Chapter

Withdrawal/Withholding of Life-Sustaining Therapies in the Intensive Care Unit

Ángel Becerra-Bolaños, Raúl Vega-Rodríguez, Héctor Trujillo-Morales, Nazario Ojeda-Betancor and Aurelio Rodríguez-Pérez

Abstract

Limitations of life-sustaining therapies in the Intensive Care Unit (ICU) are usually applied when therapeutic measurements are considered futile. Withholding and withdrawal therapies are then applied because therapies cannot achieve the desired outcomes. When implemented, several aspects should be taken into consideration, such as cultural, sociological, or personal preferences regarding end-of-life care. Withholding is the decision not to start or increase a treatment if the benefit is not clear, and is the most common measure applied, including orders such as do-not-resuscitate, do-not-intubate, or non-renal-replacement therapies. Withdrawal is a less frequent approach, and it is defined as the decision to stop a treatment. Decision-making should be multidisciplinary and consensual. It must respect the wishes of the patient and/or their relatives. These decisions usually carry a substantial emotional burden, especially for healthcare professionals, who might consider limitation of life-sustaining therapies as a failure, even though this perception should evolve. In addition, the implementation of these measures may lead to stressful situations for professionals, which need to be addressed to avoid a negative impact. Mortality is the most common outcome that emerges from the use of these measures. However, a significant number of patients survive to hospitalization. Survival can have consequences that may affect the patient's subsequent quality of life. Due to the potential concerns, the difficulty of implementation, and the challenges in the decision-making process, communication between healthcare professionals, patients, and families/relatives is an important issue when it comes to limiting life-sustaining therapies.

Keywords: intensive care unit, life-sustaining therapies, futility, limitation of therapeutic effort, withholding, withdrawal, advance directives, end-of-life, frailty, ethics

1. Introduction

Every country is facing an increase in the size and the proportion of elderly in their population [1]. Improved society and healthcare have resulted in more

elderly patients in intensive care units (ICUs) [2], leading to higher multimorbidity and frailty. These conditions contribute to poorer clinical outcomes and higher healthcare costs [3, 4]. Cognitive and technological advances have made it possible to replace vital functions during critical situations, and have shifted therapeutic efforts toward managing the worsening of chronic conditions [5, 6]. However, patients' baseline status is often suboptimal, and ICU admission may lead to devastating consequences [7].

The primary objective of ICU treatment is to preserve life while avoiding unnecessary suffering or the prolongation of the dying process [8]. Therefore, evaluating the appropriateness of ongoing treatment is crucial to avoid therapeutic obstinacy and to focus on preserving the patient's dignity, in alignment with the bioethical principles of autonomy, beneficence, justice, and non-maleficence [9].

1.1 Futility

A treatment is deemed futile when physicians determine that achieving the desired outcome is highly improbable, based on clinical practice, shared experiences, or empirical data. It is also important to differentiate between the effect on a specific part and the overall benefit to the patient [10]. A futile treatment is one that fails to achieve its intended objectives, either because it does not provide a reasonable chance of survival, proves to be clinically ineffective, does not improve the patient's quality of life, or does not align with the patient's goals [11].

The definition of *medical* futility is based on two criteria involving independent variables: quantitative and qualitative criteria. *Quantitative* or *physiological* futility refers to the numerical probability that a medical intervention will achieve the desired effect. Since it relates to alterations in organ function, its assessment presents relatively few challenges or debates among physicians. On the other hand, *qualitative* futility refers to the probability that the physiological effect will provide meaningful benefit to the patient [12], making its assessment more holistic and significantly more complex [13]. The overall futility of a treatment can be calculated as the product of quantitative and qualitative futility. Both components are essential in determining the futility of a therapy. If the chance of a treatment influencing one of the two components (qualitative or quantitative) approaches zero, the medical intervention is considered futile [14].

The perception of the futility of a therapy can be influenced by physicians' goals, sociocultural and religious values, and characteristics of both doctors and patients [15]. However, continuing ineffective treatment affects patients, their families, other patients, healthcare professionals, and systems negatively, increasing the economic costs [16]. Thus, futility justifies limiting life-sustaining therapies that offer no patient benefit while potentially increasing suffering.

1.2 Definition of limitation of life-support therapies

The limitation of life-sustaining therapies can be applied in two modalities: withholding and withdrawal. Withholding refers to the decision not to initiate additional life-sustaining measures, whereas withdrawal involves discontinuing previously implemented supportive interventions. Although both approaches are ethically equivalent, they may be perceived differently by healthcare professionals, especially

those less experienced with end-of-life care in the ICU setting. Withdrawal is often seen as a more direct action leading to the patient's death. Nevertheless, both strategies are recognized as ethically sound alternatives to therapeutic obstinacy, striving to achieve a balance between the quantity and quality of life [17].

The primary challenge in implementing limitations on life-sustaining therapies lies in the fact that determining the futility of a therapy is not always clear-cut. While clinicians may estimate the likely course of an illness, accurately predicting a precise prognosis is often elusive. This uncertainty can lead to conflicts among professionals or between healthcare providers and the patient's family members [9]. Besides, surveys conducted among ICU professionals highlight the challenges in determining which treatment goals are realistically achievable and what constitutes an unfavorable risk-benefit balance [18].

If it is justified to not start a treatment, then it is also justified to stop that same treatment, assuming the patient's condition and values remain consistent. Certain clinical conditions define an irreversible dying process, such as progressive multiorgan failure with no prospect of successful treatment of the underlying cause, or the possibility of adequately and durably replacing organ function. Other scenarios include potentially fatal diseases or complications leading to complete loss of vital functions, as well as the terminal stage of chronic or malignant diseases that can no

Withholding	Decision made not to start or increase a life-sustaining intervention
Withdrawal	Decision made to actively stop an intervention already given
Active shortening of the dying process	Circumstance in which someone performs an act with the intention of shortening the dying process
Palliative care	Specialized medical care for people with a serious illness, focused on providing relief from the symptoms and stress associated with the illness. It is aimed at improving quality of life for both the patients and their families
End-of-life care	Includes the decision-making as to the limitation of life-sustaining therapies and the physical, emotional, social, and spiritual support for patients and their families
Advanced directives	Legal document that states a person's wishes about receiving medical care if that person is no longer able to make medical decisions; it may also give a person the authority to make medical decisions for another person when the patient can no longer make decisions (power of attorney)
Conflict	Dispute, disagreement, incompatibility, opposition, or difference of opinion related to the patient's management
Appropriate care	A patient care proportional to his/her expected survival and quality of life and in line with the patient's and relatives' values
Burnout	A psychological syndrome arising in response to chronic emotional and interpersonal stressors on the job, characterized by three different features: emotional exhaustion, depersonalization, and lack of personal and professional completion
Decision-making	A stepwise practice of gathering and interpreting information, weighing different options, and ultimately making a shared, evidence-based, and personalized decision

Adapted from the European Society of Intensive Care Medicine Guidelines on end-of-life and palliative care in the intensive care unit [24].

Table 1.
Definitions.

longer be managed [8]. However, this is not solely a technical judgment. It is also essential to assess the current circumstances and consequences, considering the patient's values and the available resources [19].

The interaction between personal and professional spheres in decision-making regarding the limitation of life-sustaining therapies imposes a significant psychological burden on both healthcare professionals and the patient's family and loved ones. This process may evoke feelings of guilt or regret [20]. Therefore, the implementation of these measures should be approached in an individualized and holistic manner. To prevent conflicts in their application, recommendations have been made for hospitals and medical centers to establish mechanisms that support this decision-making process [21].

Although the limitation of life-sustaining therapies is widely accepted by professionals, it is sometimes perceived as a form of euthanasia [22]. Euthanasia involves an explicit and repeated request from the patient for an act intended to cause death to prevent further suffering [23]. However, during the limitation of life-sustaining therapies, it is the underlying disease that causes the patient's death, not the actions of healthcare professionals. Some key definitions relevant to this topic are presented in **Table 1**.

The objective of this chapter is to provide a guide to limiting life-sustaining therapies, acknowledging that a universal approach is not feasible, and that individualized decision-making must be the basis of these measures.

2. Limitation of life-sustaining therapies

2.1 Epidemiology

There is wide variability in the limitation of life-sustaining therapies, ranging from 5 to 15% of patients admitted to ICUs [6, 17, 25–27]. The frequency of these practices varies depending on geographic region and the healthcare setting in which the facility is located [28]. A study conducted across 199 ICUs in 36 countries demonstrated that the practice of limiting life-sustaining therapies differs significantly among regions [29]. Contextual factors contribute to the regional variation in decisions regarding withholding or withdrawing treatment in critically ill patients. A multicenter study conducted in Poland on ICU patients over the age of 80 reported an incidence of limitation of life-sustaining therapies of 17.9% [30]. This percentage was lower than the 24.6% observed in a German cohort [31] and significantly lower than the 41.9% reported in a Norwegian cohort [32].

Issues related to the patient's pathology or the type of unit in which the study is carried out also influence the frequency and epidemiology of these measures. In 4671 critically ill patients with COVID-19 admitted to the ICU between February and May 2020, the prevalence of limitation of long-term therapies was 14.5% [33]. In patients who received cardiopulmonary resuscitation maneuvers after out-of-hospital cardiac arrest, its prevalence was 30.7% [34], while a study carried out in septic patients detected an incidence higher than 35% [35]. On the other hand, ICUs with a greater number of post-surgical patients generally have lower rates of limitation of life-support therapies than ICUs with a higher number of patients with decompensated medical pathologies [25].

The percentage of limitation of life-support measures increases between 43 and 81% of patients who die in the ICU [17, 36].

2.2 Factors associated with the limitation of life-support therapies

The variables associated with the implementation of life-sustaining therapy limitation measures are multifaceted, including medical, ethical, and individual factors [6]. The most frequently reported factors are:

- Age: Older patients are more likely to be prescribed limitation of life-sustaining therapies [36, 37]. Age over 80 years is significantly associated with the decision to limit life-sustaining therapies [6, 26, 30]. Paradoxically, in a sub-analysis conducted across 12 ICUs participating in a multicenter study, the clinical characteristics of patients for whom these decisions were made revealed a profile of individuals younger than 70 years [38]. However, early decision-making is often associated with the patient's age and chronic poor health [39].

- Functional status: Functional dependence, assessed by the Barthel index, is also an important variable. Patients with total dependence (Barthel index less than or equal to 20) are more likely to be subject to limitation of life-sustaining therapies [40].

- Comorbidities: The Charlson Comorbidity Index has also been associated with the probability of limiting life-sustaining therapies [37]. This index is quite useful, given its correlation with the expected 10-year survival rate of the patient. Cardiovascular comorbidities were present in more than half of the patients who underwent limitation of life-sustaining therapies in a multicenter study carried out in Spanish ICUs [38].

