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REVIEW

Diagnostic workup for ARDS patients

Laurent Papazian[1,2*], Carolyn S. Calfee[3], Davide Chiumello[4,5], Charles-Edouard Luyt[6,7], Nuala J. Meyer[8], Hiroshi Sekiguchi[9], Michael A. Matthay[3] and Gianfranco Umberto Meduri[10]

Abstract

Acute respiratory distress syndrome (ARDS) is defined by the association of bilateral infiltrates and hypoxaemia following an initial insult. Although a new definition has been recently proposed (Berlin definition), there are various forms of ARDS with potential differences regarding their management (ventilator settings, prone positioning use, corticosteroids). ARDS can be caused by various aetiologies, and the adequate treatment of the responsible cause is crucial to improve the outcome. It is of paramount importance to characterize the mechanisms causing lung injury to optimize both the aetiological treatment and the symptomatic treatment. If there is no obvious cause of ARDS or if a direct lung injury is suspected, bronchoalveolar lavage (BAL) should be strongly considered to identify microorganisms responsible for pneumonia. Blood samples can also help to identify microorganisms and to evaluate biomarkers of infection. If there is no infectious cause of ARDS or no other apparent aetiology is found, second-line examinations should include markers of immunologic diseases. In selected cases, open lung biopsy remains useful to identify the cause of ARDS when all other examinations remain inconclusive. CT scan is fundamental when there is a suspicion of intra-abdominal sepsis and in some cases of pneumonia. Ultrasonography is important not only in evaluating biventricular function but also in identifying pleural effusions and pneumothorax. The definition of ARDS remains clinical and the main objective of the diagnostic workup should be to be focused on identification of its aetiology, especially a treatable infection.

Keywords: ARDS, CT scan, Ultrasonography, BAL, Diffuse alveolar damage, Personalized medicine, Phenotype–endotype

Introduction

Acute respiratory distress syndrome (ARDS) is defined by the association of bilateral infiltrates and hypoxaemia following an initial insult. A new definition has been recently proposed [1, 2]. However, one can consider that this definition lacks specificity. The recent Lungsafe survey showed that ARDS is frequently underdiagnosed by clinicians [3]. As a consequence protective mechanical ventilation is not always implemented in patients who are not identified as having ARDS. Another key point is that there are various forms of ARDS with potential differences regarding their management (i.e. positive end-expiratory pressure [PEEP] setting, prone positioning use, neuromuscular blockade and occasionally corticosteroids). Furthermore, adequate treatment of the responsible cause is a crucial element in ARDS outcome. Common risk factors associated with ARDS are the following: pneumonia, non-pulmonary sepsis, aspiration of gastric contents, major trauma, pulmonary contusion, pancreatitis, inhalational injury, severe burns, non-cardiogenic shock, drug overdose, multiple transfusions or transfusion-associated acute lung injury (TRALI), pulmonary vasculitis and drowning [1].

Recent improvements in ARDS outcome are mainly related to the decrease in iatrogenic events rather than

*Correspondence: laurent.papazian@ap-hm.fr
[1] Assistance Publique - Hôpitaux de Marseille, Hôpital Nord, Réanimation des Détresses Respiratoires et des Infections Sévères, 13015 Marseille, France
Full author information is available at the end of the article

Take-home message: Although a new definition has been recently proposed, there are various forms of ARDS with potential differences regarding their management. The main objective of the diagnostic workup is to focus on the identification of its aetiology.

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specific treatments, including but not limited to a decreased incidence of ventilator-induced lung injury, reduced use of sedation, reasonable fluid management and improved management of infections. It is therefore mandated to recognize the insult causing lung injury to better adapt both the aetiological treatment and the symptomatic treatment (mainly mechanical ventilation). In the following sections, we will identify which priorities in diagnostic procedures to do to identify the cause of ARDS and to improve the management.

Initial microbiological assessment of ARDS

As pneumonia is the leading cause of ARDS [4], there is the need to adequately identify the pathogen(s) responsible for infection. Bacteria but also viruses, parasites and fungi can cause pneumonia and ARDS. It is also important to consider the context including local epidemiology, travel history of the patient, recent hospitalization, exposure history/sick contacts and immunocompetency. Thus, the initial diagnostic workup of ARDS should include a systematic microbiological assessment that screens for all potential pathogens.

Bacteriological cause of pneumonia

Community-acquired bacterial pneumonia is the most frequent cause of direct injury leading to ARDS [4]. There is no bacterial specificity, and the usual bacterial causes of pneumonia may be responsible for ARDS (Table 1). In case of ARDS that develops in mechanically ventilated patients, nosocomial pneumonia should be considered as a potential cause or aggravating factor [5].

Viral aetiologies of pneumonia

Viruses were historically held responsible for 5–10 % of community-acquired pneumonia (CAP) cases, influenza being the most frequent [6–8]. However, a recent study in patients with severe CAP requiring ICU admission found, using polymerase chain reaction (PCR), a 36 % rate of virus recovery from the respiratory tract, the vast majority being respiratory viruses (Table 1) [9]. These viruses can cause severe pneumonia and ARDS. They are at best diagnosed on RT-PCR on bronchoalveolar lavage [10]. Besides the usual respiratory viruses, herpesviruses are an increasing recognized cause of ARDS. In 1982, Tuxen et al. showed that 30 % of their 46 patients with ARDS had virological and histological evidence of herpes simplex virus (HSV) tracheobronchitis, which could be a trigger or an aggravating factor for ARDS [11]. More recently, HSV bronchopneumonitis was diagnosed in 42 (21 %) out of 201 non-immunocompromised patients on prolonged mechanical ventilation (after a median of 12 days of mechanical ventilation), some patients having developed ARDS [12]. The diagnosis can be made when HSV-specific nuclear inclusion is observed in cells recovered by bronchoalveolar lavage (BAL) fluid and/or by assessing viral load on BAL (threshold at 10^5 copies/10^6 cells) [12]. Cytomegalovirus (CMV) is also a well-recognized cause of nosocomial pneumonia in non-immunocompromised ICU patients and could be associated with ARDS [12, 13]. As for HSV, CMV could reactivate in ICU patients as a result of sepsis-induced immunoparalysis [14]. While the reactivation is asymptomatic in most patients, a true CMV pneumonia can occur in some patients [15, 16].

