Neurocritical Care

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Editor

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Preface

Intensive care of patients with severe conditions requires systemic management that takes into account the continuous impact of the whole body on the brain and of the brain on the whole body. Neurological outcomes, including higher-order brain functions, must be improved if we are to help more patients return to a fully functional role in society, but there has been little discussion of methods to manage patients that reflect the impact on the brain from clinical conditions like post-cardiac arrest syndrome (PCAS), sepsis, or multiple organ failure. This special edition summarizes the basic knowledge needed for intensive care and discusses 18 topics relevant to the field of neurocritical care today. These topics cover essential areas for neurocritical care, including sedation and analgesia, respiratory therapy, fever management, infection control, fluid management, glycemic control, and nutrition support. The content is discussed from the perspective of the brain rather than from conventional patient management perspectives in general intensive care.

The topics cover not only the pathology of head injury and coagulopathy, cerebral hemorrhage, multiple trauma, and central nervous system infection but also nonconvulsive status epilepticus, the specific characteristics of PCAS after cardiac arrest, neurocritical care in infants, sepsis-associated brain dysfunction, and post-intensive care syndrome. This special edition includes a detailed discussion of patients who cannot be saved even with neurocritical care, using actual case studies for consideration.

Having already described the topics covered in each chapter, I omit further discussion of the detailed contents here. Suffice to say, all the chapters contain up-to-date information and are worth reading. The special edition provides accessible descriptions of basic clinical conditions, and a single sitting will provide readers with a better understanding of the notoriously difficult field of intensive care for the central nervous system and why certain procedures are necessary.

Many intensive care specialists use respiratory and circulatory monitoring in their attempts to treat sepsis, multiple organ failure, and other conditions but tend not to consider brain damage caused by sepsis or multiple organ failure. The clinical significance of such effects on the brain has also not been fully identified. Through the publication of this special edition, I hope that readers will understand

the clinical conditions and diseases that require neurocritical care and will pay more attention to brain damage as a therapeutic target, alongside sepsis and multiple organ failure, rather than simply treating any primary brain damage. I hope that this special edition prompts discussion of the usefulness of neurocritical care and prospects for the future in this field.

Tokyo, Japan Kosaku Kinoshita

Contents

Chapter 1
Sedation and Analgesia for Patients with Acute Brain Injury

Atsushi Sakurai

Abstract Neuro-critical care doctors should be familiar with the topics of sedation and analgesia for patients with acute brain injury (ABI) in the intensive care unit (ICU). Patients with elevated intracranial pressure (ICP) should be managed by intubation and mechanical ventilation with sedation of barbiturates, propofol, and midazolam. When propofol is used, special attention should be given to propofol infusion syndrome. To regulate sympathetic nerve activity and avoid hypertension, the rationale is to use opioids for ABI patients. Treatment with sedation interruption strategy should be avoided in all patients at risk for ICP elevation, who are undergoing TTM and treatment of refractory status epilepticus. Administration of ketamine has been associated with a reduction in the progress of spreading depression. Use of ketamine and dexmedetomidine for ABI patients may be optimized in selected cases.

Keywords Acute brain injury · Sedation for elevated intracranial pressure
Propofol infusion syndrome · Sedation interruption · Spreading depression
Ketamine · Dexmedetomidine · Paroxysmal sympathetic hyperactivity

1.1 Introduction

It is important for neuro-critical care doctors to acquire information regarding neurological topics of sedation and analgesia when treating patients with acute brain injury (ABI; including traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), ischemic/hemorrhagic stroke, comatose cardiac arrest, and status epilepticus [1]) in the intensive care unit (ICU) with sedation and analgesia. In this chapter, the author will discuss interesting topics of sedation and analgesia for ABI patients, such as sedation for patients with elevated intracranial pressure, the need

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for analgesia for ABI patients, sedation interruption in cases involving ABI patients, the effect of sedation and analgesia on the progress of spreading depression, and use of ketamine and dexmedetomidine for ABI cases.

1.2 Sedation for Patients with Elevated Intracranial Pressure

One of the most important concerns for patients with brain injury is intracranial pressure (ICP) control. Patients with elevated ICP may have impaired consciousness and require intubation and ventilation to secure the airway and respiration [2]. Endotracheal intubation is recommended for patients with severe TBI and a Glasgow Coma Scale (GCS) value ≦8 [3]. When intubating such patients, sedation and analgesia is necessary for management in the ICU. Consequently, ABI patients who require the control of elevated ICP are usually ventilated with sedation and analgesia. Actually, in the staircase approach to treat increased ICP in TBI patients, step 1 includes intubation and normocarbic ventilation, and step 2 involves the regulation of a sedative drug [4]. Sedation and analgesia are used to treat pain and agitation and to prevent arterial hypertension and patient–ventilator dyssynchrony.

Barbiturates have a long history of use to control ICP, presumably by suppressing metabolism, altering cerebral vascular tone, and improving the coupling of regional blood flow to the metabolic demands as a result of higher brain oxygenation with lower cerebral blood flow. According to the Brain Trauma Foundation Level II B Recommendations (based on limited evidence), barbiturate administration is not recommended as prophylaxis against the development of intracranial hypertension monitored by EEG. High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard treatment but cautions to monitor hemodynamic stability [5].

Another alternative sedation drug to control elevated ICP is propofol. In a double-blinded randomized trial, Kelly et al. reported ICP control for patients with severe TBI and who received either propofol or morphine sulfate; ICP was lower in the propofol group compared to the morphine sulfate group [6]. Chiu et al. reported in their retrospective study that mean ICP of patients with TBI for the first 3 days in the ICU was significantly lower in the propofol group than in the non-propofol group [7].

When using propofol, special consideration to the possibility of the complication, propofol infusion syndrome (PRIS), is needed. PRIS is commonly presented as an unexplained high anion gap metabolic acidosis, rhabdomyolysis, hyperkalemia, acute kidney injury, elevated liver enzymes, and cardiac dysfunction [8–12]. In most cases, propofol infusions in doses greater than 4 mg/kg/h for more than 48 h should be avoided [8, 10, 12]. Special attention should be given to pediatric patients for RRIS, according to various reports [10]. The use of propofol for pediatric patients in the ICU setting is contraindicated in some countries [11, 12]. Among case reports of PRIS in adult patients, primary diseases are mainly brain injury, including TBI, status epilepticus, cerebral sinus thrombosis, and arteriovenous

malformation [8, 9]. This is partially due to use of propofol to control elevated ICP by increasing the infusion dose and extending infusion duration. Careful monitoring for PRIS is needed.

Midazolam is also used for patients with elevated ICP. In a systematic review, no difference between midazolam and propofol in the control of ICP and cerebral perfusion pressure (CPP) [13] was observed. When using midazolam, careful attention is needed regarding tachyphylaxis at higher doses and withdrawal symptoms at discontinuation [1].

1.3 Needs Regarding Analgesia in Patients with Brain Injury

A fundamental question regarding use of analgesia in ABI patients is "If a patient has conscious disturbance, is the use of an analgesia necessary? Does the patient feel pain?" There is a myth that unconscious patients do not respond to external stimulation [14]. Arbour et al. reported that TBI patients exhibited atypical behaviors, such as eye opening or wincing during nociceptive procedures, and suggested that use of standardized behavioral pain tools may not be optimal in the assessment of the analgesic needs of TBI patients with conscious disturbance [15]. To regulate sympathetic nerve activity and avoid hypertension, use not only of sedative drugs but of also analgesia is rationalized. In the neuro-ICU textbook "analgesia first" or "A-1" approach [16], use of opioids is recommended for ABI patients [17]. Candidate opioid narcotics for use on patients with brain injury are morphine, hydromorphone, fentanyl, sufentanil, and remifentanil [1, 17, 18].

1.4 Sedation Interruption in ABI Patients

Several studies have reported that in the general ICU setting, improved outcome can be achieved by sedation minimization strategies such as daily sedation interruption (SI) [19, 20]. A protocol of no sedation for critically ill patients receiving mechanical ventilation is associated with fewer days of ventilation in the ICU, in comparison with daily interruption of sedation until consciousness [21]. However, in a randomized controlled study comparing protocol sedation to daily SI, difference in the duration of mechanical ventilation or ICU length of stay was not observed [22]. According to a systematic review and meta-analysis comparing protocol sedation and daily sedation interruption, no difference in mortality at the ICU and the hospital, duration of mechanical ventilation, intensive care unit, and hospital length of stay was observed [23]. Efficacy of sedation minimization strategies is debatable in general ICU.

Since ABI patients are generally excluded from randomized trials on sedation [21, 22], there is limited evidence regarding the efficacy of SI in ABI patients. Skoglund et al. reported that mean ICP and cerebral perfusion pressure (CPP) levels modestly increased with discontinuous propofol in a neurological wake-up test

(NWT) on severe TBI or SAH patients. In this study, reduced CPP during NWT was observed in some patients due to increased ICP [24]. These facts suggest that SI may induce brain ischemia in patients with severe brain injury and impaired autoregulation of blood pressure (Bp). Oddo et al. recommended avoiding treatments which include SI for all patients who are at risk for or who show clinical and radiological signs of brain edema or elevated ICP, as well as patients undergoing TTM and treatment for refractory status epilepticus [1].

1.5 Effect of Sedation and Analgesia on Spreading Depression and Spreading Depolarization

Spreading depression (SD) is a wave of electrocorticographic silence originating from a focal electrical or mechanical stimulus that slowly propagated across the cortex [25]. This phenomenon actually indicates transient wave propagation of near-complete neuronal and glial depolarization associated with massive transmembrane ionic and water shifts [26]. Hence this phenomenon is also called spreading depolarization (SDL) according to its pathophysiological features [27]. In the classification of this phenomenon, SDL may refer to the mechanism of SD, and SD is clinical features according to EEG.

Under specific conditions, SDL may be associated with neuronal injury. For example, an inverse hemodynamic response is a marked, prolonged hypoperfusion due to severe arteriolar constriction and is linked to SDL under pathological conditions [28]. Therefore SDL may be a candidate, along with secondary brain damage with spreading depolarization-related hypoperfusion (spreading ischemia), for ABI [29]. Hartings et al. reported that SD was associated with unfavorable outcome in TBI patients. They suggested that SD may have an adverse effect on TBI patients, and consequently, targeting SD in the treatment of TBI should be considered [30]. Treatment of SD may be a promising target in the therapeutic intervention for ABI patients.

In the reaction–diffusion model of SDL propagation and regenerative processes, basic mechanisms are believed to be responsible for the self-regenerating propagation of SDL. Elevated extracellular levels of strongly depolarizing excitatory amino acid glutamate further fuels SDL and contributes to its propagation by activating *N*-methyl-D-aspartate (NMDA) receptors [26]. Hence, use of ketamine, an NMDA receptor antagonist, to block wave propagation of SDL is reasonably assumed [27]. In experimental studies, ketamine blocked SDL propagation [31–33]. Sánchez-Porras et al. reported that a low-dose ketamine infusion did not alter subsequent oligemic/vasoconstrictive responses, and only a high-dose infusion of ketamine suppressed SD and the coupled hemodynamic response [34]. Therefore an ischemic hemodynamic response, caused by SD, may require a high dose of ketamine, and the effect of brain protection by ketamine, by inhibiting SD, may require continuous infusion.

Sakowitz et al. reported inhibition of SD by continuous infusion of ketamine (2–3 mg/kg/h) in two cases of ABI (traumatic and spontaneous intracranial hemorrhage) [35]. The international multicenter observational study group, Cooperative Study of Brain Injury Depolarizations (COSBID), reported on the effectiveness of blocking SD using ketamine based on 115 sets of patient data from seven centers [36]. In this study, administration of ketamine was associated with a reduction of SD, while midazolam anesthesia showed an increased number of SD clusters. In the clinical setting, ketamine may block SD.

If ketamine does actually suppress SD, the effect of other drugs on SD is also of interest. In an experimental study among four anesthetics (propofol, dexmedetomidine, isoflurane, and pentobarbital), isoflurane and dexmedetomidine suppressed SD [37]. Currently, multimodal continuous bedside monitoring, including intracranial electrocorticography (ECoG), is used as a method to monitor SD, ICP, CPP, and oxygen availability (local tissue partial pressure of oxygen) [29]. Further studies to determine the activity of sedative, anesthetic, and analgesic drugs on SD and spreading ischemia are needed in order to clarify clinical effectiveness of these drugs for ABI patients with SD.