- Frailty: A syndrome defined by increased vulnerability due to decreased physiological reserve. It affects the ability to adapt to stressors, such as acute illness [41]. Patients who undergo life-sustaining therapy are often frailer [37]. Assessment of frailty using tools such as the Clinical Frailty Scale has been associated with increased 30-day mortality [32], reinforcing the importance of considering this variable in the decision-making process.

- Quality of life: A poorer quality of life prior to ICU admission also increases the likelihood of a decision to limit life-sustaining therapies [6, 26]. Considering quality of life prior to admission is controversial, since patients' perception does not usually coincide with professionals' perceptions, who tend to underestimate it [42]. A survey showed that 85% of physicians and 93% of nurses agreed that it was important to consider quality of life after ICU admission to establish limitation of therapeutic effort [43]. Currently, quality of life after ICU admission is one of the main determinants [44]. Since it is related to mortality after discharge [45], the application of an objective tool for its evaluation could shed light on a patient's prognosis.

- Severity of illness leading to ICU admission: Scales such as Glasgow Coma Scale, Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score II (SAPS II), and Mortality Probability Model II (MPM II) help evaluate survival probability and reduce prognostic uncertainty in decisions regarding life-sustaining therapy limitations [26, 30, 36, 37, 46, 47]. Both the SOFA score and disease

progression within the first 5 days after ICU admission have been associated with 100% mortality rate [48]. APACHE-II score is also an independent predictor of mortality [49]. Other scales, such as Nine Equivalents of Nursing Manpower Use Score (NEMS), have shown association with life-support therapies limitation [6]. In patients over 60 years old who suffer from traumatic brain injury, the Extended Glasgow Outcome Scale (EOS) score lower than 5 has been associated with an unfavorable neurological outcome [50]. So, this scale could be used in these patients to decide on limiting life-support therapies. Poor prognosis [34] along with the perception of patient suffering are determining factors in many of the proposals for limiting therapies [44].

- Admission characteristics: Patients admitted due to decompensations of medical conditions have a higher likelihood of limiting life-sustaining therapies [25]. This may be because patients with medical decompensations tend to have greater severity at the time of ICU admission and a poorer quality of life. Consequently, these patients are often considered to have a lower likelihood of improvement. Additionally, there is a perception that surgical treatment may be curative, fully resolving the condition that led to ICU admission. Decision-making for surgical patients also requires the surgeon's agreement, and surgeons may be more reluctant to withdraw therapy [6], as this could be perceived as a failure of the surgical intervention. Furthermore, patients who are subjected to therapeutic effort limitation are frequently admitted for non-elective reasons [51].

- Other patient- or disease-related variables identified include ICU length of stay and duration of mechanical ventilation. These factors may be interrelated or associated with age, the presence of comorbidities or frailty, poorer baseline status, or greater disease severity [20, 30, 52, 53].

- External and organizational factors: Socioeconomic factors may influence decision-making regarding life-sustaining therapy limitations. In the United States, decisions to limit life-sustaining therapies are made earlier for uninsured trauma patients compared to those with private health insurance [54]. Inequities in healthcare provision not only accelerate withdrawal of life-sustaining treatment but also impact overall mortality in patients with traumatic brain injury [55]. Additionally, financial constraints within families may lead caregivers to discharge critically ill children from the hospital against treating physicians' recommendations. This affects 1.4 to 5.7% of pediatric patients in low-income countries and leads to almost certain death of the patient [56], during which the comfort and care of the patient's symptoms or family are not assured. For this reason, it is essential to establish international standards to minimize geographic and economic variability in providing optimal end-of-life care.

- Given the influence of ethical and individual factors, it is important to highlight that some of the most decisive elements in decision-making process include both the patient's family and healthcare professionals. Studies have shown that patient desires influenced the decision in 2–63% of cases, while families were involved in 2–90%. Regarding healthcare professionals, in emergency departments, decisions were made jointly with at least one other physician in 80% of cases, while nursing staff participated in up to 30% of cases [20]. Regarding religious factors, a study conducted in Lebanon showed that both Christian and Muslim

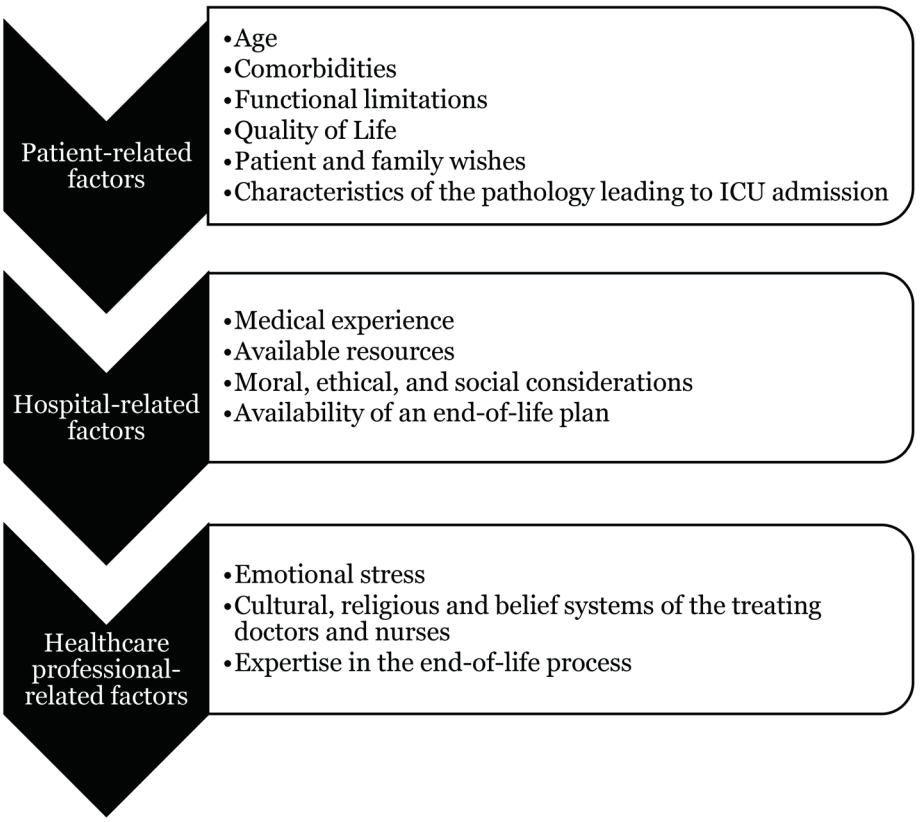

Figure 1.
Key factors influencing decisions.

physicians accepted both withholding and withdrawing life-sustaining therapies when appropriate [57].

Therefore, decisions are mainly influenced by factors related to the patient and disease, factors related to the hospital, and factors related to the healthcare professionals (**Figure 1**) [20, 58].

2.3 Decision-making

2.3.1 Advance directives

Advance directives are legal documents that state the will of the patient, safeguarding the bioethical principle of autonomy. Autonomy is the right of individuals to make decisions about their health and illness without coercion and with all the necessary information. It therefore implies knowledge of the different treatment options available and the consequences of using or not using them [9]. It is estimated that only 1.6% of patients have advance directives in Spanish ICUs. However, up to 62% of patients would accept limitations on life-sustaining therapies in cases of a poor prognosis or a significant decline in quality of life [59]. This is confirmed in other countries, where the patient's wishes are unknown in more than 40% of cases [60].

These documents allow patients to express their personal preferences regarding future medical treatments in the event that they are unable to communicate their wishes actively [61]. The content of an advance directive depends on the patient's condition, varying based on whether the individual is healthy, has chronic illnesses, or faces an advanced disease with an imminent risk of death [62]. When completed under favorable prognostic conditions, advance directives are frequently modified over time [63]. Conversely, advance directives completed within the last 3 months of life are associated with a greater likelihood of opting for aggressive care [64]. However, the presence of an acute, potentially reversible condition can impair the patient's capacity to make decisions. Despite the limitations of advance directives, understanding a patient's previously expressed wishes—regardless of how distant they may be from the circumstances leading to ICU admission—is invaluable, if not essential, in the current decision-making process. Therefore, these directives should not only be considered, but should also serve as the guiding framework to uphold patient autonomy when the patient is unable to exercise it. In such cases, this responsibility often falls to family members and close contacts.

The clinical condition during ICU admission, due to the underlying pathology or the effects of administered medications, often prevents patients from rationally expressing their preferences regarding ICU management. This situation becomes particularly challenging when it is unclear whether the patient has fully understood physicians' explanations about their prognosis. Whenever possible, decisions regarding the limitation of life-sustaining therapies should involve all individuals responsible for the patient's treatment and care [8], while considering the patient's potential wishes as perceived by those who know them best and their prior lifestyle before the critical illness.

The physician overseeing the patient's clinical management likely has the most comprehensive perspective on patient's condition, recent progression, and short- to medium-term prognosis based on the course of the disease. Although the "physician in charge" of the patient management must have the necessary tools to coordinate the conversation regarding their own proposal or that of the patient or their family members, the decision must always be discussed with the healthcare team and aligned with the explicit wishes of the patient's family [65]. Empowering those close to the patient in decision-making can be considered surrogate decision-making. This can extend the autonomy of the incapacitated person, allowing professionals to understand their previously expressed values and preferences. However, it is not easy to distinguish between the choices family members would make for themselves and those they are asked to make on behalf of someone else [66].

2.3.2 When to make the proposal

The timing of the proposal to limit life-sustaining therapies is influenced by several factors, including the state of mind of the professionals, their previous experience with death, or their knowledge of how to cope with extreme experiences. It is essential that both patients and their representatives are well informed about the prognosis of the current situation and the available therapeutic options [22]. This will allow them to consider what type of consequences they are willing to accept and at what risk. An interprofessional approach that involves both physicians and nurses in decision-making helps to maintain consistent messages and reduces moral distress among healthcare providers [67].

Proposing the limitation of life-sustaining therapies too early may be perceived by family members or close contacts as an abandonment of responsibility or as a consequence of deficiencies in the healthcare system. However, considering the possibility of limiting life-support measures early after ICU admission can reduce anxiety for both the patient and their family [37]. It is therefore crucial to identify the appropriate moment to initiate discussions leading to a shared decision-making process. Deciding within the first 48 hours of ICU admission that a patient is not a candidate for cardiopulmonary resuscitation has been associated with fewer interventions, reduced suffering, and a lower likelihood of loss of dignity as perceived by nurses. Additionally, nurses were less likely to perceive that the patient was in distress or not peaceful in cases where the patient ultimately died in the ICU. Importantly, such early decisions did not accelerate death compared to cases where the decision was made later [68]. Thus, delaying such discussions longer than necessary should be avoided. However, decision-making should be started only after gathering sufficient information regarding the patient's pre-existing conditions and the factors leading to ICU admission. This period also allows for the initiation of therapeutic measures and provides both the patient and their family an opportunity to recognize a worsening evolution. Time-limited trials recognize clinical uncertainties and prevent the extension of invasive interventions in the ICU.