Table 1 Most common pathogens responsible for acute respiratory distress syndrome that should be included in the diagnostic workup

	Pathogen
Bacteria	*Streptococcus pneumoniae* Haemophilus influenza Enterobacteriaceae Staphylococcus aureus Legionella pneumophila Chlamydia pneumoniae Mycoplasma pneumoniae Pseudomonas aeruginosa[a] *Acinetobacter baumannii*[a] *Stenotrophomonas maltophilia*[a]
Virus	Influenza A and B Rhinovirus RSV Parainfluenza Metapneumovirus Coronavirus Enterovirus Adenovirus Bocavirus Polyomavirus Herpes simplex virus[a] Cytomegalovirus[a]
Fungi	*Pneumocystis jirovecii*[b] *Aspergillus fumigatus*[b]
Parasites	*Toxoplasma gondii*[b]

MV mechanical ventilation, *CAP* community-acquired pneumonia, *ESBL* extended-spectrum beta-lactamase, *RSV* respiratory syncytial virus

[a] Organisms that cause nosocomial pneumonia and could be responsible for ARDS in mechanically ventilated patients

[b] In immunosuppressed patients

Fungi and parasites aetiologies

Although fungi are not the usual cause of ARDS, some pathogens like *Pneumocystis jirovecii*, *Toxoplasma gondii* or *Aspergillus fumigatus* may be responsible for ARDS in immunosuppressed patients [17]. Recognizing them as potential causes of ARDS in this setting is important because a specific treatment could change the outcome [17].

Initial diagnostic workup in ARDS patients with suspected pneumonia

Because of the potential reversibility of infection-induced ARDS, physicians need to systematically investigate an infectious aetiology. Initial assessment of a patient with ARDS should include a microbiological assessment looking for a wide range of pathogens. Blood cultures, urinary antigen testing (for *Legionella pneumophila*), serologic tests (for intracellular bacteria, i.e. *Mycoplasma pneumoniae, Chlamydia pneumoniae* and *Legionella pneumophila*), and microbial sampling of the lung [18]. Fibre optic BAL is a preferred tool for ARDS patients because it allows one to recover large amounts of intra-alveolar material, although mini-bronchoalveolar lavage is acceptable also. The first step is a direct microscopic examination of BAL fluid, which allows one to look for bacteria using Gram staining, but also to use Giemsa-modified staining which offers a number of advantages over Gram staining, including better visualization of host cell morphology (including viral cytopathic inclusions [12]), improved detection of bacteria, particularly intracellular bacteria, and detection of some protozoan and fungal pathogens [19]. The second step is to culture for bacteria using quantitative culture of BAL fluid to test for respiratory viruses (Table 1), *Pneumocystis* or other fungi such as *Aspergillus* using PCR [20, 21] (see Table 1). Moreover, specific staining (immunostaining or immunofluorescence) may be used to detect *Legionella pneumophila, Pneumocystis jirovecii*, *Toxoplasma gondii* and other pathogens responsible for pneumonia in immunocompetent or immunosuppressed patients.

Diagnostic evaluation of suspected lung infection complicating the course of ARDS

Fever alerts the clinician that an inflammatory process of infectious or noninfectious origin is in progress. Fever developing during ARDS represents a difficult diagnostic challenge, as underscored by the following. First, clinical criteria have limited value in identifying pulmonary or extrapulmonary sources of infections developing during ARDS and chest X-ray has low accuracy in this setting [22]. Second, development of multiple concurrent infectious processes is a frequent occurrence [23]. Third, progressive pulmonary fibroproliferation alone may give rise to fever and leukocytosis and be clinically indistinguishable from nosocomial pneumonia, thereby making a clinical distinction from infections challenging. In one study that deployed an extensive diagnostic protocol to identify the source of fever, histologically proven fibroproliferation was the sole cause in 25 % and ventilator-associated pneumonia (VAP) in 35 % [23]. Finally, viral infection may also cause fever [24, 25]. In this setting, HSV and CMV reactivations are frequent and may lead to lung involvement (i.e. HSV bronchopneumonitis and CMV pneumonia), mimicking bacterial disease [12, 13, 15, 26].

The diagnostic workup of ARDS patients developing fever should thus always be the same: firstly, rule out VAP (bacterial and viral), secondly rule out an extrapulmonary infection, and thirdly look for a non-infectious process. If no cause is recognized, ARDS itself (fibroproliferation) may be incriminated as the cause of fever [23]. In this setting, BAL is probably the best tool, allowing one to look for bacteria, viruses but also for cytology or histology in difficult cases. In patients with ARDS, a decision regarding the site of bronchoscopic sampling is made difficult by the presence of diffuse densities on chest radiograph. Bilateral sampling can be one strategy. In 94 ARDS patients with suspected VAP, the diagnostic yield of bronchoscopy was evaluated with bilateral BAL [27]. Thirty-three of the 55 (60 %) positive bronchoscopies had significant growth in only one side (18 right BAL, 15 left BAL). However, the impact of this strategy regarding the outcome remains to be validated. Microbiological screening should also include searches for specific microorganisms, namely *Herpesviridae*: HSV and CMV reactivation should be systematically assessed, with their virus load quantification using PCR, as well as lung involvement, using, if possible, cytologic criteria of viral infection [12]. However, the impact of an antiviral treatment regarding the outcome of ICU patients is currently under investigation.