1.6 Optimizing the Use of Ketamine and Dexmedetomidine for ABI Patients

There is some debate regarding indications to use ketamine and dexmedetomidine for ABI patients in the ICU, as some early studies have reported that ketamine may increase ICP [38] and that dexmedetomidine is more expensive than other sedatives but is not more effective [1]. Depending on the results of further studies, reconsideration of indications in the combination use of two drugs for ABI patients may be needed.

1.6.1 Ketamine

Glutamate released from neurons can contribute to neurotoxic effect by activating glutamate receptors such as *N*-methyl-D-aspartate (NMDA) and to cell death related to cerebral ischemia or TBI [39]. Blocking NMDA receptors may be a possible approach to ameliorate secondary brain injury. Ketamine is an NMDA receptor antagonist and possible candidate as a neuroprotective drug. However concerns that ketamine may increase ICP have been noted in previous studies [38] and should be used with special care in ABI patients with increased ICP [40]. Consequently ketamine has traditionally been avoided in the management of ABI patients.

Himmelseher et al. reviewed ketamine use in patients with TBI and in cases of neurosurgery for brain tumors and aneurysms and reported that ketamine reduced

ICP and improved CPP in patients with intracranial compromise under controlled normocapnic ventilation [41]. Clinically, ketamine effectively reduced ICP in ventilated pediatric patients with TBI and high ICP, without lowering Bp and CPP [42]. Zeiler et al. reviewed published literature on the use of ketamine in nontraumatic neurological illnesses, such as neurosurgery for tumors and hydrocephalus, and its effect on ICP and reported that ketamine did not increase ICP [43]. Ketamine could be used for ABI patients safely under controlled, normocapnic ventilation. Ketamine is particularly indicated as an induction agent in patients with hemodynamic instability due to its ability to stimulate sympathetic nerve activity [17]. Moreover from the viewpoint of its neuroprotective and neuroregenerative effect, ketamine may be recommended for use in ABI patients [41]. Further studies are considered needed.

1.6.2 Dexmedetomidine

Dexmedetomidine is α2-adrenoreceptor agonist. Presynaptic activation inhibits the release of noradrenaline, blocking the propagation of pain signals. Postsynaptic activation in the central nervous system inhibits sympathetic activity, decreasing Bp and heart rate. The effect of both receptors produces analgesia and sedation [44] and is referred to as analgo-sedation. James et al. reported in a pilot study that in patients with ABI (TBI, SAH, intracerebral hemorrhage (ICH)) who are mechanically ventilated, there was no difference in systemic or cerebral physiologic measurements between the propofol and dexmedetomidine groups [45]. In a multicenter retrospective cohort study by Erdman et al., difference in severe hypotension and bradycardia was not observed between ABI patients under continuous sedation with dexmedetomidine and patients treated with propofol [46]. Actually, a major advantage in the use of dexmedetomidine for mechanically ventilated patients with ABI compared to other drugs (propofol and midazolam) was not observed [47].

Korogulu et al. reported that propofol induces greater respiratory depression than dexmedetomidine in pediatric patients under sedation receiving magnetic resonance imaging without intubation [48]. Clinically, dexmedetomidine causes less respiratory depression [17] and is suitable for non-intubated patients, as respiratory depression without intubation has been indicated to increase $PaCO_2$ and elevated ICP in ABI patients. One case report suggested that the use of dexmedetomidine may be an effective strategy for non-intubated patients with TBI and patients with developing agitation or alcohol withdrawal, since a neurological exam can be performed without respiratory depression under sedation [49]. Severe excessive autonomic activity (elevated heart rate, blood pressure, respiratory rate, body temperature, sweating) and muscle hyperactivity (dystonia) have occurred in a subgroup of persons surviving ABI. This phenomenon is known as paroxysmal sympathetic hyperactivity (PSH) [50, 51]. A case report showed the efficacy of dexmedetomidine for patients with severe TBI and PSH [52]. Investigation of the potential use of dexmedetomidine for ABI patients, utilizing its specific action, is needed.

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Chapter 2
Respiratory Management in Neurological Intensive Care

Rikimaru Kogawa

Abstract Artificial ventilation is the most important management in the intensive care and neurological intensive care units. Respiratory management (including airway management) is the top priority particulars of the intensive care ABCD protocol and must be universally executed regardless of disease. It is important to maintain proper oxygenation and ventilation to prevent excessive breathing work. In particular, regarding ventilation (CO_2) management, it is important not to normalize $PaCO_2$ level but to aim for optimization of blood pH. When intracranial pressure is increased, appropriate management of ventilation is given top priority, and in cases of emergency, hyperventilation management is performed as a temporary measure. It is important that artificial ventilatory management is to ensure short duration of the procedure. To achieve the same, standard, weaning methods such as daily interruption of sedatives (DIS) and spontaneous breathing trial (SBT) should be followed.

Keywords Daily interruption of sedatives · Spontaneous breathing trial
Intracranial pressure · Work of breathing · Airway resistance and compliance
Initial setting of artificial ventilation

2.1 Introduction

Artificial ventilation is the most important management in the intensive care and neurological intensive care units. Appropriate systemic as well as intensive neurological care cannot be established in the absence of adequate respiratory support. The most important aspects of respiratory management in neurological

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intensive care are maintenance of appropriate oxygenation, ventilation, and determination of the cause of respiratory failure and its coping, as well as general intensive care. In addition, ventilatory support is crucial for management of intracranial pressure in the field of neurological emergency. In this paper, we describe the standard respiratory management in intensive care (including airway management) and specialty in respiratory management in neurological intensive care.

As with basic life support (BLS) and advanced cardiac life support (ACLS), management of ABCD, that is, A (airway), B (breathing), C (circulation), D (disability, dysfunction of CNS), is important in intensive care, and its importance is higher in this order, and usually evaluation and intervention are performed in this order. In other words, respiratory management (including airway management in this case) required universally adequate management irrespective of the presence or absence of central nervous disorder.

2.2 The Basis of Airway Management Is Avoidance of Asphyxia

Inadequate maintenance of the airway will prevent exchange of gases in the lungs as well as oxygenation and ventilation. Disturbance of consciousness may be associated with suffocation in patients either due to airway obstruction with foreign substances, vomit, or secretions or by glossoptosis. Asphyxia may occur, although rarely, due to epiglottitis or edema of the vocal cords (e.g., after extubation), external compression by tumor in the neck, or blood coagulum. Generally, status of the airway cannot be evaluated by examination of images or specimens. Evaluation through computed tomography (CT) is possible, but usually it is too late to be performed. Therefore, evaluation of old-fashioned “looking, listening, feeling” is important. Visual examination is important and must include evaluation of foreign substances and secretions in the oral cavity, swelling and deformation of the neck, paradoxical breathing, and respiratory effort. Evaluation of sounds signifying airway stenosis, hoarseness, and foreign objects (rumbling sound) is also essential. If you have a stethoscope in the neck, you may be more sharply anomalous. If vocalization is possible, pay attention to the hoarseness. Sometimes, the asphyxia state cannot be judged either visually or audibly. In case of perfect asphyxia, there is a case that no acoustic stenosis sound, and it may be misunderstood as if breathing exercise exists at first glance. This could be attributed to contraction of the diaphragm during inspiration without air entry, thereby creating abnormal negative pressure on the inside of the thoracic cavity and lowering of the chest. Following this, the expiration goes through a stage, abnormal negative pressure is released, and the thorax is lifted. Once inspiration begins, the thorax falls again. Therefore, with simple visual recognition from the top of the clothes, breathing seems to be anguish, but it is misunderstood that it is breathing. In the evaluation of the airway tract, it is important to see, hear, and feel; there is air entry in and out. In the suffocation state, there are signs called choking sign which are famous in the

universal world. However, this famous indication should be considered as having little clinical utility in patients undergoing neurological intensive care. Despite the increased risk of asphyxia, the "choking sign" cannot be observed due to disturbance of consciousness or paralysis. When there is abnormality in the airway tract, the foremost step is to secure the airway manually. Commonly, the head tilt/chin lift method is used first; however, if a possibility of an injury to the spinal cord/spine exists, the jaw thrust method is used. When liquid components such as secretions are present in the oral cavity or upper respiratory tract, suction procedures are usually performed. However, caution should be exercised as suction techniques may induce vomiting, and/or upper airway edema, and may exacerbate narrowing of the airway. Endotracheal intubation or supraglottic airway devices that secure the airway may be considered in cases where the abnormality of the airway as described above is recognized. Cricothyroidotomy/paracentesis may be considered in cases of airway emergency that cannot respond to supraglottic airway devices or cannot intubate.

2.3 Evaluation of Respiration

In addition to the evaluation of oxygenation and ventilation based on blood gases, respiratory function such as work of breathing and respiratory rhythm must also be evaluated. Oxygenation is evaluated using PaO_2 or SpO_2. Both PaO_2 and SpO_2 are frequently used, but care must be taken in that inhalation oxygen concentration (FIO_2 of ventilator or dosage condition of oxygen) together. Conventionally, in neurological intensive care, prophylactic administration of a high concentration of oxygen was a routine procedure. However, current studies have reported the harmful effects of administration of a high concentration of oxygen in resuscitated hypoxic encephalopathy after cardiopulmonary arrest or acute coronary syndrome as well as in patients with cerebral infarction [1]. With reference from these reports, in current practice administration of a high concentration of oxygen is avoided and to manage with a lower SpO_2 (target, 92–94%). Administration of a high concentration of oxygen results in increased production of active oxygen in the body, which can injure tissues and lead to collapse of the lungs, due to the influence of denitrogenation. Furthermore, it is difficult to evaluate the correct oxygenation when SpO_2 is 100%, and it is preferable to avoid this condition. Evaluation of ventilation is routinely performed using $PaCO_2$ or $ETCO_2$. Recently, medical instruments that can percutaneously measure CO_2 levels can be used, but these instruments are not generally prevalent, and now blood gas analysis continues to remain the standard for assessment of ventilation. When you cannot use blood gas analysis, you can use respiratory rate and thoracic motion for evaluation of ventilation. In hyperventilation syndrome patients, large breathing and tachypnea can easily predict low $PaCO_2$. In unconscious patients with low mandibular breathing or few thoracic motion and slow breathing, it can be easily judged that it is high $PaCO_2$ without blood gas test. The normal range of $PaCO_2$ is 35–45. However, during artificial ventilation, the appropriate range of $PaCO_2$ varies depending on the condition of the patient. In

Table 2.1 Equation of work of breathing

Work of breathing (WOB) is expressed by the following equation in respiratory physiology
$P = R \times F + V_T/C$

P WOB, *R* airway resistance, *F* respiratory flow rate, V_T tidal volume, *C* lung compliance

patients with intracranial pressure elevation or metabolic acidosis due to shock, it is essential to maintain low $PaCO_2$. In patients with metabolic alkalosis, maintaining higher $PaCO_2$ levels may be indicated. Another important parameter to be evaluated is the breathing style. Evaluation of the style of respiration refers to work of breathing and breathing rhythm abnormality. Evaluation of work of breathing is performed to assess the presence of any abnormality in airway resistance and lung compliance like respiratory function test (Table 2.1). Although it is often difficult to distinguish the causes by direct observation of the style of breathing, image findings, past and current medical history, and other parameters may aid in the assessment. Obstructive pulmonary disease in which airway resistance is elevated such as asthma and narrowing of the upper airway, and restrictive pulmonary diseases wherein compliance is lowered such as acute respiratory distress syndrome and pulmonary fibrosis, may be referred to as typical respiratory abnormalities. When abnormality in work of breathing is suspected, a respiratory function test is usually performed; however, the test cannot be applied to patients under artificial respiratory support; therefore, in such patients, diagnosis may be made using the graphic monitor of the ventilator (Fig. 2.1). Although it is a calculation using a prediction formula in ventilator, airway resistance and compliance value by dynamic measurement of a ventilator may be referred. Evaluation of breathing rhythm should be considered while assessing style of breathing. Variation at the physiological level is generally recognized in the breathing rhythm. A value that exceeds this physiological fluctuation is considered an abnormality of respiratory rhythm (Fig. 2.2). Abnormalities in respiratory rhythms are mainly caused by brain stem disorders affecting the respiratory center. Various causes such as direct damage due to cerebral hemorrhage or cerebral infarction, administration of sedatives or opioids, circulatory disorders, abnormality of respiratory compensation due to metabolic abnormality, and so on may lead to abnormalities in respiratory rhythm. Among the various breathing rhythm abnormalities, Cheyne-Stokes respiration is clinically significant, as this type of breathing is often observed as an early sign of heart failure. Direct brain injury can also cause Cheyne-Stokes breathing too; however, it is rare and challenging to treat. Therapeutic intervention for abnormalities in respiratory rhythms involves management of the underlying cause or artificial ventilation. Oxygen administration is often performed in cases of hypoxemia due to apnea or bradypnea; however, it is often ineffective in the long term.

