Chapter 41

Prognosis of neurologic complications in critical illness

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Abstract

Neurologic complications of critical illness require extensive clinical and neurophysiologic evaluation to establish a reliable prognosis. Many sequelae of intensive care unit (ICU) treatment, such as delirium and ICU-acquired weakness, although highly associated with adverse outcomes, are less suitable for prognostication, but should rather prompt clinicians to seek previously unnoticed persisting underlying illnesses. Prognostication can be confounded by drug administration particularly because its clearance is abnormal in critical illness. Some neurological complications are severe, and can last for months or years after discharge from ICU. The most important ethical aspects regarding neurologic complications in critically ill patients are prevention, recognition, and identification, and prevention of self-fulfilling prophecies. This chapter summarizes the tool of prognostication of major neurological complications of critical illness.

INTRODUCTION

Three fundamental questions can be addressed in the management of critically ill patients: (1) What is the diagnosis?; (2) What is the most appropriate treatment?; and (3) What is the prognosis?

In most patients in an intensive care unit (ICU), the first two questions are seldom troublesome, but predicting outcome is often very difficult. Often we cannot predict the course of the disease and whether or not complications will occur, but an estimate of prognosis provides guidance for continuation, withholding, or withdrawal of life-sustaining measures. Relatives of the patient expect from us a prediction of survival and outcome, but at the same time, predicting the future may engender strong emotions among relatives and even physicians and nurses themselves. Prognostication is an essential part of daily care in the ICU, but is also one of the most elaborate tasks (Christakis, 1999). Prognostication may become even more difficult when the original critical illness is complicated by medical events that have a strong impact on prognosis.

A medical complication is an unintended, harmful occurrence or condition resulting from a diagnostic, prophylactic, or therapeutic intervention, or an accidental injury occurring in the hospital setting (Rubins and Moskowitz, 1990). Critically ill patients are especially vulnerable to complications that arise from the underlying disease or comorbidities, as well as from advanced intensive care treatments. Well-known are complications resulting from mechanical ventilation and catheter-related blood stream infections, among many others. Acute and chronic neurologic complications can occur both in neurologic and nonneurologic critically ill patients, of which many are perceived as highly detrimental to survival and outcome. Survivors of critical illness are often left with neurologic and cognitive disabilities (Ortega-Guitierrez et al., 2009; Desal et al., 2011), even without evident neurologic complications during the course of their ICU stay. In a sense, it may seem that this is the price we pay for advances in critical care medicine, engaging us to keep patients alive simply because we can, in an increasingly elderly, multimorbid population prone to long-term (neurologic) sequelae.

Some neurologic complications are severe, and can last for months or years after discharge from ICU. These neurologic disabilities form a significant reason for decreased quality of life after ICU discharge (Guerra et al., 2012). Long-term cognitive and other neurologic

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disabilities resulting from critical illness constitute a personal, social, and economic burden for patients, their relatives, and society, and in most cases will result in high costs on resource consumption, such as sick leave, hospitalizations, outpatient care, drugs, social services, early retirement, and premature death. In many cases, neurologic complications after ICU admission form the basis of disability-adjusted life years. Although not many robust clinical studies exist that have included premorbid cognitive and functional status at ICU admission, the scarce data published to date have clearly indicated that the ICU phase may contribute to neurologic impairments.

Medically or surgically critically ill patients are at risk for acute neurologic and long-term cognitive complications. This is a particular concern among patients admitted with severe sepsis with multiple organ failure (MOF); immunocompromised patients, including those undergoing solid-organ or bone marrow transplantation or those who are treated with neurotoxic immunosuppressive agents; patients with severe metabolic, electrolyte, and acid–base disturbances, leading to encephalopathy; and those requiring long-term sedation. Common neurologic syndromes, such as delirium and ICU-acquired weakness (ICUAW), occur regularly in these patients, and have strong prognostic significance.

Prognostication of neurologic complications seems highly dependent on the etiology and severity of the primary condition, age of the patient, and comorbidities. This chapter deals with the prognosis of neurologic complications in critically ill patients developing neurologic manifestations. This information is aimed primarily at physicians and nurses who regularly deal with critically ill patients. The summaries of prognostic knowledge of the main neurologic complications of critical illness are intended to provide guidance in: (1) deciding when to continue treatment versus transition towards end-of-life care; (2) informing families of critically ill patients about what they may or may not expect in the short and long term; and (3) defining knowledge gaps in prognostic information (where currently only clinical experience and intense multidisciplinary consultations are available to estimate prognosis).

We will also explore the ethics behind prognostication: what is the personal and societal burden of neurologic impairment resulting from critical illness? What are the ethical issues raised by the use of the prognostic information?

**PROGNOSIS OF ICU-ACQUIRED ENCEPHALOPATHY**

Patients admitted to the ICU can suffer from several types of encephalopathy, including drug-induced, hepatic, hypoxic-ischemic, uremic, Wernicke’s, and hypertensive encephalopathy. Some of these can be seen as complications of critical care treatment, since they develop during admission to the ICU, whether iatrogenic (e.g., drug-induced encephalopathy), as a manifestation of the condition the patient is admitted for, or as a consequence of underlying comorbidity (hepatic encephalopathy (HE), uremic encephalopathy). Treating the underlying cause may reverse the symptoms, but in some cases, structural changes are irreversible. Prognosis of encephalopathy depends on many factors, including age, comorbidity, recognition of the underlying cause, and degree of organ dysfunction.

**Drug-induced encephalopathy**

Administration of certain drugs in patients with impaired cerebral metabolism can lead to serious encephalopathy. Usually, this is not attributed to structural cerebral lesions or diseases, but the drug-induced encephalopathy can form the basis of structural lesions, with disturbances of consciousness, personality, and cerebral function, and can give rise to clinical signs and symptoms (e.g., seizures), with subsequent impact on mortality and morbidity. Since many severely ill patients admitted to an ICU have impaired cerebral metabolism, and because of the widespread use of certain drugs, drug-induced encephalopathy is not uncommon, although often underrecognized.

A variety of commonly used drugs are neurotoxic and can cause drug-induced encephalopathies, among which are analgesics, sedatives, antibiotics, antivirals, anticonvulsants, chemotherapeutics, immunosuppressants, and neuroleptics. We focus on three groups of drugs in which encephalopathy is described as a complication specifically in critically ill patients: antibiotics, antiviral agents, and analgesics.

Most drug-induced encephalopathies have a good prognosis when the cause is recognized and reversed. Although fatal drug-induced encephalopathy is described (Cossaart et al., 2003), we were unable to find such a complication in the treatment of critically ill patients in the ICU.

Several antibiotics cross the blood–brain barrier, making them good treatment options for serious central nervous system (CNS) infections. On the other hand, these agents can, for the same reason, cause neurotoxicity, complicating treatment of infections in the ICU (Grill and Maganti, 2011). The toxic effects on the CNS are often initially unrecognized, and the signs and symptoms are mistakenly seen as manifestations of other neurologic conditions and complications. Since many ICU patients suffer from primary or nosocomial infections, which necessitate use of broad-spectrum antibiotics, the ICU population is at high risk of neurotoxicity associated with
various groups of antibiotics (Grill and Maganti, 2011). Severe infections, comorbidities, polypharmacy, and advanced age give rise to neurologic deterioration and hamper the diagnosis of drug-induced encephalopathy. Besides this, drug-induced encephalopathy is often ascribed to metabolic disturbances and MOF, such that the incidence is underestimated. As most antibiotic-induced encephalopathies are reversible after the drug is stopped, early recognition is essential.