End-of-life discussions have been shown to offer benefits for both patients and caregivers without significantly increasing emotional distress or psychiatric disorders [69]. Training healthcare teams in communication strategies is essential to prevent stress disorders and improve decision-making. Standardized interventions aim to reduce stress among family members and improve communication skills among healthcare professionals [70]. In addition, the entire process and the characteristics of the decision-making should be adequately recorded in the patient's medical record.

2.3.3 Conflicts that may arise

Conflicts may arise among the members of the medical team, who may consider a treatment futile, and the patient's representatives, who insist on maintaining all possible measures. A lack of understanding of the patient's current clinical situation by the patient's relatives is often the consequence of poor communication between them and the medical team. This opposition can lead healthcare professionals to fear potential legal action [71]. In such cases, it is crucial to interrupt the discussion and assess the root causes of the conflict. Conducting an appropriate differential diagnosis can help resolve potential issues and allow the focus to remain on providing appropriate care for the patient. These conflicts may stem from factors related to the family, the physician, or the healthcare organization [72].

Families may experience conflict due to a lack of understanding of the situation. This may result from insufficient psychological preparation to hear patient's diagnosis or prognosis, considering that bad news is often poorly processed. Additionally, the traditional communication style of physicians may contribute to misunderstandings or lead families to seek information from other sources. Even when families understand and acknowledge the situation, their decisions may also be influenced by feelings of guilt or secondary gains [73].

Physicians may also feel uncomfortable with prognostic uncertainty, leading them to approach these conversations either hesitantly or with excessive confidence. Additionally, they may be overburdened with work, fatigue, frustration, or stress. Discussing end-of-life matters may also be perceived as a professional failure. It is

essential for healthcare professionals to foster honest dialog, actively listening to patients or representatives, and incorporating this input as a crucial factor in proposing appropriate actions [74].

Social and organizational factors contributing to decision-making conflicts extend beyond the lack of financial compensation for discussions that are time-consuming. Restrictions on visiting hours limit contact between families and patients, hindering communication about end-of-life issues and preventing families from fully understanding the patient's condition [75]. Once a differential diagnosis of the conflict's reason has been established, it is necessary to develop interventions aimed at addressing and preventing these conflicts. Such measures promote better understanding between families and healthcare professionals, ultimately facilitating a consensual decision on the most appropriate course of action based on the patient's current condition.

Once it becomes clear that the patient's improvement is unlikely and that death may be approaching, conversation should continue. So, efforts can be redirected toward clarifying the patient's priorities and optimizing pain and symptom management [76].

2.4 Implementation: Withdrawal or withholding?

From an ethical standpoint, the decision to withdraw life-sustaining therapies is no different from the decision not to initiate or escalate them [77]. Although withdrawing interventions may seem more aggressive, as it involves the removal of all support and inevitably influences a potentially fatal outcome, a study revealed that life-sustaining interventions were withdrawn in nearly half of the cases [27]. From a practical perspective, withholding and withdrawing therapies can be considered equivalent. In fact, there may be uncertainty about whether a decision falls into one category or the other, and this distinction may not lead to any significant changes in the overall management of the patient. According to the Canadian Critical Care Society, legal and psychological differences between withholding and withdrawing life-sustaining treatment should not be overstated, as there may be no clinically significant differences between discontinuing an intervention and choosing not to escalate it [78].

2.4.1 Withholding

Withholding refers to the decision not to administer a life-sustaining treatment to a patient for whom it is unlikely to provide a clear benefit. This form of limitation is the most frequently used in surgical ICUs [25]. The rate of withholding-based limitations tends to be higher in studies conducted in Southern Europe compared to those involving hospital in Northern Europe, reinforcing the impact of cultural differences on these decisions. In Spain and Portugal, withholding was practiced in 63–83% of patients receiving end-of-life care, whereas these percentages were lower in other European multicenter studies [6, 25, 26, 29].

The most commonly used withholding measures are included in **Figure 2** [79]. Most publications exploring the application of withholding focus on the decision to forgo cardiopulmonary resuscitation [49]. This measure is common in end-of-life care, as cardiopulmonary resuscitation may cause more harm than benefit. Do-not-resuscitate orders are primarily indicated in three scenarios: patients who will not benefit from cardiopulmonary resuscitation, patients for whom resuscitation may

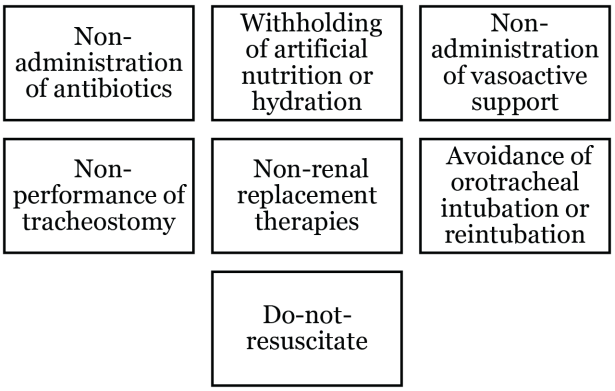

Figure 2.
Commonly employed withholding measures.

result in permanent harm or loss of consciousness, and patients with poor quality of life for whom recovery after resuscitation is unlikely [80]. This measure was significantly applied during the COVID-19 pandemic due to poor prognosis of these patients at a moment when healthcare-system demand exceeded available resources [81].

Respiratory failure accounts for nearly one-third of ICU admissions, making invasive mechanical ventilation a cornerstone of treatment for these patients. In these cases, decision-making is influenced not only by the patient's or physician's judgment but also by external factors. For example, ICU overcrowding forced many hospitals to forgo intubation in some patients due to a lack of resources during the COVID-19 pandemic [82]. The decision not to perform orotracheal intubation is generally associated with increased mortality and, in many cases, is closely aligned with a do-not-resuscitate order. The main criteria under this decision include advanced age, severe cognitive impairment, prolonged immobility, short life expectancy, limited functional capacity, or the presence of advance directives. The frequency of this decision varies across countries and published studies [82, 83]. However, up to 25% of patients for whom intubation was not performed were successfully treated with noninvasive mechanical ventilation [84].

The recommendation regarding do-not-resuscitate and do-not-intubate orders is that these directives should always be implemented in alignment with clearly defined treatment goals, ensuring consistency with the overall care plan. According to consensus guidelines, these decisions should always involve the patient, their family, and the healthcare team [24, 82]. These principles are also applicable to surgical airway management, as evidence suggests that proper palliative and end-of-life care can reduce the need for tracheostomies [85].

The complex hemodynamic and inflammatory conditions seen in ICU patients frequently lead to impaired renal function. The indication for renal replacement therapies in the ICU must distinguish between two different scenarios: patients experiencing acute kidney injury requiring renal replacement therapy due to their current condition, and those already enrolled in chronic dialysis programs who are admitted to the ICU for an intercurrent illness. These two groups have different implications when considering withholding renal replacement therapies. Only 21% of nephrologists in the United States are aware of the existence of a clinical guideline for limiting dialysis in patients with acute kidney injury and chronic kidney disease [86, 87]. The expected benefit must be considered. Despite currently increasing patient

tolerance to continuous therapies, it is important to recognize that renal replacement therapies should not be offered to all patients [86]. Among patients receiving continuous renal replacement therapy in the ICU, in-hospital mortality reached 61% for those with acute kidney injury and 54% for those with chronic kidney disease. However, renal function recovery occurred in 41–82% of survivors, with long-term outcomes being difficult to determine [88–90]. In this context, another relevant factor is the temporal window for therapeutic intervention in acute kidney injury, which is significantly shorter in patients with chronic kidney disease. The absence of advance directives further shortens this timeframe, necessitating discussions with families that, although often perceived by nephrologists as a bilateral agreement, do not always result in consensus [91]. Therefore, decisions regarding the limitation of renal replacement therapies should be made early, and the use of advance directives is particularly recommended for patients enrolled in chronic dialysis programs. One approach suggested by clinical guidelines is a trial of renal replacement therapy with predefined outcomes and duration, after which, if no improvement is observed, withdrawal may be considered [86, 87]. Additionally, dialysis withdrawal in elderly patients is generally well accepted by many physicians, even in cases where patients oppose the decision [92], despite it being a common cause of death in patients with chronic kidney disease [93]. The general acceptance of dialysis withdrawal may be attributed to the association between renal replacement therapies and a poorer quality of life.

Intravenous treatments are also frequently limited in critically ill patients with a poor prognosis, especially antibiotics and vasoactive support. To properly determine when to prescribe or withdraw an antibiotic in critically ill patients, it may sometimes be necessary to involve palliative care specialists in the patient assessment. In a cohort of 1177 cancer patients who died in the ICU, palliative care consultation led to fewer antibiotic prescriptions, a higher deprescription rate, and a lower rate of antibiotic treatment escalation [94]. Antibiotic deprescription most commonly occurs less than a day before death. In this context, the goal of end-of-life care is to improve comfort and alleviate suffering. Guidelines recommend antibiotic administration for symptomatic infections, with the aim of relieving symptoms, although there is little consensus on its usefulness in lower respiratory tract infections. Furthermore, broad-spectrum antibiotic therapy can cause patients to become reservoirs of multidrug-resistant microorganisms, with subsequent epidemiological and clinical implications. Therefore, if prolonging survival is not the primary objective, withholding antibiotics should be considered. Due to evidence of reduced symptoms and suffering, even in pneumonia, antibiotic treatment should be administered orally when possible [95–97].

Vasopressor treatment should be evaluated separately from the indication of no cardiopulmonary resuscitation and no orotracheal intubation, despite their close relationship. The administration of vasoactive drugs in patients with a poor prognosis can unnecessarily prolong life, so it should be considered as an initial measure to be limited [98]. Actually, vasopressor therapies are usually limited before more invasive therapies, such as mechanical ventilation. On the other hand, measures that must be ultimately suspended should be parenteral nutrition and hydration, since they are considered non-therapeutic measures, but rather support measures, without curative intent, that seek relief [99]. In addition, the suspension of artificial hydration and feeding has been associated with intestinal discomfort, diarrhea, and aspiration. Hence, the decision to suspend them must be made preserving the comfort and dignity of the patient, in consensus with the patient and her/his families [80].

2.4.2 Withdrawal

Withdrawal of life-sustaining treatments is a complex process that requires careful consideration of several factors, which are taken into account when organic support is considered futile [58, 100]. In this case, a treatment that is unlikely to provide any benefit to the patient is stopped. This decision should be based on an ethical assessment that considers the patient's rights, needs, and wishes. However, involving family members in the process helps mitigate emotional stress and facilitates a smoother transition [70]. Although, as previously noted, withholding and withdrawal decisions are equivalent, on a practical level, carrying out withdrawal entails a greater emotional burden for health professionals, since culturally the moral equivalence between not starting treatment and stopping treatment has not been reached [101].

