

Confusion and Delirium

Chapter 29 | Part 2: Cardinal Manifestations and Presentation of Diseases | Part 2 – Cardinal Manifestations & Presentation | DETAILED EDITION

KEY CLINICAL POINTS

1. Delirium is defined as a relatively acute decline in cognition that fluctuates over hours or days.
2. The hallmark of delirium is a deficit of attention.
3. Two subtypes exist: hyperactive (agitation, hallucinations) and hypoactive (withdrawn, quiet).
4. Risk factors include older age (>65), baseline cognitive dysfunction, and in-hospital risks (restraints, catheters, new medications).
5. Diagnosis requires acute onset, fluctuating course, inattention, and either disorganized thinking or altered level of consciousness (CAM criteria).
6. Mortality rates range from 25% to 33% in hospitalized patients, similar to sepsis.
7. Focal strokes are rarely the cause of delirium; diagnosis is often one of exclusion after other causes are investigated.
8. Management begins with treatment of the underlying inciting factor (e.g., infection, electrolyte disturbance).
9. Supportive care includes reorientation, sensory aids, sleep hygiene, and mimicking the home environment.
10. EEG is essential if seizures are considered or if etiology remains unclear after initial workup.

FIGURES IN THIS CHAPTER

No figures extracted.

1. DEFINITION & OVERVIEW

- Confusion is defined as a mental and behavioral state of reduced comprehension, coherence, and capacity to reason.
- Delirium is defined as a relatively acute decline in cognition that fluctuates over hours or days.
- Harrison's defines this as: 'Delirium is a clinical diagnosis that is made only at the bedside.'
- A multitude of terms are used to describe patients with delirium, including encephalopathy, acute brain failure, acute altered mental status, acute confusional state, and postoperative or intensive care unit (ICU) psychosis.
- The diagnosis is made based on a careful history and physical examination.
- Screening tools can aid physicians and nurses in identifying patients with delirium, including the Confusion Assessment Method (CAM), the Nursing Delirium Screening Scale (NuDESC), the Organic Brain

Syndrome Scale, the Delirium Rating Scale, and, in the ICU, the ICU version of the CAM and the Delirium Detection Score.

1.1 Clinical Manifestations

- A multitude of terms are used to describe patients with delirium, including encephalopathy, acute brain failure, acute altered mental status, acute confusional state, and postoperative or intensive care unit (ICU) psychosis.
- Delirium has many clinical manifestations, but it is defined as a relatively acute decline in cognition that fluctuates over hours or days.
- The hallmark of delirium is a deficit of attention, although all cognitive domains—including memory, executive function, visuospatial tasks, and language—are variably involved.
- Associated symptoms that may be present in some cases include altered sleep-wake cycles, perceptual disturbances such as hallucinations or delusions, affect changes, and autonomic findings that include heart rate and blood pressure instability.
- An altered level of consciousness ranging from hyperarousal to lethargy to coma is present in most patients with delirium and can be assessed easily at the bedside.
- Other features that are only sometimes present include alteration of sleep-wake cycles, thought disturbances such as hallucinations or delusions, autonomic instability, and changes in affect.
- A course that fluctuates over hours or days and may worsen at night (termed sundowning) is typical but not essential for the diagnosis.
- Observation will usually reveal an altered level of consciousness or a deficit of attention.
- In a patient with a relatively normal level of consciousness, a screen for an attentional deficit is in order, because this deficit is the classic neuropsychological hallmark of delirium.
- Attention can be assessed while taking a history from the patient.
- Tangential speech, a fragmentary flow of ideas, or inability to follow complex commands often signifies an attentional problem.
- There are formal neuropsychological tests to assess attention, but a simple bedside test of digit span forward is quick and fairly sensitive.
- In this task, patients are asked to repeat successively longer random strings of digits beginning with two digits in a row, said to the patient at one per second intervals.
- Healthy adults can repeat a string of five to seven digits before faltering; a digit span of four or less usually indicates an attentional deficit unless hearing or language barriers are present, and many patients with delirium have forward digit spans of three or fewer digits.
- More formal neuropsychological testing can be helpful in assessing a delirious patient, but it is usually too cumbersome and time-consuming in the inpatient setting.
- A Mini-Mental State Examination (MMSE) provides information regarding orientation, language, and visuospatial skills; however, performance of many tasks on the MMSE, including the spelling of 'world' backward and serial subtraction of digits, will be impaired by delirious patients' attentional deficits, rendering the test unreliable.

1.2 Subtypes of Delirium

- Two subtypes have been described—hyperactive and hypoactive—based on differential psychomotor features.
- The cognitive syndrome associated with severe alcohol withdrawal (i.e., 'delirium tremens') remains the classic example of the hyperactive subtype, featuring prominent hallucinations, agitation, and hyperarousal, often accompanied by life-threatening autonomic instability.

