INTRODUCTION — Wernicke-Korsakoff syndrome is the best known neurologic complication of thiamine (vitamin B1) deficiency [1]. The term refers to two different syndromes, each representing a different stage of the disease. Wernicke's encephalopathy (WE) is an acute syndrome requiring emergent treatment to prevent death and neurologic morbidity. Korsakoff's syndrome (KS) refers to a chronic neurologic condition that usually occurs as a consequence of WE.

In 1881, Carl Wernicke described an acute encephalopathy characterized by mental confusion, ophthalmoplegia, and gait ataxia and associated with autopsy findings of punctate hemorrhages around the third and fourth ventricles and the aqueduct. A few years later, Russian psychiatrist Sergei Korsakoff described a chronic amnestic syndrome in which memory was impaired far out of proportion to other cognitive domains. While both observations were described in the context of chronic alcoholism, neither Wernicke nor Korsakoff initially recognized the relationship between the disorders, which was not appreciated until later by other investigators.

This topic will review Wernicke's encephalopathy. Korsakoff's syndrome and other chronic neurologic complications of alcohol abuse, including alcohol withdrawal are discussed separately. (See "Overview of the chronic neurologic complications of alcohol" and see "Management of moderate and severe alcohol withdrawal syndromes").

EPIDEMIOLOGY — Typical brain lesions of Wernicke's encephalopathy (WE) are observed at autopsy in 0.8 to 2.8 percent of the general population in the Western world, and the vast majority of affected patients are alcoholic [2,3]. The prevalence of WE lesions seen on autopsy was 12.5 percent of alcohol abusers in one report [4]. Among those with alcohol-related deaths, it has been reported to be even higher, 29 to 59 percent [5,6]. Autopsy studies
have consistently revealed a higher incidence of Wernicke lesions in the general population than is predicted by clinical studies [1,7].

While cases of WE in men outnumber those in women, women appear to be more susceptible to developing WE than men. In several series, the female to male ratio for WE was higher than the ratio for alcohol dependence [1,7].

**Associated conditions** — While most often associated with chronic alcoholism, WE occurs also in the setting of poor nutrition caused by malabsorption, poor dietary intake, increased metabolic requirement (eg, during systemic illnesses), or increased loss of the water-soluble vitamin thiamine (eg, in renal dialysis). In one autopsy series, non-alcohol abusers accounted for 12 of 52 cases (23 percent) of WE [8]. Conditions associated with WE include:

- Chronic alcoholism
- Anorexia nervosa or dieting [9]
- Hyperemesis of pregnancy [10,11]
- Prolonged intravenous feeding without proper supplementation [12,13]
- Prolonged fasting or starvation, especially with refeeding [14]
- Gastrointestinal surgery (including bariatric surgery) [12,15-19]
- Systemic malignancy [20-22]
- Transplantation [23]
- Hemodialysis or peritoneal dialysis [24-26]
- Acquired immunodeficiency syndrome [27-29]

**PATHOPHYSIOLOGY** — Thiamine is a cofactor for several key enzymes important in energy metabolism, including transketolase, alpha-ketoglutarate dehydrogenase, and pyruvate dehydrogenase [1]. Thiamine requirements depend on metabolic rate, with the greatest need during periods of high metabolic demand and high glucose intake. This is manifest by the precipitation of Wernicke's encephalopathy (WE) in susceptible patients by administration of intravenous glucose before thiamine supplementation [30].

Evidence for the role of thiamine in WE is supported by observations that the thiamine antagonist pyrithiamine causes experimental thiamine deficiency in rats, resulting in a sequence of ataxia, loss of the righting reflex, and convulsions [31,32]. In some cases, low levels of magnesium, an essential cofactor of thiamine into its active diphosphate and triphosphate forms, have been implicated with thiamine deficiency in WE [33].

It is unclear how thiamine deficiency causes brain lesions. Because of its role in cerebral energy utilization, it has been proposed that its deficiency initiates neuronal injury by inhibiting metabolism in brain regions with high metabolic requirements and high thiamine turnover. Events such as blood-brain barrier breakdown, N-methyl-D-aspartic acid (NMDA) receptor-mediated excitotoxicity, and increased reactive oxygen species have been implicated in thiamine
deficiency-induced neurotoxicity [34].

