Fast Facts Core Curriculum

Neurology

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Background  This Fast Fact reviews the details of declaring death based on neurological criteria. In 1980, the Uniform Determination of Death Act (UDDA) was created which stated that “An individual who has sustained either 1) irreversible cessation of circulatory and respiratory function, or 2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination of death must be made with accepted medical standards.” The UDDA did not define “accepted medical standards,” and so the American Academy of Neurology published guidelines in 1995, and updated them in 2010. Despite these national guidelines, there is still considerable variability in local institutional guidelines.

Determined death by neurologic criteria involves two steps:

- **Step 1:** Rule out reversible causes of unconsciousness: sedative medication, neuromuscular blocking agents or hypothermia.
- **Step 2:** Rule out the presence of cortical activity and brainstem reflexes using clinical exams/tests. The exact tests done may vary by institution and one should check with their own institution’s policies. Brain death exams are typically completed by neurologists, neurosurgeons, and critical care physicians. For a person to be dead by brain death, typically all of the following tests must show lack of brain function:
  - No spontaneous movement and no movement in response to painful stimuli (movement due to spinal reflexes are acceptable).
  - No seizures, decerebrate or decorticate posturing, or dyskinetic movements.
  - Absent cranial nerve reflexes including pupillary response to light, corneal reflexes, oculocephalic reflex, caloric response, facial movement to a noxious stimulus, and gagging and cough with suctioning.
  - Caloric testing is done by first ensuring the auditory canal is clear and the tympanic membranes are intact. The head is elevated to 30°, 50 ml of ice water is slowly infused into the canals, and the eyes are observed for one minute. The normal response in an awake patient is tonic deviation of the eyes toward the cold stimulus followed by nystagmus back to the midline; the normal response in a comatose patient with an intact brainstem is tonic deviation of the eyes toward the cold stimulus without nystagmus; in brain death, the eyes do not move. Both ears must be tested with an interval of several minutes in between.
  - **Note:** At some institutions other clinical tests are done before a formal apnea test (see below). For example, some require documentation of no vagal nerve activity – an atropine test is used. The patient is given 2 mg IV atropine. In the dead patient, the parasympathetic outflow is non-functioning and the heart rate will not change (<10 beats/minute).
  - Absence of central respiratory drive is assessed using the apnea test to see if a rise of CO₂ provides a stimulus to breathe. The patient is ventilated with 100% oxygen for 10-20 minutes and a baseline blood gas is obtained. The ventilator is then removed while 100% oxygen is delivered; O₂ saturation is continuously assessed. A follow-up ABG is done after 5-10 minutes. If the PaCO₂ rises past 60mm Hg (or >20 mm Hg above
baseline), and no breathing efforts are observed, the respiratory center is not functioning. The test should be aborted if the patient develops hypoxemia (also indicates no respiratory drive), hypotension, or arrhythmias.

**Adjunctive or confirmatory tests** are needed in complex clinical situations such as uremia or hepatic encephalopathy, when apnea testing cannot be performed, when the primary brain insult is infratentorial, or if required by the local institutional brain death policy.

- Electroencephalogram: must be isoelectric, which is difficult in the ICU due to electrical artifact.
- Transcranial Doppler: intracranial arteries demonstrate either absence of diastolic flow, or small systolic peaks.
- Somatosensory Evoked Potentials: bilateral median nerve stimulation demonstrates an absence of the N20-P22 response.
- Intracranial Pressure: sustained, elevated ICP within 10 mmHg of mean arterial pressure.
- Tests of cerebral blood flow: if there is no cerebral blood flow then there is no brain function and death may be determined based on this test alone. Specific tests include cranial radionuclide angiography and conventional contrast angiography.

**References**


**Version History**: This *Fast Fact* was originally edited by David E Weissman MD and published in May 2004. Re-copy-edited in April 2009; then it was copy-edited again by Sam Maiser MD in June 2015 in which references 1 and 2 were added and incorporated into the text.

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FAST FACTS AND CONCEPTS #135
NEOPLASTIC MENINGITIS
Fareeha Siddiqui MD, Lisa Marr MD, and David E Weissman MD

Background Neoplastic meningitis (NM) – also known as *leptomeningeal metastases*, *meningeal carcinomatosis*, or *leukemic meningitis*, is a common oncologic complication representing spread of tumor cells to the subarachnoid space (SAS). It is a complication which often portends a very short prognosis.

Epidemiology NM is found in 20% of cancer patients at autopsy. Among solid tumors, NM is common in breast cancer, small cell lung cancer, and melanoma while rare in gastrointestinal and gynecologic cancers. 90% of solid tumor patients with NM have widespread metastatic disease. NM is found in 40-50% of patients with hematological malignancies, mostly commonly the acute leukemias and high-grade lymphomas (such as large cell and Burkitt lymphomas).

Signs/Symptoms Tumor reaches the SAS by hematogenous spread via arachnoid vessels or direct invasion along nerve roots. Cancer cells in the subarachnoid space have the potential to: a) settle in dependent portions of the neuraxis (base of brain/cranial nerves or lower spinal canal), b) grow into the surface of the brain and fill the sulci, and c) block normal paths of cerebral spinal fluid (CSF) flow. Thus, the hallmark of diagnosis is neurological signs/symptoms at more than one level of the neuraxis:

- Brain – headaches, nausea/vomiting, seizure, hydrocephalus.
- Cranial Nerves – diplopia, hearing loss, facial numbness, dysphagia, dysphonia.
- Spinal – radicular pain, weakness (usually legs), parenthesis, bladder and bowel dysfunction.

Diagnosis Lumbar puncture typically reveals a CSF profile of high opening pressure, low glucose, high protein, and lymphocytic pleocytosis. Sensitivity for finding malignant cells is 50-70% for one sample, increasing to 80-90% with three samples. MRI can identify nodular/bulky areas of disease, hydrocephalus, and/or enhancement of the cortex/tentorium if tumor growth along the sulci leads to neovascularization. NM commonly causes abnormal CSF flow; this can be demonstrated by a radionucleotide cisternogram.

Prognosis and Treatment Patients with breast cancer or hematological malignancies that have not been extensively treated with chemotherapy, have a reasonable chance at remission of their CNS disease if their systemic cancer can also be controlled. In contrast, patients with other cancers (e.g. lung, melanoma) typically have a dismal prognosis (1-4 months) with or without treatment. In fact, the median survival of patients who underwent placement of an implanted intraventricular reservoir (Ommaya reservoir) for intrathecal chemotherapy administration was only 72 days in a multicenter retrospective analysis. Unlike spinal cord compression or brain metastases, there is no accepted role for corticosteroids except in lymphoid malignances. Treatment options include chemotherapy and/or radiation.