- In striking contrast is the hypoactive subtype, exemplified by benzodiazepine intoxication, in which patients are withdrawn and quiet, with prominent apathy and psychomotor slowing.
- This dichotomy between subtypes of delirium is a useful construct, but patients often fall somewhere along a spectrum between the hyperactive and hypoactive extremes, sometimes fluctuating from one to the other.
- Therefore, clinicians must recognize this broad range of presentations of delirium to identify all patients with this potentially reversible cognitive disturbance.
- Hyperactive patients are often easily recognized by their characteristic severe agitation, tremor, hallucinations, and autonomic instability.
- Patients who are quietly hypoactive are more often overlooked and underdiagnosed on the medical wards and in the ICU.
- The reversibility of delirium is emphasized because many etiologies, such as infection and medication effects, can be treated easily.
- The long-term cognitive consequences of delirium remain an area of active research.
- Some episodes of delirium continue for weeks, months, or even years.
- The persistence of delirium in some patients and its high recurrence rate may be due to inadequate initial treatment of the underlying etiology, including neurodegenerative diseases.
- In other instances, delirium appears to cause permanent neuronal damage with long-term cognitive decline.
- Therefore, prevention strategies are important to implement.
- Even if an episode of delirium completely resolves, there may be lingering effects of the disorder; a patient's recall of events after delirium varies widely, ranging from complete amnesia to repeated reexperiencing of the frightening period of confusion, similar to what is seen in patients with posttraumatic stress disorder.

2. EPIDEMIOLOGY

- Delirium is common, but its reported incidence has varied widely with the criteria used to define this disorder.
- Estimates of delirium in hospitalized patients range from 10% to >50%, with higher rates reported for elderly patients and patients undergoing hip surgery.
- Older patients in the ICU have especially high rates of delirium that approach 75%.
- The condition is not recognized in up to one-third of delirious inpatients, and the diagnosis is especially problematic in the ICU environment, where cognitive dysfunction is often difficult to appreciate in the setting of serious systemic illness and sedation.
- Delirium in the ICU should be viewed as an important manifestation of organ dysfunction, not unlike liver, kidney, or heart failure.
- Outside the acute hospital setting, delirium occurs in nearly one-quarter of patients in nursing homes and in 50–80% of those at the end of life.
- These estimates emphasize the remarkably high frequency of this cognitive syndrome in older patients, a population that continues to grow.
- An episode of delirium was previously viewed as a transient condition that carried a benign prognosis.
- It is now recognized as a disorder with substantial morbidity and mortality that often represents the first manifestation of a serious underlying illness.
- Estimates of in-hospital mortality rates among delirious patients range from 25% to 33%, similar to mortality rates due to sepsis.

- Patients with an in-hospital episode of delirium have a fivefold higher mortality rate in the months after their illness compared with age-matched nondelirious hospitalized patients.
- Delirious hospitalized patients also have a longer length of stay, are more likely to be discharged to a nursing home, have a higher frequency of readmission, and are more likely to experience subsequent episodes of delirium and cognitive decline; as a result, this condition has an enormous economic cost.
- Delirium in the elderly often reflects an insult to a brain that is vulnerable due to an underlying dementia.
- A form of dementia with parkinsonism, dementia with Lewy bodies (Chap. 445), is characterized by a fluctuating course, prominent visual hallucinations, parkinsonism, and an attentional deficit that clinically resembles hyperactive delirium; patients with this condition are particularly vulnerable to delirium.
- Delirium in the elderly often reflects an insult to a brain that is vulnerable due to an underlying neurodegenerative condition.
- Therefore, the development of delirium sometimes heralds the onset of a previously unrecognized brain disorder, and after the acute delirious episode has cleared, careful screening for an underlying condition should occur in the outpatient setting.

3. ETIOLOGY & PATHOPHYSIOLOGY

- The pathogenesis and anatomy of delirium are incompletely understood.
- The attentional deficit that serves as the neuropsychological hallmark of delirium has a diffuse localization within the brainstem, thalamus, prefrontal cortex, and parietal lobes.
- Rarely, focal lesions exhibit such as ischemic strokes have led to delirium in otherwise healthy persons; right parietal and medial dorsal thalamic lesions have been reported most commonly, pointing to the importance of these areas in delirium pathogenesis.
- In most cases, however, delirium results from widespread disturbances in cortical and subcortical regions of the brain.
- Electroencephalogram (EEG) often reveals symmetric slowing, a nonspecific finding that supports diffuse cerebral dysfunction.
- Multiple neurotransmitter abnormalities, proinflammatory factors, and specific genes likely play a role in the pathogenesis of delirium.
- Deficiency of acetylcholine may play a key role, and medications with anticholinergic properties can commonly precipitate delirium.
- As noted earlier, patients with preexisting dementia are particularly susceptible to episodes of delirium.
- Alzheimer's disease (Chap. 442), dementia with Lewy bodies (Chap. 445), and Parkinson's disease dementia (Chap. 446) are all associated with cholinergic deficiency due to degeneration of acetylcholine-producing neurons in the basal forebrain.
- In addition, other neurotransmitters are also likely to be involved in this diffuse cerebral disorder.
- For example, increases in dopamine can lead to delirium, and patients with Parkinson's disease treated with dopaminergic medications can develop a delirium-like state that features visual hallucinations, fluctuations, and confusion.
- Not all individuals exposed to the same insult will develop signs of delirium.
- Even when no such history of cognitive impairment is elicited, there should still be a high suspicion for a previously unrecognized underlying neurologic disorder.
- A low dose of an anticholinergic medication may have no cognitive effects on a healthy young adult but produce a florid delirium in an elderly person with known underlying dementia, although even healthy young persons develop delirium with very high doses of anticholinergic medications.

