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EDITORIAL

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Acquiring knowledge in intensive care: merits and pitfalls of randomized controlled trials

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Randomized controlled trials (RCTs) are experiments designed to confirm or disprove a given hypothesis. As such they should be considered in the stream of acquiring knowledge, a process which finds its first explicit expression by Aristotle (384–322 B.C.) who codified the syllogism as the ideal method to sort and display the knowledge gained through experience. The syllogism is a way of reasoning that, starting from general premises, derives conclusions applicable to particular cases through a stringent logic process (deduction): "Each animal is mortal, each man is animal, each man is mortal" (*Prior Analytics* I 1,24b 18 ss). The problem of the truth in the syllogism is not in its logic deductive process but in the premises: who assures that these are universally true? In the sixteenth to seventeenth centuries Copernicus, Keplero, Tycho Brahe, Galileo, and Newton, to different degrees and in sharp contrast with "dogmas", worked along a similar pathway: the inductive processes (sense-experiences) provide general theory which has to be proved (necessary demonstrations) by experiments and described mathematically. Accordingly, the theory (the premises) is deducted from the experience, and has to be proved experimentally (the RCTs).

In extreme synthesis, it seems that in different ages and through different times, the process of deduction is undiscussed and unquestioned, while what really matters is the origin and validity of the premises: intuition, mind, and God until the Middle Ages, and abstraction from experiments beginning from the seventeenth century. More recently in Vienna, at the beginning of the twentieth century, Popper provided a new standard to establish whether a theory is scientific or not and concluded that it is impossible to prove a given theory or premise. The only possibility is to disprove them. If 100,000 swans are white we cannot conclude with certainty that all swans are white, it is just probable; it is enough for the appearance of one black swan to disprove the theory and a new theory can be advanced, new hypotheses deducted, and new experiments performed through a continuous trial and error process (Popper K, *The Logic of Scientific Discovery,* 1959).

Therefore our reasoning in acquiring new knowledge in medicine may be summarized according to the following sequence: observation, inductive processes, proposal of theories and premises, deductive hypothesis, and experiments to prove or disprove the hypothesis, which is implicit in the premises. RCTs are one of the possible experiments. Testing an hypothesis deducted from wrong or vague premises leads necessarily to inconclusive results. Hence the fundamental importance of the premises when using RCTs. Let us consider, as examples, some of the major trials performed in intensive care units (ICU), by analyzing their premises, deducted hypotheses, and outcomes (Table 1).

Table 1 RCTs in ICU, examples and considerations

	Premises	Deductive hypothesis	Outcome	Comment
Extracorporeal support, first RCT performed in intensive care by Zapol et al. [1]	Premise 1) The respiratory support must provide normal PO_2 and PCO_2 Premise 2) High FiO_2 is harmful for the lung	Providing normal blood gases by artificial lungs at reduced FiO_2 of the ventilator improves survival	Hypothesis disproved: (90 % mortality in treated (45 pts) and control (45 pts) patients	Premise 1 is wrong as normal blood gases are unnecessary for survival. Premise 2 is limited: other factors than FiO_2 may damage the lung. The interpretation was that ECMO is useless, without discussing the wrong/limited premises. As a consequence, ECMO disappeared for the next 3 decades
High versus low tidal volume ventilation (ARDS Network) [2]	Premise 1) 12 mL/kg ideal body weight causes unphysiological strain in a size-reduced ARDS lung Premise 2) This strain increases lung inflammation and inflammatory cytokines may reach distal organs	Halving the tidal volume considered harmful (and accepting hypercapnia) decreases mortality attributable to high tidal volume mechanical ventilation	On 861 randomized patients, the hypothesis was proved	A key point in this study is the size of the tidal volume, in fact 3 previous randomized trials which tested ca. 7 versus ca. 10 mL/kg did not show significant outcome differences [3]. A recent post hoc analysis [4] showed that, using the tidal volume normalized to the lung compliance (i.e., driving pressure) instead of tidal volume normalized to the ideal body weight, better previsions are provided
PEEP trials: NHLBI ARDS Clinical Trials Network [5]; LOVS [6], ExPress [7]	Premise 1) Some level of PEEP is always necessary for oxygenation Premise 2) The adverse effects of higher PEEP (overdistension) are inferior to its beneficial effects (prevention of damage induced by intratidal collapse)	Using higher PEEP improves survival	Three major RCTs, involving 2299 patients, disproved the hypothesis	As the hypothesis was not proved one or more of the premises are totally or partially wrong. In fact the premises assume that in all the patients' PEEP provides benefits by keeping the lung open. Actually, the recruitment is extremely variable and higher PEEP should logically work only in patients with higher recruitability. When the premises are too generic and wide, as in this case, the risks of trial failure are far higher than if they are more precise and robust
Prone position: Gattinoni [8], Guerin 2004 [9], Mancebo [10], Taccone [11], Guerin 2013 [12]	Premise 1) (Trials by Gattinoni [8] and Guerin 2004 [9]): better oxygenation leads to better survival Premise 2) (Trials by Mancebo [10] and Taccone [11]): prone position increases lung homogeneity decreasing the uneven distribution of stress and strain thus decreasing the lung damage Premise 3) (Trial by Guerin 2013 [12]): as premise 2, but limited to the more severe patients	Hypothesis 1) (Trials by Gattinoni [8] and Guerin 2004 [9]): 6-h prone position improves survival Hypothesis 2) (Trials by Mancebo [10] and Taccone [11]): long-term prone position decreases mortality by decreasing stress and strain maldistribution in all ARDS patients Hypothesis 3) (Trial by Guerin 2013 [12]): long-term prone position does it only in severe ARDS patents	Trials by Gattinoni [8] (304 pts), and Guerin 2004 [9] (791 pts) disproved hypothesis Trials by Mancebo [10] (136 pts) and Taccone [11] (342 pts) disproved hypothesis Trial by Guerin 2013 [12] (466 pts) proved the hypothesis 3	This sequence of trials is an example of proceeding by trial and error. The premises of trial [8] and [9] were wrong, those of trials [10] and [11] were likely right but too generic, including less severe ARDS patients in whom the stress maldistribution is limited. The trial in [12] is based on strong and well-defined premises and strongly indicates that prone position must be performed only in severe ARDS patients

