

In-Depth Clinical Review

Identifying critically ill patients with acute kidney injury for whom renal replacement therapy is inappropriate: an exercise in futility?

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Abstract

Clinicians treating critically ill patients must consider the possibility that painful and expensive aggressive treatments might confer negligible benefit. Such treatments are often described as futile or inappropriate. We discuss the problem of deciding whether to initiate renal replacement therapy (RRT) for critically ill patients with acute kidney injury (AKI) in the context of the debate surrounding medical futility. The main problems in deciding when such treatment would be futile are that the concept itself is controversial and eludes quantitative definition, that available outcome data do not allow confident identification of patients who will not benefit from treatment and that the decision on RRT in a critically ill patient with AKI is qualitatively different from decisions on other modalities of intensive care and resuscitation, as well as from decisions on dialysis for chronic kidney disease. Despite these difficulties, nephrologists need to identify circumstances in which continued aggressive care would be futile before proceeding to initiate RRT.

Keywords: acute kidney injury; critical illness; medical futility; outcome prediction; renal replacement therapy

A 64-year-old man underwent revision of prior coronary artery bypass grafting and replacement of a stenotic aortic valve. On the 4th post-operative day, respiratory failure required re-intubation, and acute kidney injury followed an episode of ventricular tachycardia. Continuous veno-venous haemofiltration (CVVH) was initiated; haemodialysis was substituted as the patient became haemodynamically more stable. However, ischaemic necrosis of fingers and toes of all extremities prompted bedside amputations. Anuria accompanied pneumonia, sepsis, intravascular coagulation and lactic acidosis. CVVH was

re-initiated on the 27th post-operative day, but the patient died shortly thereafter.

Background

Critical care decision making is influenced by many factors. These include social and cultural norms, the patient's or surrogate's values and preferences, underlying as well as acute medical conditions, the treatment setting, resource availability, and psychosocial and family circumstances [1–5]. For over two decades, medical literature has discussed the concept that there may be circumstances under which active treatment is futile. The concept has evolved over time, and the focus of discourse on futility shifted from debate over the definition of futility to an attempt to formulate policies for the determination of futility, to an emphasis on communication and mediation skills to resolve disagreements surrounding arguably futile treatment [6]. The decision whether to withhold or withdraw dialysis in critically ill patients with acute kidney injury (AKI) requires the nephrologist to merge knowledge of available outcome data with ethical considerations. He/she should recognize that outcome data offer only limited predictive information. He/she must also communicate the factual and ethical framework of dialysis to his/her fellow clinicians, the patient and the family, while skilfully avoiding and resolving disagreement and misunderstanding among all parties [7,8]. We recognize three main problems that a clinician considering withholding or withdrawing dialysis based on futility would encounter. The first is the controversial nature of the concept of medical futility, and the lack of a clear quantitative definition for futile treatment. The second is that the limitations of available outcome data impede confident identification of patients who would not substantially benefit from treatment. Finally, decisions on dialysis for AKI are different, clinically and sociologically, from decisions on other modalities of intensive care and resuscitation, as well as from decisions on dialysis for chronic kidney disease (CKD). These problems highlight the role of the nephrology consultant who must consider not only the clinical and technical aspects of the patient's condition but also recognize circumstances in which dialysis, as part

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of a continued aggressive care approach, would be futile or inappropriate.

The controversy over the definition and terminology of futile treatment

Although the terms of the discussion have changed, the early debate concerning the definition of futility remains relevant [9]. Various authors attempted quantitative definitions; they did not reach consensus, and the attempt may have been inherently problematic. One proposed definition suggested calling an intervention futile if the treatment had never worked in the last 100 cases in which it had been attempted, in which case ‘the clinician can be 95% confident that no more than three successes would occur in every 100 comparable trials’ based on the probability distribution function [10]. In addition to being arbitrary, the proposed calculation method has several limitations: first, the individual practitioner’s experience is inevitably subject to spectrum bias; second, published data regarding outcomes of treatment may not be readily applicable to individual patients outside the original cohort; and third, the setting in which physicians practice influences their perspective [11,12].

Attempts to provide a qualitative, rather than quantitative, definition of futility have proposed considering a treatment futile ‘that merely preserves permanent unconsciousness or that fails to end total dependence on intensive medical care’ [10]. This definition, however, implies a value judgment about the worth of life in a severely debilitated or chronic vegetative state that is far from universally accepted [6].

