CHAPTER 148

Ethical Considerations in Acute Renal Replacement Therapy

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OBJECTIVES

This chapter will:

1. Present the main bioethical problems associated with the management of renal replacement therapy (RRT) in critically ill patients.
2. Discuss a strategy, based on moral principles, for guiding the decision-making process.
3. Present a protocol to guide a practical possible approach to difficult decisions in critically ill patients.
4. Present and discuss some of the problems associated with clinical research in RRT in critically ill patients.
5. Present some biosocial issues related to RRT.

Renal replacement therapy (RRT) always has had a strict connection with bioethics. Information and consent for a lifesaving therapy (dialysis), clinical research, management of vital support procedures, procurement of vital organs for transplantation, and maintenance of waiting lists for expensive and scarce devices are only a few examples of how the history of RRT has marked strongly the development of bioethics. For this reason, a specific chapter dealing with some ethical considerations seems appropriate for this textbook.

The goals of this chapter are to ensure that the moral principles for delivery of care and their practical applications are understood to promote a bioethical culture for the best management of RRT for care and for research and to ensure that readers can make responsible choices in the management of RRT, even for terminally ill patients.

The chapter is divided into three parts. The first part deals with some bioethical considerations when caring for critically ill patients in need of RRT. Because renal failure in such patients is associated significantly with poor prognosis, the problem of foregoing restorative care and optimizing palliative care is examined particularly. The second part of the chapter deals with clinical research in RRT. Finally, some biosocial issues related to RRT are discussed.

RENAL REPLACEMENT THERAPY IN THE CARE OF THE CRITICALLY ILL PATIENT

Morality of Renal Replacement

The ethical management of intensive care support procedures can be difficult. A basic question refers to the question of whether RRT is moral. If it is, where does its morality stand? The answers can come only from our view of health and healthcare. Health could be considered just a physical accident (such as beauty, height, or the color of the eyes) and healthcare a commercial commodity reserved to those who can pay for it. If this were true, perhaps RRT (and, indeed, any other medical activity) would be only a technical act, one that must be managed with attention, commitment, and honesty but does not have any relevant intrinsic moral content.

On the contrary, health can be regarded as a fundamental good of every human being and healthcare as a basic human right.[1] In this sense, RRT is more than a mere technical act and has some moral content. However, what is its specific aim?

RRT, as any other medical intervention, is a means, not a goal. Many people (including clinicians) believe that the aim of medicine is to heal diseases and that hospitals are the places where diseases are fought. This means mistaking means for goals. In reality, the aim of medicine is to help people with health problems to conceive and accomplish their project of the best possible life. In case of a curable disease, trying to heal the disease is usually the best way to realize such an aim.

Unfortunately, not all diseases are curable. However, people always can be cared for, especially those in terminal conditions. For this reason, every possible intervention should undergo a twofold scrutiny to ascertain that it is clinically appropriate and ethically proportionate. A medical intervention is clinically appropriate when it will reasonably attain the beneficial clinical effect over that specific person's health problem. Assessing the clinical adequacy means determining the limit of the medical intervention to oppose a pathologic process and support the biologic frailty of the person for whom it is used. An evidence-based approach should be used to determine which possible action is the most adequate and to avoid useless or futile interventions. A medical intervention is ethically proportionate when its clinical adequacy is not only a biologic parameter but also a biographic one; it also can affect positively that person's life, helping to accomplish his or her life project. In this sense, the limit beyond which the medical intervention should be foregone is not that of the intervention to support the biologic frailty of the person, but rather the level of irretrievable frailty that the person sets as a limit for her life story.

In this sense, people with health problems deserve a twofold right: to be offered only clinically adequate interventions and to decide to what extent those clinically adequate interventions are meaningful for their life. The best decision can come only from a sharing of expertise[2]:

Clinician's Expertise	Patient's Expertise
Diagnosis	Experience of illness
Disease etiology	Social circumstances
Prognosis	Attitude to risk
Treatment options	Values
Outcome probabilities	Preferences

Caring for a suffering person and doing the most possible to help that person recover are moral actions. A clinically sound, proportionate, and compassionately administered medical action (included RRT) should be considered a good and adequate approach until proven otherwise. The best proof is the patient's valid refusal of therapy.

Three factors—clinical indication, informed consent, and compassionate administration—are the basis of the ethical foundation of RRT.

