Intensive Care Med
https://doi.org/10.1007/s00134-018-5339-x

REVIEW

Time-limited trial of intensive care treatment: an overview of current literature

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Abstract

In critically ill patients, it is frequently challenging to identify who will benefit from admission to the intensive care unit and life-sustaining interventions when the chances of a meaningful outcome are unclear. In addition, the acute illness not only affects the patients but also family members or surrogates who often are overwhelmed and unable to make thoughtful decisions. In these circumstances, a time-limited trial (TLT) of intensive care treatment can be helpful. A TLT is an agreement to initiate all necessary treatments or treatments with clearly delineated limitations for a certain period of time to gain a more realistic understanding of the patient's chances of a meaningful recovery or to ascertain the patient's wishes and values. In this article, we discuss current research on different aspects of TLTs in the intensive care unit. We propose how and when to use TLTs, discuss how much time should be taken for a TLT, give an overview of the potential impact of TLTs on healthcare resources, describe ethical challenges concerning TLTs, and discuss how to evaluate a TLT.

Keywords: Intensive care, Critical care, Prognosis, Outcome, Prediction, Medical uncertainty

Introduction

Identifying patients who will benefit from ICU admission is often challenging. Where in some countries already 20% of the people die in the ICU, a trend for an increasing number of admissions, especially in the elderly, exists [1, 2]. Medical uncertainty, involving both patient- and physician-related factors, is common on ICU admission [3]. Uncertainty can exist about the prognosis and long-term outcome, response to treatment, risk of complications, and values of the patient or their surrogates. In addition, the decision-making capacity of critically ill patients is frequently absent, and family members or surrogates are frequently unable to represent the patient because of the emotional stress and fear of losing them. A time-limited trial (TLT) of ICU can be helpful in acquiring more certainty and preventing unnecessary or disproportionate care [4]. The concept of a TLT was proposed by Vincent et al. in 2005 as 'the ICU test' [5].

In this article, we discuss current research on different aspects of TLTs in the ICU. We discuss how and when to use TLTs, how much time should be taken for a TLT, and the potential impact of TLTs on availability of healthcare and describe ethical challenges concerning TLTs and how to evaluate a TLT.

Definition of a TLT

In this article, the suggested definition of a TLT by Quill and Holloway [6] is used. They defined a TLT as: "An agreement between clinicians and a patient/family to use certain medical therapies over a defined period to see if the patient improves or deteriorates according to agreed-on clinical outcomes. If the patient improves, disease directed therapy continues. If the patient deteriorates, the therapies involved in the trial are withdrawn, and goals frequently shift more purely to palliation. If significant clinical uncertainty remains, another TLT might be renegotiated."

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How and when to use TLTs of ICU

A TLT is an agreement to initiate all indicated treatments (i.e., mechanical ventilation, renal replacement therapy, vasopressor support, extracorporeal membrane oxygenation) or treatments with clearly delineated limitations (i.e., a do-not-resuscitate order) for a certain period of time to improve uncertainty about benefit. This requires enhanced communication between all persons involved in the patient's treatment as well as with the patient and their family/surrogates. The concept of a TLT is only an option when withdrawal of life support is permissible; therefore, a TLT would not be feasible in some countries (i.e., Israel and Arabic countries).

Take home message

TLTs can, when executed well, improve quality of care and provide patients with the care they desire and can benefit from

TLTs can be initiated at two points in time. First, they may be considered on admission when outcome and/or patient preferences are (still) unclear and optimal treatment for a limited period of time is likely to improve final decision making. A TLT typically applies to patients with limited quality of life associated with limited reserves. For example, a TLT is not indicated in a young victim of polytrauma or a patient with severe septic shock and