The empirical approach extends the quantitative approach, attempting to achieve a more generally acceptable and rationally applied definition of futility [13]. It uses data and predictive instruments to identify treatments that would be considered futile according to thresholds established by the quantitative approach. Severity scores such as the Acute Physiology and Chronic Health Evaluation (APACHE) III and Acute Physiology Score (APS) have been proposed as instruments to identify patients for whom care would be futile or ineffective [14,15]. Other studies examined more specific patient populations, such as bone marrow transplant recipients who require mechanical ventilation. Among a subset of almost 400 such patients who had additional organ failure or haemodynamic instability, the survival rate was zero, which the authors considered as evidence for futility [16]. Survival was defined as being alive 30 days after extubation, and discharged from hospital. ‘Zero survival’, therefore, is not synonymous with 100% futility, since a patient may very well benefit from being alive and extubated for 29 days [13]. Therefore, even with an extremely high rate of adverse outcomes observed in a very large cohort of patients, there is a subjective, value-based judgment to be made.

The difficulty in reaching a universal definition of futility is much more than technical. The term evokes a sense of finality and certainty that is rare in clinical practice. The American Medical Association’s Council on Ethical and Judicial Affairs addressed the controversial, value-laden na-

ture of the term futility, finding ‘great difficulty in assigning an absolute definition to the term *futility* . . .’ and favoured ‘a fair process approach for determining . . .withholding or withdrawing what is felt to be futile care’ [17]. Using the term ‘inappropriate’, rather than ‘futile’, treatment may better reflect the uncertainty surrounding these issues [18]. The Society of Critical Care Medicine’s Ethics Committee’s statement favours the term ‘futility’ only where there is no physiologic benefit to the patient, and ‘inappropriate treatment’ where there is only an extremely small chance of success, extremely high cost, or uncertainty or controversy regarding the benefit of treatment [19].

The application of futility: a dialectic of autonomy and authority

The debate concerning futility extends beyond the problem of definition, and touches upon questions of physicians’ professional authority versus patients’ rights and autonomy in deciding to withhold treatment on the basis of futility [13]. In fact, the very emergence of the concept of medical futility may be viewed as a response by clinicians to families’ demands for treatment that physicians considered inappropriate [6,20]. This process reflects, at least in part, an attempt to re-assert professional judgment in an era of primacy of patient autonomy in ethics and law and backlash against medical paternalism [10].

The unilateral application of futility by physicians has been criticized as a violation of patient autonomy and dignity [20,21]. The retort asserts that requiring patient consent to withhold futile therapy actually undermines patient autonomy by sending mixed messages and making informed choice more difficult [22]. Moreover, the argument goes, the requirement to provide treatment that he considers useless and potentially harmful subordinates the physician’s conscience to societal dicta, violating personal and professional integrity [23].

Does withholding life-sustaining treatment from patients whose prognosis is poor and whose baseline functional status is very impaired mean to deprive them of autonomy? Patient autonomy may be viewed as having more than one level. The first, based on negative rights, is the right for protection from intrusion by involuntary diagnostic or therapeutic medical procedures. The second, based on positive rights, is the freedom to choose from treatments offered by the physician. Whether or not a third level exists that includes patients’ right to define the range of possible treatments from which they may choose is debatable [24]. Physicians faced with this dilemma must navigate between two extremes. The first is a paternalistic approach that dismisses patients’ self-determined interests in favour of physician-defined beneficence. The second is where physicians act solely as a conduit of information about all technically possible options. This latter approach dismisses the value of physician judgment, focus and guidance in favour of avoiding undue influence on independent patient choice [25].

Attempts at defining a balanced model stress the need for an open and equal exchange of ideas, opinions and concerns between physicians and patients, and having the final

choice made by a fully informed patient [25]. Clinicians must also acknowledge the influence of subjective experience, personal values, differences in clinical perspective, understanding of facts and concepts, miscommunication and other sources of bias in the perception of futility [11,26,27]. Many policies and guidelines require that a second physician concur with the treating physician's assessment of futility [28]. This might reduce the effect of bias and arbitrariness in this context.

The debate over the application of futility prompted clinicians, ethicists, policy makers and legislators to explore ways towards its resolution. Hospitals, professional organizations and legislators sought a solution based on policy and law. The underlying principle of this approach is to provide a clear procedural route to be followed when disputes over potentially futile treatment arise [28]. Other authors hold that the solution to these conflicts is to be found not in public policy but rather in avoiding conflict. This aim might be achieved by greater emphasis on improving physicians' communication and interaction skills when discussing end-of-life treatment with patients and families [29].