Infection surveillance during prolonged methylprednisolone treatment

Prolonged methylprednisolone treatment used in patients with ARDS blunts the febrile response and the physical findings associated with inflammation (i.e. abdominal tenderness); therefore, infection surveillance is essential to promptly identify and treat nosocomial infections [28]. Two randomized trials [29, 30] that incorporated infection surveillance (including routine BAL every 5–7 days while intubated) identified 56 % of nosocomial infections in the absence of fever. In addition to VAP and catheter-related and/or bloodstream infections, patients might be at risk of intra-abdominal infections or pancreatitis. Since findings may be misleading, in the appropriate clinical setting, computed tomography of the abdomen should be considered.

What to do in the absence of usual common risk factors for ARDS

Some patients met the radiological and clinical criteria of the Berlin definition of ARDS while having none of these risk factors. In a recent study, it was shown that the prevalence of ARDS with no risk factors was 7.5 % [31].

BAL fluid cytology, chest CT scan and specific immunologic examinations should be done when a classical risk factor is not found. Drug-induced acute respiratory failure should also be considered. In some cases, the clinical presentation is explained by a malignant aetiology (adenocarcinoma, lymphangitis). If the diagnosis cannot be done by BAL cytology, CT scan or specific biomarkers, in some instances there is a role for open lung biopsy in order to identify a malignant cause of respiratory failure (Fig. 1).

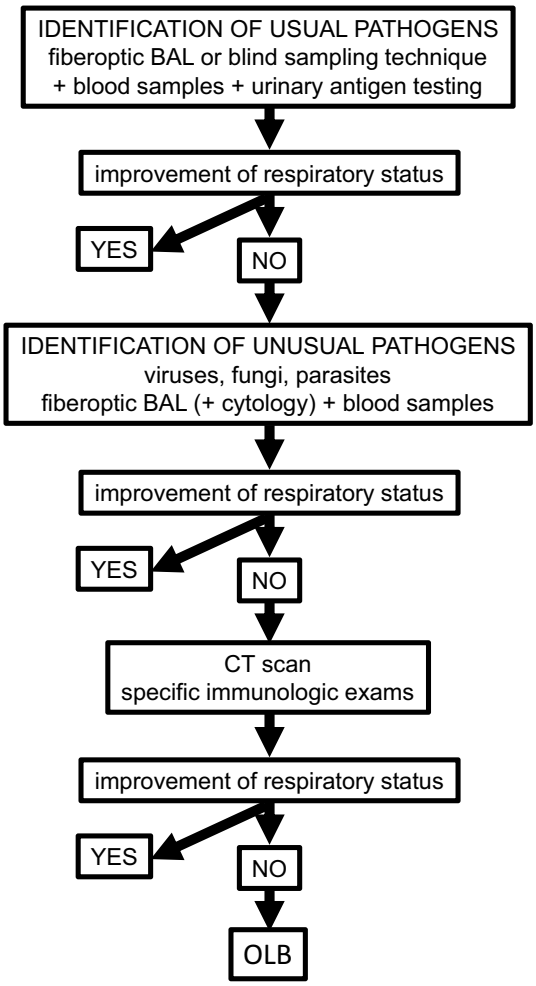

Fig. 1 Simplified representation of the diagnostic strategy for identifying the aetiology of ARDS due to pulmonary cause in non-immunocompromised patients. *BAL* bronchoalveolar lavage, *OLB* open lung biopsy

ARDS course and its evaluation

Inflammatory response

As extensively demonstrated, ARDS is often a secondary disorder that follows—usually within 6–48 h—a primary disease associated with severe systemic inflammation. In ARDS, systemic inflammation is activated by the nuclear factor-κB (NF-κB) signaling system and potentially downregulated by the activated glucocorticoid receptor alpha (GRα) [32]. Inflammatory mediators released into the systemic circulation (systemic inflammation) from the primary insult reach the pulmonary microcirculation leading to a stereotypical tissue response consisting of three simultaneously NF-κB-activated pathways: (1) tissue inflammation, (2) haemostasis (intravascular clotting and extravascular fibrin deposition [hyaline membranes]) and (3) tissue repair (regenerating native parenchymal cells, fibroproliferation and deposition of extracellular matrix) [33]. Clinicians can assess the progression of ARDS with daily measurements of variables incorporated into the lung injury score (LIS) [34]. On simple physiological criteria, the evolution of ARDS can be divided into resolving and unresolving on the basis of achieving a 1-point reduction in LIS or an increase in PaO_2/FiO_2 >100 mmHg by day 7 [34]. Patients with unresolving ARDS, in contrast to those with resolving ARDS, usually have histological evidence of maladaptive lung repair (Fig. 2) and significantly higher morbidity and mortality [33]. As shown in eTable 1 (see electronic supplementary material), measurement of biomarkers in BAL, as well as concurrent plasma samples, has demonstrated a strong cause and effect relationship between persistence vs. reduction in systemic and pulmonary inflammation-fibroproliferation and progression (unresolving) vs. resolution (resolving) of ARDS, respectively [32]. Nonimprovers have persistent elevation in circulating and BAL levels of inflammatory cytokines, chemokines, markers of lung vascular and epithelial permeability and fibrogenesis compared to improvers [35–38].

