PALLIATIVE CARE NETWORK OF WISCONSIN

Prognosis in Non-Cancer Illnesses
Fast Facts and Concepts and CME Module

FAST FACTS AND CONCEPTS: CONTINUING MEDICAL EDUCATION MODULE
PROGNOSIS IN NON-CANCER ILLNESSES
Course Description and Learning Objectives

Course Description: Prognostic indicators for patients with advanced cancer have been well-studied and described in the published medical literature. A paucity of resources, however, are available delineating prognostic considerations in non-cancer illnesses. Particularly, which clinical factors can reliably guide hospice eligibility in patients with chronic, life-limiting illnesses such as dementia, heart failure, cirrhosis, renal failure, or emphysema? Clinicians who care for patients with such illnesses should be aware of the existing medical literature regarding prognostic factors in these illnesses. With this knowledge, clinicians can better counsel patients on when to consider limits to life-prolonging interventions and/or hospice referrals. In this module, users can attain 1.0 hours of CME credit after successful completion of the following tasks:

A. Content review of ten *Fast Facts and Concepts* covering the following topics:
    a. COPD prognosis
    b. CHF prognosis
    c. Dementia prognosis
    d. CPR survival data
    e. Liver failure prognosis
    f. Dialysis prognosis
    g. Anoxic brain injury prognosis
    h. Traumatic brain injury prognosis
    i. Uremic calciphylaxis
    j. Illness trajectories
B. A score of 70% or higher on a 10 question quiz covering this content
C. Completion of a course evaluation

Learning Objectives: At the conclusion of this course, learners will:
1. Describe four common illness trajectories.
2. List three key prognostic indicators for five life-limiting non-cancer illnesses
3. Describe at least four factors predictive of failure to survive cardio-pulmonary resuscitation

FAST FACTS AND CONCEPTS #141
PROGNOSIS IN END-STAGE COPD

Julie Wilson Childers MD, Robert Arnold MD, and J Randall Curtis MD

Background Prognostic variables in COPD patients are not well described, thus decision making regarding when to move away from aggressive life-sustaining treatments is challenging. This *Fast Fact* will review prognostication in patients with advanced COPD.

Ambulatory COPD Patients The forced expiratory volume in one second (FEV_1) has traditionally been used to assess COPD severity. A FEV_1 of less than 35% of the predicted value represents severe disease; 25% of these patients will die within two years and 55% by four years. A number of other studies have shown that age, low body mass index (BMI), serum inflammatory biomarkers (such as C-reactive protein, IL-6, and fibrinogen) and low PaO_2 were independent predictors that correlated to reduced survival time. The BODE scale, consisting of BMI, exercise capacity, and subjective estimates of dyspnea, has been shown to help predict survival over 1-3 years (2).

Variable	**Points on BODE Index**			
	0	**1**	**2**	**3**
FEV1 (% predicted)	≥65	50-64	36-49	≤35
Distance walked in 6 min (meters)	>350	250-349	150-249	≤149
MMRC dyspnea scale*	0-1	2	3	4
Body-mass index (BMI)	>21	≤21		

*MMRC dyspnea scale range from 0 (none) to 4 (4 dyspnea when dressing or undressing).

BODE Index Score	**One year mortality**	**Two year mortality**	**52 month mortality**
0-2	2%	6%	19%
3-4	2%	8%	32%
4-6	2%	14%	40%
7-10	5%	31%	80%

Note: these variables do not appear to help predict prognosis within six months of death.

Hospitalized COPD Patients Mortality statistics vary for patients admitted with COPD exacerbations depending on age, functional status, co-morbidities, and physiological variables such as hypoxia and hypercarbia. Roughly 10% of patients admitted with a $PaCO_2$ >50 mmHg will die during the index hospitalization, 33% will die within six months, and 43% die within one-year (3). Patients with less severe COPD have lower in-hospital mortality rates (4). COPD patients who require mechanical ventilation have an-hospital mortality of ~25% (5,6). Poor prognostic factors include: co-morbid illnesses, severity of illness (APACHE II score), low serum albumin, and/or low hemoglobin. Previous mechanical ventilation, failed extubation, or intubation for greater than 72 hours all increase mortality (5). In one study, patients ventilated more than 48 hours had a 50% one year survival; functional status and severity of illness were associated with short term mortality while age and co-morbidities were associated with one year mortality (2).

National Hospice and Palliative Care Organization Criteria NHPCO guidelines for hospice admission in COPD include factors such as cor pulmonale and pO2 <55 mmHg while on oxygen, albumin < 2.5 gm/dl, weight loss of > 10%, progression of disease, and poor functional status. However, a study showed when using these factors, 50% of the patients were still alive at six months, implying that the NHPCO criteria have a limited role in predicting six month mortality and thus should be used with caution in determining hospice eligibility under the Medicare Hospice Benefit (7).

Summary COPD is a heterogeneous disease without a simple prognostic trajectory. For ambulatory patients, age, degree of dyspnea, weight loss (BMI), functional status, and FEV_1 are relevant prognostic

factors for predicting 1-3 year survival. For hospitalized patients, the same factors are relevant. In addition, the need for prolonged or recurrent mechanical ventilation is predictive of a shorter prognosis.

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FAST FACTS AND CONCEPTS #143
PROGNOSTICATION IN HEART FAILURE

Gary M Reisfield MD and George R Wilson MD

Background This *Fast Fact* reviews prognostication data in Heart Failure (HF). Although the Framingham Heart Study (1990-1999) showed a 5-year mortality rate of 50% for newly identified cases, providing accurate prognostic data for 6-12 month mortality in HF has been nearly impossible. Reasons cited include: 1) an unpredictable disease trajectory with high incidence (25-50%) of sudden death; 2) disparities in the application of evidence-based treatment guidelines; 3) inter-observer differences in New York Heart Association (NYHA) classification; and 4) heterogeneous study populations.