Information and Consent for Renal Replacement Therapy

People with chronic renal failure necessitating long-term ambulatory RRT (dialysis) are usually able to be informed and to give valid consent or refusal. Actually, the refusal or discontinuation of dialysis is the cause of approximately 25% of deaths of patients in irreversible renal failure.[3,4]

Such valid consent or refusal is not usually possible for the critically ill patient in an intensive care unit (ICU) who requires RRT as part of intensive support. The competence of these patients is typically inadequate at the time when important therapeutic decisions are made.[5–7] Consequently, such patients may receive care they would not have chosen and whose aim is inconsistent with their wishes.[8–11]

However, at least some patients are competent at the time of hospitalization or ICU admission. Whenever possible, their involvement in the decision-making process is mandatory. Every piece of information regarding a patient's health status is the private property of that individual patient. Healthcare workers (HCWs) have the right and duty to manage such data only to make sense of them and to give them back to the patient so that she or he can make the best choice. Once the patient has been informed adequately, it is possible to agree with her or him on the course of care that is most fitting. Obviously, the competent patient can change his or her position; in this sense, informed consent is a continuous process and not a single event.

Patients can be informed in different ways. In the process of advance care planning (ACP), the patient, after being informed of diagnosis and prognosis, agrees on a course

of therapy. Advance directives (AD) also can be drawn up by healthy people before facing a major health concern. They can include a "living will" (an instruction directive in which the patient specifies the level of acceptable therapy) and/or a proxy directive ("durable power of attorney for healthcare," in which the patient indicates the person who can make sound decisions in her or his place, should she or he become incompetent).

Unfortunately, information to the patient is often inadequate, and advance care planning and advance directives are rare in everyday clinical practice.[12] Even worse, these directives have not proved able to affect significantly the course of care of critically ill patients, because they often are ignored by HCWs.[8,13,14]

Healthcare Workers and the Relatives of the Incompetent Patient

HCWs alone are not likely to be the best decision makers for their incompetent patients, especially when end-of-life decisions have to be made.[15–20] An extreme variability exists among doctors in defining a patient's prognosis and in decision making about foregoing life-sustaining therapies (including RRT) across different countries, in different ICUs in the same country, and even between providers within the same ICU.[5,15–17,21,22]

If the patient's competence is inadequate and her or his wishes are not known, the patient's relatives should be included in the decision-making process.[23] This does not mean that the relatives should decide the course of therapy, which is always a medical decision. The family members have no clinical competence. Neither have they, in many countries, any legal authority to make surrogate decisions on behalf of an adult incompetent person. Nonetheless, the family are the upholders of their loved one's life project: they may be a precious source of information about the patient's wishes, especially when future quality of life is considered. Relatives should be helped to clarify what the patient would consider as her or his own best interest. On the other hand, what the relatives say could be conditioned by their own experience, moral and religious beliefs, or external interests, as well as anxiety and depression.[24] Relatives' and surrogates' decisions do not always reflect accurately the patient's wishes and preferences.[25–29]

For these reasons, the family of an incompetent patient and the HCWs should work together, in a shared decision-making process, to determine what the patient would have chosen in that situation.[27] This requires time, specific skills, and a great amount of attention and sensitivity. The implementation of an "intensive communication strategy" can reduce the "compassion fatigue" of carers who have to make difficult decisions regarding end-of-life issues. This strategy includes an unrestricted visiting policy (open ICU), training in end-of-life ethics, a staff psychologist available on demand for consultation, daily meetings with families, and periodic debriefing for HCWs.[30] Successful and effective communication is extremely important, and its lack is the main cause of family dissatisfaction.[31–33]

Guidelines and Moral Principles

Guidelines are very useful because they provide the clinical, moral, and legal background for decision making. However, they are not always sufficient. No guideline would be able to determine the best decision for every patient. Each situation is unique because patients, families, and relatives are always different, and so are the HCWs.

Therefore with adequate references from official guidelines, the solution to every individual situation is found best within that situation. Shared ethical principles derived from "common morality" (autonomy, beneficence/nonmaleficence, and justice) are the ones currently accepted in the Western world. They can guide reasoning and decision making according to the needs of the case. However, they must be actualized in each particular case. Ethical reasoning and ethical consultation do not aim at the *ideal* course of action but at the *best possible* course of action in that specific setting with the available resources.

The aim of decision making is promoting patients' dignity; the principles are the means to reach such a goal. In case of conflict among principles, the one that best promotes the patient's dignity in the specific situation must be privileged. Therefore the moral principles are not absolute and admit exceptions. Obviously, such exceptions always must be dealt with in the most careful way.[34] Any exception to any moral principle must be accepted only exceptionally and only if it is indispensable to best promote the patient's dignity, which is the goal of care. In such decisions, those who decide which principle should be sacrificed must assume the burden of proof. In conclusion, moral principles are clear and valid in general terms, but their specification, application, and balancing depend on circumstances.

Again, an optimal decision can be obtained only with continuous, overt, and honest circular communication among everyone involved in the care of the patient to determine clear goals of treatment, verify which therapies actually satisfy those goals, and define subsequent adequate strategies.

