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The ten diseases that look like ARDS

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Introduction

Five decades ago, Ashbaugh and colleagues first used the term "syndrome of acute respiratory distress" (ARDS) to describe 12 patients with respiratory failure [1]. The hallmarks of the syndrome were hypoxemia refractory to supplemental oxygen, diffuse radiographic opacities, and histologic evidence of diffuse alveolar damage (DAD) in most but not all fatal cases. Over three decades later, the widely adopted American–European Consensus Conference (AECC) definition of ARDS facilitated research and aided cross-study comparison and translation of research findings to clinical practice [2]. The new Berlin definition refined the AECC definition by explicitly defining acute onset. Since the majority of patients destined to develop ARDS do so within the first 72 h after recognition of a clinical risk factor, with the rest progressing within a week, the Berlin definition explicitly defined "acute onset" as 7 days [3]. It defined mild, moderate, and severe ARDS with explicit ranges of PaO_2/FiO_2. It also attempted to improve the poor interobserver agreement on the AECC radiographic criteria by explicitly describing qualifying opacities and providing example radiographs [4, 5]. As left atrial hypertension and ARDS may coexist, the Berlin definition abandoned the pulmonary artery occlusion pressures exclusion [6]. Finally, the Berlin definition added the requirement for a known clinical risk factor (e.g., pneumonia, sepsis, trauma, etc.), and if none is apparent then additional testing is recommended to exclude congestive heart failure. Both the AECC and the Berlin definition retain the central elements of Ashbaugh's original description. However, both the definitions have only moderate sensitivity and specificity for identifying patients who have DAD on post mortem examination, even in the severe subgroup of the Berlin definition [7, 8]. Moreover, lung biopsy findings in patients with what is assumed to be unresolving ARDS frequently show a number of pathologic entities other than DAD. From our clinical experience, we discuss ten of these clinical entities that may be mistaken for ARDS.

Ten diseases that may be mistaken for ARDS

Table 1 lists ten clinical entities that may be mistaken for ARDS. While it is beyond the scope of this brief report to outline a diagnostic approach to all of these entities, we offer a few observations from clinical experience. While some entities may present in an accelerated time course of several–many days, which would be consistent with the time course for ARDS, more typically they present with a longer time course. This should raise suspicion that the clinical problem is something other than ARDS. Another clinical clue is the absence of a known clinical risk factor for ARDS; or if a clinical risk factor has been identified and treated appropriately (for example, pneumonia),

Table 1 Ten clinical entities that may be mistaken for acute respiratory distress syndrome

	Typical time course for symptoms to develop	Associated symptoms and signs	Characteristic radiographic signs	Bronchoalveolar lavage findings
Acute respiratory distress syndrome (ARDS)	Up to 7 days	Cough, tachypnea with inflammatory condition such as severe infection, severe trauma, aspiration	Bilateral opacifications that may be interstitial or alveolar; ground glass and more dense opacifications on chest CT	Increased neutrophils, especially in earlier stages
Congestive heart failure, pulmonary edema	Variable from very acute (hour) to chronic (months) depending on type of heart disease	Peripheral edema, dyspnea, orthopnea, chest pain	Interstitial or alveolar opacifications, usually central but can be diffuse or asymmetric; pleural effusions right more than left, cardiomegaly, vascular congestion	Pink, frothy fluid without acute or chronic cellular inflammation
Idiopathic pulmonary fibrosis (usual interstitial pneumonitis)	Variable but usually over many weeks, months, few years	Dry cough, fine "Velcro" crackles, dyspnea on exertion and at rest in advanced stages	Diffuse interstitial markings, traction bronchiectasis, honeycombing, predominantly in bases, scattered ground glass opacification	Increased neutrophils
Cryptogenic organizing pneumonia (bronchiolitis obliterans with organizing pneumonia)	Variable, but usually over few weeks–few months	Cough, fever, dyspnea, malaise	Bilateral, frequently peripheral opacifications; CT may show diffuse or patchy ground glass opacifications, patchy air-space opacification, and small nodules	Increased cells, predominantly lymphocytes but also increased neutrophils and eosinophils
Nonspecific interstitial pneumonitis	Variable, but usually over weeks–months	Dry cough, dyspnea, fatigue; may be associated with connective tissue disease	Patchy ground glass opacification, interstitial opacifications, symmetric, peripheral, subpleural	Increased lymphocytes
Granulomatosis with polyangiitis (Wegener's granulomatosis)	Variable, but usually over weeks–months	Cough, dyspnea, malaise, hemoptysis; may present with sinusitis or glomerulonephritis	Diffuse alveolar and interstitial opacifications; multiple nodules 2–8 cm diameter, frequently with cavitation; air space consolidation; diffuse alveolar opacifications if pulmonary hemorrhage	Variable depending on activity of disease and treatment; increased neutrophils, eosinophils, and lymphocytes may be seen; increased ratio of immunoglobulin G (IgG) to albumin compared with serum
Diffuse alveolar hemorrhage	Days–few weeks	Cough, hemoptysis, dyspnea; may present with granulomatosis with polyangiitis or systemic lupus erythematosus, bone marrow transplantation, or exposure to cytotoxic drugs	Diffuse alveolar infiltrates, usually bilateral but can be asymmetric and may be associated with nodules if granulomatosis with polyangiitis, some of which may cavitate	Increasingly bloody lavage return with multiple aliquots
Goodpasture's syndrome	Variable but usually progresses over days–weeks	Cough, hemoptysis, hypoxemia; may present with acute kidney failure	Bilateral predominantly alveolar opacifications, nonspecific	Increasingly bloody lavage return with multiple aliquots
Acute hypersensitivity pneumonitis	Within several hours of exposure to offending antigen	Cough, dyspnea, fatigue	Diffuse interstitial opacifications; ground glass on CT	Increased lymphocytes
Acute eosinophilic pneumonia	Usually less than 10 days	Cough, dyspnea, chest pain, crackles, hypoxemia	Diffuse interstitial opacifications, alveolar when more advanced; small pleural effusions; ground glass and dense opacifications on CT	Eosinophilia
Drug-induced lung disease	Variable, but usually over several months	Cough, dyspnea, hypoxemia after exposure to amiodarone, bleomycin, and many others	Variable, can present as interstitial (more likely) or alveolar opacifications	Variable; amiodarone toxicity may involve alveolar proteinosis; acute and chronic inflammation

