Palliative care prioritizes symptom management and quality of life throughout the course of serious illness. Regardless of whether care is inpatient or outpatient, primary or subspecialty, a solid understanding of the basics of effective communication, symptom management, and end-of-life care is crucial. This article reviews these essentials and provides an overview of current evidence to support patient-centered palliative care.

CME Objective: To review current evidence for managing common symptoms, communication, psychosocial, ethical issues, patient education, and practice improvement of palliative care.

Funding Source: American College of Physicians.

Disclosures: Dr. Swetz, ACP Contributing Author, reports personal fees from Sage Publishing outside the submitted work. Dr. Kamal, ACP Contributing Author, has nothing to disclose. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M17-2629.

With the assistance of additional physician writers, the editors of Annals of Internal Medicine develop In the Clinic using MKSAP and other resources of the American College of Physicians.

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Palliative care (PC) focuses on improving quality of life and alleviating symptoms in patients with serious illness—that is, conditions that are chronic, incurable, and associated with high morbidity. However, it does not necessarily denote absence of treatment options or limited prognosis (e.g., near the end of life [EOL]). PC addresses the physical, mental, spiritual, and social distress caused by serious illness to maintain hope, ensure dignity, and respect the autonomy of patients and families.

PC consists of the following 3 components: primary PC, which is basic attention to quality of life provided by all clinicians; specialist PC, which is used throughout the trajectory of serious illness (ideally from the time of diagnosis); and hospice care, which is for patients approaching EOL (i.e., estimated life expectancy <6 months). All clinicians (primary care and specialty providers) can deliver primary PC by providing foundational care (e.g., basic pain management, advance care planning) that meets most patients’ needs. Complex conditions occasionally require an increased supportive infrastructure for the patient (e.g., caregivers, social services). Specialist PC can provide an extra layer of support for referring clinicians, patients, and caregivers.

With most commercial insurance or federal health coverage (Medicare/Medicaid), patients may receive hospice care if they forgo life-prolonging treatments and meet a Medicare-determined life expectancy of 6 months or less if the disease runs its normal course.

Specialist PC assesses and treats patients anywhere along the trajectory of serious disease (Table 1). Hospice and specialist PC are delivered via interdisciplinary teams, including chaplains, social workers, and pharmacists, to address patients’ and caregivers’ needs. Although hospice care is delivered in the patient’s home or long-term care facilities, most specialist PC is provided in hospitals or outpatient clinics.

Payment also differs between the 2 types of care. As a recognized board-certified subspecialty, specialist PC consultations are usually reimbursed similarly to other subspecialties through a fee-for-service model. In contrast, hospice uses a geographically pro-rated per diem payment system.

Both nonprofit and for-profit hospices receive a set daily amount (about $160 for routine home care) to provide all treatment, equipment, and services the patient requires for comfort and quality of life, with a slightly higher rate for the first 60 days. The per diem rate also covers all disease-modifying treatments that assist with symptom control, including antibiotics, transfusions, radiation therapy for pain, and inotropes. Thus, cost can be prohibitive with hospice care.

**Which patients should be considered for specialist PC?**

The criteria for specialist PC referrals are evolving as organizations update guidelines for patients with cancer (2), heart disease and stroke (3), and respiratory disease (4). Table 2 lists criteria for identifying patients who might benefit from specialist PC (5). Clinicians should periodically review a patient’s unmet needs regarding symptom management; independence and functional abilities; advance care planning; psychosocial, spiritual,
and existential issues; caregiver and family support; and prognostic awareness to determine whether specialist PC referral is indicated.

**What treatments can be given to patients receiving specialist PC?**

In general, there are no restrictions for patients receiving specialist PC regarding curative or life-prolonging treatments (e.g., supplemental oxygen for hypoxia). Disease-modifying treatments sometimes cause symptoms or burdens that negatively affect quality of life (e.g., chemotherapy or hemodialysis). If they help patients achieve their goals, hemodialysis, chemotherapy, radiation therapy, blood transfusions, surgical procedures, and participation in clinical trials may be appropriate for patients receiving specialist PC.

**What tools are available to assist in prognosticating or estimating life expectancy?**

Prognostication is difficult for many diseases, and validated scales have been developed to assist in this area. Functional status estimates with the Karnofsky Performance Score or Eastern Cooperative Oncology Group Performance Status may help prognostication in advanced cancer. However, although function correlates with survival in many chronic diseases (heart failure, chronic obstructive pulmonary disease, dementia), disease-specific markers of function are more appropriate (6).

Other tools, such as the Palliative Performance Scale, help estimate whether a patient with cancer has “days or weeks” versus “weeks or months” to live. Disease-specific prognostic tools, such as the Mitchell Mortality Index for dementia, are also available to assist with just-in-time decision making (Appendix Table, available at Annals.org) (7). Nevertheless, clinicians must understand the limitations of prognostic tools; that is, they provide estimates based on population-based data but may not incorporate all clinically relevant factors for an individual patient.

**Table 1. Comparison of Palliative Care and Hospice**

<table>
<thead>
<tr>
<th>Palliative Care</th>
<th>Hospice</th>
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</thead>
<tbody>
<tr>
<td>Both palliative care and hospice seek to maximize quality of life through meticulous symptom management, clarification of goals of care, and advance care planning</td>
<td>Can be accessed during terminal phase of disease (life expectancy of less than 6 months)</td>
</tr>
<tr>
<td>Can be accessed at any point during life-limiting illness, from diagnosis to death</td>
<td>Must forgo life-prolonging treatments</td>
</tr>
<tr>
<td>Can occur concurrently with life-prolonging or curative treatments</td>
<td>Goal of avoiding further hospitalization, unless there is no alternative to adequately manage symptoms</td>
</tr>
<tr>
<td>No limitation on treatment or hospitalization</td>
<td></td>
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</table>

**CLINICAL BOTTOM LINE**

Palliative Care vs. Hospice... PC and hospice are interrelated but distinct types of care. Specialist PC focuses on symptom management, quality of life, and delineating goals of care in patients with serious illness, whether the goal is cure, prolonging life, or maximizing function and quality of life. Hospice is a special type of PC, reserved for patients in the last 6 months of life if their disease runs its anticipated course.
Managing Common Symptoms

How should pain be evaluated and managed?