This is WOB in one breath, and when it is multiplied by the respiratory rate, it becomes the breathing work amount per minute. WOB increases with an increase in airway resistance, lowered lung compliance, or in case of tachypnea. In a ventilation mode called PAV (proportional assist ventilation), which automatically measures

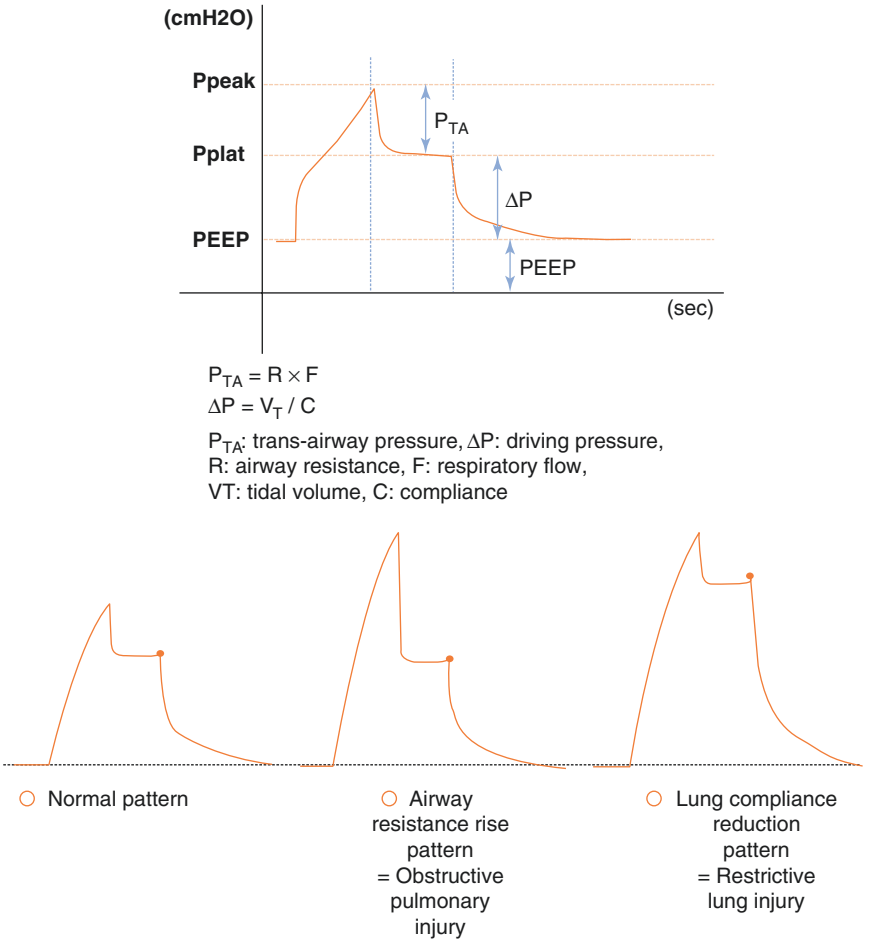

Fig. 2.1 (**a**, **b**) Evaluation of airway resistance and compliance using ventilator graphics. P_{TA} trans-airway pressure, ΔP driving pressure, R airway resistance, F respiratory flow, V_T tidal volume, C compliance, *Ppeak* peak pressure, *Pplat* plateau pressure, *PEEP* positive end-expiratory pressure

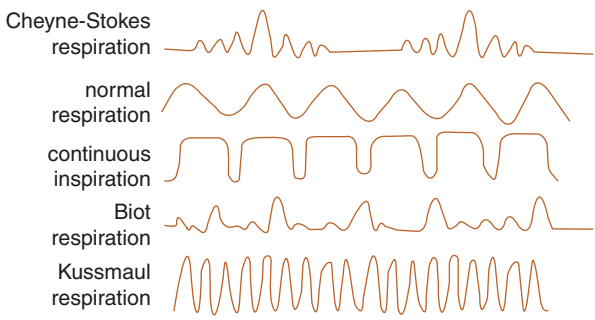

Fig. 2.2 Abnormal rhythm of respiration

the WOB and performs proportional support, the WOB is calculated based on the abovementioned equation.

In respiratory function tests, evaluation of airway resistance is usually performed using forced expiratory volume in 1 s as percent of FVC (FEV 1.0%), and compliance is evaluated using vital capacity as percent of predicted (%VC). As the respiratory function test cannot be performed during artificial ventilation, assessment is performed using waveform on the graphic monitor. As the airway resistance increases, the fraction called PTA ($= P_{peak} - P_{plat}$) increases. PTA often varies dynamically, such as in cases of secretion storage and asthma attacks, requiring frequent evaluation. Conventionally, when the PTA exceeds 10 cmH_2O, it is considered as an abnormal state. As compliance decreases, driving pressure ($= P_{plat} - PEEP$) increases. Driving pressure is also expressed as ΔP. The rise in PTA is associated with barotrauma. In addition, it is known the increase in ΔP injures the lungs and increases the subsequent mortality rate, so careful attention is required.

2.4 Intervention

Interventions for respiratory disturbance are management of the underlying cause and administration of oxygen therapy or artificial ventilation. It goes without saying that it is important to identify and eliminate the cause in all situations. However, in disorders of the central nervous system, it is often difficult to eliminate the cause; therefore, respiratory disturbances may persist in such cases. Oxygen therapy is effective against hypoxemia regardless of the cause. Artificial respiration can cope with all oxygen disorder, ventilatory disorder, and excessive respiratory work. There are two types of artificial ventilation, namely, invasive positive pressure ventilation (IPPV) with artificial airway and noninvasive positive pressure ventilation (NPPV) without using artificial airway. Although NPPV can be easily introduced, deep sedation is difficult because there is no reliable airway management. In addition, high airway pressure exceeding 20 cmH_2O is associated with a risk of aerophagia, vomiting, and aspiration, so it cannot be loaded; there are drawbacks such as poor ventilation support reliability compared with IPPV. Deep sedation can be administered safety during IPPV, thereby ensuring that restlessness and dangerous behavior due to brain injury is prevented. However, due to oral tracheal intubation in IPPV, administration of opioids or sedative drugs may result in suppression of circulation and a reduction in the level of consciousness. However deep sedation becomes a risk in central disease, because the course of original consciousness disorder cannot be followed. Sometimes we cannot notice the exacerbation and relapse of stroke. If artificial ventilation is unnecessary, but securing the airway is indicated, tracheotomy should also be considered early in order to avoid the invasive procedure of tracheal intubation and pharmacological agents such as opioids and sedatives. Deep sedation is usually required during artificial ventilation in management of refractory seizures. In such cases, since evaluation of the level of consciousness

and nonconvulsive status epilepticus is difficult, a simplified electroencephalogram may be used to monitor. In status epilepticus, the purpose is not elimination of recognizable seizures but to control epileptic waves. It is known that epileptic activity occurs in the brain. In particular, monitoring of brain waves is preferred when using muscle relaxants.

2.5 Setting and Adjustment of Ventilator

Guidelines for initial setting of the ventilator are shown in (Table 2.2). This is proposed in the FCCS [2], which is an intensive care training course provided by the Society of Critical Care Medicine (SCCM). The ventilatory mode selects what is most accustomed of the facility. Usually, synchronized intermittent mandatory ventilation (SIMV) or assist control ventilation (A/C) is used. Depending on the type of ventilator, A/C may also be known as CMV or BIPAP (A/C-PCV). The ventilation styles are VCV and PCV; These are different in the way of control method (volume or pressure) of sending the air. Because the lung stiffness (compliance) of the patient is fixed, if you specify the pressure, the amount will change. If you specify the amount the pressure will fluctuate. What is involved in ventilation is tidal volume. FIO_2 is the concentration of oxygen and can be decided between 0.21 of room air and 1.0 of pure oxygen. FIO_2 starts at 1.0 (or oxygen concentration + 10% before start of artificial ventilation) and

Table 2.2 Initial setting of artificial ventilation

1. Choose the most familiar ventilation mode. The aim of artificial respiration is to maintain adequate oxygenation and ventilation, reduce respiratory work, synchronize the patient and ventilator, and avoid high terminal alveolar pressure
2. FIO_2 starts with 1.0. Thereafter, SpO_2 is measured, and FIO_2 is reduced using 92–94% as an index. In case of severe acute respiratory failure, SpO_2 is allowed up to 88% to minimize ventilatory complications
3. For patients with normal lung compliance, the initial tidal volume (VT) should be set at 8–10 mL/kg. For patients with low lung compliance (such as ARDS) set at 6 mL/kg of PBW, to avoid hyperinflation of the lungs and to keep the intake plateau pressure below 30 cmH_2O
4. Choose respiratory rate and minute ventilation volume based on the ventilation status of the patient. The target is the optimal pH, not normal $PaCO_2$
5. Usually PEEP starts at 3–5 cmH_2O and increases according to oxygenation. For diffuse lung injury, increase PEEP to maintain alveolar opening at the end of expiration. If tidal volume is specified, PEEP will increase the maximum inspiratory plateau pressure and could adversely affect the lungs in ARDS patients. There is almost no need to raise PEEP above 15 cmH_2O
6. The trigger sensitivity is set so that the effort of the patient at the beginning of inspiration is minimized. It should be noted that if the trigger setting is too low, it will result in auto-trigger. If the trigger setting is too dull (high), it will be a miss-trigger
7. Because patients with obstructive airway disease have restricted exhalation times, avoid setting ventilators that cause auto-PEEP expression or deterioration
8. Consider consultation with an intensivist or other specialists

Table 2.3 Setting of PEEP and FIO_2

Settings for positive end-expiratory pressure (PEEP), according to the required fraction of inspired oxygen (FIO_2)	
FrO_2	PEEP
0.3	5
0.4	5–8
0.5	8–10
0.6	10
0.7	10–14
0.8	14
0.9	14–18
1.0	18–24

N Engl J Med 2007;357:1113–20

Settings are from the ARDSNet trial. The required FlO_2 is the lowest value that maintains arterial oxyhemoglobin saturation above 90%. After the corresponding level of PEEP is selected, arterial oxyhemoglobin saturation and plateau airway pressure should be monitored in the patient

gradually lowers SpO_2 to a target of 92–94%. In very severe cases that require administration of a high concentration of oxygen, SpO_2 of 88–90% may be tolerated to avoid oxygen toxicity. Generally, the respiratory rate is 10–12 times/min; however, a higher rate can be set to maintain a lower level of $PaCO_2$ in cases of severe metabolic acidosis or intracranial pressure elevation. In the initial setting guidelines, a tidal volume of 8–10 mL/kg is recommended. The tidal volume significantly exceeding this has been shown to cause high plateau pressure and exacerbate patient outcome [3], so do not set it. The inspiratory plateau pressure should be monitored after setting the tidal volume. The inspiratory plateau pressure increases in correlation with the tidal volume and inverse relation with lung compliance. PEEP starts at 3–5 cmH_2O and is increased sequentially by referring to the $PEEP/FIO_2$ correspondence table (Table 2.3) [4]. As the airway pressure becomes positive due to artificial ventilation, the intrathoracic pressure rises, causing stasis of the venous system, which in turn can raise intracranial pressure. Although mean airway pressure is known as an indicator of venous stasis, PEEP as the baseline airway pressure has a significant influence on regulation of mean airway pressure. However, the rise in mean airway pressure does not become intracranial pressure with the pressure as it is. It is known that about 13 cmH_2O PEEP level can be used safely even for brain surgery patients. In SIMV, pressure support (PS) is added to spontaneous breathing above the set number of breaths. PS usually starts from 5 to 10 cmH_2O. After the start of artificial ventilation, the suppression of circulation is evaluated with monitoring vital signs (intrathoracic pressure rise due to positive pressure ventilation, auto-PEEP, pneumothorax/tension pneumothorax may occur), and oxygenation and ventilation are properly maintained by the blood gas test. After starting artificial ventilation, items related to oxygenation and ventilation should be adjusted separately. Oxygenation is regulated by FIO_2 and mean airway pressure (MAP). Since MAP cannot be set directly, it is adjusted with

Table 2.4 Setting adjustment during artificial ventilation

Oxygenation is good: lower FIO_2 or PEEP
Oxygenation is bad: raise FIO_2 or PEEP[a]
Acidemia: increase respiratory rate or tidal volume (= lower $PaCO_2$)
Alkalemia: reduce respiratory rate or tidal volume (= raise $PaCO_2$)[b]

[a]Changes in oxygenation by PEEP have no immediate effect. In addition, avoiding high oxygen concentration is the basic concept

[b]In patients with elevated intracranial pressure, when the aim is to achieve temporary intracranial pressure reduction by artificial ventilation, alkalemia may be permitted, and low $PaCO_2$ levels may be maintained. However, considering a risk of cerebral ischemia, lowering the $PaCO_2$ level must be considered only as a short-term management in emergency situations

PEEP as the baseline pressure. First, PEEP level is raised sequentially with the goal of getting out of high concentration oxygen and is subsequently reduced as FIO_2 becomes less than 50%. Generally, it is desirable to stop a high concentration of oxygen within 24 h. Furthermore, when changing the mode of ventilation, it is necessary to adjust the PEEP level to maintain the same mean airway pressure. The goal of management of ventilation is not normalization of $PaCO_2$ but maintenance of an appropriate pH level. The respiratory rates, tidal volume (inspiratory pressure in PCV), or minute ventilation as its product is the regulating factor of ventilation. It is essential to avoid excessive tidal volume (over 10 mL/kg) and high plateau pressure (over 30 cmH_2O). Increasing respiratory rate and tidal volume results in decrease in $PaCO_2$, and blood pH shift toward alkalemia. Decreasing respiratory rates and tidal volume causes rise in $PaCO_2$, and blood pH tilts toward acidemia (Table 2.4). Maintaining optimum pH is the goal of ventilation management; however, if low $PaCO_2$ levels are required for management of intracranial pressure, some degree of alkalemia is acceptable.

