TEXTBOOK OF CRITICAL CARE

7TH EDITION

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7th Edition

BOOK

Textbook of Critical Care, Seventh Edition

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PREFACE

We are pleased to bring you the Seventh Edition of *Textbook of Critical Care*. We've listened to our readers and have retained the acclaimed features that have made this book one of the top sellers in critical care, while also making changes to the organization and content of the book to best reflect the changes in the critical care specialty since the last edition.

Our tables, boxes, algorithms, diagnostic images, and key points, which provide clear and accessible information for quick reference, will continue to be featured prominently throughout the book. The Seventh Edition contains a wealth of new information, including an entirely new section on Common Approaches for Organ Support, Diagnosis, and Monitoring. In addition, we have added new chapters on Extracorporeal Membrane Oxygenation, Biomarkers of Acute Kidney Injury, Antimicrobial Stewardship, Targeted Temperature Management and Therapeutic Hypothermia, Telemedicine in Intensive Care, and many more. Given the increased use of bedside ultrasonography, a new chapter addressing best practices with this now ubiquitous tool has been added. All chapters throughout the book have been revised to reflect new knowledge in the field and, thus, changes in the practice of critical care medicine.

Textbook of Critical Care has evolved with critical care practice over the years and is now known as the reference that successfully bridges the gap between medical and surgical intensive care practice. Unlike many critical care references, *Textbook of Critical Care* includes pediatric topics, providing a comprehensive resource for our readers who see a broad range of patients. We continue to focus on the multidisciplinary approach to the care of critically ill patients and include contributors trained in anesthesia, surgery, pulmonary medicine, and pediatrics.

The companion online book is more interactive than ever, with 29 procedural videos and 24 e-only procedural chapters, a powerful search engine, hyperlinked references, and downloadable images. The website is mobile optimized for your convenience on all portable devices. Access to the online content is included with your book purchase, so please activate your e-book to take advantage of the full scope of information available to you.

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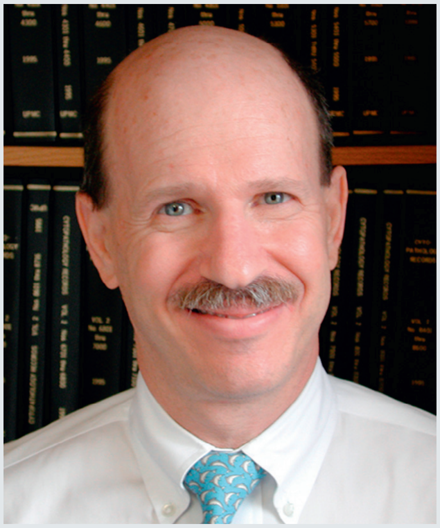
IN MEMORIAM



MITCHELL P. FINK, MD

This edition of the *Textbook of Critical Care* is dedicated to the late Mitchell P. Fink, MD. Dr. Fink was Professor of Surgery and Vice Chair for Critical Care at the University of California Los Angeles and an international leader and giant in the field of critical care medicine. He was the lead author of the Fifth Edition of this textbook. In the Fifth Edition, Dr. Fink inspired a novel, informative, user-friendly, and exciting approach to revising the textbook that served as the backbone for the Sixth and this new Seventh Edition, which he also importantly helped to formulate. Mitch was a great friend and colleague to each of us, and he will be dearly missed by us and by the entire field. We are confident that his visionary work on this book will serve, through its users, to improve the care and outcomes of critically ill adults and children worldwide for many years into the future.

To my family and friends and all who can contribute to make a better world
— *Jean-Louis Vincent*

To Norma-May, my true love. To Claire and Erin, who bring me the greatest joy, and to my mother, Dale Abraham, for her support throughout my life
— *Edward Abraham*

To my father, Ernest E. Moore, who was a family practitioner for 50 years in Butler, Pennsylvania. He inspired me by his dedication to self-education, humility, and service to his community
— *Frederick A. Moore*

To my family, friends, colleagues, and staff for their sacrifices, support, and dedication, and to the late Dr. Peter Safar for inspiring each of us to bring promising new therapies to the bedside of the critically ill
— *Patrick M. Kochanek*

1 Sudden Deterioration in Neurologic Status

Joseph M. Darby and Anupam Anupam

Patients admitted to the intensive care unit (ICU) with critical illness or injury are at risk for neurologic complications.[1-5] A sudden or unexpected change in the neurologic condition of a critically ill patient often heralds a complication that may cause direct injury to the central nervous system (CNS). Alternatively, such changes may simply be neurologic manifestations of the underlying critical illness or treatment that necessitated ICU admission (e.g., sepsis). These complications can occur in patients admitted to the ICU without neurologic disease and in those admitted for management of primary CNS problems (e.g., stroke). Neurologic complications can also occur as a result of invasive procedures and therapeutic interventions performed. Commonly, recognition of neurologic complications is delayed or missed entirely because ICU treatments (e.g., intubation, drugs) interfere with the physical examination or confound the clinical picture. In other cases, neurologic complications are not recognized because of a lack of sensitive methods to detect the problem (e.g., delirium). Morbidity and mortality are increased among patients who develop neurologic complications; therefore, the intensivist must be vigilant in evaluating all critically ill patients for changes in neurologic status.

Despite the importance of neurologic complications of critical illness, few studies have specifically assessed their incidence and impact on outcome among ICU patients. Available data are limited to medical ICU patients; data regarding neurologic complications in general surgical and other specialty ICU populations must be extracted from other sources. In studies of medical ICU patients, the incidence of neurologic complications is 12.3% to 33%.[1,2] Patients who develop neurologic complications have increased morbidity, mortality, and ICU length of stay. Sepsis is the most common problem associated with development of neurologic complications (sepsis-associated encephalopathy). In addition to encephalopathy, other common neurologic complications associated with critical illness include seizures and stroke. As the complexity of ICU care has increased, so has the risk of neurologic complications. Neuromuscular disorders are now recognized as a major source of morbidity in severely ill patients.[6] Recognized neurologic complications occurring in selected medical, surgical, and neurologic ICU populations are shown in Table 1-1.[7-41]

IMPAIRMENT IN CONSCIOUSNESS

Global changes in CNS function, best described in terms of impairment in consciousness, are generally referred to as *encephalopathy* or *altered mental status*. An acute change in the level of consciousness, undoubtedly, is the most common neurologic complication that occurs after ICU admission. *Consciousness* is defined as a state of awareness (arousal or wakefulness) and the ability to respond appropriately to changes in environment.[42] For consciousness to be impaired, global hemispheric dysfunction or dysfunction of the brainstem reticular activating system must be present.[43] Altered consciousness may result in a sleeplike state (coma) or a state characterized by confusion and agitation (delirium). States of acutely altered consciousness seen in the critically ill are listed in Table 1-2.

When an acute change in consciousness is noted, the patient should be evaluated, keeping in mind the patient's age, presence or absence of coexisting organ system dysfunction, metabolic status and medication list, and presence or absence of infection. In patients with a primary CNS disorder, deterioration in the level of consciousness (e.g., from stupor to coma) frequently represents the development of brain edema, increasing intracranial pressure, new or worsening intracranial hemorrhage, hydrocephalus, CNS infection, or cerebral vasospasm. In patients without a primary CNS diagnosis, an acute change in consciousness is often due to the development of infectious complications (i.e., sepsis-associated encephalopathy), drug toxicities, or the development or exacerbation of organ system failure. Nonconvulsive status epilepticus is increasingly being recognized as a cause of impaired consciousness in critically ill patients (Box 1-1).[44-53]

States of altered consciousness manifesting as impairment in wakefulness or arousal (i.e., coma and stupor) and their causes are well defined.[42,43,54,55] Much confusion remains, however, regarding the diagnosis and management of delirium, perhaps the most common state of impaired CNS functioning in critically ill patients at large. When dedicated instruments are used, delirium can be diagnosed in more than 80% of critically ill patients, making this condition the most common neurologic complication of critical illness.[56-58] Much of the difficulty in establishing the diagnosis of delirium stems from the belief that delirium is a state characterized mainly by confusion and agitation and that such states are expected consequences of the unique environmental factors and sleep deprivation that characterize the ICU experience. Terms previously used to describe delirium in critically ill patients include *ICU psychosis*, *acute confusional state*, *encephalopathy*, and *postoperative psychosis*. It is now recognized that *ICU psychosis* is a misnomer; *delirium* is a more accurate term.[59]

Currently accepted criteria for the diagnosis of delirium include abrupt onset of impaired consciousness, disturbed cognitive function, fluctuating course, and presence of a medical condition that could impair brain function.[60] Subtypes of delirium include hyperactive (agitated) delirium and the more common hypoactive or quiet delirium.[58] Impaired consciousness may be apparent as a reduction in awareness, psychomotor retardation, agitation, or impairment in attention (increased distractibility or vigilance). Cognitive impairment can include disorientation, impaired memory, and perceptual aberrations (hallucinations or illusions).[61] Autonomic hyperactivity and sleep disturbances may be features of delirium in some patients (e.g., those with drug withdrawal syndromes, delirium tremens). Delirium in critically ill patients is associated with increased morbidity, mortality, and ICU length of stay.[62-64] In general, sepsis and medications should be the primary etiologic considerations in critically ill patients who develop delirium.

As has been noted, nonconvulsive status epilepticus is increasingly recognized as an important cause of impaired consciousness in critically ill patients. Although the general term can encompass other entities, such as absence and partial complex seizures, in critically ill patients, *nonconvulsive status epilepticus* is often referred to as *status epilepticus of epileptic encephalopathy*.[53] It is characterized by alteration in consciousness or behavior associated with electroencephalographic evidence of continuous or periodic epileptiform activity without overt motor manifestations of seizures. In a study of comatose patients without overt seizure activity, nonconvulsive status epilepticus was evident in 8% of subjects.[51] Nonconvulsive status epilepticus can precede or follow an episode of generalized convulsive status epilepticus; it can also occur in patients with traumatic brain injury, subarachnoid hemorrhage, global brain ischemia or anoxia, sepsis, and multiple organ failure. Despite the general consensus that nonconvulsive status

TABLE 1-1 Neurologic Complications in Selected Specialty Populations

MEDICAL	
Bone marrow transplantation[7,8]	CNS infection, stroke, subdural hematoma, brainstem ischemia, hyperammonemia, Wernicke encephalopathy
Cancer[9]	Stroke, intracranial hemorrhage, CNS infection
Fulminant hepatic failure[10]	Encephalopathy, coma, brain edema, increased ICP
HIV/AIDS[11,12]	Opportunistic CNS infection, stroke, vasculitis, delirium, seizures, progressive multifocal leukoencephalopathy
Pregnancy[13,14]	Seizures, ischemic stroke, cerebral vasospasm, intracranial hemorrhage, cerebral venous thrombosis, hypertensive encephalopathy, pituitary apoplexy
SURGICAL	
Cardiac surgery[15-19]	Stroke, delirium, brachial plexus injury, phrenic nerve injury
Vascular surgery[20,21]	
Carotid	Stroke, cranial nerve injuries (recurrent laryngeal, glossopharyngeal, hypoglossal, facial), seizures
Aortic	Stroke, paraplegia
Peripheral	Delirium
Transplantation[10,22-25]	
Heart	Stroke
Liver	Encephalopathy, seizures, opportunistic CNS infection, intracranial hemorrhage, Guillain-Barré syndrome, central pontine myelinolysis
Renal	Stroke, opportunistic CNS infection, femoral neuropathy
Urologic surgery (TURP)[26]	Seizures and coma (hyponatremia)
Otolaryngologic surgery[27,28]	Recurrent laryngeal nerve injury, stroke, delirium
Orthopedic surgery[29]	
Spine	Myelopathy, radiculopathy, epidural abscess, meningitis
Knee and hip replacement	Delirium (fat embolism)
Long-bone fracture/nailing	Delirium (fat embolism)
NEUROLOGIC	
Stroke[30-34]	Stroke progression or extension, reocclusion after thrombolysis, bleeding, seizures, delirium, brain edema, herniation
Intracranial surgery[35]	Bleeding, edema, seizures, CNS infection
Subarachnoid hemorrhage[32,36-38]	Rebleeding, vasospasm, hydrocephalus, seizures
Traumatic brain injury[32,39,40]	Intracranial hypertension, bleeding, seizures, stroke (cerebrovascular injury), CNS infection
Cervical spinal cord injury[41]	Ascension of injury, stroke (vertebral artery injury)

CNS, central nervous system; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; ICP, intracranial pressure; TURP, transurethral prostatic resection.

