Time Limited Trials in Serious Illness

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Abstract:

Time limited trials (TLTs) can serve as an important tool for physicians as well as patients and family members to navigate complex medical decisions especially toward the end of life. It can be difficult to determine when and how a TLT would be appropriate in certain cases. We provide a framework for accomplishing this task using the following three steps 1) define the invasiveness and intensity of the intervention; 2) identify the purpose of the trial; and 3) understand the trial's potential impact on health outcomes and the odds of achieving the desired outcome. When applied using this framework, TLTs can help clarify goals and augment patient directed care.

Seriously ill patients and their families are frequently confronted with complex medical decisions near the end of life. The interventions may be invasive, the science and technology complex, and the outcomes uncertain. Communication between clinicians and patient/family units regarding diagnostic and prognostic uncertainty as well as establishing specific expectations and goals for various treatments is crucial. Time-limited trials (TLT) have been proposed as a useful tool to frame major treatment options in the face of prognostic uncertainty[1]. A TLT is a process by which a patient/family and clinicians reach a consensus on a temporary intervention to be implemented with the intention of improving or clarifying the patient's clinical situation and prognosis over a pre-determined period of time. If at the end of that time there is clinical improvement, the intervention may continue if needed on a time-limited or open-ended basis, but often it may no longer be needed. If the intervention fails to improve the patient's clinical situation (and the patient/family agree), the therapy is discontinued, often followed by a transition to comfort-focused care.

Time-limited trials have gained attention across a range of specialties in the management of elderly surgical patients[2], patients with end stage renal disease[3], and those with severe stroke[4]. In spite of the theoretical appeal of TLTs, a variety of barriers impede their implementation including continued prognostic uncertainty, shift-based staffing models, and lack of commitment by all involved to the initially proposed timeline and outcomes.[5] Perhaps because of these barriers, TLTs are likely underutilized.[6]

We believe TLT's have a broad role in the care of most seriously ill patients potentially nearing end of life when there is some uncertainty about the short-term benefits of burdensome invasive treatments. Prognostic uncertainty on behalf of clinicians and patient/surrogate units must exist for a successful and honest TLT to proceed, except in rare circumstances. If a clinician believes that an intervention has no chance of reversing an underlying disease process, then careful consideration should be given to whether

or not to offer the intervention at all. Here we provide a framework to help assess the appropriateness and parameters of a time-limited intervention. We suggest three important considerations when planning and implementing a time-limited trial: 1) define the invasiveness and intensity of the intervention; 2) identify the purpose of the trial; and 3) understand the trial's potential impact on health outcomes and the odds of achieving the desired outcome. Using realistic cases, this article explores each of these components in more detail in an attempt to clarify a framework for successful TLTs.

Invasiveness of intervention

The invasiveness of an intervention should be carefully considered prior to offering a TLT. The more invasive the time limited trial, the more potential there is for actual or perceived added suffering, (Table 1) thereby warranting more careful and wide ranging conversation between providers and patient/family. The perception of a treatment's invasiveness will also vary among individual patients, family members and physicians. The categorization of invasiveness may then change as a patient or family adapt to the situation and to the treatment. Invasive treatments may inherently be attached to location of care, with higher intensity treatments typically requiring an intensive care unit (ICU) or other acute care environments. This can also lead to considerations of time limited trials of ICU care in general, especially in context of data showing that, for certain subsets of patients, longer durations of stay in the ICU may not offer more survival benefit compared with shorter durations.[7]

Some interventions, such as endotracheal intubation and hemodialysis via a temporary catheter, have "built-in" time-limited trials because they often require transition to a more permanent solution if the intervention is to continue. For example, reassessing a trial of endotracheal intubation and mechanical ventilation typically occurs at the 10-14 day mark when discussions about tracheostomy and more long-term mechanical ventilation are often undertaken. Nasogastric feeding tubes are typically not used for more than 30-60 days, though the data supporting these time-limits are sparse.

Table 1. Categorizing TLTs by level of invasiveness

Level of Invasiveness	Examples
High	Endotracheal intubation, Mechanical ventilation, ECMO, VAD
Medium	BIPAP/HFNC, drainage catheters (eg, pleural, abdominal), Central venous access, Vasoactive drugs, Gastric feeding tubes, hemodialysis, ICU admission
Low	Antibiotics, Intravenous fluids, Nasogastric feeds

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device; BIPAP = bilevel positive airway pressure; HFNC = high flow nasal cannula; ICU = intensive care unit

Some very high-intensity interventions, such as extracorporeal membrane oxygenation (ECMO) for patients with acute respiratory distress syndrome (ARDS) and left-ventricular assist devices (LVAD) for patients with myocarditis, may also be offered as TLTs in carefully selected patients. An intervention such as ECMO normally serves as a bridge to recovery or transplant, but if neither end can be reached or if complications develop, the alternative is typically withdrawing life-support and transitioning to comfort oriented care. ECMO cannot be continued indefinitely, and often requires declaration of a failed trial if no improvement is seen after 3-4 weeks. In contrast, LVADs may be used as destination or long-term therapy if the patient stabilizes.

