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Clinical Trials without conceptual foundation may produce flawed results for the management of fluid therapy in the critically ill

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The 12th Consensus Conference of the Acute Dialysis Quality Initiative (ADQI XII) focused on i.v. fluid administration and removal in perioperative and critical care medicine.[1] It used a process of structured literature review, Delphi approach to consensus of a group of experts. These experts have a documented history of academic leadership and bedside medicine in fluid resuscitation and removal strategies. Fluid management is a central aspect of management of perioperative and critically ill patients. Critical illness, anaesthesia, surgery, and related therapies all may alter generalized macrovascular and regional tissue blood flow requiring prompt specific therapies, most of which are centred around specific fluid resuscitation. Furthermore, resuscitation physiology research shows clear discrepancies and divergent findings between the treatments that target macrocirculatory variables (e.g. cardiac output, arterial pressure, and oxygen delivery/consumption) or regional/cellular variables (e.g. organ function, tissue oxygen saturation, microcirculatory flow, and local energy metabolism).[2] Therefore, creating a broad summary of consensus will be useful to the clinician attempting to define rational approaches to assess fluid status, and need for fluids or their removal.

In an accompanying commentary, Dr Finfer[3] criticized the ADQI XII approach of using expert opinion based on physiological principles, personal heuristics, and clinical experience coupled to results from published literature and randomized clinical trials (RCTs). His criticisms underscore much of the present-day clinical focus of trying to define best practice clinical decision-making by tightly linking it to the results of published RCTs of groups so similar though not identical patients. Although the use of appropriately powered outcome-based RCTs is the backbone of much of clinical practice advancement, especially in the fields of cardiology and oncology, their juxtaposition onto critical care medicine rapidly degrades. Unlike acute coronary syndromes, heart failure, or cancer, critical illness creates a much more heterogeneous and dynamic interaction of the determinants of outcome than seen in single organ system processes. Furthermore, titration of care common to the management of the acutely ill and perioperative patient is much more difficult to be protocolized. The malignant academic pressure to reduce all critical care medicine practice to RCT-based positive trials and not use treatments from RCT-based negative trials deserves to be questioned.

While consensus without evidence can lead to adoption of practices that ultimately prove incorrect,[4] trials without proper grounding in conceptual frameworks can lead to erroneous conclusions. Two simple examples underscore this truth. A trial of penicillin for bacteraemia would likely only show harm without understanding the susceptibility of the infecting organisms. Similarly, a trial of norepinephrine for hypotensive shock would very likely show harm without understanding of the intravascular volume status, vasomotor tone, and cardiac contractility of the patient and an associated volume and inotrope support protocol linked to that trial. The ADQI XII view was that consensus of experts guided by evidence, and evidence acquisition guided by experts, is the best way forward.

The RCT example suggested by Dr Finfer of the ARDSNet liberal *vs* restrictive fluid trail in patients with acute lung injury (ARDS) illustrates this point nicely.[5] Though Dr Finfer gave this trial an example of how an RCT can define practice, this RCT actually gave a different outcome when studied

further by the ARDSNet investigators. Although this ARDSNet RCT showed no survival difference between patients stabilized with either restrictive *vs* liberal fluid resuscitation, the restrictive fluid group experienced a 36 h shorter time on mechanical ventilation.[6] Proponents of 'keep the lung dry' then pushed for all ARDS patents to be given a restrictive fluid strategy. However, follow-up studies in long-term survivors by these same investigators showed that the restricted fluid management approach was associated with markedly increased cognitive dysfunction at 12 months. So the restrictive fluid therapy patients were liberated from mechanical ventilation earlier only to become more dysfunctional upon recovery.[6] If restricted fluid therapy were a new drug, this harm signal would be grounds to block its future use. The reasons for these positive (shorter time receiving mechanical ventilatory support) and negative (impaired cognitive function) are probably due to the same mechanism, reduced effective circulating blood volume that in one case improves oxygenation and on the other increases drug toxicity. Clearly, some patients with isolated single organ injury may benefit from a restrictive fluid therapy, whereas those at risk for subsequent cognitive dysfunction may not. But without separating individual patients by their disease process, this distinction was lost.

Although consensus without evidence can lead to adoption of practices that ultimately prove incorrect, clinical trials without proper grounding in conceptual frameworks can lead to erroneous conclusions. This lack of a strong conceptual framework underlies much of the confusion in the interpretation of many of the existing positive RCTs. One clearly needs to understand a disease (e.g. coronary artery disease), separate from a syndrome or symptom complex (e.g. chest pain), in order to develop therapies that can ultimately be tested in clinical trials. For example, had streptokinase been given to all people presenting with chest pain, it would have failed in the same fashion that giving hydroxyethyl starch (HES) to all patients getting fluid failed. Streptokinase is far more dangerous than HES and yet it serves as a useful drug for a very specific condition. The CHEST trial failed to identify these specific conditions for which HES may be useful because the trial lacked a coherent paradigm for fluid administration.[7]

An important example is the history of drotrecogin α (activated) in the treatment of human sepsis (Prowess).[8] Activated protein C levels are decreased in critically ill patients and inversely correlate with mortality. However, giving drotrecogin α activated to septic patients did not increase activated protein C levels. Furthermore, before starting the clinical trial, few animal studies or small clinical trials were performed to define which patients or conditions would benefit from activated protein C replacement. The conceptual basis for its positive actions was developed *post hoc*, once the initial trial was positive for benefit. Regrettably, all subsequent clinical trials of this agent proved ineffective.[9] Does this mean that drotrecogin α activated is not effective in human sepsis? The answer is unknown. It is probably useful in some patients with specific physiology/inflammatory state and not in others. But without a conceptual framework, one of the most expensive clinical trials in critical care medicine places this drug in the very large ineffective treatment pile.

Similarly, tight glucose control in centres that know and understand the risks on insulin infusion improves survival in both surgical intensive care unit (ICU) patients[10] and those medical ICU patients who require prolonged ICU stay.[11] But when trialled across many hospitals wherein risk of hypoglycaemia or hypokalaemia, two common compilations of poorly monitored insulin therapy, were not included in the protocols, harm was seen. In the German SepNet trial, tight glucose control was performed by resident physicians who measured blood glucose when they were available.[12] They saw a higher level of hypoglycaemia in the tight glucose group in their study. In the NICE Sugar trial, the tight glucose control protocol did not include monitoring serum potassium levels,[13] and regrettably, they reported an increased incidence of cardiac arrhythmias in the tight glucose control group. What is the best balance in glucose control for the critically ill? We do not know. But, it is most likely to be lower than the levels routinely allowed before the start of these trials.

Realistically, is it possible to conduct massive RCTs to address important issue in critical care medicine without a strong conceptual basis for the exact mechanism of action of the defined treatment? The ADQI XII workgroup has attempted to provide a testable framework for which future studies can be based. We look forward to future RCTs based on a more nuisance and pathophysiologically based approach that will allow practicing clinicians to use those results in their own bedside clinical decision-making.

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