Encephalopathy is a common complication of systemic illness or direct brain injury. It can manifest as a spectrum that begins with subtle cognitive changes, progresses as a full-blown syndrome of brain dysfunction, and eventually leads to coma or brain death (the latter two are described in separate chapters). In this chapter, we focus on the detection, etiologic diagnosis, and management of noncomatose, critically ill, encephalopathic patients. Their condition has been traditionally known with several interchangeable names such as acute confusional state, acute organic brain syndrome, and acute cerebral insufficiency, but is most commonly referred to as delirium.

Delirium contributes significantly to lengthened hospital stay, increased morbidity and mortality, increased overall medical costs, and worse long-term neurocognitive outcomes. Despite the awareness of its existence since the earliest historical medical documents, timely detection, workup, and appropriate management continue to present challenges for the treating physicians. Delirious patients in the Intensive Care Unit (ICU) form a particularly understudied population with unique characteristics.

- Delirium has been described as an acute alteration of consciousness and higher cognitive functions.
- It typically develops over a short period of time and has a fluctuating course.
- It is a well-defined syndrome that may be precipitated by several diverse pathological processes.
- The current edition of the Diagnostic and Statistical Manual (DSM-IV TR) lists criteria for the diagnosis of delirium due to a general medical condition (Table 17.1).¹

The incidence of delirium has been estimated as between 5% and 40% for hospitalized patients in general and between 11% and 80% for critically ill patients. Other studies have reported a lower incidence of about 30%, after the exclusion of patients maintained in purposeful drug-induced sedation.

Among hospitalized, critically ill patients, delirium typically develops in those who have predisposing risk factors such as:

- Older age (older than 70 years)
- Male gender
- Poor functional status
- Malnutrition
- Substance abuse
- Premorbid medical conditions or cognitive impairment
- Polypharmacy
- Physical restraints
- Visual or hearing impairment
- Prior history of delirium

These factors have been found to correlate with the possibility and extent of functional recovery after the resolution of the acute insult.

**ETIOLOGY**

Several diverse pathological processes, which can precipitate delirium in vulnerable patients, are listed in Table 17.2. Those are broadly classified in diagnostic categories. Even though there are multiple and additive etiologies in most delirious patients, it is frequently possible to distinguish a primary disease process that can be the focus of treatment strategies.
Table 17.1. DSM-IV-TR diagnostic criteria for delirium due to a general medical condition

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, to sustain, or to shift attention.

B. A change in cognition (such as memory deficit, disorientation, or language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.

C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiologic consequences of a general medical condition.


Table 17.2. Etiology of delirium

<table>
<thead>
<tr>
<th>Category</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Ischemic stroke, transient ischemic attack, subarachnoid hemorrhage, intracerebral hemorrhage, epidural hematoma, subdural hematoma, cerebral venous thrombosis, myocardial infarction, pulmonary embolism, extreme hypertension/hypotension.</td>
</tr>
<tr>
<td>Infectious</td>
<td>Meningitis, encephalitis, cerebral abscess, neurosyphilis, Lyme disease, systemic sepsis, HIV infection and complications, pneumonia, urinary tract infection,</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>CNS lupus erythematosus, Giant cell arteritis, neurosarcoidosis.</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Systemic cancer, paraneoplastic syndromes, CNS tumors, carcinomatous meningitis.</td>
</tr>
<tr>
<td>Legal and illegal drugs</td>
<td>Anticholinergics, narcotics, benzodiazepines, barbiturates, anesthetics, digitalis, corticosteroids, antiparkinsonian, antiepileptics, immunosuppressants (tacrolimus), recreational drugs (abuse or withdrawal), over-the-counter medications, herbal preparations</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>Cardiac, orthopedic, CNS surgery, other invasive procedures</td>
</tr>
<tr>
<td>Trauma</td>
<td>Traumatic brain injury, multiple organ trauma, air or fat embolism.</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Liver failure, uremia, hypoglycemia, hyperglycemia, electrolyte abnormalities, hypercarbia, hypoxia</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Thyroid, parathyroid, pituitary, adrenal gland dysfunction, uncontrolled diabetes, pancreatitis.</td>
</tr>
<tr>
<td>Epileptic</td>
<td>Postictal conditions, status epilepticus (convulsive or nonconvulsive)</td>
</tr>
<tr>
<td>Nutritional</td>
<td>Thiamine, B₁₂, folic acid deficiencies,</td>
</tr>
<tr>
<td>Hereditary</td>
<td>Mitochondrial disorders (MELAS)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Anemia, dehydration, volume overload, burns, chronic obstructive pulmonary disease (COPD), migraine, sensory deprivation, sleep deprivation, posterior reversible encephalopathy syndrome, Reye syndrome</td>
</tr>
</tbody>
</table>