Because 50 % of ARDS patients who had an open lung biopsy (and in whom corticosteroids were potentially indicated) did not exhibit any sign of fibroproliferation by histological analysis [13], the use of a specific biomarker of pulmonary fibrosis may be useful in early identification of a population that could benefit from corticosteroids. Serial assessments of the N-terminal peptide for type III procollagen (NT-PCP-III) in BAL and blood samples are well correlated with clinical outcomes [35, 39, 40]. A recent study reported that alveolar concentrations of the NT-PCP-III in non-resolving ARDS patients was well correlated with the presence of lung fibrosis assessed by histological examination done on lung biopsies [41]. Future studies are needed to investigate the use of this biomarker to guide the corticosteroids treatment in patients with ARDS.

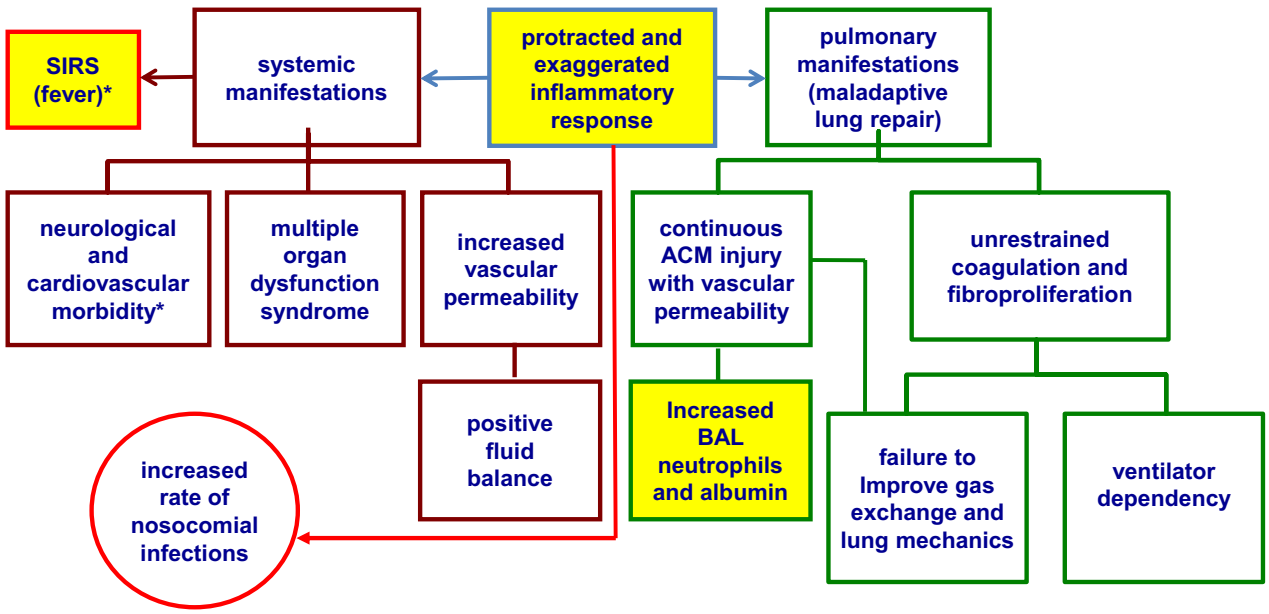

Fig. 2 Pathophysiological manifestations of dysregulated systemic inflammation in ARDS. Dysregulated systemic inflammation leads to changes at the pulmonary and systemic levels. In the lungs, persistent NF-κB activation with elevation of inflammatory mediators sustains inflammation with resulting tissue injury, alveolar-capillary membrane permeability, intra- and extravascular coagulation in previously spared lobules, and proliferation of mesenchymal cells with deposition of extracellular matrix in previously affected lobules, resulting in maladaptive lung repair. This manifests clinically with failure to improve gas exchange and lung mechanics and persistent BAL neutrophilia. Systemic manifestations include (1) systemic inflammatory response syndrome (SIRS) in the absence of infection, (2) progression of multiple organ dysfunction syndrome (MODS), (3) positive fluid balance and (4) increased rate of nosocomial infections. Elevated levels of inflammatory cytokines in the lung favour intra- and extracellular growth of bacterial pathogens and impair opsonization-dependent phagocytic neutrophil function and intracellular killing. Additional morbidity attributed to elevated cytokinemia includes hyperglycaemia, short- and long-term neurological dysfunction (delirium, neuromuscular weakness, post-traumatic stress disorder, and sudden cardiac events in those with underlying atherosclerosis. Reproduced with permission from [32, 77]

Histological description of ARDS

In their landmark description of patients with acute respiratory distress, Ashbaugh et al. reported various pathologic findings including, but not limited to, intra-alveolar haemorrhage and oedema, alveolar atelectasis, macrophages in the alveolar space, and engorged capillaries as autopsy findings [42]. The most consistent finding was the presence of hyaline membranes (HM) in ARDS patients. A decade later, Katzenstein, Bloor, and Liebow defined the term diffuse alveolar damage (DAD) as a manifestation of injury to alveolar lining and endothelial cells [43]. In addition to HM, early changes included capillary congestion, focal intra-alveolar oedema, atelectasis and intra-alveolar haemorrhage (eTable 2). A later phase of DAD past 72 h of ventilation was characterized by a mononuclear cell infiltrate of the alveolar space, alveolar epithelial cell hyperplasia and significant interstitial fibrosis for most cases ventilated for 8 days or more [43, 44]. The clinical syndrome has therefore been linked to pathologic findings of DAD, and HM in particular [42, 43]. However, there is evidence that histologic features of DAD are becoming less prevalent in the modern era. An autopsy study revealed that among patients with risk factors for ARDS, a smaller proportion met pathologic criteria for HM-positive DAD during the time period of 2001–2010 compared to the period of 1991–2000 (29 vs 44 %, $p < 0.01$) [45]. Tidal volume was also lower in the more recent decade. Even for patients with severe ARDS by the Berlin definition [2], only 58 % demonstrated DAD on autopsy [45]. Pneumonia with abundant neutrophils was the dominant pathologic finding in many of the clinically defined ARDS cases who did not have DAD [46]. Figure 3 provides histologic lung examples of ARDS patients with and without HM-positive DAD.