- Radiation: Either cranio-spinal irradiation (entire spinal column) or focused radiation therapy to sites of bulky or symptomatic areas (e.g. cauda equina for radicular leg pain).
- Chemotherapy: Options include systemic high-dose chemotherapy (Ara-C or Methotrexate) intrathecal chemotherapy (1-2 times per week) administered either by repeated lumbar puncture or via repeated puncture of an Ommaya reservoir. Commonly used intrathecal drugs include methotrexate or Ara-C.
Summary  
For many patients, NM represents a pre-terminal diagnosis and no anti-neoplastic therapy is warranted. Establishing the diagnosis in such patients may be important to help prognosticate and to anticipate future neurological problems (e.g. seizures, headache, radicular pain). The decision whether or not to begin anti-neoplastic treatment should be made in consultation with a medical, radiation, or neuro-oncologist.

References

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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
3. 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**

<table>
<thead>
<tr>
<th>Points</th>
<th>Risk factor</th>
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<tr>
<td>1.9</td>
<td>Complete dependence with ADLs</td>
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<tr>
<td>1.9</td>
<td>Male gender</td>
</tr>
<tr>
<td>1.7</td>
<td>Cancer</td>
</tr>
<tr>
<td>1.6</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>1.5</td>
<td>O₂ therapy needed w/in 14 day</td>
</tr>
<tr>
<td>1.5</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>1.5</td>
<td>&lt;25% of food eaten at most meals</td>
</tr>
<tr>
<td>1.5</td>
<td>Unstable medical condition</td>
</tr>
<tr>
<td>1.5</td>
<td>Bowel incontinence</td>
</tr>
<tr>
<td>1.5</td>
<td>Bedfast</td>
</tr>
<tr>
<td>1.4</td>
<td>Age &gt; 83 y</td>
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<tr>
<td>1.4</td>
<td>Not awake most of the day</td>
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</table>

**Risk estimate of death within 6 months**

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<th>Score</th>
<th>Risk %</th>
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<tr>
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<td>≥ 12</td>
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References

FAST FACTS AND CONCEPTS #201
PALLIATIVE CARE FOR PATIENTS WITH HUNTINGTON'S DISEASE
Sean Marks MD, Serena Hung MD, and Drew A Rosielle MD

Background
Huntington’s disease (HD) is an incurable neurodegenerative disorder inherited in an autosomal dominant fashion. It is characterized by progressive movement disorders, psychiatric manifestations, behavioral abnormalities, and cognitive impairment. This Fast Fact will focus on supportive and terminal care for patients with HD and their families.

Natural History and Prognosis
- Symptom onset is usually between 33 and 44 years; subtle cognitive and motor changes may precede diagnosis by many years. Mean duration of illness from onset to death is 15-20 years with average age of death of 60 years; there are no proven therapies which slow the progression of HD.
- Patients show signs of progressive dementia and become unable to walk, talk, take in nutrition, and care for themselves. Life threatening complications may result from aspiration, chronic infections, poor nutrition, falls, or cardiovascular disease.
- ~1/3 of all patients with HD are institutionalized in long-term care facilities.

Impact on Families
HD often begins during a time when family life is most complex and therefore most disruptive to the family structure (e.g. child-rearing, career development). Children can be particularly affected: distress is aggravated by concerns about their own genetic susceptibility, and as many as 40% of children of HD patients describe HD as splitting their family apart. Careful assessments of familial coping and psychosocial needs are an integral part of ongoing care for the HD patient.

Common Symptoms and Supportive Care
Patients are best served by an interdisciplinary team familiar with caring for patients with HD.
- Motor Manifestations: Abnormal involuntary movements include: chorea, dystonia, rigidity, bradykinesia, tremor, and myoclonus; other motor manifestations include gait and balance problems leading to frequent falls, slurred speech and swallowing difficulties.
  - First-line strategies are non-pharmacologic and include gait/balance training, speech therapy, and orthotics and leg weights to assist with upright posture.
  - Chorea is the most frequently targeted symptom for pharmacologic therapy. Tetrabenazine (a dopamine depleting agent) has been shown to reduce chorea in a well-designed placebo controlled trial; it is undergoing approval in the US. Haloperidol and other antipsychotics are also used for chorea, although trials evaluating their effectiveness have shown mixed results.
- Psychiatric manifestations are present in over half of HD patients.
  - Depression is a significant psychiatric problem and rates of suicide are higher in HD patients than the general population. Case reports support using tricyclic as well as newer antidepressants.
  - Agitation is also common, and a small number of patients develop psychosis. Atypical neuroleptics are commonly used. Emotional lability (including episodes of extreme anger) can respond to propranolol.
  - Low doses of scheduled benzodiazepines before meals or propranolol are used to control motor manifestations and anxiety related to eating.
  - Establishing strict daily and hourly routines can help lessen anxiety, short-term memory deficits, intrusive thoughts, and fear of abandonment.
- Cognitive Deficits: gradual loss of memory and executive function are common. Consequently, increasing impairments in initiating movements and conversation occur. Yes/no questions may be preferable over open-ended questions when cognitive impairments become severe.
**Advance Care Planning**  Advanced care planning should be performed as early as possible, prior to cognitive impairment. Of particular importance is establishing a health care power of attorney, as well as documenting guidance to families for likely decisions they will face (such as tube feeding and mechanical ventilation). Some states require clear evidence that a patient would want tube feeding withheld or withdrawn at the end of life and patients should be instructed to document this if consistent with their wishes. See also Fast Facts #12, 65, 162, and 178 for further discussion of advance care planning.

**Terminal Care**  There are no evidence-based criteria for determining a 6 month prognosis in HD; web-based reference 13, however, provides some guidance regarding hospice eligibility. A retrospective, multi-centered study of over 100 HD patients, suggested that the hospice length of stay is longer than non-HD hospice patients and only a significant minority of HD patients are able to die at home. Labored breathing, excessive secretions, and restlessness are common terminal symptoms – see Fast Facts #1, 60, 109, 158, and 176.

**References**


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Background  Seizure management in the dying patient without intravenous (IV) access, such as in the home environment, is challenging. In this population they can be due to primary or metastatic brain cancers, strokes, toxic/metabolic causes like hypoglycemia, or pre-existing epilepsy. The incidence of seizures in dying patients is unknown, and while likely uncommon, they can cause tremendous distress to patients and families. This Fast Fact reviews management strategies for seizures near the end of life.