TABLE 1-2 States of Acutely Altered Consciousness

STATE	DESCRIPTION
Coma	Closed eyes, sleeplike state with no response to external stimuli (pain)
Stupor	Responsive only to vigorous or painful stimuli
Lethargy	Drowsy, arouses easily and appropriately to stimuli
Delirium	Acute state of confusion with or without behavioral disturbance
Catatonia	Eyes open, unblinking, unresponsive

epilepticus is a unique entity responsible for impaired consciousness in some critically ill patients, there is no general consensus on the electroencephalographic criteria for its diagnosis or the optimal approach to treatment.[65]

STROKE AND OTHER FOCAL NEUROLOGIC DEFICITS

The new onset of a major neurologic deficit that manifests as a focal impairment in motor or sensory function (e.g., hemiparesis) or one that results in seizures usually indicates a primary problem referable to the cerebrovascular circulation. In a study evaluating the value of computed tomography (CT) in medical ICU patients, ischemic stroke and intracranial bleeding were the most common abnormalities associated with the new onset of a neurologic deficit or seizures.[66] Overall, the frequency of new-onset stroke is between 1% and 4% in medical ICU patients.[1,2] Among general surgical patients, the frequency of perioperative stroke ranges from 0.3% to 3.5%.[67] Patients undergoing cardiac or vascular surgery and surgical patients with underlying cerebrovascular disease can be expected to have an increased risk of perioperative stroke.[19]

The frequency of new or worsening focal neurologic deficits in patients admitted with a primary neurologic or neurosurgical disorder varies. For example, as many as 30% of patients with aneurysmal subarachnoid hemorrhage develop delayed ischemic neurologic deficits.[36] Patients admitted with stroke often develop worsening or new symptoms as a result of stroke progression, bleeding, or reocclusion of vessels previously opened with interventional therapy. In patients who have undergone elective intracranial surgery, postsurgical bleeding or infectious complications are the main causes of new focal deficits. In trauma patients, unrecognized injuries to the cerebrovascular circulation can cause new deficits. Patients who have sustained spinal cord injuries, and those who have undergone surgery of the spine or of the thoracic or abdominal aorta, can develop worsening or new symptoms of spinal cord injury. Early deterioration of CNS function after spinal cord injury usually occurs as a consequence of medical interventions to stabilize the spine, whereas late deterioration is usually due to hypotension and impaired cord perfusion. Occasionally, focal weakness or sensory symptoms in the extremities occur as a result of occult brachial plexus injury or compression neuropathy. New cranial nerve deficits in patients without primary neurologic problems can occur after neck surgery or carotid endarterectomy.

SEIZURES

The new onset of motor seizures occurs in 0.8% to 4% of critically ill medical ICU patients.[1,2,68] New-onset seizures in general medical-surgical ICU patients is typically caused by narcotic withdrawal, hyponatremia, drug toxicities, or previously unrecognized structural abnormalities.[3,68] New stroke, intracranial bleeding, and CNS infection

BOX 1-1 General Causes of Acutely Impaired Consciousness in the Critically Ill

INFECTION
- Sepsis encephalopathy
- CNS infection

DRUGS
- Narcotics
- Benzodiazepines
- Anticholinergics
- Anticonvulsants
- Tricyclic antidepressants
- Selective serotonin uptake inhibitors
- Phenothiazines
- Steroids
- Immunosuppressants (cyclosporine, FK506, OKT3)
- Anesthetics

ELECTROLYTE AND ACID-BASE DISTURBANCES
- Hyponatremia
- Hypernatremia
- Hypercalcemia
- Hypermagnesemia
- Severe acidemia and alkalemia

ORGAN SYSTEM FAILURE
- Shock
- Renal failure
- Hepatic failure
- Pancreatitis
- Respiratory failure (hypoxia, hypercapnia)

ENDOCRINE DISORDERS
- Hypoglycemia
- Hyperglycemia
- Hypothyroidism
- Hyperthyroidism
- Pituitary apoplexy

DRUG WITHDRAWAL
- Alcohol
- Opiates
- Barbiturates
- Benzodiazepines

VASCULAR CAUSES
- Shock
- Hypotension
- Hypertensive encephalopathy
- CNS vasculitis
- Cerebral venous sinus thrombosis

CNS DISORDERS
- Hemorrhage
- Stroke
- Brain edema
- Hydrocephalus
- Increased intracranial pressure
- Meningitis
- Ventriculitis
- Brain abscess
- Subdural empyema
- Seizures
- Vasculitis

SEIZURES
- Convulsive and nonconvulsive status epilepticus

MISCELLANEOUS
- Fat embolism syndrome
- Neuroleptic malignant syndrome
- Thiamine deficiency (Wernicke encephalopathy)
- Psychogenic unresponsiveness

CNS, central nervous system.

are other potential causes of seizures after ICU admission. The frequency of seizures is higher in patients admitted to the ICU with a primary neurologic problem such as traumatic brain injury, aneurysmal subarachnoid hemorrhage, stroke, or CNS infection.[69] Because nonconvulsive status epilepticus may be more common than was previously appreciated, this problem should also be considered in the differential diagnosis of patients developing new, unexplained, or prolonged alterations in consciousness.

GENERALIZED WEAKNESS AND NEUROMUSCULAR DISORDERS

Generalized muscle weakness often becomes apparent in ICU patients as previous impairments in arousal are resolving or sedative and neuromuscular blocking agents are being discontinued or tapered. Polyneuropathy and myopathy associated with critical illness are now well recognized as the principal causes of new-onset generalized weakness among ICU patients being treated for nonneuromuscular disorders.[5,70-73] These disorders also may be responsible for prolonged ventilator dependency in some patients. Patients at increased risk for these complications include those with sepsis, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome, as well as those who require prolonged mechanical ventilation. Other risk factors include treatment with corticosteroids or neuromuscular blocking agents. In contrast to demyelinating neuropathies (e.g., Guillain-Barré syndrome), critical illness polyneuropathy is primarily an axonal condition. Critical illness polyneuropathy is diagnosed in a high percentage of patients undergoing careful evaluation for weakness acquired while in the ICU. Because primary myopathy coexists in a large number of patients with critical illness polyneuropathy, *ICU-acquired paresis*[72] or *critical illness neuromuscular abnormalities*[5] may be better terms to describe this problem. Although acute Guillain-Barré syndrome and myasthenia gravis are rare complications of critical illness, these diagnoses should also be considered in patients who develop generalized weakness in the ICU.

NEUROLOGIC COMPLICATIONS OF PROCEDURES AND TREATMENTS

Routine procedures performed in the ICU or in association with evaluation and treatment of critical illness can result in neurologic complications.[4] The most obvious neurologic complications are those associated with intracranial bleeding secondary to the treatment of stroke and other disorders with thrombolytic agents or anticoagulants. Other notable complications are listed in Table 1-3.

EVALUATION OF SUDDEN NEUROLOGIC CHANGE

A new or sudden change in the neurologic condition of a critically ill patient necessitates a focused neurologic examination, review of the clinical course and medications administered before the change, a thorough laboratory assessment, and appropriate imaging or neurophysiologic studies when indicated. The type and extent of the evaluation depend on clinical context and the general category of neurologic change occurring. The history and physical examination should lead the clinician to the diagnostic approach best suited to the individual patient.

Essential elements of the neurologic examination include an assessment of the level and content of consciousness, pupillary size and reactivity, and motor function. Additional evaluation of the cranial nerves and peripheral reflexes and a sensory examination are conducted as indicated by the clinical circumstances. If the patient is comatose on initial evaluation, a more detailed coma examination should be performed to help differentiate structural from metabolic causes of coma.[43,55] When the evaluation reveals only a change in arousal without evidence of a localizing lesion in the CNS, a search for infection, discontinuation or modification of drug therapy, and a

TABLE 1-3 Neurologic Complications Associated with ICU Procedures and Treatments

PROCEDURE	COMPLICATION
Angiography	Cerebral cholesterol emboli syndrome
Anticoagulants/antiplatelet agents	Intracranial bleeding
Arterial catheterization	Cerebral embolism
Bronchoscopy	Increased ICP
Central venous catheterization	Cerebral air embolism, carotid dissection, Horner's syndrome, phrenic nerve injury, brachial plexus injury, cranial nerve injury
DC cardioversion	Embolic stroke, seizures
Dialysis	Seizures, increased ICP (dialysis disequilibrium syndrome)
Endovascular procedures (CNS)	Vessel rupture, thrombosis, reperfusion bleeding
Epidural catheter	Spinal epidural hematoma, epidural abscess
ICP monitoring	CNS infection (ventriculitis), hemorrhage
Intraaortic balloon pump	Lower extremity paralysis
Intubation	Spinal cord injury
Left ventricular assist devices	Stroke, seizures
Lumbar puncture or drain	Meningitis, herniation
Mechanical ventilation	Cerebral air embolism, increased ICP (high PEEP and hypercapnia), seizures (hypocapnia)
Nasogastric intubation	Intracranial placement

CNS, central nervous system; DC, direct current; ICP, intracranial pressure; ICU, intensive care unit; PEEP, positive end-expiratory pressure.

general metabolic evaluation may be indicated. Lumbar puncture to aid the diagnosis of CNS infection may be warranted in selected neurosurgical patients and immunocompromised individuals. Lumbar puncture to rule out nosocomially acquired meningitis in other patients is generally not rewarding.[74] Electroencephalography should be performed in patients with clear evidence of seizures, as well as when the diagnosis of nonconvulsive status epilepticus is being entertained. Continuous electroencephalography should be considered when the index of suspicion for nonconvulsive status epilepticus remains high and the initial electroencephalographic studies are unrevealing.

Computed tomography (CT) is indicated for nonneurologic patients with new focal deficits, seizures, or otherwise unexplained impairments in arousal.[66] In patients with primary neurologic disorders, CT is indicated if worsening brain edema, herniation, bleeding, and hydrocephalus are considerations when new deficits or worsening neurologic status occurs. In some cases, when the basis for a change in neurologic condition remains elusive, magnetic resonance imaging (MRI) may be helpful. In particular, the diffusion-weighted MRI technique can reveal structural abnormalities such as hypoxic brain injury, fat embolism, vasculitis, cerebral venous thrombosis, or multiple infarcts following cardiopulmonary bypass that are not apparent by standard CT or conventional MRI.[75-80] MRI may be the imaging modality of choice in patients with human immunodeficiency virus (HIV) and new CNS complications.[75] For patients who develop signs and symptoms of spinal cord injury complicating critical illness, MRI or somatosensory evoked potentials can be used to further delineate the nature and severity of the injury. For patients who develop generalized muscle weakness or unexplained ventilator dependency, electromyography and nerve conduction studies can confirm the presence of critical illness polyneuropathy or myopathy.

MONITORING FOR NEUROLOGIC CHANGES

The common occurrence of neurologic changes in critically ill patients emphasizes the need for vigilant monitoring. A variety of clinical techniques such as the Glasgow Coma Scale, National Institutes of Health Stroke Scale, Ramsay Sedation Scale, Richmond Agitation-Sedation Scale, and Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) can be used to monitor clinical neurologic status.[57,58,81-86] Neurophysiologic methods such as the bispectral index may provide more objective neurologic monitoring in the future for patients admitted to the ICU with and without primary neurologic problems.[87-89] For patients admitted to the ICU with a primary neurologic disorder, a variety of monitoring techniques including measurements of intracranial pressure, near-infrared spectroscopy, brain tissue Po_2, transcranial Doppler, and electroencephalography are available.[90]

ANNOTATED REFERENCES

De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit. A prospective multicenter study. JAMA 2002;288:2859–2867.

