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LESS IS MORE IN INTENSIVE CARE

Less is more: ten reasons for considering to discontinue unproven interventions

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An increasing number of practices in the Intensive Care Unit (ICU) have recently been challenged. There are several reasons why de-implementation of these practices should be considered. Before going further, it is worth pointing out that it is not our intention to suggest that every intervention needs to be validated in a randomized controlled trial (RCT). In fact, large RCTs may not be optimal for assessing interventions that are likely to benefit, and may not be feasible when dealing with rare diseases or uncommon endpoints. That said, these situations are uncommon but we would argue that most embedded practices should be validated to some extent. For the purpose of this short piece we will consider "unproven intervention" any intervention lacking a sufficient rational for the expected benefit, lacking concurrent evidences for any direct or indirect efficacy, or for which high degree evidence suggest lack of benefit. The following arguments support the call for de-implementation of unproven interventions:

1. "first do no harm"
   Non-maleficence is one of four basic principles of health care ethics. It is usually abbreviated as "primum non nocere": first do no harm [1]. The primacy of this principle, which implies strong disapproval of the use of unproven practices, is however less absolute than it may sound. Instead, a careful assessment of the benefit/risk ratio and the balance between beneficence and non-maleficence, summarized as "The patient's interests always come first" may more precisely reflect the spirit of this ethical principle [1, 2].
2. Side effects are easily overlooked/underestimated
   Assessing the risk/benefit balance of an intervention may however be challenging if the potential adverse effects are not fully described. Even high level trial data may only provide limited and potentially biased information regarding side effects due to inadequate ascertainment or classification of adverse events, or lack of statistical power to identify rare events [3]. Moreover, most RCTs are performed in carefully selected patient populations. Extrapolating a validated intervention to more general populations may potentially lead to an increase in severe or even fatal side effects [4]. Moreover, physician are likely to overestimate potential benefits while underestimating risks of given intervention [5].
3. Toxicity is frequently cumulative
   Side effects and toxicities may be cumulative [4, 6]. For instance, the risk and severity of acute kidney injury (AKI) depends on the number of potentially nephrotoxic agents [6]. As such, multiplication of intervention or drug is likely to increase risk of cumulative toxicity further disfavouring the risk–benefit ratio of interventions that have limited benefit, unknown benefits and/or limited data regarding side effects.
4. Debated toxicity remains a potential toxicity
   Another challenge arises from the difficulty to prove causality between an adverse event and the intervention. For example, renal toxicity of Vancomycin was observed more than 70 years ago but assumed to be related to a contaminant. A long debate followed until two years ago when the pathophysiological mechanisms of Vancomycin toxicity were demonstrated and replicated in animal models and the debate closed [6, 7]. The difficulty of assessing toxicity and confirming a causal relationship may lead

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to a biased assessment of the risk–benefit ratio of a poorly evaluated or unproven intervention.

5. More therapies are not necessarily more effective
The instinct to act and to do everything possible may lead to the implementation of unproven interventions in the hope they may confer benefit. However, countless interventions with promising preliminary results failed to stand up to the scrutiny of rigorous trials. It is also important to acknowledge that the discontinuation of marketed drugs, treatments and devices which had raised hopes and expectations has led to new doubts and disagreements among some clinicians, coupled with a sense of missed opportunities [8–10].
6. More is sometimes worse
Unproven interventions may not only be ineffective but also deleterious. For instance, protocolised administration of fluid to reverse oliguria may indeed worsen the risk of AKI, lead to fluid overload and an increased risk of morbidity or mortality [11]. Similarly, early initiation of continuous hemofiltration has not only failed to be beneficial in patients with shock but was also associated with worse outcomes in some studies [12].
7. More is frequently more expensive
Implementing new interventions is usually associated with increased costs. For instance, implementing a bundle of care in all patients with sepsis may be associated with an increase in cost from $2000 to $3000 per patient [9]. During times when the sustainability of health care systems is challenged worldwide, the distributive justice principle and the need to optimize judicious use of health care should discourage the use of unproven interventions [2, 13].
8. Changes to practice may be difficult
Traditional decision making processes in ICU may preclude easy and timely de-implementation of unproven interventions. Simplification of processes, protocols and heuristic thinking are powerful tools to aid decision-making processes but they may also limit flexibility and prevent change of practice [14, 15]. Status quo bias, which describes the tendency to continue "usual practice" when facing a decision, further precludes change and de-implementation [15].
9. Implementing unproven practices may mask ongoing areas of uncertainty
It is recognised that a negative trial result and lack of evidence does not completely exclude a potential benefit of an intervention. Concern about the heterogeneity of the population included in the study and/or potentially flawed study methods often underpin ongoing usage of unproven interventions. Unfortunately, the heterogeneity of patients receiving the intervention usually increases in routine clinical practice, along with the heterogeneity of the clinical context. This often hinders re-evaluating the intervention in real life scenarios and attempting to identify the population of interest that may benefit most from the intervention.

Table 1 Reasons for discontinuing unproven intervention along with their most obvious counter-arguments

Reasons for discontinuing unproven intervention	Counter-argument
First do no harm	A strict application of this principle may deter innovation, discoveries and lead to therapeutic nihilism
Side effects are easily overlooked	Implementation and close follow-up may be more efficient in detecting side effects
Toxicity is frequently cumulative	Toxicity may be overestimated and some toxic association are still debated (example Piperacillin/Tazobactam and Vancomycin Combination Therapy)
Debated toxicity remains a potential toxicity	Unwarranted fear of toxicity may deter from relevant and useful interventions (example: contrast media)
More is not necessarily better	A strict application of this principle may lead to therapeutic nihilism
More is sometimes worse	A strict application of this principle may lead to therapeutic nihilism
More is frequently more expensive	Accountability and struggle to respect distributive justice may not necessarily be in conflict with reasonable implementation of carefully chosen unproven intervention
Changing practices may be difficult	This is also true for proven interventions
Implemented unproven practices may mask ongoing areas of uncertainty	Implemented unproven practices in a carefully controlled context may help to identify subgroups that may benefit from an intervention
Implementing unproven practices may lead to excessive care	Therapeutic nihilism may deter search for solution and innovation in difficult context
Additional counter-arguments	Standardization of practices is one of the recommended organizational processes that may improve safety and patients' survival

10. Implementing unproven practices may lead to excessive care
    Lastly, offering or continuing an unproven intervention may delay acknowledging the lack of validated therapeutic options and the need for more research and innovation. Such misperception of therapeutic options may result in misleading conversations with patients, patient's families and colleagues and give false hopes, along with the risk of excess care and prolongation of suffering.

As a closing remark, the arguments listed above are relative and most of them may be opposed by sound counter-arguments (see Table 1). Nevertheless, we believe that clinicians should be encouraged to regularly assess and re-assess the benefit and risks of implemented procedures, therapeutic strategies and bundles of care in routine clinical practice, and if possible in randomized trials. Only this will identify strategies that may be unproven but effective and safe, or unproven and harmful and should be discontinued. More importantly, the evaluation of procedures and strategies should not be limited to RCTs. Validation in real life practice may need to be performed in ways that identify both obstacles to real world implementation, external validity of expected/observed benefit, and side effects/modification of risk induced by interventions.

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