Thiamine deficiency in alcohol abusers results from a combination of inadequate dietary intake, reduced gastrointestinal absorption, decreased hepatic storage, and impaired utilization [35].

Only a subset of thiamine-deficient alcohol abusers develop WE. Greater susceptibility among identical rather than fraternal twins suggests a genetic predisposition [34]. Investigators have found that in alcohol abusers with WE, the thiamine-dependent enzyme transketolase has an altered affinity for thiamine [36-44]. Variants in the high affinity thiamine transporter gene have also been implicated [45,46].

Pathology — Acute WE lesions are characterized by vascular congestion, microglial proliferation, and petechial hemorrhages. In chronic cases, there is demyelination, gliosis, and loss of neuropil with relative preservation of neurons. Neuronal loss is most prominent in the relatively unmyelinated medial thalamus [1,47]. Atrophy of the mamillary bodies is a highly specific finding in chronic WE and Korsakoff syndrome and is present in up to 80 percent of cases [1,48].

The lesions of WE occur in a characteristic, symmetrical distribution in structures surrounding the third ventricle, aqueduct, and fourth ventricle [1,48]. The mamillary bodies are involved in virtually all cases, and the dorsomedial thalamus, locus ceruleus, periaqueductal gray, ocular motor nuclei, and vestibular nuclei are commonly affected. Lesions occur less frequently in the colliculi, fornices, septal region, hippocampus, and cerebral cortex, which may show patchy, diffuse neuronal loss and astrocytic proliferation.

In about one-half of cases, sagittal sections through the cerebellum reveal selective loss of Purkinje cells at the tips of the folia of the anterior superior cerebellar vermis. The latter changes are identical to those found in alcoholic cerebellar degeneration, where they can occur in the absence of other Wernicke lesions. (See "Overview of the chronic neurologic complications of alcohol", section on Alcoholic cerebellar degeneration).

CLINICAL MANIFESTATIONS

Classic signs — The classic triad of Wernicke's encephalopathy (WE) includes:

- Encephalopathy
- Oculomotor dysfunction
- Gait ataxia

Clinical recognition of WE is straightforward when an alcoholic presents with this classic triad. However, this may be the exception, not the rule. Detailed clinical and neuropathological data from 82 autopsies and 245 patients
examined over 10 years revealed that all features of the triad were recognized in only one-third of patients; in most, elements of the clinical triad appeared alone or in combination [1]. Confusion was the most common presenting symptom, followed by staggering gait and ocular problems. A similar constellation of symptoms has been reported in smaller series [4,49]. Absence of one or more of the classic symptoms likely leads to underdiagnosis [4,50]. In one series, WE was diagnosed premortem in only 26 of 131 patients whose brains revealed chronic WE lesions. All signs of the classic triad were recorded in 17 percent; none were recorded in 19 percent [50]. Clinical records recorded a high incidence of mental status abnormalities (82 percent), but much lower incidences of ataxia (23 percent), ocular motor abnormalities (29 percent), and polyneuropathy (11 percent).

The symptoms may present more or less simultaneously. Often, however, ataxia precedes other symptoms by a few days or weeks [1].

- **Encephalopathy** — The encephalopathy is characterized by profound disorientation, indifference, and inattentiveness [1]. If these are less severe and permit higher cognitive testing, impaired memory and learning are also evident. Some patients exhibit an agitated delirium related to concomitant ethanol withdrawal. Fewer than 5 percent present with a depressed level of consciousness, although the course in untreated patients will progress through stupor and coma to death [1,51]. In one autopsy series, patients with unrecognized WE frequently had lethargy or coma.

- **Oculomotor dysfunction** — Nystagmus, lateral rectus palsy, and conjugate gaze palsies reflect lesions of the oculomotor, abducens, and vestibular nuclei. Ocular abnormalities usually occur in combination rather than alone.