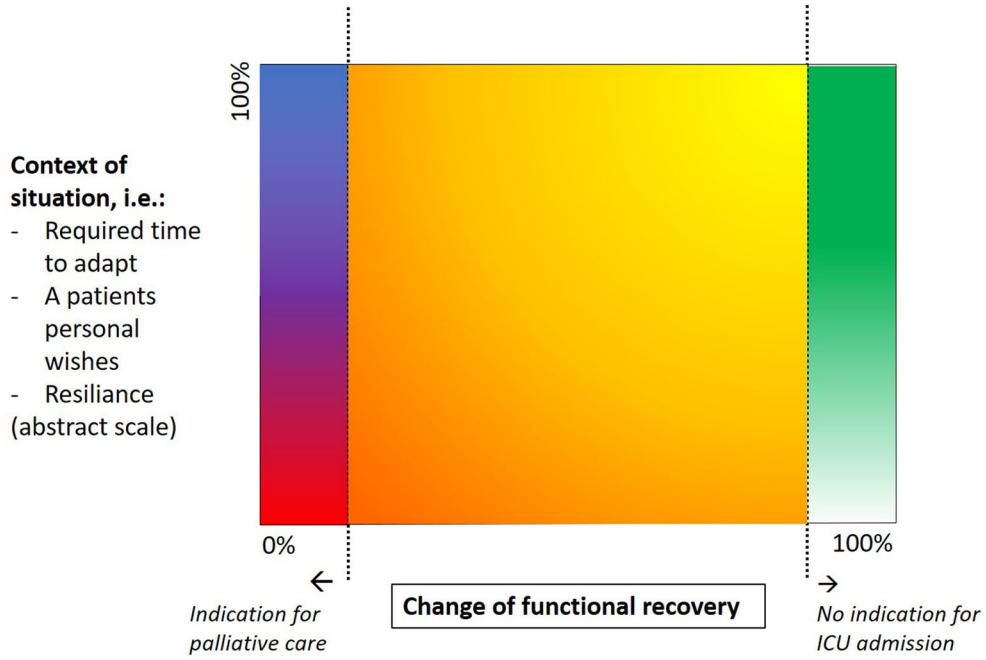

Fig. 1 Schematic view of (un)certainties in critically ill patients. Theoretically, patients admitted to the ICU can be classified based on two scales. The first scale, depicted on the X-axis of this figure, represents the change of functional survival. Patients at the right end of the spectrum are 'too well' for admission. These patients would also survive without ICU care and so admission would result in excessive care. The dashed line on the right side of the X-axis marks this point. At the left end of the X-axis, patients are 'too ill' for ICU admission. These patients would die despite optimal treatment in the ICU, and so admission would be disproportionate and could even be considered harmful; palliative care would be more appropriate. The dashed line on the left side of the X-axis marks this point. The Y-axis represents an abstract scale, the context of the situation. Multiple factors are represented, i.e., patients' preferences, resilience, and the possible required time for patients and families to adapt. At the top of the Y-axis, the context is optimal: i.e., the preferences are clear, no time is needed to adapt, and no issues need to be clarified. At the origin of the Y-axis, the context is not optimal, i.e., preferences are not clear, and time to adapt or to come to an agreement is required. Both this context (Y-axis) and the change in functional survival (X-axis) influence the correct indication for ICU admission and a TLT. The green-to-white area represents patients with a high chance of functional survival in an optimal context; ICU admission is not indicated. The white area falls outside the scope of this article (high chance of survival in a non-optimal context): preferences should be explored outside the ICU (i.e., out-patient clinic). The blue-to-red area represents patients with a high chance of mortality or non-functional recovery in a non-optimal context: i.e., patients and families might need time to adapt or preferences and effect of treatments that may need to be instituted are unclear. Palliative care with special attention to communication could be preferable over a TLT. The orange-to-yellow part of the figure represents patients with a risk of death and a chance of a beneficial effect of treatment in an optimal/suboptimal context that qualifies as appropriate ICU care. The orange part represents the patients who could benefit from a TLT: patients with a high probability of dying/non-functional recovery and uncertainty about the effect of ICU treatment on that survival and/or a suboptimal/non-optimal context

