

REVIEW

Respiratory infections and acute respiratory distress syndrome

Adrian Ceccato^{1,2,*}, Elena Campaña-Duel¹, Aina Areny-Balagueró¹, Saad Nseir³, Antoni Torres^{2,4}

¹Critical Care Center, Parc Taulí University Hospital, Parc Taulí Research and Innovation Institute I3PT, 08208 Sabadell, Spain

²CIBER of Respiratory Diseases (CIBERES), Institute of Health Carlos III, 28029 Madrid, Spain

³Critical Care Center, Lille University Hospital, F-59000 Lille, France

⁴Department of Pneumology, Hospital Clinic of Barcelona, August Pi i Sunyer Biomedical Research Institute—IDIBAPS, University of Barcelona, 08036 Barcelona, Spain

***Correspondence**

aaceccato@tauli.cat
(Adrian Ceccato)

Abstract

Respiratory infections and acute respiratory distress syndrome (ARDS) are closely related. Pneumonia is the most common cause of ARDS, and patients with ARDS usually develop infectious respiratory complications. Sixty percent of the cases of ARDS are due to pneumonia, but only some patients with pneumonia will develop ARDS. Viral pneumonia is a common cause of ARDS, especially in seasonal outbreaks or pandemics. Patients admitted with ARDS could present a secondary infection, and ventilator-associated pneumonia may impair prognosis. Several conditions that predispose patients with ARDS to respiratory infections are present. Decisions regarding antimicrobial treatment should be based on epidemiology, risk factors and current recommendations. Corticosteroids may be used as adjunctive therapy in both pathologies in selective patients.

Keywords

Pneumonia; VAP; ARDS

1. Introduction

Respiratory infections and acute respiratory distress syndrome (ARDS) are closely related. Pneumonia is the most common cause of ARDS, and patients with ARDS will often develop complications, such as respiratory infections. In the LUNG-SAFE study [1], 60% of patients presented pneumonia as the most common risk factor for ARDS. However, ARDS is usually under-recognized by clinicians, which suggests that its incidence may be higher [2]. The inflammatory environment present in ARDS leads to an impaired host defense response [3, 4], resulting in a more elevated risk of infectious complications. The recent coronavirus disease 2019 (COVID-19) pandemic saw an increased prevalence of respiratory infections in patients receiving invasive mechanical ventilation [5].

In this narrative review, we describe the closely relation between ARDS and respiratory infections, analyze common points and management of both conditions.

2. ARDS due to respiratory infections

While pneumonia is the most frequent cause of ARDS [1, 6, 7], only a few patients with community-acquired pneumonia (CAP) will develop ARDS. In a study by Cillóniz *et al.* [8] including 5334 hospitalized patients with CAP, only 125 patients met Berlin criteria for ARDS. Among those patients hospitalized for pneumonia, 930 (17%) required admission to the intensive care unit (ICU) and only 137 received invasive mechanical ventilation. Patients who developed ARDS had higher severity scores (Sepsis-related Organ Failure Assess-

ment (SOFA) and Pneumonia Severity Index (PSI)) and lower ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO₂/FiO₂). Interestingly, those patients with severe CAP who did not develop ARDS more frequently received inhaled corticosteroids. Outcomes were similar between patients with severe CAP and those who developed ARDS; there was no reported differences in etiology. In a study evaluating risk factors for acute lung injury (ALI) [9], 102 of 1234 patients with pneumonia presented ALI. The Lung injury prediction scores (LIPS) score [10] was validated in this study and included pneumonia as a risk factor as well.

Ichikado *et al.* [11] described two clinical phenotypes for those patients with fatal outcomes due to pneumonia-causing ARDS. Those patients who died early (<5 days) presented a higher Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and more commonly, disseminated intravascular coagulation. Those who died later (>5 days) had an early fibroproliferation pattern in the computerized tomography (CT) scan and disseminated intravascular coagulation as well.

Several pathogens may cause pneumonia and ARDS (Table 1). The most common pathogen isolated in patients with CAP is *Streptococcus pneumoniae* [12]. ARDS could be present in 3% of patients with pneumococcal pneumonia [13] and in 45% of patients with severe CAP due to pneumococcus [14]. The incidence of ARDS does not seem to be higher among patients with pneumococcal pneumonia or other types of bacterial pneumonia [15].

Viruses are an increasing cause of pneumonia that could

TABLE 1. Pathogens that may cause ARDS and pneumonia.