Great attention has been paid in the last few years to the appropriate shared decision-making process, to reach the best decision for people with chronic renal failure necessitating RRT.[35–37] However, the proposed approach can work as well in the acute kidney injury settings. In fact, it provides for full patient information about diagnosis, prognosis, and treatment options, and development of emphatic relationships aimed to a shared advanced care planning.

In some complex cases, a time-limited trial of dialysis can be taken into account to better define prognosis by the medical team and a shared decision by the patient or legal surrogate, also considering family involvement.

In Box 148.1, part A, a protocol is proposed to guide the decisional process for the terminally ill incompetent patient.

Managing the Refusal of Renal Replacement Treatment

Involving patients/relatives and searching for consent means accepting that a potentially life-saving treatment (e.g., RRT) can be refused. Such refusal may be expressed by the sufficiently competent patient (directly or through advance care planning) or mediated by the family or proxies. This situation can be difficult to manage if the HCWs do not subscribe to the patient's decision.

Great care should be used in evaluating whether the refusal concerns the proposed therapy or the reasonably expected outcome. The therapy is just a means; the goal is the outcome. If the informed patient refuses the proposed therapy but accepts the possible outcome of therapy, then a duty exists to make effective therapy as agreeable as possible. On the contrary, if the patient reliably refuses the outcome, there is no reason to administer any therapy save for the compassionate ones.

A reliable therapeutic refusal must be honored. Consequently, the duty of the HCW is to assess the trustworthiness of the patient's refusal. This should not lead to mistaking competence for rationality. What should be assessed is not

BOX 148.1

A Protocol for the Management of Care for Incompetent, Terminally Ill Patients in Intensive Care Units

Part A: The Decisional Phase

1. Every patient, considered in his or her particular clinical condition, should receive the best possible treatment to fulfill his or her interests. The adequate level of intensivity and palliation should be defined officially. In the absence of such definition, the patient must be considered in full treatment until officially stated otherwise.
2. In emergency conditions, such a decision can be made by the clinician and the nurse in charge, after a reasonable clarification of the diagnosis and prognosis of the patient and, whenever possible, an adequate discussion with the patient's relatives (to whom the final decision must be communicated).
3. In nonemergency conditions, the patient's course of care may be discussed on the request of the patient, with the patient's relative or an HCW (MD or RN). Such a request should activate a meeting (even informal) as soon as possible. Every HCW involved in the patient's care should be allowed to attend; among them, the clinician in charge of the ICU, the clinicians and nurses who best know the patient's case, and, if necessary, an external consultant (e.g., surgeon, nephrologist, cardiologist). If the request comes from the patient's relatives, they can be allowed to attend the meeting. The discussion will deal with the following:
   a. The clinic: Which are the relevant clinical data? Are they sufficient to define diagnosis and prognosis with reasonable certainty? Are particular data necessary and achievable for a more certain diagnosis/prognosis?
   b. The involved subjects: Are the patient's wishes and preferences known? Is it possible to meet them? Which subjects can or must be involved in the discussion? Are diagnosis and prognosis sufficiently clear for all of them? For each subject, what needs must be respected in the final decision?
   c. A possible solution: Taking into account points 3a and 3b, which solution most respects the rights and needs of all those involved (above all, those of the patient): (1) full treatment without limitation, (2) full treatment with reevaluation within a specific time interval *(time limit)* or in case of a specific event *(event limit)*, or (3) treatment with a diagnostic or therapeutic limit *(specifying what is limited)*? Are there predictable obstacles to the implementation of such a decision? Are there internal interventions (among the involved subjects) or external interventions (e.g., specialist consultant, psychologist, ethics committee) that could help increase the agreement on such a decision?
4. The final decision: Made in the patient's interest after adequate involvement of the patient's relatives, the final decision becomes operative after it has been communicated, understood, and shared by all of the subjects involved in the decision (the patient whenever possible, the patient's relatives, and all of the HCWs).
5. Such a decision must be reported and explained in the patient's chart.