NYHA Classification The NYHA classification remains the major gauge of disease severity. Based on data from SUPPORT, Framingham, IMPROVEMENT, and other studies, 1-year mortality estimates are:

- Class II (mild symptoms): 5-10%.
- Class III (moderate symptoms): 10-15%.
- Class IV (severe symptoms): 30-40%.

General Predictors of Shorter Prognosis:

- Cardiac hospitalization (triples 1-year mortality; nearly 1 in 10 die within 30 days of admission).
- Intolerance to neurohormonal therapy (i.e. beta-blockers or ACE-inhibitors) is associated with high 4 month mortality
- Elevated BUN (defined by upper limit of normal) and/or creatinine ≥1.4 mg/dl (120 µmol/l).
- Systolic blood pressure <100 mm Hg and/or pulse >100 bpm (each doubles 1-year mortality).
- Decreased left ventricular ejection fraction (linearly correlated with survival at LVEF ≤ 45%).
- Ventricular dysrhythmias, treatment resistant.
- Anemia (each 1 g/dl reduction in hemoglobin is associated with a 16% increase in mortality).
- Hyponatremia (serum sodium ≤135-137 mEq/l).
- Cachexia or reduced functional capacity.
- Orthopnea.
- Co-morbidities: diabetes, depression, COPD, cirrhosis, cerebrovascular disease, and cancer

Hospice Eligibility Guidelines The National Hospice and Palliative Care Organization's 1996 guidelines for heart disease admission criteria include: a) symptoms of recurrent HF at rest (NYHA class IV) *and* b) optimal treatment with ACE inhibitors, diuretics, and vasodilators (*contemporary optimal treatment now includes β-blockers, aldosterone antagonists, and device therapies*). The NHPCO guide indicates that an ejection fraction $\leq$ 20% is "helpful supplemental objective evidence," but not required. The NHPCO guidelines also assert that each of the following further decreases survival: treatment resistant ventricular or supraventricular arrhythmias, history of cardiac arrest in any setting, history of unexplained syncope, cardiogenic brain embolism, and concomitant HIV disease.

Prognostic Models Since publication of the NHPCO's guidelines, several models have been developed for predicting short- and/or long-term mortality among HF patients. Two recent models purport to predict mortality among patients *hospitalized with acutely decompensated HF.* Fonarow et al (2005), using a model based on admission BUN (≥ 43 mg/dl), creatinine (≥ 2.75 mg/dl), and systolic BP (< 115 mmHg), identified in-hospital mortality rates ranging from about 2% (0/3 risk factors) to 20% (3/3 risk factors). Lee et al (2003), using a model based on admission physiologic variables and co-morbidities (almost all from above list of indicators) identified 30-day mortality and 1-year mortality rates ranging from <1% and <10%, respectively, for the lowest risk patients to >50% and >75%, respectively, for the highest risk patients. While both models are applicable to bedside use, neither has been applied prospectively or in independent patient samples, nor do they address HF treatments as predictive variables. More recently, Levy et al (2006) developed a 24-variable risk model using the PRAISE1 (*n*=1125) database and validated it on preexisting ELITE2, ValHeFT, UW, RENAISSANCE, and IN-CHF (*n*=9942) databases.

The model purports to accurately estimate mean 1-, 2-, and 3-year survival and, importantly, *dynamically* incorporates clinical and laboratory variables, HF medications, and device therapies. It awaits independent, prospective evaluation in unselected HF patients. A web-based interactive calculator can be accessed at http://www.seattleheartfailuremodel.org.

Bottom Line Meticulous application of medication and device therapies can and will continue to change HF prognosis. HF follows an unpredictable disease trajectory, one which is highly mutable by application of evidence-based therapies, yet still marked by a high incidence of sudden death. The 1996 NHPCO criteria are not accurate predictors of 6-month mortality. Several models have recently been developed to aid in determining short- and long-term mortality in HF patients. These models await independent, prospective validation in unselected ambulatory HF patients and will need periodic updating to control for continually evolving standards of HF care. At present, accurate prognostication remains problematic.

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FAST FACTS AND CONCEPTS #150
PROGNOSTICATION IN DEMENTIA
Sing Tsai MD and Robert Arnold MD

Background Dementia is a syndrome of acquired and persistent impairment in cognition and intellectual functioning (1). When caused by certain diseases or injury, dementia is irreversible, leading to progressive brain failure and death. This *Fast Fact* reviews issues of prognostication in dementia.

Natural history of dementia Olson (2003) classifies dementia into four functionally defined categories: mild, moderate, severe, and terminal. 'Terminal dementia' is defined as loss of communication, ambulation, swallowing, and continence. Others use the term "end-stage" or "advanced" making interpretation of prognostic data challenging. Many prognostic factors have been associated with shortened survival: male gender, age, diabetes mellitus, CHF, COPD, cancer, cardiac dysrhythmias, peripheral edema, aspiration, bowel incontinence, recent weight loss, dehydration, fever, pressure ulcers, seizures, shortness of breath, low oral intake, not being awake for most of the day, low Body Mass Index, and recent need for continuous oxygen. A 2012 systematic review found that malnutrition, feeding issues, and dysphagia were the strongest associated factors with 6 month mortality in elderly patients with advanced dementia. Simply being admitted to the hospital with acute illness and end-stage or terminal dementia is associated with a particularly poor prognosis: the six month mortality after hospitalization for pneumonia was 53% compared with 13% for cognitively intact patients. For patients with a new hip fracture, 55% of end-stage dementia patients died within 6 months compared with 12% for cognitively intact patients (Morrison 2000).