- This concept of delirium developing as the result of an insult in predisposed individuals is currently the most widely accepted pathogenic construct.
- Therefore, if a previously healthy individual with no known history of cognitive illness develops delirium in the setting of a relatively minor insult such as elective surgery, a urinary tract infection, or hospitalization, an unrecognized underlying neurologic illness such as a neurodegenerative disease, multiple previous strokes, or another diffuse cerebral cause should be considered.
- In this context, delirium can be viewed as a 'stress test for the brain' whereby exposure to known inciting factors such as systemic infection and offending drugs can unmask a decreased cerebral reserve and herald a serious underlying and potentially treatable illness.
- New blood-based biomarkers for specific dementias may soon be available to help predict people at risk for delirium prior to surgical procedures or hospitalization.
- Other important elements of the history include screening for symptoms of organ failure or systemic infection, which often contributes to delirium in the elderly.
- A history of illicit drug use, alcoholism, or toxin exposure is important, particularly in younger delirious patients.
- Finally, asking the patient and collateral source about other symptoms that may accompany delirium, such as depression or anxiety, may help identify potential therapeutic targets.
- Some etiologies can be easily discerned through a careful history and physical examination, whereas others require confirmation with laboratory studies, imaging, or other ancillary tests.
- A large, diverse group of insults can lead to delirium, and the cause in many patients is multifactorial.
- Common etiologies are listed in Table 29-1.
- Prescribed, over-the-counter, and herbal medications all can precipitate delirium.
- Drugs with anticholinergic properties, narcotics, and benzodiazepines are particularly common offenders, but nearly any compound can lead to cognitive dysfunction in a predisposed patient.
- Whereas an elderly patient with baseline dementia may become delirious upon exposure to a relatively low dose of a medication, in less susceptible individuals, delirium occurs only with very high doses of the same medication.
- This observation emphasizes the importance of correlating the timing of recent medication changes, including dose and formulation, with the onset of cognitive dysfunction.
- In younger patients, illicit drugs and toxins are common causes of delirium.
- In addition to more classic drugs of abuse, the availability of fentanyl (Chap. 467), synthetic cannabis (Chap. 466), 'bath salts,' methylenedioxymethamphetamine (MDMA, ecstasy), γ -hydroxybutyrate (GHB), and the phencyclidine (PCP)-like agent ketamine has led to an increase in delirious young persons presenting to acute care settings (Chap. 468).
- Many common prescription drugs such as oral narcotics and benzodiazepines are often abused and readily available on the street.
- Alcohol abuse leading to high serum levels causes confusion, but more commonly, it is withdrawal from alcohol that leads to a hyperactive delirium (Chap. 464).
- Alcohol and benzodiazepine withdrawal should be considered in all cases of delirium, including in the elderly, because even patients who drink only a few servings of alcohol every day can experience relatively severe withdrawal symptoms upon hospitalization.
- Metabolic abnormalities such as electrolyte disturbances of sodium, calcium, magnesium, or glucose can cause delirium, and mild derangements can lead to substantial cognitive disturbances in susceptible individuals.
- Other common metabolic etiologies include liver and renal failure, hypercarbia and hypoxemia, vitamin deficiencies of thiamine and B12, autoimmune disorders including central nervous system (CNS) vasculitis, and endocrinopathies such as thyroid and adrenal disorders.

- Systemic infections often cause delirium, especially in the elderly.
- A common scenario involves the development of an acute cognitive decline in the setting of a urinary tract infection in a patient with baseline dementia.
- Pneumonia, skin infections such as cellulitis, and frank sepsis also lead to delirium.
- This so-called septic encephalopathy, often seen in the ICU, is probably due to the release of proinflammatory cytokines and their diffuse cerebral effects.
- CNS infections such as meningitis, encephalitis, and abscess are less common etiologies of delirium, as are cases of autoimmune or paraneoplastic encephalitis; however, in light of the high morbidity and mortality rates associated with these conditions when they are not treated, clinicians must always maintain a high index of suspicion.
- In some susceptible individuals, exposure to the unfamiliar environment of a hospital itself can contribute to delirium.
- This etiology usually occurs as part of a multifactorial delirium and should be considered a diagnosis of exclusion after all other causes have been thoroughly investigated.
- Many primary prevention and treatment strategies for delirium involve relatively simple methods to address infectious, metabolic, and pharmacologic complications that can accompany hospitalization after stroke.
- Cerebrovascular etiologies of delirium are usually due to global hypoperfusion in the setting of systemic hypotension from heart failure, septic shock, dehydration, or anemia.
- Focal strokes in the right parietal lobe and medial dorsal thalamus rarely can lead to a delirious state.
- A more common scenario involves a new focal stroke or hemorrhage causing confusion in a patient who has decreased cerebral reserve.
- In these individuals, it is sometimes difficult to distinguish between cognitive dysfunction resulting from the new neurovascular insult itself and delirium due to the infectious, metabolic, and pharmacologic complications that can accompany hospitalization after stroke.