2.6 Artificial Ventilation in the Neurological Intensive Care

In addition to standard artificial ventilation, CO_2 management that is conscious of intracranial pressure management is important. In particular, when performing artificial ventilation for neurological intensive care patients, care must be taken to prevent hypoxemia and CO_2 storage until endotracheal intubation and subsequent care. If severe hypoxemia, circulatory failure, CO_2 storage, or severe acidosis are present, NPPV or sufficient BVM ventilation should be performed prior to tracheal intubation. This is because progression of hypoxemia and ventilatory disorder may occur during tracheal intubation. When starting artificial ventilation, initial setting should be based on general ventilator guidelines, and care must be taken to maintain ventilation (especially respiratory rate) according to intracranial pressure. However, very

low $PaCO_2$ levels must be prevented as it may contract cerebrovascular vessels and cause ischemia in the brain tissue. Conversely, in a patient with elevated intracranial pressure, if a ventilatory disorder ($PaCO_2$ storage) occurs due to conditions such as disturbance of consciousness, sudden intracranial pressure rise, and progression of consciousness disturbance progresses, the patient's condition deteriorates.

2.7 Column $AaDO_2$

$AaDO_2$ is expressed by the following equation. Because $AaDO_2$ contains items of oxygenation and ventilation, it is used as an index of the respiratory condition that is stricter than the PF ratio.

$$AaDO_2 = (760 - 47) \times FIO_2 - PaCO_2/0.8 - PaO_2$$

At atmospheric pressure (760 mmHg) and 37 °C (water vapor pressure 47 mmHg).

$AaDO_2$ represents the ability of the respiratory system to perform gas exchange in the lungs; lower $AaDO_2$ signifies better respiratory condition. In some neurointensive care patients, $AaDO_2$ may be normal, even though PaO_2 may be low along with high $PaCO_2$. This could signify that the respiratory condition is not favorable, despite the ability to maintain gas exchange in the lungs. Therefore, it is presumed that the extra-lung lesion. It is caused by stenosis of the upper airway or the like and suppression of respiration (such as respiratory arrest and slow breathing) due to brain injury.

2.8 Weaning from Artificial Ventilation

Various complications including ventilator-associated pneumonia (VAP), respiratory muscle atrophy, and disuse syndrome may occur sequentially due to prolonged artificial ventilation. Therefore, a protocol to shorten artificial ventilation is paramount. The process of weaning from the ventilator has started since the beginning of artificial ventilation. During weaning from invasive positive pressure ventilation, evaluation of the following three elements must be conducted simultaneously. Depending on the severity of the disease condition, the underlying cause may not be eliminated. It is important not to stepwise weaning method like the conventional one but to automatically control of goal-directed method like daily interruption of sedatives (DIS) [5, 6] and spontaneous breathing trial (SBT) [7].

1. Withdrawal from artificial airway.

   Evaluate the necessity of a tracheal tube. The subsequent step during weaning from artificial airway is extubation. However, in neurological intensive care patients, disturbance of consciousness is often prolonged, and extubation (with-

drawal from artificial airway) is difficult. In doing so, tracheotomy should be considered. The cuff leak test is useful for evaluating whether it is possible to withdraw from the artificial airway. The cuff leak test is a technique to collapse the cuff of the tracheal tube while continuing the artificial ventilation management. As a result, narrowing of the upper airway and risk of asphyxiation can be evaluated by air leak from the side of the tracheal tube. Additionally, the existence of cough reflex and the risk of aspiration can also be evaluated.

2. Withdrawal from sedative drugs.

   In order to withdraw from artificial ventilation, it is also necessary to evaluate the necessity of sedative drugs. Even if spontaneous breathing is solid and artificial ventilation is unnecessary, continuation of deep sedation may be indicated as a neurological intensive care procedure, in cases of early stage subarachnoid hemorrhage or a persistent convulsive seizure attack. The daily interruption of sedatives (DIS), also known as spontaneous awakening trial (SAT), is a standard method for withdrawal from sedation.

   This is the way to discontinue sedative medication once a day and evaluate its necessity. See the guideline for details [8]. In DIS, the sedative drugs are suspended, and the condition of the patient is evaluated including the state of consciousness at arousal, the possibility of independently securing the airway, and maintenance of spontaneous breathing. If sedation is required despite withdrawal from ventilator support, a change to sedative drugs (such as dexmedetomidine) with less respiratory depression effects must be considered.

3. Withdrawal from ventilatory support.

   This aspect refers to the evaluation of withdrawal from ventilatory support or weaning. This is a standardized method called spontaneous breathing trial (SBT), which involves putting the on spontaneous breathing (CPAP or T piece) once a day. In this CPAP management, minimal ventilation support (minimum pressure support for tracheal tube cancellation, usually 4–5 cmH_2O or using automatic tube compensation function, ATC) may be used. Cancellation criteria is determined by SBT in advance and is stopped if the patient falls below the set limit, following which there is return to the original ventilator setting. SBT may be considered successful if 30–120 min elapse without falling below the cancellation criteria.

2.9 Summary

As mentioned in this article, respiratory management (including airway management) is the top priority particulars of the intensive care ABCD protocol and must be universally executed regardless of disease. It is important to maintain proper oxygenation and ventilation to prevent excessive breathing work. In particular, regarding ventilation (CO_2) management, it is important not to normalize $PaCO_2$ level but to aim for optimization of blood pH. When intracranial pressure is increased, appropriate management of ventilation is given top priority, and in cases of emergency,

hyperventilation management is performed as a temporary measure. The key to the success of artificial ventilatory management is to ensure short duration of the procedure. To achieve the same, standard, weaning methods such as DIS and SBT should be followed.

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Chapter 3
Body Temperature Care for Comatose Patients with Post-cardiac Arrest Syndrome

Takashi Moriya and Masahiro Kashiura

Abstract Most clinicians know that increasing body temperature may worsen neurological prognosis. Although the appropriate period for temperature management remains unclear, Nielsen et al. described a protocol to control body temperature at 37.5 °C or lower for up to 72 h after cardiac arrest. Targeted temperature management (TTM) was divided into four phases, introduction (cooling), maintenance, rewarming, and subsequent rewarming. In the introduction to maintenance phase in TTM, cation imbalance due to hypothermia-induced polyuria and water balance is recognized. In rewarming and subsequent rewarming phases, temperature control is essential for patients, and to understand mechanism of fever in central nervous system diseases might be important. Current points regarding temperature management of post-cardiac arrest syndrome are discussed.

Keywords Induced hypothermia · Therapeutic hypothermia · Targeted temperature management · Post-cardiac arrest syndrome · Post-hypothermia hyperthermia

3.1 Introduction

In order to determine pharmacological intervention methods to protect an injured brain from secondary damage, many animal studies have been carried out. One well-known method to protect the brain is to lower body temperature [1]. However, significant therapeutic effect was not shown in clinical studies until after the twentieth century.

At the beginning of the twenty-first century, two randomized clinical trials were carried out. Therapeutic hypothermia (32–34 °C for 12–24 h) treatment significantly showed neurologically better results than standard treatment [2, 3]. Eleven years after this significant medical evidence, a "targeted temperature management

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[4]" was proposed, consisting of four phases, introduction (cooling), maintenance, rewarming, and subsequent rewarming. Most clinicians know that increasing body temperature may worsen neurological prognosis. However, the appropriate period for temperature management in comatose patients with complications such as post-cardiac arrest syndrome (PCAS) remains unclear. In this chapter, current points regarding temperature management of PCAS are discussed.

3.2 Changes in Thinking Regarding Technological Methods: From Therapeutic Hypothermia to Targeted Temperature Management (TTM)

In the 1990s, Busto et al. [5] reported that elevation of extracellular glutamate concentration could be suppressed by lowering body temperature by only 2 °C in the rat middle cerebral artery occlusion model. In the twenty-first century, the protective effect of brain hypothermia obtained at return of spontaneous circulation (ROSC) was clinically verified in comatose patients with PCAS. These results were epoch-making facts in the history of clinical treatments defined as induced hypothermia (IH) or therapeutic hypothermia (TH) [2, 3]. Hypothermia treatment essentially lowered body temperature to the targeted value rapidly, and temperature was maintained within a few hours. Although the criteria of the two studies somewhat differed, the duration and cooling temperature for TH was for 12 h at 33 °C according to Bernard et al. [2] and over 24 h at 32–34 °C according to the Hypothermia after Cardiac Arrest Study Group [3].

Hundreds of IH and TTM for critical CNS diseases have been handled at two hospitals, Nihon University Itabashi Hospital and Jichi Medical University Saitama Medical Center, since 1996. In particular, emphasis has been placed on circulation management after cardiac arrest. In general, the targeted body temperature is reached within 3–6 h from the start of cooling phase, with a body temperature fluctuation within 0.3 °C (Fig. 3.1). Differences in individual body temperature between 0.1 and 0.3 °C depended on each measurement part, and the variations are consistent. Temperature fluctuation sometimes is caused by hypothermia-induced polyuria [6] which may occur in the cooling phase in TH (Fig. 3.2). In 32 patients who obtained ROSC after cardiac arrest, urine volume during cooling phase (371 ± 54 mL/h) was more than twice than before cooling phase (163 ± 39 mL/h). These findings depended on disease-non-specific factors such as severe traumatic injury and comatose PCAS. This phenomenon may induce the temperature fluctuation due to circulatory disturbance, for which temperature control may be more difficult. This mechanism is based, not on the change in secretion of antidiuretic hormone (ADH) in CNS but on decreased sensitivity of the peripheral receptor (V2 receptor) to ADH [7]. Polyuria resulted from the in-out imbalance of free water and affected cation metabolism from the glomerulus to the collecting duct. Although decreased serum potassium induced lethal arrhythmia, decreased serum phosphorus and magnesium

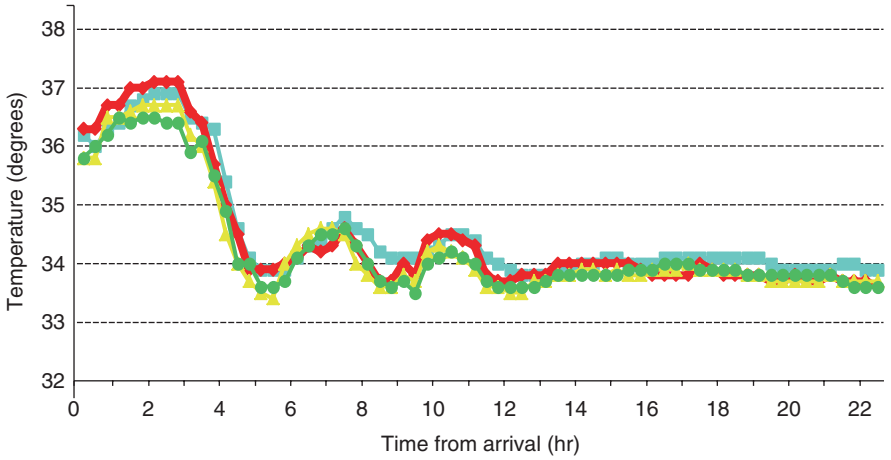

Fig. 3.1 Changes in individual body temperatures in the induction of therapeutic hypothermia. Blue, bladder; red, internal jugular vein; yellow, pulmonary artery; green, tympanic membrane