This prospective multicenter study of critically ill patients was the first to assess the clinical incidence, risk factors, and outcomes of mechanically ventilated patients developing ICU-acquired weakness, emphasizing a central role for corticosteroid use in its genesis and prolonged mechanical ventilation as a relevant ICU outcome.

Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients. Validity and reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). JAMA 2001;286:2703–2710.

Recognizing that the diagnosis of delirium is often difficult in the critically ill patient receiving mechanical ventilation, the authors adapted a common method for assessing delirium using the Confusion Assessment Method to critically ill patients receiving mechanical ventilation. This prospective evaluation revealed high sensitivity, specificity, and inter-rater reliability in detecting delirium in 80% of the patient population they studied.

McGuire BE, Basten CJ, Ryan CJ, et al. Intensive care unit syndrome. A dangerous misnomer. Arch Intern Med 2000;160:906–909.

In an effort to dispel the myth that environmental conditions lead to "ICU psychosis," the authors of this article argue that ICU psychosis is more appropriately described as delirium. The etiology and management of delirium in critically ill patients are reviewed.

Naik-Tolani S, Oropello JM, Benjamin E. Neurologic complications in the intensive care unit. Clin Chest Med 1999;20:423–434.

The authors of this article present an overview of central nervous system (CNS) complications of critical illness and ICU procedures in critically ill patients without primary disorders of the CNS.

Sundgren PC, Reinstrup P, Romner B, et al. Value of conventional diffusion- and perfusion-weighted MRI in the management of patients with unclear cerebral pathology, admitted to the intensive care unit. Neuroradiology 2002;44:674–680.

This retrospective study of 21 critically ill patients undergoing MRI because of a disparity in clinical neurologic findings and CT imaging revealed that additional useful diagnostic and prognostic information can be obtained, especially when diffusion- and perfusion-weighted MR sequences are obtained.

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2 Agitation and Delirium

Kwame Frimpong, E. Wesley Ely, and Arna Banerjee

Agitation and delirium are commonly encountered in the intensive care unit (ICU). They are more than just an inconvenience; these conditions can have deleterious effects on patient and staff safety and contribute to poor outcomes. It is therefore important for clinicians to be able to recognize agitation and delirium and to have an organized approach for its evaluation and management.

AGITATION

Agitation is a psychomotor disturbance characterized by excessive motor activity associated with a feeling of inner tension.[1,3] The activity is usually nonproductive and repetitious, consisting of behaviors such as pacing, fidgeting, wringing of hands, pulling of clothes, and an inability to sit still. Careful observation of the patient may reveal the underlying intent. In the ICU, agitation is frequently related to anxiety or delirium. Agitation may be caused by various factors: metabolic disorders (hypo- and hypernatremia), hyperthermia, hypoxia, hypotension, use of sedative drugs and/or analgesics, sepsis, alcohol withdrawal, and long-term psychoactive drug use to name a few.[4,5] It can also be caused by external factors such as noise, discomfort, and pain.[6] Associated with a longer length of stay in the ICU and higher costs,[4] agitation can be mild, characterized by increased movements and an apparent inability to get comfortable, or it can be severe. Severe agitation can be life threatening, leading to higher rates of self-extubation, self-removal of catheters and medical devices, nosocomial infections,[4] hypoxia, barotrauma, and/or hypotension due to patient/ventilator asynchrony. Indeed, recent studies have shown that agitation contributes to ventilator asynchrony, increased oxygen consumption, and increased production of CO_2 and lactic acid; these effects can lead to life-threatening respiratory and metabolic acidosis.[5]

DELIRIUM

Delirium can be defined as follows: (1) A disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention. (2) A change in cognition (e.g., memory deficit, disorientation, language disturbance) or development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia. (3) The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day. (4) There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of a general medical condition, an intoxicating substance, medication use, or more than one cause (Fig. 2-1).[3] Delirium is commonly underdiagnosed in the ICU and has a reported prevalence of 20% to 80%, depending on the severity of illness and the need for mechanical ventilation.[7-10] Recent investigations have shown that the presence of delirium is a strong predictor of longer hospital stay, higher costs, and increased risk of death.[11-13] Each additional day with delirium increases a patient's risk of dying by 10%.[14] Longer periods of delirium are also associated with greater degrees of cognitive decline when patients are evaluated after one year.[13] Thus, delirium can adversely affect the quality of life in survivors of critical illnesses and may serve as an intermediate recognizable step for targeting therapies to prevent poor outcomes in survivors of critical illness.[13,15]

Unfortunately, the true prevalence and magnitude of delirium have been poorly documented because myriad terms including *acute confusional state*, *ICU psychosis*, *acute brain dysfunction*, and *encephalopathy*, have been used to describe this condition.[16] Delirium can be classified according to psychomotor behavior into hypoactive delirium, hyperactive delirium, or a mixed subtype. Hypoactive delirium, which is the most prevalent form of delirium, is characterized by decreased physical and mental activity and inattention. In contrast, hyperactive delirium is characterized by combativeness and agitation. Patients with both features have mixed delirium.[17-19] Hyperactive delirium puts both patients and caregivers at risk of serious injury but fortunately only occurs in a minority of critically ill patients.[17-19] Hypoactive delirium might actually be associated with a worse prognosis.[20,21] The Delirium Motor Subtype Scale may assist in making this diagnosis.[22]

Although healthcare professionals realize the importance of recognizing delirium, it frequently goes unrecognized in the ICU.[23-30] Even when ICU delirium is recognized, most clinicians consider it an expected event that is often iatrogenic and without consequence.[23] However, it needs to be viewed as a form of organic brain dysfunction that has consequences if left undiagnosed and untreated.

Risk Factors for Delirium

The risk factors for agitation and delirium are many and overlap to a large extent (Table 2-1). Fortunately there are several mnemonics that can aid clinicians in recalling the list; two common ones are IWATCH-DEATH and DELIRIUM (Table 2-2). In practical terms, risk factors can be divided into three categories: the acute illness itself, patient factors, and iatrogenic or environmental factors. Importantly, a number of medications that are commonly used in the ICU are associated with the development of agitation and delirium (Box 2-1). A thorough approach to the treatment and support of the acute illness (e.g., controlling sources of sepsis and giving appropriate antibiotics; correcting hypoxia, metabolic disturbances, dehydration, and hyperthermia; normalizing sleep/wake cycles), as well as minimizing iatrogenic factors (e.g., excessive sedation), can reduce the incidence and/or severity of delirium and its attendant complications. A retrospective study conducted on postoperative delirium, specifically in patients undergoing cardiopulmonary bypass, has alluded to a decreased incidence of delirium in patients pre-treated with statins.[31] Furthermore, ICU statins have been associated with decreased delirium, most significantly in the early stages of sepsis; in contrast to this, discontinuation of statins has been shown to be associated with increased delirium.[32,33]

PATHOPHYSIOLOGY

The pathophysiology of delirium is poorly understood, although there are a number of hypotheses:

- **Neurotransmitter imbalance.** Multiple neurotransmitters have been implicated, including dopamine (excess), acetylcholine (relative depletion), γ-aminobutyric acid (GABA), serotonin, endorphins, norepinephrine, and glutamate.[34-37]
- **Inflammatory mediators.** Inflammatory mediators, such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and other cytokines and chemokines, have been implicated in the pathogenesis of endothelial damage, thrombin formation, and microvascular dysfunction in the central nervous system (CNS), contributing to delirium.[37] Recently, a study in the ICU has strengthened the evidence of a role for endothelial dysfunction in increasing the duration of delirium.[38]

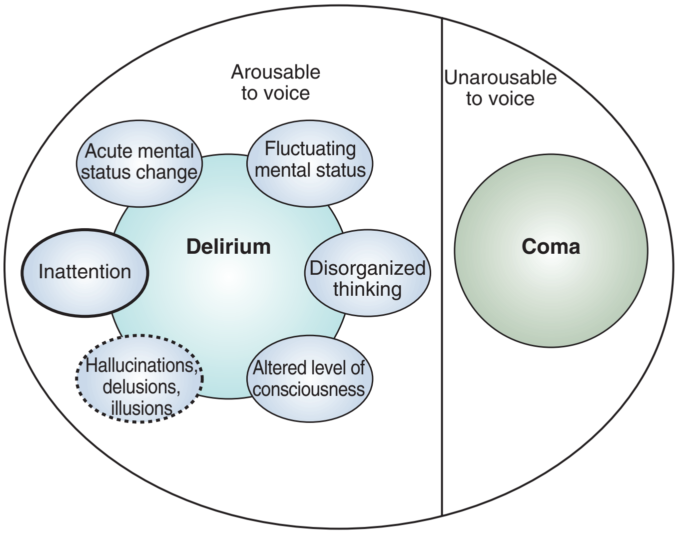


FIGURE 2-1 ■ Acute brain dysfunction. Patients who are unresponsive to voice are considered to be in a coma. Patients who respond to voice can be further evaluated for delirium using validated delirium monitoring instruments. Inattention is a cardinal feature of delirium. Other pivotal features include a change in mental status that fluctuates over hours to days, disorganized thinking, and altered levels of consciousness. While hallucinations, delusions, and illusions may be part of the perceptual disturbances seen in delirium, they on their own are not synonymous with delirium, a diagnosis of which requires the presence of inattention and other pivotal features outlined above. (With permission from E. Wesley Ely and A. Morandi) (www.icudelirium.org).

TABLE 2-1 Risk Factors for Agitation and Delirium

Age >70 years	BUN/creatinine ratio ≥18
Transfer from a nursing home	Renal failure, creatinine > 2.0 mg/dL
History of depression	Liver disease
History of dementia, stroke, or epilepsy	CHF
Alcohol abuse within past month	Cardiogenic or septic shock
Tobacco use	Myocardial infarction
Drug overdose or illicit drug use	Infection
HIV infection	CNS pathology
Psychoactive medications	Urinary retention or fecal impaction
Hypo- or hypernatremia	Tube feeding
Hypo- or hyperglycemia	Rectal or bladder catheters
Hypo- or hyperthyroidism	Physical restraints
Hypothermia or fever	Central line catheters
Hypertension	Malnutrition or vitamin deficiencies
Hypoxia	Procedural complications
Acidosis or alkalosis	Visual or hearing impairment
Pain	Sleep disruption
Fear and anxiety	

BUN, blood urea nitrogen; CHF, congestive heart failure; CNS, central nervous system; HIV, human immunodeficiency virus.

- **Impaired oxidative metabolism.** According to this hypothesis, delirium is a result of cerebral insufficiency secondary to a global failure in oxidative metabolism.[39]
- **Large neutral amino acids.** Increased cerebral uptake of tryptophan and tyrosine can lead to elevated levels of serotonin, dopamine, and norepinephrine in the CNS. Altered availability of these amino acids is associated with increased risk of development of delirium.[40]

TABLE 2-2 Mnemonic for Risk Factors for Delirium and Agitation

IWATCHDEATH	DELIRIUM
Infection	**D**rugs
Withdrawal	**E**lectrolyte and physiologic abnormalities
Acute metabolic	**L**ack of drugs (withdrawal)
Trauma/pain	**I**nfection
Central nervous system pathology	**R**educed sensory input (blindness, deafness)
Hypoxia	**I**ntracranial problems (CVA, meningitis, seizure)
Deficiencies (vitamin B_{12}, thiamine)	**U**rinary retention and fecal impaction
Endocrinopathies (thyroid, adrenal)	**M**yocardial problems (MI, arrhythmia, CHF)
Acute vascular (hypertension, shock)	
Toxins/drugs	
Heavy metals	

CHF, congestive heart failure; CVA, cerebrovascular accident; MI, myocardial infarction.