no major comorbidity. Theoretically, patients admitted to the ICU can be classified based on two scales (Fig. 1). The first scale, depicted on the X-axis of this figure, represents the chance of functional recovery. Patients at the right end of the spectrum are 'too well' for admission. These patients would also survive without ICU care and so admission would result in excessive care. The dashed line on the right side of the X-axis marks this point. These patients should not be admitted to the ICU, unless for logistical reasons, i.e., some post-elective surgery patients [7]. Uncertainty about excessive treatment can exist. This could be solved by admitting the patient to another level of care (medium care, post-anesthesia care unit). At the left end of the X-axis, patients are 'too sick' for ICU admission. These patients would die irrespective of ICU care and so admission would be disproportionate and could even be considered harmful. In these cases, palliative care would be more appropriate. The dashed line on the left side of the X-axis marks this point. There are exceptions to this classification: e.g., admission of a patient with a large intracerebral hematoma can be appropriate in light of a possible brain-dead organ donation procedure where the patient has no chance of survival. The point where excessive treatment and disproportionate treatment start on the X-axis is not fixed and influenced by hospital context and social structures. The Y-axis represents an abstract scale, the context of the situation. Multiple factors are represented here, i.e., the patients' preferences, resilience, and time for patients and families to adapt. At the top of the Y-axis, the context is optimal: i.e., the preferences are clear, no time is needed to adapt, and no issues need to be clarified. At the origin of the Y-axis, the context is not optimal: i.e., preferences are not clear, and time to adapt or to come to an agreement is required. Both this context (Y-axis) and the change of functional recovery (X-axis) influence the indication for ICU admission and a TLT. The green-to-white area represents patients with a high chance of functional recovery in an optimal context; ICU admission is not indicated. The white area falls outside the scope of this article (high chance of functional recovery in a non-optimal context): preferences should be explored outside the ICU (i.e., out-patient clinic). The blue-to-red area represents patients with a high chance of mortality or non-functional recovery in a non-optimal context: i.e., patients and families might need time to adapt or preferences and effect of treatments that may need to be instituted are unclear. Palliative care with special attention to communication could be preferable to a TLT. The orange-to-yellow part of Fig. 1 represents patients with a risk of death and the chance of a beneficial effect of treatment in an optimal/suboptimal context, which qualifies as appropriate ICU care. The orange part represents the patients that could benefit from a TLT: patients with a high probability of dying/non-functional recovery and uncertainty about the effect of ICU treatment on that survival and/or a suboptimal/non-optimal context. The extent of this area is, however, not easily defined. An international group of experts could not agree on a survival cutoff below which patients should no longer be admitted to the ICU [8]. Moreover, the majority (52%) of experts surveyed was not even unwilling to deny admission of patients with a 1% chance of survival [8]. In addition, some doctors have prognostic pessimism regarding ICU survival, which would lead to inappropriate denial of ICU admission. In a recent study, patients deemed to have a less than 10% change of survival actually had a 40% survival rate [9]. Although patients deemed 'too ill' to survive ICU admission are frequently denied ICU admission, their actual survival rate was 20% [10] in adult patients and 13% in patients older than 85 years [11]. In these patients a TLT could be helpful, and 94% of experts agreed that a TLT would give these patients the optimal chance of benefit [8].

Second, besides initiating a TLT at the moment of ICU admission, a TLT may be used during an ICU stay when unexpected complications occur or an untoward clinical course evolves resulting in increased uncertainty about the final outcome. In both these cases, a TLT could benefit the patient, relatives, and treatment team in situations where the patient and his or her relatives do not agree on treatment choices with each other or with the treatment team. A TLT is primarily used to give a patient the optimal chance for benefit. Moreover, it can potentially improve patient-centered decision making and prevent disproportionate care [4]. A TLT can thus also be initiated for surrogate/family/patient-centered reasons. Many surrogates and patients feel overwhelmed when faced with decisions about complex treatments and decisions to withhold or withdraw life support [12]. Some surrogates simply need time to process options and determine the most benevolent course in keeping with their loved one's values [12]. In case of uncertain prognosis on admission, surrogates may feel that clinicians are not willing to initiate all necessary treatments because of doubt, prejudice, or cost. In addition, families or surrogates may be overly optimistic about ICU care and prognosis [13]. This often results in disconnected communication and occasional mistrust, which may end up in surrogates insisting on continuing treatment despite the medical team's advice to focus on comfort measures. TLTs can reassure surrogates that every available and warranted option is utilized. Moreover, TLTs give surrogates the opportunity to get better informed and provide family members time to adjust emotionally. In addition, TLTs can prepare surrogates and clinicians for