Limitations to predicting outcome in critically ill patients with AKI

The first step towards assessment of quantitative futility in these patients is examination of the empirical data regarding their prognosis, and identifying factors associated with the worst patient outcome. One retrospective cohort study stratified intensive care unit (ICU) patients with AKI requiring dialysis by prognosis [30]. In-hospital mortality was 70% and about two-thirds of deaths occurred within 30 days of dialysis initiation. Mechanical ventilation, malignancy and non-respiratory organ failure independently and significantly predicted mortality. Diabetes and higher creatinine levels were associated with lower mortality, which, although counterintuitive, could be explained physiologically or methodologically [31]. Using a multivariate regression model, and a 95% positivity criterion, 24% of deaths were correctly predicted with no misclassification of survivors. Using the 100-sample bootstrap method, prediction of mortality at the 95% confidence cut-off was 0.5%. Theoretically, 1 in 200 patients who were destined to survive was incorrectly classified as having being destined to die [30]. If this degree of precision in predicting mortality were applicable for individual patients outside the original cohort, this model would approximate the original threshold proposed for quantitative futility [10].

Subsequent prospective studies that assessed outcome in AKI found an overall in-hospital mortality rate ranging from 37 to 85% [32–40].

Risk factors for mortality vary among these studies but often include older age, severe uraemia, AKI of septic origin, respiratory or hepatic failure, thrombocytopenia, oliguria, history of hypertension, lower baseline serum creatinine, haemodynamic instability, abnormal consciousness and RIFLE score in the 'failure' category [41].

A further analysis of data from the Program to Improve Care in Acute Renal Disease (PICARD) was performed

to identify predictive variables at three time points: onset of AKI, nephrology consultation and initiation of dialysis. The predictive power of variables obtained at the onset of AKI was extremely low, but improved somewhat at the time of nephrology consultation and was best at the initiation of dialysis. Models incorporating analysis of variation over time, day-to-day changes in extra-renal system organ failure and accounting for provision of dialysis over the course of AKI enhanced predictive power in this analysis [33]. While overall in-hospital mortality in PICARD was relatively low (37%), in some study centres it remained very high (80–100%) in subgroups such as those with four or more organ system failure or who were intermittently dialyzed, and then switched to continuous mode. Considerable inter-institutional variation in patient characteristics and treatment practices was observed [42]. Even at the initiation of dialysis, no generic or disease-specific predictive model had an area under the receiver operating characteristic (ROC) curve >0.73 [33].

A recent multinational trial examined AKI-related outcomes of 29 269 ICU patients in 54 countries. AKI occurred in 5.7% of patients; 1260 (4.3%) required RRT. Overall hospital mortality was 60.3%; 13.8% were still continuing dialysis when discharged from hospital [34]. Analysis of two generic (Simplified Acute Physiology - SAP II, Sequential Organ Failure Assessment - SOFA) and four renal-specific (Chertow [35], Mehta [36], Liano [37], Paganini [39]) scoring systems showed none of them to have a high level of calibration or discrimination [38]. A randomized controlled trial did not show continuous veno-venous haemodiafiltration to significantly increase survival compared to intermittent haemodialysis; the former was associated with 32% 60-day survival, and the latter with 33% [40]. These findings were confirmed in a recent meta-analysis [43].

Despite this abundance of available data, several methodological problems limit its usefulness for clinicians confronted with the problem of futility. First, application of a regression model to patient populations other than the original cohort from which it was developed is problematic and increases uncertainty [38]. Second, relative risk or odds ratio does not directly address the issue of futility, since the group with the worse prognosis may still have an absolute probability of survival high enough to justify treatment. Third, many articles that report mortality rates approaching 100% do so for groups that are too small to allow for confident generalization. In fact, only a handful of articles identify groups of more than 10 patients with mortality rates exceeding 95% [36,44]. Thus, even for some of the best available models—58/60 deaths in the worse prognostic decile of the PICARD model [36] and 45/46 in the worse prognostic quintile of the Liano score [44]—the lower 95% confidence limit is only 88–89%.

Aspects of futility specific to dialysis in AKI

The challenge of determining futility of dialysis in AKI is not limited to the difficulty in interpreting the available outcome data. The unique temporal and clinical characteristics of the decision required in this setting render it distinct from both the decision making regarding dialysis in CKD and

decisions about other intensive care treatments for critically ill patients.