BOX 2-1 Commonly Used Drugs Associated With Delirium and Agitation

Benzodiazepines
Opiates (especially meperidine)
Anticholinergics
Antihistamines
H_2 blockers
Antibiotics
Corticosteroids
Metoclopramide

ASSESSMENT

Recently, the Society of Critical Care Medicine (SCCM) published guidelines for the use of sedatives and analgesics in the ICU.[41] The SCCM has recommended the routine monitoring of pain, anxiety, and delirium and the documentation of responses to therapy for these conditions.[42]

There are many scales available for the assessment of agitation and sedation, including the Ramsay Scale,[43] the Riker Sedation-Agitation Scale (SAS),[44] the Motor Activity Assessment Scale (MAAS),[45] the Richmond Agitation-Sedation Scale (RASS),[46] the Adaptation to Intensive Care Environment (ATICE)[47] scale, and the Minnesota Sedation Assessment Tool (MSAT).[47] Most of these scales have good reliability and validity among adult ICU patients and can be used to set targets for goal-directed sedative administration. The SAS, which scores agitation and sedation using a 7-point system, has excellent inter-rater reliability (kappa = 0.92) and is highly correlated (r^2 = 0.83 to 0.86) with other scales. The RASS (Table 2-3), however, is the only method shown to detect variations in the level of consciousness over time or in response to changes in sedative and analgesic drug use.[48] The 10-point RASS scale has discrete criteria to distinguish levels of agitation and sedation. The evaluation of patients consists of a 3-step process. First, the patient is observed to determine whether he or she is alert, restless, or agitated (0 to +4). Second, if the patient is not alert and does not show positive motoric characteristics, the patient's name is called and his or her sedation level scored based on the duration of eye contact (−1 to −3). Third, if there is no eye opening on verbal

TABLE 2-3 Richmond Agitation-Sedation Scale

+4	Combative	Combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent nonpurposeful movement; fights ventilator
+1	Restless	Anxious, apprehensive, but movements not aggressive or vigorous
0	Alert and calm	
–1	Drowsy	Not fully alert but has sustained (>10 sec) awakening (eye opening/contact) to voice
–2	Light sedation	Drowsy; briefly (<10 sec) awakens to voice or physical stimulation
–3	Moderate sedation	Movement or eye opening (but no eye contact) to voice
–4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
–5	Unarousable	No response to voice or physical stimulation

PROCEDURE FOR ASSESSMENT

1. Observe patient. Is patient alert, restless, or agitated?	(Score 0 to +4)
2. If not alert, state patient's name and tell him or her to open eyes and look at speaker. Patient awakens, with sustained eye opening and eye contact.	(Score –1)
3. Patient awakens, with eye opening and eye contact, but not sustained.	(Score –2)
4. Patient does not awaken (no eye contact) but has eye opening or movement in response to voice.	(Score –3)
3. Physically stimulate patient by shaking shoulder and/or rubbing sternum. No response to voice, but response (movement) to physical stimulation.	(Score –4)
4. No response to voice or physical stimulation	(Score –5)

From Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166(10):1338-1344.

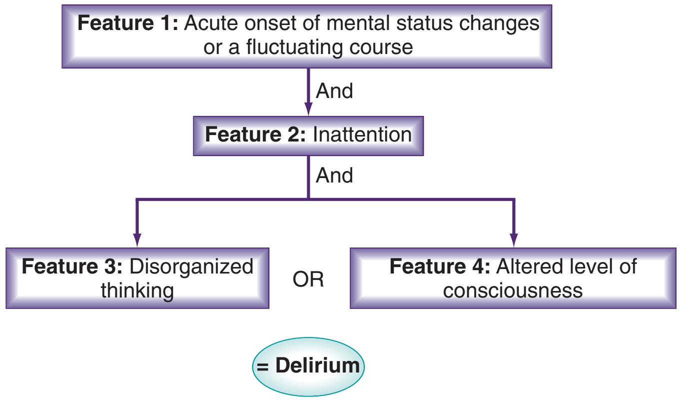


FIGURE 2-2 ■ Confusion Assessment Method in the Intensive Care Unit (CAM-ICU).

TABLE 2-4 Intensive Care Delirium Screening Checklist

PATIENT EVALUATION	
Altered level of consciousness	(A–E)*
Inattention	Difficulty in following a conversation or instructions. Easily distracted by external stimuli. Difficulty in shifting focus. Any of these scores 1 point.
Disorientation	Any obvious mistake in time, place, or person scores 1 point.
Hallucinations-delusions-psychosis	The unequivocal clinical manifestation of hallucination or behavior probably attributable to hallucination or delusion. Gross impairment in reality testing. Any of these scores 1 point.
Psychomotor agitation or retardation	Hyperactivity requiring the use of additional sedative drugs or restraints to control potential danger to self or others. Hypoactivity or clinically noticeable psychomotor slowing.
Inappropriate speech or mood	Inappropriate, disorganized, or incoherent speech. Inappropriate display of emotion related to events or situation. Any of these scores 1 point.
Sleep/wake cycle disturbance	Sleeping less than 4 h or waking frequently at night (do not consider wakefulness initiated by medical staff or loud environment). Sleeping during most of the day. Any of these scores 1 point.
Symptom fluctuation	Fluctuation of the manifestation of any item or symptom over 24 h scores 1 point.
Total Score (0-8)	

*Level of consciousness:
A—No response: score 0.
B—Response to intense and repeated stimulation (loud voice and pain): score 0.
C—Response to mild or moderate stimulation: score 1.
D—Normal wakefulness: score 0.
E—Exaggerated response to normal stimulation: score 1.
Available at: http://www.acgme.org/acgmeweb/tabid/445/GraduateMedicalEducation/SingleAccreditationSystemforAOA-ApprovedPrograms.aspx. Accessed November 12.

stimulation, the patient's shoulder is shaken or pressure applied over the sternum by rubbing, and the response noted (–4 or –5). This assessment takes less than 20 seconds in total and correlates well with other measures of sedation (e.g., Glasgow Coma Scale [GCS], bispectral electroencephalography, and neuropsychiatric ratings).[46]

Until recently, there was no valid and reliable way to assess delirium in critically ill patients, many of whom are nonverbal owing to sedation or mechanical ventilation.[51,58] A number of tools have been developed to aid in the detection of delirium in the ICU. These tools have been validated for use in both intubated and nonintubated patients and measured against a "gold standard," the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria. The tools are the Confusion Assessment Method for the ICU (CAM-ICU)[51-55] and the Intensive Care Delirium Screening Checklist (ICDSC).[8]

The CAM-ICU (Fig. 2-2) is a delirium measurement tool developed by a team of specialists in critical care, psychiatry, neurology, and geriatrics.[51,58] Administered by a nurse, the evaluation takes only 1 to 2 minutes to conduct and is 98% accurate in detecting delirium as compared with a full DSM-V assessment by a geriatric psychiatrist.[51,52]

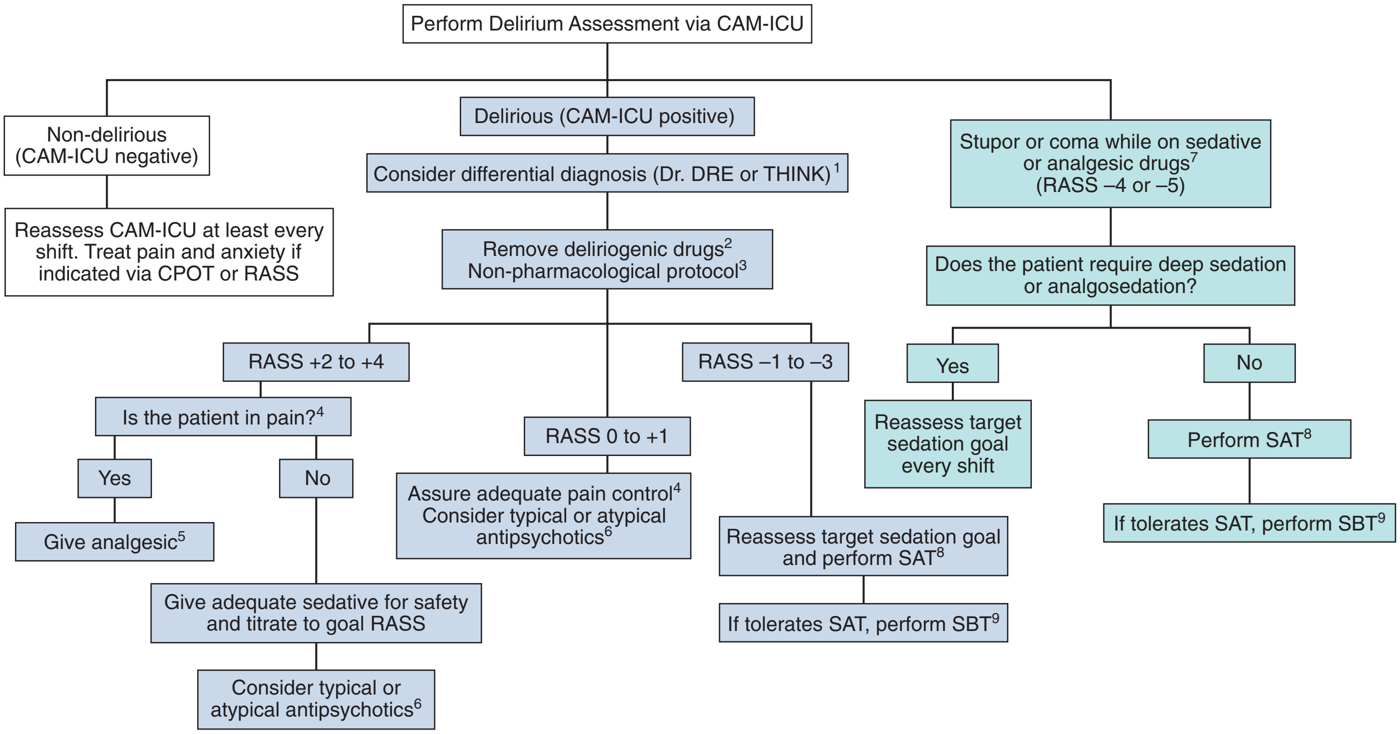
To perform the CAM-ICU, patients are first evaluated for level of consciousness; patients who respond to verbal commands (a RASS score of –3 or higher level of arousal) can then be assessed for delirium. The CAM-ICU comprises four features: (1) a change in mental status from baseline or a fluctuation in mental status, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. Delirium is diagnosed if patients have features 1 and 2, and either feature 3 or 4 is positive (see Fig. 2-2).

The ICDSC[8] (Table 2-4) is a checklist-based assessment tool that evaluates inattention, disorientation, hallucination, delusion or psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbances, and fluctuations in these symptoms. Each of the eight items is scored as absent or present (0 or 1), respectively, and summed. A score of 4 or above indicates delirium, while 0 indicates no delirium. Patients with scores between 1 and 3 are considered to have subsyndromal delirium,[59] which has worse prognostic implications than the absence of delirium but a better prognosis than clearly present delirium.

Recent studies have called into question the usefulness of delirium evaluations for patients under sedation.[60,61] A small subset of patients (approximately 10%) were noted to have rapidly reversible sedation-related delirium, but unfortunately in this study the majority of patients continued to have persistent delirium even after interruption of sedation. Thus, when feasible, delirium evaluation should be performed after interruption of sedation; however delirium evaluations should not be forgone just because a patient is under sedation since the omission of the diagnosis would be far worse than overdiagnosing delirium in a handful of patients.