Prognostic Systems (see table below):

I. The National Hospice and Palliative Care Organization (NHPCO) recommends the *Functional Assessment Staging* (FAST), a 7-step staging system, to determine hospice eligibility. The FAST identifies progressive steps and sub-steps of functional decline. NHPCO guidelines state that a FAST stage 7A is appropriate for hospice enrollment, based on an expected six month or less prognosis, if the patient also exhibits one or more specific *dementia-related co-morbidities* (aspiration, upper urinary tract infection, sepsis, multiple stage 3-4 ulcers, persistent fever, weight loss >10% within six months). Luchins (1997) studied the relationship of FAST to survival in 47 patients enrolled in hospice with advanced dementia and one or more dementia-related co-morbidities. The median survival for all patients was 6.9 months; 38% survived beyond six months. Of note, 41% of patients did not demonstrate dementia progression in a manner that allowed for assigning a FAST stage. For those patients who could be assigned a FAST stage (n = 12), and who were at stage 7C or greater, mean survival was 3.2 months. The generalizability and clinical relevance of this data are greatly compromised by this very low patient number.
II. The *Mortality Risk Index* (MRI), a composite score based on 12 risk factor criteria obtained from using the MDS (Minimum Data Set), has been suggested as an alternative to FAST. Mitchell (2004) developed and then validated the MRI by examining data from over 11,000 newly admitted nursing home patients. Among patients with a MRI score of ≥ 12, 70% died within 6 months (mean survival time not reported). Compared to FAST Stage 7C, the MRI had greater predictive value of six month prognosis. The MRI as only been evaluated in newly admitted nursing home residents; it has yet to be validated in the community setting or for previously established long-term nursing home residents.

Medical Interventions Estimation of prognosis in severe/terminal dementia is in part dependent on the goals of care and decisions regarding the level of intervention that will be provided to treat acute medical problems such as urosepsis and malnutrition.

Summary Although many prognostic risk factors have been identified there is no gold standard to help clinicians determine a less than six months prognosis with any degree of certainty. The criteria adopted by NHPCO for hospice eligibility is based on very limited research and lacks important studies to determine FAST scale reliability and validity among referring physicians and hospice staff. The MRI is a promising new scale but more research is needed. Physicians can best help their patients by working with families to help them establish goals of care and levels of medical intervention that are most consistent with current medical research and family/patient preferences.

Functional Assessment Staging (FAST)

Stages

1. No difficulties
2. Subjective forgetfulness
1. Decreased job functioning and organizational capacity
4. Difficulty with complex tasks, instrumental ADLs
5. Requires supervision with ADLs
6. Impaired ADLs, with incontinence
7. A. Ability to speak limited to six words
   B. Ability to speak limited to single word
   C. Loss of ambulation
   D. Inability to sit
   E. Inability to smile
   F. Inability to hold head up

Mortality Risk Index Score (Mitchell)

Points	Risk factor
1.9	Complete dependence with ADLs
1.9	Male gender
1.7	Cancer
1.6	Congestive heart failure
1.6	O_2 therapy needed w/in 14 day
1.5	Shortness of breath
1.5	<25% of food eaten at most meals
1.5	Unstable medical condition
1.5	Bowel incontinence
1.5	Bedfast
1.4	Age > 83 y
1.4	Not awake most of the day

Risk estimate of death within 6 months

Score	Risk %
0	8.9
1-2	10.8
3-5	23.2
6-8	40.4
9-11	57.0
≥ 12	70.0

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FAST FACTS AND CONCEPTS #179
CPR SURVIVAL IN THE HOSPITAL SETTING
David H Ramenofsky and David E Weissman MD

Background Survival to discharge following cardiac arrest occurring in the hospital is infrequent. This *Fast Fact* will review data on CPR outcomes in hospitalized patients.

I. A 2003 report of in-hospital CPR outcomes from the National Registry of Cardiopulmonary Resuscitation, reported data from 14,720 resuscitation attempts (2000-2002) in adults from 207 U.S. hospitals (1). The uniform case inclusion definition included cardiac and respiratory arrests requiring an emergency response from hospital personnel.

- Survival 20 minutes after CPR was 44%, but only 17% of all CPR patients survived to discharge. The survival to discharge for ventricular fibrillation and pulseless ventricular tachycardia was 34% and 35%, respectively, but only 10% for asystole and pulseless electrical activity.
- Pre-CPR, 84% of patients came from home. Among survivors, 51% returned home, the remainder being discharged to another hospital, a rehabilitation facility, or a nursing home. Two percent were discharged to hospice care.
- Neurological function of survivors was assessed using a five point scale (1 = good performance to 5 = brain death). Pre-CPR, 68% were in category 1, falling to 59% at discharge. In other words, 86% of category 1 patients remained at this level if they survived CPR, whereas 14% had neurological decline.
- Overall functional performance was assessed using a similar five point scale (1 = good to 5 = brain death). Overall performance declined: 49% of survivors were category 1 pre-CPR compared to only 37% after CPR, a 25% decline in overall function.

II. A meta-analysis of CPR outcomes was reported in 1998; it included data from 49 research publications after 1980, totaling 9,838 patients (2).