**Metronidazole**

Administration of the antibiotic metronidazole can lead to a variety of neurologic adverse effects, including peripheral neuropathy, seizures, cerebellar dysfunction, and encephalopathy (Kusumi et al., 1980; Ahmed et al., 1995; Horlen et al., 2000; Woodruff et al., 2002; Heaney et al., 2003; Seok et al., 2003; Kim et al., 2007, 2011; Mulcahy and Chaddha, 2008; Graves et al., 2009; Sarna et al., 2009; Huang et al., 2012). Metronidazole is a nitroimidazole antibiotic commonly used as treatment for anaerobic-related infections, *Clostridium difficile* colitis, and in patients with HE (to remove the nitrogenous load in the gastrointestinal tract). After discontinuation of the medication, patients in case reports usually made a rapid recovery. The hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images were found to be completely or partially reversible (Horlen et al., 2000; Cecil et al., 2002; Heaney et al., 2003; Kim et al., 2007; Mulcahy and Chaddha, 2008). Metronidazole-induced encephalopathy must be differentiated from osmotic demyelination and other transient T2-hyperintense lesions, as these will lead to different therapeutic strategies. When adequately recognized using brain magnetic resonance imaging (MRI), prognosis of metronidazole-induced encephalopathy is favorable, disappearing a few days to weeks after discontinuation of the medication.

**Cephalosporins**

Cephalosporin-induced neurotoxicity may manifest as encephalopathy, among other neurologic signs and symptoms. Elderly patients, those with renal failure, and patients with prior neurologic conditions are especially prone to cephalosporin-induced encephalopathy (Abanades et al., 2004; Lam and Gomolin, 2006; Grill and Maganti, 2008). Cefepime is a parenterally administered fourth-generation cephalosporin antibiotic used for the treatment of Gram-positive and Gram-negative infections in critically ill patients. Approximately 3% of patients treated with cefepime experienced adverse neurologic reactions (Neu, 1996). Cefepime-induced status epilepticus has been reported in more than 25 cases (Primavera et al., 2004; Maganti et al., 2006; Thabet et al., 2009). Sonck and colleagues (2008) described 8 patients with renal failure showing slowly progressive neurologic symptoms after initiation of cefepime. The mortality in this series was 100%, with death occurring shortly after neurologic deterioration in 3 cases. Three patients who survived longer showed neurologic improvement after drug discontinuation. Partial or complete recovery after early recognition and withdrawal of cefepime appear to be the most common outcome (Jallon et al., 2000; Martinez-Rodriguez et al., 2000; Chattelier et al., 2002; Chow et al., 2003; Ferrara et al., 2003).

Ceftriaxone has also been described as inducing a reversible encephalopathy (Klion et al., 1994; Herishanu et al., 1998; Martinez-Rodriguez et al., 2000; Dakdouki and Al-Awar, 2004; Roncon-Albuquerque et al., 2009; Grill and Maganti, 2011; Kim et al., 2012; Sharma et al., 2012; Sadafi et al., 2014). As with cefepime, toxicity is more common with previous CNS disease and renal failure (Denysenko and Nicolson, 2011; Kim et al., 2012; Sadafi et al., 2014). Latency of ceftriaxone-induced encephalopathy is 1–10 days after drug initiation, and regression of all neurologic symptoms usually follows within 2–7 days following drug suspension (Roncon-Albuquerque et al., 2009; Kim et al., 2012; Sharma et al., 2012).

Other cephalosporins (cefoxime, cefazidime, cefazolin) have been described to cause encephalopathy as well (Schwankhaus et al., 1985; Josse et al., 1987; Geyer et al., 1988; Pascual et al., 1990; Ortiz et al., 1991; Jackson and Berkovic, 1992; Herishanu et al., 1998). After withdrawal or reduction in dosage, most patients show recovery of signs and symptoms of encephalopathy. In some cases, symptoms persisted for more than a week after withdrawal of the antibiotics (Jackson and Berkovic, 1992).

**Clarithromycin**

Clarithromycin is an antibiotic of the macrolide family, used widely in respiratory infections. Clarithromycin may give rise to psychiatric symptoms (Négrin-González et al., 2014), but may also induce encephalopathy, appearing 1–10 days after drug intake (Bandettini di Poggio et al., 2011). Early detection of clarithromycin-induced encephalopathy and discontinuation of the drug result in full recovery.

**Cycloserine**

Cycloserine is a broad-spectrum antibiotic used for the treatment of drug-resistant tuberculosis. Excessive doses can give rise to serious neurologic complications (Kwon et al., 2008; Kim et al., 2014). A characteristic finding is
reversible cytotoxic edema in the dentate nuclei, visible on MRI. Discontinuation of cycloserine usually gives complete resolution.

**Linezolid**

Linezolid is an antibiotic used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to other antibiotics, including vancomycin-resistant Enterococcus species and methicillin-resistant Staphylococcus aureus. In the ICU, it is often used in the treatment of life-threatening pneumonia and serious skin infections. Linezolid has been described in a small number of patients as inducing peripheral and central neurotoxicity (Ferry et al., 2005; Fletcher et al., 2010), among which is posterior reversible encephalopathy syndrome (PRES) (Hinchey et al., 1996; Nagel et al., 2007). In one series of 4 patients, linezolid-induced peripheral neuropathy resulted in persistent neurologic damage, while central neurotoxicity was transient after discontinuation of linezolid (Ferry et al., 2005).

**Penicillin**

Penicillin encephalopathy has been, since 1952 (Bateman et al., 1952), described in many patients (Conway et al., 1968). As with other antibiotic-induced encephalopathies, it is often associated with renal failure, which leads to drug accumulation. In every case where penicillin has been stopped or reduced, considerable improvement, usually resulting in complete recovery of encephalopathic symptoms, occurred (Conway et al., 1968).

**Antiviral Drugs**

In critically ill patients with renal failure, neurotoxicity of acyclovir leading to encephalopathy is described in several case reports (Revankar et al., 1995; Ernst and Franey, 1998; Dulerme et al., 2002; Dulluc et al., 2004; Carlon et al., 2005; Onuigbo et al., 2009; Van Kan et al., 2009). Prevention is especially important in patients with renal failure. With the prompt initiation of hemodialysis, neurotoxicity is reversible, making prognosis favorable in many cases (Laskin et al., 1982; Almond et al., 1995). However, Van Kan et al. (2009) could not exclude, however unlikely, the contribution of acyclovir neurotoxicity in the death of a critically ill patient.

**Analgesics**

Opioids can induce neurotoxicity, especially in severely ill patients secondary to dehydration, infection, or drug interactions (Gallagher, 2007). Morphine-induced encephalopathy is described as a complication in patients with severe liver dysfunction, which interferes with the metabolism of morphine (Hasselström et al., 1990; Dumont et al., 1998). Therefore, it is a challenge to ensure adequate analgesia and pain treatment in patients with liver failure. Shinagawa et al. (2008) described a case of morphine-induced encephalopathy where the excess of ammonia due to constitutional constipation in this patient was exacerbated by the use of morphine. The patient regained consciousness by receiving amino-leban and a suppository for constipation.