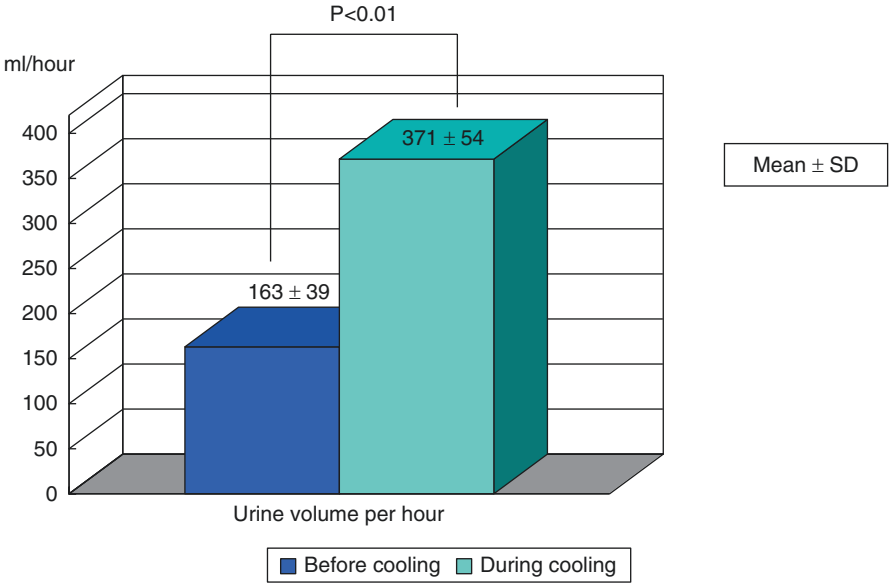

Fig. 3.2 Changes in urine volume in the induction of therapeutic hypothermia

also seriously affected migration into cells and extracorporeal loss in the same mechanism [8]. In our experience, serum phosphorus (2.1 ± 0.22–1.5 ± 0.36 mmol/L) and magnesium (1.0 ± 0.18–0.6 ± 0.22 mmol/L) decreased by 30–40%. On the other hand, urine phosphorus (1.9 ± 0.6–10.5 ± 2.2 mmol/h) and magnesium (0.11 ± 0.04–0.73 ± 0.31 mmol/h) increased by 500% (Figs. 3.3 and 3.4). Imbalance of some

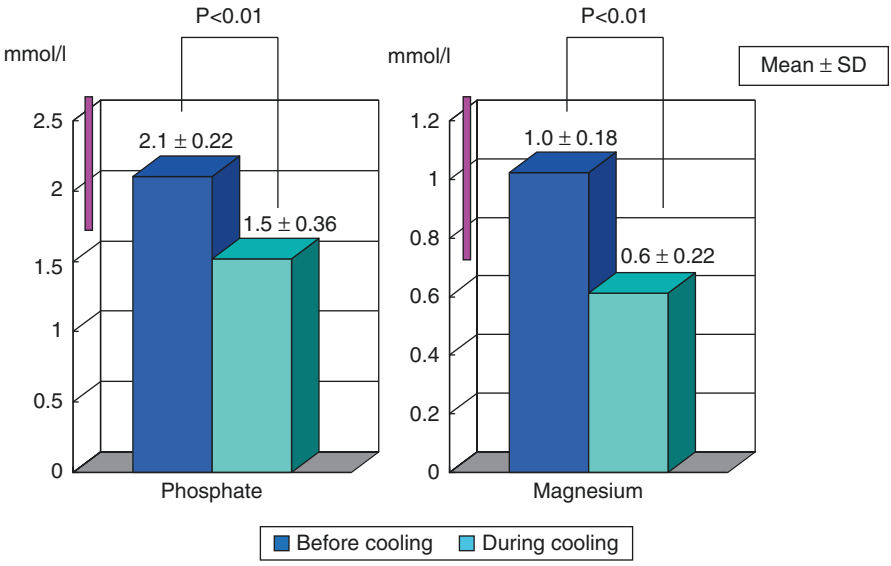

Fig. 3.3 Changes in serum phosphate and magnesium in the induction of therapeutic hypothermia. Each red bar means normal value range

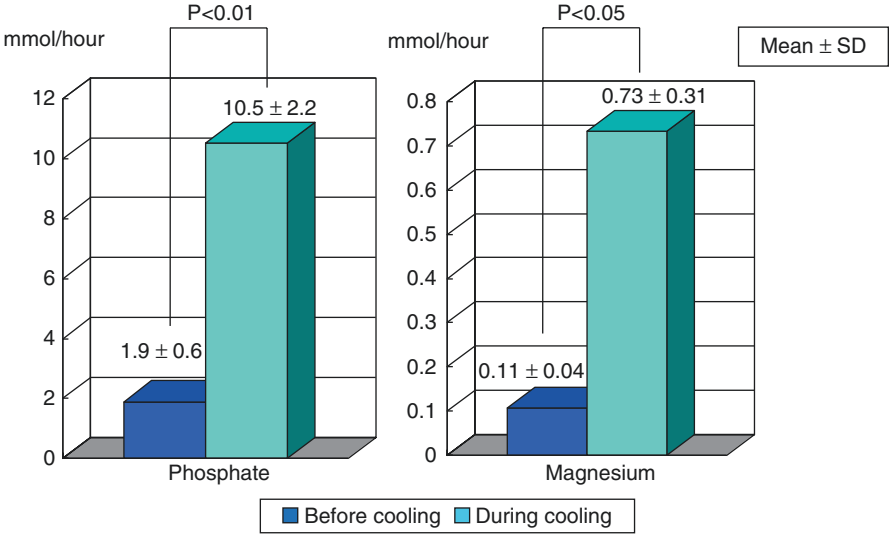

Fig. 3.4 Changes in urine electrolytes in the induction of therapeutic hypothermia

serum cations comprehensively induced severe fatal arrhythmia or respiratory muscle failure [7, 9]. For these reasons, frequent blood examination tests during cooling should be scheduled.

In the surface cooling method for patients receiving IH, stability of circulation dynamics may be considered indispensable since body temperature is regulated in

the heat exchange of peripheral blood vessels. However, Bernard et al. [2] and the HACA study group [3] observed obvious temperature fluctuations. Nielsen et al. [4] reported that even in the intravascular cooling method, which is the most reliable method to control body temperature, similar fluctuations were observed. In their findings, there was much fluctuation in bladder temperature in each temperature group [10]. These results were not referred to in reference with circulatory disturbance due to polyuria. Management of analgesic and sedative agents and muscle relaxants also was not indicated.

3.3 Mechanism of Fever in Central Nervous System Diseases (CNS)

All mechanisms in which hyperthermia causes secondary brain damage in CNS diseases have not yet been elucidated [11]. Epidemiologically, the probability of fever was high due to diffuse axonal injury and focal injury of the frontal lobe in severe head injury [12]. Sympathetic response and inflammation for stress are involved in the acute phase within 24 h of injury. Fever was recognized in most patients as caused by infection and partially by direct damage to preoptic nucleus of hypothalamus and focal center of pons as a thermoregulatory center [13]. Forty percent showed damage to the hypothalamus in a cadaver study [14]. The cause of hyperthermia complicated with CNS injury can be divided into infectious pyrexia and neurogenic fever [15]. Incidence of hyperthermia and its causes were prospectively examined in 387 consecutive patients who were admitted to the neuro-intensive care unit [16]. A body temperature of 38.3 °C or more was observed in 23% of patients of which 52% had infectious diseases such as pneumonia and bronchitis. On the other hand, 28% had unknown causes of fever despite receiving a complete prognostic examination. Intraventricular hemorrhage was also listed as a risk factor related to hyperthermia without infection. The hypothalamus, which is located in the thermoregulatory center, was stimulated by mixture of blood and cerebrospinal fluid in the ventricle.

3.4 Significance of TTM and Future Direction

TTM was used not only to lower body temperature for critical CNS diseases but also to control body temperature. The concept of temperature management has existed for a long time and has also been defined [1]. For comatose PCAS patients, if TTM is administered to global ischemia due to cardiac arrest along with early reperfusion up to 20 min from ROSC and late reperfusion from 4 h to 7 days, management comprised of shivering, electrolyte imbalance, stress-induced hyperglycemia, early coronary intervention, stunning myocardium, sepsis-like syndrome, low cardiac output, and hypothermia-induced polyuria from cooling phase to maintenance phase, and hemodynamic change, oxygen metabolism, electrolytes, blood sugar,

and hyperthermia during rewarming phase should be considered [17]. Time interval from admission to body temperature maintenance and temperature degree in IH was emphasized. Currently, Nielsen et al. [3] clearly describe a protocol to control body temperature at 37.5 °C or lower for up to 72 h after cardiac arrest in TTM intervals.

Mechanisms of hyperthermia that worsen damaged neuronal injury have been reported. Hyperthermia after head injury increases inflammatory cytokines, enhances accumulation of neutrophils at injury site [18], increases the release of excitatory amino acids, and induces the influx of calcium into nerve cells. In addition, sensitivity of nerve cells to excitatory amino acids changed [19]. Extracellular glutamate concentration increased with hyperthermia [20]. Intracellular acidosis and depolarization effect in ischemic penumbra were also reported [21].

3.5 Fever After IH Completion

Increased body temperature after IH completion has been observed clinically. This phenomenon is called "hyperthermia after rewarming from induced hypothermia," "post-rewarming hyperthermia," "pyrexia after induced hypothermia for cardiac arrest," "post-hypothermia fever," "post-rewarming (rebound hyperthermia) after induced hypothermia," or "post-induced hypothermia hyperthermia" [22]. Pathophysiology of post-hypothermia hyperthermia indicates that actual "rebound" hyperthermia is a reaction to IH and simply the unmasking of postarrest hyperthermia after IH completion. Finally, whether treating post-hypothermia hyperthermia is beneficial remains unknown [22].

3.6 Conclusion

To protect an injured brain from secondary damage, temperature control is definitely essential for patients with critical CNS diseases. T.T.M. should be applied as a therapeutic measure needed in neuro-intensive care.

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Chapter 4
Infection Control for Neurocritical Care

Yuki Uehara

Abstract Infection control in the field of neurocritical care is essential because hospital-associated infections among the patients who require neurointensive care are correlated with long stay in neuro-ICU and high mortality. Standard precaution is most important, and high adherence of all healthcare providers is necessary. Specific infectious diseases in neuro-ICU are surgical site infections penetrating to intracranial space and ventriculostomy-associated infections, both of which need specific precautions. Other HAI should be prevented as same as other wards.

Keywords Standard precautions · Surgical site infections · Ventriculostomy-associated infections · Healthcare-associated infections

4.1 Infection in Neurocritical Care Settings

Infectious diseases in the field of neurocritical care can be differentiated into several groups: primary central nervous system (CNS) infections as the causes of admission to neurological intensive care unit (neuro-ICU), contaminated head trauma followed by secondary CNS infections, any types of healthcare-associated infections (HAIs), and diseases associated with antimicrobial usage such as *Clostridioides difficile*-associated diseases (CDAD). Especially, HAIs among the patients who require neurointensive care are correlated with long stay in neuro-ICUs and high mortality [1–4]. These previous reports repeatedly showed the importance of infection control in the field of neurocritical care.

Diagnosis and management of CNS infections will be described elsewhere in detail in this book, so this chapter is focusing on the issues for controlling infectious diseases mainly based on the recommendations from the Centers for Disease Control and Prevention (CDC) in the United States.

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4.2 Infection Control Basics

4.2.1 Standard Precautions

Standard precautions are indicated for all patients, at any time, without regarding situations, which can prevent the spread of infection from patient to patient as well as protect healthcare providers from infections. They are formed with common sense hygienic practices and use of personal protective equipment, based on a risk assessment of the exposure to any biological substances of patients except for sweat.

CDC included the items in standard precautions listed in Table 4.1, and especially the first two items are essential.