Dialysis for CKD and dialysis for AKI

In the case of dialysis for patients with CKD, the guidelines published by the American Society of Nephrology (ASN) and Renal Physicians Association (RPA) for withholding and withdrawing dialysis in patients with end-stage renal disease (ESRD) [45] as well as the K/DOQI guidelines on initiation of haemodialysis and peritoneal dialysis [46] may help clinicians decide on the appropriateness of initiating treatment. The ASN/RPA guidelines emphasize the importance of a patient–physician relationship that promotes shared decision making, informed consent and refusal, estimating prognosis, conflict resolution, advanced directives, advanced health planning, a checklist for withdrawal, consideration of special groups with particularly poor prognosis, time-limited trials of dialysis and the application of palliative care principles [45]. The K/DOQI guidelines emphasize tradeoffs between benefits and harms inherent in initiating chronic dialysis treatment at varying levels of kidney function, and the dependence of this decision on systems of care.

How applicable are these guidelines to decisions regarding RRT for critically ill patients with AKI? While many of the principles in the RPA/ASN guidelines are certainly relevant in the acute setting as they are in ESRD [8], certain key differences render them less relevant to critically ill patients with AKI. The potential for shared decision making, for example, may differ widely between the two scenarios: in the case of CKD progressing to ESRD, the decision-making process is ideally the result of a long-standing relationship between the patient, family and the attending nephrologist that may develop over the span of many years as the disease slowly progresses.

Although many patients with CKD still come late to nephrologists' attention, even in the emergency department, 70% of ESRD patients in the United States have been followed by a nephrologist for more than 4 months prior to dialysis; the median follow-up time prior to initiation of dialysis is 346 days [47]. Repeated outpatient visits over months and years allow patient and physician to form a relationship and to make plans together. Patients who have longer contact with a nephrologist before ESRD survive longer, and are more likely to begin haemodialysis treatment using an arterio-venous fistula than are those who have only brief care, or who are dialyzed emergently [47,48]. The situation of the patient with AKI is very much like that of the patient with CKD that is first recognized in the emergency department. Decisions are often urgent, and clinicians usually have no previous relationship with the patient and family; it is much harder truly to share decision making. In a survey of ICU physician–family conferences about end-of-life decisions, criteria for shared decision making were only met in 2% of cases, and the rate of shared decision making was lower with lower family level of education [49]. In this respect, decision making about the treatment of AKI and about the emergency treatment of CKD are probably much more similar to other acute care decision making than to

dialysis preparation for CKD patients who have been under a nephrologist's care for months or years. Finally, in deciding on dialysis in the chronic setting, the nephrologist occupies the position of primary clinician. In the treatment of critically ill ICU patients, decisions regarding RRT require co-operation and agreement with intensive care colleagues, regardless of the expanding role of nephrologists in this setting [50].

Differences between dialysis and other life-sustaining modalities

The decision to dialyze a critically ill patient with AKI also differs in quality from decisions regarding other modalities of life-sustaining intensive care such as intubation, mechanical ventilation, and basic and advanced cardiac life support.

The first important difference relates to the temporal dimension of decision and action. In respiratory or circulatory failure, the interval between the clinical indication and the need to act is usually seconds to minutes, whereas in acute kidney injury it can range from hours to weeks [33]. This allows for more time to deliberate on the appropriateness of dialysis, not just as an isolated treatment module but also as part of continued aggressive treatment as a whole. This approach would require nephrology consultants to take a more active role in raising the question of futility with their ICU colleagues *before* proceeding to dialysis [8].

The second difference is that the indications for dialysis in AKI, optimal timing, dosage and modality and even the very definition of AKI are all controversial and unclear [43,51], and are farther from consensus and standardization than those for other resuscitative modalities (e.g. ACLS protocols for cardiac resuscitation). Furthermore, signs of physiological futility in dialysis are less immediate. When mechanical ventilation or cardiac resuscitation fails to achieve its physiological goals (i.e. the patient remains severely hypoxic, or does not regain effective circulation), it is evident immediately, whereas the effects (or lack thereof) of dialysis on the patient's volume status, uraemic signs and symptoms, and acid base and electrolyte abnormalities are often delayed.