Table 1 Problems associated with TLTs that last too long or are too short

	Too long	Too short
Patient/surrogates/family	The impact of a too long TLT depends: It could be a huge emotional burden especially if they wanted to stop treatment earlier but the team wanted to go on If the family wants survival whatsoever then there is no too long	Inadequate assessment of potential benefit, thus leading to inappropriate limitation of care Emotional burden of being rushed Regret/deceit feelings afterwards, negative effect on mourning process Losing trust in doctors/system
Nurses/doctors	Potential loss of compassion (compassion fatigue) Emotional burden Burn-out contributor Decreased quality of care	Rushed to a definite decision May impose precedent for future patients if not recognized Providing inadequate care Emotional burden when recognized Burn-out potential
Hospital directors/organization	When family perceives as too long it will result in the loss of confidence in the organization Increased costs for DRG-like systems	When recognized by family/surrogates they might lose trust in the organization as a whole On the other hand, a decrease in costs and maximal gain in profit (short duration and full refund in DRG-like systems)

DRG diagnosis-related group

discussions on a possible shift toward comfort-care strategies when the desired outcome seems unreachable [14].

Clear and concise communication is very important for a successful TLT where proactive communication with family members of critically ill patients, including family members' presence during rounds and subsequent family conferences, may lessen the burden of bereavement [15]. Some have proposed a five-step framework for initiating TLTs: the clinical problem and prognosis have to be defined, patient goals and priorities clarified, objective markers of improvement or deterioration determined, a time frame for reevaluation suggested, and finally potential actions at the end of a TLT defined [6]. A recent study, however, showed that TLTs are infrequently offered in conferences with surrogates of patients with a high risk of dying. When they are offered, they are incompletely discussed: clinicians frequently do not inform surrogates about how to value a TLT or its rationale and variable scenarios on how to move forward [16].

How much time is needed for a TLT?

Although time is an essential element of the TLT, only few studies have actually addressed this. In a recent editorial comment, Quill and Holloway made suggestions on the duration of a TLT in critically ill patients [6]. In patients requiring mechanical ventilation, the optimal duration of the TLT increased from 3 days (patients with hypoxic ischemic encephalopathy) to 3–7 days in patients with end-stage congestive heart failure and 7–14 days for patients with severe stroke. As these recommendations were not based on studies, they urged using considerable discretion as severity of illness, comorbidities, preferences, and time needed to assess effects were important elements in defining the optimal duration. Lecuyer et al. investigated the effect of a 5-day full-code TLT in 188 patients with hematologic malignancies or solid tumors requiring mechanical ventilation and having at least one additional organ failure [17]. Forty-five percent ($n=85$) of these patients died during the TLT. Of the patients that survived the TLT, an increasing number of failing organs 1 day after the TLT was linearly related to mortality. Only 5% of the patients with six failing organs survived to hospital discharge. All patients requiring initiation of mechanical ventilation, vasopressors, or dialysis more than 3 days following admission died [17]. This study suggests that increases in severity of disease within the first 3–5 days of a TLT could serve as a reliable endpoint for the TLT. Using a stage-transition model of 920 cancer patients with poor-prognosis solid tumors or hematologic neoplasms validated in 624 patients, Shrime et al. [18] modeled the effect of using a 3-, 8-, or 15-day TLT versus unlimited ICU care on 30-day survival stratified by the sequential organ failure assessment (SOFA) score. They found that cancer patients with lower severity of illness benefited most from a longer duration of a TLT (up to 15 days). Although a 3-day TLT always resulted in lower survival duration, the incremental survival durations were very small (up to 3 days). For patients with solid tumors, a 1–4-day TLT resulted in equivalent survival duration compared with unlimited ICU treatment [18]. From these studies, it can be concluded that the duration of a TLT should take into account the pre-existing conditions of the patient and the average time needed to show a response, or the lack thereof, to a treatment. Therefore, at least 24–72 h should be reserved for a TLT.

Finding the optimal duration for a TLT is challenging. Both TLTs that are too short and too long are associated with problems (Table 1). When at the end of a TLT uncertainty remains, another TLT can be renegotiated [6]. Ethical challenges associated with another TLT are discussed below.