Streptococcus pneumoniae
Mycoplasma pneumoniae
Pseudomonas aeruginosa
Staphylococcus aureus
Rhinovirus
Parainfluenza virus
Metapneumovirus
Influenza
Respiratory syncytial virus
Coronavirus
Adenovirus
Varicella-Zoster Virus
Hanta virus

ARDS: Acute respiratory distress syndrome.

induce ARDS [16]. Influenza virus may lead to seasonal disease—mainly fall or winter—or, in some cases, pandemic disease. In the world occurred 4–8.8 deaths per 100,000 individuals by Influenza [17]. The last influenza pandemic disease was in 2009 due to influenza A (H1N1) virus that emerged in Mexico and originated in swine [18]. ARDS is commonly diagnosed in patients with severe pneumonia due to influenza virus [19].

Adenovirus, metapneumovirus and the syncytial respiratory virus may also cause ARDS [20–22]. Hantavirus is a less common cause of pneumonia but may induce severe disease, characterized by severe respiratory and cardiovascular failure [23].

In the last two decades, three coronaviruses (CoV) have emerged as causing severe acute respiratory syndrome (SARS). In 2003, SARS-CoV was found to cause severe disease with ARDS, mainly in southeastern Asia [24], while Middle East respiratory syndrome (MERS) was described in Saudi Arabia in 2012 [25]. At the end of 2019, SARS-CoV-2 appeared in China, spreading quickly and triggering a pandemic. Almost all patients admitted to ICU due to COVID-19—the disease caused by SARS-CoV-2—presented ARDS [26–28]. Mortality associated with COVID-19 reached rates higher than 45% in patients receiving invasive mechanical ventilation [29]. Older age, high fever, comorbidities, neutrophilia, lymphocytopenia, elevated end organ-related indices (e.g., aspartate aminotransferase, urea, lactate dehydrogenase) and inflammatory biomarkers, and coagulation disorders were significantly associated with a higher risk of ARDS onset [30]. COVID-19-related may cause lung sequelae [31, 32] in the long term; however, mortality rates have not been reported to significantly increase after discharge [33]. Alveolar-capillary microthrombi, microangiopathy, angiogenesis and classical diffuse alveolar damage were found in lung samples obtained during autopsies of patients with COVID-19 [34]. A possible cause for such observations is the release of procoagulant factors from injured

endothelial cells [35, 36]. Patients with COVID-19 may also have a co-infection when admitted to the ICU. In a study comparing the prevalence of co-infections among patients with either COVID-19 or influenza, the rate was significantly lower in those with COVID-19 [37]. It is worth noting, though, that this prevalence may be higher if more sensitive tests are performed. In a study where bronchoalveolar lavage was obtained and analyzed using a multiplex polymerase chain reaction (PCR) panel, 21% of patients presented co-infections within 48 hours of undergoing invasive mechanical ventilation [38].

Co-infections are common in patients with pneumonia-related ARDS. In a study by Kao *et al.* [39] including 902 patients with ARDS due to any cause, microbiological isolation of the causative agent occurred in 142 patients with pneumonia. Twenty-nine percent (n = 41) presented a co-infection with a virus, fungus or bacteria (having been isolated in bronchoalveolar lavage samples). No differences in ARDS severity were observed among patients with either a co-infection or only viral infection; however, mortality was higher in those individuals with co-infections.

Respiratory infections that cause ARDS may be nosocomial or community-acquired. In a study analyzing community-, hospital- or ICU-acquired ARDS, Kao *et al.* [40] observed that ICU-acquired ARDS was the most common and patients with community-acquired ARDS had the lowest mortality.

Barbeta *et al.* [41] analyzed the characteristics and outcomes of patients with ventilator-associated pneumonia (VAP) who did and did not develop ARDS. Of the 302 patients with VAP, 41 (14%) presented ARDS. These patients were younger, with lower severity scores at admission and increased severity at VAP diagnosis. The most frequently isolated pathogen in both groups was *Pseudomonas aeruginosa*. Interestingly, no differences in 28- and 90-day mortality were found between groups.

3. Secondary respiratory infections in patients with ARDS

Ventilator-associated lower respiratory tract infections (VA-LRTI) are common complications in patients with ARDS [42]. VAP and ventilator-associated tracheobronchitis (VAT) fall within the definition of VA-LRTI.

Several conditions that facilitate the onset of respiratory infections are present in patients with ARDS. Also, diagnosing VA-LRTI in patients with ARDS is difficult, given the presence of bilateral infiltrates in chest x-rays and, in many cases, colonization of the airway by pathogens.

VAP must be suspected when there is an impairment in the clinical condition, the onset of fever, changes in respiratory secretions, or higher requirements for oxygen or positive end-expiratory pressure levels [43, 44]. Increased levels of biomarkers such as C-reactive protein may help in diagnosing VAP [45, 46].