Nystagmus is the most common finding and is typically evoked by horizontal gaze to both sides [1]. Vertical nystagmus can also occur, usually evoked by upward, rather than downward, gaze. Rotatory and vertical nystagmus alone are uncommon. Lateral rectus palsy is virtually always bilateral. Vertical gaze palsies are less common than conjugate gaze palsies, and isolated vertical gaze palsy, internuclear ophthamoplegia, and complete ophthalmoplegia are rare. Pupillary abnormalities, usually sluggish or unequal pupils, may be present. A light-near dissociation is sometimes seen. In advanced cases, there may be complete loss of eye movements with miotic, nonreactive pupils. Ptosis is uncommon.

- **Gait ataxia** — Ataxia primarily involves stance and gait and is likely due to a combination of polyneuropathy, cerebellar involvement, and vestibular dysfunction [1,52]. When severe, walking is impossible. Less
affected patients walk with a wide-based gait and slow, short-spaced steps. Gait abnormalities are appreciated only on tandem gait in some patients.

Cerebellar pathology is generally restricted to the anterior and superior vermis; thus, ataxia of the legs or arms and dysarthria or scanning speech are uncommon [1]. Vestibular dysfunction may be the major cause of acute gait ataxia in WE, also explaining the dissociation between gait and limb abnormalities [1,52,53]. These findings contrast with those reported in patients with alcoholic cerebellar degeneration, in whom lower extremity ataxia is common [54]. (See "Overview of the chronic neurologic complications of alcohol", section on Alcoholic cerebellar degeneration).

**Other signs** — In addition to the classic triad, stupor or coma, hypotension, and hypothermia were prominent findings in unsuspected cases [50]. Patients with WE may also present with the following findings:

- Evidence of protein-calorie malnutrition is observed frequently in patients with WE [1]. However, not all patients are malnourished; in Australia, some beer drinkers with WE were even reported to be overweight [55].

- Vestibular dysfunction without hearing loss is a common finding [1,52,53,56]. In one study of 17 patients with acute WE, cold caloric responses were absent on at least one side in all, and abnormalities were bilateral in 11 [52]. The presence of spontaneous nystagmus with absent caloric responses appears to be a relatively specific finding in WE [53]. Vertigo is unusual. Some vestibular dysfunction is permanent after WE.

- Peripheral neuropathy is common and typically involves just the lower extremities [1]. Patients complain of the gradual onset of weakness, paresthesias, and pain affecting the distal lower extremities. In many patients there are no symptoms of neuropathy, but examination reveals diminished or absent ankle jerks and patchy distal sensory loss.

- Hypothermia has been described in 1 to 4 percent of patients with WE who went to autopsy, and it has been noted in numerous case reports [1,50,57]. Hypothermia may cause unreactive pupils [58], a finding rarely encountered in normothermic patients with WE [1]. Lesions in the posterior and posterolateral hypothalamus were noted in two patients with WE and hypothermia in one report [59]. This location is consistent with the known thermoregulatory functions of the hypothalamus. Other signs of autonomic involvement may include hypotension and syncope. In one autopsy series, hypotension and
hypothesis were prevalent in unsuspected cases of WE [50].

- While overt beriberi heart disease is rare in WE, other cardiovascular signs and symptoms are common and include tachycardia, exertional dyspnea, elevated cardiac output, and EKG abnormalities [1]. These reverse with thiamine administration.

**DIAGNOSIS —** Wernicke's encephalopathy (WE) is primarily a clinical diagnosis. Laboratory studies and neuroimaging studies can be helpful, but the biggest barrier to diagnosis is a low index of suspicion when all clinical symptoms are not present and in the nonalcoholic patient. Institution of treatment takes priority over diagnosis, and response to treatment may be diagnostic. (See "Treatment" below).

**Differential diagnosis —** WE should be considered in the differential diagnosis of all patients presenting with acute delirium or acute ataxia. It follows that other causes of delirium are considered in the diagnosis of a patient presenting with WE (show table 1). (See "Diagnosis of delirium and confusional states").

