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ARDS and Precision Medicine

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What is the path forward for treatment of acute respiratory distress syndrome (ARDS)? Is it big trials (favoured by clinical scientists) or further insight into disease physiopathology (favoured by basic scientists)? Or both? Funding resources are limited and the debate is wide open. In the post-genomic era, a new direction is needed. On 20 January 2015, then U.S. President Barack Obama announced the Precision Medicine Initiative® (PMI), the main focus of which is a clear call for a more organised, systematic approach for disease treatment and prevention that takes into account individual variability in environment and genetics for each person (obamawhitehouse.archives.gov/precision-medicine).

Precision medicine is a promising strategy for many complex diseases that have proven difficult to prevent or treat using a population approach. This is especially true for intensive care medicine, where syndromic diagnoses are common and randomised controlled trials frequently include heterogeneous patient populations (Vincent et al. 2016). For example, many recent clinical studies in intensive care units erred on the side of large sample sizes, ignoring heterogeneity in the selected study population for lack of accurate molecular biomarkers. Promising therapeutic approaches might have harmed as many patients as they helped. ARDS is arguably one of the most poorly characterised diseases in intensive care units (ICUs) (Sheu et al. 2010). We frequently deal with the dilemma that the patients we treat in our ICUs may or may not reflect the syndrome diagnosis that is used to include patients in clinical trials.

For decades, there was no common definition for ARDS, which resulted in a very wide range of reported prevalence. In 1994 the American-European Consensus Conference (AECC) definition became globally accepted and addressed some of the problems of clinical characterisation. In the AECC definition ARDS was graded based on oxygenation relative to the fraction of inspired O2 (PaO_2/FiO_2) (Bernard et al. 1994; Artigas et al. 1998). Treatment bundles fostering what became known as “protective lung ventilation” were the most important achievements that followed. Difficulties in interpretation of chest radiography and the lack of a standardised positive end-expiratory pressure (PEEP) level, however, limited the application and utility of the AECC definition. In 2012 the new Berlin Definition of ARDS was established to solve the aforementioned limitations. This definition improved the interpretation of the chest radiograph and established a minimum level of PEEP (Costa and Amato 2013; ARDS Definition Task Force 2012). Despite these improvements, the definition still lacks differentiation based on underlying aetiology, a direct measure of lung injury, and markers that identify early patients who may benefit from preventive therapies (Bellani et al. 2012). Another unresolved conundrum is the lack of agreement between ARDS and lung histology. One would hope that pathological studies would help better characterise the disease and therefore improve clinical phenotyping. Yet Thille et al. found (Thille et al. 2013a; 2013b) that in 712 autopsies analysed 356 patients had pathological criteria for ARDS at the time of death, showing a very poor specificity (63%) in identifying ARDS using the Berlin Definition. Moreover, diffuse alveolar damage (DAD) at autopsy was found in less than half of the patients with clinical criteria for ARDS (Guerin 2011). The limitations of the Berlin Definition largely reflect the limitations of clinical characterisation. Ultimately, this lack of agreement with lung pathology will ultimately impact in less-than-optimal customisation of the patient’s care, incongruent with the goals of precision medicine (decisions, practices, and/or products being tailored to the individual patient).

We, therefore, need to consider introducing new tools to better characterise ARDS. Currently available bedside diagnostic tools should be evaluated in clinical studies and if they have added value implemented in daily clinical practice. One of the challenges is that a novel diagnostic test for lung injury would be applied using the Berlin Definition, which fails for the reasons described above as a “gold standard” for classification. Thus, clinical trials should be constructed to test a regimen of novel diagnostics as compared to standard clinical diagnostics for prediction of

successful treatment intervention.

See Also: Personalised Medicine in Intensive Care

Patient selection for trials should also be tested based on physiological parameters that measure the underlying pathophysiology. For example, tools such as electrical impedance tomography and thermodilution-estimated extravascular lung water (EVLW) might provide better insight into the physiopathology and therefore direct a more individualised treatment approach. ARDS is defined by a histopathology pattern of diffuse alveolar damage and correlated with an increased EVLW, which can be measured at the bedside by the trans-pulmonary single-indicator thermo-dilution method. EVLW should be tested as a diagnostic criterion for ARDS, and might easily predict disease severity and outcome, adding value as a diagnostic criterion of ARDS (Camporota et al. 2012).

Another method for the bedside monitoring of lung pathophysiological processes is the analyses of exhaled breath (Nseir et al. 2011). Breath contains hundreds of volatile organic compounds that are produced during normal metabolism of the host, bacterial metabolism, or as a result of lipid peroxidation during an inflammatory response (Bos et al. 2014a). The octane concentration in exhaled breath was shown to be higher in patients with ARDS. This molecule is linked to peroxidation of oleic acid (Bos et al. 2014b). Both lipid peroxidation and oleic acid have been implicated in the pathogenesis of ARDS. Additionally, ethylene, another compound associated with the peroxidation of oleic acid, significantly increased during periods of oxidative stress in cardiac surgery. These two observations combined suggest that breath analysis might be used to evaluate lipid peroxidation in patients with ARDS (Boots et al. 2015). Because exhaled breath is available continuously for rapid analysis in mechanically ventilated patients, this approach might be useful as a continuous assessment of the pathophysiological process that is central to the development of ARDS.

Finally, another approach to test is a “mixed model” of ARDS classification which relies on phenotyping based on clinical characteristics, causes of lung injury, and/or individual or sets of biomarkers (Calfee et al. 2015). Since there is considerable heterogeneity between patients with ARDS, some patients might benefit from an intervention that harms others (Papazin et al. 2016). Stratification on biological responses to lung injury (i.e., the biological phenotype) may allow for better selection of patients for a certain intervention, allowing exclusion of patients that have a low chance of benefit (or even harm) (Beitler et al. 2016). Measuring a wide range of markers in a group of ARDS patients and clustering those patients together that have a similar biological profile could help identify biological phenotypes (Calfee et al. 2014). In a posthoc analysis of two randomised controlled trials, this approach identified two groups of patients that respond differently to increased PEEP and fluid therapy. We believe that these biological phenotypes might also be used in future studies to target immunomodulatory treatment (Beitler et al. 2016).

Conclusion

While big clinical trials of ARDS have provided important treatment benefits over the last two decades, precision medicine in the post-genomic era, based on novel molecular diagnostics and better phenotyping, is more likely to provide the next big advances in ARDS diagnosis, treatment and outcomes.

Conflict of Interest

Ignacio Martin-Loeches declares that he has no conflict of interest. Lieuwe Bos declares that he has no conflict of interest. J. Perren Cobb declares that he has no conflict of interest.

Abbreviations

ARDS acute respiratory distress syndrome

EVLW extravascular lung water

PEEP positive end-expiratory pressure

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