Our understanding of DAD as a pathologic hallmark of ARDS is skewed because most pathologic descriptions of ARDS derive from autopsy findings. We know very little about whether pathologic findings of DAD are prominent in milder cases of ARDS or in patients who survive the syndrome. In a prospective observational study of open lung biopsy for patients with nonresolving ARDS without clear aetiology persisting more than 7 days, it was shown that the majority demonstrated fibrosis, consistent with the fibroproliferative stage of ARDS [13]. However, these patients proceeded to biopsy precisely because their cause for ARDS was not apparent and their ARDS was

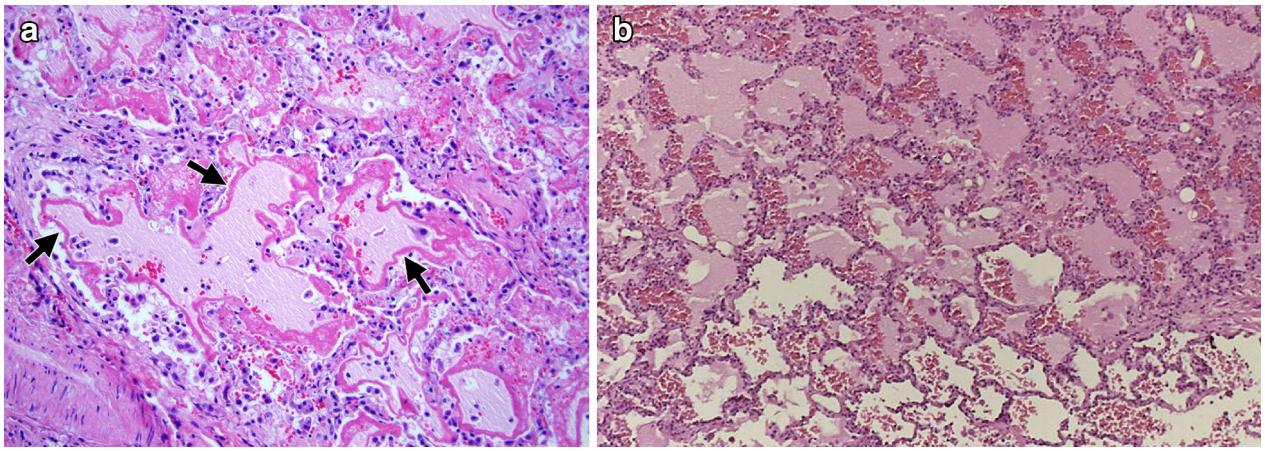

Fig. 3 Representative pathology from two patients with ARDS. **a** From the post-mortem lung examination of a 25-year-old man who died with severe H1N1 influenza confirmed by PCR after 9 days of lung-protective ventilation. Histology demonstrates extensive hyaline membranes (*arrows*) with evidence of diffuse alveolar damage and a mononuclear cell infiltrate, with apparent loss of alveolar epithelial cells. **b** Representative section from a lung biopsy in a 49-year-old woman with moderate ARDS for 5 days and an extensive travel history. All cultures and stains were negative, and history demonstrates protein-rich alveolar oedema with haemorrhage and neutrophils and no hyaline membranes

prolonged; thus, they may not reflect the overall population with ARDS. Consonant with the European autopsy study, biopsy frequently disclosed infection [13, 45]. Histologic patterns may also vary depending on the duration of ARDS, with oedema and congestion becoming less prevalent after a few days with the syndrome while fibrosis becomes more prevalent [47], though fibrosis is relatively rare among autopsy-diagnosed ARDS [48]. In conclusion, it seems unreasonable to conclude that pathologic evidence of DAD is the gold standard for ARDS diagnosis.

Still a place for open lung biopsies in ARDS patients?

There are two different situations in which lung histology could be useful: (1) to diagnose early in the course of ARDS a curable aetiology when results from less invasive examinations such as BAL, blood samples and CT scan are inconclusive and/or (2) towards the end of the first week of evolution, to identify fibroproliferation in order to consider corticosteroids to improve the outcome in the absence of concomitant nosocomial infection. In a series of 100 surgical lung biopsies for non-resolving ARDS with non-contributive BAL, the presence of fibrosis was reported in only 53 % of the cases [13]. Additionally, more than half of patients with fibrosis had a concomitant infection [13]. However, it is important to note that there has been a significant improvement in the microbiologic diagnosis of infectious pneumonia using BAL and blood samples. Biomarkers of fibroproliferation such as NT-PCP-III measured in BAL were also demonstrated to be helpful in the clinical decision-making to initiate corticosteroids. Therefore, only a few indications remain for open lung biopsy for non-resolving ARDS in current clinical practice [49].

Lung imaging

As chest X-ray is part of the ARDS definition and detailed elsewhere, its accuracy will be excluded from this review.