Table 1 Table 29-1 Differential Diagnosis of Delirium

Category	Specific Etiologies
Toxins	Prescription medications: especially those with anticholinergic properties, narcotics, and benzodiazepines Drugs of abuse: alcohol intoxication and alcohol withdrawal, opiates, ecstasy, LSD, GHB, PCP, ketamine, cocaine, 'bath salts,' marijuana and its synthetic forms Poisons: inhalants, carbon monoxide, ethylene glycol, pesticides
Metabolic Conditions	Electrolyte disturbances: hypoglycemia, hyperglycemia, hyponatremia, hypernatremia, hypercalcemia, hypocalcemia, hypomagnesemia Hypothermia and hyperthermia Pulmonary failure: hypoxemia and hypercarbia Liver failure/hepatic encephalopathy Renal failure/uremia Cardiac failure Vitamin deficiencies: B12, thiamine, folate, niacin Dehydration and malnutrition Anemia
Infections	Systemic infections: urinary tract infections, pneumonia and other respiratory infections, skin and soft tissue infections, sepsis CNS infections: meningitis, encephalitis, brain abscess
Endocrine Conditions	Hyperthyroidism, hypothyroidism Hyperparathyroidism Adrenal insufficiency

Category	Specific Etiologies
Cerebrovascular Disorders	Global hypoperfusion states Hypertensive encephalopathy Focal ischemic strokes and hemorrhages (rare): especially nondominant parietal and thalamic lesions
Autoimmune Disorders	CNS vasculitis Cerebral lupus Neurologic paraneoplastic and autoimmune encephalitis
Seizure-Related Disorders	Nonconvulsive status epilepticus Intermittent seizures with prolonged postictal states
Neoplastic Disorders	Diffuse metastases to the brain Diffuse glioma Carcinomatous meningitis CNS lymphoma
Hospitalization	Terminal end-of-life delirium

3.1 Risk Factors

- An effective primary prevention strategy for delirium begins with identification of high-risk patients.
- Some hospital systems have initiated comprehensive delirium programs that screen most or all patients upon admission or before elective surgery; positive screens trigger a host of focused prevention measures.
- Multiple validated scoring systems have been developed as a screen for asymptomatic patients, many of which emphasize well-established risk factors for delirium.
- The two most consistently identified risk factors are older age and baseline cognitive dysfunction.
- Individuals who are aged >65 or low scores on standardized tests of cognition develop delirium upon hospitalization at a rate approaching 50%.
- Whether age and baseline cognitive dysfunction are truly independent risk factors or are related is uncertain.
- Other predisposing factors include sensory deprivation, preexisting hearing and visual impairment, as well as indices of poor overall health, including baseline immobility, malnutrition, and underlying medical or neurologic illness.
- In-hospital risks for delirium include the use of physical restraints, bladder catheterization, sleep and sensory deprivation, and the addition of three or more new medications.
- Avoiding such risks remains a key component of delirium prevention as well as treatment.
- Surgical and anesthetic risk factors for the development of postoperative delirium include procedures such as those involving cardiopulmonary bypass, inadequate or excessive treatment of pain in the immediate postoperative period, and perhaps specific agents such as inhalational anesthetics or benzodiazepines.
- The relationship between delirium and dementia (Chap. 31) is complicated by significant overlap between the two conditions, and it is not always simple to distinguish between them.
- Dementia and preexisting cognitive dysfunction serve as major risk factors for delirium, and at least two-thirds of cases of delirium occur in patients with coexisting underlying dementia.
- Patients with a more hypoactive, apathetic presentation with psychomotor slowing may be identified as being different from baseline only through conversations with family members.
- A number of validated instruments have been shown to diagnose cognitive dysfunction accurately using a collateral source, including the modified Blessed Dementia Rating Scale and the Clinical Dementia Rating (CDR).

3.2 Pathogenesis

- The attentional deficit that serves as the neuropsychological hallmark of delirium has a diffuse localization within the brainstem, thalamus, prefrontal cortex, and parietal lobes.
- Rarely, focal lesions exhibit such as ischemic strokes have led to delirium in otherwise healthy persons; right parietal and medial dorsal thalamic lesions have been reported most commonly, pointing to the importance of these areas in delirium pathogenesis.
- In most cases, however, delirium results from widespread disturbances in cortical and subcortical regions of the brain.
- Electroencephalogram (EEG) often reveals symmetric slowing, a nonspecific finding that supports diffuse cerebral dysfunction.
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- In addition, other neurotransmitters are also likely to be involved in this diffuse cerebral disorder.
- For example, increases in dopamine can lead to delirium, and patients with Parkinson's disease treated with dopaminergic medications can develop a delirium-like state that features visual hallucinations, fluctuations, and confusion.