MANAGEMENT

The development of effective evidence-based strategies and protocols for prevention and treatment of delirium awaits data from ongoing randomized clinical trials of both nonpharmacologic and



1. Dr. DRE:
   - **D**iseases: Sepsis, CHF, COPD
   - **D**rug **R**emoval: SATs and stopping benzodiazepines/narcotics
   - **E**nvironment: Immobilization, sleep and day/night orientation, hearing aids, eye glasses, noise

   THINK:
   - **T**oxic Situations – CHF, shock, dehydration – Deliriogenic meds (tight titration) – New organ failure (liver, kidney, etc.)
   - **H**ypoxemia
   - **I**nfection/sepsis (nosocomial), immobilization
   - **N**onpharmacological interventions[3]
   - **K**$^+$ or Electrolyte problems
2. Consider stoppinig or substituting deliriogenic medications such as benzodiazepines, anticholinergic medications (metoclopramide, H2 blockers, promethazine, diphenhydramine), steroids, etc.
3. See non-pharmacological protocol – see below.
4. If patient is non-verbal assess via CPOT, or if patient is verbal assess via visual analog scale.
5. Analgesia – Adequate pain control may decrease delirium. Consider opiates, non-steroidals, acetaminophen, or gabapentin (neuropathic pain).
6. Typical or atypical antipsychotics. Discontinue if high fever, QTc prolongation, or drug-induced rigidity.
7. Consider non-benzodiazepine sedation strategies (propofol or dexmedetomidine)
8. Spontaneous Awakening Trial (SAT) – If meets safety criteria (no active seizures, no alcohol withdrawal, no agitation, no paralytics, no myocardial ischemia, normal intracranial pressure, $FiO_2 \leq 70\%$)
9. Spontaneous Breathing Trial (SBT) – If meets safety criteria (no agitation, no myocardial ischemia, $FiO_2 \leq 50\%$, adequate inspiratory efforts, O_2 saturation $\geq 88\%$, no vasopressor use, PEEP ≤ 7.5 cm)

Non-pharmacological protocol[3]

Orientation
- Provide visual and hearing aids
- Encourage communication and reorient patient repetitively. Have familiar objects from patient's home in the room
- Attempt consistency in nursing staff
- Family engagement and empowerment

Environment
- Sleep hygiene: Lights off at night, on during day.
- Control excess noise (staff, equipment), earplugs
- Early mobilization and exercise
- Music

Clinical parameters
- Maintain systolic blood pressure > 90 mm Hg
- Maintain oxygen saturations >90%

Treat underlying metabolic derangements and infections

FIGURE 2-3 ■ Delirium Protocol as a part of ABCDEF Bundle.

pharmacologic strategies. Refer to Chapter 51 for a detailed description of management strategies of delirium, including an empiric sedation and delirium protocol. A brief overview is provided here.

When agitation or delirium develops in a previously comfortable patient, a search for the underlying cause should be undertaken before attempting pharmacologic intervention. A rapid assessment should be performed, including assessment of vital signs and physical examination to rule out life-threatening problems (e.g., hypoxia, self-extubation, pneumothorax, hypotension), or other acutely reversible physiologic causes (e.g., hypoglycemia, metabolic acidosis, stroke, seizure, pain). The previously mentioned IWATCHDEATH and DELIRIUM mnemonics can be particularly helpful in guiding this initial evaluation.

Once life-threatening causes are ruled out as possible etiologies, aspects of good patient care such as reorienting patients, improving sleep and hygiene, providing visual and hearing aids if previously used, removing medications that can provoke delirium, and decreasing the use of invasive devices if not required (e.g., bladder catheters, restraints), should be undertaken.

The use of ABCDEs (Awakening and Breathing Trials, Choice of appropriate sedation, Delirium monitoring and management, and Early mobility and Exercise) has been shown to decrease the incidence of delirium and improve patient outcome (Fig. 2-3). This algorithm based on the PAD 2013 guidelines[41] involves the following: (1) Routine *assessment* of agitation, depth and quality of sedation and delirium using appropriate scales (RASS and SAS for agitation and sedation and CAM-ICU or ICDSC for delirium). They recommend using protocol target-based sedation and targeting the lightest possible sedation, thus exposing the patient to lower cumulative doses of sedatives[62] and/or daily awakening trials[63] and spontaneous breathing trials[64] to reduce the total time spent on mechanical ventilation. Coordination of daily awakening and daily breathing was associated with shorter durations of mechanical ventilation, reduction in length of hospital stay, and no long-term neuropsychologic consequences of waking patients during critical illness.[65,66] (2) *Treatment* should start with treating analgesia first. Choosing the right sedative regimen in critically ill patients is important. Numerous studies have confirmed that benzodiazepines are associated with poor clinical outcomes.[67,68,69] The guidelines also recommend avoiding rivastigmine and antipsychotics if there is an increased risk of Torsades de Pointes. (3) *Prevention* also plays an important role. Exercise and early mobility in ICU patients is associated with decreased length of both ICU and hospital polypharmacy.[70,71] Risk factors for delirium need to be identified and eliminated. Promoting sleep and restarting baseline antipsychotic medications are also important. Data from the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS)[67] study and the Safety and Efficacy of Dexmedetomidine Compared to Midazolam (SEDCOM) trial[69] also support the view that dexmedetomidine can decrease the duration and prevalence of delirium when compared to lorazepam or midazolam. Pharmacologic therapy should be attempted only after correcting any contributing factors or underlying physiologic abnormalities. Although these agents are intended to improve cognition, they all have psychoactive effects that can further cloud the sensorium and promote a longer overall duration of cognitive impairment. Patients who manifest delirium should be treated with traditional antipsychotic medication. Newer "atypical" antipsychotic agents (e.g., risperidone, ziprasidone, quetiapine, olanzapine) may decrease the duration of delirium.[76]

Benzodiazepines are not recommended for the management of delirium because they can paradoxically exacerbate delirium. These drugs can also promote oversedation and respiratory suppression. However, they remain the drugs of choice for the treatment of delirium tremens (and other withdrawal syndromes), and seizures.

At times, mechanical restraints may be needed to ensure the safety of patients and staff while waiting for medications to take effect. It is important to keep in mind, however, that restraints can increase agitation and delirium, and their use may have adverse consequences, including strangulation, nerve injury, skin breakdown, and other complications of immobilization.

SUMMARY

Agitation and delirium are very common in the ICU, where their occurrence puts patients at risk of self-injury and poor clinical outcomes. Available sedation and delirium monitoring instruments allow clinicians to recognize these forms of brain dysfunction. Through a systematic approach, life-threatening problems and other acutely reversible physiologic causes can be rapidly identified and remedied. A strategy that focuses on early liberation from mechanical ventilation and early mobilization can help reduce the burden of delirium. Use of antipsychotics should be reserved for patients who pose an imminent risk to themselves or staff.

KEY POINTS

1. Delirium
2. Agitation
3. Confusion
4. Assessment
5. Risk factors
6. Management
7. Sedation

ANNOTATED REFERENCES

Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291(14):1753-1762.

This large cohort study showed that delirium in the ICU was an independent risk factor for death at 6 months and that each day with delirium increased the hazards of dying by 10%.

Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med 2001;27(5):859-864. (Available at: http://www.acgme.org/acgmeweb/tabid/445/GraduateMedicalEducation/SingleAccreditationSystemforAOA-ApprovedPrograms.aspx. Accessed November 12.)

The ICDSC provides health care providers with an easy to use bedside delirium monitoring instrument that can be incorporated into the daily work flow of bedside nurses. It provides the ability to diagnose subsyndromal delirium.

Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. Am J Respir Crit Care Med 2009;180(11):1092-1097.

This cohort study demonstrated a dose-response curve between days of delirium and the risk of dying at 1 year.

Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;286(21):2703-2710.

A landmark study validating for the first time an easy to use bedside delirium-monitoring instrument for nonverbal mechanically ventilated patients. Delirium monitoring with the CAM-ICU can be performed in less than 2 minutes and does not require a psychiatrist.

Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373(9678):1874-1882.

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3 Management of Acute Pain in the Intensive Care Unit

David Boldt

Critically ill patients frequently experience acute pain, which can have multiple causes in the intensive care unit (ICU) setting including surgical and posttraumatic wounds, the use of invasive monitoring devices and mechanical ventilators, prolonged immobilization, and routine nursing care (e.g., dressing changes). The experience of pain differs among patients, but the physiologic consequences of inadequately treated pain are relatively predictable and potentially deleterious. Some physiologic responses to acute pain and stress are mediated by neuroendocrine activation and increased sympathetic tone. Patients may develop tachycardia, increased myocardial oxygen consumption, immunosuppression, hypercoagulability, persistent catabolism, and numerous other metabolic alterations.[1] Additional morbidity may be incurred by pain-related functional limitations such as impaired pulmonary mechanics or delayed ambulation.

ACUTE PAIN ASSESSMENT

The assessment of acute pain in the ICU can be challenging. Unfortunately, many ICU patients cannot provide full or even partial information regarding their pain. However, the inability of ventilated, sedated ICU patients to report pain should not preclude its assessment and management. A number of scales and assessment tools for the evaluation of pain in ICU patients have been developed, such as the visual analog scale, the numeric rating scale, behavioral pain scale, and critical care pain observation scale (Fig. 3-1). In heavily sedated or paralyzed patients, caregivers must use signs of heightened sympathetic activity like hypertension, tachycardia, lacrimation, diaphoresis, and restlessness as surrogate indicators for the presence of pain. Favorable trends in these signs following analgesic administration provide a measure of the success of a given intervention.

OPTIONS FOR ACUTE PAIN THERAPY

Acute pain is triggered by stimulation of peripheral nociceptors in the skin or deeper structures and is a complex process involving multiple mediators at various levels of the neuraxis (Fig. 3-2). Different parts of the pain pathway can be targeted either individually or as part of a comprehensive "multimodal" strategy aimed at multiple sites for additive or synergistic effects. Thus, nociception can be influenced peripherally by the use of nonsteroidal antiinflammatory drugs (NSAIDs) and nerve blocks, at the spinal cord level by the use of epidural or intrathecal medications, and centrally by the use of systemic medications.

Nonsteroidal Antiinflammatory Drugs

Drugs in this class inhibit cyclooxygenase (COX) enzymes, which are involved in synthesis of prostaglandins and related inflammatory mediators in response to injury. COX-1 is a constitutive enzyme that is present in most tissues and, through the production of prostaglandins E2 and I2, serves homeostatic and protective functions. COX-2 is an inducible enzyme that is expressed in response to inflammation. As a class, NSAIDs can cause adverse effects that include gastrointestinal (GI) ulceration and GI bleeding, inhibition of platelet function, renal injury, and bronchospasm in aspirin-sensitive patients (triad of asthma, nasal polyposis, and aspirin allergy).

Ketorolac is one of only two parenteral NSAIDs available in the United States. Although it has been shown to reduce postoperative opioid requirements, prolonged use may be associated with a significant incidence of the aforementioned side effects, primarily GI bleeding and renal injury. Consequently, it is recommended that ketorolac therapy be limited to a maximum of 5 days. In addition, ketorolac, as with all NSAIDs, should be used at decreased dosages or avoided altogether in patients at higher risk of such complications (e.g., advanced age, hypovolemia, or preexisting renal insufficiency).

Intravenous ibuprofen (Caldolor) has recently been approved by the Food and Drug Administration (FDA) as the only other parenteral NSAID for the treatment of pain. It has been demonstrated in several studies to be a safe and well-tolerated adjunctive agent in a multimodal approach of pain management, reducing opioid requirements and decreasing the incidence of opioid-related side effects.[2-4] As with other nonselective NSAIDs, there is risk of GI bleeding and renal injury.

Due to the concern for an increased risk of cardiovascular thrombotic complications, myocardial infarction, and stroke demonstrated with COX-2 selective NSAIDs, there is a Black Box Warning contraindicating the use of both intravenous ibuprofen and ketorolac in perioperative coronary artery bypass graft (CABG) patients. In addition, their use is contraindicated in patients with active or recent GI bleeding or perforation. Unfortunately, the unfavorable adverse effect profile of these agents limits their use in the ICU setting.