**Prognosis of Hepatic Encephalopathy in Acute Liver Failure**

Acute liver failure (ALF) is a feared condition in critically ill patients, resulting in rapid and severe decline in liver function (impaired synthetic parameters, such as international normalized ratio (INR) > 1.5) and HE, the latter resulting from reduced detoxification. ALF may be observed as a complication of critical illness. Although ALF is most commonly drug-induced and starts outside the ICU, it can also result from severe shock, MOF, viruses, vascular origin, or autoimmunity. Rare causes of ALF with HE include pregnancy and Reye’s syndrome. In more than 80% of cases, the cause of ALF can be determined. ALF is always life-threatening and may affect relatively young patients. Liver transplantation is often the only possible therapeutic option impacting survival, without which patients may die within days, despite all supportive ICU treatments. Before the era of liver transplantation, mortality of ALF was as high as 85%, but in the last several decades, survival rates have risen to 60–80%. Recovery with only standard intensive care treatment is seen in more than half of the patients admitted with ALF due to an overdose with acetaminophen and pregnancy-related (fatty) liver failure. On the other end of the spectrum, poor prognosis is often seen in hepatitis B infection, other drug intoxications (e.g., ecstasy), and autoimmune liver failure.

HE is an important factor for predicting survival in ALF. HE is characterized by decrease in level of consciousness, asterixis, myoclonus and may progress to coma with extensor motor responses, and a variety of precipitating factors that can affect the prognosis. Renal failure with electrolyte and acid–base imbalance, respiratory failure, and sepsis are common. Neurologic features of HE in ALF include the presence of raised intracranial pressure, which can complicate the outcome, even with complete recovery of liver function or after liver transplantation. The grade of HE is an important prognostic factor. Low-grade HE (I–II) is associated with spontaneous recovery in up to 70%,
but recovery is below 20% in grade IV HE (O’Grade et al., 1989).

In the acute phase, the outcome of ALF is often unpredictable, making prognostication very difficult. Age, the etiology of ALF, severity of illness, long periods of raised intracranial pressure, and comorbidities are independent factors in prognostication.

Several prognostic scoring systems have been developed and are in use for screening before liver transplantation (García-Martínez et al., 2011). The most commonly used prediction model is the King’s College criteria, which were developed using data from 588 patients with ALF. The model separates acetaminophen-induced ALF from other causes. In acetaminophen-induced ALF, criteria for transplantation include an arterial pH < 7.3 (irrespective of grade of HE) or all three of serum creatinine > 3.4 mg/dL, prothrombin time (PT) > 100 seconds (INR > 6.5), and grade III–IV HE. In patients with other causes of ALF, transplantation is indicated in patients with PT > 100 seconds (INR > 6.5, irrespective of the grade of HE) or three of the following five variables: idiosyncratic drug reactions, > 7 days’ jaundice prior to onset of HE, PT > 50 seconds (INR > 3.5), age < 10 or > 40 years, and serum bilirubin > 18 mg/dL.

**PROGNOSIS OF ICU-ACQUIRED UREMIC ENCEPHALOPATHY**

Uremic encephalopathy may complicate severe acute and chronic renal failure. Especially in patients with acute renal failure, the symptoms are generally more pronounced and progress more rapidly (Van Dijck et al., 2012). Renal failure is fatal if left untreated. Uremic encephalopathy reflects the severity of renal failure. If the renal failure is not treated, or cannot be treated any more, uremic encephalopathy progresses to coma and death. On the other hand, uncomplicated uremic encephalopathy is reversible, making prompt recognition and treatment (hemodialysis) important. An important note is the fact that there is scarce literature on the effects of treatment of uremic encephalopathy with renal replacement therapies (RRT) on clinically relevant outcomes. Although patients may certainly improve in level of consciousness after RRT has been initiated, robust prospective studies are lacking.

**PROGNOSIS OF ICU-ACQUIRED WEAKNESS**

ICUAW is the most common modern terminology for the syndrome of weakness that is also referred to by other names, such as “critical illness polynuromyopathy.” The many terms used to identify this syndrome have hampered robust outcome research. Only relatively recently proposed criteria have been published for ICUAW, which may be regarded as a starting point for more robust short- and long-term outcome studies, now that definitions have become more uniform (Stevens et al., 2009; Farhan et al., 2016). Nevertheless, ICUAW in its previous diverse connotations is a well-recognized complication since the first description in the 1980s (Bolton et al., 1984), which has been associated with long-term morbidity and mortality in survivors (van der Jagt, 2010; Kress and Hall, 2014). Current studies on prognosis, many with intrinsic limitations with regard to definitions and terminology, will be summarized in this section.

In general it is difficult to truly separate the influence of ICUAW from outcomes from other prognostic factors, such as age, cognitive status, and various comorbidities. Moreover, the fact that ICUAW is heterogeneous in itself (polyneuropathic ICUAW seems to have a worse prognosis than predominantly myopathic ICUAW (Koch et al., 2014; Hermans and Van den Berghe, 2015)) complicates matters further. Finally, a plethora of interventions in the ICU seem to impact on the occurrence and course of ICUAW (e.g., medications such as corticosteroids, early mobilization practices, and nutrition), although true prospective randomized studies that reveal cause-and-effect relationships are scarce (Schweickert et al., 2009; Farhan et al., 2016). Therefore, at present, it is unclear whether ICUAW is merely a marker of severity of illness, or that it independently contributes to eventual adverse clinical outcomes, although the truth most probably lies somewhere in between (Hermans and Van den Berghe, 2015). Nonetheless, ICUAW and cognitive dysfunction together represent the most important long-term ICU sequelae (Kress and Hall, 2014), and therefore deserve our attention. In other words, there is more to ICU-related outcomes than just “discharge from ICU alive.” In ICU survivors, functional outcome is of major interest. In addition, ICU length of stay (ICU-LOS) is of importance both from the perspective of the patient and cost-effectiveness.

Earlier investigations have reported highly variable mortality risk associated with ICUAW, ranging from 7 to 61%, depending on the target population and the time frame of evaluation after ICU admission (van der Jagt, 2010). Adjustment for confounders has shown a statistically independent relationship between ICUAW and 30-day mortality, which may be fivefold higher compared to patients without ICUAW. In addition, ICU-LOS may double after a diagnosis of ICUAW (Ali et al., 2008). Importantly, easy-to-perform bedside tests may assist in the evaluation of muscle strength in suspected ICUAW and unveil an increased risk of death (Ali et al., 2008; Lee et al., 2012). More recent investigations by separate research groups have confirmed the
strong and independent association between ICUAW and extended ICU and hospital LOS, as well as long-term risk of death, suggesting a causal relation (Hermans et al., 2014). The finding enhances this notion that there seems to be a dose–response relationship between the severity of muscle weakness at ICU discharge and mortality (Hermans et al., 2014). These studies suggest that scrutiny is indicated in the follow-up of these patients after the ICU period because of their higher risk for adverse outcomes. However, studies evaluating the benefit of follow-up programs have not been performed.