The history and physical examination are crucial for appropriate pain management. A focused history of opioid and sedative-hypnotic use, a social history that includes a personal and family history of substance abuse, and laboratory test results and x-rays can guide management. The cause of pain may vary and include myofascial, neuropathic, osseous, or visceral sources. Even for seriously ill patients, a careful history is important to determine opioid misuse or diversion, and use of nonpharmacologic treatments (e.g., mindfulness, physical therapy, transcutaneous nerve stimulation) should be considered for all patients as appropriate. Nonopioid analgesics, including acetaminophen or nonsteroidal anti-inflammatory drugs, are used for mild pain (score of 1-3 on a pain intensity scale of 0-10). Moderate pain (pain score of 4-6) is commonly treated with a combination of opioids and nonopioid analgesics. If these agents are combined in a single pill (such as oxycodone and acetaminophen), clinicians should avoid inadvertently overdosing the nonopioid (acetaminophen) component if needed for the opioid increases. Similarly, clinicians should caution patients about simultaneous use of over-the-counter acetaminophen (or other nonopioid component) formulations to avoid unintentional overdose. The daily cumulative dose of acetaminophen (<4 g) is the limiting factor in combination preparations, particularly for patients with liver disease—the dose for these patients should not exceed 2 g/day.

Severe pain (pain score of 7-10) is treated predominantly with opioids. Adjunct therapies, such as nonsteroidal anti-inflammatory drugs, corticosteroids, antiepileptics, and antidepressants, can be beneficial in certain pain syndromes (e.g., neuropathic pain) and can be added if appropriate. Commonly used noninjected opioids are detailed in Table 3 (see the Box for morphine equivalents).

Oral opioid administration is preferred because it is convenient, is inexpensive, and produces stable blood levels. Intramuscular injections are not recommended because of associated pain, unreliable absorption, and longer interval to peak drug concentrations. If parenteral administration

Table 2. Suggested Criteria for Consideration of Specialist Palliative Care Assessment at Time of Hospital Admission*

<table>
<thead>
<tr>
<th>Criteria for Consideration of Palliative Care Consultation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Surprise</td>
<td>You would not be surprised if the patient died within 12 months</td>
</tr>
<tr>
<td>Frequent admissions</td>
<td>Repeated admission for same condition within several months</td>
</tr>
<tr>
<td>Complex symptoms</td>
<td>Admission for difficult symptom or psychological need</td>
</tr>
<tr>
<td>Complex care requirement</td>
<td>Functional dependence or complex home support needed</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>Decline in functional status, weight, or ability to care for self</td>
</tr>
<tr>
<td>Advance care planning needs</td>
<td>No history of completing an advance care planning document or having a discussion</td>
</tr>
<tr>
<td>Limited social support</td>
<td>Family stress, chronic mental illness, lack of caregivers</td>
</tr>
<tr>
<td>Limited prognosis</td>
<td>Metastatic or locally advanced cancer, hip fracture with cognitive impairment, out-of-hospital cardiac arrest. Any one of these criteria may be sufficient to warrant consultation; multiple criteria need not be present</td>
</tr>
</tbody>
</table>

* Data from reference 5.

20. Wood GI, Shega JW, Lynch B, Von Roenn JH. Management of intractable nausea and vomiting in patients at the end of life. “I was feeling nauseous all of the time...nothing was working”. JAMA. 2007;298:1796-207. [PMID: 17946654]
is needed, intravenous or subcutaneous injection is preferred. Intravenous administration has the most rapid onset but the shortest duration of action. Transdermal opioid patches are useful for chronic pain management in opioid-tolerant patients. Short-acting opioids alone are often insufficient to manage chronic or neoplasm-related pain. Long-acting opioids, such as extended-release morphine, extended-release oxycodone, and transdermal fentanyl patches, often ensure basal pain relief throughout the day. However, shorter-acting opioids should be utilized as needed to relieve breakthrough pain.

To avoid overmedication, the dose of the long-acting basal pain medication should be determined by calculating the total short-acting opioid dose in a 24-hour period (based on morphine equivalents); and the long-acting drug should be dosed at 50%–75% of the 24-hour total (see the Box: Calculating Short- and Long-Acting Opioid Doses). The dose of the long-acting opioid may be increased every 3–4 days if medication for breakthrough pain is frequently required. When calculating a breakthrough opioid dose, clinicians should consider the patient’s total opioid dose in a 24-hour period and prescribe 10%–15% of that daily requirement as an immediate-release medication on an as-needed basis. Because long-acting opioids may take 1–3 days to take full effect, clinicians should monitor the patient’s mental status closely. Ideally, to facilitate dose titration, the same agents should be used for both breakthrough and basal pain.

Several opioids should be avoided or used cautiously under certain circumstances. Codeine, tramadol, and morphine should be used with caution in patients with renal insufficiency. Meperid-
Morphine Equivalents
The "1:2:3" rule
The following drugs are equivalent:
- 1 mg IV or SQ morphine
- 2 mg PO oxycodone
- 3 mg PO morphine
The "30:20:10:7.5:1.5" rule is a corollary of the "1:2:3 rule" but includes:
- 30 mg PO morphine
- 20 mg PO oxycodone
- 10 mg IV or SQ morphine
- 7.5 mg PO hydromorphone
- 1.5 mg IV or SQ hydromorphone
Rather than memorizing individual drug potencies, using these ratios allows clinicians to calculate equivalent doses using stoichiometry. For example, if a patient is receiving 30 mg of ER oxycodone every 12 hours and 10 mg of IR morphine every 4 hours, 4 times a day, how many OMEs is this?
- Oxycodone 30 mg / 2 doses = 60 mg × (30 mg PO morphine / 20 mg PO oxycodone) = 90 OMEs
- Morphine 10 mg / 4 doses = 40 OMEs
The patient is receiving 130 OMEs.
ER = extended release; IR = immediate-release; IV = intravenous; OME = oral morphine equivalent; PO = oral; SQ = subcutaneous.

Dine has variable oral bioavailability, and neurotoxic metabolites accumulate with prolonged use at high doses or in patients with renal failure, reducing the seizure threshold and causing neurotoxicity. Buprenorphine, a mixed opioid agonist-antagonist, may be used for analgesia in patients at risk for opioid misuse or diversion, whether administered alone or combined with naloxone. Methadone is difficult to titrate, has an onset of action far shorter than its half-life, and poses risk for inadvertent overdose; thus, it should be prescribed only by providers who are experienced with its use.