In one case series of 36 hospitalized geriatric patients, thiamine deficiency was common and associated with delirium [60]. In another small series, thiamine deficiency appeared to contribute to postoperative confusion in older patients after hip surgery [61]. These results appear to be contradicted by a larger series of 118 older inpatients in which there was no association between thiamine deficiency and delirium; however, the inclusion of patients with dementia and a broader definition of delirium in this study may have influenced these results [62].

Also, structural disease in the medial thalami or inferior medial temporal lobes such as occurs with top of the basilar stroke, hippocampal damage after cardiac arrest, herpes simplex encephalitis, and third ventricular tumors are likely considered because of the neuroanatomic overlap with WE [63,64].

**Clinical criteria —** Clinical recognition of WE is likely when an alcoholic presents with the classic symptom triad. However, autopsy-based series suggest that many patients lack one or more elements of this triad, and in some, lethargy or coma is the predominant clinical feature [1,4,50]. (See "Classic signs" above).

While autopsy studies likely underestimate the presence of classic signs that were not properly elicited, recognized, or recorded, it is clear that the diagnosis of WE can be missed when reliance is placed on the presence of all three of the typical symptoms.

One group proposed criteria for the diagnosis of WE and KS in chronic alcohol abusers based upon clinical-neuropathological correlation [65]. WE is diagnosed in patients with two of the following four Caine criteria:
• Dietary deficiency  
• Oculomotor abnormalities  
• Cerebellar dysfunction  
• Either altered mental status or mild memory impairment

Applying these criteria to a cohort of 106 autopsied alcohol abusers increased the diagnostic sensitivity for WE from 22 percent using the classic triad, to 85 percent.

The Caine criteria are clearly more sensitive than the classic triad, but given the high morbidity and mortality associated with the disorder, they are not sensitive enough. Specificity is low, and these were not intended to apply to nonalcoholics in whom the diagnosis is further impeded by a lower index of suspicion.

**Laboratory testing** — There are no laboratory studies that are diagnostic of WE. Thiamine deficiency can be most reliably detected by measurement of erythrocyte thiamine transketolase (ETKA) before and after the addition of thiamine pyrophosphate (TPP). A low ETKA, along with a more than 25 percent stimulation, establishes the diagnosis of thiamine deficiency [66]. This test is often not readily available, especially in the emergency setting. A serum thiamine or thiamine pyrophosphate level in serum or whole blood can also be measured by chromatography [67]. (See "Overview of water-soluble vitamins", section on Thiamine). The sensitivity and specificity of these blood tests in symptomatic patients are unclear.

Results from these measurements are not considered necessary for patient management. When the diagnosis of WE is entertained, immediate thiamine replacement takes precedence over laboratory diagnosis. (See "Treatment" below).

Patients with WE will likely also be tested for other toxic and metabolic conditions that can lead to delirium. (See "Diagnosis of delirium and confusional states"). In the setting of fever, or other suspicion for central nervous system infection, a lumbar puncture is required. In WE, the cerebrospinal fluid may be normal or may show a mild protein elevation [1]. Pleocytosis or protein >100 mg/dL suggest alternative diagnoses. An EEG may be ordered if nonconvulsive seizures are suspected. In WE, only about half of patients will demonstrate abnormalities, usually diffuse mild to moderate slow wave activity [1].

**Imaging studies** — Imaging studies are not necessary in all patients with suspected WE and should not delay treatment. (See "Treatment" below). However, diagnostic imaging can be helpful by providing evidence of WE in many patients and may rule out alternative diagnoses.
Abnormalities on computerized tomography (CT) scans or magnetic resonance imaging (MRI) have been reported in small numbers of patients with acute WE [68]. CT may show symmetric, low density abnormalities in the diencephalon, midbrain, and periventricular regions that enhance after the injection of contrast [69-72]. Gross hemorrhages are uncommon in acute WE, but they have also been detected by CT [73]. These findings are uncommon in other disorders, and when present, should strongly suggest the diagnosis. However, CT is an insensitive test for WE; a normal CT scan does not rule out the diagnosis [49].