Critical illness portends long-term functional disabilities in those who are sensitive to the adversities of both the critical illness itself and the aggressive treatment approaches. Long-term neurophysiologic abnormalities (e.g., nerve conduction abnormalities) found in survivors of critical illness up to 5 years after ICU discharge illustrate the potential long-term impact of treatment in the ICU (Fletcher et al., 2003). These often subtle abnormalities may go unnoticed for ICU physicians, who are frequently focused primarily on “saving lives,” but may have an important impact on functional recovery, activities of daily living, and quality of life after ICU discharge.

Previous health status seems to have an important impact on the relationship between ICUAW and long-term functional outcome, with younger, relatively healthy patients suffering least from the consequences of ICUAW (Semmler et al., 2013). After discharge from ICU, mortality risk in ICU survivors with ICUAW may differ less significantly compared to those without ICUAW, but in this subset of ICUAW patients, lower physical functioning has been found as an important outcome difference (Wieske et al., 2015). In spite of the significant functional impairments months after ICU discharge, there is also a prolonged potential for ongoing recovery when patients’ physical reserve is sufficient (De Jonghe et al., 2002). Although observational studies confirm an association between early mobilization and improved functional outcomes, it remains to be seen in future studies whether such mobilization programs improve physical functioning for sure (TEAM Study Investigators et al., 2015). Further, current randomized and nonrandomized studies on early rehabilitation in critically ill patients that include a control group are difficult to interpret, due to varying interventions and outcome definitions, although a signal seems to be present in favor of early rehabilitation, at least with regard to walking distance at discharge from the hospital (Castro-Avila et al., 2015). Ongoing controlled studies on early rehabilitation will likely provide more insight into efficacy of specific early interventions on functional outcomes after ICU.

There is a need for structured outcome prediction of ICUAW for several reasons: (1) early rehabilitation may benefit those destined for adverse functional outcomes the most, and better prognostic tools may aid in the design of future intervention studies; and 2) prognostic information helps patients and next of kin to have realistic expectations on the time course of the recovery process. To develop prediction models for outcome, internal and external validations are needed in large, preferably prospective datasets examining various outcomes of interest. For this purpose, pooling data from prospective intervention studies has been shown to be appropriate in other settings (Walgaard et al., 2010; Roozenbeek et al., 2012), and should be considered for future studies of ICUAW.

Risk factors have been identified for the development of ICUAW in several studies and include sepsis, disease severity at admission, poor nutritional status, treatment with corticosteroids or neuromuscular blocking agents, prolonged sedation, mechanical ventilation, hyperglycemia, and female sex (De Jonghe et al., 2002; Hermans et al., 2014). Recently, a prediction model has been reported for ICUAW, with fair discriminative performance (area under the curve for model of >0.70, compared with 0.64 and 0.66, respectively, for Acute Physiology and Chronic Health Evaluation (APACHE-IV) compared with the Sequential Organ Failure Assessment (SOFA) score) (Wieske et al., 2014). However, external validity has not yet been demonstrated.

Although ICUAW is undoubtedly a relevant clinical entity, there are no known interventions that are supported by rigorous evidence that improve recovery from it. Nevertheless, recognition of ICUAW is of utmost importance, as has been shown in a landmark paper by Latronico et al. (1996). This study showed that, in patients who were comatose after sustaining different kinds of brain injuries, the presence of ICUAW might severely confound prognostic estimations, because of underestimating the motor response as part of the Glasgow Coma Scale. This may lead to unreasonably pessimistic prognostication that may even result in inadvertent withdrawal of treatment orders when there is in fact a salvageable brain. Therefore, it seems especially pertinent to establish protocols for the standardized evaluation of ICUAW in ICUs where neurologic patients are cared for (Latronico and Bolton, 2011; Farhan et al., 2016). In a more general sense, it seems sensible to avoid oversedating patients without a strict indication, in order to avoid muscle wasting and catabolism. Ideally, intensivists should strive for awake, but comfortable, patients who are evaluated on a daily basis for suitability for early physiotherapy and mobilization (Hermans and Van den Bergh, 2015). However, such practices are often hampered by implementation issues and scarce resources (Trogrlic et al., 2015). Further, ICUAW has been associated with extubation failure,
which highlights that diagnosing ICUAW is clinically relevant (Jung et al., 2016), although obviously ICUAW is not the only relevant factor (Thille et al., 2015).

**PROGNOSIS OF POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME**

PRES, also known as reversible posterior leukoencephalopathy syndrome or hypertensive encephalopathy, was first described in 1996 (Hinchey et al., 1996). Signs and symptoms include confusion, depressed consciousness, visual loss, and headache. Despite its name, PRES is seldom isolated only to the posterior parts of the brain. On MRI, areas of edema are visible mostly in the occipital and parietal regions, but also frontal, temporal, cerebellar, and brainstem. PRES can, especially in cases related to a severe hypertensive crisis, lead to cardiac stunning (Banuelos et al., 2008).

The pathophysiology of PRES is largely unknown, but hypotheses include impaired autoregulation of the brain, endothelial dysfunction, and vasospasm resulting in ischemia. Underlying conditions are eclampsia, malignant hypertension, cytotoxic medications, sepsis, MOF, renal failure, low serum magnesium, immunosuppressive therapy (e.g., tacrolimus, cyclosporine), and chemotherapy. Acute kidney injury has been reported in 10–15% of patients with PRES (Ni et al., 2011). Autimmune disease is present in more than 40% of cases (Fugate et al., 2010).

The diagnosis is clinical, and in critical care patients it is often suspected based on MRI findings. As many patients admitted to the ICU with serious illness are unconscious or pharmacologically sedated, the diagnosis may go unrecognized. In these unrecognized cases, seizures may deteriorate into status epilepticus (Riggael et al., 2013).

Since many patients admitted to an ICU have conditions that are risk factors for PRES, the diagnosis is not uncommon. PRES can be viewed as a complication of underlying conditions that are often treated on ICUs.

Recently, Muhammed et al. (2016) described an illustrative case of PRES in a patient admitted with subarachnoid hemorrhage (SAH), who was treated with induced hypertension for cerebral vasospasm. Besides their own case, the authors found seven articles describing 10 patients with PRES after hypertensive therapy of vasospasm and delayed cerebral ischemia. The time to development of PRES after starting hypertensive treatment was 7.8 ± 3.8 days (range 1–13 days). In all patients, the clinical symptoms reversed within days of normalization of the blood pressure.

As more than 60% of patients with SAH develop vasospasm, often treated with induced hypertension, in some cases maintaining mean arterial pressure above 110 mmHg, PRES is probably sometimes overlooked, given the rarity of published case reports. Because the prognosis of PRES complicating induced hypertension is generally favorable after normalization of the blood pressure, recognition is paramount. Therefore, in patients with SAH and symptomatic vasospasm in whom clinical symptoms worsen after induced hypertension, PRES should be considered.