Seizure Prophylaxis  Up to 40% of patients with brain tumors have a seizure at the time of diagnosis and another 20% eventually develop seizures. Although antiepileptic drugs (AEDs) are commonly started as prophylaxis at the time of brain tumor diagnosis, they have not been found to prevent seizures and the American Academy of Neurology Clinical Practice Guidelines do not support this practice (1). Thus, prophylactic AEDs can be safely discontinued in patients with brain tumors who have never had a seizure. For brain tumor patients with a seizure history (especially those with a history of status epilepticus), AEDs should be continued when possible. In one study, tapering AEDs in the last week of life was associated with seizures in 35% of patients with high-grade gliomas. For patients who lose an enteric route and have no intravenous access, rectal administration of prophylactic AEDs is possible. Clinical judgment should be used as to whether to continue AEDs in this setting as it can be appropriate to simply stop them, particularly if the patient’s prognosis is very short. Phenobarbital, pentobarbital, carbamazepine, valproic acid, and lamotrigine can all be given rectally. Rectal absorption of other prophylactic AEDs is undefined and they should not be administered. No AEDs need dose adjustments for rectal administration. Carbamazepine should be divided into small doses administered 6-8 times a day. Lamotrigone is administered rectally by crushing and suspending the chewable tablets in 10 mL of water. When clinically indicated, drug levels of lamotrigine should be monitored as rectal absorption is erratic. There is no data for the use of rectal levetiracetam in humans.

Seizure Management  

- **Single self-limited seizure:** Check for treatable causes such as hypoglycemia. If no reversible cause is identified, initiation of maintenance AED therapy should be considered, particularly if the patient is expected to survive more than a few weeks.

- **Acute seizure or status epilepticus:**
  - Non-IV routes: Studies, mainly in the pediatric population, have shown intranasal (IN) midazolam at a dose of 0.2 mg/kg to be an effective and convenient agent to abort an acute seizure. It has a quick onset of action of only 4-8 minutes and a time to maximal concentration of 15-30 minutes. Rectal diazepam (0.3 mg/kg) used to be the drug of choice for this indication and can be considered, but it has a longer onset of action, is more expensive, and appears to be less preferred by patients compared with IN midazolam. Once the initial seizure is controlled, diazepam 20 mg PR nightly should be considered to reduce the occurrence of further seizure events. Other rectal benzodiazepines are available (clonazepam, lorazepam, and midazolam), but take longer to reach peak serum levels. Sublingual lorazepam is also available, but is not well-studied.
  - IV routes: When available, IV or subcutaneous (SC) benzodiazepines should be used to stop a seizure in progress; IV lorazepam is preferred due to its onset of action and half-life. SC dosing is equivalent to IV for lorazepam, midazolam, and clonazepam. If seizure activity persists, additional anti-epileptic medication should be provided using a loading and then maintenance dose. Patients with refractory seizures who have short prognoses and comfort-oriented goals of care should be considered for an anti-epileptic sedative such as a continuous midazolam or barbiturate infusion with the goal of deep sedation (see Fast Facts #106,107).

Parenteral AED Dosing and Routes.
Levetiracetam: Doses up to 2,500 mg IV have been used successfully and safely when added to standard status epilepticus regimens. A typical maintenance dose is 500-1500 mg PO or IV BID.

**Family Education**

Family members should be counseled that all medications used to manage seizures can cause sedation and cardiopulmonary depression. Family members who have witnessed prior seizures often have great fear about seizure recurrence. Many hospice agencies have established seizure protocols and medication kits which can be stored at home, and will collaborate with physicians and families on establishing a ‘seizure plan’ for acute seizures. Review seizure safety with families, including not putting anything in the patient’s mouth and making sure the patient is in a safe environment.

**References**


**Author Affiliations:** Medical College of Wisconsin, Milwaukee, WI.
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FAST FACTS AND CONCEPTS #234
PROGNOSIS OF ANOXIC-ISCHEMIC ENCEPHALOPATHY 3RD EDITION

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 pupillary 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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Author Affiliation: Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY.

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EVALUATION OF SPINAL CORD COMPRESSION
Rohtesh S Mehta MD, MPH and Robert Arnold MD

Background  Malignant epidural spinal cord compression (SCC) is a common and devastating complication of cancer (see Fast Fact #62). If not diagnosed and treated in a timely manner, SCC can lead to permanent weakness, paraplegia, and loss of bowel and bladder control. This Fast Fact discusses the clinical features and diagnosis of SCC in adults. Fast Fact #238 discusses its management.

Epidemiology  Breast, lung, prostate, and multiple myeloma are the most common cancers causing SCC. Cumulative incidence of SCC in the 5 years preceding death is roughly 8% in multiple myeloma, 7% in prostate cancer, 5.5% in breast and 3% in lung cancer patients. The thoracic spine (70%) is the most common site of SCC because of its narrow epidural space and dense vascularization, followed by the lumbosacral (20%) and cervical spines (10%). Hematogenous spread (both arterial and venous) to the vertebral bone and subsequent growth into the epidural space is the most common mechanism of metastasis to the epidural space, although and direct invasion through the neural foramen can also occur. Once in the epidural space, tumor may spread in any direction, including pressing on the dura mater causing ischemia and demyelination of the spinal cord.

Symptoms  Symptoms usually present in a progressive manner from pain to neurologic deficits. Back pain is the most common and the most sensitive symptom in SCC (>90%), but is non-specific. It can be localized (20-80%), radicular (40-60%), or mechanical (14%), and can worsen with recumbent position (20%) or coughing or sneezing (35-40%). Back pain that is new or changing should raise one’s suspicion of SCC. Pain may be present for 2-3 months before neurological symptoms develop. Motor deficits are more specific for SCC than pain, but present late in its course. The time from the onset of weakness to frank paraplegia can range from less than 24 hours to many weeks. Motor symptoms include progressive motor weakness (60%-95%), ataxia, and subsequently total paralysis. Sensory deficits are less common than motor symptoms (40%-60%). Autonomic symptoms, including bladder (50%) and bowel (75%) complaints occur last in the disease process. These include urinary hesitancy (14%), retention (25%), incontinence (15%), constipation (66%), and fecal incontinence.

Signs  Physical examination can reveal weakness (85%) and a sensory level of deficit (50-60%), but there is poor correlation between the level of pain and the actual level of compression. More than half of patients with upper thoracic compression present with lumbosacral pain and vice-versa (7). A clinically detected sensory level abnormality is also poorly correlated (16%) with the level of compression identified on MRI.