Opioid misuse, diversion, and addiction have led to heightened scrutiny of prescription practices. Guidelines from the Centers for Disease Control and Prevention urge prescribers to screen patients for aberrant use behaviors (8). Of note, persons with serious illness can display these behaviors. Regardless of the nature of the illness or its effect on prognosis, clinicians are ultimately responsible for safe opioid prescribing and may need to consider abuse-deterrent preparations, limited-quantity prescriptions with frequent pill counts, routine confirmatory urine drug testing, or use of agents with low risk for aberrant use.

How should opioid side effects be managed?
Opioids have predictable side effects, including nausea, constipation, pruritus, and sedation. Sedation usually dissipates over a 1- to 2-day period as tolerance develops and can often be alleviated with dose reduction or rotation to another opioid. Clinicians should prescribe a prophylactic stimulant (e.g., senna, bisacodyl) or osmotic laxatives for patients using opioids daily to treat constipation and adjust the dosage on the basis of the patient's bowel habits. Stool softeners (docusate) alone are ineffective (9). Osmotic laxatives, such as lactulose and polyethylene glycol, should be used if the prophylactic regimen does not produce bowel movements at least every other day. Polyethylene glycol is inexpensive, well-tolerated, and effective; lactulose is highly effective but less well-tolerated.

In most cases, opioid-related pruritus and urticaria result from histamine release rather than a true drug allergy. Symptoms may be alleviated by changing the opioid or adding a non sedating antihistamine. Opioid-induced nausea typically abates in 3-5 days. It is best treated with anti dopaminergic antiemetics, such as metoclopramide or prochlorperazine; ondansetron may be useful in refractory cases (discussed further below). Some patients have less nausea if the opioid blood level remains steady rather than peaking intermittently. Giving the immediate-release preparation regularly or at shorter intervals may stabilize blood levels and reduce nausea and vomiting. Changing to extended release or the transdermal route also produces more constant opioid blood levels.

What measures are available for specific pain syndromes?
Visceral pain is usually dull, colicky, and poorly localized, and the discomfort may be associated with autonomic symptoms, such as nausea or diaphoresis. Visceral pain is typically caused by distention, torsion, or inflammation and most frequently occurs in conjunction with pancreatic, hepatic, renal, or intestinal cancer. It may be caused by severe constipation due to medications, immobility, and underlying disease. Anticholinergic agents can be used adjunctively for colic but are associated with xerostomia, constipation, and sedation.
Palliative surgery can be useful to relieve visceral pain caused by bowel obstruction. Sympathetic blockade of the celiac plexus or splanchnic nerves may be useful for patients with pain that is refractory to opioids.

Neuropathic pain is described as constant or episodic; is usually characterized as burning, tingling, stabbing, or shooting; and often is caused by direct damage to the central or peripheral nervous system. Patients with cancer may experience such pain from nerve root compression or neural encroachment; it also may be seen in patients with HIV or diabetes or in chemotherapy recipients. In cases of nerve compression, corticosteroids are effective in reducing tumor swelling or lysing certain tumors, thus reducing pain from compression and inflammation while increasing appetite and energy levels. Corticosteroids are the mainstay of managing spinal cord compression, as well as headache and nausea from intracranial swelling. As an adjunct, lower doses of dexamethasone (2-4 mg twice daily) are usually sufficient; spinal cord compression requires higher doses.

Peripheral neuropathy or radiculopathy is common in patients with or without cancer. Several therapies are effective for neuropathic pain, including gabapentin and pregabalin (10). Dose escalation should be based on age, renal function, or previous titration tolerance. Duloxetine may be useful in patients with neuropathic pain and depression; venlafaxine also has been used on an off-label basis in the United States (10).

Musculoskeletal manifestations may occur, including referred pain (e.g., shoulder pain from a visceral tumor) or gout in patients with cancer or those receiving chemotherapy. For bone metastases, adjunctive therapies, such as radiation therapy, corticosteroids, bisphosphonates, or interventional procedures (e.g., cryoablation or radiofrequency ablation), may be highly effective.

What treatments are most effective for relieving dyspnea?
Dyspnea is commonly associated with cardiac and/or pulmonary processes. However, it can also be related to debility, wasting syndromes, neurodegenerative disorders, anxiety and depression, or chronic disease. Potentially reversible causes, including effusion, pneumonia, anemia, and ascites, should be treated accordingly. Dyspnea is subjective—the patient’s report of it (rather than vital signs) should prompt treatment. Severity correlates poorly with respiratory rate, arterial blood gas levels, oxyhemoglobin saturation, or accessory muscle use.

Evidence supports nonpharmacologic treatment interventions including interventions such as radiation therapy, corticosteroids, bisphosphonates, or interventional procedures (e.g., cryoablation or radiofrequency ablation), may be highly effective.

Calculating Short- and Long-Acting Opioid Doses
1. Sum all doses of opioids the patient is taking in 24 hours; consider converting all doses to OMEs for ease and a common point of reference.
2. If the short-acting agent differs from the long-acting agent, the calculated dose of the short-acting agent in OMEs should be reduced by 50% because of incomplete cross-tolerance.
3. If the long- and short-acting agents are the same, no adjustment for incomplete cross-tolerance is required.
4. Provide a dose for the breakthrough pain between 10%-15% of the combined total daily OME dose; this may be given as a short-acting opioid every 1-2 hours. No reduction in this calculation is required for incomplete cross-tolerance.

For example, a patient receiving 20 mg of ER oxycodone PO every 12 hours continues to require 4 mg of hydromorphone PO every 4 hours as needed for breakthrough pain (a total of 4 doses a day). How do we calculate the new long-acting dose for the breakthrough pain dose?

Step 1: Calculate OMEs for each drug:
- Long-acting agent: (2 × 20 mg oxycodone per day) × (30 mg PO morphine/20 mg PO oxycodone) = 60 OMEs
- Short-acting agent: (4 × 4 mg hydromorphone per day) × (30 mg PO morphine/7.5 mg PO hydromorphone) = 64 OMEs

Steps 2 and 3: Here, the short- and long-acting agents are different drugs, so the short-acting daily dose in OMEs should be reduced by 50% (64 × 0.5 = 32 OMEs). Add the short- and long-acting daily doses of OMEs (60 + 32 = 92 OMEs). Calculate the new total daily dose of the long-acting agent to be given: 92 OMEs × (20 mg oxycodone/30 mg PO morphine) = 61 mg oxycodone. This may be given as 30 mg ER oxycodone every 12 hours.