Potential impact of TLTs on availability of healthcare

ICU costs continue to rise because of the increasing number of beds, days spent at the ICU, bed occupancy, and costs per day [19]. Admission to the ICU with the prospect of ultimate non-survival is deemed inappropriate care in most cases (except organ donation procedures, providing time for the family to arrive in the hospital, delivery of the unborn baby in a brain-dead patient, etc.) [4]. In addition, using resources to deliver inappropriate care should thus be limited. In general, patients do not prefer ICU admission when the likelihood is only to delay the inevitable death during that hospital admission. Therefore, advanced care planning could reduce inappropriate ICU care. In a systematic review, Khandelwal et al. [20] showed that advance care planning and palliative care interventions resulted in a reduction in ICU admissions and ICU length of stay before death. Lilly et al. showed that the introduction of proactive communication with patients and families resulted in a sustained increase in overall ICU survival [21, 22]. The majority of this improvement could be related to the improved survival of seriously ill patients who only improved slowly, whereas also more less sick patients where admitted. Although Daly et al. [23] failed to show a significant effect of improved communication strategies, they were only able to involve 75% of the patients/families, whereas Lilly et al. [21] were able to vertically include all patients/families (99%). A TLT could also serve to limit inappropriate care by allowing patients who are unlikely to achieve their goals to gain insight into their prognosis [24]. Therefore, when conducted carefully, TLTs could also reduce the length of ICU stay [21, 22, 25]. A TLT should be a package where communication with the patient/family has a key role, and timely end-of-life discussions and involvement of palliative care together can help reduce inappropriate care and improve optimal delivery of care to a larger group of patients. Since communication is the cornerstone of not only a successful TLT but also of successful ICU treatment, research should focus on decision-making models used by ICU clinicians and families.

Ethical challenges concerning TLTs

Treatment of critically ill patients with an uncertain prognosis often balances between life-prolonging measures and their possible complications versus non-beneficial interventions and changing to comfort care too early (Table 1). When at the end of a TLT uncertainty remains, another TLT can be renegotiated [6]; although this provides more time, the evaluation of the balance between disproportionate and beneficial care remains. This becomes especially problematic when the goal of the patient or his surrogates is merely: "not to be dead" [26]. A TLT in this context may give the patient/surrogate time to better evaluate the patient's condition so that goals may change. Especially in cancer patients, who initially may just focus on survival and more so than patients without cancer [27], families may change their perspective when faced with a poor prognosis [28–30]. For surrogates, especially when the patient is unable to communicate, a TLT is especially challenging [14, 31]. Although the consequences of a conflict based on these aspects may vary between different countries and states the question may arise: 'Who is in control?': the medical team or family/surrogate. A recent statement of multiple European and American ICU societies recommended first using intensive communication to resolve a conflict about potentially inappropriate treatments followed by a fair process of conflict resolution that could contain a second medical opinion and review by an interdisciplinary hospital ethics committee [31]. Where the consensus statement stated that clinicians should not provide futile interventions, the definition of these interventions was far more restrictive than frequently used in clinical practice [31]. Although 90% of families/surrogates desire recommendations from the intensivist, only 50% of intensivists actually provide them with wide variation between practices [32–34].

When the outcome of a TLT is that recovery is no longer feasible, this can be perceived as a form of patient abandonment by both surrogates and staff, and withdrawal of life support can be perceived as a non-beneficent act. In family meetings and discussions, it should be emphasized that abandonment never occurs, but that at this stage, emphasis is placed on comfort and palliation. Care for patients after withdrawal of life support at the end of a TLT therefore requires specific skills to allow a patient to die in comfort, meeting his end-of-life goals [35] while at the same time gaining the trust of both surrogates and staff.

How to evaluate a TLT

At the end of a TLT, there are three possible outcomes. First, the patient has improved and moved into the green or yellow area in Fig. 1. Second, the situation of the patient has not changed significantly since the start of the TLT. If this is related to unknown preferences of the patient or a still ongoing dispute with the family/surrogates, ongoing communication and additional psychologic support should be provided [35]. When, however, the lack of

