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EDITORIAL

Focus on ventilation and ARD: recent insights

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The year 2018 in mechanical ventilation and acute respiratory distress syndrome (ARDS) was marked by the struggle to develop personalized or precision medicine, defined as "the tailoring of medical treatment to the individual characteristics of each patient with ARDS". Despite many recent efforts made performing large randomized clinical trials, their results often remain indeterminate in unselected ARDS patients [1]. In a randomized trial involving patients with very severe ARDS [2], early application of venovenous extracorporeal membrane oxygenation (VV-ECMO) did not result in a statistically significant reduction in the primary endpoint of 60-day mortality. However, the large absolute 11% reduction in mortality seen despite the fact that 28% of control patients crossed over to ECMO for refractory hypoxemia, suggests that many patients with severe ARDS could benefit from VV-ECMO therapy. On the other hand, therapies with proven efficacy for decreasing mortality in ARDS patients remain inconsistently applied in clinical practice. A prospective international prevalence study found that prone position was used in only 32.9% of severe ARDS patients [3]. The discordance between the application of therapies at the bedside and results of large trials might reflect the use of precision medicine by bedside physicians. Moreover, it is worth noting that a lot of patients were excluded from large ARDS studies according to their comorbidities [4], which further increases the gap between clinical trials and actual clinical practice.

The literature from 2018 provided new insights to differentiate patient and ARDS characteristics in relation to diagnosis, prognosis and response to treatment. They are detailed below and outlined in Fig. 1, and could help physicians move closer to performing precision medicine.

Baseline clinical characteristics

Body mass index has to be taken into account in the management of ARDS patients. Higher driving pressure [plateau pressure minus positive end expiratory pressure (PEEP)] has been associated with higher mortality in ARDS patients. However, a recent retrospective study found no impact of driving pressure on 90-day mortality in 100 obese (BMI $\geq$ 30) patients, in contrast to 262 non-obese ARDS patients [5]. These results suggest that ARDS in obese patients (often excluded from large studies assessing therapies in ARDS) may differ from ARDS in non-obese patient. Habits, like smoking, have also strong importance. After severe blunt trauma, a history of smoking was related to lung microbiota composition, at the time of ICU admission and at 48 h [6]. ARDS development was correlated with respiratory microbial community structure at 48 h and with taxa that are relatively enriched in smokers at ICU admission [6]. Moreover, a comorbidity assessment could help the physician for the diagnosis, prognosis and treatment of ARDS. In an unselected population with ARDS from 1997 to 2014, Azoulay et al. found that half had major comorbidities (chronic respiratory diseases, chronic heart failure, solid tumors, liver cirrhosis, drug-related immunodeficiency, hematological malignancies, and HIV infection) [4]. In the group with major comorbidities, hypoxemia was more severe, mortality higher, extrapulmonary organ dysfunction more common, and ICU resource consumption greater. In patients undergoing noninvasive ventilation (NIV) for acute respiratory failure, a recent study aimed to explore the appropriateness of NIV use in different diagnostic groups [7]. The NIV failure rate varied among diagnostic groups, ranging from 0 to 58%. Through exploratory

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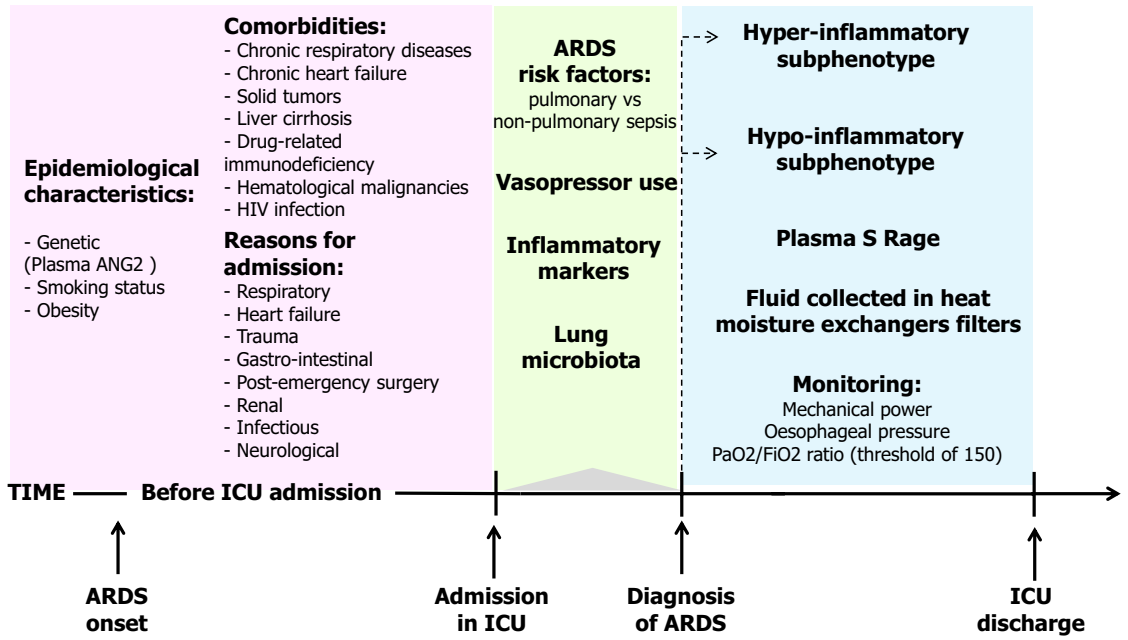