Step 4: Calculate the new breakthrough dose: use total current OMEs from step 1 (no adjustment): 60 OMEs + 64 OMEs = 124 OMEs. Use 10%-15% for breakthrough: (about 12-18 OMEs) × (20 mg oxycodone/30 mg PO morphine) = 8-12 mg PO immediate-release oxycodone as needed every 1-2 hours for breakthrough pain in seriously ill patients, less frequently as pain is controlled. This may be given orally as 10-15 mg tablets of immediate-release oxycodone.

ER = extended release; OME = oral morphine equivalent; PO = oral.
Benzodiazepines may be beneficial for some patients whose dyspnea is exacerbated by anxiety. Evidence supports low-dose opioids as safe for treatment of dyspnea; however, concurrent use of benzodiazepines and opioids is more often associated with adverse outcomes. Thus, the patient’s goals of care and prognosis need to be considered. Supplemental oxygen is useful in relieving dyspnea in terminally ill patients with hypoxemia but is no better than medical air in patients without hypoxemia.

A double-blind, randomized, placebo-controlled study of 239 patients with refractory dyspnea and baseline PaO2 greater than 55 mm Hg compared 7 days of oxygen or 2 L of room air per minute via nasal cannula. No difference in dyspnea relief was observed between the 2 groups.

**How should clinicians treat nausea?**

Nausea may result from several processes, and understanding its origin helps guide effective therapy. Most recommendations come from small studies or expert opinion based on putative neurotransmitters (20, 21). Opioid-induced nausea may respond best to dopaminergic blockade with either metoclopramide or prochlorperazine. Chemotherapy-induced nausea is more often responsive to serotonin antagonists (e.g., ondansetron) or olanzapine, which has a wide range of activity (21, 22). Corticosteroids are additive to other antiemetics in chemotherapy regimens (20, 21) and for primary treatment of nausea due to increased intracranial pressure. For incomplete mechanical bowel obstruction, the standard of care is dexamethasone and metoclopramide; findings on the efficacy of octreotide have varied (23). Higher-grade obstructions may require venting gastrostomy tubes in addition to octreotide. Reduced gastrointestinal motility may best be relieved by metoclopramide, whereas radiation-associated nausea responds best to serotonin antagonists. Anticholinergic antihistamines (e.g., scopolamine, meclizine) are effective for motion-associated nausea and vomiting or for posterior fossa lesions (e.g., cerebellar stroke or metastases) (20). If nausea or vomiting is persistent, adding an agent from a different class that works synergistically, rather than switching to one with a similar mechanism of action, is recommended.

**How should delirium and agitation be managed in terminally ill patients approaching EOL?**

Delirium is common in terminally ill patients and is associated with worse outcomes (survival and morbidity) in elderly patients (24); those with advanced cancer (25); and patients with concurrent depression—even those who are not dying (26, 27).

A meta-analysis of 42 high-quality observational studies of elderly patients with delirium evaluated “poor outcomes,” defined as mortality, institutionalization, or dementia. The authors concluded that delirium was associated with a poor outcome independent of other factors, such as age, sex, or comorbid conditions.

Delirium, an acute fluctuation in mental status, presents with inattention and agitation or hypoactivity and must be distinguished from the chronic cognitive changes of dementia. Whether the patient is agitated or hypoactive, identification and appropriate treatment of delirium are crucial to ensure comfort and safety and to relieve loved ones’ distress. Potentially reversible causes of delirium (e.g., side effects of such psychoactive drugs as benzodiazepines, untreated pain, urinary obstruction or bowel impaction, sensory deprivation from missing eyeglasses or earwax) should be approached nonpharmacologically first. Low-dose haloperidol is commonly used, although some
Indicators of Depression in Seriously Ill Patients

**Psychological symptoms**
- Dysphoria
- Depressed mood
- Sadness
- Tearfulness
- Anhedonia
- Hopelessness
- Helplessness
- Social withdrawal
- Guilt
- Suicidal ideation

**Other indicators**
- Intractable pain or other symptoms
- Somatic preoccupation
- Poor adherence to or refusal of treatment
- Treatment with corticosteroids, interferon, or other agents

**Historical indicators**
- Personal or family history of psychiatric illness
- Pancreatic cancer

Data from reference 36.

studies suggest neuroleptics do not provide additional benefit over nonpharmacologic measures, such as reorientation. Agitation and restlessness that are refractory to haloperidol typically respond to the more sedating agents.

Patients at EOL may experience a multifactorial, terminal delirium. Benzodiazepines are typically avoided for patients not at EOL, primarily because of greater incidence of paradoxical reactions, including worsened delirium (28). However, recent evidence suggests that adding benzodiazepines to neuroleptics for hospitalized patients with advanced cancer and agitated delirium may be beneficial (29, 30).

Patients approaching EOL may become agitated for various reasons, including delirium, pain, anxiety, and dyspnea. The patient should be evaluated for reversible causes (e.g., pain) before the agitation is assumed to be due to delirium. Patients at EOL may be hyperactive or apathetic and withdrawn; moan or grunt; use accessory muscles for breathing; or have tachypnea, tachycardia, or diaphoresis. However, these signs and symptoms are nonspecific, do not always correlate with distress, and warrant further evaluation and appropriate intervention. Irregular breathing patterns (e.g., Cheyne-Stokes respiration, tachypnea after a stroke or in the setting of acidosis) and tracheal secretions (“death rattle”) may be interpreted by loved ones as distress or struggle. The clinician plays a key role in educating family members on normal, expected EOL processes versus what is atypical and may require intervention. Patients in the final 1–2 days of life often receive anticholinergics (preferably glycopyrrolate) to treat noisy breathing. However, the evidence for this practice is equivocal and recent data recommend against routine pharmacologic treatment with agents like atropine drops or scopoline patches (31).

Is depression a normal part of serious illness, and when should it be treated?