CT scan

Lung CT scan has been used to understand the pathophysiology and the interplay with mechanical ventilation. CT scan clearly showed that ARDS is a non-homogeneous lung disease with the following classically reported morphological patterns: consolidated regions (defined by a homogenous increase in density without vessels or bronchi), ground glass areas (with an increase in density with still recognizable vessels) and the normal aerated regions [50]. These three morphological features are usually simultaneously present. Air bronchograms and small pleural effusions are also common. The dependent localization of consolidated areas is related to the increase in lung oedema (i.e. increase in lung weight) during the initial phase of ARDS which raises the hydrostatic pressure transmitted throughout the lung, causing a reduction in lung gas volume and the development of non-aerated lung regions [51]. These poorly or non-aerated lung regions are characterized by a higher inflammation than normally ventilated lung regions [52]. The presence of non-inflated areas causes a major expansion of the neighbouring lung regions and generation of higher local pressures which act as a "stress raiser" [52]. Higher amounts of inhomogeneities are accompanied by higher stress raisers and severity of ARDS and worse outcome. Pulmonary ARDS presents

a similar amount of consolidated and ground glass areas while extrapulmonary ARDS has a higher amount of ground glass areas [53]. However, trying to diagnose a pulmonary or extrapulmonary ARDS only on the basis of CT findings is not accurate. According to lung-protective strategy, higher levels of PEEP may be indicated in patients with more severe disease and higher amounts of lung oedema and recruitability [1]. Unfortunately the application of PEEP may simultaneously induce a further inflation and expansion of the well-inflated regions and a decrease in the amount of poorly and non-aerated regions (lung recruitment) [54]. Thus higher PEEP levels were suggested only in patients with higher recruitability (Fig. 4a), avoiding unnecessary higher PEEP levels in patients with low recruitability (Fig. 4b). In this way CT scan can be useful in describing the distribution of lung opacities in order to adapt mechanical ventilation settings. In some instances CT scan is also able to identify unsuspected pneumothorax or to help the clinician to identify the cause of ARDS (typical lung lesions or intra-abdominal process causing ARDS).

However the use of CT scan requires the transportation of the patients to the radiological department, the use of ionizing radiation and dedicated software with

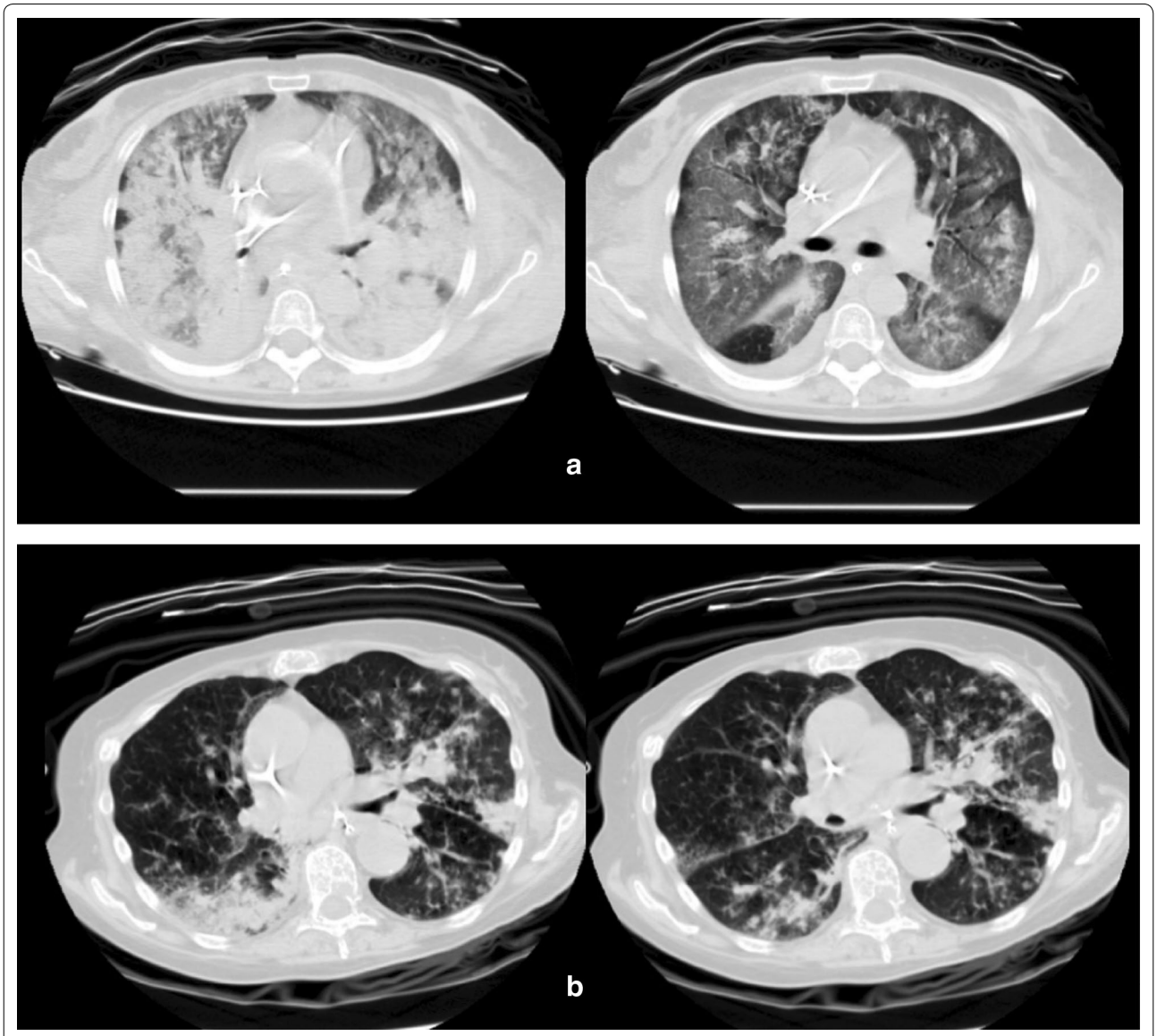

Fig. 4 Representative CT scan imaging from two patients with ARDS. **a** Patient presenting with homogeneous opacities with a high potential for recruitment. **b** Patient presenting with lung inhomogeneity with a low potential for recruitment

up to 6 h of work for a complete lung CT scan quantitative computation. Possible solutions include the application of a low dose CT scan acquisition protocol (able to reduce up to 70 % of the effective dose reduction) [55] and the use of a visual anatomical analysis which can classify, with a sufficient sensitivity and specificity, the patients on the basis of lung recruitability [56].