Acetaminophen is a para-aminophenol derivative with analgesic and antipyretic properties similar to those of aspirin. The mechanism of action of acetaminophen is still poorly defined. Recent evidence has suggested that it may selectively act as an inhibitor of prostaglandin synthesis in the central nervous system (CNS) rather than in the periphery. When combined with opioids, acetaminophen may be a useful adjunct in pain relief, especially as an alternative to NSAIDs in high-risk patients because of the lower incidence of adverse effects.

An intravenous (IV) form of acetaminophen was approved in 2010 for the management of fever and mild to severe pain. Studies have proven it to be safe and effective in the reduction of pain, leading to decreased opioid requirements and fewer opioid-related side effects.[4-7] Compared head-to-head in the setting of acute pain, IV acetaminophen has been shown to be equal and in some cases even more effective than IV morphine.[8-10] The increased analgesic effects of IV, compared to oral acetaminophen, likely has to do with more favorable pharmacokinetics and avoidance of the hepatic first pass effect. When compared with oral or rectal acetaminophen in equal doses, intravenous administration results in a more rapid elevation in plasma concentrations and higher peak levels of acetaminophen.[10] In fact, the mean peak concentration after infusion of IV acetaminophen is 70% higher than that seen with an equivalent oral dose.[10] These higher plasma concentrations result in a more rapid and significant diffusion across the blood-brain barrier, as demonstrated by significant differences in the peak and total amount of acetaminophen in the cerebrospinal fluid with intravenous versus oral administration.[11] Although there are concerns about the use of acetaminophen in patients with liver disease, it has proven to be safe even in this population, although

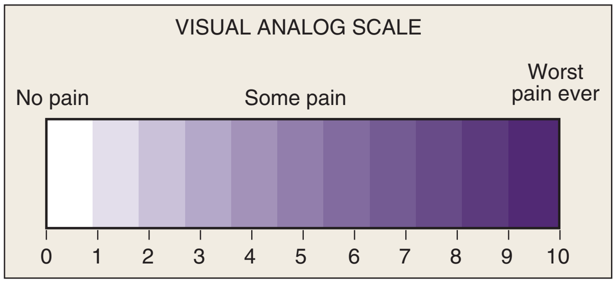

FIGURE 3-1 ■ **Visual analog scale.** Pain can be rated between 0 (no pain) and 10 (extreme pain). Use of a graphic such as this allows an intubated patient to indicate his or her level of discomfort by pointing. Other scales use cartoon faces that are either smiling or frowning. (From Higgins TL, Jodka PG, Farid A. Pharmacologic approaches to sedation, pain relief and neuromuscular blockade in the intensive care unit. Part II. Clin Intensive Care. 2003;14[3-4]:91-98.)

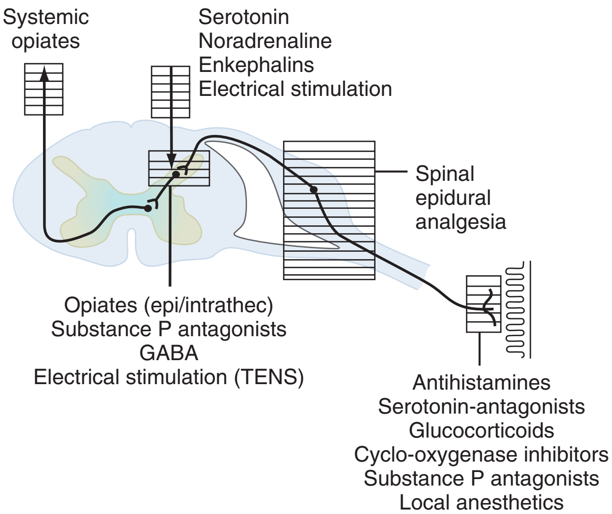

FIGURE 3-2 ■ **"Map" of the path of nociceptive information from periphery to central nervous system.** Modification of information can occur at any point of information transfer. GABA, gamma-aminobutyric acid; TENS, transcutaneous electrical nerve stimulation. (From Kehlet H. Modification of responses to surgery by neural blockade: clinical implications. In: Cousins MJ, Bridenbaugh PO, editors. Neural blockade in clinical anesthesia and pain management. 2nd ed. Philadelphia: Lippincott; 1988:145.)

a reduction of the daily dosage limit is recommended by the manufacturer in cases of mild to moderate hepatic impairment.[12] Its use is contraindicated, however, in cases of severe hepatic impairment.

Opioid Analgesics

This drug class remains the mainstay of ICU analgesia. Although a number of parenteral opioids are available, morphine, hydromorphone, and fentanyl are most commonly used, often as infusions in intubated patients along with a sedative agent. Opioids bind to a variable degree with opioid receptor subtypes (μ, δ, κ) located in the brain, spinal cord, and peripheral sites and modulate the transmission and processing of nociceptive signals. The clinical and pharmacologic properties of opioids depend on several variables, including chemical and solubility properties, dosing regimen, patient characteristics (e.g., age, tolerance, hepatic or renal dysfunction), and presence of active metabolites.

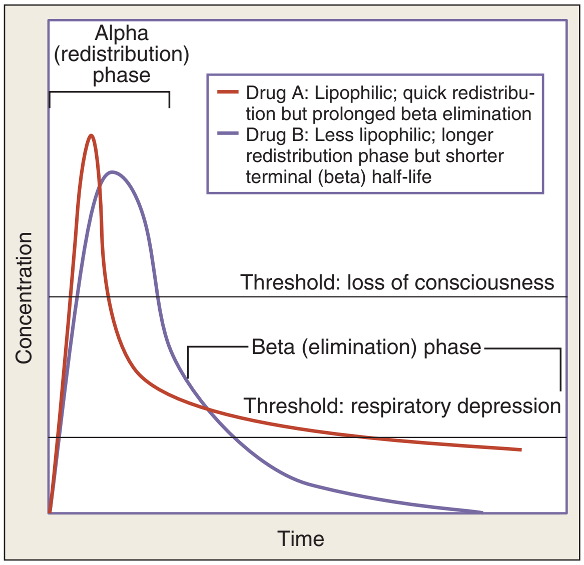

FIGURE 3-3 ■ **Pharmacokinetics.** A lipophilic drug (drug A) may have a rapid onset and an initially quick distribution, but a prolonged beta-elimination (metabolism) phase resulting in respiratory depression with repeated doses or constant infusion. A less lipophilic drug (drug B) may take longer to redistribute, giving the impression of a prolonged initial duration of action, but it does not accumulate owing to a shorter elimination half-life. Fentanyl is like drug A, whereas morphine is similar to drug B. (From Higgins TL, Jodka PG, Farid A. Pharmacologic approaches to sedation, pain relief and neuromuscular blockade in the intensive care unit. Part II. Clin Intensive Care 2003;14[3-4]:91-98.)

Opioids are excellent analgesics, but they are not amnestic agents. As a class they may suppress respiratory drive and promote sedation, GI symptoms (ileus, nausea and vomiting, constipation), urinary retention, pruritus, or hypotension as a result of the ablation of pain-mediated sympathetic stimulation. In actual practice, however, opioids are relatively neutral in their hemodynamic effects, so long as they are used judiciously in euvolemic patients. Of note, morphine additionally causes hypotension by triggering the release of histamine. This side effect, along with its hepatic metabolism to an active compound, morphine-6-glucuronide, which can accumulate in patients with renal insufficiency, are the main disadvantages of morphine when compared with other parenteral opioids.

Opioids are most commonly administered intravenously in critically ill patients and titrated to effect, either on a scheduled, intermittent basis or as a continuous infusion. This strategy avoids concerns regarding unpredictable bioavailability associated with intramuscular, enteral, or transdermal administration and favors more stable analgesic drug concentrations. The benefits of administering analgesics in this fashion, however, must be balanced against the possibility of unintentional overdosing resulting in excessive sedation, respiratory depression, and in turn, prolonged intubation. To avoid this problem, scheduled daily interruptions of sedative and analgesic drug infusions, often referred to as "sedation vacations" or "sedation holidays," are recommended as they have been shown to result in shorter durations of mechanical ventilation and ICU stays.[13] Drugs that are often thought of as short acting, like fentanyl, actually have a markedly prolonged duration of action if given as an infusion, even in patients without significant renal or hepatic dysfunction due to its accumulation in fat (Fig. 3-3). This concept is referred to as the "context-sensitive half-life," which is defined as the time it takes for the plasma concentration of a drug to decrease by one-half following cessation of a continuous infusion.

Remifentanil is a potent synthetic opioid with a rapid onset and short duration of action, owing to its unique organ-independent metabolism and the absence of active metabolites or drug accumulation, even following prolonged infusion. Unlike other opioids that rely heavily on hepatic metabolism, remifentanil is rapidly hydrolyzed within a matter of minutes by nonspecific plasma and tissue esterases (not plasma cholinesterase or pseudocholinesterase notably, meaning that patients with atypical cholinesterase do not experience a prolonged duration of action). This rapid hydrolysis also prevents drug accumulation during continuous administration. Furthermore, although its major metabolite is renally eliminated, it is virtually devoid of opioid activity, resulting in a stable pharmacokinetic profile even in the presence of severe renal impairment. All of these qualities result in a drug with an extremely short context-sensitive half-life, irrespective of infusion duration. Although this may be particularly useful in critically ill patients who often have comorbid hepatorenal dysfunction and who require prolonged opioid infusions, there are a couple of drawbacks to this drug that limit its widespread use in the ICU setting: First, its potent nature often leads to dose-dependent hypotension and bradycardia if not carefully titrated. Second, its ultrashort duration of action of several minutes can result in abrupt recurrence of pain after an infusion is stopped, which may result in unwanted acute sympathetic stimulation. This may be particularly pronounced in those with a large pain burden, such as postoperative or trauma patients. Other adverse effects of remifentanil are similar to those of other opioids. Of these, chest wall rigidity resulting in the inability to ventilate is arguably the most worrisome and deserves a brief mention. Although a possible adverse effect of any IV opioid, it may be slightly more common with remifentanil, particularly when it is given as a bolus or infused at higher rates. This can be treated by administering a neuromuscular blocking agent and reducing or discontinuing the infusion.[14-16]

Ketamine

Ketamine is a well-known general anesthetic and analgesic. With the discovery of the *N*-methyl-D-aspartate (NMDA) receptor and its links to nociceptive pain transmission and central sensitization, there has been renewed interest in utilizing ketamine as a potential antihyperalgesic agent. Ketamine is a noncompetitive NMDA receptor antagonist. Although high doses (>2 mg/kg) of ketamine have been implicated in causing psychomimetic effects (excessive sedation, cognitive dysfunction, hallucinations, nightmares), subanesthetic or low doses (<1 mg/kg) of ketamine have demonstrated significant analgesic efficacy without these side effects. Furthermore, there is no evidence to indicate that low doses of ketamine exert any adverse pharmacologic effects related to respiration or cardiovascular function. Low doses of ketamine have not been associated with development of nausea, vomiting, urinary retention, or impaired intestinal motility. Ketamine, in combination with IV opioids, has been shown not only to reduce postoperative opioid consumption but also to improve analgesia.[5,17]

Methadone

The use of methadone in the outpatient setting in treating opioid addiction and providing relief in chronic pain and palliative care is well established.[18] Its long duration of action (up to 8 hours) compared to other opioids and its dual effects on both opioid and NMDA receptors make it an ideal agent in these settings. In addition to these features, methadone differs pharmacologically from other opioids in several important ways. Its elimination half-life, which is considerably longer than its duration of action, varies dramatically among individuals from 8 to 90 hours, due largely to its highly lipophilic properties leading to drug accumulation.[18] This results in three important considerations regarding drug titration and side effects: First, dosage increases should only be made once every several days, since steady-state plasma concentrations, and therefore full analgesic effects, are not attained until 3 to 5 days after initiation. Second, peak respiratory depressant effects usually occur later and last longer than the peak analgesic effect, especially during the drug initiation phase. Third, when attempting to discontinue the drug after long-term use the dose should be gradually tapered off, as abrupt discontinuation can lead to withdrawal symptoms. These factors should be kept in mind when dosage adjustments are being made. The delayed respiratory depressant effect is due to drug accumulation rather than the presence of active metabolites as with morphine, since methadone is hepatically metabolized to inactive metabolites. Other than respiratory depression, the most commonly seen serious adverse effect is QT prolongation, which makes regular monitoring of the EKG necessary especially during initiation of therapy, dosage increases, or addition of other medications with QT prolonging effects. Although traditionally used for chronic pain and addiction, there is recent interest in the use of this drug acutely in the inpatient setting in patients who are displaying signs of either opioid tolerance or opioid-induced hyperalgesia.