Depression may be present in terminally ill patients, and physicians should have a low threshold for assessment and treatment. It can be difficult to differentiate depression from a demoralized or transiently depressed mood lasting a few days to a few weeks, which may be normal in patients facing serious, life-threatening illness. Symptoms persisting for several weeks and meeting diagnostic criteria for depression are neither normal nor expected (see the **Box:** Indicators of Depression in Seriously Ill Patients). Treatment with selective serotonin reuptake inhibitors is usually safe, but drug–drug interactions should be considered, particularly if the patient is also

receiving hormonal agents (e.g., tamoxifen) (32). Psychostimulants (e.g., methylphenidate) are fast-acting and effective in medically ill populations without major contraindications (e.g., unstable tachyarhythmia). Methylphenidate has mixed evidence for depression in serious illness (33, 34), but pooled data suggest benefits for patients with cancer who have opioid-induced sedation and fatigue (35). Mirtazapine at low doses may help treat depression in patients with concomitant insomnia or anorexia. Tricyclic antidepressants, duloxetine, or venlafaxine may be considered for depression with concomitant neuropathic pain; however, prognosis must be considered because treatment requires several weeks to achieve optimal effect (36).

Beyond pharmacotherapy, studies of specialist PC interventions demonstrated improved mood-related quality of life for seriously ill patients with cancer (37–39), with lower symptom burden from depression and posttraumatic stress disorder or anxiety. Although several studies have shown benefits of specialist PC for patients with mood symptoms and psychological distress (38, 40–42), pooled data show unclear benefit (39).

Seriously ill patients with active suicidal ideation, including those requesting hastened death, often have fears of unmanageable symptoms and loss of control. Such requests should prompt an immediate assessment for suicidality by clinicians while eliciting the patients’ concerns about EOL. Referral to a mental health or specialist PC professional should be considered (36).

When and how should providers treat anorexia in serious illness? Reduced appetite and weight loss are common in patients with cancer or advanced illness who are approaching EOL. Because eating and enjoying food are essential components of social interaction, lack of interest in food and poor nutrition are distressing to many families. Patients may feel pressured to eat more, even if it causes discomfort, because caregivers conflate not eating with “giving up.” Patients may feel guilty about the stress their anorexia causes family members. Educating patients and caregivers about the sources of anorexia and cachexia is helpful in relieving guilt and promoting acceptance of altered eating habits. Caregivers should allow the patient to participate in the social aspects of meals, realizing that the patient may enjoy just a bite or two of a favorite food.

If prognosis is uncertain and EOL is not imminent, appetite stimulants may be considered. In cancer-related anorexia, megestrol (400–800 mg orally per day) has been most commonly studied. In a systematic review, megestrol reduced anorexia and promoted weight gain but had no impact on mortality and unclear effects on quality of life (43). Side effects include thromboembolic disease, hyperglycemia, adrenal suppression, and vaginal bleeding. Prokinetic agents, such as metoclopramide (10 mg 4 times daily by mouth at meals and at bedtime), can reduce nausea but do not facilitate weight gain or relieve anorexia. Short-term corticosteroids (e.g., dexamethasone 2–4 mg orally before breakfast and at midday) have reduced nausea and anorexia in patients with advanced cancer in several trials.

A randomized study of 475 patients with cancer-related anorexia and cachexia found that megestrol and dexamethasone had similar appetite enhancement and nonfluid weight gain. Dexamethasone was discontinued more frequently because of steroid toxicity; megestrol...
had a higher rate of venous thromboembolism (5% vs. 1%) (44).

It is widely reported that cannabinoids can improve appetite and sense of well-being. Synthetic cannabinoids, such as nabixim and dronabinol, are indicated for chemotherapy-induced nausea and vomiting; however, evidence supporting their use as appetite stimulants is minimal. With increased legalization of marijuana use in several jurisdictions, clinicians should be aware of the limited and complex evidence underpinning cannabis use and should regularly ask patients whether they use it as an adjunct to prescription medications.

Do artificial nutrition and hydration help patients to live longer or feel better?

Use of enteral and parenteral nutrition in patients approaching EOL is controversial. Benefits (e.g., increasing weight or strength) are most pronounced in patients with good functional status or when nutritional intake is limited in aerodigestive cancer (e.g., esophageal cancer for which the patient is undergoing concurrent radiation and chemotherapy).

Evidence suggests that enteral feeding has no benefit in patients with advanced dementia in terms of survival, quality of life, or decreased risk for aspiration pneumonia. Parenteral nutrition is associated with such risks as line-associated infection, electrolyte imbalance, and fluid overload. No current evidence has demonstrated that enteral or parenteral nutrition prolongs life or improves quality of life for patients in the final weeks of life, and some evidence suggests harm. Discussing a patient’s nutritional preferences before extreme weight loss and anorexia occur is important and may help to prevent distress for the patient and family later (45). Oral nutritional supplements may be considered if they are consistent with the patient’s goals of care (46, 47).

Managing Common Symptoms... Moderate to severe pain in patients with life-limiting illness may best be managed with opioids; these drugs also effectively treat dyspnea. Appropriate monitoring, selection, and dosing can eliminate significant respiratory depression. Treatment of nausea is most effective when tailored to the putative associated neurotransmitters. Anxiety can be problematic for patients, but contributors to distress should be investigated before instituting pharmacotherapy. Delirium is common in patients approaching EOL and should be recognized early and treated with neuroleptics. Persistent depression in patients with serious illness warrants antidepressant treatment. Encouraging oral intake for patient comfort and enjoyment should take preference over parenteral or enteral nutrition, particularly in late-stage illness.

CLINICAL BOTTOM LINE

Communication and Psychosocial and Ethical Issues

How should clinicians approach discussions about EOL?

Seriously ill patients may be reluctant to initiate discussions about goals of care and prognosis with their families and clinicians but often want to have these discussions with their clinicians (1). Patients may fear physician abandonment, withdrawal of supportive measures and treatments, and emotional reactions.
from loved ones. Physicians should facilitate conversations among patients, families, and other providers to address patients’ wishes and concerns with regard to life-sustaining technologies, supportive treatments, and desire for care at home versus inpatient care (1) (Table 4). Such conversations may evoke emotional responses (48) and often require several visits to appropriately address these issues.

Many physicians and families incorrectly believe that initiating discussions about goals of care “takes away hope” (49, 50). Patients should be assured that these discussions do not imply “giving up,” “losing hope,” or that there is “nothing left to do.” Reminding patients that hope is relative to the current situation and can be preserved by setting achievable goals (e.g., controlling pain, enabling walks or other activities that provide enjoyment) often alleviates anxiety and fosters ongoing discussion. Studies suggest that hope is maintained when patients are given truthful prognostic information and treatment options, even when the news is bad (49). Avoiding such discussions may limit treatment of burdensome symptoms or evaluation of other concerns. Such avoidance may also rob a patient of the opportunity to complete important tasks related to life closure.