progression should stimulate consideration of other entities. Occasional signs and symptoms (e.g., hemoptysis, association with rheumatologic conditions, or with glomerulonephritis) may distinguish an entity from ARDS. There is substantial overlap in the radiographic findings between ARDS and these entities, but some findings may distinguish some entities from ARDS (e.g., honeycombing in pulmonary fibrosis and cavitary nodules in granulomatosis with polyangiitis) [9]. Some bronchoalveolar lavage findings may also help to distinguish some of these entities from ARDS as noted in Table 1 [10]. A single-center study suggested that open lung biopsy in patients with suspected ARDS may improve outcomes if it contributes to management [11]. In general, the combination of a careful history and physical examination, serologic testing for connective tissue disease and vasculitis, computed tomography (CT) scan, and bronchoscopy findings as presented in Table 1 should limit the need for open lung biopsy to establish a diagnosis in enigmatic cases that masquerade as ARDS.

Implications for treatment

If a patient with one of these ten ARDS mimics requires mechanical ventilation, there may be a substantial risk of ventilator-induced lung injury because inflammatory processes increase the vulnerability of the lung parenchyma to mechanical stress. Moreover, the volume of aerated lung is reduced, making the aerated lung vulnerable to overdistension. Therefore, we recommend using a lung-protective approach, as in ARDS, with an initial tidal volume goal of approximately 6 ml/kg predicted body weight [12]. The optimal level of positive end-expiratory pressure (PEEP) in ARDS is still controversial, and we know of no data to guide us in the use of PEEP in patients with the entities described in Table 1.

Whereas use of steroids in unresolving ARDS remains a matter of debate [13, 14], some of the disease entities in Table 1 should prompt clinicians to start steroids without delay. This holds true for systemic lupus, alveolar hemorrhage complicating polyangiitis and Goodpasture's syndrome, acute eosinophilic pneumonia, and most patients with nonspecific interstitial pneumonitis. Other diagnoses will require additional therapies (such as plasmapheresis and immunosuppressive therapy for Goodpasture's syndrome and additional immunosuppressive therapy for polyangiitis). Some require a careful search for an environmental or occupational exposure (hypersensitivity pneumonitis) or an offending drug exposure to prevent recurrence or progression and improve clinical outcomes. Close interaction with a pneumologist and/or a physician skilled in systemic diseases is often helpful to coordinate care.

The distinction between ARDS and some of the other entities may have important prognostic implications. Although the mortality rate from ARDS is high, most patients recover from the acute process, and many return to productive lives. In contrast, idiopathic pulmonary fibrosis (IPF) progresses relentlessly, leading to irreversible respiratory failure. If the diagnosis of IPF can be established before onset of respiratory failure, patients can be counseled about their condition and make more informed decisions about end-of-life care.

Conflicts of interest On behalf of all authors the corresponding author states that there is no conflict of interest related to this manuscript.

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