OPIOID TOLERANCE AND OPIOID-INDUCED HYPERALGESIA

Although at first glance their presentation is quite similar, it is clinically important to distinguish these two situations in terms of the differences in their treatment. Both may result from high-dose opioid consumption and present with uncontrolled pain despite increasing opioid doses. The difference, however, is that patients with opioid-induced hyperalgesia display signs of increasing sensitivity to painful stimuli (hyperalgesia), and the pain is more diffuse (allodynia) and present in an area or distribution that is beyond the initial site. Differentiation of these two scenarios can be difficult, and consultation with a pain management specialist may be necessary.

Opioid tolerance results from repeated exposure to an opioid causing a decreased therapeutic effect through desensitization of antinociceptive mechanisms. Treatment options involve further uptitration of the current opioid regimen, the addition of adjunctive agents with different mechanisms of pain control in a multimodal approach, and attempting an opioid switch or “rotation” to a different opioid analgesic. Although there is debate about the efficacy of the latter approach, methadone in particular has demonstrated particular efficacy when attempting an opioid switch.[19,20] This is likely due to its dual mechanism of action as an opioid agonist and NMDA receptor antagonist, a quality that is unique among other opioids. Its action at the NMDA receptor not only provides an additional mechanism for pain control but also attenuates hyperalgesia, which arguably also plays a part in many cases of opioid tolerance.[19,20]

Opioid-induced hyperalgesia, on the other hand, results from repeated exposure to an opioid causing increased pain due to the central sensitization of pronociceptive mechanisms. This has been termed the *wind-up* phenomenon, and presents a challenging problem for the clinician. As its mechanism is different from opioid tolerance, the treatment also differs. Rather than uptitration of opioid agents, attempts should be made to reduce and even discontinue them. This is accomplished through the addition of nonopioid analgesics and through the use of NMDA-receptor antagonists, in particular ketamine. The NMDA receptor is a ligand-gated calcium channel that plays a major role in the development of central sensitization. Through antagonism of this receptor, ketamine has been shown to reverse this phenomenon and effectively treat the hyperalgesia.[19,20] In addition to its effectiveness in treating opioid-induced hyperalgesia, the use of low-dose ketamine in the treatment of acute pain has been shown to reduce opioid requirements, as previously discussed. This may be particularly beneficial in the postoperative setting.[5] The opioid-sparing effect of ketamine is partly due to its own intrinsic analgesic effect, but when combined with opioid treatment regimens, it is also likely due to prevention of hyperalgesia.[17,19] In addition to ketamine, methadone has been shown to improve opioid-induced hyperalgesia, likely in part due to its own action at the NMDA receptor.[19,20] Initiation of methadone in this setting may also facilitate the tapering and removal of other opioid agents contributing to the hyperalgesia.

Tramadol

Tramadol is a centrally acting synthetic analgesic with two distinct mechanisms of action: It is a weak μ-opioid agonist and a reuptake inhibitor of norepinephrine and, to a lesser extent, serotonin. This results in augmentation of descending inhibitory pathways of pain control. Tramadol has proven to be an effective analgesic, especially when combined with acetaminophen, with fewer opioid-related side effects, most notably gastrointestinal.[21-24] Tramadol is a racemic mixture of two enantiomers with different pharmacologic effects. One isomer is responsible for the norepinephrine effect and the other the serotonin effect. In addition, its μ-opioid effect is dependent on metabolism by P4502D6 enzyme to an active metabolite. Unfortunately, 5% to 15% of the population are poor metabolizers.[25]

Tapentadol is a newer agent with a similar dual mechanism of action as a μ-opioid agonist and a norepinephrine uptake inhibitor. Unlike tramadol, it does not require metabolic activation and is a nonracemic molecule, only affecting the reuptake of norepinephrine. These features may increase the efficacy of this agent compared to tramadol. Although tapentadol has 20 times less affinity for the μ-opioid receptor than morphine, it has been demonstrated to have an analgesic effect only three times less than morphine, which is likely explained by its action on norepinephrine.[26] When compared with several opioid analgesics including oxycodone in the setting of both acute and chronic pain, tapentadol has shown comparable efficacy with fewer GI adverse effects.[27-30]

Gabapentin

The gabapentanoids gabapentin and pregabalin are analogs of gamma-aminobutyric acid (GABA). Although initially developed as antiepileptic agents, an indication for which they have not shown great efficacy, these agents have become well established for the long-term treatment of chronic neuropathic pain. Although not completely understood, their mechanism of action involves binding to voltage-gated calcium channels in the central nervous system, downregulating their action and subsequently decreasing neurotransmitter release. This results in inhibition of central sensitization and hyperalgesia, which is responsible for the development of chronic neuropathic pain. Recent studies, however, have investigated the use of these agents as an adjunct to opioid analgesics in the treatment of acute pain, in particular postsurgical pain.

A single preoperative dose of gabapentin has been shown to improve postoperative pain scores and decrease postoperative opioid requirements in a variety of surgical populations.[31,32] This is theorized to be due to the prevention of surgery-induced central sensitization, which is believed to also play a significant role in acute postoperative pain. There is also evidence that continuation of gabapentanoids in the postoperative period may help to provide increased pain relief and reduce opioid requirements.[32,33]

Studies using pregabalin in the treatment of acute postoperative pain have demonstrated similar efficacy with this agent.[5,17,33,34]

Alpha-2 Adrenergic Agonists

In addition to the opiate system, alpha-2 (α2) adrenergic activation represents another inherent pain-control network in the CNS. The α2 adrenergic receptor exists in the substantia gelatinosa of the dorsal horn, which is a primary site of action by which this class of drugs can inhibit somatic pain. This receptor system also exists in the brain, where its stimulation can produce sedation. Cardiovascular depression from α2 adrenergic agonists can occur at both brain and spinal cord sites. These side effects of sedation and sympathetic inhibition limit α2 adrenergic agonists to only an adjuvant role as analgesics.

Clonidine was originally used to control blood pressure and heart rate. It binds to α2 adrenergic and imidazole receptors in the CNS. It has been hypothesized that clonidine acts at α2 adrenergic receptors in the spinal cord to stimulate acetylcholine release, which acts on both muscarinic and nicotinic receptor subtypes for postoperative pain relief. Clonidine can be administered by oral, IV, or transdermal routes.

A newer centrally acting α2 agonist is the parenteral agent dexmedetomidine, which possesses a higher affinity for the α2 receptor than clonidine. Although FDA approved only for sedation, it is being studied as an adjunctive analgesic based on its mechanism and several studies that have demonstrated decreased opioid requirements and improved pain scores with its use.[35,36]

Neuraxial Analgesic Techniques

The administration of narcotics, local anesthetics, and other agents via intrathecal or epidural catheters targets the processing of pain signals at the level of the spinal cord or nerve root. The use of epidural catheters for regional analgesia in ICU patients may be quite useful, assuming that the pain pattern is regionalized and that there are no contraindications to catheter placement (e.g., coagulopathy, uncontrolled infection, unstable spinal skeletal fractures). In some patients, epidural analgesia may be preferable to IV-administered medications because this approach affords dense regional pain control while largely avoiding the sedative and respiratory side effects of systemic medications. In trauma patients with rib fractures and postsurgical thoracotomy patients, the use of epidural catheters may be particularly helpful in achieving pain control while minimizing respiratory depression in a patient population that is prone to develop respiratory insufficiency and failure due to hypoventilation as a result of uncontrolled pain.

Peripheral Nerve Blocks

Peripheral nerve blocks are an attractive method of providing postoperative analgesia for many orthopedic surgical procedures. The use of peripheral nerve blocks achieved by either a single injection or by continuous infusion via a catheter may provide superior analgesia, reduce opioid consumption, and reduce opioid-related side effects. Unfortunately, this technique is not commonly used in the ICU setting. Due to the aforementioned benefits, however, it should be strongly considered as an alternative to opioids when appropriate.

Multimodal Analgesia

Multimodal analgesia is a concept that was developed as a technique to improve the quality of pain relief while minimizing the adverse effects of opioids. The idea is to use a combination of agents with different mechanisms in an additive and often synergistic effect to achieve adequate analgesia with lower doses of each agent. Utilizing this concept in the ICU can be vitally important, since the adverse effects of drugs are often magnified in the critically ill, especially in the setting of polypharmacy. As we increase our understanding of the etiology of pain, newer agents with different mechanisms of action are being developed, and hopefully one day the concept of treating pain with several agents in a multimodal approach will be common practice in every clinical setting.

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4 Fever

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Fever is defined as an increase in body temperature. Normal body temperature is 36.8°C ± 0.4°C. Normally, body temperature varies in a circadian fashion by about 0.6°C, being lowest in the morning and highest in the late afternoon or early evening. A core body temperature of ≥38.3°C is generally accepted to represent fever.[1] In 2008, a task force from the Society of Critical Care Medicine and the Infectious Disease Society of America concluded that "because fever can have many infectious and noninfectious etiologies, a new fever in a patient in the intensive care unit should trigger a careful clinical assessment rather than automatic orders for laboratory and radiologic tests. A cost-conscious approach to obtaining cultures and imaging studies should be undertaken if indicated after a clinical evaluation."[1]

Fever is a common finding in patients admitted to an intensive care unit (ICU), being present at one time or another in almost 50% of cases. Moreover, fever is an independent risk factor for mortality in patients admitted to ICUs.[2]

The pathogenesis of fever triggered by infectious agents is complex.[2,3] Classically, fever was thought to be triggered by the peripheral release of various cytokines—notably, interleukin 1-beta (IL-1β), tumor necrosis factor (TNF), IL-6, and possibly interferon-alpha (IFN-α)—that are capable of up-regulating the expression of two key enzymes that are involved in the production of prostaglandin E_2 (PGE_2), namely: cyclooxygenase (COX)-2 and microsomal prostaglandin E synthase-1 (mPGES-1). The central role of PGE_2 in the pathogenesis of fever is supported by the following findings: first, febrile responses to lipopolysaccharide (LPS) and other inflammatory stimuli are depressed by drugs that inhibit PG synthesis; second, mice that are genetically deficient in either COX-2 or mPGES-1 do not become febrile after an LPS challenge. Although PGE_2 can be produced by immunostimulated macrophages in the periphery, the PGE_2 that is responsible for fever is probably generated in the central nervous system (CNS). PGE_2 binds to prostaglandin receptors located on a cluster of neurons in the preoptic region of the hypothalamus. Although there are four subtypes of PGE_2 receptors, only one, PGE_2 receptor 3 (EPR3), is required for the development of fever in response to IL-1β, LPS, or PGE_2.[4] The activation of EPR3 triggers a number of neurohumoral and physiologic changes that lead to increased body temperature. The antipyretic effects of various nonsteroidal antiinflammatory drugs (NSAIDs), such as aspirin and ibuprofen, are due to the inhibition of COX-2-dependent PGE_2 biosynthesis in the CNS. The mechanism by which acetaminophen reduces fever might involve COX-2 inhibition in the CNS, but it remains controversial and poorly understood.[5-7]

The classical view of the pathogenesis of fever associated with infection has been updated by the proposal that pyrogenic stimuli trigger the activation of vagal afferent signals originating from the liver and travelling to the nucleus tractus solitarius in the brainstem. These signals are subsequently transmitted to the hypothalamus, where an early increase in temperature is mediated in a PGE_2-independent fashion via an α_1-adrenergic receptor–dependent pathway. A secondary (delayed) increase in temperature is mediated via an α_2-adrenergic–dependent pathway that leads to an increase in PGE_2 production secondary to the increased expression of COX-2.