The prognosis of PRES depends on the cause, but in most cases clinical signs and symptoms resolve within several weeks after controlling the underlying condition. Findings on MRI imaging usually also resolve within days to weeks. However, in other cases, signs and symptoms may be long-lasting and give rise to prolonged neurologic disturbances, mostly visual (Roth and Ferber, 2011). In critically ill patients, especially when there is an inadequately treated underlying condition, PRES can potentially be life-threatening. This is especially described in initially unrecognized cases in which PRES causes ischemia and infarction. Recurrent episodes of PRES have been reported in the literature, especially in patients requiring dialysis (Ergün et al., 2008; Hobson et al., 2012). MRI provides not only a means of diagnosing PRES, but also prognostic information. Covarrubias et al. (2002) have found that some patients develop foci of high signal intensity in the cortex on diffusion-weighted images, consistent with infarction. Apparent diffusion coefficient values in these areas are normal or only slightly elevated, perhaps because of pseudonormalization, resulting from intravoxel averaging of values in cytotoxic and vasogenic edema. The extent of T2 and diffusion-weighted imaging signal intensity correlates well with outcome and can provide guidance in decision making.

**PROGNOSIS OF DELIRIUM IN CRITICALLY ILL PATIENTS**

Delirium in critically ill patients is regarded as a highly lethal form of vital organ failure and is highly prevalent, especially in mechanically ventilated patients (Ely et al., 2004). Emergence or presence of delirium has implications for prognosis, which will be exacerbated with prolonged duration (Pisani et al., 2009). Therefore delirium may be viewed as a complication of critical illness, although it is certainly not exclusive to critically ill patients alone.

Delirium has been firmly linked to several adverse clinical outcomes in critically ill patients (Salluh et al., 2015).
Delirium has been reported to increase the risk of death approximately threefold compared to nondelirious critically ill patients in a seminal study by Ely and coworkers (2004), when statistical adjustments were incorporated into the analyses to diminish the potential for confounding. It was further shown that delirium arising after a state of coma (often due to sedatives in a patient receiving mechanical ventilation) was still associated with death, whereas such a comatose state that was not followed by a delirious state did not have a worse prognosis. This signifies that comatose state and delirium may not be viewed as a continuum of impaired brain function, but rather that delirium and coma are different both in a pathophysiologic and prognostic sense (Skrobik et al., 2013). The strong association of delirium with mortality in mechanically ventilated patients has been corroborated by others, who have reported even higher risks associated with delirium (Lin et al., 2004). However, since there are essentially three states of consciousness in critically ill patients (coma, delirium, no delirium), it is important to scrutinize whether, in studies on associations of delirium and adverse outcomes, the presence of coma has been accounted for. For instance, delirium may occur more frequently when sedation practices are mitigated towards less sedation use because this may result in fewer patients being comatose due to sedatives and more delirium simply because more patients can be assessed for it. Therefore, some studies have focused on “acute brain dysfunction” as a composite risk factor (i.e., delirium or coma), which still is associated with mortality (Almeida et al., 2014).

Recently, two studies from the same research group have challenged the independent association of delirium with mortality in ICU survivors using advanced statistical methods to adjust for time-varying variables (Klein Klouwenberg et al., 2014; Wolters et al., 2014). In the latter study, the association with mortality could not be established for a single day of delirium, but was still present for delirium persisting for 2 or more days.

In spite of the vast number of studies in recent years, a pathophysiologic explanation for the association of delirium with death is still elusive (few ICU physicians will have ever seen a patient acutely die from delirium), and measures that reduce delirium in controlled trials have not been consistently shown to reduce mortality (Al-Qadheeb et al., 2014). Therefore it seems more likely that focusing on preventive measures that act in concert to decrease both mortality and delirium will prove beneficial, rather than solely focusing on decreasing delirium as a syndrome of solitary organ failure (Al-Qadheeb et al., 2014; van der Jagt et al., 2014).

Emerging evidence links ICU delirium to significant cognitive impairment in ICU survivors (Pandharipande et al., 2013). Especially delirium duration is an important variable predicting future cognitive impairment. The degree of cognitive impairment up to 1 year after ICU stay may, in severe cases, be comparable to that seen in mild forms of Alzheimer’s disease, or mild traumatic brain injury. This may be true even in younger patients. Although one may argue that the effects of delirium on cognition may simply represent additional pathologic “hits” on those with already vulnerable brains before their ICU stay, several studies suggest that a bidirectional interaction exists, linking cognitive decline to susceptibility towards infection and critical illness on the one hand, but also infection or sepsis to further decline of cognitive function on the other hand (Robinson et al., 2012; Shah et al., 2013).

Delirium has also been linked to functional impairment and reduced quality of life in ICU survivors, although it is hard to truly separate cognitive and functional impairment (Abelha et al., 2013; Svenningsen et al., 2014). Functional impairment is not limited to frail elderly patients, but may also be very significant in younger patients who were healthy at baseline (Iwashyna et al., 2010). Such functional impairments, especially in elderly ICU survivors, may result in increased rates of discharge to long-term care facilities (Balas et al., 2009).

Severity of delirium seems to predict the risk for adverse outcomes, in terms of mortality risk, functional outcome, or place of discharge (home vs. other) (Ouimet et al., 2007). Therefore, delirium should be regarded as a syndrome with a disease spectrum, rather than a type of organ failure that is either present or absent. Practically, the Intensive Care Delirium Screening Checklist (ICDSC), composed of a scoring form listing specific delirium symptoms, is more suitable to “grade” delirium severity than the Confusion Assessment Method for the ICU (CAM-ICU), which regards delirium as a dichotomous syndrome being either present or absent (Devlin et al., 2007). Further, some data indicate that the hypoactive subtype of delirium, rather than the hyperactive or mixed subtype, predicts worse prognosis (Robinson et al., 2011; Stranský et al., 2011). A distinction between 1-day versus prolonged delirium seems to be prognostically and pathophysiologically sound, since prolonged delirium as opposed to 1-day delirium seems more firmly linked to mortality (Klein Klouwenberg et al., 2014). Finally, sedation-associated delirium manifestations that resolve after halting the sedatives (so-called rapidly reversible, sedation-related delirium) have been found to be more “benign” compared with delirium symptoms that persist after sedatives have been stopped (Patel et al., 2014). Obviously, delirium comes in different “sizes” and also here the adage “one size fits all” does not entirely apply.
PROGNOSIS OF COMA AFTER CARDIOPULMONARY RESUSCITATION

Patients who remain comatose after cardiopulmonary resuscitation (CPR) and return of spontaneous circulation (ROSC) pose the dilemma to intensivists whether or not return of consciousness will occur. This issue usually becomes relevant after the first 24 hours of ICU management, which generally includes targeted temperature management (TTM) with sedation and analgesia. Several prognostic factors are known, such as initial heart rhythm, underlying disease and severity, previous medical history, and whether the resuscitation took place in an out-of-hospital or in-hospital setting. However, such prognostic factors can, on their own, not be used to determine with certainty whether individual patients will have a favorable or poor outcome. Therefore, recent guidelines have adopted a multimodal approach to prognostication (Nolan et al., 2015). Estimation of prognosis is useful to inform next of kin and discuss appropriateness of medical treatments or limitations thereof.