Part B: The Operational Phase

6. The decision (see points 2 and 3) should be communicated to the relatives by the clinician and nurse who are in charge of care for that patient.
7. Whenever possible, the decision to limit intensive support will be implemented by trying to wean the patient and transfer him or her to a normal ward, where the presence of relatives and friends can be ensured more easily.
8. If discharge from the ICU appears to be impossible because of the patient's strict dependence on intensive life support, every drug, instrumentation, and monitoring device that is not indispensable for the patient's comfort will be foregone, according to the previous decision (point 3c). The management of the endotracheal tube will be decided in each case, according to the patient's conditions and wishes and the relatives' understanding of the situation. However, there are no contraindications to the extubation of a terminal patient.
9. Whenever indicated, adequate analgesia and sedation will be provided. There are neither clinical, moral, nor legal reasons why a patient should die with pain or discomfort.
10. The patient's relatives should be informed constantly and adequately of what is being done.
11. Except for exceptional situations, the relatives' access to the patient's bed will be more unrestrained. In particular, it is recommended to call relatives in time, to relax restrictions on visitation, and to remove every obstacle to physical contact (e.g., lowering bed rails and other restraints and obstacles to hand holding).
12. The relatives' needs should be taken into consideration. Some of the most important of these are the need to be with the dying person, to feel helpful to the dying person, to be informed of the dying person's changing condition, to understand what is being done to the patient and why, to be assured of the patient's comfort, to be comforted and to express emotions, to be assured that the final decision was right, to find meaning in the dying of their loved one, to be involved in the caring activities (e.g., mouth care), and to be fed, hydrated, and rested.
13. Times and modalities of the relatives' presence at the patient's bedside will be managed by the nurse in charge of the patient, in relation to his or her global caring engagements and obligations.
14. The relatives always should be offered the possibility of being present at the moment of the patient's death, together with the clinician and nurse who are in charge of care for that patient.
15. Opportunity for debriefing always should be considered.

HCW, Healthcare worker; *ICU,* intensive care unit.

whether the family or the HCW agrees with the patient's decision but whether the patient's decision is coherent with his or her view of life and moral and religious beliefs (as witnessed by the patient's relatives and friends).

In this sense, a few words on the difference between "facts" and "values" must be elucidated. HCWs may be expert on the facts, but they are not always experts on the underlying values. Furthermore, many HCWs believe that questions such as foregoing life supports can be based on purely factual grounds (e.g., by claiming that treatments are "not clinically appropriate"), when in fact these questions have many value dimensions that must be taken into consideration. In other words, making end-of-life decisions often involves many assumptions about values that must be taken into careful consideration.

As a practical approach, the consequence of refusal of an effective therapy should be weighed against the patient's acceptability of the predictable outcome. If the consequence of the refusal is clearly in contrast with the patient's view of life and moral and religious beliefs, so much so that the decision can be considered unreliable, every effort should be undertaken to make the therapy acceptable. Adequate sedation, if clinically indicated, can be a final but acceptable resource in the patient's best interest. Actually, cases

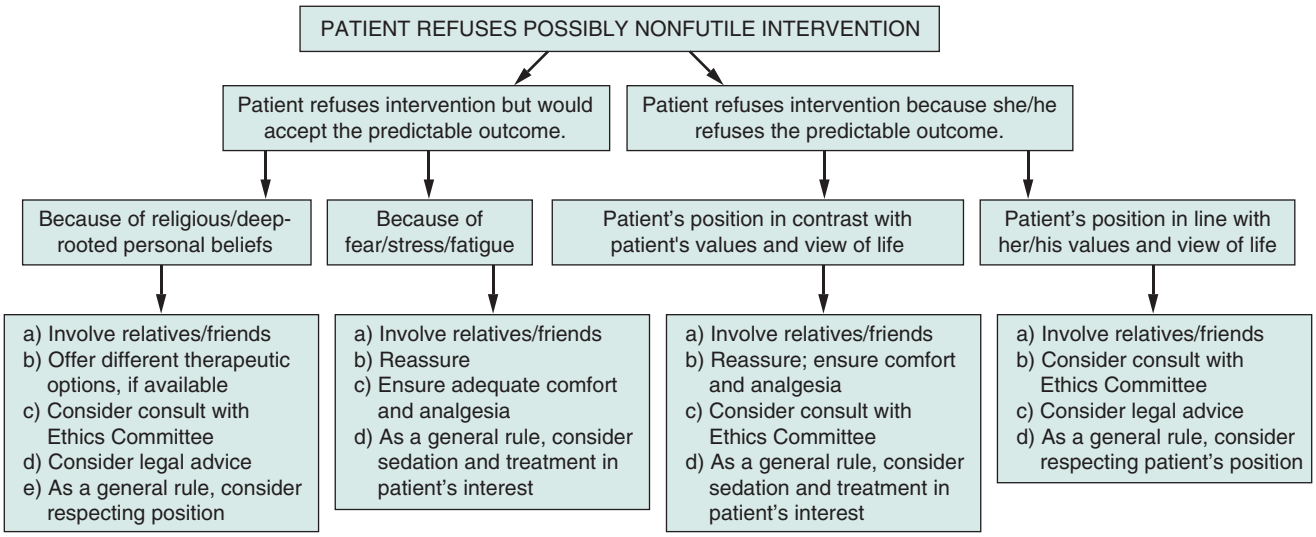

FIGURE 148.1 Suggested management of the patient's refusal of possibly nonfutile intervention (see text for discussion).

of patients who were happy to have received successful treatment despite their previous rejection of it have been reported.[38,39]

On the contrary, if the patient does refuse the outcome, and such a decision can be considered reliable, then this position should be respected until the end. The same should be done even if the outcome is desirable but is obtainable only through means that the patient refuses because of religious or well-grounded personal beliefs (Fig. 148.1).