A multisite, prospective, longitudinal cohort study of 332 patients and associated caregivers demonstrated that only 37% of patients reported having EOL discussions before baseline and that these discussions were associated with fewer aggressive interventions near death. A key conclusion was that aggressive care was associated with worse quality of life for the patient and greater bereavement for family members (50).

How can clinicians assist with advance care planning, including advance directives? In addition to assessing goals of care and ensuring that symptoms are managed, patients’ preferences regarding disease-targeted interventions and surro-gate decision making should be addressed. State laws vary regarding default surrogate decision makers if one was not previously designated by the patient (51); an advance directive that appoints a durable health care power of attorney or health care proxy may prevent conflict or confusion. Free online resources are available to promote advance care planning and have been shown to improve documentation rates (52). Surrogates should be informed of and agree to support a patient’s wishes regarding symptom management and care preferences as illness progresses. Surrogates should know what to do if the patient’s condition suddenly deteriorates and should be assured that their role is to represent the patient’s expressed wishes when he or she can no longer do so, not to determine the outcome. The surrogate experience can be positive, therapeutic, and less stressful when this person is empowered to execute a patient’s wishes (53). Patients with medical devices (e.g., pacemakers, cardioverter-defibrillators) or those receiving long-term, life-sustaining treatments (e.g., hemodialysis) require special consideration and careful advance care planning to prevent unwanted medical interventions. Ideally, treatments that no longer achieve the patient’s goals should be discussed when the patient’s functional status and quality of life are still intact but declining. Some physicians may feel uncomfortable honoring a patient’s request to discontinue treatment for a disorder not related to the underlying cause of death (e.g., hemodialysis in a patient with cancer). A clinical ethics consultation may help in such situations.

What are the legal and ethical differences between withholding or withdrawing life-sustaining treatments and euthanasia or assisted suicide?

Goal-directed, voluntary withdrawal of medical treatment is ethically and legally sound and differs from physician-aid in dying (PAID, previously known as physician-assisted suicide) or euthanasia (Table 5). The U.S. Supreme Court and lower courts have consistently articulated that there is no moral, legal, or ethical difference between withdrawing life-sustaining treatments and having never started them. Because patients ultimately die of their underlying illness, withholding or withdrawing interventions, such as mechanical ventilation, feeding tubes, and hemodialysis, is considered legally allowable and ethnically neutral.

PAID is morally different for many persons because it introduces an intervention with the primary goal of hastening death that is independent of the terminal disease process. Direct administration of a lethal drug by a clinician is not legal in the United States. As more jurisdictions legalize PAID, clinicians should be aware of their personal position regarding participation. Conscientious objection is permitted regardless of the legal status of this practice. The American College of Physicians, which is committed to improving care for patients throughout and approaching the end of life, does not support PAID and encourages clinicians to engage in dialogue with patients (54). A request for PAID should prompt clinical evaluation to better understand the reasons for the request (55).

Is palliative sedation ever acceptable?

Palliative sedation with benzodiazepines, barbiturates, or anesthetic agents is acceptable and justified for alleviation of symptoms that cannot be managed any other way (55). Sedation may unintentionally hasten death due to possible side effects, often referred to as “double effect” (56) (Table 5). The intent of palliative treatments should be congruent with patient wishes to relieve symptoms, must follow standards of care, and must be documented alongside the patient’s or surrogate’s understanding of the potential risks. Palliative sedation is ethically and legally acceptable because its primary intent is to relieve suffering that is refractory to all reasonable treatments, and it is consistent with physicians’ responsibility to provide comfort. Such care, however, should include multidisciplinary discussions and specialist PC consultation.

Table 4. Examples of Clinician Statements to Guide Conversations Regarding Goals of Care*

<table>
<thead>
<tr>
<th>REMAP</th>
<th>Addressing Goals of Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reframe: Why the status quo isn’t working</td>
<td>(You may need to discuss serious news, such as a scan first.) “Given this news, it seems like a good time to talk about what to do now. We’re in a different place.”</td>
</tr>
<tr>
<td>Expect: Emotion. Respond with empathy</td>
<td>“It’s hard to deal with all this.” “I can see you are really concerned about [x].” “Tell me more about that—what are you worried about?” “Is it ok for us to talk about what this means?”</td>
</tr>
<tr>
<td>Map out what’s important</td>
<td>“Given this situation, what’s most important for you?” “When you think about the future, are there things you want to do?” “As you look toward the future, what concerns you?”</td>
</tr>
<tr>
<td>Align with the patient’s values</td>
<td>“As I listen to you, it sounds the most important things are [x-y-z].”</td>
</tr>
<tr>
<td>Plan to match values</td>
<td>“Here’s what I can do now that will help you do those important things.” “What do you think about it?”</td>
</tr>
</tbody>
</table>


Patient Education

What do patients and their families need to understand about specialist PC?
Patients and families commonly (and mistakenly) believe that hospice and specialist PC are the same, both focusing exclusively on EOL care. Misunderstandings regarding eligibility (e.g., only for EOL), purpose (pursuit of treatment prohibited), or philosophy (fastening death) are common and discourage patients from having specialist PC consultations. Explaining the rationale for such consultation and explicitly discussing the goals of specialist PC with patients may increase their receptiveness to these interventions.

When is the best time to discuss PC?
Patient education is a fundamental component of PC, whether primary or specialist. Clinicians should introduce PC options long before the patient becomes terminally ill. Planning helps introduce uncomfortable topics, such as death and dying, and physicians should emphasize its importance. They should seek opportunities to routinely address advance directives and durable health care power of attorney documents with patients. When situations evolve, it is important to keep patients and surrogates informed about clinical changes, prognosis, and treatment options.