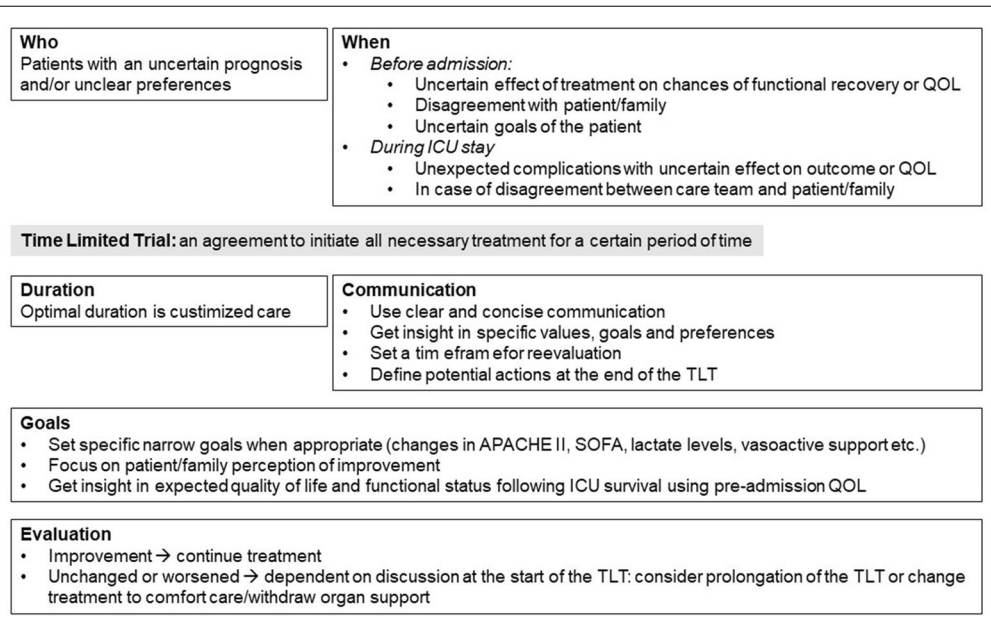

Fig. 2 A proposal of the clinical and practical use of a TLT. *QOL* quality of life

progress is related to the absence of improvement in the overall clinical condition of the patient, this should be considered similar to the third option where the patient's condition actually worsened during the TLT. Studies on lactate show that no improvement in the clinical condition implies a worse outcome [36]. This scenario should thus be explained and discussed at the start of the TLT where clear concrete and measurable goals should be set when discussing the evaluation of the TLT [14]. Bruce et al. [14] defined narrow and broad goals for a TLT. Narrow goals, more frequently used in surgical/anesthesia ICUs, would be focused on for example trends in laboratory values or weaning efforts, organ failure scores, dependence on circulatory support, etc. Changes in APACHE II scores [37] and Sequential Organ Failure Scores [38, 39], as well as lactate levels [40, 41] and level of vasoactive support [42], may provide important information in these conditions. Broad goals, more frequently used in medical/neuro ICU's, would focus more on aspects related to quality of life like wakefulness, mobility, responsiveness, and independence. The difference in focus (broad versus narrow goals) is unit (surgical vs. nonsurgical) specific, but also specialty (internal vs. surgical/anesthesia specialists) dependent.

Surrogates are often too optimistic regarding expectations compared with physicians. Cox et al. [13] showed that where clinicians expected a chance of survival of 44% in specific critically ill patients, surrogates expected a 93% chance of survival. Although physicians are more accurate in predicting outcome and surrogates perform better than chance alone, surrogates frequently disagree based on religious beliefs and hope [43]. Next to the patient, family/surrogates have an important role in these evaluations as ultimately when survival is likely, the likelihood of attaining an acceptable quality of life or functional status is important [28]. Relatives in close contact with the patient can adequately reflect the patient's functional status on admission to the ICU [44] where a poor health-related quality of life before admission is already an important predictor of survival [45]. However, ultimately the patient is the only person who can truly value the gap between their actual and anticipated quality of life [46].

Palliative care

Whenever doubt about the appropriateness of ICU admission is in question, involving palliative care might be considered. Palliative care should surely be involved as soon as a TLT is started. Relief of symptoms is a key component of critical care for all ICU patients, regardless of condition or prognosis. When the outcome of a TLT is however negative, relief of symptoms should be the only focus of treatment, with special attention to treatment of distress, agitation, delirium, dyspnea, pain, and thirst, which is described in more detail in other articles [47–50]. Life-prolonging treatments without effect on distress, i.e., mechanical ventilation, renal replacement therapy, vasopressor support, and extracorporeal membrane oxygenation, should be ceased, and a do-not-resuscitate order should be in place. Also during this phase of treatment communication with patients and family/surrogates is of utmost importance.