For hand hygiene, there are two choices of practice. One is handwashing using soap and water, and another is hand rubbing using alcohol-based formulation. Handwashing with soap and water is necessary when healthcare workers obviously notice touching certain or visible amount of biological substances. Another indication of handwashing with soap and water is possible exposure to microorganisms which cannot be disinfected by alcohol-based formulation such as spore-forming bacteria or virus without envelope. In contrast, hand rubbing using alcohol-based formulation can be used widely and conveniently unless the situation needs handwashing with soap and water. Though the importance of hand hygiene is widely recognized by healthcare workers, appropriateness of the timing and practice is always the concern. Recently, practical recommendations for hand hygiene are described by the World Health Organization (WHO). WHO shows the five moments to do hand hygiene practice:

1. Before patient contact.
2. Before an aseptic task.

Table 4.1 Items inclded in standard precautions by Centers for Disease Control and Prevention: https://www.cdc.gov/infectioncontrol/basics/standard-precautions.html

1. Perform hand hygiene
2. Use personal protective equipment (PPE) whenever there is an expectation of possible exposure to infectious materials
3. Follow respiratory hygiene/cough etiquette principles
4. Ensure appropriate patient placement
5. Properly handle and properly clean and disinfect patient care equipment and instruments/devices
6. Clean and disinfect the environment appropriately
7. Handle textiles and laundry carefully
8. Follow safe injection practices
9. Wear a surgical mask when performing lumbar punctures
10. Ensure healthcare worker safety including proper handling of needles and other sharps

3. After body fluid exposure risk.
4. After patient contact.
5. After contact with patient surroundings.

This simple recommendation of timing can be easily followed by healthcare workers and is getting popular in healthcare settings. WHO's hand hygiene promotion toolkits are available in http://www.who.int/gpsc/tools/Five_moments/en/.

Use of PPEs is not a special practice and is recognized as a part of standard precautions. When healthcare providers are at risk of exposure to wet biological substances of patients, appropriate use of PPE is necessary, in case of intubation, suction of sputum, changing dressings of wound or catheter insertion site, changing diapers, handling infusion lines, transporting laboratory samples, etc.

4.2.2 Transmission-Based Precautions

Transmission-based precautions are used in addition to standard precautions for patients who may be infected or colonized with certain microorganisms for which additional precautions are necessary to prevent infection transmission to other patients. In acute care settings, it is reasonable to add transmission-based precautions for suspected pathogens to standard precautions, waiting for the confirmation of causative pathogens.

4.2.2.1 Contact Precautions

Contact precautions are indicated for patients with known or suspected infections that represent an increased risk for contact transmission.

4.2.2.2 Droplet Precautions

Droplet precautions are indicated for patients known or suspected to be infected with pathogens transmitted by respiratory droplets that are generated by patients' coughing, sneezing, or talking.

4.2.2.3 Airborne Precautions

Airborne precautions are indicated for patients known or suspected to be infected with pathogens transmitted by the airborne route.

Summary of the practices of each transmission-based precaution recommended by CDC is shown in Table 4.2.

Table 4.2 Detailed practices and comparison of contact precautions, droplet precautions and airborne precautions: https://www.cdc.gov/infectioncontrol/basics/transmission-based-precautions.html (except for Pathogens/diseases)

Practices and pathogens	Contact precautions	Droplet precautions	Airborne precautions
Patient placement	Single patient space or room if available	Single room if possible	Airborne infection isolation room, or in settings where airborne precautions cannot be implemented due to limited engineering resources, masking the patient and placing the patient in a private room with the door closed is necessary
Use of PPE	Wear a gown and gloves for all interactions that may involve contact with the patient or the patient's environment	Mask upon entry into the patient room or patient space	N95 or higher level respirator for healthcare personnel
Limitted transport and movement of patients	When transport or movement is necessary, cover or contain the infected or colonized areas of the patient's body	If transport or movement outside of the room is necessary, instruct patient to wear a mask and follow respiratory hygiene/cough etiquette	If transport or movement outside of the room is necessary, instruct patient to wear a mask and follow respiratory hygiene/cough etiquette
Use of disposable or dedicated patient-care equipment	If common use of equipment for multiple patients is unavoidable, clean and disinfect such equipment before use on another patient		
Prioritizing cleaning and disinfection of the rooms	Should be frequently cleaned and disinfected (e.g., at least daily) focusing on frequently-touched surfaces and equipment in the immediate vicinity of the patient		
Source control		Put a mask on the patient	Put a mask on the patient
Restriction of susceptible healthcare personnel from entering the room			Necessary

Immunize susceptible persons as soon as possible following unprotected contact		Necessary (and *Neisseria meningitidis* needs prophylactic antimicrobial treatment for contacts)	Necessary
Pathogens/diseases (examples)	methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* spp., *Clostridium difficile*, ESBL-producing *Enterobacteriaceae*, Carbapenem-resistant *Enterobacteriaceae*, multidrug-resistant *Pseudomonas aeruginosa/Acinetobacter* spp., toxic-shock like syndrome (β-hemolytic streptococci), enterohemorrhagic *Escherichia coli*, *Salmonella* spp., *Shigella* spp., *Vibrio cholerae*, adenovirus, varicella-zoster virus, norovirus, rotavirus, Coxackievirus, etc.	all acute respiratory infections, invasive infections caused by *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis*, β-hemolytic streptococci, *Corynebacterium diphtheriae, Bordetella pertussus*, mumps, rubella, Coxackievirus, influenzavirus, adenovirus, etc.	*Mycobacterium tuberculosis*, Measles, Smallpox and disseminated herpes zoster (varicella-zoster virus), etc.

4.3 Infectious Diseases and Their Prevention in Neurocritical Care

4.3.1 Primary CNS Infections on Admission and Contaminated Head Trauma Followed by Secondary CNS Infections

CNS infections such as meningitis/encephalitis sometimes need critical management in neuro-ICU. Diagnosis, causative pathogens, and management of primary CNS infections and secondary CNS infections after contaminated head trauma will be described in elsewhere in this book.

4.3.2 Healthcare-Associated Infections and Their Prevention

Neurocritical care is often provided in neuro-ICU, where many types of invasive devices and procedures were used to take care of patients. Infections can be associated with the devices used in medical procedures, such as catheters or ventilators. These are called as healthcare-associated infections (HAIs), which include central line-associated bloodstream infections (CLABSIs), catheter-associated urinary tract infections (CAUTI), and ventilator-associated pneumonia (VAP). Infections may also occur at surgery sites, known as surgical site infections (SSI). In addition, ventriculostomy-associated infection is a unique infectious disease in neuro-ICU.

Numerous measures to prevent each HAI were recommended by CDC and other specialist groups such as the Society for Healthcare Epidemiology of America (SHEA). To control HAIs in neuro-ICU in each facility, close collaboration with the infection control department is strongly recommended to implement these recommendations in real practice.

4.3.3 Healthcare-Associated Infections (HAIs) Specific for Neurocritical Care

4.3.3.1 Infection After Neurosurgery (Surgical Site Infection: SSI)

Surgical site infection (SSI) is defined as infection that occurs after surgery in the part of the body where the surgery took place. SHEA and CDC provided the updated guidelines for the prevention of SSI in 2014 and 2017, respectively, but the important contents are common in both guidelines [5, 6].

SSI are classified into three types based on the depth of infected sites. Superficial incisional SSI is limited in skin to subcutaneous tissue, deep incisional SSI reaches

deep soft tissue such as fascia and muscle, and organ/space SSI is in the deepest organ space. In the neurocritical care, SSI can happen in any of these three classifications: superficial incision site infections to intracranial site infections. Seriousness of SSI is related with depth of involvement.

Here the essential components of the latest CDC guideline to prevent SSI are described.

- Antiseptic and other prophylaxes.

  Generally, it is recommended that patients should shower or bathe (full body) with soap (antimicrobial or nonantimicrobial) or an antiseptic agent on at least the night before the operative day. But in neurocritical care, CNS surgeries are often performed urgently, so this practice can only be implemented for rare scheduled surgeries. Skin preparation in the operating room should be performed using an alcohol-based agent unless contraindicated. In the SHEA guideline, timing and procedure of hair removal is also described. SHEA guideline says, "Do not remove hair at the operative site unless the presence of hair will interfere with the operation, and do not use razors. If hair removal is necessary, remove hair outside the operating room using clippers or a depilatory agent." For neurosurgery, it is almost always necessary to remove hair of incision site, so SHEA's recommendation should be followed for the timing and procedures to remove hair before neurosurgery.
- Parenteral antimicrobial prophylaxis.

  Antimicrobial prophylaxis should be administered only when indicated based on published clinical practice guidelines and timed such that a bactericidal concentration of the agents is established in the serum and tissues when the incision is made. In neurosurgery, SSI is mainly caused by staphylococci or streptococci, so the American Society of Health-System Pharmacists recommends cefazolin as the parenteral antimicrobial prophylaxis and clindamycin or vancomycin as alternatives for beta-lactam allergy patients [7]. For patients with known carriage of MRSA, vancomycin can be used for prophylaxis. For cefazolin, 2 g of dose should be started 60 min before skin incision and redosed every 4 h during surgery. For clindamycin, 900 mg of dose should be started 60 min before skin incision and redosed every 6 h during surgery. For vancomycin, 15 mg/kg of dose should be started 120 min before skin incision, but redosing is generally unnecessary. In clean and clean-contaminated procedures, additional prophylactic antimicrobial agent doses are not necessary after the surgical incision is closed in the operating room, even in the presence of a drain.
- Nonparenteral antimicrobial prophylaxis.

  Topical antimicrobial agents should not be applied to the surgical incision. The benefits and harms regarding intraoperative antimicrobial irrigation for the prevention of SSI are controversies.
- Glycemic control.

  During surgery, glycemic control should be implemented using blood glucose target levels less than 200 mg/dL.

- Normothermia.
  Normothermia (temperature of 35.5 °C or more) during the perioperative period should be maintained in all patients.
- Oxygenation.
  Supplemental oxygen is most effective when combined with additional strategies to improve tissue oxygenation, including maintenance of normothermia and appropriate volume replacement. Increased fraction of inspired oxygen should be administered during surgery and after extubation in the immediate postoperative period for patients with normal pulmonary function undergoing general anesthesia with endotracheal intubation.
- Blood transfusion.
  Transfusion of blood products should not be withheld from surgical patients as a means to prevent SSI.

4.3.3.2 Ventriculostomy-Associated Infections

- Intraventricular catheters are used for diagnostic and therapeutic purposes in patients with hydrocephalus and elevated intracranial pressure, which are usually managed in neuro-ICU. A meta-analysis of ventriculostomy-associated infections (VAIs) showed the infection rates ranged from 1% to 45%, though the common definition of VAI was not used in the studies [8]. Risk factors for VAIs include prolonged intraventricular catheterization, leakage of cerebrospinal fluid, intracranial hemorrhage, a recent neurosurgical procedure, the insertion of multiple catheters, and the lack of a strict protocol for drain management, and prolonged neuro-ICU stay [9–12].
- Prevention.
  Various bundle practices were reported to prevent VAIs. Honda et al. proposed that similar practices for the prevention of CLABSIs were effective to prevent VAIs [13]. All medical personnel in the patient's room or in the operating room who were not directly involved in the placement of the intraventricular catheter should wear a mask and cap, while the patient underwent intraventricular catheterization and, in addition, standardized dressing protocol including three components such as use of sterile gauze dressing with adhesive tape to cover the catheter site, changing of the intraventricular catheter site dressing every 48 h by neuro-ICU nurses who received standard training, and documentation of the date and time of gauze-dressing change. They also reported that antibiotic-impregnated catheter might have some effects to prevent VAIs. Gozal et al. emphasized that post-placement nursing care for ventriculostomy should be standardized: appropriate use of sterile occlusive dressing; management of hair growth in the sterilized scalp; appropriate choice of and procedures to the use of antiseptics, to avoid kinking or excessive tension to the catheters; and monitoring signs of infections at insertion sites, leakage of cerebrospinal fluid, etc. [14]. Darrow et al. reported that they would start the strict bundle of practices for VAIs, uniquely including preprocedural antibiotics administered (cefazolin,

clindamycin, or vancomycin), subcutaneous tunnel formation longer than 5 cm, BIOPATCH at exit site, barrier island dressing, and cerebrospinal fluid tests on day 5 after placement and at removal of the catheter [4]. It might be difficult to identify the most important practice to reduce VAIs via these studies, but the effectiveness of the bundle approaches would be confirmed in the near future.