Table 5.  Legal and Ethical Differences Among Withholding and Withdrawing Life-Sustaining Treatment, Palliative Sedation, Physician-Aid in Dying, and Euthanasia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Withhold Life-Sustaining Treatment</th>
<th>Withdraw Life-Sustaining Treatment</th>
<th>Palliative Sedation and Analgesia</th>
<th>Physician-Aid in Dying</th>
<th>Euthanasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause of death</td>
<td>Underlying disease</td>
<td>Underlying disease</td>
<td>Underlying disease†</td>
<td>Intervention prescribed by physician and used by patient</td>
<td>Intervention administered by physician</td>
</tr>
<tr>
<td>Intent/goal of intervention</td>
<td>Avoid burdensome intervention</td>
<td>Remove burdensome intervention</td>
<td>Relieve symptoms</td>
<td>Termination of life</td>
<td>Termination of life</td>
</tr>
<tr>
<td>Legal in United States?‡</td>
<td>Yes§</td>
<td>Yes§</td>
<td>Yes</td>
<td>Legal in some states; prohibited in some states; being considered in some states§</td>
<td>No</td>
</tr>
</tbody>
</table>

† Note “double-effect” (see text).
‡ Several states limit the power of surrogate decision makers regarding life-sustaining treatments.
§ Refer to your state’s medical guidelines for current policy.

Communication and Psychosocial and Ethical Issues... Early, regular discussions of goals of care among physicians, patients, and families help to set expectations regarding treatment goals and disease progression and help maintain hope. Advance care planning and potential roles for surrogate decision makers should be addressed. If a patient perceives that the burden of a treatment outweighs its benefits, withdrawing the treatment is morally equivalent to never having started it.

CLINICAL BOTTOM LINE
Clinical Guidelines
The fourth edition of the National Consensus Project Clinical Practice Guidelines for Quality Palliative Care. The full version is expected to be published in July 2018.

The full third edition of the Hospice & Palliative Nurses Association guidelines.

General Information
http://oahpm.org
Information from the American Academy of Hospice and Palliative Medicine.

www.capc.org
Information for providers, payers, and policymakers from the Center to Advance Palliative Care.

www.gpcqa.org
Information from the Global Palliative Care Quality Alliance.

www.pcqn.org
Information from the Palliative Care Quality Network.

Patient Information
Fact sheet for patients and families.

https://getpalliativecare.org/handouts-for-patients-and-families
Information for families about both adult and pediatric palliative care; discusses palliative care according to disease.

www.prepareforyourcare.org
A Web site for patients to document their wishes in advance and have a voice in medical decisions. The tools are available in both English and Spanish.

http://gowish.org
Printable cards that are used in a game that facilitates discussions about advance care planning. The cards can be used by patients and family members as well as health providers.
WHAT YOU SHOULD KNOW ABOUT PALLIATIVE CARE

What Is Palliative Care?
When you have a serious health condition (a chronic disorder that cannot be cured), you need special care and attention. Living with a serious health condition can be hard in many ways. It can affect:
• How your body feels
• Your emotional health
• Your family’s and friends’ emotional health
Palliative care provides the special care you need while living with a serious health condition. You can get palliative care while you are in a hospital or at your doctor’s office, and it includes the following:
• Help learning how to manage your health condition
• Symptom relief
• Help feeling better day-to-day
• Support for you and your loved ones
• Answers to your questions about care planning or the future
• Support in having conversations about your wants, needs, and wishes with your doctor and loved ones
• Help making plans for the future

Who Is on My Palliative Care Team?
Your palliative care team will teach you about treatments and support you in making decisions about your health. This team can also help educate and give support to your loved ones. Your care team will usually include:
• A doctor
• A nurse
• A chaplain
• A social worker

What Is the Difference Between Palliative Care and Hospice Care?
• Hospice, while also a special type of care for persons who have a serious health condition, is for those expected to die within 6 months.
• Palliative care is for all patients in all stages of a serious health condition. This can mean right after you are diagnosed and any time after that.

How Will It Help My Symptoms?
It can be very hard to live with a serious health condition. Many people have:
• Pain that won’t go away
• Trouble breathing
• Nausea
• Confusion or anger
• Sadness or depression
• Less appetite
• Weight loss
There are treatments, medicines, and therapies that can help you feel better and provide relief from:
• Pain. For mild or moderate pain, your doctor may suggest over-the-counter pain medicines like acetaminophen or nonsteroidal anti-inflammatory drugs. For more severe pain, you may be prescribed strong pain medicines like opioids. Be sure to follow your doctor’s instructions on how to take them.
• Breathing trouble. Your doctor may prescribe medicines to help with your breathing. He or she may also suggest pulmonary rehabilitation, which helps you learn how to breathe better and cope with breathing problems.
• Depression or anxiety. There are medicines that might help you feel better on a day-to-day basis. It might also help to talk to your palliative care team about how you feel.
• Nausea or vomiting. There are medicines that can help you feel less nauseous and prevent vomiting. Some medicines might even help you feel hungry again.
Your treatment will depend on your symptoms. Ask your palliative care team about what treatment options are right for you.

Questions for My Doctor
• What is the best way to plan for my future?
• Where can I find support for me and my loved ones?
• Can we discuss what I want for my future?
• How will I feel as my health condition progresses?
• Who can I talk to about my wants and needs?
• What is the best way to manage my symptoms now?

For More Information
American College of Physicians
www.acponline.org/practice-resources/patient-education/online-resources/end-of-life
MedlinePlus
https://medlineplus.gov/palliativecare.html
National Institute of Nursing Research
### Appendix Table. A Survey of Evidence Regarding Prognostication Tools