- Depending on the rigor of CPR event definition, immediate survival was 41-44% and survival to discharge was 13-15%.
- Of the five studies reporting discharge information, 78% of 93 survivors returned to their home.
- Factors associated with survival to discharge were: myocardial infarction, coronary heart disease, and hypertension.
- Factors predicting a failure to survive to discharge:
  - Sepsis the day prior to the CPR event
  - Serum creatinine >1.5 mg/dl
  - Metastatic cancer
  - Dementia or dependent status

III. In 2013, the American Heart Association (AHA) published a consensus statement reviewing in-hospital cardiac arrest results in the US. Major take-home points were:

- There is a lack of consistency with how investigators report survival after inpatient CPR. Some studies exclude patients made DNR after the CPR attempt from data analysis, others do not.
- Regardless, survival to hospital discharge has remained essentially unchanged for decades.
- Despite the rising prevalence of “rapid response teams”, there is no convincing evidence these teams have improved survival rates. Rather, these teams likely spare the need for non-ICU CPR attempts via earlier identification of critically ill patients and more efficient ICU transfer.

IV. Historically, the CPR success rate in cancer patients has been thought to be less than 2%. A meta-analysis of 42 studies from 1966-2005 suggests that 6.7% of cancer patients (localized: 9.1%; metastatic: 5.6%) survived CPR to discharge (4). Survival to discharge for ward patients was better than ICU patients: 10.1% vs.2.2%. Data on neurological outcome were not included.

V. Renal dialysis patients: 3 studies have looked at CPR outcomes in a total of 137 dialysis patients. Survival to discharge was seen in 14% of patients. One study examined long-term survival: of 74 patients undergoing CPR, only 2 (3%) survived six months (vs. 9% of non-dialysis controls) (5).

Summary CPR for hospitalized patients is associated with poor outcomes, as the cause of arrest is usually associated with advanced chronic illness rather than an easily reversible acute cardio-pulmonary event (e.g. isolated arrhythmia). The AHA recommends the widespread use of advance directive for all patients admitted to the hospital as well as "frank" discussions about prognosis and survival rates from CPR. When talking with patients about CPR, physicians can say roughly 15%, or 1 in 6 patients, who undergo CPR in the hospital may survive to discharge. However, specific co-morbidities will reduce the chance of survival, and surviving patients are at risk for a range of CPR-related complications including permanent neurological and functional impairment.

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FAST FACTS AND CONCEPTS #189
PROGNOSIS IN DECOMPENSATED CHRONIC LIVER FAILURE

Brigid Dolan MD and Robert Arnold MD

Background In 2009, chronic liver disease and cirrhosis resulted in approximately 30,000 deaths, making it the twelfth leading cause of death in the United States. Patients with compensated chronic liver failure (without ascites, variceal bleeding, encephalopathy, or jaundice) have a median survival of 12 years. After decompensation, median survival drops to ~ 2 years. This *Fast Fact* reviews prognosis in chronic liver failure, focusing on two validated prognostic indices. Of note, these indices predict prognosis for patients without liver transplantation.

The ***Child's-Turcotte-Pugh (CTP)*** score includes 5 variables, each scored 1-3:

	Numerical Value		
Variable	1	2	3
Ascites	None	Slight	Moderate/Severe
Encephalopathy	None	Grade 1-2	Grade 3-4
Bilirubin (mg/dL)	< 2.0	2.0-3.0	>3.0
Albumin (mg/L)	> 3.5	2.8-3.5	<2.8
Increase in seconds from normal Prothrombin time	1-3	4-6	>6.0

Patients are grouped into three classes based on the total CTP score, which is simply the sum of the scores for each of the 5 variables. Patients scoring 5-6 points are considered to have *'Class A'* failure*;* their 1 and 2 year median survivals are 95% and 90%, respectively. A score of 7-9 is considered *Class B* with median survivals of 80% at 1 year and 70% at two years. *Class C* patients (10-15) have far greater mortality: 1-year median survival is 45% and 2-year is 38%. Variations in the timing and subjectivity inherent in the scoring of the CTP (e.g. in grading ascites or encephalopathy) are its major limitations. In addition, the scale does not include renal function, an important prognostic factor in liver failure.

The ***Model for End-stage Liver Disease (MELD)*** score was developed in 2000 to overcome the above-mentioned limitations and determine survival benefit from transjugular intrahepatic portosystemic shunting. It is currently used to help determine organ allocation for liver transplantation, and there is increasing evidence that it can also be used generally to predict survival in patients with chronic liver failure. The MELD score relies on laboratory values alone (serum creatinine, total bilirubin, and INR). An additional benefit over CTP is that it can predict prognosis on the order of months with more precision – making it helpful for determining hospice eligibility in the US. The formula to calculate MELD score is complex, and a calculator can be found at: http://reference.medscape.com/calculator/meld-score-end-stage-liver-disease.

MELD Score	**Predicted 6 month survival**	**Predicted 12 month survival**	**Predicted 24 month survival**
0-9	98%	93%	90%
10-19	92%	86%	80%
20-29	78%	71%	66%
30-39	40%	37%	33%

Other important prognostic variables The hepatorenal syndrome (HRS) – renal failure from renal arterial under-filling due to decompensated liver failure – portends a particularly poor prognosis. Most patients with type-1 HRS (rapid and severe renal failure) die within 8-10 weeks even with therapy. Median survival with type-2 HRS (chronic, less severe renal failure with serum creatinine usually 1.5-2 mg/dL) is around 6 months. Both older age and hepatocellular carcinoma also adversely affect survival. While the CTP and MELD systems provide objective guidance to prognostication in liver failure, clinical judgment, patient comorbidities, the rate of decompensation, and the likelihood of transplantation all should additionally affect the assessment and communication of a patient's prognosis in liver disease.