The question of whether AKI is more of a factor in the demise of critically ill patients or a marker of disease severity remains unanswered [52,53]. Thus, when the utility of dialysis for AKI is questionable, assessing its futility in a specific patient becomes even more problematic.

Futility, resource allocation and dialysis

The debate concerning futility shares some common ground with the question of just rationing of resources, since defining an intervention as futile can be used to support an argument for withdrawing, withholding or not offering such treatment [8,54] in the interest of a more just and efficient allocation policy. Others argue that futility and resource allocations belong to different ethical and social paradigms and are best kept separate [13,55–57]. There is paucity

of data concerning the cost-effectiveness of management of critically ill patients. It has been suggested that high-quality cost-effectiveness analysis is particularly important in assessing the effects and utility of costly interventions such as RRT [57]. A secondary analysis of the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) Trial studied the impact of dialysis on outcomes and its cost-effectiveness in seriously ill hospitalized patients prospectively [58]. Dialyzed patients tended to be those in whom a generally aggressive approach to treatment was adopted. The median survival was 32 days; 6-month survival was 27%. Estimated cost per quality adjusted life-year (QALY) of initiating dialysis was \$128 200, although the authors comment that overall cost in those patients was driven not so much by the cost of dialysis itself but rather by the continuation of aggressive treatment. Cost per QALY was higher with worse *a priori* prognosis [58].

It is important to recognize, however, that cost-effectiveness analyses based on QALY's can have significant flaws. They rely heavily on assumptions, some of which do not correspond with actual behaviour patterns and choices in empirical studies [59]. Furthermore, QALY-based analyses measure individual utility to elicit values that are meant to support social choice, most notably resource allocation. These problems limit the utility of QALY's in informing clinical decision making and health policy [60].

The imposing cost of dialysis for patients has been cited in the context of withholding or withdrawing dialysis in certain critically ill patients with AKI [8]. We consider the meaning of these numbers from a different perspective. The main determinant of the cost of dialysis in the SUPPORT trial was considered to be continued aggressive care, rather than dialysis *per se* [58]. Our interpretation of this analysis is that the economic reality reflects a clinical one: the futility and benefits of dialysis are inextricable from those of intensive care as a whole.

Conclusion

The problem of potentially futile or inappropriate medical treatment poses a formidable challenge to physicians, patients and their families, and society at large. Its definition is elusive, and the application of these concepts in medical practice may prompt controversy among professionals and conflict between clinicians, patients and families. A nephrologist required to determine futility or inappropriateness of RRT in a critically ill patient must overcome obstacles inherent to this clinical setting.

The high mortality rates in patients with AKI who are treated with RRT indicate that treatment is futile in a significant portion of cases. However, despite a considerable corpus of empirical evidence on outcomes in AKI, the calibration and discrimination of predictive variables and scoring systems remain limited. The identification of patients in whom treatment is potentially futile is, therefore, problematic. While guidelines on withholding and withdrawing dialysis have been published, they appear to be much more readily applicable to patients with CKD progress-

ing to ESRD. Their limitations in the care of critically ill patients with AKI include the common lack of personal patient-physician relationships as a basis for shared decision making, the rapid clinical course and the need to mobilize a medical team to reverse the acute condition. In addition, the nephrology consultant is generally in a secondary position in overall patient management, as opposed to his or her primary role in ESRD. Dialysis for AKI differs from other common organ failure treatments in that there is usually a relatively long interval between recognition of the indication for treatment and the absolute need to act on it, in that the response to treatment is much slower and harder to determine and in that the optimal timing, dosing and modality of RRT are largely unknown.

Despite these inherent difficulties, nephrologists can and should take an active role in promoting discussion of futility in circumstances where clinical impression and objective parameters indicate that the prospects for a meaningful recovery are no more than minimal. Uncertainty, arbitrariness and bias are major concerns that must be acknowledged and addressed. Given the time-dependent nature of certain predictive models [33], decisions to dialyze made at the time of the initial consultation should be reviewed immediately before dialysis is actually initiated. Truly shared decision making is not always feasible in the face of acute, rapidly progressive, critical illness. Clinicians need to communicate their position in a consistent, clear and timely manner and make a genuine attempt at reaching agreement. Resorting to policy or legal mechanisms for resolving disputes is much less preferable than shared decision making, and usually unnecessary [61]. A cogent, compassionate assertion of futility, where appropriate, should not be viewed as dismissive of patient autonomy or the wishes and concerns of their families, but rather as an expression of professional responsibility and integrity.

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