Risk Factors  In cancer patients with suspected SCC, the following factors have been associated with an increased risk of having SCC compared to patients without these characteristics: age less than 60 years, inability to walk, middle or upper back pain, abnormal neurologic examination, presence of spinal metastases, radiographically diagnosed compression fractures, bone metastases diagnosed more than 1 year earlier, and metastatic disease at initial cancer diagnosis (3,4).

Imaging  Because symptoms poorly correlate with compression level, and SCC can occur at multiple levels simultaneously, imaging of the entire spine is recommended. MRI (without contrast) is the imaging modality of choice because of its high sensitivity (93%) and specificity (97%). In addition, MRI reveals if there is compression of the cord versus nerve roots and can provide useful information about the spine’s stability. CT myelography has sensitivity and specificity close to that of MRI, and can be used in patients who cannot get an MRI. Plain films are not sensitive and cannot rule out either vertebral metastases or SCC. If they show vertebral lesions in a suspected area, however, that should increase one’s suspicion of SCC and prompt further investigation. Bone and PET scans can show the presence of vertebral metastases but do not provide information about compression of the spinal cord. CT scans are not recommended due to poor revelation of the epidural space and spinal cord.

Conclusion  New or worsening back pain in cancer patients with or without neurologic deficits should be evaluated urgently for SCC. Clinicians should have a very low threshold to image a patient’s entire spine with MRI. If a patient has developed any neurologic deficits, glucocorticoids should be administered (see Fast Fact #238) and total spine MRI should be performed emergently.
References

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Background  Metastatic spinal cord compression (SCC) is a medical emergency; early treatment is associated with less functional disability. Treatment options include corticosteroids, radiotherapy and surgery. This Fast Fact discusses management of SCC in adults. Fast Fact #237 discusses its diagnosis.

Corticosteroids  Dexamethasone is the most tested steroid in clinical trials. Studies have shown that steroids provide analgesia and reduce vasogenic edema which may lead to better neurological outcomes. Treatment should be started as soon as diagnosis is made; studies in acute spinal cord injury suggest significant neurological improvement when used within 8 hours of injury. Historically, debate existed between using high dose dexamethasone (100 mg loading, then 96 mg daily) versus moderate dose (10 mg loading, then 16 mg daily). A randomized controlled trial comparing the two doses found no differences in efficacy and thus most give the lower dose. (1) Many studies give the steroids divided 4 times a day (total 16 mg daily), tapered over 10-14 days. Most generally start IV and then switch to PO when patients are “clinically stable” and more definitive therapy (radiation or surgery) has been initiated. Steroids should be tapered as soon as possible to prevent long term toxicities (2). Common short term side effects include hyperglycemia, insomnia and gastric distress. Serious acute adverse effects such as gastrointestinal perforation or bleeding, psychosis, risk of infections and death are associated with high doses only (17%) (3).

Radiotherapy (RT)  In the absence of bony instability, RT has historically been the treatment of choice, preferably started within 24 hours of diagnosis. Dose schedule for RT ranges from single fraction 8 Gy to 20 fractions of 40 Gy. One or two fractions of 8 Gy may be preferable in patients with short prognoses and, in one study, had a similar outcome to more prolonged treatment (4). RT results in pain relief in 40-80% of patients, sphincter control in 45-90% of cases (3, 4) when instituted in time. About 90% of ambulatory patients retain ambulation with RT alone, but less than 30% of patients who have lost the ability to walk by the time RT is initiated regain ambulation (3).

Surgery  Until recently, surgery was reserved for cases with SCC in a previously irradiated area, neurologic deterioration during RT, spinal instability, or bony compression. However a recent meta-analysis (5) and a randomized controlled trial (6) found better functional outcomes with surgery plus post-operative RT as compared to RT alone. This trial used a newer surgical technique (circumferential decompression, reconstruction and immediate stabilization). 84% of the patients in the surgery group were ambulatory and retained ambulation for a longer time (a median of 122 days) after treatment compared to 57% in the RT group (median 13 days). 62% of the non-ambulatory patients regained the ability to walk after the surgery compared to 19% in the RT groups. The surgery group also maintained continence for a significantly longer time (median 156 days vs. 17 days). A more recent retrospective matched pair analysis of cancer patients with SCC comparing RT alone to surgery plus RT did not find any significant differences in outcome between the two treatments (7). Prompt, interdisciplinary evaluation by radiation oncologists and spine surgeons is indicated in order to identify the best treatment course.

Other treatments  Spinal Stereotactic Radiosurgery (SRS) has an investigational role in adult non-surgical patients with radio-resistant tumor or those with previously irradiated areas. Studies suggest more than 80% improvement in overall neurological function (8). Transarterial embolization is another novel investigational treatment. It is generally used preoperatively for hypervascular spinal tumors causing compression, is safe and effective, and can make radical tumor resection possible at times (9). In adults, chemotherapy has no role in acute management even in chemo-sensitive cancers because of its slow effect. Although bisphosphonates reduce
the incidence of skeletal complications of cancer, there are no data to suggest a benefit in treating SCC.

**Prognosis**

Median survival after developing SCC is between 3-6 months in adults. Poor prognostic factors for survival include non-ambulatory status, SCC within 15 months of original cancer diagnosis, presence of visceral or other bone metastases, cancer type (survival is worse for lung cancer and better for myeloma/lymphoma), and rapidity of developing motor symptom (worst if <7 days and better if more than 2 weeks after the onset of symptoms).

Conclusion  A loading dose of dexamethasone 10 mg IV should be given as soon as possible after diagnosis, followed by maintenance dose of 4 to 6 mg every 6-8 hours, and referral made for primary surgery (if feasible) with adjuvant RT. If surgery is contraindicated, palliative RT alone is indicated.

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

Stacy M Kessler MD and Keith M Swetz MD

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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**Background**  Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disorder leading to weakness, spasticity, and incoordination of the muscles involved in speaking, swallowing, breathing, and ambulation. Currently, there is no cure for ALS and the disease progresses inexorably toward death. Despite the lack of cure, there are available treatments that can improve quality of life. This Fast Fact will discuss non-pharmacologic therapies for common challenges faced by ALS patients. See Fast Fact ### for pharmacologic therapies and Fast Fact ### for management of sialorrhea specifically.