The European Resuscitation Council (ERC) guidelines have recently been updated (Nolan et al., 2015) and the International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support Task Force published its consensus in parallel (Callaway et al., 2015). Since the 2010 guidelines (Deakin et al., 2010), which stressed increased uncertainties rather than fixed truths with regard to prognostication due to the uncertain effects of widespread use of therapeutic hypothermia as compared with the 2005 guidelines (Nolan et al., 2005), outcome assessment has now become a multimodal approach, using several clinical and electrophysiologic variables to guide clinical judgment with greater confidence. A practical guide to prognostication is elaborated on in the next paragraph, but some general remarks apply. In general, decisions on halting or limiting treatment because of estimated poor prognosis are made in a multidisciplinary setting involving intensivists and neurologists, and such decisions may also involve other consulting specialists depending on the initial or underlying disease (e.g., cardiologists and nurses). It is of utmost importance that a locally implemented protocol is in use, which is strictly adhered to with the goal of minimizing variability in clinical practice. This implies that intensivists and neurologists, as the most pertinent specialists with regard to decision making based on estimated prognosis, are well versed with regard to mutual practices. For instance, when benzodiazepines and/or muscle relaxants have been administered during the initial TTM period, this may imply residual sedation, which should render consulting neurologists cautious in their prognostic assessments.

In this multidisciplinary setting, the protocol should be strictly followed, because even small deviations may complicate clinical decision making, especially when family members perceive inappropriate suggestions indicating dismal prognosis. For instance, early electroencephalography (EEG) to assess the presence of seizures (<72 hours after ROSC) in a patient with daily improving Glasgow Coma Scale motor scores, but persistent unresponsiveness, may yield a low-voltage EEG, suggesting poor prognosis, when in fact the clinical course signifies that progressive brain functioning is occurring, justifying daily clinical follow-up, rather than use of information from electrophysiologic tests to establish a definitive prognostic verdict. In general, it is wise not to use information from tests that were executed for an indication other than prognostic assessment, since this may complicate prognostication, rather than being helpful. This is also in line with the explicit admonition in the newest guidelines (Callaway et al., 2015), stating that any doubts about prognosis should be met with a low threshold for treatment continuation to allow more time for follow-up on neurologic status, rather than institution of tests to confirm poor prognosis.

Figure 41.1 from the ERC guideline publication shows a prognostication algorithm (Nolan et al., 2015). Importantly, patients eligible for prognostication according to the algorithm are those with ROSC and persistent coma, but the guidelines do not further specify with regard to specific subgroups, such as in-hospital versus out-of-hospital cardiac arrest. However, the robust evidence focuses mainly on out-of-hospital witnessed cardiac arrest victims, such that the management advice described in the guidelines is supported more for these patients than those who had cardiac arrest in different circumstances. In this section, for the purpose of uniformity, the situation of a comatose survivor is presumed to have been one that was managed with TTM, in line with Figure 41.1. However, we acknowledge that some patients will still be managed without TTM on an individual basis and depending on the organization of local care.

A comatose survivor of cardiac arrest will most commonly be managed with 24 hours of TTM between 32 and 36°C, after which rewarming will occur slowly. However, the whole process of cooling and rewarming will take less than 48 hours after ROSC, after which the first question should be whether there could be a confounder present for the comatose state. The most common confounders include residual sedation or metabolic disturbances, which should be firmly ruled out before concluding too soon that severe brain damage is present. No uniform guidelines are available to assess such potential confounders. A pharmacist may be helpful in cases of possible residual sedation, if there is doubt regarding its presence. When confounders are excluded,
and the patient is still comatose after 72 hours of ROSC (Fig. 41.1), there should be assessment of the pupillary and corneal reflexes. When both are absent, poor outcome is extremely likely (this is also true when only the pupillary reflexes are absent, only very slightly less so). Otherwise, bilaterally absent somatosensory evoked potentials (SSEPs) indicate a poor prognosis. When bilateral SSEPs and brainstem reflexes are present, more time is needed to determine prognosis, as indicated by the algorithm. Although the algorithm subsequently suggests including two or more of several variables (status myoclonus <48 hours after ROSC, high neuron-specific enolase levels, nonreactive burst suppression, status epilepticus on EEG, or diffuse anoxic injury on brain computed tomography (CT) or MRI), it should be noted that this advice is based on expert opinion, without very robust evidence. Apart from the low level of evidence for this latter part of the algorithm, applicability of this advice may be hampered by several issues depending on local settings: (1) implementation problems (e.g., neuron-specific enolase assessments may not be widely available); and (2) external validity (inherent to the lower level of evidence, these variables have been based on low numbers, from only a few hospitals, and applicability to other settings is disputable until further studies confirm the robustness of the predictive value of the variables).

Absence of EEG reactivity, a burst suppression pattern, and very low voltage seem to be relatively good indicators of poor prognosis after 72 hours of normothermia being reached and in the absence of confounders, although the guideline mentions a study reporting 3 patients who awoke in spite of absent EEG reactivity (Bouwes et al., 2012b). However, no further details were provided on these patients (e.g., could there have been residual sedation?). Status epilepticus also is not invariably a sign of poor prognosis and may be a reason to start a trial of aggressive treatment with antiepileptic drugs (AEDs). Whether this is indeed useful is currently being investigated (Ruijter et al., 2014), since many more patients with status epilepticus in this setting die than survive. More data on the prognostic value of EEG patterns are becoming available, and it is expected that their prognostic value will gain importance; not only to predict poor outcomes but also to help identify patients with good outcomes at an earlier stage (Hofmeijer et al., 2015; Westhall et al., 2016).

A vexing problem can be the patient with severe myoclonic jerking, with positive SSEPs and brainstem reflexes, which can only be managed with continuous intravenous sedatives to obtain an acceptable level of suppression of the myoclonus. In such a patient it may be best to treat with several AEDs, potentially in high dosages (e.g., valproate, levetiracetam, and when necessary, one or two other AEDs), to try and diminish the myoclonus, yet also abolish the sedatives to be able to assess the neurologic status. When this regimen is unsuccessful, most
physicians will feel the inclination to stop treatment aimed at recovery, but theoretically early severe myoclonus may constitute Lance–Adams syndrome, which is compatible with awakening.

The guideline mentions that any doubt on ultimate prognosis should lead to consideration of prolonged treatment. Clearly, absence of any subsequent improvement of neurologic status suggests an ultimately worse prognosis. Reference is made to several studies reporting “late awakening” (up to 25 days after ROSC), but these cases did not provide any detail on the presence or absence of important confounders (Rittenberger et al., 2012) and, in one unexpected case of late awakening, an early EEG showed reactivity, which is a strong reason to suspect brain recovery, and in that sense the positive outcome may have been so unexpected (Greer, 2013).