4. CLINICAL FEATURES

- A multitude of terms are used to describe patients with delirium, including encephalopathy, acute brain failure, acute altered mental status, acute confusional state, and postoperative or intensive care unit (ICU) psychosis.
- Delirium has many clinical manifestations, but it is defined as a relatively acute decline in cognition that fluctuates over hours or days.
- The hallmark of delirium is a deficit of attention, although all cognitive domains—including memory, executive function, visuospatial tasks, and language—are variably involved.
- Associated symptoms that may be present in some cases include altered sleep-wake cycles, perceptual disturbances such as hallucinations or delusions, affect changes, and autonomic findings that include heart rate and blood pressure instability.
- An altered level of consciousness ranging from hyperarousal to lethargy to coma is present in most patients with delirium and can be assessed easily at the bedside.
- Other features that are only sometimes present include alteration of sleep-wake cycles, thought disturbances such as hallucinations or delusions, autonomic instability, and changes in affect.
- A course that fluctuates over hours or days and may worsen at night (termed sundowning) is typical but not essential for the diagnosis.
- Observation will usually reveal an altered level of consciousness or a deficit of attention.
- In a patient with a relatively normal level of consciousness, a screen for an attentional deficit is in order, because this deficit is the classic neuropsychological hallmark of delirium.
- Attention can be assessed while taking a history from the patient.
- Tangential speech, a fragmentary flow of ideas, or inability to follow complex commands often signifies an attentional problem.

- There are formal neuropsychological tests to assess attention, but a simple bedside test of digit span forward is quick and fairly sensitive.
- In this task, patients are asked to repeat successively longer random strings of digits beginning with two digits in a row, said to the patient at one per second intervals.
- Healthy adults can repeat a string of five to seven digits before faltering; a digit span of four or less usually indicates an attentional deficit unless hearing or language barriers are present, and many patients with delirium have forward digit spans of three or fewer digits.
- More formal neuropsychological testing can be helpful in assessing a delirious patient, but it is usually too cumbersome and time-consuming in the inpatient setting.
- A Mini-Mental State Examination (MMSE) provides information regarding orientation, language, and visuospatial skills; however, performance of many tasks on the MMSE, including the spelling of 'world' backward and serial subtraction of digits, will be impaired by delirious patients' attentional deficits, rendering the test unreliable.
- The remainder of the screening neurologic examination should focus on identifying new focal neurologic deficits.
- Focal strokes or mass lesions in isolation are rarely the cause of delirium, but patients with underlying extensive cerebrovascular disease or neurodegenerative conditions may not be able to cognitively tolerate even relatively small new insults.
- Patients should be screened for other signs of neurodegenerative conditions such as parkinsonism, which is seen not only in idiopathic Parkinson's disease but also in other dementing conditions including Alzheimer's disease, dementia with Lewy bodies, and progressive supranuclear palsy.
- The presence of multifocal myoclonus or asterix on the motor examination is nonspecific but usually indicates a metabolic or toxic etiology of the delirium.
- The general physical examination in a delirious patient should include careful screening for signs of infection such as fever, tachypnea, pulmonary consolidation, heart murmur, and meningismus.
- The patient's fluid status should be assessed; both dehydration and fluid overload with resultant hypoxemia have been associated with delirium, and each is usually easily rectified.
- The appearance of the skin can be helpful, showing jaundice in hepatic encephalopathy, cyanosis in hypoxemia, or needle tracks in patients using intravenous drugs.

4.1 Physical Examination Findings

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- The appearance of the skin can be helpful, showing jaundice in hepatic encephalopathy, cyanosis in hypoxemia, or needle tracks in patients using intravenous drugs.
- The neurologic examination requires a careful assessment of mental status.
- Patients with delirium often present with a fluctuating course; therefore, the diagnosis can be missed when one relies on a single time point of evaluation.
- For patients who worsen in the evening (sundowning), assessment only during morning rounds may be falsely reassuring.
- An altered level of consciousness ranging from hyperarousal to lethargy to coma is present in most patients with delirium and can be assessed easily at the bedside.
- In a patient with a relatively normal level of consciousness, a screen for an attentional deficit is in order, because this deficit is the classic neuropsychological hallmark of delirium.
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4.2 History Taking

- It may be difficult to elicit an accurate history in delirious patients who have altered levels of consciousness or impaired attention.
- Information from a collateral source such as a spouse or another family member is therefore invaluable.
- The three most important pieces of history are the patient's baseline cognitive function, the time course of the present illness, and current medications.
- Premorbid cognitive function can be assessed through the collateral source or, if needed, via a review of outpatient records.
- Delirium by definition represents a change from a cognitive baseline that is relatively acute and usually develops over hours to days.
- An acute confusional state is nearly impossible to diagnose without some knowledge of baseline cognitive function.
- Without this information, many patients with dementia or longstanding depression may be mistaken as delirious during a single initial evaluation.
- Patients with a more hypoactive, apathetic presentation with psychomotor slowing may be identified as being different from baseline only through conversations with family members.
- A number of validated instruments have been shown to diagnose cognitive dysfunction accurately using a collateral source, including the modified Blessed Dementia Rating Scale and the Clinical Dementia Rating (CDR).

