping product use-associated lung injury is a very recently described inhalation pneumonitis<sup>52</sup> that occurs in patients with history of vaping within the preceding 90 days,<sup>53,54</sup> likely owing to toxicity from vitamin E acetate, a component of e-liquids.<sup>55,56</sup> E-cigarette or vaping product use-associated lung injury should be suspected especially in teenagers or young adults (who are less likely to have other risk factors for ARDS), particularly if accompanied by gastrointestinal symptoms and/or lung function testing abnormalities. Although no clinical trials have yet tested the usefulness of steroids, most cases are so treated based on expert opinion.

Finally, acute interstitial pneumonia, although often listed as a separate entity, is a likely form of idiopathic ARDS with fulminant course and high mortality.<sup>57</sup> Although again lacking evidence to support the approach, high-dose steroids are often attempted.

## **PRACTICAL SUGGESTIONS FOR IDENTIFYING ACUTE RESPIRATORY DISTRESS SYNDROME AND MAKING THE SPECIFIC DIAGNOSIS**

To identify ARDS, we recommend an initial focus on the exclusion of cardiogenic pulmonary edema and inclusion of ARDS based on Berlin criteria. Once the syndrome is recognized and appropriate ARDS-directed supportive therapy initiated, we recommend proceeding to a consideration of the cause of ARDS. To that end, we begin with an investigation of classic etiologies using history, examination, and basic laboratory studies, followed by a consideration of rare causes (zebras) and the performance of further diagnostic maneuvers when an underlying diagnosis is not evident with initial studies (**Fig. 2**). For the purposes of this discussion, we assume that radiographic findings and the degree of hypoxemia are consistent with the Berlin criteria, with one exception. If the patient requires 15 to 20 LPM of 100% O<sub>2</sub> delivered by HFNC or nonrebreather to maintain a hemoglobin saturation of 90% to 95%, we would strongly consider the possibility of ARDS even in the absence of noninvasive or invasive mechanical ventilation with PEEP. Accordingly, careful monitoring of such patients in the intensive care unit for the need for intubation and lung protective ventilation is recommended.

An evaluation for ARDS and its causes should begin with a thorough history and examination. The history should review the duration of illness and precipitating events, as well as the relevant past medical, family, and social history, including substance use, malignancy, and connective tissue disease. A history of cardiac, renal, or liver disease, and/or of substantial volume resuscitation before intensive care unit arrival should increase suspicion for cardiogenic pulmonary edema.



**Fig. 2.** A suggested approach to recognition and treatment. In caring for the hypoxemic patient with bilateral opacities on either plain radiograph or CT scan, clinicians should determine whether opacities qualify for ARDS and evaluating for cardiogenic pulmonary edema. A workup for specific underlying etiologies should follow and may include advanced imaging, bronchoscopy, specific laboratory testing, biopsy, and/or empiric trials of therapy. A suggested algorithm is presented here with the recognition that clinician preference or resource limitations may require alternative or parallel approaches. BAL, bronchoalveolar lavage; CTD, connective tissue disease; PCR, polymerase chain reaction; TTE, transthoracic echocardiogram.

The examination should start with an evaluation for pulmonary or extrapulmonary infection and a systemic inflammatory response or shock; whereas cardiogenic shock may favor the diagnosis of cardiogenic pulmonary edema, distributive shock would favor sepsis and ARDS. In the absence of shock, the examination should focus first on identifying signs of heart failure or systemic volume overload. Pulmonary examinations are often nonspecific. Rales may or may not be present. Egophany, bronchial breath sounds, or dullness to auscultation/percussion may suggest effusions or atelectasis (which are insufficient to diagnose ARDS and could suggest volume overload), or alternatively, consolidations consistent with ARDS owing to pneumonia. Dental, joint, and skin examinations may reveal potential causes of infection or stigmata of vasculitis, connective tissue disease, or coagulopathy. Point-of-care ultrasound examinations can reasonably be considered an extension of the modern critical care examination<sup>58</sup> and can aid in the qualitative characterization of a decrease in left ventricular ejection fraction, a plethoric inferior vena cava and/or jugular veins, dense pulmonary consolidations, and pericardial, pleural, or intra-abdominal fluid collections.

As a part of the initial workup, we recommend obtaining a complete blood count; basic metabolic panel; coagulation and liver function tests; respiratory, blood, and urine cultures for bacterial pathogens; direct fluorescent antibody testing or polymerase chain reaction panel for common viral and atypical bacterial pathogens; and BNP or NT-proBNP and troponin. Procalcitonin is not required but can be valuable in patients who are suspected to have sepsis without a clear source.

If, after the initial workup as described, the possibility of cardiogenic pulmonary edema remains, we recommend a trial of diuresis when possible (ie, not contraindicated by other organ failure such as distributive shock, and renal function sufficient to achieve diuresis). If this is not possible, or the possibility of cardiogenic pulmonary edema remains even after a reasonable volume of diuresis, we suggest formal transthoracic echocardiography. If none of these evaluations is sufficient to evaluate cardiac function and ensure normal fluid status, right heart catheterization may occasionally be helpful.