Some interventions are less frequently framed as TLTs, such as a percutaneous endoscopic gastrostomy (PEG) tube or tracheostomy. These treatments should generally not be presented in a TLT context except where there is legitimate though uncertain possibility for clinical improvement over time, and active consideration is being given for discontinuation of these therapies whether or not improvement occurs. An example of such a case may be a ventilator dependent patient with Guillain-Barre syndrome who may have very slow improvement over the course of months with the goal of gaining functional independence, but does not want to be permanently ventilator

dependent. If the patient is still ventilator dependent at the end of the trial, a decision is made whether to withdraw treatment or initiate another TLT or accept permanent ventilator dependence. Conventional endotracheal intubation and nasogastric feeding should generally be considered the time limited trials, and patients with an uncertain outcome and their families should be made aware of the timeframes and markers for improvement, and the full range of options if the patient is not improving. Therefore, for the majority of patients an initial TLT should precede the decision to pursue interventions like tracheostomy or PEG tube which have no inherent endpoint and have the potential for long term dependence on invasive medical intervention.

Classifying a TLT Based on Its Purpose

Initiating a therapeutic intervention

Case: TK is a 75 year old nursing home resident with mild dementia and heart failure who is admitted to the hospital with sepsis and acute kidney injury. Because of refractory hyperkalemia and volume overload, hemodialysis (HD) is discussed as the next step of care if the goal was to prolong her life. Her family agrees to a trial of dialysis to see if her kidneys recover with treatment of her infection. At the start of the trial, they do not see long term dialysis as something the patient would want.

In this case TK has a potentially reversible problem as well as a proposed therapy that the family is in favor of trying. This scenario potentially involves different end-points/goals of the trial: 1) HD as a bridge to renal recovery; 2a) a desire to avoid committing her to long term hemodialysis, or 2b) a desire to assess whether TK can tolerate HD on a more long-term basis. The expected timeframe for potential renal recovery would set time parameter of this trial, but the trial might also clarify how well the patient adapts to dialysis treatment. These discussions should include what an acceptable baseline would be for TK given that her age, underlying dementia and additional illnesses which now put her at very high risk for permanent and progressive functional decline following this hospitalization. At the end of the proposed trial period a pre-arranged meeting between the family and the

medical team should be scheduled to review the outcome of the trial and next steps. In the interim, if she is unable to tolerate hemodialysis or clinically deteriorates in spite of the intervention, the trial has failed and recommendations should be made for a purely palliative approach. Anticipatory guidance and regular updates for the family regarding progress toward the potential outcomes of the trial will minimize the risk of surprises or disagreements during the course of the trial.

Withdrawal of a therapeutic intervention

Case: LF is a 64 year old male with metastatic pancreatic cancer admitted with hypoxemic respiratory failure secondary to pneumonia. His medical order for life-sustaining treatment (MOLST) form clearly indicated he wanted a "trial of intubation" in the event of respiratory failure, but did not specify what that trial might entail. His hypoxemia gradually improved with antibiotics and low-tidal volume ventilation, but he developed worsening weakness and volume overload. After two weeks of mechanical ventilation, he continues to "fail" pressure support trials. The family is clear that he would not want a tracheostomy and long-term mechanical ventilation. They planned to meet with the medical team to discuss withdrawal of ventilator support.

There are two TLT's in this scenario. The first, a TLT of endotracheal intubation and mechanical ventilation as a "natural" duration of two weeks in the absence of clinical deterioration. The initial trial has likely failed, though he has been weaned to minimal settings. The second potential trial in this case begins after discontinuation of mechanical ventilation. The medical team outlines a plan for "sink or swim" extubation: LF may "swim" with sustained independent respiratory effort on his own without the ventilator and continue to clinically improve. It is also possible that he may "sink" without more invasive ventilator support and deteriorate rapidly and die. The family should be warned about the very disparate potential possible outcomes as well as which is most likely to occur. Given any likelihood of "sinking", the family should be offered the option to gather other loved ones and have people say goodbyes prior to extubation.

It is also imperative to establish a specific management plan in case of recurrent respiratory distress after extubation among medical team members and share this plan with the family. This would mark the unsuccessful end of a TLT of breathing independently off the ventilator, and his transitioning to actively dying (given his desire not to be permanently dependent of mechanical ventilation). Use of opioids during the initial phase should be conservative so as not to compromise respiratory effort, whereas symptoms might be more aggressively palliated if and when the patient begins to experience respiratory failure and death is inevitably approaching.