Table 2 Core elements of a time-limited trial

Element	Comment
Advanced care planning	The presence of advanced care directives would make it much easier to design a TLT and address more precisely the personal preferences of the patient
Multidisciplinary team	A TLT should be a team effort that involves all parties participating in the care of the patient (intensivists, nurses, referring specialists, palliative care, religious/spiritual support persons if applicable, etc.)
Palliative care	A palliative care team could be involved early in patient care when pre-existing problems of frailty, quality of life,and pre-admission permanent organ disfunction are present. Ideally, the palliative care team should already be involved before ICU admission (if possible)
Ethics committee and legal department	In some cases, involvement of the Ethics Committee to review the case on its ethical merits or the legal department to review possible legal aspects of the case might be relevant. Ideally, these consultations should take place before discussing a TLT with the patient and/or relatives
Communication	Clear and concise communication is important for a successful TLT. Proactive communication with family members of critically ill patients, including family members' presence during rounds and subsequent family conferences are preferred

Table 3 Problem solving in the process of a TLT

What do you say to families on a daily basis?	Show sympathy, empathy and compassion Inform on preferences Explore needs, i.e., spiritual or moral support Short update on the status of the patient; however, when unexpected events occur (i.e., acute deterioration) requiring a change of plans, a family meeting should be arranged
How long should a TLT be?	Treatment of critically ill patients with an uncertain prognosis often balances between life-prolonging measures and their possible complications versus non-beneficial interventions and changing to comfort care too early The duration of a TLT should take into account the pre-existing conditions of the patient and the average time needed to show a response, or the lack thereof, to a treatment. Therefore, at least 24–72 h should be reserved for a TLT
How frequently should a TLT be discussed by the staff?	During a TLT, the patient's situation, potential problems, and adaptation by the family/surrogates should be discussed on a daily basis Just before the end of a TLT, the outcome of the TLT should be discussed during a staff meeting in more detail

Table 4 Pitfalls of a TLT

Starting a TLT when the goal should actually be palliative care In this case, initiating a TLT would result in non-beneficial interventions and disproportionate care. Potentially, patients, families, and surrogates can get false hope for recovery. A TLT would only postpone the inevitable death
Not immediately starting a TLT when indicated When a TLT is not immediately initiated when indicated, a barrier to start a TLT can be experienced
Lack of communication during a TLT Communication and evaluation are of utmost importance for a successful TLT. Without special attention to communication to explore preferences and update on the situation, a TLT cannot be successful. Especially in case of a conflict, even more attention should be paid to communication
Incorrect duration of a TLT A too short duration of a TLT will not provide optimal chances for survival. On the other hand, a too long duration when palliative care should be initiated will result in improved survival but non-beneficial interventions and disproportionate care
Failure to keep the family/surrogates updated or informed When families/surrogates are not aware of the current situation, the discussion of the outcome at the end of a TLT can potentially surprise the patient/family and could potentially result in a conflict and inability to proceed to palliative care

How to implement a TLT

Based on the topics discussed in this overview, a proposal of the clinical and practical use of a TLT is given in Fig. 2. Table 2 shows the core elements of a TLT, Table 3 shows some of the most frequently asked questions on TLTs, and Table 4 shows the most important pitfalls of a TLT.

Conclusion

A TLT is an agreement among the patient, surrogates and treating clinicians to initiate certain life-sustaining treatments for a certain period of time to better assess patients' response to ICU care and the possibilities of a meaningful outcome. TLTs can give better insight into prognosis when outcome is difficult to assess on admission or when unexpected complications occur during admission, resulting in doubt about their impact on the final outcome. Communication, clearly defined measurable goals, and evaluation are of utmost importance for a successful TLT. TLTs can, when executed well, improve quality of care and quality of dying when intensive care can no longer provide a meaningful outcome.

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Compliance with ethical standards

Conflicts of interest

The authors declare that they have no conflict of interest.

Received: 17 February 2018 Accepted: 23 July 2018
Published online: 22 August 2018

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