In addition to new imaging (chest radiograph or CT scan of the chest), it is imperative that clinicians review any prior imaging, because persistent abnormalities argue for underlying subacute or chronic conditions. Plain radiographs are sufficient to evaluate most cases of ARDS, but CT scanning may be useful if there is no typical risk factor for ARDS, cardiogenic pulmonary edema is unlikely, a disqualifying pulmonary finding (such as nodular or cavitary disease) is suspected, or an atypical cause of ARDS such as hemorrhage or interstitial lung disease is suspected. A CT scan can also be helpful in identifying findings that may be missed on plain radiograph (such as mild ground glass, reticulations, or honeycombing suggestive of interstitial lung disease, or bilateral opacities that were obscured by a diaphragmatic dome or mediastinal structures). Additionally, CT scans may assist with bronchoscopic planning.

When, despite the examinations as described, the underlying etiology of ARDS cannot be identified, bronchoscopy is suggested. In practice, high  $\text{FiO}_2$  or PEEP requirements often preclude the ability to perform bronchoscopy. However, when possible, bronchoscopy with BAL can identify aspirated or inhaled material, provide a substrate to test for infectious etiologies, and provide cell counts to evaluate for entities such as eosinophilic pneumonia or DAH. When safe, we recommend bronchoscopy in patients with ARDS in whom a specific underlying etiology has not been identified, including in which an initial infectious workup is negative or the patient is not improving with empiric treatment, and/or when there is high suspicion for DAH based on classic presenting symptoms.

Lung biopsy has no role in confirming the diagnosis of ARDS, because the diagnosis is clinical rather than histologic.<sup>59</sup> However, biopsy may rarely be considered when treatable causes are suspected—for instance, when the patient has no typical risk factors for ARDS, is very young without comorbid disease, there is a high suspicion for a specific diagnosis such as interstitial lung disease—or the patient is worsening rather than improving after several days of appropriate ARDS care without other available explanation.<sup>59</sup> One important exception to this general approach is in suspected AEIPF; in those cases, owing to high associated morbidity, biopsy is usually avoided in favor of empiric therapy.<sup>49</sup> AEIPF aside, case reports and meta-analyses do support the value of biopsy in a very limited set of patients to guide therapy.<sup>60–62</sup> In these studies, however, the majority of cases in which biopsy guided therapy were atypical infections or interstitial processes with possible steroid responsiveness. With the advent of increasingly sensitive diagnostic modalities for atypical infections—such as universal polymerase chain reaction—the relative usefulness of biopsy may decline. Moreover, a significant proportion of patients undergoing biopsy may already be undergoing a therapeutic steroid trial.<sup>61</sup> Because the risk of complications from lung biopsy is significant, the pursuit of biopsy versus a therapeutic trial of steroids when infection is ruled out must be considered on an individual basis, generally in multidisciplinary consultation.<sup>59</sup>

## SUMMARY

ARDS is a syndrome, not a disease. To save lives, it is essential to recognize ARDS and provide optimal supportive care with lung protective ventilation<sup>8</sup> and sensible fluid management.<sup>10</sup> ARDS can be the manifestation of myriad underlying conditions, however, and optimal outcomes require identification and treatment of the underlying cause or causes, in addition to recognition of the syndrome itself. An improved understanding of the diverse cellular and molecular processes that lead to ARDS will foster the development of biomarkers and new treatments, and usher in the era of personalized medicine for our patients with this devastating syndrome.

## CLINICS CARE POINTS

- The diagnosis of ARDS is based purely on clinical criteria (currently defined by expert consensus according to the Berlin criteria), and does not require any knowledge of the underlying cause or histopathology.
- Clinicians should maintain a high index of suspicion for ARDS in any patient with hypoxia. Although the Berlin criteria require arterial blood gas measurements and PEEP, clinicians may recall that a patient with normal hemoglobin dissociation curve has a  $\text{PaO}_2/\text{FiO}_2$  ratio of 300 mm Hg or greater if their peripheral saturation is less than 90% on room air. Therefore, the likelihood of hypoxemia qualifying for ARDS further increases with increasing levels of supplemental oxygen needed to maintain a saturation of 90% to 95%.
- Any bilateral airspace opacities that can be captured on plain radiographs or a CT scan qualify if not entirely explained by collapse or effusion. They need not be diffuse, of particular density, or in any specific distribution.
- The overlap between ARDS and DAD is incomplete; neither histology nor a radiographic correlate to DAD are required.
- Although classic causes of ARDS are well-described, almost any pulmonary insult can cause ARDS. Specific diseases that have been called mimics are still consistent with a diagnosis of ARDS if clinical criteria are met.

- Cardiogenic pulmonary edema and ARDS frequently coexist. An index of suspicion for ARDS should remain unless the opacities and hypoxemia that might qualify for ARDS are resolved with treatment of cardiogenic edema alone
- Recognizing ARDS and implementing appropriate supportive care is just the start. Once the syndrome is recognized, clinicians should work to identify and treat the underlying cause using tools such as serology, specialized microbial detection methods, bronchoscopy, radiographic modalities, biopsy, and/or empiric trials of treatment.

## DISCLOSURE

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