5. DIFFERENTIAL DIAGNOSIS

- A large, diverse group of insults can lead to delirium, and the cause in many patients is multifactorial.
- Common etiologies are listed in Table 29-1.
- Some etiologies can be easily discerned through a careful history and physical examination, whereas others require confirmation with laboratory studies, imaging, or other ancillary tests.
- Prescribed, over-the-counter, and herbal medications all can precipitate delirium.
- Drugs with anticholinergic properties, narcotics, and benzodiazepines are particularly common offenders, but nearly any compound can lead to cognitive dysfunction in a predisposed patient.
- Whereas an elderly patient with baseline dementia may become delirious upon exposure to a relatively low dose of a medication, in less susceptible individuals, delirium occurs only with very high doses of the same medication.
- This observation emphasizes the importance of correlating the timing of recent medication changes, including dose and formulation, with the onset of cognitive dysfunction.
- In younger patients, illicit drugs and toxins are common causes of delirium.
- In addition to more classic drugs of abuse, the availability of fentanyl (Chap. 467), synthetic cannabis (Chap. 466), 'bath salts,' methylenedioxymethamphetamine (MDMA, ecstasy), γ -hydroxybutyrate (GHB), and the phencyclidine (PCP)-like agent ketamine has led to an increase in delirious young persons presenting to acute care settings (Chap. 468).
- Many common prescription drugs such as oral narcotics and benzodiazepines are often abused and readily available on the street.
- Alcohol abuse leading to high serum levels causes confusion, but more commonly, it is withdrawal from alcohol that leads to a hyperactive delirium (Chap. 464).
- Alcohol and benzodiazepine withdrawal should be considered in all cases of delirium, including in the elderly, because even patients who drink only a few servings of alcohol every day can experience relatively severe withdrawal symptoms upon hospitalization.
- Metabolic abnormalities such as electrolyte disturbances of sodium, calcium, magnesium, or glucose can cause delirium, and mild derangements can lead to substantial cognitive disturbances in susceptible individuals.
- Other common metabolic etiologies include liver and renal failure, hypercarbia and hypoxemia, vitamin deficiencies of thiamine and B12, autoimmune disorders including central nervous system (CNS) vasculitis, and endocrinopathies such as thyroid and adrenal disorders.
- Systemic infections often cause delirium, especially in the elderly.
- A common scenario involves the development of an acute cognitive decline in the setting of a urinary tract infection in a patient with baseline dementia.
- Pneumonia, skin infections such as cellulitis, and frank sepsis also lead to delirium.
- This so-called septic encephalopathy, often seen in the ICU, is probably due to the release of proinflammatory cytokines and their diffuse cerebral effects.
- CNS infections such as meningitis, encephalitis, and abscess are less common etiologies of delirium, as are cases of autoimmune or paraneoplastic encephalitis; however, in light of the high morbidity and mortality rates associated with these conditions when they are not treated, clinicians must always maintain a high index of suspicion.
- In some susceptible individuals, exposure to the unfamiliar environment of a hospital itself can contribute to delirium.
- This etiology usually occurs as part of a multifactorial delirium and should be considered a diagnosis of exclusion after all other causes have been thoroughly investigated.
- Many primary prevention and treatment strategies for delirium involve relatively simple methods to address infectious, metabolic, and pharmacologic complications that can accompany hospitalization after

stroke.

- Cerebrovascular etiologies of delirium are usually due to global hypoperfusion in the setting of systemic hypotension from heart failure, septic shock, dehydration, or anemia.
- Focal strokes in the right parietal lobe and medial dorsal thalamus rarely can lead to a delirious state.
- A more common scenario involves a new focal stroke or hemorrhage causing confusion in a patient who has decreased cerebral reserve.
- In these individuals, it is sometimes difficult to distinguish between cognitive dysfunction resulting from the new neurovascular insult itself and delirium due to the infectious, metabolic, and pharmacologic complications that can accompany hospitalization after stroke.

Table 2 Table 29-1 Differential Diagnosis of Delirium

Category	Specific Etiologies
Toxins	Prescription medications: especially those with anticholinergic properties, narcotics, and benzodiazepines Drugs of abuse: alcohol intoxication and alcohol withdrawal, opiates, ecstasy, LSD, GHB, PCP, ketamine, cocaine, 'bath salts,' marijuana and its synthetic forms Poisons: inhalants, carbon monoxide, ethylene glycol, pesticides
Metabolic Conditions	Electrolyte disturbances: hypoglycemia, hyperglycemia, hyponatremia, hypernatremia, hypercalcemia, hypocalcemia, hypomagnesemia Hypothermia and hyperthermia Pulmonary failure: hypoxemia and hypercarbia Liver failure/hepatic encephalopathy Renal failure/uremia Cardiac failure Vitamin deficiencies: B12, thiamine, folate, niacin Dehydration and malnutrition Anemia
Infections	Systemic infections: urinary tract infections, pneumonia and other respiratory infections, skin and soft tissue infections, sepsis CNS infections: meningitis, encephalitis, brain abscess
Endocrine Conditions	Hyperthyroidism, hypothyroidism Hyperparathyroidism Adrenal insufficiency
Cerebrovascular Disorders	Global hypoperfusion states Hypertensive encephalopathy Focal ischemic strokes and hemorrhages (rare): especially nondominant parietal and thalamic lesions
Autoimmune Disorders	CNS vasculitis Cerebral lupus Neurologic paraneoplastic and autoimmune encephalitis
Seizure-Related Disorders	Nonconvulsive status epilepticus Intermittent seizures with prolonged postictal states
Neoplastic Disorders	Diffuse metastases to the brain Diffuse glioma Carcinomatous meningitis CNS lymphoma
Hospitalization	Terminal end-of-life delirium

6. INVESTIGATIONS & DIAGNOSIS

- Because a fluctuating course often is seen in delirium, intermittent seizures may be overlooked when one is considering potential etiologies.
- Both nonconvulsive status epilepticus and recurrent focal or generalized seizures followed by postictal confusion can cause delirium; EEG remains essential for this diagnosis and should be considered

whenever the etiology of delirium remains unclear following initial workup.