MRI is more sensitive than CT in detecting acute diencephalic and periventricular lesions [49,74,75]. Typical findings include areas of increased T2 and decreased T1 signal surrounding the aqueduct and third ventricle and within the medial thalamus and mamillary bodies [75-78]. Diffusion-weighted imaging (DWI) is abnormal in these areas as well [79,80]. The distribution of these findings is consistent with the pathologic lesions. (show radiograph 1 and show radiograph 2).

In one report comparing 15 patients with acute WE to 15 asymptomatic alcohol abusers and 15 controls, the sensitivity and specificity of MRI were 53 and 93 percent, respectively [49]. Other series have reported a higher prevalence of MRI abnormalities in patients with acute WE [75,81]. Abnormal T2 signal disappears within as little as 48 hours after treatment with thiamine [81].

Mamillary body atrophy is a relatively specific abnormality in patients with chronic lesions of WE [82]. A large decrease in the volume of the mamillary bodies can be identified by MRI in approximately 80 percent of alcohol abusers with a history of classic WE, and it is not found in controls, patients with Alzheimer disease (AD), or alcohol abusers without a history of WE [82-84]. Mamillary body atrophy can be detected within one week of the onset of WE [81].

**TREATMENT** — The diagnosis of Wernicke's encephalopathy (WE) is difficult to confirm and, untreated, most patients progress to coma and death. Fortunately, intravenous administration of thiamine is safe, simple, inexpensive, and effective [85]. Adverse reactions, including anaphylaxis and bronchospasm are reported but are extremely rare; in the United Kingdom, there were four reported cases for every five million intramuscular doses used and one report for every one million intravenous doses used [86-89].

Diagnostic testing should not delay treatment; treatment should immediately follow consideration of the diagnosis.

For patients with suspected WE, we recommend 100 mg of thiamine intravenously or intramuscularly for five consecutive days. Administration of glucose without thiamine can precipitate or worsen WE; thus, thiamine should
be administered before glucose. Because gastrointestinal absorption of thiamine is erratic in alcoholic and malnourished patients, oral administration of thiamine is an unreliable initial treatment for WE [35]. Some advocate higher doses of thiamine as more effective, but there is no evidence to conclusively support a recommendation of one dose over another [86,89-91].

Although dietary requirements for thiamine are only 1 to 2 mg daily, absorption and utilization of thiamine are incomplete, and some patients have genetically determined requirements for much larger doses [37,92]. Daily oral administration of 100 mg of thiamine should be continued after the completion of parenteral treatment and after discharge from the hospital until patients are no longer considered at risk. Magnesium and other vitamins are replaced as well, along with other nutritional deficits if present.

By establishing a sufficiently low threshold for treatment, all patients with WE will receive thiamine, including those whose diagnosis is unsuspected. For practical purposes, all patients with undiagnosed altered mental status, oculomotor disorders, or ataxia should receive parenteral thiamine.

**CLINICAL COURSE AND PROGNOSIS** — Prompt administration of thiamine leads to improvement in ocular signs within hours to days [1]. If ocular palsies fail to respond, other diagnoses should be considered. In one report, recovery of vestibular function began during the second week after thiamine treatment; improvement in gait ataxia coincided with recovery of vestibular function [52]. Confusion subsides over days and weeks. Signal abnormality on MRI resolves with clinical improvement [81,93]. This early therapeutic response likely represents the recovery from a biochemical rather than a structural lesion.

In the largest cohort of patients reported on, residual deficits were the rule [1]. While gaze palsies recovered completely in most cases, 60 percent had permanent horizontal nystagmus. Only about 40 percent recovered from ataxia; remaining deficits ranged from inability to walk at all to a wide-based slow shuffling gait. As the acute encephalopathy and confusion receded, deficits in learning and memory become more obvious; the latter recovered completely or substantively in only about 20 percent; the remainder had a permanent amnestic syndrome. (See "Overview of the chronic neurologic complications of alcohol", section on Korsakoff's amnestic syndrome).

Case reports and small case series suggest that prognosis may be less dismal [55,80,94]. One exceptional case reports near complete recovery in a severely affected patient whose treatment was delayed for four months [95].