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FAST FACTS AND CONCEPTS #191
PROGNOSTICATION IN PATIENTS RECEIVING DIALYSIS
Matthew Hudson, Steven Weisbord MD, Robert Arnold MD

Background End stage renal disease (ESRD) is a highly prevalent and rapidly increasing condition. While dialysis prolongs life in patients with ESRD, life expectancy remains only a third to a sixth as long as similar patients not on dialysis. The overall one and five year mortality rates are 25% and 60%, respectively. Approximately 20% of ESRD patient deaths occur after a decision to stop dialysis, highlighting the importance of discussions of prognosis and goals of care with this chronically ill population. This *Fast Fact* reviews the current data regarding prognostication in patients receiving chronic hemo- and peritoneal dialysis. **Note:** renal transplantation reduces mortality and the following data do not consider patients with functioning kidney transplants.

Prognostic Factors Several patient-specific factors influence prognosis:

- *Age:* For 1-year increments beginning at age 18, there is a 3 to 4% increase in annual mortality compared to the general population. 1 and 2 year mortality rates go from 10 and 12% at 25-29 years of age, to 25% and 42% at 65-69 years, to 39% and 61% at 80-84 years of age.
- *Functional status:* the relative risk of dying within 3 years of starting dialysis is 1.44 for those with Karnofsky Performance Status scores of <70 compared to a score ≥70 (see *Fast Fact* #13).
- *Albumin:* a low serum albumin level, both at baseline and during the course of dialysis treatment, is a consistent and strong predictor of death. For example, the 1 and 2 year survival of patients with an albumin of >3.5 g/dL is 86% and 76% respectively, compared to 50% and 17% if less than 3.5.
- *Surprise question*: in a multivariate analysis, the likelihood of death in 6 months was significantly greater when nephrologists answered no to the question "*would I be surprised if this patient died within 6 months*?"

Prognostic Tools It has long been recognized that patient comorbidity is strongly correlated with prognosis in ESRD. An age-modified Charlson Comorbidity Index (CCI), which stratifies patients based on medical comorbidities and age, has been successfully used to predict mortality in dialysis-dependent patients (8):

Modified Charlson Comorbidity Index: Total score is the sum of the comorbidity points

Comorbidity Points				
1 point each for coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, mild liver disease, diabetes **1** point for every decade over 40 (e.g. a 65 year old would receive 3 points).				
2 points each for hemiplegia, moderate-to-severe renal disease (including being on dialysis), diabetes with end-organ damage, cancer (including leukemia or lymphoma)				
3 points for moderate-to-severe liver disease				
6 points each for metastatic solid tumor or AIDS				
Modified CCI Score Totals	Low score (≤3)	Moderate (4-5)	High (6-7)	Very High (≥8)
Annual mortality rate	0.03	0.13	0.27	0.49

For example, a 66-year old male on dialysis with a history of CHF, COPD, and diabetes with retinopathy would have a CCI score of 9 and a nearly 50% chance of dying within a year. Using this, a provider could discuss with the patient his prognosis and use this to facilitate further discussion regarding planning for the future, including end-of-life decisions. The Index of Coexistent Disease (ICED), a general illness severity index, has also shown predictive power in ESRD. The scale's complexity and length however (it entails asking over 100 questions) limit its clinical usefulness.

Summary The age-modified CCI, in conjunction with other prognostic factors such as serum albumin and functional status, can be used to help facilitate discussions with dialysis-dependent patients and their families regarding goals of care and end-of-life planning.

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FAST FACTS AND CONCEPTS #234
PROGNOSIS OF ANOXIC-ISCHEMIC ENCEPHALOPATHY

James Fausto MD

Introduction Cardiac arrest, experienced by approximately 450,000 Americans annually, has a very poor survival rate (see *Fast Fact* #179). Some patients who initially survive cardiopulmonary resuscitation remain comatose, demonstrating obvious impairments in consciousness and neurologic function. This syndrome, called anoxic-ischemic encephalopathy (AIE, also known as 'anoxic brain injury,' or 'hypoxic-ischemic coma'), can result in outcomes ranging from full recovery to permanent unconsciousness to death. This *Fast Fact* discusses prognostic factors in adults with AIE after cardiac arrest.

"Neurologic Outcome" A challenge in interpreting the literature on AIE is the use of variable or imprecise definitions of a 'poor neurologic outcome.' The American Academy of Neurology practice parameter paper defines poor outcome as: death, persistent unconsciousness (such as a vegetative state), or severe disability requiring full nursing care after 6 months (6). This is the definition used in this *Fast Fact*.

Predictors of Neurologic Outcome A review of the current literature reveals that data obtained by careful neurologic exam, electrophysiologic studies, and biochemical markers are most predictive of outcome (see below). Other factors not strongly predictive of outcome include: age, sex, cause of arrest, type of arrhythmia, total arrest time, duration of CPR, geographic location of arrest, elevated body temperature, elevated intracranial pressure, concurrent respiratory failure, and early brain imaging findings (3,6,7,8).

Note: the data below assume patients are not receiving medications which would significantly confound their neurologic examination such as high-dose barbiturates. In all cases, specialist neurologic examination and input is advised.

Strong Indicators of Poor Outcome (false positive rates of 0% based on current literature):

- Absent pupillary light reflexes 24 hours after CPR, or 72 hours after CPR for those who initially had intact papillary light reflexes (3,6,7).
- Absent corneal reflexes 72 hours post-CPR (6,7).
- Short-latency Somatosensory Evoked Potentials (SSEP, an electrophysiologic study): bilateral absence of the N20 potentials on SSEP of the median nerve in AIE patients greater than 24 hours post-CPR (1,6,7,8).
- Neuron-Specific Enolase (NSE, a blood test): serum NSE > 33 mcg/L on day 1 to 3 (6,7,8). While this biomarker is promising, it has not been studied in large trials, nor is the assay itself standardized, so its current clinical role remains undefined (7).