In a study published by Chastre *et al.* [47], VAP was the most frequent condition occurring in patients with ARDS compared to ventilated patients without ARDS. Patients with ARDS had a more elevated incidence of VAP due to methicillin-resistant *Staphylococcus aureus*. Mortality was

also higher in patients with VAP and ARDS.

Incidence of VAP was analyzed in a post-hoc study including patients from a randomized controlled trial (RCT) of cisatracurium besilate in patients with severe ARDS [48]. VAP occurred in 98 (29%) patients, and mortality was higher in those individuals who developed the condition (41% vs. 31%). However, when analyses were adjusted for severity and plateau pressure, VAP was not associated with ICU mortality. In a separate post-hoc analysis of a clinical trial evaluating prone position in ARDS [49], incidence of VAP was 1.18 (0.86–1.60) per 100 days of invasive mechanical ventilation; it was similar to that reported in patients included in the prone position arm. VAP was, furthermore, associated with higher mortality, with a hazard ratio of 2.2 95% CI 1.39–3.52 $p < 0.001$ after adjusting for position group, age, SOFA score, McCabe score and immunodeficiency.

A model of VAP prediction in patients with ARDS was developed using data from the EDEN trial [50]. Use of neuromuscular blocking agents, severe ARDS, admission for an unscheduled surgery, and trauma as primary causes of ARDS constituted independent risk factors for VAP.

An inflammatory environment present in the lungs of patients with ARDS may predispose them to developing VA-LRTI [4, 51–53]. An impaired host defense—including innate and acquired immune response—or the use of immunomodulatory drugs such as glucocorticoids may provide an explanation for this observation. Also, inflammatory patterns could be related to changes in microbiota as well [54]: dysbiosis observed in patients with ARDS may facilitate the development of VAP [55–57]. Finally, a low level of positive end-expiratory pressure and hyperoxia may increase the risk of VAP [58, 59], warranting consideration during the management of patients with ARDS.

Recently, critically ill patients with COVID-19 have been observed to present a higher incidence/prevalence of VA-LRTI [60, 61]. In a multicenter study evaluating both patients with COVID-19 or influenza and mechanically ventilated patients without non-viral pneumonia, Rouze *et al.* [5] observed an incidence of 50% of VA-LRTI in patients with COVID-19. This incidence was significantly higher even after being adjusted for confounders. VAP was associated with poor outcomes [62, 63].

Less common secondary pulmonary infections could be found in patients with severe viral pneumonia. Pulmonary aspergillosis may complicate ARDS caused by influenza or COVID-19 [64–67].

Combining novel microbiological tests and routine Gram staining and cultures may help diagnose VAP early and accurately and promote prompt and adequate treatment. Gram staining has good accuracy in diagnosing *S. aureus* [68], and multiplex PCR may reduce exposure to broad-spectrum antibiotics, especially if testing for resistance mechanism genes occurs [69, 70]. Bronchoalveolar lavage may promote better diagnoses and should be performed when possible [43, 71]. Diagnosing infections due to aspergillus is a challenge. However, detection of galactomannan in serum and bronchoalveolar lavage may help [72].

4. Managing ARDS due to or complicated by respiratory infections

ARDS must be managed according to current recommendations [73]. Protective mechanical ventilation and the use of prone positions have shown benefits in this population. Extracorporeal membrane oxygenation (ECMO) should be used in selective populations [7], and clinicians should consider the risks and benefits of neuromuscular blocking agents [74–78]. For respiratory infections, current guideline recommendations may help choose early and adequate antimicrobial treatments (Table 2) [43, 44, 79]. Local data about multidrug-resistant (MDR) pathogens and individual risk factors must be considered. ARDS was included as a risk factor for MDR pathogens in the last American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines [44]. However, in a study validating this particular guideline, ARDS had poor accuracy in relation to MDR pathogen prediction (high specificity (81%) and low sensitivity (24%)) [80].

Corticosteroids have been tested in several trials for both ARDS and pneumonia. Potent anti-inflammatory medications [81], corticosteroids may play a role as an immunomodulatory drug in the exacerbated inflammatory response observed in patients with either ARDS or pneumonia. In 1986, methylprednisolone was tested at high doses in patients with ARDS, conferring no benefits [82]. The same was found at intermediate doses in patients with prolonged ARDS (more than seven days since onset) [83]. In an analysis including data from four RCT, prolonged treatment (>25 days) with corticosteroids improved outcomes with fewer ventilator- and ICU-free days, and lower ICU mortality. Villar *et al.* [84] performed an RCT evaluating dexamethasone 10 mg per day for 10 days in patients with moderate or severe ARDS according to the Berlin definition [85]. Two hundred and seventy-seven patients were randomized to dexamethasone or placebo. Ventilator-free days were higher in the dexamethasone arm, and mortality decreased by 15.3% in those patients who received corticosteroids.