4.3.4 Healthcare-Associated Infections (HAIs) Non-specific for Neurocritical Care

4.3.4.1 Central Line-Associated Bloodstream Infections (CLABSIs)

- CLABSI is a serious infection that occurs when microorganisms enter the bloodstream through the central venous catheter. In CLABSI, pathogens mainly enter the bloodstream streaming outside of the catheter surface or rarely by contaminated fluid injection through the catheter. It is easy to notice CLABSI if patients have a fever with inflammatory findings such as redness and tenderness around catheter insertion site, but such local inflammation signs are not always apparent. We have to consider CLABSI as a differential diagnosis of fever for any patients with intravenous catheters, regardless of local inflammation signs.
- Prevention.
  - CDC states that healthcare providers must follow a strict aseptic protocol when inserting the line. In addition, stringent infection control practices to check the line and to change the dressing are highly recommended by CDC [15].
  - When inserting the central venous line:
    - Perform hand hygiene.
    - Apply appropriate skin antiseptic.
    - Ensure that the skin prep agent has completely dried before inserting the central line.
    - Use all five maximal sterile barrier precautions:

      Sterile gloves.
      Sterile gown.
      Cap.
      Mask.
      Large sterile drape.
  - Once the central line is in place:
    - Follow recommended central line maintenance practices.
    - Wash their hands with soap and water or an alcohol-based hand rub before and after touching the line.
    - Remove a central line as soon as it is no longer needed.

4.3.4.2 Catheter-Associated Urinary Tract Infections (CAUTI)

- CAUTI is an infection involving any part of the urinary system among patients with placement of urinary tract catheter. It is estimated that approximately 70–80% of urinary tract infections acquired during hospitalization are associated with urinary tract catheter [16].
- Prevention.

  The most important risk factor for developing CAUTI is prolonged use of the urinary catheter. Therefore, catheters should only be used for appropriate indications and should be removed as soon as they are no longer needed. Alternative management of urinary tract such as intermittent catheterization to bladder or condom-type catheter should be considered to avoid placing the catheter in bladder for days. Aseptic procedure should be used for insertion of catheter, and the system should be maintained as sterile and continuously closed drainage. Detailed information is available in CDC and SHEA guidelines [16, 17].

4.3.4.3 Ventilator-Associated Pneumonia (VAP)

Neurocritical patients with altered consciousness level are frequently on mechanical ventilation and recognized as high-risk population of VAP.

- Prevention.

  The components of preventive measures of VAP recommended by SHEA are summarized here [18]. Briefly, (a) avoid intubation if possible, (b) minimize sedation, (c) maintain and improve physical conditioning, (d) minimize pooling of secretions above the endotracheal tube cuff, (e) elevate the head of the bed, and (f) maintain ventilator circuits without obstruction. These basic components should be implemented for patients on mechanical ventilation in all neuro-ICUs. Some special measures, such as selective oral or digestive decontamination, regular oral care with chlorhexidine, or administration of prophylactic probiotics, can be considered when benefits seem overwhelming disadvantages.

4.3.4.4 *Clostridioides difficile*-Associated Diseases (CDAD)

CDAD is one of the serious nosocomial infectious diseases which mainly affects compromised patients with predisposing antimicrobial use. As noted in Table 4.2, *C. difficile* needs strict contact precaution because *C. difficile* can form spores which cannot be disinfected by alcohol hand rub and need "removal" from healthcare providers' body surface using PPE and washing hand with soap and water. Neuro-ICU patients often need excretion care, so healthcare providers should keep adherence to precaution practices not to spread *C. difficile* in ICU.

Recently, SHEA and Infectious Diseases Society of America released the updated guideline of management of CDAD [19]. The latest recommendations are as

follows: use of a private room, strict contact precaution measures needed for at least 48 hours after diarrhea has resolved, handwashing with soap after direct contact with feces or contaminated area around patients, use of disposable equipment for each patient as much as possible, adequate room cleaning, etc.

Appropriate antimicrobial use is most important to prevent the occurrence of CDAD. Minimizing the frequency and duration of high-risk antimicrobial therapy and the number of antimicrobial agents prescribed, and implementation of antimicrobial stewardship program including restriction of fluoroquinolones, clindamycin, and cephalosporins, should be considered based on local epidemiology.

4.4 Protect Healthcare Providers from Unexpected Infections from Patients

Some pathogens are highly risky for healthcare providers to contract after unexpected exposure. Adequate prediction of highly pathogenic microorganisms is usually difficult in the settings of emergency room or critical care, because it is impossible to obtain the history of illness and other related factors, such as travelling overseas, exposure to dirty waters, and risky behaviors, from unconscious patients.

As shown in Table 4.2, the majority of infectious diseases can be controlled by standard precautions and management of respiratory excretion from patient. In addition, routine vaccination recommended for healthcare providers is essential to protect them from unexpected job-related infectious diseases. Keeping adherence to standard precautions, appropriate management of respiratory droplets from patients, and vaccination to healthcare providers are the essential measures. Postexposure chemoprophylaxis is recommended in some particular pathogens related with CNS infections.

- *Neisseria meningitidis*.

  For healthcare providers who have heavy exposure to patients (e.g., by resuscitation of patients, etc.), they are recommended to take chemoprophylaxis. For nonpregnant personnel, rifampin (600 mg po q12h for 2 days) is the first line of chemoprophylaxis. Alternative regimen is oral ciprofloxacin (500 mg po once) if personnel is nonpregnant and there is no concern about quinolone-resistant *N. meningitidis*. Ceftriaxone (250 mg im once) is another choice, and it can be used for pregnant women.
- *Haemophilus influenzae*.

  Prevalence of invasive infection of *H. influenzae* is decreased by the wide implementation of vaccination for children, but if healthcare providers have heavy exposure to infected patients (e.g., by resuscitation of patients, etc.), they can be considered as the candidates for chemoprophylaxis. Rifampin (600 mg po q24h for 4 days) is the first choice but is limited for nonpregnant personnel. Ceftriaxone or cefotaxime might be an alternative regimen. In contrast, ampicillin, cefaclor, trimethoprim/sulfamethoxazole, and erythromycin are thought to have insufficient effects to eradicate colonization.

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Chapter 5
Fluid Management for Neurocritical Care

Akira Utagawa

Abstract Fluid management in neurocritically ill patients has an impact on the neurological outcome. The blood-brain barrier (BBB) plays an important role in brain volume regulation, because an intact BBB is only water permeable and electrolyte filtration is strictly regulated. In contrast, BBB disruption leads to impaired autoregulation and induces an increase in transcapillary hydrostatic pressure (P_C). Therefore, the control of P_C may be an important therapeutic target. In clinical practice, intensivists should pay attention to the fluid osmolality before infusion. In fact, physiological plasma osmolality is 288 ± 5 mOsm/kg, whereas the osmolality of 4% albumin is only 260 mOsm/kg, which represents a hypotonic solution. Infusing such a hypotonic fluid under a disrupted BBB may result in a brain edema. Therefore, albumin administration in patients with acute brain injury should not be recommended routinely. Furthermore, although many investigations and meta-analysis with respect to osmotherapy were published, its beneficial evidence on outcome was not yet shown to be reliable. In both the resuscitation and maintenance phases, the most recommended fluid to be used in neurocritical care is simply the crystalloid. Additionally, hemodynamic monitoring is necessary for patients with acute brain injury, as the volume status is correlated to the neurological outcome. Finally, both the transpulmonary thermodilution and the arterial pulse contour analysis techniques seem feasible to guide fluid management for neurocritical care.

Keywords Brain injury · Blood-brain barrier · Hydrostatic pressure · Osmolality Osmotherapy · Fluid responsiveness

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5.1 Introduction

The aim of fluid management in neurocritical care is to both maintain the adequate organ blood flow and to deliver oxygen and nutrients to the brain and the other organs. Recent data show that fluid management in neurocritically ill patients has an impact on neurological outcome. However, compared to general critically ill patients, fluid management in neurocritically ill patients has several distinctive features: (1) the intact BBB strictly regulates fluid balance; (2) fluid osmolality is an increasingly important issue after BBB disruption; (3) the term of euvolemia is subject to interpretation; (4) fluid management is context-sensitive; (5) the transpulmonary thermodilution (TPT) technique seems feasible to guide fluid management.

In this chapter, the author tries to address fluid management in neurocritical care by tackling the abovementioned matters.

5.2 Principles Underlying Brain Volume Regulation

5.2.1 Blood-Brain Barrier

The brain's most important anatomical characteristic is its surrounding rigid cranium, which leaves only a minor space for brain expansion. Intracranial pressure (ICP) dynamics are regulated by the contributing volumes that are the cerebral blood volume (CBV), the cerebrospinal fluid (CSF) volume, and, most significantly, the brain tissue volume itself. Brain volume regulation is mainly obtained by controlling the fluid exchange across the capillary endothelium. In fact, in all extracranial organs, capillaries are passively permeable to smaller molecules, including Na^+ and Cl^- ions, and to some extent also to larger molecules, such as proteins. The permeability of BBB to Na^+ and Cl^- is 1000 folds lower than that of peripheral microvessels, and it plays a crucial role for the brain water shift [1]. In contrast, electrolytes and larger molecules cannot passively cross the normal BBB. Hypotonic fluids administration causes water shifts to the interstitium as the BBB is only water permeable. However, neurons can compensate for these fluid shifts through active depression of intracellular osmotic solutions, which causes a reactive shrinkage.

In contrast, both electrolytes and some larger molecules can passively cross a disrupted BBB. Acute brain injuries (ABI), including traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), ischemic stroke, intracranial hemorrhage, sepsis associated encephalopathy, and post cardiac arrest syndrome (PCAS), promote BBB disruption. In fact, various permeability-promoting inflammatory substances released after ABI are involved in the BBB disruption. While a disrupted BBB may be essential for the development of the vasogenic brain edema, the cytotoxic brain edema is caused by a cell membrane damage induced by hypoxia, cytokines, and reactive oxygen species. Hypoxia is presumed to be an important trigger of

cytotoxic brain edema, and it may also deteriorate the ICP via increasing the interstitial osmotic pressure from both the cellular and molecular disintegration, including transcapillary filtration [2].

An imbalance in the Starling fluid equilibrium, which is explained by the increased P_C and/or decreased transcapillary oncotic pressure (P_{onc}), will promote filtration. When the BBB is intact, the filtrate is only comprised of water; therefore, the filtration terminates soon, as the water filtrated into the interstitium both decreases the interstitial osmotic pressure through dilution and generates an absorbing osmotic counter-pressure. In contrast, in the disrupted BBB, passive electrolyte filtration continues until an elevation in the ICP is reached. In addition, impaired autoregulation alters the vascular tone in the injured brain, leading to an increase in the arterial inflow pressure (P_A) and to a subsequent increase in the P_C.

5.2.2 The Starling Fluid Equilibrium

Although normal tissue pressure of extracranial organs is about 0–2 mmHg, the normal intracranial pressure is 8–11 mmHg. Previous experimental studies used the plethysmograph to help intensivists understand the relation between the P_C and intracranial hypertension [3].

The venous pressure right outside the dura (P_V) is close to 0 mmHg in the upright position. In contrast, a pressure fall exists in veins between the subdural and extradural space, which generates a passive subdural venous collapse (PSVC) prior to the veins leaving the brain (Fig. 5.1) [4, 5]. This PSVC was shown to have a subdural venous outflow vascular resistance (R_{out}). Subdural passive venous outflow pressure right before PSVC (P_{out}) and tissue volume do not change as long as the P_V is below the brain tissue pressure (P_{tissue}). However, when the P_V increases above the P_{tissue}, the protecting PSVC is no longer present and P_{out} increases. Subsequently, both the P_C and tissue volume increase, while the cerebral blood flow is reduced due to a reduction in perfusion pressure.

Intracranial hypertension caused by the vasogenic brain edema may be much higher than the imbalance in Starling fluid equilibrium following both the increase in the P_C and the decrease in the P_{onc}. This phenomenon is explained through plethysmograph studies, as follows. The disturbance in the Starling fluid equilibrium following the BBB breakdown initiates the filtration and the slow increase in ICP, which causes the rise of the pressure gradient ICP-P_V, leading to an elevation in the P_{out}, which is transferred to the capillaries retrogradely. The increasing P_C results in further filtration and greater ICP elevation. Previous experimental studies demonstrated that the highest increase in the ICP due to the vasogenic brain edema is eight times larger than the initial imbalance between the P_C and the P_{onc} [5].