Lung ultrasonography

Recent analyses of ultrasonographic artefacts produced by air, chest wall, pleura and parenchyma have highlighted ultrasonography as a valuable tool in the diagnosis and management of ARDS [57, 58]. eTable 3 summarizes examples of normal and abnormal findings seen with thoracic ultrasonography. The most important finding in the diagnosis of respiratory failure is a B line (Fig. 5), which is defined as a discrete laser-like vertical hyperechoic reverberation artefact that arises from the pleural line [58]. It extends to the bottom of the ultrasound screen without fading and moves synchronously with lung sliding. The presence of three or more B lines in one intercostal space is considered abnormal and referred to as B pattern [58]. It has been shown that B lines correlate with interstitial involvement of the lungs, and B-pattern-predominant lungs are suggestive of alveolar processes such as ARDS, cardiogenic pulmonary oedema, and unilateral pneumonia, rather than nonalveolar causes, such as airway obstructive disease and vascular disorders [59]. However, the presence of bilateral B pattern per se does not differentiate ARDS from cardiogenic pulmonary oedema as an aetiology of the alveolar process [60]. Ultrasonographic characteristics such as nonhomogeneous distribution of B pattern, pleural line abnormalities (absent or reduced lung sliding, thickening or irregularity) and C (consolidative) pattern were observed more commonly in ARDS compared to cardiogenic pulmonary oedema [61]. Combined cardiac and thoracic ultrasonography is able to help in differentiation of ARDS from other aetiologies of acute respiratory failure. While both ARDS and cardiogenic pulmonary oedema present with B-pattern-predominant lungs, it was shown that left pleural effusion, moderately or severely decreased left ventricular function, and a large inferior vena cava minimal diameter can help in identifying cardiogenic pulmonary oedema compared to ARDS in acutely hypoxaemic patients [62]. Table 2 summarizes common ultrasonographic findings in ARDS and cardiogenic pulmonary oedema. Sequential thoracic ultrasonography can be used in monitoring lung parenchymal changes after the diagnosis of ARDS or when there is a sudden severe haemodynamic and/or respiratory change suggesting the presence of a pneumothorax. A few studies suggested that the evolution of ARDS and VAP could also be successfully followed over time with thoracic ultrasonography [63, 64]. Measurement of the ultrasound lung reaeration score based on the ultrasonographic findings before and after the application of PEEP could be as reliable as the pressure–volume curve method for assessing lung recruitment [65]. In summary, ultrasonography has a role in both the diagnosis and management of ARDS. Its portability, non-invasiveness and lack of radiation make bedside ultrasonography an attractive adjunctive tool to physical examination, laboratory data and other imaging studies.

Importantly, new non-invasive promising techniques such as electrical impedance tomography may be contributive for diagnosing regional inhomogeneity and lung recruitability [66]. Technological improvements would contribute to increase its accuracy.

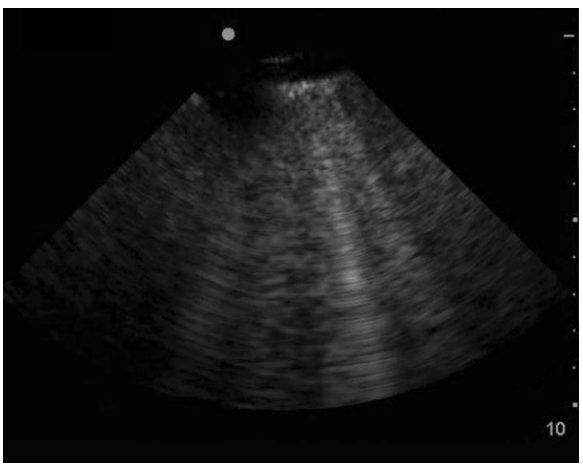

Fig. 5 Thoracic ultrasonography showing multiple B lines

Phenotype identification: personalized medicine for ARDS patients?

In asthma, as in many types of cancer, the identification of subphenotypes of disease with distinct clinical and biological features, different natural histories and differential response to therapy—also known as "endotypes"—has dramatically advanced both research and clinical care. Over the past several years, there has been increasing evidence for distinct subphenotypes of ARDS, classified by severity, biology, aetiology, timing, radiographic appearance or combinations thereof. How should clinicians attempt to incorporate phenotype identification at the bedside, now and in future years?