Moderate Predictors of Poor Outcomes (these all predict a poor outcome, but not as invariably as the above factors based on current literature):

- Clinical exam findings: no spontaneous eye movements or absent oculocephalic reflexes at 72 hours post-arrest (3,6,7). No, or extensor-only, motor response to painful stimuli at 72 hours also implies a very poor chance of recovery (3,6).
- Electroencephalogram findings: certain findings can be strongly associated with poor outcomes but are highly subject to institutional/technician variability. Myoclonic status epilepticus within 1 day of cardiac arrest is the most predictive of a poor outcome (3,6,7,8).

The Therapeutic Hypothermia Protocol The majority of the evidence for prognosis in the comatose patient after CPR predates the widespread use of therapeutic hypothermia in patients after cardiac arrest. It remains unclear how this intervention will change prognostication. While the above factors will likely still indicate poor prognosis, the timing of when the evaluations should be done, as well as if they will predict a *uniformly* poor outcome is uncertain. One European study advises that patients have an initial neurological assessment as soon as possible, but that the second assessment occurs *no earlier* than 48-72 hours after the return of normal blood temperature and not 48-72 hours after the discontinuation of

active cooling (2). Zandbergen et al suggest that serum NSE >33 mcg/L occurring while hypothermic still consistently predicts poor outcomes accurately (8). Initial data (4,8) on the predictive value of SSEPs in patients who underwent hypothermia confirmed that bilateral absent N20 responses is highly predictive of a poor outcome. There has been a case report of an isolated patient with absent N20 responses who made a full recovery, highlighting the importance of ongoing investigation into the impact of the hypothermia protocol on the prognosis of AIE (4).

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FAST FACTS AND CONCEPTS #239
PROGNOSTICATION IN SEVERE TRAUMATIC BRAIN INJURY IN ADULTS

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Background Traumatic brain injury (TBI) is defined as brain injury caused by an external force – most commonly falls, struck by/against events, motor vehicle collisions, and assaults. The vast majority of patients with mild to moderate TBIs have substantial recoveries; this is not true of severe TBIs. This *Fast Fact* discusses prognostication in severe TBI in adults.

Initial TBI severity TBI severity is most commonly graded by the initial Glasgow Coma Scale (GCS) score. The GCS rates the patient's best verbal response, best motor response and the stimulus needed to elicit eye opening. Scores range from 3-15, with score ≤ 8 representing coma. 'Mild' TBI (accounting for ~80% of cases) is manifest by a 30 minute post-injury GCS of 13-15. 'Moderate' TBI consists of immediately altered or loss of consciousness for > 30 minutes and 6 hour post-injury GCS of 9-12. 'Severe TBI' involves immediate loss of consciousness for > 6 hours with residual GCS of 3-8.

Long-term outcomes The Glasgow Outcome Scale (GOS) is a five-point scale used widely in brain injury research. An eight-point Extended Glasgow Outcome Scale (GOS-E) is available with more sensitivity to change in function, but most outcome studies reference the GOS. The GOS range is (1) death, (2) persistent vegetative state (unconscious and unable to interact), (3) severe disability (conscious; cannot live independently; requires daily assistance due to physical or mental impairment), (4) moderate disability (able to live independently; able to work in a supported environment), and (5) good recovery (minimal or no deficits; able to work and socialize normally). In addition to global functional impairments, survivors of severe TBIs often have impairments in memory, executive functioning, impulse control, sensory processing, and communication skills. Mental health problems are common.

Predicting outcomes Overall 30-day mortality following TBI is estimated to be 20% with the highest mortality corresponding to the worst initial GCS scores. For patients with reliable initial GCS scores of 3-5, only 20% will survive and less half of those survivors will have what is often referred to in the research literature as a 'good outcome' (GOS 4-5). Older age, lower initial GCS score, abnormal initial pupil reactivity, longer length of coma and duration of post-traumatic amnesia, and certain computed tomography findings all indicate a smaller chance of recovery to GOS 4-5. Kothrari proposed the following prognostic guidelines, based on a comprehensive review of studies that looked at outcome in adults 6 months or later after severe TBI [8]:

- Favorable outcome (GOS 4-5) likely when the time to follow commands is less than 2 weeks after injury, and the duration of post-traumatic amnesia is less than 2 months.
- Poor outcome (GOS <4) is likely when the patient is > 65 years old, the time to follow commands is longer than 1 month, or the duration of post-traumatic amnesia is greater than 3 months.
- Notably, 10% of patients will not have the outcome predicted by the guidelines above.

A multinational collaborative trial developed a prognostic model (referred to as the CRASH prognostic mode) which has been validated to predict outcomes in TBI (9,10). The model is available online and uses age, GCS, pupil reactivity, presence of major extracranial injury, and (optional) computed tomography findings to give rates of death at 14 days post-injury and GOS at 6 months for survivors (11).