- Seizure activity spreading from an electrical focus in a mass or infarct can explain global cognitive dysfunction caused by relatively small lesions.
- It is extremely common for patients to experience delirium at the end of life in palliative care settings.
- This condition must be identified and treated aggressively because it is an important cause of patient and family discomfort at the end of life.
- It should be remembered that these patients also may be suffering from more common etiologies of delirium such as systemic infection.
- A cost-effective approach allows the history and physical examination to guide further tests after initial screening laboratory studies are obtained.
- No single algorithm will fit all delirious patients due to the staggering number of potential etiologies, but one stepwise approach is detailed in Table 29-2.
- If a clear precipitant such as an offending medication is identified, further testing may not be required.
- If, however, no likely etiology is uncovered with initial evaluation, an aggressive search for an underlying cause should be initiated.
- Basic screening lab tests, including a complete blood count, electrolyte panel, and tests of liver and renal function, should be obtained in all patients with delirium.
- In elderly patients, screening for systemic infection, including chest radiography, urinalysis and culture, and possibly blood cultures, is important.
- In younger individuals, serum and urine drug and toxicology screening may be appropriate earlier in the workup.
- Additional laboratory tests addressing other autoimmune, endocrinologic, metabolic, and infectious etiologies should be reserved for patients in whom the diagnosis remains unclear after initial testing.
- Multiple studies have demonstrated that brain imaging in patients with delirium is often unhelpful.
- If, however, the initial workup is unrevealing, most clinicians quickly move toward imaging of the brain to exclude structural causes.
- A noncontrast computed tomography (CT) scan can identify large masses and hemorrhages but is otherwise unlikely to help determine an etiology of delirium.
- The ability of magnetic resonance imaging (MRI) to identify nearly all acute ischemic strokes as well as to provide neuroanatomic detail that gives clues to possible infectious, inflammatory, neurodegenerative, and neoplastic conditions makes it the test of choice.
- Because MRI techniques are limited by availability, speed of imaging, patient's cooperation, and contraindications, many clinicians begin with CT scanning and proceed to MRI if the etiology of delirium remains elusive.
- Lumbar puncture (LP) must be obtained immediately after neuroimaging for all patients in whom CNS infection is suspected.
- Spinal fluid examination can also be useful in identifying autoimmune, other inflammatory, and neoplastic conditions.
- As a result, LP should be considered in any delirious patient with a negative workup.
- EEG remains invaluable if seizures are considered or if there is no cause readily identified.
- Using the well-validated CAM, a diagnosis of delirium is made if there is (1) an acute onset and fluctuating course and (2) inattention accompanied by either (3) disorganized thinking or (4) an altered level of consciousness.

Table 3 Table 29-2 Stepwise Evaluation of a Patient with Delirium

Evaluation Tier	Tests/Procedures
Initial Evaluation	History with special attention to medications (including over-the-counter and herbals) General physical examination and neurologic examination Complete blood count Electrolyte panel including calcium, magnesium, phosphorus Liver function tests, including albumin Renal function tests
First-Tier Further Evaluation Guided by Initial Evaluation	Systemic infection screen Urinalysis and culture Chest radiograph and tests for respiratory pathogens Blood cultures Electrocardiogram Arterial blood gas Serum and/or urine toxicology screen (perform earlier in young persons) Brain imaging with MRI with diffusion and gadolinium (preferred) or CT Suspected CNS infection or other inflammatory disorder: lumbar puncture after brain imaging Suspected seizure-related etiology: electroencephalogram (EEG) (if high suspicion, should be performed immediately)
Second-Tier Further Evaluation	Vitamin levels: B12, folate, thiamine Endocrinologic laboratories: thyroid-stimulating hormone (TSH) and free T4; cortisol Serum ammonia Sedimentation rate Autoimmune serologies: antinuclear antibodies (ANA), complement levels; p-ANCA, c-ANCA, consider paraneoplastic/autoimmune encephalitis testing in the serum and CSF Infectious serologies: rapid plasmin reagin (RPR); fungal and viral serologies if high suspicion; HIV antibody Lumbar puncture (if not already performed) Brain MRI with and without gadolinium (if not already performed)

