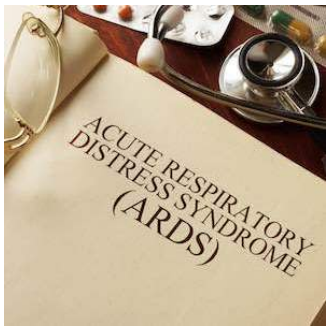
ICU
MANAGEMENT & PRACTICE

Precision Therapies for Heterogeneous ARDS Patients



ARDS is a heterogeneous syndrome rather than a distinct disease. It is this heterogeneity that often makes it difficult to study treatments for patients with ARDS. Literature on ARDS is rife with clinical trials that do not show any mortality benefit.

Recent evidence suggests different sub-phenotypes within the heterogeneous patient population. These sub-phenotypes have variable clinical responses to specific therapies. This concept is commonly referred to as heterogeneity of treatment effect (HTE). Realising the importance of these different sub-phenotypes and HTE could have important implications for the clinical management of patients with ARDS.

In a recent review, researchers present studies that have identified different sub-phenotypes and discuss how they can modify the effects of therapies evaluated in these clinical trials that are commonly considered to have no benefit in patients with ARDS.

The potential of HTE is an important factor to consider when designing and evaluating clinical trials. Trials that have a more heterogeneous study population are more generalisable to clinical practice and may have more external validity. But they are also likely to have more heterogeneous treatment effects among the study participants. On the other hand, clinical trials that include more a homogenous study population are less likely to have heterogeneous treatment effects but may have lower external validity.

As far as clinical trials for ARDS are concerned, therapies evaluated in clinically heterogeneous patient populations have been more or less unsuccessful. This could be due to truly ineffective therapies, but it is also possible that the therapies that were used may have helped some patients but harmed others resulting in non net clinical effect. That is why identifying different sub-phenotypes among patients with ARDS is extremely important. Potential sub-phenotypes that have been identified as effect modifiers include physiological, clinical and biological variables.

In this review, the authors summarise key trials of therapies for ARDS. Many of these trials are incorrectly referred to as negative. They present evidence for HTE according to the severity of disease, cause of ARDS and inflammatory sub-phenotypes and review the circumstances under which these treatments could potentially be useful.

The first strategy that is evaluated is open lung ventilation. Only two clinical studies show a mortality benefit associated with this strategy. However, as the authors highlight, while no mortality benefit was shown, the trials did not reveal any harm either. Patient-level analysis of the ALVEOLI, ExPress and LOVS trials show that open lung ventilation was associated with lower mortality when delivered to patients with PaO2/FIO2 ratios ≤200 mmHg.

Similarly, early trials of prone positioning did not decrease mortality in patients with PaO2/FIO2 ratios <300 mmHg or <150 mmHg. But the application of a longer duration of prone positioning led to non-significant trends towards mortality in patients with PaO2/FIO2 <100 mmHg and 132±74 mmHg.

There are studies that suggest an association between spontaneous modes of ventilation and increased ventilator-free days and shorter length of stay in the ICU. But again, no mortality benefit has been reported with this strategy. But as the authors point out, the HTE for spontaneous breathing is driven by the severity of ARDS.

These are just a few examples of the various strategies discussed by the authors in this review. The main point of their analysis is that it is

important to recognise different phenotypes among patients with ARDS and understand how they can modify the different treatments. Understanding the role of HTE and delivering therapies that are personalised to heterogeneous ARDS patients could be a significant paradigm shift in the clinical management of these patients. Treatments that may have been considered ineffective previously could, in fact, reduce mortality under certain circumstances if they are applied and used in the right patients.

Source: CHEST

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