Helping families make decisions Families of patients with severe TBIs may be confronted with decisions about medical care (e.g. gastrostomy tube placement, chronic ventilatory support, dialysis). Such decisions often depend on a family's understanding of a patient's long-term functional outcome. The above-mentioned prognostic indicators can help clinicians provide objective information for families about the likelihood of recovery after a TBI. As with all prognostic tools, however, clinicians can only predict what would happen to a population of patients with a similar injury (e.g. 'only 10% of patients would recover such that they could live independently'); this is different from predicting any particular patient's course. It is important to communicate the uncertainty that accompanies most prognostic estimations. Counseling families about long-term functional prognosis, as well as the expected treatment course (what rehabilitation would involve) is important. While the research literature often defines a 'good recovery' as GOS 4-5, that may not constitute a 'good' recovery for an individual patient. Clinicians should avoid such language at the bedside and instead use detailed descriptive language of expected

functional and cognitive outcomes. Early and frequent family meetings can facilitate communication, built rapport, and are vital in expectation setting and establishing goals of care. If life sustaining treatments are initiated, framing the treatments in the context of time-limited trials is helpful. This empowers family members to discontinue certain cares after a specified period of time if the prognosis remains unchanged or if the treatment is not meeting the goals of care (e.g. helping to restore a patient to a functional status which is acceptable to the patient). Interdisciplinary team members including speech, occupational, and physical therapists, physiatrists, neurologists, palliative care clinicians, and neurosurgeons can be important in letting family members more fully understand a patient's likely future. See *Fast Fact* #226 about helping surrogates make decisions.

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FAST FACTS AND CONCEPTS #325
UREMIC CALCIPHYLAXIS

Katherine Roza MD, Jason C. George DO, Maria Bermudez MD and Zankhana Mehta MD.

Calciphylaxis is a poorly understood disorder in which calcification of small blood vessels causes painful ischemic skin and visceral lesions most often in patients with end-stage renal disease (ESRD). This *Fast Fact* will review its clinical presentation and offer recommendations for advance care planning and symptom management.

Epidemiology: Calciphylaxis occurs in 4% of ESRD patients on peritoneal dialysis or hemodialysis and can occasionally occur in pre-dialysis renal disease (1). Risk factors include: female sex; Caucasian race; obesity; diabetes mellitus; hyperparathyroidism; albumin < 3; hypercoagulable states; and exposure to certain medications such as warfarin, iron, vitamin D, and corticosteroids (2-7).

Pathophysiology: Uremia, calcium products, and reactive oxygen species (ROS) associated with ESRD are thought to increase vascular calcium deposition and fibrosis, leading to calciphylaxis (1,3). Over time this process likely precipitates arteriolar remodeling and progressive stenosis, causing ischemia and skin infarcts. The one-year mortality rate for calciphylaxis is estimated to be 45-80%, which may be even higher when ulcerative skin lesions are present (7,8). Ischemic complications and difficult to treat infections given incomplete antibiotic penetrance and poorly perfused tissues are potential mechanisms for the increased mortality risk.

Clinical Presentation: Early signs include pain and a lace-like purplish discoloration of the skin (livedo reticularis). This is often followed by painful subcutaneous nodules or plaques that progress to necrotic ulcerations. Areas of greatest fat tissue -- abdomen, buttocks, and inner thighs -- are most commonly involved, although visceral organs, skeletal muscle, and heart muscle can also be affected (5, 9). Calciphylaxis can be challenging to distinguish from a vasculitis. Intact pulses, bilateral upper extremity involvement, and calcification seen on X-rays or CT scans are suggestive indicators of calciphylaxis.

Diagnosis: Calciphylaxis is a clinical diagnosis. Laboratory findings are non-specific. In certain circumstances, a dermatology consult and/or skin biopsy may be needed. However, skin biopsy is usually deferred due to risk of pain, a false negative result, and poor wound healing (**Error! Bookmark not defined.**,10). Imaging studies can support the diagnosis by identifying calcification, but they do not confirm a diagnosis and may lead to unnecessary discomfort (10).

Treatment: No randomized control trials exist for the treatment of calciphylaxis. In general, most experts recommend a multi-modal approach involving adequate wound care, pain control, and treatment of hyperparathyroidism. This includes a low phosphate diet, use of non-calcium based phosphate binders (i.e., sevelamer), and cessation of vitamin D supplementation. In hemodialysis patients, calcimimetics (i.e. cinacalcet) and increasing dialysis frequency to 4 to 6 sessions per week may help but evidence is limited to case reports (3,11). Other less established options include sodium thiosulfate infusion during hemodialysis, oxygen therapy (10-15 liters via face mask 2 hours/day), and hyperbaric oxygen directed to the wound (3,5,12,13). Providing these therapies may be logistically challenging for hospice agencies.

Pain Management: The mechanism of pain is poorly understood, but is thought to be due to ischemia and resultant nerve damage. No controlled studies have confirmed an optimal analgesic approach. However, case series suggest that combining aggressive wound care with an analgesia regimen consisting of opioids, ketamine, and non-opioid adjuvants (e.g., gabapentin or tricyclic antidepressants) can be effective (14). Fentanyl, buprenorphine and methadone do not have known renal metabolites and thus may be associated with less opioid toxicity. The use of topical ketamine or topical opioids, such as morphine-infused gels may offer local pain control with potentially less systemic side effects, but this has not yet been studied (see *Fast Facts* # 185). Amputation remains an option in cases of refractory pain.

Advance Care Planning: Considering the one-year mortality risk, the diagnosis of calciphylaxis should prompt clinicians to engage patients and families in a larger discussion regarding advance directives, prognosis, and goals of care. A potential decision-point is whether to withhold or withdraw hemodialysis

when calciphylaxis is diagnosed. Patients may not be aware that stopping dialysis is a viable care option unless raised by a clinician. Clinicians, however, should be aware that the decision to stop hemodialysis can be exceedingly complex and dependent upon a variety of factors such as patient-defined quality of life, symptom burden, prognosis, and care location preferences (see *Fast Fact* #163). While the Medicare Hospice Benefit (MHB) can provide important care resources and support for patients with calciphylaxis, MHB patients are typically unable to continue dialysis with a hospice admitting diagnosis of ESRD. Thus, even a discussion of hospice can be challenging to navigate for many clinicians. Given their skills in managing complex analgesic regimens and their multidisciplinary approach to clinical, psychological, spiritual, and social care, the involvement of a specialist palliative care team can be helpful when discussing withholding or withholding dialysis.

