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EDITORIAL

Definitions, guidelines and opinions: the white, the black and the grey

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Due to demographic reasons, I have had the opportunity to participate in all the international consensus conferences, up to Berlin [1], for the definition of acute respiratory distress syndrome (ARDS) and the development of guidelines for its management. The current tendency is to simplify both the definition and the management approach, primarily focussing on oxygenation or haemoglobin oxygen saturation [2], whilst other physiological variables, as respiratory mechanics or haemodynamics, are downplayed or ignored. It is, therefore, worthwhile to question the real value of guidelines in defining and managing ARDS, especially today when two leading societies have issued markedly different recommendations for three key aspects: positive end-expiratory pressure (PEEP) selection, venovenous extracorporeal membrane oxygenation (VV-ECMO) indications, and use of neuromuscular blockade [3, 4]. Before addressing these issues, it is crucial to reflect on the value of guidelines in managing syndromes such as ARDS, which is a collection of signs and symptoms with various causes and not a single disease.

Guidelines are a collaborative effort by experts who, through a combination of scientific evidence and personal opinions, produce recommendations. The generation of evidence relies heavily on the analysis of randomised clinical trials (RCTs), and methods like the Delphi technique for consensus building, culminating in a "democratic" vote. Consequently, the limitations of clinical trials become the limitations of the evidence, and the democratic process generates the majority's opinion, not necessarily the truth. The major limitations of RCTs in providing scientific evidence are clear: they typically include a small fraction of screened patients (about 10%) and overlook fundamental aspects of medicine such as patient history, age, prior health status, and comorbidities, which are theoretically neutralised by randomisation. Identical entry criteria in sepsis studies led to mortality rates ranging from 25% to 60%, in supposedly similar populations [5]. Unfortunately, current thinking often ignores these limitations, and RCTs and meta-analyses remains "dogmatic". The production of "evidence" has become a profession and an industry, characterised by rising costs, and rules dictated by professional trialists. Consequently, common clinical sense is sometimes lost.

One of the principles of statistical analysis is to exclude prior experiences, placing expert opinion at the lowest level of the evidence hierarchy. However (as you may have guessed, I am not a statistician!), I humbly believe that all our experience is nothing else than a "post-hoc analysis" and, most of decisions in our lives, including medical ones, are based on previous experiences. This highlights the limitations of relying solely on RCTs for guideline development. However, the "recent evidence" from guidelines suggests that opinions frequently outweigh the evidence provided by RCTs [6].

The recent differences in the guidelines produced by the American Thoracic Society (ATS) and the European Society of Intensive Care Medicine (ESICM) clearly underline these issues. I will limit my discussion to PEEP selection and VV-ECMO indication. When two expert panels, sharing 33% of participants and the same evidence, reach different conclusions, it suggests that opinions outweigh evidence. In two editorials published in this issue of Intensive Care Medicine [7, 8], the authors of the guidelines attempt to persuade readers that the differences are more apparent than substantial. However, for the "average" reader, the absence of a PEEP recommendation for all ARDS patients [4], or the recommendation to use high PEEP in moderate to severe ARDS [3] is substantially different.

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In real life, despite these contradictory recommendations, the trial results indicate that a general population benefits equally from a PEEP around 7 cmH_2O and PEEP around 12 cmH_2O. This suggests that in a population (not in a single individual), the risk/benefit ratio of atelectrauma (lower PEEP) is similar to the risk/benefits of volutrauma (higher PEEP) [9–11]. But, mortality increases with PEEP over 15 cmH2O, suggesting higher volutrauma risks in a significant patient subset [12]. From this simple "evidence", a complicated methodological approach led ESICM to conclude, and I paraphrase: "choose the PEEP you prefer" and the ATS: "you should use higher PEEP" (following the PEEP/FiO_2 table, which recommend, as an example, a PEEP of 16 when the set FiO_2 is 40%!) [11]. Similar reasoning may be applied to the use of neuromuscular agents.

The recommendation on extracorporeal support is a curious one and illustrates this issue further. From the Zapol's study to the EOLIA trial, classic RCTs failed to show a statistical benefit for VV-ECMO in severe ARDS. However, whilst initial trials led to a discontinuation of ECMO use, the EOLIA trial, despite being stopped for futility, was seen as "the positive amongst the negatives" [13, 14]. This reflects a shift in opinion rather than evidence, underscoring the influence of contemporary views on the use of ECMO. Although I am personally convinced that ECMO is a powerful tool to buy time until disease resolution and this is self-evident in clinical practise. In this framework, with similar levels of evidence (negative trial!), the ESICM strongly recommended against extracorporeal CO_2 removal and strongly recommended in favour of ECMO when in accordance with the EOLIA protocol. In contrast, the ATS opted for a more prudent recommendation. Once again, the evidence is largely overcome by the panel opinion. In summary, the recent guidelines for ARDS treatment from ATS and ESICM cast reasonable concerns about their usefulness and applicability.

Therefore, we may ask ourselves how to proceed to select the most adequate treatment for a given patient. Before doing so, it is interesting to consider that the ARDS approach currently undertaken by the intensivists is the exact opposite to that of oncologists. Indeed, we began with an "obsessive" characterisation (mechanics, haemodynamic, gas-exchange, etc.,) of individual patients (personalization), but later we shifted in a U-turn towards studying population behaviour through randomised studies, whilst oncologists moved from RCTs towards a more personalised approach (focussing on individual receptors and specific patient characteristics). My belief is that in the intensive care practise, which focuses on symptomatic treatment to sustain life until the underlying disease is resolved, the most logical approach is to identify the mechanisms at play in a given patient. For example, ventilatory treatment in ARDS cannot be rationally applied without understanding lung volumes and esophageal pressures, which are crucial for estimating lung strain and stress. Whilst guidelines can be useful in certain situations, their creation and application should not replace medical reasoning, which is aimed at addressing individual patient needs rather than population-wide issues.

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