Particularly in the ICU population, most underlying processes are the ones responsible for the initial hospitalization and ICU admission. However, ICU delirium is often the result of environmental factors or iatrogenic interventions. The use of psychoactive medications (especially opiate narcotics and benzodiazepines) is common in critically ill patients and strongly correlates with the development of
delirium. Other important factors are the sleep dis-
ruption in an ICU environment, bladder catheter-
ization, physical restraints, sensory deprivation, and
frequent invasive vascular access procedures.

CLINICAL FEATURES OF DELIRIUM
Delirium syndromes share many common clinical
features, regardless of the underlying etiology. As
described in the DSM-IV criteria:

- An alteration in the level of consciousness should
  be present. This is not as severe as in coma, where
  there is a profound impairment of arousal. It may
  range from paradoxical agitation (hyperactive
  delirium) to sedation and stupor (hyposactive
  delirium).
- Attention impairment is one of the hallmarks of
delirium. This can manifest as difficulty main-
taining attention (distractibility) or shifting the
focus of attention (perseveration). This is typically
tested by asking the patient to perform serial sub-
tractions, multistep commands or assessing digit
span.
- Fluctuation of symptomatology is also a promi-
nent characteristic of delirium. Symptoms fre-
quently worsen at night, often in association with
a sleep–wake reversal. At times, patients may
intermittently seem cognitively intact, something
that may contribute to the delayed detection of
the condition.
- Hallucinations, disorientation, and perceptual
distortions often dominate the clinical picture,
particularly in the hyperactive type. Visual halluci-
nations and illusions are most common and may
result in attempts to dislodge endotracheal tubes
or IV lines, thus compromising patient safety.
- Disorders of thought processes and memory are
frequent and may need to be differentiated from
an underlying dementia. Patients with delirium
are more likely to have disorganized thinking,
even to the point of incoherent speech, as well as
immediate and recent memory impairment.

STANDARDIZED DETECTION
Delirium is frequently diagnosed in a delayed fash-
ion, particularly in the ICU setting. Often, other life-
saving procedures take precedence in the patient’s
management and preclude serial assessments of
the mental status. Many critically ill patients are
nonverbal or even mechanically ventilated, and
the evaluation of their higher cognitive functions is,
thus, extremely difficult. Moreover, pharmacologic
sedation is often an integral part of treatment in
the neurocritical setting and further confounds the
clinical presentation.

Several standardized delirium detection scales
have been devised to assist in the early detection
and management of delirium. They are, ideally, per-
formed in a short amount of time, can be applied
repeatedly, and can be delivered by nursing care
providers. Only two of them have been specifically
developed to assess critically ill patients:

1. The Confusion Assessment Method for the
   Intensive Care Unit (CAM-ICU), which is an
   adaptation of the original Confusion Assess-
   ment Scale for mechanically ventilated
   patients and
2. The Intensive Care Delirium Screening
   Checklist (ICDSC)

The implementation of these screening tools
depends on local institutional criteria. Both scales
are easy to use, have high accuracy and inter-rater
reliability and assist communication between
members of the healthcare team. The effect of early
detection and management in achieving improved
long-term outcomes remains to be proven.