Body temperature can be measured using an oral, axillary, or rectal mercury-filled glass thermometer. These traditional approaches, however, have been largely replaced by a variety of safer and more environmentally friendly methods that use thermistors located on catheters or probes placed in the pulmonary artery, distal esophagus, urinary bladder, or external ear canal. Infrared detectors can be used to measure tympanic membrane temperature. Forehead skin temperature can be measured using a temperature-sensitive patch.

Fever is a cardinal sign of infection. Accordingly, any new onset of fever should trigger a careful diagnostic evaluation for investigating the source of infection. The diagnostic evaluation should be thorough and tailored to the recent history of the patient. For example, the possibility of a CNS infection should receive greater attention in a patient with recent or ongoing CNS instrumentation. By the same token, if a patient recently underwent a gastrointestinal surgical procedure, the clinician should have a high index of suspicion for an intraabdominal source of infection. Key elements in the assessment of new-onset fever in the ICU are listed in Box 4-1. Common sources of infection in ICU patients are listed in Box 4-2.

Although fever in the ICU is most commonly due to infection, myriad noninfectious causes of systemic inflammation (Box 4-3) can also result in hyperthermia. Some authors claim that noninfectious causes of fever rarely result in a core temperature above 38.9°C,[8,9] but rigorous data in support of this view are lacking. Still, infections are rarely if ever associated with core temperatures over 41.1°C. When the core temperature is this high, the clinician should suspect malignant hyperthermia, neuroleptic malignant syndrome, or heat stroke.

On theoretical grounds, the routine treatment of fever would seem to be ill-advised. Hyperthermia is an adaptive response that enhances the host's ability to fight infection.[10] In addition, body temperature becomes an unreliable clinical parameter when patients are receiving antipyretic therapy. Still, currently available data are insufficient to determine whether fever should be routinely treated in ICU patients. In one randomized clinical trial that enrolled 82 surgical ICU patients, the protocolized administration of acetaminophen when body temperature exceeded 38.5°C was compared to the treatment of fever only when temperature exceeded 40°C. More aggressive treatment of fever in this study was associated with a trend toward higher mortality ($P = 0.06$).[11] In contrast to these findings, Schortgen et al. randomized febrile patients with septic shock requiring vasopressors, mechanical ventilation, and sedation to either external cooling ($n = 101$) for 48 hours to achieve normothermia (36.5°C to 37°C) or no external cooling ($n = 99$).[12] Day 14 mortality was significantly lower in the group randomized to external cooling ($P = 0.013$). In another study, 120 febrile adults (not all critically ill) were randomized to treatment with intravenous ibuprofen (100, 200, or 400 mg) or placebo every 4 hours for a total of 6 doses. There was no significant difference in the rate of serious adverse events, such as acute kidney injury, bleeding, or mortality, between the groups.[13]

Although it is unclear whether hyperthermia should be routinely treated in ICU patients, antipyretics should be administered to selected patients with fever, notably those with acute coronary syndromes (i.e., myocardial infarction or unstable angina), because the tachycardia that usually accompanies the febrile response can exacerbate imbalances between myocardial oxygen delivery and demand. Febrile patients with head trauma, subarachnoid hemorrhage, or stroke should receive cooling (using antipyretics and/or external cooling devices) to prevent temperature-related increases in cerebral oxygen utilization. Children with temperatures higher than 40°C or with a history of seizures should also be treated.

[†] Deceased

BOX 4-1 Key Elements in the Evaluation of New-Onset Fever in ICU Patients

- Be familiar with the patient's history. Pay particular attention to possible predisposing causes of fever.
- Perform a careful physical examination. Pay particular attention to surgical wounds and vascular access sites. Look for evidence of pressure-induced skin ulceration. In patients with recent median sternotomy, evaluate the stability of the chest closure. Perform a careful abdominal examination.
- Obtain or review a recent chest X-ray, looking for evidence of new infiltrates or effusions.
- Obtain appropriate laboratory studies. At a minimum, these studies should include a peripheral white blood cell count and cultures of blood and urine. If the patient is endotracheally intubated or has a tracheotomy, obtain a sample of sputum for Gram stain. In some centers, sputum is routinely cultured. In other centers, bronchoalveolar lavage or bronchial brushing for quantitative microbiology is performed using blind or bronchoscopic methods.
- In patients receiving antibiotics for more than 3 days, a stool sample should be analyzed for the presence of *Clostridium difficile* toxin, unless a high sensitivity assay for the toxin was performed recently and was negative.
- More extensive diagnostic evaluation should be considered in a graded fashion based on history, physical examination findings, laboratory results, persistence of fever despite presumably appropriate antimicrobial chemotherapy, or clinical instability. These additional tests and procedures include diagnostic thoracentesis, paracentesis, and lumbar puncture. Imaging studies should be considered, including abdominal or cardiac ultrasonography and head, chest, or abdominal computed tomography.

Hypothermia blankets are often used to lower the core temperature in febrile ICU patients, although these blankets are no more effective for cooling patients than antipyretic agents.[14,15] Hypothermia blankets can cause large temperature fluctuations and are associated with rebound hyperthermia when removed. Additionally, external cooling can augment hypermetabolism and actually promote persistent fever. Lenhardt and colleagues demonstrated that active external cooling in volunteers with induced fever increased oxygen consumption by 35% to 40% and was associated with a significant increase in circulating epinephrine and norepinephrine concentrations.[16]

In view of these phenomena, the administration of an antipyretic agent is the recommended approach when the treatment of fever is warranted. Commonly used antipyretics include isoform nonselective COX inhibitors, such as ibuprofen or aspirin, or acetaminophen. Because corticosteroids (hydrocortisone, methylprednisolone) are potent antiinflammatory agents, these drugs can suppress the febrile response to infection. Other antiinflammatory agents have a similar effect, so absence of fever should not be used to rule out infection, especially in patients receiving corticosteroids or other potent antiinflammatory drugs.

A reasonable approach for evaluating fever in ICU patients was described by Marik.[8] Blood cultures should be obtained whenever an ICU patient develops a new fever. The sensitivity of blood cultures for detecting bacteremia depends to a large extent on the volume of blood inoculated into culture media. Whenever possible, at least 10 to 15 mL of blood should be withdrawn and inoculated into 2 or 3 bottles or tubes at a ratio of 1 mL of blood per 5 mL of medium.[1]

A comprehensive physical examination should be carried out, and a chest X-ray obtained and reviewed. Noninfectious causes of fever should be excluded. In patients with an obvious focus of infection, a directed diagnostic evaluation is necessary. However, if there is no obvious source of infection and the patient is not clinically deteriorating, it is reasonable to obtain blood cultures and observe the patient for 48 hours before ordering additional diagnostic studies or starting empirical antibiotics. This approach is not reasonable, however, if new fever is accompanied by other signs of worsening clinical status such as arterial hypotension, oliguria, increasing confusion, rising serum lactate concentration, falling platelet count, or worsening coagulopathy. Nor is this approach reasonable if the core temperature is above 39°C but below 41.1°C. Patients in this category should receive empirical antimicrobial chemotherapy while aggressive attempts are made to diagnose the source of infection. All febrile neutropenic patients should receive broad-spectrum empirical antimicrobial chemotherapy after appropriate cultures are obtained.

Intravascular catheters are commonly suspected as a source of infection and fever in ICU patients and can cause fever due to localized or systemic (bloodstream) infection. In patients with a new onset of fever but without other ominous signs (e.g., hypotension, profound thrombocytopenia, acute respiratory distress syndrome), it is unnecessary to remove all intravascular catheters. In contrast, if one or more of these (or other) ominous signs are present, the most prudent course of action is to remove all vascular access catheters, including tunneled and/or cuffed devices. In many institutions, routine culturing of catheter tips (using semiquantitative methods on solid media) is no longer thought to be cost effective because the results of such studies rarely change the subsequent therapy strategy.[17,18]

BOX 4-2 Common Infectious Causes of Fever

CENTRAL NERVOUS SYSTEM
Meningitis
Encephalitis
Brain abscess
Epidural abscess

HEAD AND NECK
Acute suppurative parotitis
Acute sinusitis
Parapharyngeal and retropharyngeal space infections
Acute suppurative otitis media

CARDIOVASCULAR
Catheter-related infection
Endocarditis

PULMONARY AND MEDIASTINAL
Pneumonia
Empyema
Mediastinitis

HEPATOBILIARY AND GASTROINTESTINAL
Diverticulitis
Appendicitis
Peritonitis (spontaneous or secondary)
Intraperitoneal abscess
Perirectal abscess
Infected pancreatitis
Acute cholecystitis
Cholangitis
Hepatic abscess
Acute viral hepatitis

GENITOURINARY
Bacterial or fungal cystitis
Pyelonephritis
Perinephric abscess
Tubo-ovarian abscess
Endometritis
Prostatitis

BREAST
Mastitis
Breast abscess

CUTANEOUS AND MUSCULAR
Cellulitis
Suppurative wound infection
Necrotizing fasciitis
Bacterial myositis or myonecrosis
Herpes zoster

OSSEOUS
Osteomyelitis

BOX 4-3 Noninfectious Causes of Fever

CENTRAL NERVOUS SYSTEM
Subarachnoid hemorrhage
Intracerebral hemorrhage
Infarction

CARDIAC
Myocardial infarction
Pericarditis

PULMONARY
Atelectasis
Pulmonary embolism
Fibroproliferative phase of acute respiratory distress syndrome

HEPATOBILIARY AND GASTROINTESTINAL
Acalculous cholecystitis
Acute pancreatitis
Active Crohn's disease
Toxic megacolon
Alcoholic hepatitis

RHEUMATOLOGIC SYNDROMES
Vasculitides (e.g., polyarteritis nodosa, temporal arteritis, Wegener's syndrome)
Systemic lupus erythematosus
Rheumatoid arthritis
Goodpasture's syndrome

ENDOCRINE
Hyperthyroidism
Adrenal insufficiency
Pheochromocytoma

OTHER
Drug reactions ("drug fever")
Transfusion reactions
Neoplasms (especially lymphoma, hepatoma, and renal cell carcinoma)
Malignant hyperthermia
Neuroleptic malignant syndrome
Serotonin syndrome
Opioid withdrawal syndrome
Ethanol withdrawal syndrome
Transient endotoxemia or bacteremia associated with procedures
Devitalized tissue secondary to trauma
Hematoma

Fever is a common feature of the systemic inflammatory response syndrome (SIRS), irrespective of whether the underlying cause is infectious or noninfectious.[19] Procalcitonin, a precursor of the polypeptide hormone, calcitonin, has been studied extensively as a circulating marker that can be used to differentiate infectious from noninfectious causes of SIRS in ICU or emergency department patients. A recent meta-analysis concluded that "procalcitonin represents a good biological diagnostic marker for sepsis, severe sepsis, or septic shock."[20] Several randomized controlled trials have investigated the feasibility of using the results of procalcitonin assays for making decisions regarding starting or stopping antibiotics for patients with proven or suspected respiratory infections. According to a recent meta-analysis of these studies, the "use of procalcitonin to guide the initiation and duration of antibiotic treatment was not associated with higher mortality rates or treatment failure, [and] antibiotic consumption was significantly reduced."[21] Thus, measurements of procalcitonin can be a useful adjunct for the evaluation of fever in ICU patients, but this assay is not a replacement for other key diagnostic modalities: careful physical examination, chest X-ray, assessment of sputum Gram stain findings, and appropriate cultures of blood, urine, sputum, or bronchoalveolar lavage fluid.

References for this chapter can be found at expertconsult.com.

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