The ERC/European Society of Intensive Care Medicine guidelines (Nolan et al., 2015) mention the very small possibility of awakening in spite of absent SSEPs (i.e., false-positive results) with referral to three publications (Young et al., 2005; Bouwes et al., 2012a; Dragancea et al., 2015). In the first study, reference details on the single patient who awoke in spite of absent SSEPs were not provided (Young et al., 2005), and the study concerned patients who were not managed with therapeutic hypothermia. In the second study, the discussion refers to the risk of technically indeterminate SSEP results, but the results of the study itself did not include false positives in patients with SSEPs after rewarming (Bouwes et al., 2012a). In the third study (Dragancea et al., 2015), there was mention of one SSEP that proved to be false positive, but this was done in a patient who was actually following commands, and the SSEP itself was reported to be technically insufficient (in addition to the fact that it was obviously not indicated). Based on these insufficient data, one may therefore still argue that a technically well-performed SSEP, in a patient in whom there is a strong clinical suspicion of neurologic damage compatible with persistent comatose state (i.e., motor score 4 or less at least 72 hours after ROSC) and no residual sedation, muscle relaxants, or other potential confounders such as uremic encephalopathy, is a reliable tool to confirm poor prognosis, indicating that further treatment is inappropriate. Thus, it is important that a multidisciplinary team, including at least a clinical neurophysiologist, neurologist, and intensivist, establishes this verdict, and that intensivists should decide on withdrawal of treatment only after having certified that the other team members have corroborated and confirmed their assessment in the medical file.

There has been a point of discussion as to whether absent SSEPs truly indicate irreversible brain damage, or that SSEPs, being an intricate part of decision making, actually constitute a real risk with regard to a self-fulfilling prophecy. Proponents of the dangers of the self-fulfilling prophecy indicate that treatment limitations based on bilaterally absent SSEPs may result in potentially premature treatment cessation in patients who would still have a small chance of recovery. However, inappropriate withdrawal of life support with negative SSEPs only seems possible when technical artifacts of the SSEP and/or residual sedation are present; otherwise extubation may give a spontaneously breathing patient the opportunity to show neurologic improvement in the course of the following days, at least when sedatives are withheld. If unanticipated awakenings in such situations had been described in the medical literature, the fear of the self-fulfilling prophecy would be substantiated, but such reports are not known, and should not be mixed up with observational series reporting late awakenings (e.g., more than 3 days after rewarming), in which details of sedation practices and protocols for withdrawal of treatment practices have not been extensively described (Gold et al., 2014).

One may argue that a patient who cannot sustain patency of the airway in spite of intact brainstem function and absence of residual sedation must have sustained damage to the cortical structures so severe that it is essentially incompatible with a meaningful recovery, but studies on natural disease course of patients who have been certified to fulfill these criteria are also absent. However, it is very unlikely that a trial will ever be conducted in patients with absent SSEPs comparing standard practice with a strategy of sustained intensive care treatment, which will be arguably the only way to definitely establish whether fear of a self-fulfilling prophecy is justified.

Although chances of survival of in-hospital (nonper- operative) cardiac arrest and coma are lower than those associated with out-of-hospital cardiac arrest (Nolan et al., 2007), this knowledge does not generally impact on prognostic decision making. To a certain extent, the cerebral prognosis may be considered as separate from other organ failures, because the first consideration of prognostication focuses on whether or not the patient will regain consciousness. This means that, when the patient will not regain consciousness, treatment may be stopped independently of other organ failures, whereas when cerebral prognosis is regarded as indeterminate or good, the extent of organ failure may be much more important in the assessment of overall prognosis. In line with this, the new guidelines only stratify in the prognostication process based on whether patients have been managed with TTM or not, and do not stress the distinction between in- or out-of-hospital cardiac arrest patients, or initial rhythms as crucial factors for prognostication.

In conclusion, clinical variables other than those indicated by the algorithm in Figure 41.1 and paragraph 4.2.2...
of the ERC guidelines should generally not be used for prognostication with regard to cerebral short-term outcomes. An exception may exist for in-hospital cardiac arrest survivors, since a very large population-based validation study proposed practical criteria to predict favorable outcome, which may be usable for clinical and “family-shared” decision making on treatment continuation or limitation (Chan et al., 2012). However, further external validation seems necessary.

We conclude with a case which exemplifies that the absence of clinical indicators of dismal prognosis, such as bilaterally absent SSEPs, warrants extreme caution, especially when potential confounders for neurologic assessment are present.

Illustrative case

A 24-year old woman was admitted to an academic ICU after prolonged cardiac arrest and CPR (90 minutes) in another institution caused by massive pulmonary embolism after recent start of oral contraceptives. The patient had been cannulated for venaarterial extracorporeal life support by a mobile extracorporeal membrane oxygenation (ECMO) team due to lack of persistent ROSC in spite of ongoing resuscitation efforts, but had some instances of nonsustained spontaneous output during the whole resuscitation period. She had been treated with thrombolytics, with no apparent effect. After transfer for ECMO support to an academic ICU, a laparotomy was performed because of abdominal compartment syndrome due to intra-abdominal bleeding caused by liver rupture as a result of prolonged chest compressions and intense anticoagulant therapies. After surgery, temperature control with avoidance of fever was initially chosen as a treatment strategy rather than hypothermia.

The subsequent course was as follows:

- Initially, she had absent pupillary and corneal reflexes, and status myoclonus.
- SSEPs were bilaterally present.
- EEG at 72 hours after ROSC was not low-voltage (>20 μV), but was nonreactive, although the patient was still receiving sedatives (opiate and propofol) in order to attenuate the severe myoclonus.
- The course was complicated by septic shock with acute kidney injury, which further hampered detailed assessment of her neurologic status, although pupillary and corneal reflexes returned.
- Some members of the treatment team doubted whether further treatment was indicated because of perceptions of a very poor prognosis, but others favored continuing treatment since important confounders were present.
- Over the subsequent week, after RRT had normalized the serum urea, the motor response improved to withdrawal, and the patient seemed to open her eyes to voice, but still did not track. A repeat EEG showed return of reactivity. She still required low dosages of sedatives because of frequent myoclonus, which had not disappeared despite treatment with two AEDs (valproate and levetiracetam).
- Although there was still some doubt about the prognosis, a tracheostomy was performed.
- Over the next week, her neurologic status improved, and she followed commands after sedation was tapered. It was concluded that the severe myoclonus was a combination of Lance–Adams syndrome and possibly the uremia earlier in the course.

According to the ERC algorithm (Fig. 41.1), one might argue that only status myoclonus was present, but a second criterion for poor prognosis was absent, indicating a strategy to “observe and re-evaluate.” This strategy proved justified in this case.

PROGNOSIS OF NEUROLOGIC COMPLICATIONS OF LIVER TRANSPLANTATION

Orthotopic liver transplantation is a life-saving procedure for liver failure. All patients with ALF, and all patients after orthotopic liver transplantation are treated in ICUs.

Neurologic complications after liver transplantation surgery are reported in 13–47% of patients, especially in those receiving cadaveric grafts. Key topics in this setting include: immunosuppressive neurotoxicity; seizures; osmotic demyelination; neuromuscular complications; cerebrovascular complications; and CNS infections (Guarino et al., 2011).

The most commonly used immunosuppressive drugs after liver transplantation are cyclosporine and tacrolimus, which are well known for their complicating neurotoxicity (Guarino et al., 2006; Saner et al., 2007). Other, more recently introduced agents, such as sirolimus and everolimus, lack this neurotoxicity. Neurotoxicity can become evident soon after initiation of these medications, even while patients are still in the ICU. Guarino et al. (2011) distinguish “minor” events, (e.g., headache, tremor, insomnia, and paresthesias) and “major” events (e.g., encephalopathy, seizures, akinetic mutism, and polynuropathy). Severe complications are often preceded by hypertension, hypomagnesemia, and HE (Saner et al., 2007). The prognosis of immunosuppressive neurotoxicity is favorable in most cases, but is highly dependent on timely discontinuation and a switch to nonneurotoxic agents. Irreversible neurologic damage is possible if the culprit drug is not stopped.