DIAGNOSTIC EVALUATION
No single cognitive manifestation of delirium is
specific to a particular etiology. “Hepatic enceph-
halopathy,” “septic encephalopathy,” and “uremic
encephalopathy” can all present with the same
mental status impairments. Uncertain associations
have been proposed between motoric subtypes
(hyposactive, hyperactive or mixed delirium) and
pathophysiology. Anticholinergic drug intoxication
has been correlated with hyposactive delirium, while
alcohol withdrawal or thyroid hyperactivity with
hyperactive delirium.

However, additional historical, clinical, labora-
tory and imaging data are almost always required
for differential diagnosis.

1. History: This can be of invaluable help, particu-
larly in cases of drug intoxication, withdrawal,
Encephalopathy

Table 17.3. Laboratory investigations

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count with differential, ESR and CRP</td>
<td>Complete blood count with differential, ESR and CRP.</td>
</tr>
<tr>
<td>Serum electrolytes, BUN, glucose</td>
<td>Serum electrolytes, BUN, glucose.</td>
</tr>
<tr>
<td>Thyroid hormone evaluation</td>
<td>Thyroid hormone evaluation.</td>
</tr>
<tr>
<td>Liver function tests, amylase, lipase, ammonia</td>
<td>Liver function tests, amylase, lipase, ammonia.</td>
</tr>
<tr>
<td>Troponin levels</td>
<td>Troponin levels.</td>
</tr>
<tr>
<td>HIV ELISA</td>
<td>HIV ELISA.</td>
</tr>
<tr>
<td>Arterial blood gases</td>
<td>Arterial blood gases.</td>
</tr>
<tr>
<td>Cerebrospinal fluid evaluation including cytology.</td>
<td>Cerebrospinal fluid evaluation including cytology.</td>
</tr>
<tr>
<td>Body fluid cultures (blood, urine, stool, sputum, CSF)</td>
<td>Body fluid cultures (blood, urine, stool, sputum, CSF).</td>
</tr>
<tr>
<td>Culture of indwelling catheters.</td>
<td>Culture of indwelling catheters.</td>
</tr>
<tr>
<td>Serum and urine toxicology</td>
<td>Serum and urine toxicology.</td>
</tr>
</tbody>
</table>

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; BUN = blood urea nitrogen; ELISA = enzyme-linked immunosorbent assay.

2. Clinical examination: A thorough general and neurologic clinical examination is very important. Alterations of vital signs are very frequent in infections or drug intoxications. A detailed examination of organ systems (gastrointestinal, genitourinary, pulmonary, cardiac, skin) can reveal an otherwise occult source of infection.

- Nuchal rigidity is a sensitive indicator of meningeal irritation.
- Cranial nerve dysfunction and lateralized neurologic signs are highly suggestive of a focal structural process (particularly a lesion in the right hemisphere or the territory of the posterior circulation).
- Fluent aphasia, psychosis, or mood disorders can mimic delirium.
- The patient should be carefully observed for the presence of subtle convulsive activity in previously undetected complex partial status epilepticus.

3. Laboratory investigations: Laboratory tests that can be considered are included in Table 17.3.

- Laboratory evidence of infection should be aggressively pursued, particularly in elderly, debilitated patients who may not demonstrate clinical signs of inflammation.

- Serum and urine toxicology may reveal the presence of many drugs of abuse, as well as toxic levels of tricyclic antidepressants, antiepileptics, anticholinergics, digoxin, and other medications.
- Hypoxia and hypoglycemia are life-threatening conditions and their immediate identification and treatment are important for a good outcome.
- Cerebrospinal fluid evaluation should be performed even the lowest suspicion of primary CNS involvement from infection and inflammation, or if the etiology is uncertain. There are very few contraindications to the procedure and they can be safely excluded by appropriate clinical examination and neuroimaging.

4. Other studies: An electrocardiogram (EKG) and a chest radiograph are inexpensive tests, which should always be performed in the evaluation of delirium.