Perhaps the best-accepted and longest-standing approach to subphenotyping patients with ARDS is by severity of oxygenation impairment i.e. by the PaO_2/FiO_2 ratio. This simple and practical approach has been incorporated into both the original and newer

Table 2 Common point-of-care ultrasonography findings in ARDS and cardiogenic pulmonary oedema (CPO)

ARDS	CPO
Thoracic ultrasonography	
Bilateral B pattern	Bilateral B pattern
Non-homogenous distribution	Homogenous distribution
Pleural line abnormalities	Pleural effusion ≥20 mm
Thickening or irregularity	Left-sided predominance
Absent or reduced lung sliding	
C pattern	
Cardiac ultrasonography	
Preserved or unchanged left ventricular function from the previous examination	New or moderate to severe left ventricular dysfunction
Normal or small inferior vena cava minimal diameter ≤23 mm	Large inferior vena cava minimal diameter >23 mm
E/*e*′ ≤8	*E*/*e*′ ≥14

Berlin definitions of ARDS [2, 67]. Focusing on moderate–severe ARDS in clinical trials has led to some notable successes, including the recent positive trials of neuromuscular blockade and prone positioning, with a significant impact on clinical practice [68, 69].

Another approach to the identification of distinct ARDS subtypes has been to begin with clinically evident subgroups—e.g. trauma-related ARDS vs. sepsis-related ARDS, or direct vs. indirect lung injury—and to ask whether these subgroups have different biomarkers of disease, different histopathology or different clinical outcomes [46, 70]. This approach has yielded important insights that highlight both the clinical and biological heterogeneity within ARDS. For example, patients with ARDS from direct pulmonary causes (e.g. pneumonia, aspiration) have a biomarker profile that reflects more severe lung epithelial injury, while patients with indirect ARDS (e.g. non-pulmonary sepsis) have biomarker evidence of more severe endothelial injury and inflammation [71, 72]. Likewise, in a series of elegant studies, patients with diffuse ARDS by chest computed tomography have lower lung compliance, better response to PEEP, and higher levels of the receptor for advanced glycation endproducts (RAGE), a marker of lung epithelial injury and inflammation, compared to patients with focal ARDS [73, 74].

Yet another promising approach has been to adapt well-established statistical methods to identify meaningful subgroups within ARDS, free from presupposition about what those subgroups might be. By applying latent class models in two large randomized controlled trial samples of ARDS patients, investigators found strong evidence in both cohorts for two distinct endotypes of ARDS, a hyper-inflammatory endotype and a hypo-inflammatory endotype [75]. These two endotypes had different clinical and biological features, widely divergent clinical outcomes and, perhaps most importantly, differential response to randomly assigned treatment with higher vs. lower PEEP. Another group of investigators used similar approaches to analyse data on the timing of ARDS in patients with severe trauma; they found evidence for early and late ARDS subtypes, as well as some evidence of biological differences between the two groups [76].

At the moment, the clinical impact of ARDS phenotype identification hinges on whether the division of ARDS into specific subphenotypes will improve clinical outcomes. Assessment of severity of ARDS using the PaO_2/FiO_2 ratio already has important implications for clinical practice and should be carefully considered in all patients. For most of the other proposed subphenotypes of ARDS, the question of clinical impact remains open. Studies are ongoing to determine if patients with diffuse versus focal ARDS respond differently in a randomized controlled trial of mechanical ventilation practices (NCT02149589), and if the hyper- and hypo-inflammatory subtypes respond differently to randomly assigned therapies other than PEEP.

Conclusions

If there is no obvious cause of ARDS or if a direct lung injury is suspected, bronchoscopic BAL (or mini-BAL) is the pivotal examination in order to identify microorganisms responsible for pneumonia (routine cultures, PCR, cytology, direct examination). Blood samples are also helpful to identify a microorganism and evaluate biomarkers of infection. If there is no infectious cause of ARDS and no other apparent aetiology, second-line examinations should include common markers of immunologic diseases. In selected instances, open lung biopsy remains useful to identify the cause of ARDS when all the previous examinations remain inconclusive. CT scan is a fundamental examination when there is a suspicion of intra-abdominal sepsis and when some agents of pneumonia such as *Aspergillosis* are suspected. Although there is a role of CT scan

in adjusting ventilator settings, its routine use only for this objective is not recommended. Ultrasonography is important to evaluate left (and right) ventricular function, and also helps in identifying pleural effusions and the presence of a pneumothorax. In the presence of non-resolving ARDS or when there is a secondary deterioration of the respiratory status, BAL (and blood samples) should be used to identify the microorganisms that may be responsible for VAP. It may also be useful in evaluating biomarkers indicating fibroproliferation. In this context, open lung biopsy is indicated only if there is reasonable suspicion of an undiagnosed infection or another process that is masquerading as ARDS such as malignancy or immunologic disorders. The ARDS phenotype identification sorting ARDS into specific subphenotypes could improve clinical outcomes. Ongoing and future studies will attempt to assess this latter topic.

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Author details
[1] Assistance Publique - Hôpitaux de Marseille, Hôpital Nord, Réanimation des Détresses Respiratoires et des Infections Sévères, 13015 Marseille, France. [2] Aix-Marseille Université, Faculté de médecine, URMITE UMR CNRS 7278, 13005 Marseille, France. [3] Departments of Medicine and Anesthesia, Cardiovascular Research Institute, University of California San Francisco, San Francisco, CA, USA. [4] Dipartimento di Anestesia, Rianimazione ed Emergenza-Urgenza, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy. [5] Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy. [6] Service de Réanimation, Institut de Cardiologie, Groupe Hospitalier Pitié–Salpêtrière, Assistance Publique–Hôpitaux de Paris, Paris, France. [7] Sorbonne Universités, UPMC Université Paris 06, INSERM, UMRS 1166-ICAN Institute of Cardiometabolism and Nutrition, Paris, France. [8] Pulmonary, Allergy, and Critical Care Division, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA, USA. [9] Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA. [10] Division of Pulmonary Critical Care, and Sleep Medicine, Departments of Medicine, Memphis Veterans Affairs Medical Center, Memphis, TN, USA.

Compliance with ethical statements

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None.

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