The futility of cardiopulmonary resuscitation in critically ill patients is a complex issue. Only 17–22% of patients with in-hospital cardiac arrest survive to hospital discharge, and a significant percentage of these patients are prone to suffer any associated neurological dysfunction [102]. Therefore, the precise moment to stop resuscitation remains a matter of debate. According to clinical guidelines, discontinuation of cardiopulmonary resuscitation maneuvers should be considered in the absence of return of spontaneous circulation after an adequate period of resuscitation and advanced life support. Retrospective studies have shown that the probability of survival is less than 1% when resuscitation is prolonged beyond 39 minutes, and that significant neurological recovery is unlikely if cardiopulmonary resuscitation is prolonged beyond 32 minutes [103, 104]. However, recent medical advances, such as the use of cardiopulmonary bypass systems, have allowed documented cases in which return of spontaneous circulation has been achieved after more than 150 minutes of cardiopulmonary resuscitation. Therefore, it is essential to evaluate each case individually before deciding to discontinue the maneuvers [105].

Patients frequently reach the end of life while connected to invasive mechanical ventilation. When the situation is irreversible, withdrawal of mechanical ventilation should be considered. Ventilatory support can be removed in two ways: terminal weaning (consists of gradually reducing the dose of oxygen and ventilatory support) or terminal extubation (cessation of ventilatory support and removing the endotracheal tube in a single time). These two methods are often used, either together or separately, and there is no evidence as to which one is better [106]. However, dyspnea is predictable in ventilator-dependent patients in the process of weaning, especially at the end of life. Dyspnea is a common and distressing symptom that should be managed appropriately to ensure patient comfort [107]. The pharmacological and non-pharmacological measures for maintaining comfort after weaning are difficult to achieve. Many patients who are weaned off ventilation can be treated with noninvasive ventilation or high-flow oxygen therapy [108]. Patients with signs of respiratory distress in whom it is decided to withdraw mechanical ventilation are usually treated with morphine or fentanyl [107]. The most frequent causes reported for disconnection of ventilatory support were the physician's decision as the survival expectancy is less than 10%, the prediction of a severe cognitive function deficit, and the perception that the patient does not want advanced life support. Given the characteristics of invasive mechanical ventilation, this decision is usually made by consensus with the family, without the patient's participation [109, 110]. The published literature suggests that terminal extubation was associated with higher rates of airway obstruction, gasping, and a higher behavioral pain scale score, whereas terminal weaning involved more opioids, hypnotics, and neuromuscular blocking agents, suggesting more active

comfort management. Although both methods were similar in time to patient death [111], contrasting results have been reported regarding the psychological impact of these interventions on both families and healthcare professionals. Families tended to show high levels of satisfaction with the management of the situation in both cases, but ICU staff showed higher levels of stress with immediate extubation. The fact that this modality was associated with higher rates of gasping may indicate the need for better palliative management in this type of patient [111]. Pain is the most frequently reported distressing symptom in patients at high risk of death [112], so it is usually the main objective and continuous attention is usually given to it.

In developed countries, dialysis withdrawal is a cause of mortality in 15–22% of patients who die while on renal replacement therapy. In the ICU, stopping renal replacement therapy is one of the most frequent decisions to limit therapeutic effort at the end of life [113, 114]. The cessation of dialysis therapy and transition to palliative care is recommended for those patients with poor quality of life and poor prognosis [115].

Vasopressors and comfort medications should be withdrawn gradually, ensuring that the patient receives adequate treatment of pain and other symptoms so that he/she is comfortable [100]. General well-being is multidimensional and encompasses symptoms other than pain.

The timing of withdrawal of life support is influenced by several factors, which are crucial for setting expectations, managing resources, and considering organ donation possibilities. This process must be carefully planned and executed. This includes mechanical ventilation, administration of vasoactive support, and the use of extracorporeal assist devices. Measures that may seem simpler should be considered equivalent to organ support measures, but any therapeutic measure that is no longer justified on medical grounds should be discontinued. Thus, from an ethical and legal point of view, each of the measures shown in **Figure 3** should be considered equivalent in relation to the fact that the process of irreversible death should not be prolonged [8].

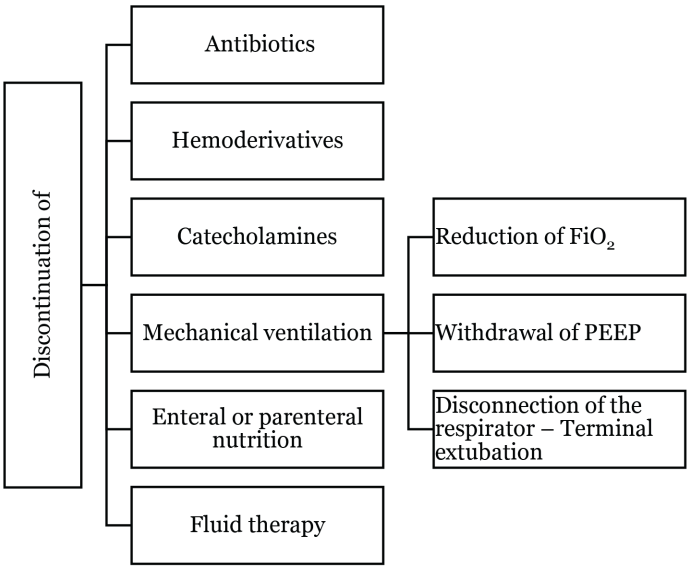

Figure 3.
Withdrawal.

Predicting the time to asystole from the withdrawal of life support is important for setting expectations and planning resource use. Some factors, such as deteriorating oxygenation or the absence of reflexes, are indicators that asystole is imminent [100]. Although the process should last long enough for the family to be able to accept the outcome, it should not be prolonged unnecessarily. The unpredictability of the dying process is a challenge for families and healthcare providers [116]. The following factors influence the withdrawal process's duration:

- Physiologic indicators: In adults, impending asystole (considered within the first 60 minutes) is associated with impaired oxygenation, absence of corneal and cough reflexes, decreased blood pressure, and the use of vasopressors and analgesics [100]. It is difficult to make accurate predictions in children because the physiological process is less well understood [116].

- Predictive models: Several predictive models exist for estimating time to asystole in adults. However, their generalizability and accuracy vary, and further validation is needed [100]. Few tools are available for pediatric patients.

- Emotional and logistical considerations: The unpredictability of the patient's time to death can cause emotional distress for families and healthcare professionals, affecting the potential organ donation after death [116]. Healthcare providers should assist families with logistics, medications, and setting expectations during the process [117].

- Cultural and ethical tensions: There might be tensions between maintaining a dignified dying process and therapeutic interventions, and between the role of healthcare professionals and the wishes of families [118].

2.5 Implications of implementation

The implementation of limiting life-sustaining therapies in the ICU is complex, infrequent, emotionally charged, and usually occurs at a point when various therapeutic interventions have been exhausted and futility has been demonstrated. Despite being the group in closest contact with the critically ill patient, nurses recognize that the decision to initiate life-sustaining interventions is usually made by the physician and feel that their opinion is almost never considered [71]. Although the physician may be the appropriate person to lead discussions about initiating the withholding or withdrawal of life-sustaining therapies, it is advisable to involve the entire team of professionals responsible for the patient's care (nurses, physiotherapists). In addition, families should feel involved in any changes in the patient's treatment, as both healthcare professionals and family members play a fundamental role in these situations [119]. The importance of involving all personnel responsible for the patient's care is that the decision to withdraw life-sustaining treatment can raise a moral dilemma for the nursing staff, who are often the ones responsible for withdrawing these therapies [120]. However, despite an obvious imbalance between medical and nursing staff decision-making, ICU nurses report relief when implementing life-sustaining therapy limitation measures [121].

The implementation of decisions can be interpreted by many professionals as a professional failure, as it is usually followed by the death of the patient [22]. This can affect emotional and professional well-being [58, 121]. The main effects of these decisions on ICU staff are included in **Table 2**.

Emotional stress and ethical dilemmas	Nurses may experience ethical conflicts due to disagreements among medical teams and the perception that physicians prolong unnecessary treatments rather than allowing for a dignified death. They acknowledge that physicians occasionally avoid applying irreversibility criteria, opting instead to extend interventions in an effort to defeat death, rather than facilitate a peaceful end-of-life process [71]. As a result, staff members often struggle to balance their duty to preserve life against the recognition of the patient's suffering [22, 58].
Feelings of frustration and powerlessness	Professionals may feel frustrated when their opinions are not considered in the decision-making process. This can lead to a sense of professional devaluation and make it more difficult for them to engage in a care plan they do not feel a part of [71, 122]. Poor communication can increase anxiety and depression among both professionals and the patient's relatives [70, 123].
Difficulty in withdrawing treatments	The discontinuation of previously prescribed treatments often adds stress to the decision-making process [71].
Risk of burnout and moral distress	Providing futile treatments can cause moral distress, emotional exhaustion, and even lead to a desire to leave the profession [58]. The emotional burden associated with limiting life-sustaining therapies combined with the high demands of the ICU environment increase the risk of burnout [122].
Need to provide comfort and relief	Nurses focus on ensuring patient comfort and relief during the end-of-life process, with the aim of securing a "good death." This includes creating a dignified and respectful environment, ensuring the presence of family, and alleviating pain and distress [71].

Table 2.
Effects of implementation on ICU staff.

Before implementing any decisions, it is advisable to avoid confusion between limiting life-sustaining therapies and euthanasia. Clearly distinguishing between these two concepts enables healthcare providers to make sound decisions that can benefit the patient during moments of great uncertainty [22]. Training in bioethics and the creation of spaces for reflection and dialog can help healthcare professionals face these challenges. Furthermore, emotional support and inclusion in the decision-making process are essential to mitigating the negative impact of limiting life-sustaining therapies on staff and family's well-being [19].

2.6 Outcomes

Despite the vast amount of medical information that intensive care physicians handle, significant uncertainty remains in clinical practice. This inevitably leads to differing outcomes among patients despite limited therapeutic measures, and consequently, a range of different results that can be obtained after implementing these decisions [124]. Clinical consequences after implementing life-sustaining therapies limitation may include survival, disability, or death—in the ICU, during the hospital stay, or after hospital discharge.

Mortality is probably the most common and sometimes most expected outcome. However, a causal relationship between the limitation of measures and patient death has not been clearly defined. During the COVID-19 pandemic, it was found that withholding was associated with a 75% mortality rate in ICU patients, while withdrawal was associated with a 95% mortality rate. In British ICUs, a study that included almost 800,000 patients found a 26% higher mortality difference in those patients who were withheld or withdrawn compared to those who were not [29, 33, 124, 125].

Healthcare professionals often associate this decision-making with mortality [29]. However, patient death is not always the outcome. One in five ICU admissions where therapeutic effort limitation measures are applied survives the hospitalization. Paradoxically, in a study of a cohort of over one million patients, those hospitals with higher rates of end-of-life treatment had slightly better survival rates [126].

Thus, after limiting life-sustaining treatment, ICU survival remains high (22%), with hospital survival at 16% [60]. Limitation of life-sustaining therapies does not always result in the patient's death. In up to 20% of cases, the implementation of these measures is associated with clinical improvement. This may be due to reversible diseases, misdiagnoses, a positive outcome from treatments administered prior to the decision, or because the decision involved limiting interventions that the patient ultimately did not need. For example, establishing a therapeutic ceiling by not initiating renal replacement therapies in patients who do not experience acute kidney failure during their hospital stay [29].