5. Electroencephalogram (EEG): Several EEG characteristics are associated with etiologies of delirium, although most of them are not entirely specific.

- Ongoing electrographic seizures are diagnostic of nonconvulsive status epilepticus and are necessary in the correct detection
and treatment of this condition. Otherwise, focal epileptiform discharges are associated with a higher risk of localization-related epilepsy but do not necessarily indicate the cause of the current event.

- Increased beta activity is associated with use of sedating medications, particularly benzodiazepines.
- Lateralized slowing and asymmetry could be the result of a hemispheric lesion.
- Triphasic waves are observed in metabolic encephalopathies, particularly of hepatic or uremic etiology.
- Finally, EEG is very useful in assessing the severity of encephalopathy and the response to medical interventions.

6. Neuroimaging: Computed tomography (CT) imaging of the brain is readily available in most settings and can exclude many structural abnormalities responsible for delirium. Recent advances of CT imaging with CT angiography can provide detailed images of the intracranial circulation in a noninvasive manner. Magnetic resonance imaging (MRI) can provide significantly more information than CT, but many critically ill patients cannot tolerate the study. Diffusion-weighted MRI can reveal areas of acute ischemia, while diffuse gadolinium enhancement is highly sensitive for blood-brain barrier disruption, even without a focal lesion. Neuroimaging has become an irreplaceable component of the diagnostic workup of delirium. 

MANAGEMENT

The management of delirium in the ICU setting is particularly challenging. Many of the medically necessary procedures can precipitate delirium. The need for analgesia and sedation should be balanced against the risk of delirium, which is a side effect of all psychoactive medications. Optimally, management involves several different steps that can be implemented simultaneously through the coordinated efforts of the entire healthcare team.

1. Primary prevention of delirium. The patient, if awake, should be frequently oriented to time and place. Dim lighting at night can help maintain normal sleep patterns. Eyeglasses and hearing aids should be asked for and brought by family members. Sensory stimuli should be kept at a comfortable level, avoiding overstimulation or sensory deprivation. If continuous iatrogenic sedation is required, daily awakening trials should be attempted to facilitate timely ventilator weaning, mobilization, and clinical monitoring. Clinical protocols can help prevent infection spread and fluid volume depletion. The presence of family members or a sitter should be encouraged and physical restraints should be avoided, when possible.

2. Identification of patients at high risk for developing delirium. Patients with multiple risk factors are particularly susceptible to developing delirium and have worse cognitive and overall clinical outcomes. Flexible clinical protocols that target these patients should be in place, providing a better yield for the resources of each institution.

3. Early detection of syndrome, even when only prodromal symptoms are evident. It is possible, but not clearly proven yet, that early detection in the ICU setting allows for better long-term outcomes. The presence of fragments of the delirium syndrome may alert physicians to the possibility of a subclinical process that will soon complicate clinical management.

4. Identification and treatment of underlying etiologies. Early treatment of infections, volume status maintenance, and reversal of other treatable causes are paramount to the treatment of delirium. Particular attention should be directed to life-threatening conditions such as hypoxia or hypoglycemia. IV thiamine should be administered before dextrose in suspected hypoglycemia.

5. Environmental modifications, nonpharmacologic management. The same principles for primary prevention should continue to be applied after delirium has been identified. Physical restraints are often necessary in this setting, but the continued need for them should be assessed frequently.