Table 1 continued

	Premises	Deductive hypothesis	Outcome	Comment
Early goal-directed therapy: by Rivers [13], ProCess [14], ARISE [15], ProMISe [16]	Premise 1) Imbalance between oxygen demand and oxygen supply causes, with time, organ dysfunction and failure Premise 2) The signs of imbalance are metabolic acidosis, increased lactate values, and low SvO_2 (if mitochondrial function is intact) Premise 3) The standard criteria for severe sepsis and septic shock define a population with the same characteristics, in whom oxygen imbalance is always present or predominant	If severe sepsis and septic shock patients are treated, targeting adequate central venous pressure, arterial pressure, and SvO_2, tissue ischemia is prevented/corrected thus improving survival (this is how the hypothesis was formulated, not how it should have been)	RCT by Rivers [13] (263 pts) proved the hypothesis ProCess [14] (1341 pts), ARISE [15] (1600 pts) and ProMISe RCTs [16] (1260 pts) disproved the hypothesis	Premise 3 is too generic and wrong in its formulation. In fact the severe sepsis/septic shock criteria pick up subgroups of patients with different mortality (from 18 to 45 %), different incidence of mechanical ventilation (from 10 to 80 %), and likely different incidence of patients with oxygen imbalance The logical deduction from premises 1 and 2 should have been to reserve the treatment to the patients with actual oxygen imbalance. May be by chance the first RCT [13] picked a population with baseline SvO_2 of 48 %, while in the remaining trial the baseline SvO_2 (when quoted) was already higher than 70 %, suggesting that oxygen imbalance was not the primary problem in the majority of the patients. Therefore, on the basis of these trials it is inappropriate to conclude that SvO_2 is a useless monitoring or target

RCT randomized controlled trial, PO_2 partial oxygen pressure, PCO_2 partial carbon dioxide pressure, FiO_2 inspired oxygen fraction, *ECMO* extracorporeal membrane oxygenation, *ARDS* acute respiratory distress syndrome, *NHLBI* National Heart, Lung, and Blood Institute, *PEEP* positive end expiratory pressure, SvO_2 venous oxygen saturation, *pts* patients

As shown, the successful trials are based on robust and well-defined hypotheses, sometimes refined with time. Good examples are the prone position trials and the low tidal volume ventilation. Many other trials, in our opinion, failed either because they were based on wrong premises (the first RCT on extracorporeal support) or were based on premises that were too vague and generic. Possible examples are the PEEP trials and the trials on early goal-directed therapy. Practical problems of the trials such as "population heterogeneity" or time of enrollment often hypothesized as an explanation of failing trials are implicit in the premises. If too generic, the heterogeneity of the population is an unavoidable consequence. Other series of trials, not analyzed in the table, concentrated on anti-inflammatory therapy in severe sepsis and septic shock, either by using corticosteroids or by blocking a large series of inflammatory mediators. These trials, in general, suffered from weak premises and hypotheses: sepsis is a generalized inflammatory reaction and blocking inflammation would improve survival. This approach does not consider a number of co-factors which should be included in the premises to make them credible and effective. In other trials the premises are inconsistent and lacking any physiological or clinical meaning. We found it difficult to identify credible premises in the trials of simvastatine in ARDS or fixed pressure levels in septic shock.

Considering the number of expensive and time-consuming trials performed in intensive care which failed to show differences between treated and control patients, it is tempting to say that in the ICU setting the trial is the wrong tool to advance our knowledge. However, a closer look at the structure and meaning of this methodology clearly suggests that the tool is not wrong per se, but the way we apply it. As the trials became a sort of dogma in ICU research, the trialists spent a lot of effort in improving their internal validity, by increasing the number of rules and caveats to avoid possible biases in the conduct of the trials. This contrasts sharply with the lower attention in clearly identifying and making explicit the premises of the trials, which are the core of the problem.

RCTs are successful, in general, only when the premises are well defined. This obviously makes the results valid only for the restricted patient population enrolled in the study and the generalization of the results (the external validity) is problematic. Using thousands of patients, studies with weak premises are usually inconclusive as the presence of subgroups in which the intervention could be of benefit may be obscured by subgroups in which the same intervention may be harmful. Therefore the effort to conduct the trial in a large population unavoidably carries the high risk of vague premises and useless results.

In conclusion we believe that trials may be an extremely effective method to advance our knowledge when "positive". This usually occurs when the premises are carefully considered and defined, the hypothesis logical, and the target population (unfortunately "restricted") adequate to test the hypothesis. In contrast the negative trials do not indicate that a given intervention per se is useless or wrong, but simply disproves the premises. This usually occurs when they are too generic or wrong.

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