6.1 Diagnostic Algorithm

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7. MANAGEMENT & TREATMENT

- Management of delirium begins with treatment of the underlying inciting factor (e.g., patients with systemic infections should be given appropriate antibiotics, and underlying electrolyte disturbances should be judiciously corrected).
- These treatments often lead to prompt resolution of delirium.
- Blindly targeting the symptoms of delirium pharmacologically only serves to prolong the time patients remain in the confused state and may mask important diagnostic information.
- Relatively simple methods of supportive care can be highly effective (Fig. 29-1).
- Reorientation by the nursing staff and family combined with visible clocks, calendars, and outside-facing windows can reduce confusion.
- Sensory isolation should be prevented by providing glasses and hearing aids to patients who need them.
- Sundowning can be addressed to a large extent through vigilance to appropriate sleep-wake cycles.
- During the day, a well-lit room should be accompanied by activities or exercises to prevent napping.
- At night, a quiet, dark environment with limited interruptions by staff can assure proper rest; melatonin can be considered before bed to promote sleep.
- These sleep-wake cycle interventions are especially important in the ICU setting as the usual constant 24-h activity commonly provokes delirium.
- Attempting to mimic the home environment as much as possible also has been shown to help treat and even prevent delirium.
- Visits from friends and family throughout the day minimize the anxiety associated with the constant flow of new faces of staff and physicians.
- Allowing hospitalized patients to have access to home bedding, clothing, and nightstand objects makes the hospital environment less foreign and therefore less confusing.
- Simple standard nursing practices such as maintaining proper nutrition and volume status as well as managing pain, incontinence, and skin breakdown also help alleviate discomfort and resulting confusion.

7.1 Supportive Care Interventions

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8. PROGNOSIS & COMPLICATIONS

- The long-term cognitive consequences of delirium remain an area of active research.
- Some episodes of delirium continue for weeks, months, or even years.
- The persistence of delirium in some patients and its high recurrence rate may be due to inadequate initial treatment of the underlying etiology, including neurodegenerative diseases.
- In other instances, delirium appears to cause permanent neuronal damage with long-term cognitive decline.
- Therefore, prevention strategies are important to implement.
- Even if an episode of delirium completely resolves, there may be lingering effects of the disorder; a patient's recall of events after delirium varies widely, ranging from complete amnesia to repeated reexperiencing of the frightening period of confusion, similar to what is seen in patients with posttraumatic stress disorder.
- Estimates of in-hospital mortality rates among delirious patients range from 25% to 33%, similar to mortality rates due to sepsis.
- Patients with an in-hospital episode of delirium have a fivefold higher mortality rate in the months after their illness compared with age-matched nondelirious hospitalized patients.
- Delirious hospitalized patients also have a longer length of stay, are more likely to be discharged to a nursing home, have a higher frequency of readmission, and are more likely to experience subsequent episodes of delirium and cognitive decline; as a result, this condition has an enormous economic cost.

9. SPECIAL CONSIDERATIONS

- Delirium in the ICU should be viewed as an important manifestation of organ dysfunction, not unlike liver, kidney, or heart failure.
- Outside the acute hospital setting, delirium occurs in nearly one-quarter of patients in nursing homes and in 50–80% of those at the end of life.
- These estimates emphasize the remarkably high frequency of this cognitive syndrome in older patients, a population that continues to grow.
- An episode of delirium was previously viewed as a transient condition that carried a benign prognosis.
- It is now recognized as a disorder with substantial morbidity and mortality that often represents the first manifestation of a serious underlying illness.
- Delirium in the elderly often reflects an insult to a brain that is vulnerable due to an underlying dementia.
- A form of dementia with parkinsonism, dementia with Lewy bodies (Chap. 445), is characterized by a fluctuating course, prominent visual hallucinations, parkinsonism, and an attentional deficit that clinically

resembles hyperactive delirium; patients with this condition are particularly vulnerable to delirium.

- Therefore, the development of delirium sometimes heralds the onset of a previously unrecognized brain disorder, and after the acute delirious episode has cleared, careful screening for an underlying condition should occur in the outpatient setting.
- It should be remembered that these patients also may be suffering from more common etiologies of delirium such as systemic infection.
- In some susceptible individuals, exposure to the unfamiliar environment of a hospital itself can contribute to delirium.
- This etiology usually occurs as part of a multifactorial delirium and should be considered a diagnosis of exclusion after all other causes have been thoroughly investigated.
- Many primary prevention and treatment strategies for delirium involve relatively simple methods to address infectious, metabolic, and pharmacologic complications that can accompany hospitalization after stroke.

10. KEY PEARLS & CLINICAL TRAPS

- The hallmark of delirium is a deficit of attention.
- A course that fluctuates over hours or days and may worsen at night (termed sundowning) is typical but not essential for the diagnosis.
- Patients who are quietly hypoactive are more often overlooked and underdiagnosed on the medical wards and in the ICU.
- The diagnosis is especially problematic in the ICU environment, where cognitive dysfunction is often difficult to appreciate in the setting of serious systemic illness and sedation.
- Focal strokes or mass lesions in isolation are rarely the cause of delirium.
- In some susceptible individuals, exposure to the unfamiliar environment of a hospital itself can contribute to delirium.
- This etiology usually occurs as part of a multifactorial delirium and should be considered a diagnosis of exclusion after all other causes have been thoroughly investigated.
- EEG remains invaluable if seizures are considered or if there is no cause readily identified.
- Using the well-validated CAM, a diagnosis of delirium is made if there is (1) an acute onset and fluctuating course and (2) inattention accompanied by either (3) disorganized thinking or (4) an altered level of consciousness.
- Blindly targeting the symptoms of delirium pharmacologically only serves to prolong the time patients remain in the confused state and may mask important diagnostic information.
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