6. Symptomatic pharmacologic management. Pharmacologic management for delirium should be initiated with low doses of medications, and titrated according to clinical response. Patients should be monitored
Table 17.4. Common medications used to treat delirium

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>Younger patients 2–5 mg IV q2h</td>
<td>Extrapyramidal side effects</td>
</tr>
<tr>
<td></td>
<td>Older patients 0.5–1 mg IV q2h</td>
<td>QTc prolongation</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Younger patients 0.75–3 mg PO/day</td>
<td>Can induce delirium</td>
</tr>
<tr>
<td></td>
<td>Older patients 0.25–0.5 mg PO q12h</td>
<td>QTc prolongation</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Younger patients 3–7.5 mg PO/day</td>
<td>Not to be used with age &gt;70 years</td>
</tr>
<tr>
<td></td>
<td>Older patients 2.5–5 mg PO at night</td>
<td>Increases glucose levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less QTc prolongation</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Younger patients 25–100 mg PO/day</td>
<td>QTc prolongation, but can be used</td>
</tr>
<tr>
<td></td>
<td>Older patients 12.5 mg PO at night</td>
<td>following haloperidol-induced prolonged QTc.</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.5–2 mg IV/PO q8h</td>
<td>Monitor sedation level and respiratory rate.</td>
</tr>
</tbody>
</table>

QTc = QT interval corrected for heart rate.

serially for improvement of symptoms or clinical toxicity. Table 17.4 shows the most common medication used. Available classes include:

a. First-generation (typical) antipsychotics: These remain the first line of pharmacologic treatment for delirium.

- High-potency antipsychotics (haloperidol, droperidol) are preferable to the low-potency ones (phenothiazines) because they cause less sedation. Specifically, a titrating regimen of IV haloperidol has been recommended for the treatment of delirium in critically ill patients. A baseline EKG should be obtained for any patient who is treated for delirium with antipsychotics. QT prolongation (>450 ms or >25% of baseline) could lead to torsades de pointes even with low doses.

- Oral administration of medications is often impossible. The IV route is usually preferred, but IM administration may be necessary in case of severe agitation or lack of IV access. The IM or PO routes, however, may increase the risk for extrapyramidal side effects compared to IV administration (due to hepatic “first pass”).

b. Second-generation (atypical) antipsychotics: Increasing clinical and research data support the use of atypical antipsychotics in delirium. Increased efficacy over typical antipsychotics in the treatment of delirium has not been clearly demonstrated.

- There are concerns of increased mortality in patients with concurrent dementia (which frequently predisposes to or coexists with delirium).

- The lack of IV formulations limits their use in critically ill patients who need acute symptomatic control. Risperidone is available in a liquid form and can be administered through nasogastric tubes. Clozapine should not be used because of its anticholinergic effects, a contraindication in delirium, which is considered a state of increased dopamine and decreased acetylcholine levels.

c. Benzodiazepines: These have a role in the treatment of delirium associated with withdrawal of alcohol, benzodiazepines or b-hydroxybutyric acid (GHA), intoxication of sympathomimetic substances (cocaine, phenycyclidine), neuroleptic malignant syndrome, as well as seizure-related delirium.

- Benzodiazepines are not recommended in the routine management of delirious patients and they may, in fact, precipitate paradoxical agitation in vulnerable patients.
Combination therapy with antipsychotics has been proposed, but, particularly in the elderly, a simplified regimen should be used.

The risk of respiratory depression is significant in the critical care setting.

If benzodiazepines are used, shorter-acting agents (midazolam, lorazepam) without active metabolites are preferable to longer-acting ones (chlordiazepoxide).

7. Mechanical ventilation: Extreme agitation can be associated with cardiovascular instability and hypoxia in the critical care setting. If such symptoms are not effectively controlled with medications, mechanical ventilation with sedation and, even, muscle paralysis becomes an option, until underlying etiologies are identified and reversed. Propofol infusion up to 75 μg/kg per minute has been recommended because of its immediate onset and fast elimination.

CONCLUSIONS

Encephalopathy is an index of acute CNS dysfunction, in susceptible patients. It is usually precipitated by multiple underlying etiologies, which are not immediately apparent and should be actively investigated. If untreated, neurologic damage may progress to coma or brain death. Early detection and treatment has the potential of improving long-term outcomes. Effective management is multimodal and requires coordination of the entire healthcare team. Standardized evaluation and treatment protocols have been recommended, but treatment should be individualized to the particular needs of the critically ill patient.

REFERENCES