Psychosocial time limited trial

Case: WH is a 78 yo male with dementia and dysphagia admitted with pneumonia secondary to aspiration. He has an existing do not resuscitate/do not intubate (DNR/DNI) order, but had no other limits on aggressive treatment. He is started on IV antibiotics for pneumonia and placed on bilevel positive airway pressure (BiPAP) in the emergency department due to severe respiratory distress. The medical team speaks with the patient's family in the presence of the patient and all understand his limited prognosis and options considering his expressed wishes. All agree on a 24 hour trial of BiPAP to see if he turns around and also to allow time for additional family members to arrive to "say goodbye".

In this case the parameters of the trial would be to see if he tolerates the BiPAP without extreme discomfort with the goal of potentially giving the family time for closure. This is an atypical time limited trial because in this case the medical team and the family understand and accept the prognosis of likely death without ventilator support. The purpose of the trial is to serve as a bridge to allow the family more time to prepare for and come to terms with the patient's inevitable death. On a similar note, a psychosocial TLT may also be useful in situations where the prognosis is clear to the medical team, but the family still needs time to accept it. A psychosocial TLT in this case may help to find some common ground through a systematic approach.[3] When non-invasive ventilation (or mechanical ventilation) is initiated as a bridge to arrival of family,

physicians should strongly recommend placing a DNR if not already in place.

Better Aligning Preferences and the Odds of Achieving the Desired and Un-Desired Outcomes

The appropriateness of a time limited trial and the length of follow-up needs to carefully consider the trade-offs in patient outcomes. It is important to carefully consider underlying disease prognosis and trajectory, as this would affect the potential impact of a TLT on both survival and quality of life outcomes. The underlying disease process will likely limit the extent to which a patient may recover as well as the amount of benefit an intervention may provide. For example, a young patient with a severe stroke may survive years after a TLT compared to a patient with advanced cancer with an infection and delirium who may only survive days to weeks. The impact on these health outcomes, as well as the uncertainty surrounding them, should be understood to best determine the appropriateness of initiating a TLT as well as the potential length of follow up needed to provide sufficient clarity for the team to make future decisions. Especially in cases where a patient's wishes are not clearly defined or understood, and medical decisions are being made by a health care proxy or family members, there is the risk of making a decision that the patient may not have agreed with if the patient could have spoken for herself. This could present as risk of prolonging a life that the patient would not find tolerable, or, on the flip side, an equivalent risk of not prolonging a life the patient would have found worth living.

Given the high stakes of these decisions, we have found that integrating TLTs in the care of seriously ill patients near the end of life can help facilitate the quality of joint decision-making as well as family, patient, and physician satisfaction. Maintaining good communication throughout the TLT between clinicians and patients/surrogates, as well as among the members of the medical teams, is important to facilitate successful completion of the TLT.[5,8] When the purpose of the trial is outlined with a clear and mutual understanding of the invasiveness of treatment and its associated risks and benefits as well as the odds of achieving desired and un-

desired outcomes, a TLT can provide a useful structure for preference-sensitive care in the face of potentially life-threatening illness.

References

1. T.E. Quill, R. Holloway. "Time-Limited Trials Near the End of Life," JAMA 306(13):1483-1484 (2011).

2. M.D. Neuman, S. Allen, M.L. Schwarze, J. Uy. "Using time-limited trials to improve surgical care for frail older adults," Annals of Surgery 261(4):639-641 (2015).

3. A. Rinehart. "Beyond the futility argument: The fair process approach and time-limited trials for managing dialysis conflict," Clinical Journal of the American Society of Nephrology 8(11):2000-2006 (2013).

4. C.J. Creutzfeldt, R.G. Holloway. "Treatment Decisions After Severe Stroke – Uncertainty and Biases," Stroke 43(12): 3405-3408 (2012).

5. C.R. Bruce, C. Liang, J.S. Blumenthal-Barby, J. Zimmerman, A. Downey, L. Pham, L. Theriot, E.D. Delgado, D. White. "Barriers and Facilitators to Initiating and Completing Time-Limited Trials in Critical Care," Critical Care Medicine 43(12):2535-2543 (2015).

6. Y. Schenker, G.A. Tiver, S.Y. Hong, D.B. White. "Discussion of treatment trials in intensive care," Journal of Critical Care 28(5):862-869 (2013).

7. M.G. Shrime, B.S. Ferket, D.J. Scott, J. Lee, D. Barragan-Bradford, T. Pollard, Y.M. Arabi, H.M. Al-Dorzi, R.M. Baron, M.G. Hunink, L.A. Celi, P.S. Lai. "Time-Limited Trials of Intensive Care for Critically Ill Patients With Cancer: How Long Is Long Enough?" JAMA Oncology 2(1):76-83 (2016).

8. J.S. Scherer, J.L. Holley. "The Role of Time-Limited Trials in Dialysis Decision Making in Critically Ill Patients," Clinical Journal of the American Society of Nephrology 11(2):344-353 (2016).