Ethical consultation can be useful. Legal advice also is recommended, such as for adequate application of domestic laws.

Right to Die Without Renal Replacement Therapy

Honoring the patient's refusal of a possibly lifesaving RRT means acknowledging a right to die without RRT. Such right can have at least three different meanings, applying to different categories of patients.

In terminally ill patients, for whom an intensive approach could only unduly prolong the process of dying, RRT could be defined as incorrect because it infringes on the principles of *beneficence, nonmaleficence*, and *distributive justice*.[40,41] Clinically inadequate treatments neither should be offered.[42] In such situations, even the term *lifesaving* supports can be misleading when supports turn out to be just *agony prolonging*. The term *intensive* supports may be preferable, and it is the one used in this chapter. As for patients in these conditions, dying without RRT means that the method and the time of dying should be respected and dignified. A corresponding clinician's duty to fulfill the patient's wish can be affirmed. Every communicative effort should be made to reduce the request for futile treatment from relatives of the patient who has become incompetent.[27] However, when patients or surrogates request a treatment that the HCW believes is futile, the HCWs should not limit treatment on the basis of their personal view of futility; rather, they should rely on institutional and professional policies.[43]

The second category consists of those patients who have poor life expectancy, even if it is not unequivocally definable. These are, for instance, patients with severe chronic obstructive pulmonary disease in fleeting compensation, patients with critical inoperable cardiac disease, and cancer patients who have multimetastatic disease but are still nonmoribund. In these situations, an acute crisis (e.g., a septic episode) can be cured and overcome with intensive care, but without a substantial improvement in prognosis. For this group, the right to not prolong an untreatable and terminal disease or condition against the will of the sufferer should be acknowledged. Again, a corresponding HCW duty should be affirmed.

The third category covers those patients who have a fair prognosis for survival, usually thanks to chronic care, but at the expense of a quality of life that they judge unacceptable. Quadriplegic patients and patients in a vegetative state with previously ascertained refusal of invasive therapies are typical representatives of this group, for which a right of not being kept alive by artificial means is admissible. Such a right can pose particular bioethical and legal problems. Each situation should be approached in light of the individual circumstances.

Justifying Foregoing of Renal Replacement Therapy

Justifying foregoing of intensive supportive measures such as RRT is rarely painless. Actually, such supports tend to be self-justifying for the mere reason that they are at least temporarily lifesaving. They tend also to expand from the acute to the chronic phase of the illness and from single to the multiorgan support. Decisions to limit supportive therapy often are hindered by prognostic uncertainty because the available prognostic indexes cannot predict the outcome of the individual patient with sufficient accuracy to justify end-of-life decisions.[44,45] Finally, such decisions are made even more difficult by the usual temporal correlation with the death of the patient.

Nevertheless, a fundamental concept is that the aim of intensive supportive care is not to cure diseases. If this were the case, it would be impossible to recognize any diagnostic or therapeutic limit. Even worse, the patient would become an accident of the illness, the mere biologic substrate necessary for the disease to occur and by which the disease can be fought. In reality, the object (or, better, the subject) of the curing/caring process is the patient. If this is true (and we believe it is), intensive support procedures

should be used as long as they are useful to the patient, according to the patient's wishes and project of life. Beyond that point, they should be limited.[46]

Several clinical patterns may demand the use of acute RRT in an intensive care setting. However, mere survival may not be the unique factor to address when challenging the best patient's option. In addition, the idea that acute kidney injury implies RRT for every patient in every situation could be an oversimplistic and inadequate paradigm. Based on their education, clinicians may believe that their job is exactly to do things in the best possible way. Consequently, they could retain that the decision to start treatment is good (intensive support is a good way to promote surviving and strive against death) and that the decisions to forego intensive supports should be justified openly and carefully. However, in some critical situations near the end of life, clinicians are responsible for every decision they take and should give clear good reasons of every action. The crucial point is not doing things, but doing the right things. Better, the decision is not between doing and not doing, but among doing the best things possible. Sometimes an invasive approach means overtreating diseases, which is much different from caring for persons. If clinicians decide to start invasive treatments, they should be able to identify more valid reasons for that than for palliative care.

Practice of Foregoing Renal Replacement Therapy

Recognizing the patient's right to die without RRT can have little meaning if it does not lead to adequate actions. In particular, the rights of the patient and the needs of all the involved subjects must be recognized.