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FAST FACTS AND CONCEPTS #326
ILLNESS TRAJECTORIES: DESCRIPTION AND CLINICAL USE
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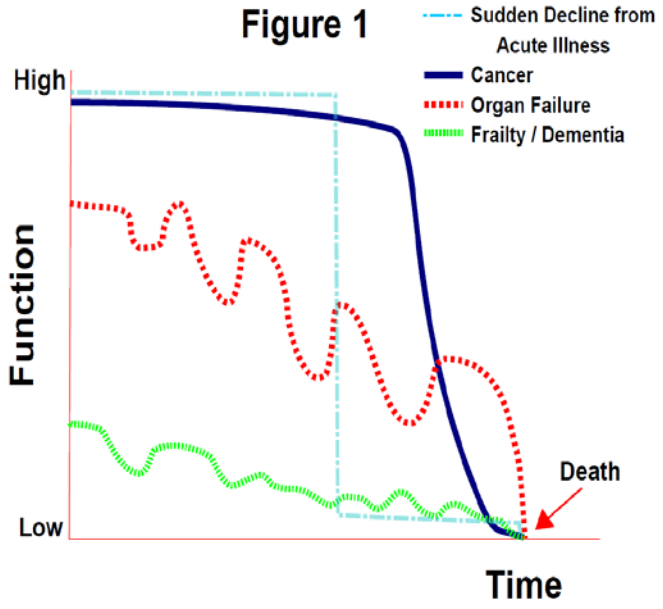
Illness trajectories can provide a framework for addressing patient and family expectations of what will happen with regards to their anticipated health. Distinct illness trajectories have been recognized in the medical literature (see Figure 1). This *Fast Fact* will review the medical evidence of these trajectories as well as their utility as a patient teaching tool.

General Evidence: A large observational study, described distinct illness trajectories at the end of life for frailty/dementia, cancer, and organ failure (1). Subsequent research has cast some controversy about the validity of these findings, particularly whether hospitalizations may have a more significant role on the pattern of decline than the specific illness itself (2-4).



Illness Trajectories:
Frailty / Dementia: A pattern of dwindling cognitive and/or physical disability that may progress over several years (1). Seventy percent of dementia patients require assistance in ≥3 ADLs, in the last year of life, making these patients at heightened risk for nursing home placement and caregiver breakdown (2). Many clinicians and families may not recognize that dementia by itself is a terminal illness.

Cancer: A relatively stable period of physical function followed by an acute decline in the last few months of life. Multiple studies have supported this trajectory however, the timing of steep decline ranges between 1 to 5 months before death depending on the study (1,5-7). Cancer patients may also experience more predictable patterns of spiritual distress with peaks at diagnosis, disease recurrence, and the terminal phase of illness (8). Because the physical decline and psycho-spiritual distress can be better anticipated, especially in solid tumors, more accurate prognostication and implementation of specialized palliative care services can occur. One study of Medicare patients showed that cancer patients were more likely to utilize hospice in comparison to other chronic illnesses because of the more predictable trajectory (9). More research is needed to validate this trajectory in the face of new targeted treatment modalities.

Organ failure: A more erratic trajectory with punctuated periods of decline likely correlating with acute exacerbations (1). Each exacerbation may result in death but is often survived with gradual deterioration in health and functional status. Timing of death is less certain than in cancer. Perhaps as a result, patients with congestive heart failure (CHF) and chronic obstructive pulmonary disorder are more likely to die in the hospital and less likely to receive hospice services nor understand the likely progression of their illness (9-12). Other take home points regarding the organ failure trajectory include:

- The functional decline for CHF has been shown to be particularly heterogeneous (2,13). Some hypothesize this may be related to co-morbidities and/or research methodologies (13).
- Often prognosis is more centered around patient specific goals regarding acceptance or not of repeat hospitalizations and treatment of potentially reversible complications.
- Although observational studies have shown inconsistent findings, elderly end stage renal disease patients who forgo initiating hemodialysis may be more likely to have an illness trajectory similar to sudden death – stable function for months with a rapid end of life deterioration (14-16).

Sudden Death or Decline: An abrupt change from normal physical function to either death or significant medical disability, often as a result of trauma or an acute cardiopulmonary/neurologic event. Many times there is little or no prior interaction with the health system nor a recognizable pattern of functional decline preceding the event (1,9). Thus, intense displays of shock or anger are common from family members when clinicians break bad news. See *Fast Fact* #305. Loved ones are at increased risk for depression and complicated grief as they adjust to the new medical reality after the event (17,18).

Clinical Use: Although there is no known published data assessing the effectiveness of utilizing the illness trajectories as a clinical teaching tool, describing or even diagramming these illness trajectories with patients and families may be a concise communication technique to set expectations and offer guidance regarding the anticipated impact of chronic illness on daily life. Clinicians should be aware of the significant variability in the medical literature regarding the validity of these illness trajectories as well as the limitations in the way functional decline is measured between studies. Therefore, it is vital that illness trajectories be reevaluated as the condition evolves. In particular, certain patterns such as an abrupt functional decline or frequent hospitalizations may indicate the need to readdress goals of care.

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