**PREVENTION** — Wernicke's encephalopathy (WE) may be iatrogenically precipitated by glucose loading in patients with unsuspected thiamine deficiency [30]. To avoid this complication, it has become standard practice in emergency departments to administer thiamine prior to or along with glucose
infusion, particularly in those who are at risk for thiamine deficiency (see "Associated conditions" above).

The prevention of WE and Korsakoff's amnestic syndrome (KS) might be possible through the widespread oral administration of thiamine to outpatients at risk. Enrichment of flour with thiamine decreased the autopsy prevalence of WE in Australia [96]. There is also interest in whether preventing thiamine deficiency would also reduce the high prevalence of cognitive deficits in alcohol abusers without known episodes of WE [97]. The low cost and safety of oral thiamine argues for widespread supplementation in alcohol abusers and others at risk for developing thiamine deficiency. Fortification of alcoholic beverages has also been proposed.

SUMMARY AND RECOMMENDATIONS — Wernicke's encephalopathy (WE) and Korsakoff's amnestic syndrome (KS) are, respectively, acute and chronic brain disorders that result from thiamine deficiency.

- WE is most often associated with alcoholism but can also occur in other situations including malnutrition from any cause (particularly at the time of refeeding) and in dialysis patients. (See "Associated conditions" above).

- WE produces hemorrhagic necrosis in midline brain structures and corresponding deficits in mentation, oculomotor function, and gait ataxia. All three of these classic symptoms are present in only one-third of patients. Any one of these, but most often encephalopathy, may be seen in isolation. WE should be considered when one or more occur. (See "Clinical manifestations" above).

- While laboratory measurements and neuroimaging are often abnormal in WE, the first imperative is to administer thiamine rather than confirm the diagnosis, whenever WE is considered. (See "Diagnosis" above).

- Untreated, WE leads to coma and death. Prognosis is improved by prompt administration of thiamine. Whenever the diagnosis of WE is entertained, we recommend immediate parenteral administration of thiamine (Grade 1A). The usual dose is 100 mg intravenous (IV) or intramuscular (IM), repeated daily for five consecutive days. Oral thiamine and multivitamin supplementation are recommended thereafter as long as the patient remains at risk (Grade 1A). (See "Clinical course and prognosis" above).

- WE may be precipitated by administration of intravenous glucose solutions to individuals with thiamine deficiency. In susceptible individuals glucose administration should be preceded or accompanied by thiamine 100 mg IV (Grade 1A). (See "Prevention" above).
Thiamine supplementation, along with other multivitamin supplementation, is recommended for patients at risk for thiamine deficiency. (See "Prevention" above).

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REFERENCES

14. Suzuki, Y, Matsuda, T, Washio, N, Ohtsuka, K. Transition from upbeat to downbeat nystagmus observed in a patient with Wernicke's


**GRAPHICS**

**Common causes of delirium and confusional states**

<table>
<thead>
<tr>
<th>Drugs and toxins</th>
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<tbody>
<tr>
<td>Prescription medications (eg, opioids, sedative-hypnotics, antipsychotics, lithium, skeletal muscle relaxers, polypharmacy)</td>
</tr>
<tr>
<td>Non-prescription medications (eg, antihistamines)</td>
</tr>
<tr>
<td>Drugs of abuse (eg, ethanol, heroin, hallucinogens, nonmedicinal use of prescription medications)</td>
</tr>
<tr>
<td>Withdrawal states (eg, ethanol, benzodiazepines)</td>
</tr>
<tr>
<td>Medication side effects (eg, hyperammonemia from valproic acid, confusion from quinolones, serotonin syndrome)</td>
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<tr>
<td>Poisons:</td>
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<tr>
<td>Atypical alcohols (ethylene glycol, methanol)</td>
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<tr>
<td>Inhaled toxins (carbon monoxide, cyanide, hydrogen sulfide)</td>
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<tr>
<td>Plant-derived (eg, Jimson weed, salvia)</td>
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<tr>
<th>Infections</th>
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<tr>
<td>Sepsis</td>
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<td>Systemic infections; fever-related delirium</td>
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<tr>
<th>Metabolic derangements</th>
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<tr>
<td>Electrolyte disturbance (elevated or depressed): sodium, calcium, magnesium, phosphate</td>
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<td>Endocrine disturbance (depressed or increased): thyroid, parathyroid, pancreas, pituitary, adrenal</td>
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<tr>
<td>Hypercarbia</td>
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<td>Hyperglycemia and hypoglycemia</td>
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<td>Hyperosmolar and hypoosmolar states</td>
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<tr>
<td>Hypoxemia</td>
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<tr>
<td>Inborn errors of metabolism: porphyria, Wilson's disease, etc.</td>
</tr>
<tr>
<td>Nutritional: Wernicke's encephalopathy, vitamin B12 deficiency, possibly folate and niacin deficiencies</td>
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**Brain disorders**