Fig. 1 Patient and ARDS characteristics highlighted in papers published in 2018 for individualizing ARDS management. This figure details patient and ARDS characteristics highlighted in papers published in 2018 which could help the physician to personalize ARDS management and apply precision medicine: (i) patient characteristics before intensive care unit admission: epidemiological characteristics, comorbidities, reasons for ICU admission; (ii) disease characteristics: ARDS risk factors, vasopressor use, inflammatory markers, lung microbiota; (iii) ARDS characteristics: hyper-inflammatory versus hypo-inflammatory subphenotypes, plasma S rage, fluid collected in heat moisture exchangers filters, and ventilatory parameters (mechanical power, esophageal pressure, PaO_2/FiO_2 ratio with a threshold of 150 mmHg)

analyses, the standardized mortality rate was lower than the median for the trauma and chronic obstructive pulmonary disease (COPD) groups and higher than the median for the gastrointestinal and post-emergency surgery groups. Interestingly, despite a zero-failure rate, NIV conferred no survival benefit in the renal group, and despite having the highest NIV-failure rate, the neurological group had average mortality. The future will probably include individualized management according to genetic characteristics. In European ancestry subjects with sepsis, higher plasma angiopoietin-2 (ANG2) levels were associated with higher ARDS risk [8].

Biomarkers and microbiological sampling

In a meta-analysis of individual data, Jabaudon et al. provided evidence that alveolar epithelial injury at baseline, as assessed by biomarker plasma sRAGE, was an independent variable associated with 90-day mortality in ARDS, independent of driving pressure and tidal volume [9]. In addition, individualized microbiological sampling could help diagnosis of ARDS. A new method was recently described, based on fluid collected from heat–moisture exchanger filters attached to mechanical ventilators of ARDS patients [10]. It was found that this fluid accurately represented fluid in the distal airspace. Heat–moisture exchanger fluid might be a novel, simple, noninvasive method to repeatedly sample the distal airspace in patients with ARDS and provided personalized management strategy according to the results of this simplified sampling. However, it is worth noting that heat-and-moisture exchangers are not recommended during mechanical ventilation for ARDS due to instrumental dead space enhancement.

Ventilatory management

In patients who receive invasive ventilation for more than 48 h, a post hoc analysis found that mechanical power in the second 24 h of ventilation was independently associated with higher in-hospital mortality, independent of the presence of ARDS or use of neuromuscular blocking agents, and even at low tidal volume and low driving pressure [11]. However, mechanical power was not associated to mortality in the subset of ARDS patients. These results suggest that mechanical power might help to further individualize ventilatory settings and use of other therapeutics. Similarly, esophageal pressure manometry could be a method of choice for personalized ventilatory settings [12].

Identification of subphenotypes

Using a statistical method named latent class analysis (LCA), a two-subphenotype model was found to best describe the SAILS population, with the hyper-inflammatory subphenotype being associated with increased inflammatory biomarkers, a higher prevalence of shock, and worse clinical outcomes [13]. Two similar ARDS subphenotypes (hyper-inflammatory and hypo-inflammatory) were also identified in the HARP-2 cohort, with distinct clinical and biological features and disparate clinical outcomes [14]. The hyper-inflammatory subphenotype had improved survival with simvastatin compared with placebo [14]. These findings further validate the presence of two subphenotypes in ARDS and suggest that they could be used for precision medicine in these patients. In a study performed by Maiolo et al., ARDS patients were separated into two groups using a PaO_2/FiO_2 ratio threshold of 150 mm Hg (measured at 5 cm H_2O PEEP), with resulting different anatomical and physiological characteristics [15]. This classification in mild–moderate and moderate–severe ARDS subgroups may help to identify specific indications for ventilator settings and for the use of alternative therapies such as prone positioning and extracorporeal carbon dioxide removal.

To conclude, it is time to apply personalized medicine to ARDS patients. Many tools based on baseline characteristics, new biomarkers and sampling, ventilatory parameters and subphenotypes identification were developed in the year 2018. Individualizing diagnosis and therapeutic strategies are more and more feasible in clinical practice and could lead to improved patient outcomes.

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Compliance with ethical statement

Conflicts of interest

Dr. Ferguson reports personal consulting fees from Getinge, Baxter, and Sedana Medical. Pr. Jaber reports receiving consulting fees from Drager, Xenios, Medtronic, and Fisher & Paykel. No potential conflict of interest is reported for Dr. De Jong.

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