The patient's needs and rights are usually well known, and adequate care usually is best aimed at the relief of physical, psychologic, and emotional suffering. Whenever necessary, an adequate sedation is recommended, as long as the true intention of the HCW is to alleviate pain and distress even if a shortening of the terminal process of dying may result. However, adequate palliation must be kept distinct from active shortening of the dying process.[47] The doctrine of the *double effect* regulates this aspect of care. Withdrawal of treatments with associated palliative/terminal sedation is different from shortening of dying process (SDP) or euthanasia. They have different intentions, different means, and different goals.[48,49]

Great regard must be paid to the family's needs. Many little considerations are necessary to gratify these needs,[50] which cannot be included in any guideline but which can come only from the careful presence of the healthcare team. The commitment of the HCW should not be to give a corpse back to the family, but to help the patient's relatives to accompany their loved one in the dying process and to participate in it. This can be done only with a "caring for the family while caring for the patient" approach. In this regard, nurses, as the HCWs who spend the most time at the bedside, play a pivotal role in communication.[51] Unfortunately, disagreement between clinicians and nurses in end-of-life decisions has been described,[52–55] and it, together with dissatisfaction because of inadequate involvement in the decision-making process,[56,57] can lead to frustration on the part of nurses. The needs of the clinical team also must be recognized and satisfied; these include cooperation among team members, competence in the care of patients and relatives, administrative support, and opportunity for debriefing. A protocol is proposed in Box 148.1, part B, wherein the operative phase (how to implement what has been decided) is considered.

Limiting Treatments, Not Care

Finally, three concepts must be emphasized. The first one is that the patient's decision to give up treatments that she or he considers disproportionate should never lead to abandonment. Caring opportunities exist even after the attainment of a therapeutic limit. "No RRT" should never come to mean "No care." However, it is also fundamental to remember that palliation is not a separate option to be reserved for the terminal phase. There is not one time for invasive restorative care and a separate time (and perhaps separate HCW) for palliation. In every moment of care, HCWs always should act as intensivists and palliativists at the same time. The prevalence of intensive care and palliative care should vary according to the patient's conditions. Restorative care is justified as long as it is useful to the patient. Palliation always should be present. At the end, when there is no more meaning for intensivity, palliation alone remains as the most adequate form of caring.

The coexistence of palliative care and critical care may seem paradoxic in the technologic ICU. However, contemporary critical care should be as concerned with palliation as with the prevention, diagnosis, monitoring, and treatment of life-threatening conditions.[58]

In 2014 the Institute of Medicine emphasized the urgent need for improvement in the quality of end-of-life care in their report, *Dying in America.* Among the challenges to the provision of high-quality care, it identified a poor understanding of palliative care among health professionals. The report recommended that end-of-life care be delivered in an integrated, person-centered, family-oriented manner.[59]

The issue of dignity conserving care, which has been proposed recently, cannot be overemphasized.[60]

The second aspect is that a decision to limit supportive procedures is made with the intention of avoiding futile therapies, not to lead a patient to death. Actually, limiting support does not imply the immediate death of the patient[5] and is consequently well compatible with maintaining other therapies, if indicated. A decision to forego futile continuous RRT, for instance, does not conflict with the use of diuretics to stimulate a residual diuresis (if present) or with careful treatment of distressing symptoms of fluid overload.

Finally, clinicians always should be ready to reevaluate the patient's situation. The decision to forego an intensive care procedure is adequate as much as it is based on clinical facts and on the wishes of the patient; if clinical facts change, the decision should be revised. Indeed, survival of patients after revision of end-of-life decisions has been described.[61]

Clinical Research in Renal Replacement Therapy

RRT cannot exist without good research, which means adequate study design, good research conduct, and patients' informed consent. Unfortunately, patients' incompetence is common in clinical research in the intensive setting, which makes informed consent impossible. Introduction of a waiver of consent in clinical trials perhaps could increase patients' recruitment[63,64] and reduce the time needed to achieve satisfactory research end points,[65] yet it is not a viable solution.

The problem is complex also because clinical research regarding critical conditions treatable with RRT cannot be performed on healthy volunteers; inducing renal failure or sepsis in healthy people for mere research purposes would be simply inconceivable.

Perhaps going back to the core question can help: Why is patients' consent so important?

Informed consent is a way of honoring the principle of *autonomy*. Perhaps more important, informed consent usually is considered a form of patient self-protection.[66,67] However, studies of cancer patients demonstrate unacceptably low comprehension by patients of the protocols they consented to enter.[68,69] The competence of critically ill patients in need of RRT is much less adequate. If the patient is not adequately competent, the only acceptable decision should be the one that corresponds to what the patient would have decided. Unfortunately, the reliability of HCWs and relatives[70] to predict patients' wishes is still unclear.