The postoperative course of liver transplantation is complicated by tonic-clonic seizures in up to 40% of patients (Guarino et al., 2006, 2011; Saner et al.,
et al. reported that all 6 of their patients had some clinical improvement, since patients who
impose on their cause. Seizures due to metabolic derangements or immunosuppressive neurotoxicity have a favorable outlook, but seizures attributable to sepsis, acute transplant rejection, or cerebrovascular events may have a more guarded prognosis.

Central pontine and extrapontine myelinolysis (CPEPM), first described in 1959, is a feared complication, which may be associated with rapid correction of hyponatremia (>15 mmol/L in 24 hours or 18 mmol/L in 48 hours when the sodium concentration was <120 mmol/L) (Abbasoglu et al., 1998; Yu et al., 2004). It was first described after liver transplantation in 1978 (Starzl et al., 1978). The incidence of CPEPM after liver transplantation was reported to be 5–10% (Yu et al., 2004), but in a recent series was found in only 1.4% of 1378 consecutive patients (Morard et al., 2014).

CPEPM is the most serious neurologic complication after liver transplantation. In the ICU, CPEPM occurs in malnourished, usually alcoholic patients and in those with cirrhosis. Other risk factors are chronic renal failure necessitating hemodialysis and adrenal insufficiency (Morais et al., 2009). After liver transplantation, CPEPM is seen in patients with cirrhosis with pretransplantation serum hyponatremia, where large volumes of intravenous fluids were given in the operating theatre, resulting in an increase in plasma osmolality. Effective treatment modalities in the acute phase of CPEPM are lacking. Despite the absence of any compelling evidence, treatment has been attempted with corticosteroids, plasmapheresis, and intravenous immunoglobulin.

The prognosis of CPEPM has traditionally been considered to be poor. In one series, CPEPM occurred 3–18 days after liver transplantation, and had a 100% case fatality rate, with a median survival of 25 days (Yu et al., 2004). In a series described by Abbasoglu et al. (1998), all patients expired within 3 months. Others report a mortality rate >50% in the first 2 weeks and 90% after 6 months (Morais et al., 2009). However, some recent reports are less pessimistic. Musana (2005) reported that all 6 of their patients had some clinical improvement over time. In another series of 25 patients, 11 had a favorable outcome, of which 7 had a full recovery, and the remaining 4 were independent in activities of daily living with some mild cognitive or extrapyramidal deficits (Kallakatta et al., 2011). Because most published series have shown a grim prognosis, there may also be a degree of self-fulfilling prophecy, since patients who undergo withdrawal of life support measures usually die. In a recent series of 36 patients with CPEPM (not as a complication after liver transplantation), 11 (31%) were dead 1 year after withdrawal of life-sustaining measures, whereas 14 (56%) of the survivors were still alive with a Rankin score less than 1 (Louis et al., 2012). The reason for withdrawal of life-sustaining measures in the 11 patients was, in all cases, severe motor deficits. Improvements in neurologic function may be seen over the course of months after onset of CPEPM. When individuals are offered time to recover, many show gradual improvement, and can even recover completely (Niehaus et al., 2001), while other surviving patients have residual deficits, ranging from minor functional and cognitive difficulties to locked-in syndrome, quadriplegia, and pseudobulbar paralysis (Newell and Kleinschmidt-DeMasters, 1996; Brown, 2000). Patients with CPEPM often have other complications, such as MOF, infection, and gastrointestinal hemorrhage, making the prognosis more unfavorable (Brito et al., 2006). Kallakatta et al. (2011) showed that three factors were significantly correlated with poor prognosis: sodium concentration <115 mmol/L, associated hypokalemia, and Glasgow Coma Scale <10. Prevention of CPEPM, recognizing a patient at risk with slow correction of hyponatremia, is paramount (Abbasoglu et al., 1998; Yu et al., 2004).

The diagnosis, treatment, and prognosis of muscular weakness, stroke, and CNS infections after liver transplantation are similar to other settings, and will not be discussed here.

**ETHICAL CONSIDERATIONS**

Critically ill patients are subject to many complications connected with life-sustaining treatment and measures required for their serious conditions. As complications can worsen outcome and even cause death, they are of ethical concern. High-quality medical care can be defined as evidence-based care based on the results of well-conducted research and delivered by well-trained clinicians. A complication is usually defined as an unintended, harmful occurrence or condition resulting from a diagnostic, prophylactic, or therapeutic intervention, or an accidental injury occurring in a hospital setting. However, when a complication is a result of medical care that was not indicated, or not well applied, it can be labeled as unethical. The three most important ethical aspects regarding complications in critically ill patients are prevention, identification, and avoidance of self-fulfilling prophecies.

Efforts to prevent complications of intensive care should be vigorously pursued. This includes adequate monitoring of signs and symptoms, educational
programs for physicians and nurses, and the provision of adequate staffing. Due to the severity of the medical conditions of patients, their multiple comorbidities, and the complexity of the intensive care environment, many complications can never be completely prevented. For example, although some ICU patients develop delirium due to a single preventable cause, delirium more often occurs when a vulnerable patient with multiple predisposing risk factors encounters a serious course of illness (Brummel and Girard, 2013). Early identification and treatment of conditions leading to MOF, avoidance of deep sedation, treatment of hyperglycemia, promotion of early mobilization, and carefully weighing the administration of corticosteroids might help reduce the incidence and severity of ICUAW (De Jonghe et al., 2009).

Correct identification of neurologic complications in critically ill patients can be challenging, but can have a significant impact on outcomes. For example, initially unrecognized cases of PRES can progress to cerebral infarction. Early recognition of risk factors and symptoms is paramount and can, for some complications, make the difference between a good or bad outcome. Physicians and nurses should have knowledge of the possible risk factors associated with neurotoxicity of drugs. Monitoring of neurologic signs and symptoms potentially associated with the administration of drugs should be routine, but also correct identification that the symptoms are, in fact, drug-related, and not a sign of underlying neurologic disease (George et al., 2010).

Prognostication in critically ill patients can raise additional ethical concerns. As with all prognostication in medicine, how sure are we when we predict outcome? This is especially important in cases where a perceived poor prognosis leads to withholding or withdrawing of life-sustaining measures. Predictions of poor outcome may become self-fulfilling if life-sustaining measures, such as mechanical ventilation, are subsequently withheld or withdrawn on the basis of that prediction (Wilkinson, 2009). Predictions of poor outcome may also affect the perception of patients, relatives, and healthcare providers. Physicians make decisions on the basis of available evidence. If the evidence is not based on the most relevant knowledge, or is based on the presumption that the signs and symptoms are those of the underlying disease, and not of a (reversible) complication, this can lead to unethical decisions. It is accepted that it is ethically permissible to withhold or withdraw life-sustaining measures in the face of uncertainty in critical care medicine based on clinical signs and symptoms pointing to a poor prognosis, but it is unethical to do this based on wrong assumptions.

**References**