Patients who survive ICU admission suffer numerous complications and marked deterioration, which makes it difficult to regain pre-admission functional capacity. This may be exacerbated in patients who have undergone limited life-sustaining therapies, who tend to be more fragile, with multiple comorbidities and a worse prognosis [29]. For example, patients undergoing mechanical ventilation in the ICU experience a loss of up to 40% in their ability to perform some activities of daily living after admission. Cognitive impairment, brain fog, muscle weakness, fatigue, anxiety, and depression are some of the other symptoms that patients often present with upon discharge from the ICU [127]. Therefore, it is expected that patients who have received withholding or withdrawal of life-support measures will also experience a deterioration in their quality of life after discharge from the unit.

Limiting life-sustaining therapies often allows for earlier transitions to palliative care, which reduces ICU congestion [128] and costs without compromising the ethics of care [129]. Furthermore, when care goals are aligned and decision-making is consensual, ICU teams function more cohesively and with less internal conflict.

The implementation of structured approaches, such as time-limited trials, reduces the duration and intensity of non-beneficial treatments and the length of ICU stays without affecting overall mortality, improving the quality of experience for the families of critically ill patients [130]. Families generally appreciate honest and empathetic communication and sharing decision-making. Furthermore, clear communication reduces anxiety and improves the grieving experience [131], as they are more likely to feel that the patient died with dignity and that their values were respected [69]. Fear of legal liability and accusations of unethical behavior are common concerns among healthcare professionals, as observed in a Polish cross-sectional study [132]. However, when decision-making is well documented and agreed upon, legal risks are minimal [133].

It is mandatory to emphasize that the limitation on life-sustaining therapies does not imply the abandonment of the patient. Awareness of this principle can bring relief and comfort both to the professionals carrying out these practices and to the families of the patients involved. The fundamental components of a dignified death include ensuring the patient is free from pain, suffering, and distress, and is accompanied by family members throughout the process [71]. In the final stages of life, opioids are the most commonly used analgesics, with morphine the most frequent, followed by fentanyl. Among benzodiazepines, midazolam is the most used sedative. The average doses of analgesics and sedatives tend to increase both before and after the withdrawal of life support [134]. Patients admitted to the ICU typically have intravenous

access and continuous monitoring in place. The intravenous administration of both opioids and sedatives is often the most efficient route for effective symptom management. The use of continuous intravenous drug infusion allows for a stable blood concentration that can be adjusted according to the infusion rate. This rate can be increased as needed to alleviate discomfort during the end-of-life process [66].

3. Conclusions

When a therapy is found to be futile, limiting life-sustaining therapies that do not benefit the patient should be considered. Both withholding and withdrawing therapies already given are equally valid ways of avoiding unnecessary prolongation of ICU stay and, eventually, life. However, the use of one of these methods depends on certain patient-related, cultural, or clinician-related factors. The decision should be multidisciplinary, taking into account the wishes of the patient and family in accordance with the principle of autonomy. Decision-making should begin as soon as sufficient information has been gathered to know the patient's prognosis, to avoid unnecessary delays, and to facilitate the active involvement of families to prevent stress and reduce uncertainty. Adequate and compassionate communication will prevent conflicts between families and doctors or among health professionals.

Withholding refers to the decision not to provide life-sustaining treatment to a patient for whom it is unlikely to provide clear benefit. Withdrawing refers to the discontinuation of a treatment that is unlikely to benefit the patient. The implementation of both methods can be complex, emotionally charged, and have consequences for healthcare professionals. In addition, the clinical consequences often lead to the patient's death, requiring active support with pharmacological and non-pharmacological therapies to facilitate end-of-life care. Sometimes the patient survives despite the limitation of life-sustaining therapies because of reversible diseases, misdiagnosis, a positive outcome of treatments administered prior to the decision, or because the decision involved limiting interventions that the patient may not need. In these cases, the possibility of complications or disability after discharge is a possibility that will affect the quality of life of the patient and their caregivers.

Conflict of interest

The authors declare no conflict of interest.

Thanks

We would like to thank Peter Mangiaracina and Bruno Rodríguez-Reveggino for their assistance in preparing this chapter.

DOI: http://dx.doi.org/10.5772/intechopen.1010899

Author details

Ángel Becerra-Bolaños[1,2*], Raúl Vega-Rodríguez[1], Héctor Trujillo-Morales[1], Nazario Ojeda-Betancor[1] and Aurelio Rodríguez-Pérez[1,2]

1 Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Spain

2 Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain

*Address all correspondence to: angbecbol@gmail.com

IntechOpen

References

[1] WHO. Ageing and Health. 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health [Accessed: February 28, 2025]

[2] Ruiz C, Díaz MÁ, Zapata JM, Bravo S, Panay S, Escobar C, et al. Características y evolución de los pacientes que ingresan a una Unidad de Cuidados Intensivos de un hospital público [Characteristics and evolution of patients admitted to a public hospital intensive care unit]. Revista Médica de Chile. 2016;**144**(10):1297-1304. DOI: 10.4067/S0034-98872016001000009

[3] Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: Implications for clinical practice and public health. Lancet. 2019;**394**(10206):1365-1375. DOI: 10.1016/S0140-6736(19)31786-6

[4] Becerra-Bolaños Á, Hernández-Aguiar Y, Rodríguez-Pérez A. Preoperative frailty and postoperative complications after non-cardiac surgery: A systematic review. The Journal of International Medical Research. 2024;**52**(9):3000605241274553. DOI: 10.1177/03000605241274553

[5] Patrícia KR, Lenise PM, do, Almeida Cabral Patrícia Fernanda de, Jatobá de Souza Ana Izabel, Anders Jane Cristina. El cuidado y la tecnología en las unidades de cuidados intensivos. Index de Enfermería. 2013;**22**(3):156-160. Available from: http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1132-12962013000200009&lng=es. DOI: 10.4321/S1132-12962013000200009

[6] Iribarren-Diarasarri S, Latorre-García K, Muñoz-Martínez T, Poveda-Hernández Y, Dudagoitia-Otaolea JL, Martínez-Alutiz S, et al. Limitación del esfuerzo terapéutico tras el ingreso en una Unidad de Medicina Intensiva. Análisis de factores asociados [limitation of therapeutic effort after ICU admission. Analysis of related factors]. Medicina Intensiva. 2007;**31**(2):68-72. DOI: 10.1016/s0210-5691(07)74778-2

[7] Boelens YFN, Melchers M, van Zanten ARH. Poor physical recovery after critical illness: Incidence, features, risk factors, pathophysiology, and evidence-based therapies. Current Opinion in Critical Care. 2022;**28**(4):409-416. DOI: 10.1097/MCC.0000000000000955

[8] Valentin A, Druml W, Steltzer H, Wiedermann CJ. Recommendations on therapy limitation and therapy discontinuation in intensive care units: Consensus paper of the Austrian associations of intensive care medicine. Intensive Care Medicine. 2008;**34**(4):771-776. DOI: 10.1007/s00134-007-0975-6

[9] García MÁG, Arenas MÁR, Cornejo AM. Bioethics in critical care patients. In: Reflections on Bioethics. London, UK: InTech; 2018. DOI: 10.5772/intechopen.75565

[10] Schneiderman LJ. Defining medical futility and improving medical care. The Journal of Bioethical Inquiry. 2011;**8**(2):123-131. DOI: 10.1007/s11673-011-9293-3

[11] Jecker NS, Pearlman RA. Medical futility. Who decides? Archives of Internal Medicine. 1992;**152**(6):1140-1144

[12] Schneiderman LJ, Jecker NS, Jonsen AR. Medical futility: Its meaning and ethical implications. Annals of

Internal Medicine. 1990;**112**(12):949-954. DOI: 10.7326/0003-4819-112-12-949

[13] Aghabarary M, Dehghan NN. Medical futility and its challenges: A review study. The Journal of Medical Ethics and History of Medicine. 2016;**9**:11

[14] Bernat JL. Medical futility: Definition, determination, and disputes in critical care. Neurocritical Care. 2005;**2**(2):198-205. DOI: 10.1385/NCC:2:2:198

[15] Cardona-Morrell M, Kim J, Turner RM, Anstey M, Mitchell IA, Hillman K. Non-beneficial treatments in hospital at the end of life: A systematic review on extent of the problem. International Journal for Quality in Health Care. 2016;**28**(4):456-469. DOI: 10.1093/intqhc/mzw060

[16] Aksoy E, Ilkilic I. Medical futility at the end of life: The first qualitative study of ethical decision-making methods among Turkish doctors. BMC Medical Ethics. 2024;**25**(1):122. DOI: 10.1186/s12910-024-01120-1

[17] McPherson K, Carlos WG 3rd, Emmett TW, Slaven JE, Torke AM. Limitation of life-sustaining care in the critically ill: A systematic review of the literature. Journal of Hospital Medicine. 2019;**14**(5):303-310. DOI: 10.12788/jhm.3137

[18] Jox RJ, Schaider A, Marckmann G, Borasio GD. Medical futility at the end of life: The perspectives of intensive care and palliative care clinicians. Journal of Medical Ethics. 2012;**38**(9):540-555. DOI: 10.1136/medethics-2011-100479

[19] Hernando P, Diestre G, Baigorri F. Limitación del esfuerzo terapéutico: "cuestión de profesionales o también de enfermos?" [limitation of therapeutic effort: A "question for professionals or for patients as well?"]. Anales del Sistema Sanitario de Navarra. 2007;**30**(Suppl. 3):129-135. DOI: 10.23938/ASSN.0207

[20] Walzl N, Sammy IA, Taylor PM, Smith JE, Lowe DJ. Systematic review of factors influencing decisions to limit treatment in the emergency department. Emergency Medicine Journal. 2022;**39**(2):147-156. DOI: 10.1136/emermed-2019-209398

[21] Bosslet GT, Pope TM, Rubenfeld GD, Lo B, Truog RD, Rushton CH, et al. An official ATS/AACN/ACCP/ESICM/SCCM policy statement: Responding to requests for potentially inappropriate treatments in intensive care units. American Journal of Respiratory and Critical Care Medicine. 2015;**191**(11):1318-1330. DOI: 10.1164/rccm.201505-0924ST

[22] González-Castro A, Azcune O, Peñasco Y, Rodríguez JC, Domínguez MJ, Rojas R. Opinión de los profesionales de una unidad de cuidados intensivos sobre la limitación del esfuerzo terapéutico [Opinion of professionals in an intensive care unit on the limitations of therapeutic effort]. Revista de Calidad Asistencial. 2016;**31**(5):262-266. DOI: 10.1016/j.cali.2015.12.007

[23] Pantoja ZL. Problemas éticos al final de la vida:¿ todo es eutanasia? Seminarios de la Fundación Española de Reumatología. 2009;**10**:128-131