**Head Drop**  Axial muscle involvement, particularly neck extensor can lead to disabling head drop and kyphosis. A soft collar may be helpful early in the course of disease, but as the disease progresses, a semi-rigid collar is often needed to stabilize the neck and restrict motion. Individualized collars and adjustable head rests on wheelchairs may be needed considering the significant variability in neck anatomy (1,2,3).

**Dysphagia**  Dysphagia is a common bulbar manifestation of ALS and should be assessed each visit (4). Poor nutritional status at diagnosis or disease progression has been associated with higher mortality (5).
- Early referrals to a dietitian and speech pathologist are recommended. Use of thickened fluids, high-protein/high-calorie supplements, and modified swallowing techniques can mitigate the malnutrition associated with dysphagia (4,6).
- Gastrostomy tubes do not prevent aspiration, but they have been shown to improve nutritional status and may prolong survival. It is highly recommended that if patients are agreeable to getting a gastronomy tube, it be done before vital capacity falls below 50% of predicted (4,7).
- Nasogastric tubes have been used as a short-term alternative, but they are uncomfortable and may worsen sialorrhea (4,8).

**Ventilatory Compromise**  The most common cause of death in ALS is ventilatory failure (9). Symptoms of ventilatory compromise, such as poor nighttime sleep, daytime somnolence, anorexia, morning headache, and weak cough, often precede dyspnea.
- Noninvasive ventilation (NIV) with bilevel positive airway pressure has been shown to prolong survival and improve quality of life in patients with ALS who can maintain their airway (10). Nasal masks/pillows and sip/puff devices may improve tolerability.
- Mechanical in-exufflators alternate positive and negative pressures to improve airflow and clearance of secretions. These devices may reduce pulmonary morbidity and associated hospitalizations in muscular dystrophy (11), but there are no similar studies specific to ALS.
- Diaphragmatic pacemakers can be surgically implanted to stimulate more forceful muscle contractions in patients with some degree of residual diaphragm function. Their effectiveness has yet to be confirmed in randomized controlled trials.
- When NIV is no longer adequate or tolerated (i.e. inability to clear one’s own secretions), a small percentage of patients pursue long-term mechanical ventilation. See Fast Fact #73.

**Impairment of Mobility**  Physical therapy and use of equipment such as canes, walkers, and ankle-foot orthoses can minimize foot-drop, improve gait, and help prevent falls (12-14). Occupational therapy with assistive devices such as modified cutlery, Velcro fasteners for dressing, and bathroom modifications such as grab bars and higher toilet seats help maintain function (12-14). In patients with prominent distal weakness, wrist braces at 30 to 35 degrees can improve grip efficiency while a universal cuff can assist with eating and typing (14). Early intermittent use of a wheelchair is recommended for energy conservation (14). Modifiable controls, such as a joystick that requires minimal arm/hand strength (12), make power wheelchairs a better long-term option than power scooters for maintaining mobility. Modified remote controls and security systems may allow patients to maintain employment (12).

**Impairment of Communication**  Communication boards can be useful even after hand motor function is lost. Computer, tablet, or smartphone applications can be used to generate electronic speech from typed language. Patients can preemptively record their speech using voice banking
systems to preserve the personalization, inflection, and accent of the electronic speech (15). Eye-tracking software can be used to generate typewritten language and electronic speech.

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Background  Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disorder which can affect the muscles involved in swallowing, speaking, breathing, and ambulation (1). This Fast Facts discusses pharmacologic management strategies for patients with ALS; see Fast
Fact #300 for non-pharmacologic management strategies and Fast Fact #299 for management of sialorrhea specifically.

Pseudobulbar Affect (PBA)  This term refers to disordered emotional expressions caused by disruption of cortico-pontine-cerebellar tracts. It typically manifests as inappropriate and uncontrollable laughing or crying inconsistent with the patient’s mood and can be socially debilitating.

• The combination drug dextromethorphan/quinidine is the only FDA approved treatment of PBA. Its mechanism of action for pseudobulbar affect seems to be related to its anti-glutamatergic and anti-NMDA actions (2). The recommended dose is 20 mg dextromethorphan/10 mg quinidine twice daily. The rationale for combination therapy is that dextromethorphan is rapidly metabolized by an enzyme that is inhibited by quinidine.

• Tricyclic and SSRI anti-depressants have shown benefit, but clinical trial data is limited by small numbers of patients and poor standardization of PBA diagnostic and severity criteria (3).

Depression  Major depressive disorder is a common in ALS. Selective serotonin reuptake inhibitors are often used; however, there are no randomized controlled trials specific to ALS (4). Although the American Academy of Neurology advocates treatment of depression in ALS, there are insufficient data to recommend any specific treatment with regard to particular SSRIs, SNRIs, etc. (5).

Spasticity  Damage to the upper motor neurons in ALS leads to spasticity, which can be associated with cramps and incoordination of movement. There are no high-quality, controlled trials evaluating pharmacologic treatments for spasticity (6) and clinicians should be aware that some degree of spasticity can be useful for maintenance of posture. Although baclofen and tizanidine are both commonly used, experts tend to reserve tizanidine for more severe cases (4).

• Baclofen: initial dosing is 5-10 mg BID-TID; doses up to 120 mg per day may be needed (7).

• The starting dose for tizanidine is 2-4 mg BID with 24 mg as the maximum daily dose (7).

• Intrathecal baclofen pumps are considered only for patients with medically refractory spasticity.

Pain  Spasticity, muscle spasms, joint stiffness and skin breakdown related to immobility are all potential sources of pain in ALS, which occurs in the later stages in up to 80% of patients (8). There is insufficient evidence on which to base specific recommendations for the treatment of pain in ALS. However, as in other conditions, non-opioid analgesics and anti-inflammatory medications are generally considered first-line. When these medications fail, opioids are used commonly.

Dyspnea  Air hunger due to ventilatory failure is common in the later stages of ALS, occurring in up to 85% of patients (9). According to the American Academy of Neurology, there are insufficient data to support specific treatments for dyspnea in ALS (5). In addition to non-invasive ventilation, opioids are used commonly to relieve air hunger. One small, non-randomized prospective study demonstrated that morphine appears to be both safe and effective in this patient population (10). Furthermore, studies evaluating the safety of opioids for dyspnea in general have not demonstrated any excess mortality (11).

Riluzole  It is the only proven disease-modifying pharmacologic agent in ALS, providing a modest survival benefit of 2-3 months and likely works via inhibition of glutamate release (12). Unfortunately, its cost can often be prohibitive and it does not palliate any ALS-associated symptoms or improve quality of life. In fact, side effects such as fatigue can be significant enough to warrant discontinuation (5). Given these factors, it is reasonable to discontinue the medication at the time of hospice enrollment (or when a patient becomes ventilator-dependent), although there are no published guidelines regarding these considerations.