Corticosteroids have been extensively tested in patients with pneumonia [86, 87]. Several trials [88–91] and a meta-analysis [92–101] reported heterogeneous results about the efficacy of corticosteroids in reducing mortality and improving outcomes in patients with CAP. Benefits regarding mortality were observed mainly in patients with severe CAP [95, 96, 99–101]. Nonetheless, concerns about the reproducibility of these results have limited applicability thereof [79]. Recently, in a propensity score matching study using real-life data [102], our group observed significantly lower mortality in those patients with severe CAP criteria per ATS/IDSA guidelines [79]. Corticosteroids also reduced the risk of disease progression to ARDS [97]. Special considerations should be made for some cases of viral pneumonia. Corticosteroids showed impaired outcomes in patients with severe CAP due to influenza or MERS [103–105]. Conversely, though, corticosteroids have served as the main treatment drug for patients with severe or critical COVID-19. Corticosteroids have shown efficacy in reducing mortality in patients with COVID-19 when treatment was started after seven days since symptom onset [106, 107]. Most critically ill patients experienced higher benefits. Corticosteroids were described as a risk factor for ICU-acquired

TABLE 2. Recommended antimicrobial treatments for pneumonia.

Community-acquired pneumonia				Nosocomial pneumonia (HAP and VAP)
β -lactam	plus	macrolides	or	Higher prevalence of MDR pathogens (>25% of GNEB or 10% of MRSA), septic shock, high mortality risk or risk factors for MDR pathogens: double coverage with antipseudomonal agents and MRSA coverage: β -lactams/aminoglycosides +/- linezolid or vancomycin.
If MDR pathogens are suspected based on risk factors and local epidemiology: antipseudomonal β -lactams +/- linezolid or vancomycin.				If patient does not have septic shock and one agent is active against 90% of isolated pathogens in the ICU, a single agent could be administered.
Oseltamivir must be added if influenza is suspected or confirmed.				

Based on recommendations from ATS/IDSA [44, 79] and European respiratory society/European Society of Intensive Care Medicine/European Society of Clinical Microbiology and Infectious Diseases/Latin American Thoracic Society (ERS/ESICM/ESCMID/ALAT) [43] guidelines. Abbreviations: HAP: Hospital-acquired pneumonia; MDR: multidrug-resistant; VAP: ventilator-associated pneumonia; GNEB: Gram negative entero bacteriace; MRSA: Methicillin-resistant staphylococcus aureus; ICU: Intensive care unit. Note that ARDS may be considered as a risk factor for MDR pathogens according to ATS/IDSA guidelines.

pneumonia [108].

Corticosteroids should be used with caution in patients with VAP, given that the drug was associated with lower survival in an observational study by Ranzani *et al.* [109].

5. Future perspectives

ARDS is a heterogeneous condition [110], which means that not all measures could be of benefit. ARDS due to respiratory infections may differ in terms of the causative agent, previous condition or host-pathogen interaction (*e.g.*, inflammatory response) [111]. Thus, several aspects should be taken into account before recommending a treatment or measure. Knowing different phenotypes may allow clinicians to adjust treatment according to risks and benefits [112]. Platform or adaptive trials taking place during the last pandemic have demonstrated the possibility of evaluating several treatments, with quick results changing clinical practice (*e.g.*, the use of corticosteroid for COVID-19). Predictive and prognostic enrichment might improve clinical trials, increasing effect sizes; however, results may not be generalizable [113].

Given that many clinical trials have failed to improve clinical practice, future studies should be designed in a way that acknowledge the varying components and implement enrichment. Adaptive trials should be considered, mainly in those conditions with high prevalence.

6. Conclusions

Pneumonia is the most common cause of ARDS. Community- or hospital-acquired pneumonia can trigger ARDS. Patients admitted with ARDS could present a secondary infection. Antimicrobial treatment must be based on epidemiology, risk factors and current recommendations. Corticosteroids can be used as adjunctive therapy in both pathologies.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

FUNDING

Adrian Ceccato acknowledges receiving financial support from Instituto de Salud Carlos III (ISCIII; Sara Borrell 2021: CD21/00087).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Adrian Ceccato, Elena Campaña-Duel, Aina Areny-Balaguero, Saad Nseir, Antoni Torres. Respiratory infections and acute respiratory distress syndrome. *Signa Vitae.* 2022. doi:10.22514/sv.2022.054.