<table>
<thead>
<tr>
<th>Prognostic Index</th>
<th>Description of Cohort or Population From Which Derived</th>
<th>Data Used for Calculation</th>
<th>Utility and Prognostic Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer and general conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karnofsky Performance Status</td>
<td>Deduced initially to describe functional status and likelihood of tolerance of antineoplastic toxicity in clinical trials.</td>
<td>Developed in 1948, 0-100 scale with 10-point intervals. Rough estimate of functional status regarding self-care, daily activity and ambulation. 100 is “normal, no complaints; no evidence of disease” and 0 is “dead.”</td>
<td>Has been further derived to estimate survival in terms of “days, weeks or months.”</td>
<td>63</td>
</tr>
<tr>
<td>Eastern Cooperative Oncology Group</td>
<td>Like Karnofsky Performance Status, used to describe functional status and likelihood of tolerance of antineoplastic toxicity in clinical trials.</td>
<td>Developed in 1960 and further defined in 1982, 0-5 scale by 1-point intervals. Rough estimate of functional status regarding self-care, daily activity and ambulation. 0 is “Fully active, able to carry on all pre-disease performance without restriction” and 5 is “dead.”</td>
<td>Has been further derived to estimate survival in terms of “days, weeks or months.”</td>
<td>64, 65</td>
</tr>
<tr>
<td><strong>Palliative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palliative Performance Scale</td>
<td>Initial cohort evaluated 119 cancer patients on home hospice, 213 patients admitted to hospice unit.</td>
<td>Degree of ambulation, ability to do activities/extent of disease, ability to care for self, food/fluid intake, and level of consciousness.</td>
<td>Has been derived to estimate survival in terms of “days, weeks or months”</td>
<td>66</td>
</tr>
<tr>
<td>Palliative Prognostic Score</td>
<td>Prospective study of 519 patients with cancer.</td>
<td>Clinical prediction of survival (weeks), Karnofsky Performance Status, total white blood cell count, lymphocyte percentage, and presence of shortness of breath and anorexia.</td>
<td>Probability of survival at 30 days</td>
<td>67</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BODE Index</td>
<td>Initial validation with 207 patients to determine predictive factors. Prospective tool validated in cohort of 625 patients with COPD.</td>
<td>B: Body mass index O: Degree of airflow obstruction by FEV1% D: Dyspnea severity by Modified Medical Research Council Scale for Dyspnea E: Exercise capacity by 6-minute walk</td>
<td>Approximate 4-year survival</td>
<td>68</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seattle Heart Failure Model</td>
<td>Derived from cohort of 1125 patients using multivariate Cox model, prospective validation in an additional 9942 patients with heart failure.</td>
<td>Various “clinical, pharmacological, device, and laboratory characteristics.”</td>
<td>1, 2, and 3-year survival estimated.</td>
<td>69</td>
</tr>
<tr>
<td>Multiple estimation of risk based on the emergency department score in patients with acute heart failure</td>
<td>Derivation cohort of 4867 consecutive emergency room patient from 2009-2011, validated in 3229 patients admitted during 2014.</td>
<td>Thirteen independent risk factors identified. Barthel Score (calculated by functional status with activities of daily living), age, systolic blood pressure, respiratory rate, lab values (NT-proBNP, potassium, troponin, creatinine), oxygen saturation; presence or absence of; acute coronary syndrome, hypertrophy on electrocardiography, New York Heart Association Class IV status, low-output symptoms.</td>
<td>30-day mortality risk</td>
<td>70</td>
</tr>
</tbody>
</table>

Continued on following page
<table>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Dementia</strong></td>
<td>Functional Assessment Staging Tool (FAST)</td>
<td>Continuum of 16 stages/substages (Stage 1-7f) that describe cognitive impairment and behaviors associated with decline range from normal to severe.</td>
<td>Score of 7c correlates with survival of ≤6 months</td>
<td>71</td>
</tr>
<tr>
<td>Mortality Risk Index</td>
<td>Retrospective cohort study from minimum data set between 1994-1998. Derivation cohort of 6799 patients, validation cohort of 4631 patients.</td>
<td>Twelve variables including age, sex, oral intake, bowel continence, mobility, and level of alertness, as well as presence or absence of cancer, unstable medical conditions, congestive heart failure.</td>
<td>6-month mortality risk</td>
<td>72</td>
</tr>
<tr>
<td>ePrognosis</td>
<td>Systematic review of literature.</td>
<td>Collection based on systematic review of multiple prognostic indices for older adults across community, nursing home, hospice and hospital settings.</td>
<td>Variable, based on tool used</td>
<td>7</td>
</tr>
<tr>
<td><strong>End-stage renal disease</strong></td>
<td>6-month mortality on hemodialysis</td>
<td>4802 incident patients evaluated via retrospective cohort study.</td>
<td>Surprise question (Would I be surprised if this patient died within the next 6 months?), albumin, age, presence of dementia, and peripheral vascular disease</td>
<td>6-month survival on maintenance hemodialysis</td>
</tr>
<tr>
<td></td>
<td>12-month mortality with stage 4 or 5 chronic kidney disease</td>
<td>749 patients with stage 4 or 5 chronic kidney disease evaluated in prospective, observational study.</td>
<td>Surprise question for 6 months and 12 months, age, Modified Karnofsky Performance Index (score 0 as normal, 1 as cannot work and needs frequent care, and 2 as disabled or requiring special care).</td>
<td>12-month mortality in advanced chronic kidney disease</td>
</tr>
<tr>
<td><strong>End-stage liver disease</strong></td>
<td>Child-Turcotte-Pugh</td>
<td>Originally used to predict perioperative mortality for abdominal surgery in setting of cirrhosis, later modified to classify risk of bleeding from esophageal varices.</td>
<td>Total bilirubin, albumin, INR, presence/severity of encephalopathy and ascites.</td>
<td>Describes severity of liver disease, not directly correlated with prognosis</td>
</tr>
<tr>
<td>Model for End-Stage Liver Disease (later Model for End-Stage Liver Disease–Na when sodium incorporated).</td>
<td>Multivariate analysis of several cohorts with advanced liver disease. Initially used to predict 3-month mortality in patients undergoing transjugular intrahepatic portosystemic shunt procedures. Later validated in cohort of 73 patients to predict 90-day mortality risk in patients with alcoholic hepatitis.</td>
<td>Uses serum bilirubin, serum creatinine and INR for prothrombin time. 2006 study demonstrated adding serum sodium as a variable improved accuracy of predicted survival.</td>
<td>90-day mortality risk</td>
<td>77-79</td>
</tr>
<tr>
<td><strong>Multisystem and critical illness</strong></td>
<td>Charlson Comorbidity Index</td>
<td>Derived from cohort of 559 medical patients.</td>
<td>Total score based on presence or absence of 19 different medical conditional or diagnoses, each weighted as 1, 2, 3, or 6 to produce a total score.</td>
<td>1-year and 10-year mortality risk</td>
</tr>
<tr>
<td>Acute Physiology and Chronic Health Evaluation (APACHE)</td>
<td>805 admissions to intensive care units at university and community hospitals; APACHE II enrolled 5815 patients and prophetically validated the tool, and is the actively used version.</td>
<td>Uses physiologic measurements, age, and previous health status to provide general measure of disease severity.</td>
<td>Mortality Prediction in the ICU both with and without operative intervention</td>
<td>81, 82</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; INR = international normalized ratio; NT-proBNP = N-terminal pro-B-type natriuretic peptide.
Web-Only References