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Background: Locked-in Syndrome (LIS) is a rare neurologic condition characterized by quadriplegia and an inability to articulate speech, but with preserved self-awareness (1,2). It is easily misdiagnosed and once identified, a constellation of medical, psychological, social, and ethical issues may ensue (3,7).

Pathophysiology and Prognosis: LIS is caused by the disruption of motor tracts in the ventral brainstem. At least 60% of cases are caused by an acute stroke (4). LIS patients have a high risk of dying within the first several months; however, those that survive that period are likely to live 10 years or more (3, 5-7). They often have limited motor recovery of their extremities, but with long-
term survival, many patients eventually have their tracheostomy and gastrostomy tubes safely removed (7). The severe neurologic disability results in a low health-related quality of life, yet, the global quality of life and rate of depression may be no different than healthy controls (7-9). There are no particular symptoms associated with LIS other than those expected from immobility. The prevalence of bodily pain is felt to be similar to healthy controls, although inadequate pain relief is associated with suicidal thoughts (9). Because the etiology is often restricted to the brainstem, LIS typically does not affect cognition (10-12).

**Diagnosis:** Diagnosis is dependent upon the physical examination, but unless the examiner is familiar with LIS, LIS may be mistaken for coma (eyes closed, does not follow commands) or a vegetative state (eyes may open and move, but not to command) (7). Therefore, physical exam is best performed by a neurologist. If LIS is suspected, clinicians should assess for abnormal brainstem respiratory patterns such as central neurogenic hyperventilation (rapid and deep breaths 20-40/min), apneustic breaths (prolonged inspiratory pause) or ataxic respirations (irregularly irregular). A complete coma exam including cranial nerves and volitional eye/eyelid movements should be performed. Cranial imaging is typically performed to elucidate the diagnosis with magnetic resonance imaging as the preferred modality.

**Care Decisions:** The common care decisions in LIS are related to the consequences of the severe impairment of muscles that control eating and breathing. Thus, decisions about the use of mechanical ventilation, artificial nutrition and hydration, and 24 hour nursing care will be paramount. Considering the communication challenges clinicians may encounter, consultation with neuropsychology to assess decision-making capacity should be done early in the patient’s course, especially since delirium can be a confounding variable. Though prior wishes expressed in advance care planning documents may be useful, misunderstandings regarding LIS patient’s cognition and care preferences are common.

**Communication Strategies:** As portrayed in the 1997 book *The Diving Bell and the Butterfly*, written by a locked-in patient, communication is possible but it requires patience (13) and for the patient, it may be limited to vertical/lateral eye movements or blinking of the upper eyelid (2). Hence, consultation with speech language pathology is advised. The following communication strategies are recommended:

- Establish a reliable and consistent communication method, such as a vertical eye movement up means “yes,” and vertical eye movement down means “no.”
- Phrase questions so that the answers must be “yes” or “no.”
- Present a list of words (i.e. symptoms), and allow the patient time to respond.
- To improve reliability of the decisionality assessment, present questions in both an affirmative and negative manner: “Do you want a PEG tube?” and “Do you want to refuse PEG tube placement?” An orientation question might be, “Is the year 1999? 2019? 2015?” Comprehension can be tested with questions such as “Can a shark fly? Can a hammer pound a nail?”
- Apply the basic principles of determining decisionality as in any other patient (see Fast Fact #55)
- Utilize augmentative communication tools such as alphabet boards or eye-tracking devices when available.
- Permit extra time for fluctuating arousal and fatigue.
- Family members and/or primary caregivers may have insights into communication and subtle signals of distress on the part of the patient. These can be elicited and posted at the bedside.

**Cautions:**

- LIS patients are at risk for being talked about at the bedside as if they are dead or in a coma by hospital staff (1). Always assume the patient can hear you.
- Assess decisionality and the patient’s care preferences as soon as possible. If an advance directive is available, review for care preferences that may guide decision making if the patient is deemed non-decisional.
- Be aware that surrogates and clinicians may wrongly assume that quality of life is poor and not worth living and thereby advocate for the early withdrawal of life sustaining
therapies (7, 14-16).

• Clinicians should be aware of their own values and personal responses to a LIS patient, and be careful not to assume they are shared by the patient. Efforts should be made to ensure alignment of goals of care between the patient and surrogate throughout the disease trajectory.

• Clinicians should be transparent with patients/surrogates about what the future may look like and discuss a full range of care options such as life prolongation (PEG tube, tracheostomy, nursing home placement) vs a comfort plan of care.

References:

Author Affiliations: Hennepin County Medical Center; Medical College of Wisconsin

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**Background** Glioblastoma (previously known as glioblastoma multiforme or GBM) is the most common incurable primary brain malignancy in adults. This Fast Fact addresses symptom management, prognosis, and medical decision-making in glioblastoma patients.

**Prognosis** Median age at diagnosis is 64; median survival from diagnosis is 15 months. Extended survival may be seen with favorable genetic mutations (e.g. MGMT and IDH), age < 50 years, and a fully independent postoperative functional status (1,2). Two-year survival after diagnosis is 27%; 5-year survival is 10% (3). Its illness trajectory is associated with a rapid rate of cognitive decline preceding the steep functional decline indicative of the usual dying phase of cancer.
Symptom Presentation and Management  Tumor size, tumor location, and cancer treatment side effects are the most common determinants of how symptoms manifest.

• **Focal deficits.** Hemiparesis, aphasia, paresthesias, dysarthria, dysphagia, visual changes, and neglect are common. Management includes physical, occupational and speech therapy, psychosocial support, and corticosteroids (e.g. dexamethasone 2-4 mg daily or twice a day) (2,4).

• **Cognitive changes.** Depression and anxiety are common; hence many glioblastoma patients are initiated on antidepressants. Memory loss, personality changes, fatigue, agitation, and delirium are also common. Management options include psychotropics, assessment of decision-making capacity, and off-label use of psychostimulants for depression, apathy, or drowsiness (see Fast Fact #173) (5,6). While corticosteroids can help with vasogenic-related symptoms such as headaches or nausea, they can exacerbate behavioral changes via psychiatric side effects (see Fast Fact # 323).