The situation is even more complicated in case of emergency research on incompetent subjects. In this situation, a *previously* collected informed consent is not feasible (by definition, as the subjects are incompetent) and relatives are usually ineffectual: a next-of-kin is usually unavailable in the therapeutic window time frame,[71] different family members could give different versions of the patient's wishes and/or may fail to accurately report them,[72] and emotional stress can bias significantly the decision of relatives in emergency situations.[73,74] *Deferred* consent has been proposed as a possible solution. However, consent can work only if given before an action is performed. Deferred consent could be useful only for the subsequent treatments and for the use of personal data but can have little space in practice to protect the patient.[75] Nevertheless, patients must be protected.[76] Relatives are not always an adequate protection and could be unavailable for emergency research.[69] Researchers can have nonfinancial and financial conflicts of interest.[77–79] Randomized controlled trials (RCTs) have proved to be possibly subject to bias and potentially dangerous to patients in many ways. Inadequate or ineffective control treatment,[80] useless RCTs,[81] overemphasized statistical significance of clinically meaningless results,[82] use of composite outcomes in which good minor results rarely affect major ones,[83] publication bias,[84] and influence of pharmaceutical industries[85–87] have been described.

For all these reasons and in spite of all obvious difficulties, informed consent should not be abandoned, because it clarifies that clinical research is for the patients (and not the other way around) and promotes respect for critically ill patients and their rights.[69]

Protecting Incompetent Patients Through Risk/Benefit Ratio Evaluation: The Role of Research Ethics Committees (RECs)

Measures regarding the acceptability of the risk/benefit ratio of the study design can protect the incompetent subjects of emergency trials much more than information and consent. A new EU Regulation (n. 536/2014) sets suitable rules for this aim. In fact, it states that clinical trials on an incapacitated subject (Article 31) and on minors (Article 32) may be conducted only where at least either the "direct clinically relevant benefit for the subject" or the "minimal risk to, and minimal burden on, the subject in comparison with the standard treatment" standard is respected. On the contrary, clinical trials in emergency situations (Article 35) demand the respect of both standards, to protect the incompetent subjects of emergency research, when they are incompetent and a guardian is not (yet) available. In this situation, the role of the REC/IRB (Institutional Review Board) is crucial because it has the task to verify that the clinical trial design really respects these requirements. In this way, the REC/IRB can ensure effective protection of research subjects and promote good clinical research in emergency settings. No other people, and surely not the subject's relatives pressed in an emergency situation, can make a better evaluation. Clinicians who perform clinical research have specific legal and moral responsibilities. However, at the same time, the strengthened criteria verified by the REC/IRB in evaluating the design of an emergency trial involving incompetent subjects should be sufficient for the inclusion.

Promoting Better Research

Informed consent is not enough. Also, the quality of research should be improved as much as possible. This includes many aspects. Less-than-optimal therapy for the control group of patients should be avoided carefully. The number of research protocols in RRT (and in general in critical care) could be reduced and their quality increased. A few large, multicenter trials are more desirable than many statistically underpowered studies. Great care is needed in designing, conducting, and evaluating protocols of clinical studies. Also, other methodologic options (e.g., using different treatments separately at different times or in different centers and then comparing them[88]) have been suggested.

Ethics Committees and Institutional Review Boards must ensure careful evaluation of research protocols. Thorough discussion and evaluation of protocol from all the staff involved in the research also is recommended.

Finally, the introduction of a registry of protocols[90,91] is an extremely positive step.

As for local situations, readers are invited to refer to national specific documents. One is the result of a conference on the ethical conduct of clinical research involving critically ill patients in the United States and Canada.[92] Ethical requirements for clinical research were specified (Box 148.2), and an ethical checklist for clinical research design, implementation, and monitoring was proposed (Box 148.3). Other reports take into account also the European situation.[93,94]

BOX 148.2

Ethical Requirements for Clinical Research

1. Social value: The research must improve health or advance knowledge.
2. Scientific validity: The research must be scientifically rigorous and provide reliable results.
3. Fair participant selection: The research must expose the vulnerable and the privileged to the same risks and benefits.
4. Favorable risk/benefit ratio: The research must minimize risk and maximize benefit to participants whenever possible.
5. Independent review: The research must be reviewed, approved, amended, or terminated by unaffiliated observers.
6. Informed consent: The research participants or their surrogates must be informed about the research, must understand it, and must agree to it voluntarily and without coercion.
7. Respect for enrolled participants: The research participants' privacy must be respected, their withdrawal permitted, and their safety monitored.

From Luce JM, Cook DJ, Martin TR, et al. American Thoracic Society: the ethical conduct of clinical research involving critically ill patients in the United States and Canada: principles and recommendations. *Am J Respir Crit Care Med.* 2004;170:1375–1384.