<table>
<thead>
<tr>
<th>CNS infections: encephalitis, meningitis, brain or epidural abscess</th>
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<tr>
<td>Epileptic seizures, especially nonconvulsive status epilepticus*</td>
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<td>Head injury*</td>
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<tr>
<td>Hypertensive encephalopathy</td>
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<tr>
<td>Psychiatric disorders*</td>
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**Systemic organ failure**

<table>
<thead>
<tr>
<th>Cardiac failure</th>
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<tr>
<td>Hematologic: thrombocytosis, hypereosinophilia, leukemic blast cell crisis, polycythemia</td>
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<td>Liver failure: acute, chronic</td>
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<tr>
<td>Pulmonary disease, including hypercarbia and hypoxemia</td>
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<tr>
<td>Renal failure: acute, chronic</td>
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**Physical disorders**

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<tr>
<th>Burns</th>
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<tr>
<td>Electrocution</td>
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<td>Hyperthermia</td>
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</table>
Hypothermia

Trauma: with systemic inflammatory response syndrome, *head injury, fat embolism

* Disorders that, while not truly systemic or "medical", may produce the clinical picture of delirium or confusional state in all other aspects.

**MRI findings wernicke's encephalopathy**
A 20-year-old pregnant female with severe emesis and presumed Wernicke's encephalopathy. Flair images demonstrate typical findings of hyperintensity in the periaqueductal region of the midbrain (A), mammillary bodies (B), and thalamus (C). Additionally, the patient had bilateral symmetrical hyperintensity in the frontal-parietal cortices (D), which has also been reported in these patients. *Courtesy Eric D Schwartz, MD.*
Diffusion-weighted imaging (A) and ADC map (B) show restricted diffusion in the thalami, suggestive of cytotoxic edema. Other reports show hyperintensity on diffusion images without restriction seen on ADC maps, more suggestive of vasogenic edema. The underlying pathology and prognostic significance of diffusion findings are unclear. Post-contrast images (C) indicate breakdown of the blood-brain barrier with enhancement of the mammillary bodies. Courtesy Eric D Schwartz, MD.

Grade 1A recommendation

A Grade 1A recommendation is a strong recommendation, and applies to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.

Explanation:

A Grade 1 recommendation is a strong recommendation. It means that we believe that if you follow the recommendation, you will be doing more good than harm for most, if not all of your patients.

Grade A means that the best estimates of the critical benefits and risks come from consistent data from well-performed, randomized, controlled trials or overwhelming data of some other form (eg, well-executed observational studies with very large treatment effects). Further research is unlikely to have an impact on our confidence in the estimates of benefit and risk.

Recommendation grades
1. Strong recommendation: Benefits clearly outweigh the risks and burdens (or vice versa) for most, if not all, patients
2. Weak recommendation: Benefits and risks closely balanced and/or uncertain

Evidence grades
A. High-quality evidence: Consistent evidence from randomized trials, or overwhelming evidence of some other form
B. Moderate-quality evidence: Evidence from randomized trials with important limitations, or very strong evidence of some other form
C. Low-quality evidence: Evidence from observational studies,
unsystematic clinical observations, or from randomized trials with serious flaws

For a complete description of our grading system, please see the UpToDate editorial policy which can be found by clicking "About UpToDate" and then selecting "Policies".