• **Seizures.** Even though seizures are a common presenting sign of glioblastoma, prophylactic antiepileptic drugs (AEDs) are not recommended. Instead, active seizures are treated with benzodiazepines, and AEDs are initiated thereafter. Consultation with a clinical pharmacist or a neurologist is advised to minimize drug interactions and identify appropriate routes of administration for AEDs. At the end-of-life, oral administration may not be feasible. See Fast Fact #229 for more information on rectal, sublingual, subcutaneous, or intravenous routes (2,11,2).

• **Headache, nausea, and fatigue.** These symptoms can result from the effects of chemotherapy or radiation therapy or from a disease-related increase in the intracranial pressure (ICP). Beyond conventional treatments, corticosteroids may help if vasogenic edema is present; radiation therapy and ventriculoperitoneal shunts can help manage increased-ICP-related symptoms (2,4,7).

Cancer-Directed Therapy  For newly diagnosed patients with a preserved performance status, standard treatment involves maximal safe surgical resection followed by concomitant temozolomide (TMZ) chemotherapy and 6 weeks of radiotherapy (2,3). Essentially all patients will experience disease recurrence for which no standard treatment exists (1,2). Instead, various strategies are individualized.

• Any combination of repeat surgical resection, re-irradiation, and chemotherapy (TMZ or other) (8).

• Bevacizumab: A monoclonal antibody that can yield radiographic improvement of the tumor and thereby reduce functional deficits and the need for corticosteroids. Although it may improve quality of life, current data shows it does not prolong survival and can precipitate strokes and cardiovascular events via side effects including bleeding and clotting (9,10).

• Tumor Treating Fields (TTF): A headpiece that is worn 24 hours per day and applies low-intensity alternating electric fields to disrupt cell division of cancer cells. TTF is a new treatment with relatively limited evidence to suggest it can prolong survival when combined with TMZ for newly diagnosed and recurrent glioblastoma (12). The cosmetic appearance and burden of wearing a device all day, is a considerable trade-off that may impact quality of life.

• Hospice is an appropriate care plan for any patient with recurrent glioblastoma, particularly those with comfort-based goals of care and/or a poor performance status.

Medical-Decision Making  Deciding when to stop life prolonging treatment can be challenging in glioblastoma. As with any other type of cancer or life-limiting illness, this should be a shared-decision between patients and clinicians based on performance status, treatment expectations, and quality of life preferences. Below are additional medical-decision-making elements worth highlighting for glioblastoma:

• In most cases, patients will not be able to enroll in hospice if they are continuing anti-cancer treatments like radiation or chemotherapy. There is some controversy around abruptly stopping bevacizumab for fear of rebound vasogenic edema contributing to a faster decline. Despite these concerns, bevacizumab is associated with its own side effects (loss of appetite, nausea, constipation, bleeding, clotting) and burdens. Hence, most experts recommend its discontinuation in the event of tumor progression so that patients can maximize their access to hospice support (11).
Close collaboration with treating oncologists is crucial when interpreting tumor status on radiologic imaging, as microscopic progression may make radiologic interpretation challenging (11).

Given the high risk for early cognitive changes, early advance care planning (ACP), including identification of a surrogate decision-maker, is critical with glioblastoma. ACP discussions should begin at diagnosis, and be revisited at oncologic touch points such as completion of first-line treatment, disease recurrence, hospitalizations, and any decline in functional status (6,13,14).

Disease-related behavioral and/or cognitive changes can lead to caregiver burden and make home hospice dispositions challenging. This can create caregiver guilt, especially for patients who expressed a wish to die at home. Clinicians may need to support surrogates by highlighting the patient care needs and the safety benefits of a more supervised care setting.

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Author Affiliations: University of Minnesota Medical School, Minneapolis, MN (RP, EN, SM), Hennepin County Medical Center, Minneapolis, MN (SM).

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**FAST FACTS AND CONCEPTS #361**

PARKINSON’S DISEASE: PART 1 DISEASE TRAJECTORY

Danny Estupinan MD¹; Alva Roche’-Green MD²; Maisha Robinson MD²; Robert P. Shannon MD²

This **Fast Fact** will address the natural history and illness trajectory of Parkinson’s Disease (PD). See **Fast Fact #362** for information on palliation strategies of non-motor symptoms associated with PD.

**Illness Background**  PD is a degenerative central nervous system disorder which disproportionately affects the motor system leading to asymmetric muscle rigidity, bradykinesia, and a resting “pill-rolling” tremor (1). It involves a section of the midbrain called the substantia nigra which leads to a depletion of the neurotransmitter dopamine. Dopamine derivatives (levodopa) and agonists are pharmacologic mainstays for the motor symptoms. The illness trajectory varies by Parkinsonian syndrome. Typically PD has a longer prognosis and progresses slower with less nonmotor symptoms and cognitive impairment early in the disease course compared with atypical Parkinsonism which includes a variety of disorders such as Multisystems Atrophy, Corticobasal Degeneration, and Lewy Body Dementia (2).

**Impact of Illness**  While the progression of functional impairment and disability is quite variable, typically PD progresses over many years, not months. In general, patients begin to have levodopa related treatment complications such as dyskinesia (irregular, jerky movements), psychosis,
and dystonia, within 5 years of diagnosis (3-5). Within 12 years of disease onset, most PD patients have issues with falls, gait disturbance, and balance; within 15-20 years of disease onset, issues with either hallucinations or dementia are common (6). The symptom burden from the motor and non-motor symptoms of PD has been shown to be comparable to metastatic cancer (3,4). The slow erosion of functional capacity and the increased dependence on caregivers leads many PD patients to suffer from a diminished sense of personhood and identity (1). This can lead to significant caregiver distress, financial hardship, and consequently a high utilization of nursing home placement in the last years of life (7). These factors plus a variable and long prognosis can lead many PD patients to make requests for a hastened death to their clinicians and caregivers. See Fast Facts 156 and 159. Involvement of an interdisciplinary team is often necessary to address the unmet spiritual, psychological, and social needs of PD patients (3,4).

**Prognosis** With the improvement in disease-modifying therapies such as deep brain stimulators, life expectancy is only modestly decreased compared to aged-matched controls and is roughly 6 to 22 years at disease onset (8,9). The long illness prodrome should allow for early advance care planning and appropriate palliative care interventions prior to late complications. Late-term PD complications are listed below. When encountered, they should prompt clinicians to help patients and families prepare for a peaceful death and should also prompt clinicians to consider hospice care (10).