[24] Kesecioglu J, Rusinova K, Alampi D, Arabi YM, Benbenishty J, Benoit D, et al. European Society of Intensive Care Medicine guidelines on end of life and palliative care in the intensive care unit. Intensive Care Medicine. 2024;**50**(11):1740-1766. DOI: 10.1007/s00134-024-07579-1

[25] Becerra-Bolaños Á, Ramos-Ahumada DF, Herrera-Rodríguez L,

Valencia-Sola L, Ojeda-Betancor N, Rodríguez-Pérez A. Withdrawal/withholding of life-sustaining therapies: Limitation of therapeutic effort in the intensive care unit. Medicina (Kaunas, Lithuania). 2024;**60**(9):1461. DOI: 10.3390/medicina60091461

[26] Monteiro NF, Simões I, Gaspar I, Carmo E. Do-not-resuscitate and treatment limitation decisions - six years of experience from a Portuguese general intensive care unit. Revista da Associacao Medica Brasileira (1992). 2019;**65**(9):1168-1173. DOI: 10.1590/1806-9282.65.9.1168

[27] Feldman C, Sprung CL, Mentzelopoulos SD, Pohrt A, Hartog CS, Danbury C, et al. Richards GA; Ethicus-2 study group. Global comparison of communication of end-of-life decisions in the ICU. Chest. 2022;**162**(5):1074-1085. DOI: 10.1016/j.chest.2022.05.007

[28] Löfmark R, Nilstun T, Cartwright C, Fischer S, van der Heide A, Mortier F, et al. Physicians' experiences with end-of-life decision-making: Survey in 6 European countries and Australia. BMC Medicine. 2008;**6**:4. DOI: 10.1186/1741-7015-6-4

[29] Avidan A, Sprung CL, Schefold JC, Ricou B, Hartog CS, Nates JL, et al. Variations in end-of-life practices in intensive care units worldwide (Ethicus-2): A prospective observational study. The Lancet Respiratory Medicine. 2021;**9**(10):1101-1110. DOI: 10.1016/S2213-2600(21)00261-7

[30] Pasieka P, Surówka A, Fronczek J, Skwara E, Czuczwar M, Borys M, et al. Prevalence of life-sustaining treatment limitations in polish very old intensive care patients (VIPs). A post-hoc analysis of two prospective observational studies. Journal of Critical Care. 2024;**79**:154439. DOI: 10.1016/j.jcrc.2023.154439

[31] Bruno RR, Wernly B, Beil M, Muessig JM, Rahmel T, Graf T, et al. Therapy limitation in octogenarians in German intensive care units is associated with a longer length of stay and increased 30 days mortality: A prospective multicenter study. Journal of Critical Care. 2020;**60**:58-63. DOI: 10.1016/j.jcrc.2020.07.024

[32] Andersen FH, Ariansen Haaland Ø, Klepstad P, Flaatten H. Frailty and survival in elderly intensive care patients in Norway. Acta Anaesthesiologica Scandinavica. 2021;**65**(8):1065-1072. DOI: 10.1111/aas.13836

[33] Giabicani M, Le Terrier C, Poncet A, Guidet B, Rigaud JP, Quenot JP, et al. COVID-ICU study investigators. Limitation of life-sustaining therapies in critically ill patients with COVID-19: A descriptive epidemiological investigation from the COVID-ICU study. Critical Care. 2023;**27**(1):103. DOI: 10.1186/s13054-023-04349-1

[34] Naito H, Sakuraya M, Hongo T, Takada H, Yumoto T, Yorifuji T, et al. Prevalence, reasons, and timing of decisions to withhold/withdraw life-sustaining therapy for out-of-hospital cardiac arrest patients with extracorporeal cardiopulmonary resuscitation. Critical Care. 2023;**27**(1):252. DOI: 10.1186/s13054-023-04534-2

[35] Chang YC, Fang YT, Chen HC, Lin CY, Chang YP, Chen YM, et al. Effect of do-not-resuscitate orders on patients with sepsis in the medical intensive care unit: A retrospective, observational and propensity score-matched study in a tertiary referral hospital in Taiwan. BMJ Open. 2019;**9**(6):e029041. DOI: 10.1136/bmjopen-2019-029041

[36] López González UA, Bautista Rentero D, Crespo Gómez M, Cárcamo

Ibarra P, Míguez Santiyán AM. Factors associated with limitation of life support: Post-ICU mortality case study of a tertiary hospital. Revista española de anestesiología y reanimación (English edition). 2024;**71**(5):387-393. DOI: 10.1016/j.redare.2024.02.007

[37] Lacoste-Palasset T, Sutterlin L, M'Rad A, Modestin L, Mourman V, Pepin-Lehalleur A, et al. Impact of early limitation of therapeutic effort in elderly COVID-19 patients admitted to the intensive care unit-a cohort study. Journal of Personalized Medicine. 2022;**12**(9):1501. DOI: 10.3390/jpm12091501

[38] Estella Á, Lagares C, Furones MJ, Martínez López P, Lázaro Martín NI, Estebánez B, et al. Limitation of life support treatments in Spanish intensive care units: Analysis of the ETHICUS II study. Medicina Intensiva (English Edition). 2024;**48**(5):247-253. DOI: 10.1016/j.medine.2024.02.013

[39] Adamski J, Weigl W, Musialowicz T, Lahtinen P, Reinikainen M. Predictors of treatment limitations in Finnish intensive care units. Acta Anaesthesiologica Scandinavica. 2022;**66**(4):526-538. DOI: 10.1111/aas.14035

[40] Toyas Miazza C, Martínez-Álvarez RM, Díez-Manglano J, Ezpeleta Galindo AI, Laín Miranda ME, Aspiroz SC. Limitación del esfuerzo terapéutico en pacientes con bacteriemia [limitation of therapeutic effort in patients with bacteremia]. Revista Española de Geriatría y Gerontología. 2018;**53**(5):262-267. DOI: 10.1016/j.regg.2018.02.005

[41] Hernández-Aguiar Y, Becerra-Bolaños Á, Rodríguez-Pérez A. Preoperative diagnosis of frailty. The Journal of International Medical Research. 2024;**52**(5):3000605241251705. DOI: 10.1177/03000605241251705

[42] Spanish Group for the Epidemiological Analysis of Critical Patients (PAEEC), Mata GV. Quality of life: A tool for decision-making in the ICU. Intensive Care Medicine. 1994;**20**(4):251-252. DOI: 10.1007/BF01708958

[43] Abizanda R, Almendros Corral L, Balerdi PB. Aspectos éticos de la medicina intensiva. Resultados de una encuesta de opinión [Ethical aspects of intensive medicine. Results of an opinion survey]. Medicina Clínica (Barcelona). 1994;**102**(14):521-526

[44] Bueno Muñoz MJ. Limitación del esfuerzo terapéutico: aproximación a una visión de conjunto [Limitation of therapeutic effort: Approach to a combined view]. Enfermería Intensiva. 2013;**24**(4):167-174. DOI: 10.1016/j.enfi.2013.04.003

[45] Rivera-Fernández R, Sánchez-Cruz JJ, Abizanda-Campos R, Vázquez-Mata G. Quality of life before intensive care unit admission and its influence on resource utilization and mortality rate. Critical Care Medicine. 2001;**29**(9):1701-1709. DOI: 10.1097/00003246-200109000-00008

[46] Teres D, Lemeshow S, Avrunin JS, Pastides H. Validation of the mortality prediction model for ICU patients. Critical Care Medicine. 1987;**15**(3):208-213. DOI: 10.1097/00003246-198703000-00005

[47] White DB, Pope TM. Medical futility and potentially inappropriate treatment. In: Youngner AJ, Arnold RM, editors. The Oxford Handbook of Ethics at the End of Life. New York, USA: Oxford University Press; 2016

[48] Cabré L, Mancebo J, Solsona JF, Saura P, Gich I, Blanch L, et al. Multicenter study of the multiple organ

dysfunction syndrome in intensive care units: The usefulness of sequential organ failure assessment scores in decision making. Intensive Care Medicine. 2005;**31**(7):927-933. DOI: 10.1007/s00134-005-2640-2

[49] Wang AY, Ma HP, Kao WF, Tsai SH, Chang CK. Characteristics and outcomes of "do not resuscitate" patients admitted to the emergency department-intensive care unit. Journal of the Formosan Medical Association. 2019;**118**(1 Pt 2):223-229. DOI: 10.1016/j.jfma.2018.03.016

[50] Launey Y, Coquet A, Lasocki S, Dahyot-Fizelier C, Huet O, Le Pabic E, et al. Factors associated with an unfavourable outcome in elderly intensive care traumatic brain injury patients. A retrospective multicentre study. BMC Geriatrics. 2022;**22**(1):1004. DOI: 10.1186/s12877-022-03651-x

[51] Ramos JGR, Tourinho FC, Borrione P, Azi P, Andrade T, Costa V, et al. Effect of a palliative care program on trends in intensive care unit utilization and do-not-resuscitate orders during terminal hospitalizations. An Interrupted Time Series Analysis. Rev Bras Ter Intensiva. 2018;**30**(3):308-316. DOI: 10.5935/0103-507X.20180042

[52] Brunker LB, Boncyk CS, Rengel KF, Hughes CG. Elderly patients and management in intensive care units (ICU): Clinical challenges. Clinical Interventions in Aging. 2023;**18**:93-112. DOI: 10.2147/CIA.S365968

[53] Muscedere J, Waters B, Varambally A, Bagshaw SM, Boyd JG, Maslove D, et al. The impact of frailty on intensive care unit outcomes: A systematic review and meta-analysis. Intensive Care Medicine. 2017;**43**(8):1105-1122. DOI: 10.1007/s00134-017-4867-0

[54] Hoit G, Wijeysundera DN, Hamad DM, Nauth A, Atrey A, Halai M, et al. Insurance type and withdrawal of life-sustaining therapy in critically injured trauma patients. JAMA Network Open. 2024;**7**(7):e2421711. DOI: 10.1001/jamanetworkopen.2024.21711

[55] Malhotra AK, Shakil H, Essa A, Mathieu F, Taran S, Badhiwala J, et al. Influence of health insurance on withdrawal of life sustaining treatment for patients with isolated traumatic brain injury: A retrospective multi-center observational cohort study. Critical Care. 2024;**28**(1):251. DOI: 10.1186/s13054-024-05027-6

[56] Feleke H, Moges T. Critical insights into pediatric care: Unveiling trends and outcomes of discharge against medical advice at Ethiopia's premier hospital: A retrospective cross-sectional survey. The Ethiopian Journal of Pediatrics and Child Health. 2023;**18**(2):149-161

[57] El Jawiche R, Hallit S, Tarabey L, Abou-Mrad F. Withholding and withdrawal of life-sustaining treatments in intensive care units in Lebanon: A cross-sectional survey of intensivists and interviews of professional societies, legal and religious leaders. BMC Medical Ethics. 2020;**21**(1):80. DOI: 10.1186/s12910-020-00525-y

[58] Choi HR, Ho MH, Lin CC. Futile life-sustaining treatment in the intensive care unit - nurse and physician experiences: Meta-synthesis. BMJ Supportive & Palliative Care. 2024;**14**(1):36-46. DOI: 10.1136/spcare-2023-004640

[59] Muñoz Camargo JC, Hernández-Martínez A, Rodríguez-Almagro J, Parra-Fernández ML, Prado-Laguna MDC, Martín M. Perceptions of patients and their families regarding limitation of therapeutic effort in the intensive care unit. Journal of Clinical Medicine.