BOX 148.3

Ethical Checklist for Clinical Research

Research Design

1. Will the study results provide social or scientific value?
2. Is the study design scientifically valid?
3. Is the intended participant selection fair and suitable for the research question?
4. Is there a favorable risk/benefit ratio?
5. Has the design undergone, or will it undergo, independent review before the study is started?
6. Are adequate procedures in place to ensure informed consent, and have they been reviewed?
7. Are adequate procedures in place to ensure respect for potential and enrolled participants?
8. Are data and safety monitoring in place?
9. Have conflicts of interest been identified and minimized?

Research Implementation and Monitoring

1. Do new data or hypotheses undermine the social or scientific value of the ongoing study?
2. Do new results from this or other studies unfavorably alter the risk/benefit ratio?
3. Is the participant selection process working as intended and designed?
4. Are investigators carrying out the study as intended and designed?
5. Are the data and safety monitoring procedures, including the detection and reporting of adverse events, working as intended and designed?

From Luce JM, Cook DJ, Martin TR, et al. American Thoracic Society: the ethical conduct of clinical research involving critically ill patients in the United States and Canada: principles and recommendations. *Am J Respir Crit Care Med.* 2004;170:1375–1384.

BIOSOCIAL ASPECTS OF RENAL REPLACEMENT THERAPY

RRT is a fundamental component of modern high-technology medicine. High-technology medicine can be extremely effective in individual cases, but it also poses important biosocial problems. One of them relates to the possibility of manipulating virtually every aspect of the process of dying and prolonging low-quality lives. HCWs should be aware that all they actually manage is not life or death but clinical data, drugs, and devices to reach the best possible quality of life for their patients. Because death is an inevitable event, the quality of each death and of the relationships involved in each death are major indicators of quality of care.

Another problem is related to the extraordinary amount of resources necessary for high-technology medicine.[95–98] For this reason, it is likely that HTM will be increasingly available only to those patients who can have access to it. We proposed the word *presentism* to describe the fact that a huge amount of money is spent to cure a limited number of patients (those who are "present" to receive it), whereas much less is offered to all those who are "absent."[99]

As a consequence, high-technology medicine can work only in highly developed countries. As a mere example, 90% of the 100,000 patients who develop end-stage renal disease each year in India die without seeing a nephrologist, and only 4% of those who begin hemodialysis still are being treated after 1 year, often with unacceptable standards of treatment.[100]

On the other hand, in the United States, total spending on healthcare is increasing and already accounts for 16% of the gross domestic product.[101] Critical care alone consumes more than 1% of the gross domestic product.[102] However, in spite of its enormous costs, this system has negligible positive impact on global health and life expectancy of the U.S. population.[99] The risk is that, for many patients, high-technology medicine could be reduced to an extremely expensive way to manage unavoidable death: by now, one out of five Americans already dies in an ICU,[103] often in relation to the refusal or limitation of supportive care.[5,6]

Obviously, the solution cannot be abolishing high-technology medicine (and consequently RRT). We must avoid "throwing the baby out with the dirty bathwater." However, even if causes and remedies are above all political and societal, it is important that every HCW be aware of these biosocial issues.

Key Points

1. A clinically sound and compassionately administered medical approach should be considered good and adequate unless refused by the patient. Clinical indication, informed consent, and compassionate administration are the bases of the ethical foundation of renal replacement therapy.
2. Decisions regarding the course of therapy for an incompetent patient are always a medical task; the relatives or surrogate and healthcare workers should work together to determine the patient's desires and expectations. The aim of the decisions always should be promoting patients' dignity; guidelines and principles are the means to reach such a goal. They are not absolute, and exceptions can be admitted; guidelines can be ignored and principles can be sacrificed, if this is necessary to best promote patient dignity in a specific situation.
3. The aim of intensive life support is to care for patients, not to cure diseases; consequently, such procedures should be used only so long as they are useful to the patient. A right to die without renal replacement therapy exists, and a reliable request should be honored. To carry out a decision to limit intensive supports, the rights of the patient and the needs of all the involved subjects must be recognized and satisfied.
4. Informed consent clarifies the fact that clinical research is for the patients and promotes respect for critically ill patients and their rights. However, it cannot solve all the problems related to research in continuous renal replacement therapy. The role of the RECs/IRBs is crucial because they can ensure effective protection of research subjects and promote good clinical research in emergency settings. Also, the maximum possible quality of research should be ensured.
5. Healthcare workers should be aware that renal replacement therapy (like all the other components of modern high-technology medicine) also raises important biosocial problems; the most important ones relate to the possibility of manipulating the process of dying and to the amount of resources necessary.

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