- **Dementia**: approximately 40% of PD patients develop dementia (11). It is a significant risk factor for nursing home placement and one-year mortality (7,9).
- **Delirium**: Visual hallucinations and delirium are common in the last years of life. They are also a predictor of nursing home admission (7).
- **Extrapyramidal symptoms**: the presence of muscle rigidity and dyskinesia despite best medical management is associated with an elevated one-year mortality (9).
- **Dysphagia**: this may occur from progression of motor symptoms or dementia. Recurrent hospitalizations and/or aspiration events are common. There is no evidence that feeding tubes improve survival at this stage nor quality of life. Honey-thickened liquids and encouraging a “chin-down” feeding posture are more effective strategies for managing dysphagia in advanced PD (12).

**Hospice Considerations** There are no specific hospice criteria for PD nor are there reliable indicators to help clinicians predict a < 6 month survival. Medicare claims data suggest that only 54% of PD patients utilize hospice prior to death; although, nursing home residents and patients seen by an outpatient neurologist may be more likely to utilize hospice care (13). To better identify hospice-eligible PD patients, clinicians should look for a pattern of recurring hospitalizations, dysphagia, and/or progressive dementia. See Fast Facts #125 and #150 for hospice admission guidelines for general neurologic illnesses.

**End of Life Pharmacologic Considerations** There are no current PD specific guidelines regarding end-of-life care medication management, however, many experts recommend continuing levo-dopa derivatives and agonists as long as the patient is able to swallow pills. Abrupt discontinuation of these medications can be associated with intense and uncomfortable muscle rigidity. Although levo-dopa associated symptoms like dyskinesia may fluctuate dramatically throughout the day and be difficult to observe, patients often prefer these symptoms to the underlying muscle rigidity associated with PD.

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Authors’ Affiliations: ¹Cleveland Clinic, Cleveland OH; ²Mayo Clinic College of Medicine, Rochester, MN.

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PARKINSON’S DISEASE: PART 2 PALLIATION FOR COMMON NON-MOTOR SYMPTOMS
Danny Estupinan MD1; Alva Roche-Green MD2; Maisha Robinson MD2; Robert P. Shannon MD2

Background Nonmotor symptoms likely affect overall quality of life in Parkinson Disease (PD) as much as motor symptoms (1). Fast Fact #361 discussed the natural trajectory of PD. This Fast Fact will focus on management strategies of common non-motor symptoms in PD patients.

Pain Nearly 85% of PD patients report pain (2). Musculoskeletal pain from limitations in mobility is the most commonly reported pain type. While there are no comparative analgesic studies for PD, NSAIDs, acetaminophen, physical rehabilitation, and low dose opioids are commonly utilized analgesic strategies. Dystonia is a prolonged involuntary muscle contraction which often leads to foot cramping, muscle spasms, and a sensation of muscles twisting. In addition to the analgesic strategies listed above, skeletal muscle relaxants and botulinum toxin injections may be warranted (see Fast Facts #340 & 324). Neuropathic pain, which is often described as a shooting pain or a sensitivity to light touch within a dermatome, is a less common pain reported in PD. Gabapentin, pregabalin, duloxetine, venlafaxine, and/or interventional strategies (e.g. spinal cord stimulator or a nerve block) are preferred over tricyclic antidepressants (TCAs) due to the risk for delirium and falls in PD patients.

Neuropsychiatric Symptoms As many as 40% of patients with advanced PD experience neuro-psychiatric symptoms, most commonly visual hallucinations (3). The assessment and treatment is similar to delirium in general (see Fast Fact #1) with a few special considerations (3-10):
Several PD medications are associated with psychosis: amantadine; monoamine oxidase type B (MAOB) inhibitors, catechol-O-methyl transferase inhibitors (e.g. entacapone); and dopamine agonists (e.g. pramipexole). Before initiating new pharmacotherapies, reduce or discontinue offending medications as appropriate. Pharmacy and neurology input may be necessary.

Common neuroleptics used to treat delirium such as haloperidol, risperidone, and olanzapine should be avoided as they may worsen motor symptoms by blocking dopamine and raise mortality risk.

Quetiapine is the preferred pharmacologic treatment in PD because it seems to have the least effect on motor symptoms. Because PD patients may be more prone to somnolence, many experts recommend initiating at a low dose such as 12.5 mg to 25 mg at bedtime or BID.

Clozapine has the most compelling evidence of all anti-psychotics for treating PD-related psychosis; however, its use is reserved to psychiatrists due to its association with agranulocytosis.

Pimavanserin is a FDA approved oral medication for PD-related hallucinations at a usual dose of 34 mg a day. Although randomized, placebo controlled trials show efficacy with little worsening of motor symptoms or other adverse effects (12-14), its use is limited by its cost which is >$80/day.

Daytime Sleepiness Excessive daytime somnolence is common in PD. Beyond best nocturnal sleep hygiene practices (see Fast Facts 101, 104 & 105), expert considerations include (15-17):

- AM intake of caffeine or a prescribed psychostimulant such as methylphenidate 5-10 mg twice a day or modafinil 100-200 mg per day.
- Screen for comorbid sleep disorders such as rapid eye movement behavior sleep disorder, restless leg syndrome, and obstructive sleep apnea as roughly 85% of PD patients have a sleep disorder. Refer to a sleep specialist when appropriate.
- Screen for sudden bouts of excessive daytime drowsiness or sleep (often referred as a “sleep attacks”) which can be common and hazardous in PD. If present, patients should avoid driving.

Depression There is no clear consensus regarding the best antidepressant in PD. Duloxetine, venlafaxine, bupropion, sertraline, and escitalopram are preferred by many experts over mirtazapine and TCAs which have higher anticholinergic activity. Clinicians should be cautious when combining any antidepressants with MAOB inhibitors to avoid serotonin syndrome (10,18,19).

Dementia The only FDA-approved treatment for PD-related dementia is rivastigmine. It has been associated with moderate improvements in cognition and anxiety in mild to moderate dementia. Its cholinergic properties can lead to significant rates of nausea, vomiting, and worsening tremor (10,20).

Orthostatic Hypotension Nonpharmacologic interventions like increased fluid/salt intake and compression stockings are first-line treatments as are a reduction of antihypertensive medications if medically appropriate. Fludrocortisone or midodrine can be added in refractory cases (5).

Sialorrhea Sialorrhea and drooling are common in PD because of the reduced oromotor control and autonomic dysfunction. Chewing gum or hard candy may encourage swallowing and reduce drooling in mild cases (21). For moderate to severe symptoms, the use of glycopyrrolate 1-2 mg by mouth three times a day; sublingual atropine 1% ophthalmic solution 1-2 drops once to twice a day; ipratropium spray, or botulinum toxin injections into salivary glands has been described (20-22)

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