2021;**10**(21):4900. DOI: 10.3390/jcm10214900

[60] Denke C, Jaschinski U, Riessen R, Bercker S, Spies C, Ragaller M, et al. End-of-life practices in 11 German intensive care units: Results from the ETHICUS-2 study. Medizinische Klinik – Intensivmedizin und Notfallmedizin. 2023;**118**(8):663-673. DOI: 10.1007/s00063-022-00961-1

[61] Orentlicher D. From the Office of the General Counsel. Advance Medical Directives. JAMA. 1990;**263**(17):2365-2367. DOI: 10.1001/jama.263.17.2365

[62] Sedini C, Biotto M, Crespi Bel'skij LM, Moroni Grandini RE, Cesari M. Advance care planning and advance directives: An overview of the main critical issues. Aging Clinical and Experimental Research. 2022;**34**(2):325-330. DOI: 10.1007/s40520-021-02001-y

[63] Wong HJ, Seow H, Gayowsky A, Sutradhar R, Wu RC, Lim H. Advance directives change frequently in nursing home residents. Journal of the American Medical Directors Association. 2024;**25**(8):105090. DOI: 10.1016/j.jamda.2024.105090

[64] Enguidanos S, Ailshire J. Timing of advance directive completion and relationship to care preferences. Journal of Pain and Symptom Management. 2017;**53**(1):49-56. DOI: 10.1016/j.jpainsymman.2016.08.008

[65] Melltorp G, Nilstun T. Decisions to forego life-sustaining treatment and the duty of documentation. Intensive Care Medicine. 1996;**22**(10):1015-1019. DOI: 10.1007/BF01699221

[66] Tanaka Gutiez M, Efstathiou N, Innes R, Metaxa V. End-of-life care in the intensive care unit. Anaesthesia. 2023;**78**(5):636-643. DOI: 10.1111/anae.15908

[67] Blythe JA, Kentish-Barnes N, Debue AS, Dohan D, Azoulay E, Covinsky K, et al. An interprofessional process for the limitation of life-sustaining treatments at the end of life in France. Journal of Pain and Symptom Management. 2022;**63**(1):160-170. DOI: 10.1016/j.jpainsymman.2021.06.016

[68] Ouyang DJ, Lief L, Russell D, Xu J, Berlin DA, Gentzler E, et al. Timing is everything: Early do-not-resuscitate orders in the intensive care unit and patient outcomes. PLoS One. 2020;**15**(2):e0227971. DOI: 10.1371/journal.pone.0227971

[69] Wright AA, Zhang B, Ray A, Mack JW, Trice E, Balboni T, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. Journal of the American Medical Association. 2008;**300**(14):1665-1673. DOI: 10.1001/jama.300.14.1665

[70] Termoz A, Subtil F, Drouin P, Marchal M, Verroul M, Langlois C, et al. Evaluating the impact of a standardised intervention for announcing decisions of withholding and withdrawing life-sustaining treatments on the stress of relatives in emergency departments (DISCUSS): Protocol for a stepped-wedge randomised controlled trial. BMJ Open. 2024;**14**(9):e087444. DOI: 10.1136/bmjopen-2024-087444

[71] Paredes Escobar MC. Limitación del esfuerzo terapéutico en la práctica clínica: Percepciones de profesionales médicos y de enfermería de unidades de pacientes críticos de un hospital público de adultos en la Región Metropolitana. Acta bioeth. 2012;**18**(2):163-171. DOI: 10.4067/S1726-569X2012000200004. Available from: http://www.scielo.cl/scielo.

php?script=sci_arttext&pid=S1726-569X2012000200004&lng=es

[72] Goold SD, Williams B, Arnold RM. Conflicts regarding decisions to limit treatment: A differential diagnosis. Journal of the American Medical Association. 2000;**283**(7):909-914. DOI: 10.1001/jama.283.7.909

[73] Ness DE, Ende J. Denial in the medical interview, Recognition and Management. JAMA. 1994;**272**(22):1777-1781

[74] Heyland DK, Dodek P, Rocker G, Groll D, Gafni A, Pichora D, et al. What matters most in end-of-life care: Perceptions of seriously ill patients and their family members. CMAJ. 2006;**174**(5):627-633. DOI: 10.1503/cmaj.050626

[75] Rosenczweig C. Should relatives witness resuscitation? Ethical issues and practical considerations. CMAJ. 1998;**158**(5):617-620

[76] Quill TE. Perspectives on care at the close of life. Initiating end-of-life discussions with seriously ill patients: Addressing the "elephant in the room". Journal of the American Medical Association. 2000;**284**(19):2502-2507. DOI: 10.1001/jama.284.19.2502

[77] Cabré Pericas L, Solsona Durán JF. Limitación del esfuerzo terapéutico en medicina intensiva. Medicina Intensiva. 2002;**26**(6):304-311

[78] Canadian Critical Care Society Ethics Committee, Bandrauk N, Downar J, Paunovic B. Withholding and withdrawing life-sustaining treatment: The Canadian critical care society position paper. Canadian Journal of Anaesthesia. 2018;**65**(1):105-122. DOI: 10.1007/s12630-017-1002-1

[79] Penders YWH, Bopp M, Zellweger U, Bosshard G, Swiss Medical End-of-Life Decisions Study Group. Continuing, withdrawing, and withholding medical treatment at the end of life and associated characteristics: A mortality follow-back study. Journal of General Internal Medicine. 2020;**35**(1):126-132. DOI: 10.1007/s11606-019-05344-5

[80] Pan H, Shi W, Zhou Q, Chen G, Pan P. Palliative care in the intensive care unit: Not just end-of-life care. Intensive Care Research. 2022;**3**:77-82. DOI: 10.1007/s44231-022-00009-0

[81] Oliveira HC, Sauthier M, Silva MMD, Crespo MDCA, Seixas APR, Campos JF. Do-not-resuscitate order in COVID-19 times: Bioethics and professional ethics. Revista Gaúcha de Enfermagem. 2021;**42**(spe):e20200172. DOI: 10.1590/1983-1447.2021.20200172

[82] Wilson ME, Mittal A, Karki B, Dobler CC, Wahab A, Curtis JR, et al. Do-not-intubate orders in patients with acute respiratory failure: A systematic review and meta-analysis. Intensive Care Medicine. 2020;**46**(1):36-45. DOI: 10.1007/s00134-019-05828-2

[83] Vilaça M, Aragão I, Cardoso T, Dias C, Cabral-Campello G. The role of noninvasive ventilation in patients with "do not intubate" order in the emergency setting. PLoS One. 2016;**11**(2):e0149649. DOI: 10.1371/journal.pone.0149649

[84] Levy M, Tanios MA, Nelson D, Short K, Senechia A, Vespia J, et al. Outcomes of patients with do-not-intubate orders treated with noninvasive ventilation. Critical Care Medicine. 2004;**32**(10):2002-2007. DOI: 10.1097/01.ccm.0000142729.07050.c9

[85] Hsu NC, Huang CC, Hsu CH, Wang TD, Sheng WH. Does hospitalist care enhance palliative care and reduce

aggressive treatments for terminally ill patients? A propensity score-matched study. Cancers (Basel). 2023;**15**(15):3976. DOI: 10.3390/cancers15153976

[86] Claure-Del Granado R, Mehta RL. Withholding and withdrawing renal support in acute kidney injury. Seminars in Dialysis. 2011;**24**(2):208-214. DOI: 10.1111/j.1525-139X.2011.00832.x

[87] Patel SS, Holley JL. Withholding and withdrawing dialysis in the intensive care unit: Benefits derived from consulting the renal physicians association/ American society of nephrology clinical practice guideline, shared decision-making in the appropriate initiation of and withdrawal from dialysis. Clinical Journal of the American Society of Nephrology. 2008;**3**(2):587-593. DOI: 10.2215/CJN.04040907

[88] Allegretti AS, Steele DJ, David-Kasdan JA, Bajwa E, Niles JL, Bhan I. Continuous renal replacement therapy outcomes in acute kidney injury and end-stage renal disease: A cohort study. Critical Care. 2013;**17**(3):R109. DOI: 10.1186/cc12780

[89] Chen JCY, Hu B, Frank RD, Kashani KB. Inpatient kidney function recovery among septic shock patients who initiated kidney replacement therapy in the hospital. Nephron. 2020;**144**(8):363-371. DOI: 10.1159/000507999

[90] Stevens JS, King KL, Robbins-Juarez SY, Khairallah P, Toma K, Alvarado Verduzco H, et al. High rate of renal recovery in survivors of COVID-19 associated acute renal failure requiring renal replacement therapy. PLoS One. 2020;**15**(12):e0244131. DOI: 10.1371/ journal.pone.0244131

[91] van Biesen W, van de Luijtgaarden MW, Brown EA, Michel JP, van Munster BC, Jager KJ, et al. Nephrologists' perceptions regarding dialysis withdrawal and palliative care in Europe: Lessons from a European renal best practice survey. Nephrology, Dialysis, Transplantation. 2015;**30**(12):1951-1958. DOI: 10.1093/ ndt/gfv284

[92] Clement R, Chevalet P, Rodat O, Ould-Aoudia V, Berger M. Withholding or withdrawing dialysis in the elderly: The perspective of a western region of France. Nephrology, Dialysis, Transplantation. 2005;**20**(11):2446-2452. DOI: 10.1093/ndt/gfi012

[93] Chan S, Marshall MR, Ellis RJ, Ranganathan D, Hawley CM, Johnson DW, et al. Haemodialysis withdrawal in Australia and New Zealand: A binational registry study. Nephrology, Dialysis, Transplantation. 2020;**35**(4):669-676. DOI: 10.1093/ndt/ gfz160

[94] Kim JH, Yoo SH, Keam B, Heo DS. Antibiotic prescription patterns during last days of hospitalized patients with advanced cancer: The role of palliative care consultation. The Journal of Antimicrobial Chemotherapy. 2023;**78**(7):1694-1700. DOI: 10.1093/jac/ dkad156

[95] Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an antibiotic stewardship program: Guidelines by the infectious diseases society of America and the society for healthcare epidemiology of America. Clinical Infectious Diseases. 2016;**62**(10):e51-e77. DOI: 10.1093/cid/ciw118

[96] van der Steen JT, Ooms ME, van der Wal G, Ribbe MW. Pneumonia: The demented patient's best friend? Discomfort after starting or withholding antibiotic treatment.

Journal of the American Geriatrics Society. 2002;**50**(10):1681-1688. DOI: 10.1046/j.1532-5415.2002.50460.x

[97] van der Steen JT, Pasman HR, Ribbe MW, van der Wal G, Onwuteaka-Philipsen BD. Discomfort in dementia patients dying from pneumonia and its relief by antibiotics. Scandinavian Journal of Infectious Diseases. 2009;**41**(2):143-151. DOI: 10.1080/00365540802616726

[98] Ramazzotti D, Clardy P, Celi LA, Stone DJ, Rudin RS. Withholding or withdrawing invasive interventions may not accelerate time to death among dying ICU patients. PLoS One. 2019;**14**(2):e0212439. DOI: 10.1371/journal.pone.0212439

[99] Morgan CK, Varas GM, Pedroza C, Almoosa KF. Defining the practice of "no escalation of care" in the ICU. Critical Care Medicine. 2014;**42**(2):357-361. DOI: 10.1097/CCM.0b013e3182a276c9

[100] Nicolson C, Burke A, Gardiner D, Harvey D, Munshi L, Shaw M, et al. Predicting time to asystole following withdrawal of life-sustaining treatment: A systematic review. Anaesthesia. 2024;**79**(6):638-649. DOI: 10.1111/anae.16222

[101] Aita K, Kai I. Physicians' psychosocial barriers to different modes of withdrawal of life support in critical care: A qualitative study in Japan. Social Science and Medicine. 2010;**70**(4):616-622. DOI: 10.1016/j.socscimed.2009.10.036

[102] Beck K, Vincent A, Cam H, Becker C, Gross S, Loretz N, et al. Medical futility regarding cardiopulmonary resuscitation in in-hospital cardiac arrests of adult patients: A systematic review and meta-analysis. Resuscitation. 2022;**172**:181-193. DOI: 10.1016/j.resuscitation.2021.11.041

[103] Okubo M, Komukai S, Andersen LW, Berg RA, Kurz MC, Morrison LJ, et al. Duration of cardiopulmonary resuscitation and outcomes for adults with in-hospital cardiac arrest: Retrospective cohort study. BMJ. 2024;**384**:e076019. DOI: 10.1136/bmj-2023-076019

[104] Panchal AR, Bartos JA, Cabañas JG, Donnino MW, Drennan IR, Hirsch KG, et al. Part 3: Adult basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2020;**142**(16 suppl. 2):S366-S468. DOI: 10.1161/CIR.0000000000000916

[105] Kim YS, Choi W, Hwang J. Resuscitation of prolonged cardiac arrest from massive pulmonary embolism by extracorporeal membrane oxygenation. European Journal of Cardio-Thoracic Surgery. 2017;**51**(6):1206-1207. DOI: 10.1093/ejcts/ezw413

[106] Orr S, Efstathiou N, Baernholdt M, Vanderspank-Wright B. ICU clinicians' experiences of terminal weaning and extubation. Journal of Pain and Symptom Management. 2022;**63**(5):e521-e528. DOI: 10.1016/j.jpainsymman.2022.01.016

[107] Obarzanek L, Campbell ML. Withholding and withdrawal of life support in critically ill patients at the end of life: Pain is not the only symptom to manage. Intensive Care Medicine. 2021;**47**(4):489-490. DOI: 10.1007/s00134-020-06345-3

[108] Nava S, Ferrer M, Esquinas A, Scala R, Groff P, Cosentini R, et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: A randomised feasibility trial. The Lancet Oncology. 2013;**14**(3):219-227. DOI: 10.1016/S1470-2045(13)70009-3

[109] Cook D, Rocker G, Marshall J, Sjokvist P, Dodek P, Griffith L, et al. Withdrawal of mechanical ventilation in anticipation of death in the intensive care unit. The New England Journal of Medicine. 2003;**349**(12):1123-1132. DOI: 10.1056/NEJMoa030083

[110] Chen YC, Fan HY, Curtis JR, Lee OK, Liu CK, Huang SJ. Determinants of receiving palliative care and ventilator withdrawal among patients with prolonged mechanical ventilation. Critical Care Medicine. 2017;**45**(10):1625-1634. DOI: 10.1097/CCM.0000000000002569

[111] Robert R, Le Gouge A, Kentish-Barnes N, Cottereau A, Giraudeau B, Adda M, et al. Terminal weaning or immediate extubation for withdrawing mechanical ventilation in critically ill patients (the ARREVE observational study). Intensive Care Medicine. 2017;**43**(12):1793-1807. DOI: 10.1007/s00134-017-4891-0

[112] Puntillo KA, Arai S, Cohen NH, Gropper MA, Neuhaus J, Paul SM, et al. Symptoms experienced by intensive care unit patients at high risk of dying. Critical Care Medicine. 2010;**38**(11):2155-2160. DOI: 10.1097/CCM.0b013e3181f267ee

[113] Neto MJA, Moura AFS, Suassuna JHR. Renouncement of renal replacement therapy: Withdrawal and refusal. Jornal Brasileiro de Nefrologia. 2017;**39**(3):312-322. DOI: 10.5935/0101-2800.20170054

[114] Metaxa V, Lavrentieva A. End-of-life decisions in burn intensive care units - an international survey. Burns. 2015;**41**(1):53-57. DOI: 10.1016/j.burns.2014.05.018

[115] Ramakrishnan C, Widjaja N, Malhotra C, Finkelstein E, Khan BA, Ozdemir S, et al. Unravelling complex choices: Multi-stakeholder perceptions on dialysis withdrawal and end-of-life care in kidney disease. BMC Nephrology. 2024;**25**(1):6. DOI: 10.1186/s12882-023-03434-5

[116] Francoeur C, Hornby L, Silva A, Scales NB, Weiss M, Dhanani S. Paediatric death after withdrawal of life-sustaining therapies: A scoping review protocol. BMJ Open. 2022;**12**(9):e064918. DOI: 10.1136/bmjopen-2022-064918

[117] Francoeur C, Silva A, Hornby L, Wollny K, Lee LA, Pomeroy A, et al. Pediatric death after withdrawal of life-sustaining therapies: A scoping review. Pediatric Critical Care Medicine. 2024;**25**(1):e12-e19. DOI: 10.1097/PCC.0000000000003358

[118] Choi HR, Ho MH, Lin CC. Navigating tensions when life-sustaining treatment is withdrawn: A thematic synthesis of nurses' and physicians' experiences. Journal of Clinical Nursing. 2024;**33**(6):2337-2356. DOI: 10.1111/jocn.17059

[119] Pérez Pérez FM. Adecuación del esfuerzo terapéutico, una estrategia al final de la Vida [the suitability of therapeutic effort: An end-of-life strategy]. SEMERGEN. 2016;**42**(8):566-574. DOI: 10.1016/j.semerg.2015.11.006

[120] Birchley G. Angels of mercy? The legal and professional implications of withdrawal of life-sustaining treatment by nurses in England and Wales. Medical Law Review. 2012;**20**(3):337-361. DOI: 10.1093/medlaw/fws007

[121] Velarde-García JF, Luengo-González R, González-Hervías R, Cardenete-Reyes C, Álvarez-Embarba B, Palacios-Ceña D. Limitation of therapeutic effort experienced by intensive care nurses.

Nursing Ethics. 2018;**25**(7):867-879. DOI: 10.1177/0969733016679471

[122] Restrepo BD, Cossio C, Ochoa JFL, Jaramillo JC, Bedoya J, Duque D, et al. Conocimientos, actitudes y prácticas frente a la limitación de esfuerzos terapéuticos en personal de salud de un hospital universitario. Persona y Bioética. 2013;**17**(2):216-226

[123] Douplat M, Jacquin L, Frugier S, Tazarourte K, Le Coz P. Difficulty of the ethical decision-making process in withholding and withdrawing life-sustaining treatments in French EDs during COVID pandemic. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 2020;**28**(1):78. DOI: 10.1186/s13049-020-00772-3

[124] Maharaj R, Harrison DA, Rowan K. The association between the decision to withdraw life-sustaining therapy and patient mortality in U.K. ICUs. Critical Care Medicine. 2022;**50**(4):576-585. DOI: 10.1097/CCM.0000000000005306

[125] Azoulay E, Pochard F, Garrouste-Orgeas M, Moreau D, Montesino L, Adrie C, et al. Decisions to forgo life-sustaining therapy in ICU patients independently predict hospital death. Intensive Care Medicine. 2003;**29**(11):1895-1901. DOI: 10.1007/s00134-003-1989-3

[126] Lin CY, Farrell MH, Lave JR, Angus DC, Barnato AE. Organizational determinants of hospital end-of-life treatment intensity. Medical Care. 2009;**47**(5):524-530. DOI: 10.1097/MLR.0b013e31819261bd

[127] Rosa RG, Teixeira C, Piva S, Morandi A. Anticipating ICU discharge and long-term follow-up. Current Opinion in Critical Care. 2024;**30**(2):157-164. DOI: 10.1097/MCC.0000000000001136

[128] Halpern NA, Pastores SM. Critical care medicine in the United States 2000-2005: An analysis of bed numbers, occupancy rates, payer mix, and costs. Critical Care Medicine. 2010;**38**(1):65-71. DOI: 10.1097/CCM.0b013e3181b090d0

[129] Khandelwal N, Curtis JR. Economic implications of end-of-life care in the ICU. Current Opinion in Critical Care. 2014;**20**(6):656-661. DOI: 10.1097/MCC.0000000000000147

[130] Chang DW, Neville TH, Parrish J, Ewing L, Rico C, Jara L, et al. Evaluation of time-limited trials among critically ill patients with advanced medical illnesses and reduction of nonbeneficial ICU treatments. JAMA Internal Medicine. 2021;**181**(6):786-794. DOI: 10.1001/jamainternmed.2021.1000

[131] Heyland DK, Rocker GM, Dodek PM, Kutsogiannis DJ, Konopad E, Cook DJ, et al. Family satisfaction with care in the intensive care unit: Results of a multiple center study. Critical Care Medicine. 2002;**30**(7):1413-1418. DOI: 10.1097/00003246-200207000-00002

[132] Damps M, Gajda M, Kowalska M, Kucewicz-Czech E. Limitation of futile therapy in the opinion of nursing staff employed in polish hospitals-results of a cross-sectional study. International Journal of Environmental Research and Public Health. 2022;**19**(24):16975. DOI: 10.3390/ijerph192416975

[133] White DB, Curtis JR, Lo B, Luce JM. Decisions to limit life-sustaining treatment for critically ill patients who lack both decision-making capacity and surrogate decision-makers. Critical Care Medicine. 2006;**34**(8):2053-2059. DOI: 10.1097/01.CCM.0000227654.38708.C1

[134] Laserna A, Durán-Crane A, López-Olivo MA, Cuenca JA, Fowler C, Díaz DP, et al. Pain management during the withholding and withdrawal of life support in critically ill patients at the end-of-life: A systematic review and meta-analysis. Intensive Care Medicine. 2020;**46**(9):1671-1682. DOI: 10.1007/s00134-020-06139-7