Under such an intracranial hypertension, the brain tissue may compress or collapse both capillaries and venules. This venous congestion may lead to a more severe ICP elevation. Additionally, outflow obstruction also contributes to blood

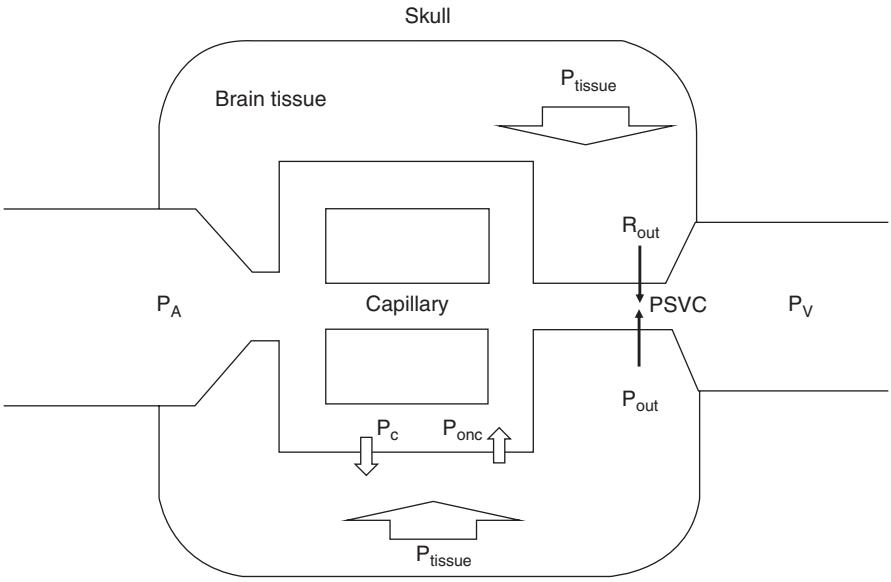

Fig. 5.1 Schematic representation of the cerebrovascular components and their associated physiological variables: arterial inflow pressure (P_A), extracranial venous pressure (P_V), transcapillary hydrostatic pressure (P_C), transcapillary oncotic pressure (P_{onc}), passive subdural venous collapse (PSVC), subdural passive venous outflow pressure (P_{out}), subdural passive venous outflow resistance (R_{out}), and brain tissue pressure (P_{tissue})

stasis. Considering that vessel lumina contain leukocytes-platelet aggregations, endothelial cell injury, and microthrombi, it was suggested that microcirculation disturbance contributes to the secondary brain injury.

The balance between arterial blood inflow and venous outflow has an important role in brain homeostasis. Therefore, when this balance is impaired, aggressive fluid administration causes overflow, ICP elevation, and worsen patient outcome. Consequently, the reduction in transcapillary hydrostatic pressure may be one of the therapeutic targets for refractory intracranial hypertension in neurocritical care. In fact, the P_C may be decreased through precapillary vasoconstriction. Even though this agent is expected in CBF reduction, these interventions may aggravate the secondary brain injury and dysfunction of other organs (e.g., ARDS, AKI). Barbiturate therapy reduces the ICP by inducing precapillary vasoconstriction; furthermore, the reduction in cerebral energy metabolism is also a major cause of vasoconstriction. However, considering that the CBF depression is changing in parallel to the reduction in energy metabolism, this vasoconstriction may not increase the risk of ischemia.

5.2.3 Venous Outflow Impedance in Multiple Compartments

In accordance with Hagen-Poiseuille's law, both the lower arterial pressure and the higher venous pressure will theoretically result in a lower perfusion pressure. Clinically, whether central venous pressure (CVP) elevation may impede venous

outflow from the brain and contribute to ICP elevation represents an interesting issue for intensivists. In fact, increased CVP may not be transferred to the brain tissue through PSVC protection as long as the ICP is higher than either the CVP or the positive end-expiratory pressure (PEEP) in the mechanical ventilation. Although intensivists tend to pay attention to the influence of high PEEP on ICP on a venous perspective via venous back-pressure, high PEEP may influence ICP on the arterial side. In fact, when cerebral autoregulation is intact, high PEEP impedes venous return, followed by both arterial hypotension with cerebral vasodilation and ICP impairment [6].

Adverse circumstances, including massive hypotonic fluid administration, recent brain injury with edema, and high PEEP under intra-abdominal hypertension, lead to an increase in the venous outflow impedance and deteriorate the brain compliance. Several experimental and clinical studies reported a correlation between intra-abdominal pressure (IAP) and ICP, for which the transmission of IAP to the thorax is suspected to lead to an increase in CVP and venous outflow impedance from the brain [7, 8]. In the case of an abdominal trauma with severe TBI, an abdominal insufflation for laparoscopy with mechanical ventilation showed the elevation in ICP [9].

5.3 Properties of Solutions

In the clinical practice, intensivists should distinguish between osmolarity (in mOsm/L) and osmolality (in mOsm/kg). In fact, osmolarity is obtained by calculating the sum of all the dissociable particles, whereas osmolality refers to the amount of osmotically active solutes and is directly measured by an osmometer through the freezing point depression method. Considering the incomplete dissociation of soluble molecules, osmolality is lower than osmolarity in administered solutions. Table 5.1 shows the characteristics of available fluid preparations. Physiological

Table 5.1 Characteristics of commonly used fluid preparations

	Theoretical osmolarity (mOsm/l)	Measured osmolality (mOsm/kg)	Tonicity
Plasma	291	287	Isotonic
NaCl 0.9%	308	286	Isotonic
Dextrose 5%	278	290	Hypotonic in vivo[a]
Ringer's lactate	276	256	Hypotonic
Ringer's acetate	276	256	Hypotonic
Plasmalyte®	294	273	Hypotonic
6% HES 130/0.4 in normal saline	308	304	Hypertonic, slightly
6% HES 130/0.4 in buffered solution	286	283	Hypertonic, slightly
Albumin 4%	269	260	Hypotonic
Albumin 25%	312	312	Hypertonic

[a]Since glucose is quickly metabolized, dextrose solutions behave hypotonically in vivo

plasma osmolality is 288 ± 5 mOsm/kg, whereas, for example, the osmolality of 4% albumin is only 260 mOsm/kg, representing a hypotonic solution. Therefore, infusion of such a hypotonic fluid following BBB disruption may induce brain edema.

5.3.1 Crystalloid

A normal saline solution is recommended to treat ABI patients, considering that no benefits of using other solutions in the acute phase are known.

However, massive infusion of normal saline solution may lead to adverse effects, as follows: (a) hyperchloremic acidosis, (b) renal dysfunction following interstitial edema, (c) reduced glomerular filtration following renal arterial vasoconstriction [10, 11], (d) dilution coagulopathy, (e) hyperchloremia-induced inflammatory response [12, 13].

Additionally, a negative linear relationship between the amount of chloride administration and base excess exists [14]. In a 70 kg patient, the massive infusion (9 L) of normal saline decreases the base excess by 10 mmol/L.

5.3.2 Balanced Crystalloids

In all balanced crystalloids (BC), cations are buffered by anions, such as lactate, acetate, citrate, or malate, to decrease the chloride concentration. Compared to normal saline solutions, the BCs electrolyte composition is similar to that of the plasma. Therefore, isotonic BC is expected to reduce hyperchloremic acidosis and not to aggravate intracranial hypertension [15]. Additionally, direct irrigation on an injured brain by a normal saline solution may lead to neuronal damage due to a decrease in pH and rapid electrolyte disorders in the cerebral interstitial fluid. Therefore, the use of BC may prevent these deleterious effects [16].

5.3.2.1 Citrate

Although citrate is metabolized in the liver, its metabolic rate may be impaired during shock, hypothermia, and liver dysfunction. Considering that post-traumatic coagulopathy was more frequently reported in patients with isolated TBI when compared to patients' injuries without TBI, it can be concluded that severe TBI occurs from coagulopathy which develop within the first 24 h. Citrate, contained in some BCs, binds ionized calcium in the blood and induces coagulopathy. Massive blood transfusion shows similar coagulation disorders due to the high citrate concentration. In the case of severe TBI accompanied by

hemorrhagic shock, when the BC with citrate is infused massively, the control of ionized calcium was strongly recommended in some guidelines [17].

5.3.2.2 Lactate

Lactate is mainly metabolized in the liver. Given that 70% of the infused lactate is metabolized for glyconeogenesis, the exogenous lactate may be a fuel for the brain in situations of increased energy demand. In contrast, hyperglycemia is promoted by infused lactate. Under the conditions of shock or severe acidosis (pH < 7.1), the lactate metabolism is suppressed. Additionally, tissue hypoxia is aggravated, the reason why oxygen consumption is accentuated by lactate degradation.

5.3.2.3 Acetate

Even though patients suffered from shock, acetate is rapidly metabolized in the skeletal muscles, myocardium, kidney, and liver. During the process of acetate metabolism, the amount of carbon dioxide production is low; therefore, it would not affect hyperglycemia. Massive BC containing acetate (2–4 L within 1 h) may promote both a vasodilation-induced hypotension and an alteration of myocardial contractility due to ATP production suppression.

5.3.2.4 Evidence of BC

Although the adverse effects of BC have been reported to be fewer when compared to normal saline solutions, an absence of evidence with respect to the predominance of long-term prognosis is present. Therefore, further studies are required on the matter.

5.3.3 Hypertonic Saline Solutions

In previous experimental studies, hypertonic saline infusions resulted in a significant improvement of outcome associated with a reduction in the inflammatory response [18]. Hypertonic saline solutions are, in fact, suspected to reduce the expression of proinflammatory cytokines [19]. However, although hypertonic saline solutions were demonstrated to decrease the ICP, a significant improvement in the neurological outcomes was not found [20, 21]. Consequently, alternative guidelines do not recommend using hypertonic saline solutions routinely.

5.3.4 Albumin

Albumin is a negatively charged plasma protein, with a molecular weight of 69 kDa, which is commercially available in different concentrations: hypotonicity (4–5% albumin) and hypertonicity (20–25% albumin).

The Saline versus Albumin Fluid Evaluation (SAFE) randomized study administered to critically ill patients either the normal saline solution or 4% albumin. This study did not provide any evidence in support of the usage of 4% albumin [22]. Additionally, the SAFE-TBI study showed a less favorable outcome for TBI patients treated with 4% albumin [23]. Normal saline solutions have an osmolality of 286 mOsm/kg; in contrast, the albumin used in this study had an osmolality of only 260 mOsm/kg. Therefore, the albumin investigated in the SAFE/SAFE-TBI study was a significantly hypoosmotic solution. Therefore, there is no reliable evidence that albumin is harmful for patient with TBI, considering that the SAFE-TBI study might only suggest that hypoosmotic solutions were deleterious in TBI patients [24]. Albumin is also expected to assume a neuroprotective role due to the improvement in penumbra microcirculation during ischemic stroke [25]. However, the albumin present in acute stroke (ALIAS) multicenter clinical trials could not provide any evidence in support of the usage of albumin. As a matter of fact, adverse incidents, including symptomatic intracranial hemorrhage, congestive heart failure, and pulmonary edema, occurred in patients infused with albumin [26–29]. For this reason, 25% albumin is not recommended for patients with acute ischemic stroke.

5.3.5 Synthetic Colloids

5.3.5.1 Dextrans

Dextrans are long-chain glucose polysaccharides of various relative molecular weights (MW). For example, the MW of dextran 40 and 70 is 40 kDa and 70 kDa, respectively. Dextrans are retained in the intravascular space and act as a plasma expander, similarly to albumin. They are mainly eliminated through the kidney, with the rest of it (20%) being metabolized by dextranase. Unlike albumin, dextran 70, when given in large amounts (over 1.5 g/kg), suppresses platelet aggregation and facilitates fibrinolysis.

5.3.5.2 Hydroxyethyl Starch (HES)

HES are often used as plasma volume expanders following acute blood loss. The mean MW ranges between 70 and 670 kDa, depending on the difference in HES preparations. Their elimination depends on the molar substitution degree. Molecules smaller than 60 kDa are excreted in the urine, while large molecules are metabolized by plasma α-amylase. However, the detailed metabolism remains unclear.

HES were demonstrated to both have increased rates of adverse effects, including coagulopathy and AKI, and to decrease long-term survival. Therefore, it was recommended not to use HES routinely for critically ill patients [30].

5.4 Fluid Strategy

All intensivists should perpend the goal of fluid maintenance from the standpoints of both cerebral perfusion and cardiovascular hemodynamics. With regard to cerebral perfusion, hypovolemia may be defined as an intravascular volume that is insufficient to maintain an adequate cerebral perfusion. In contrast, euvolemia may be defined as an intravascular volume that can deliver adequate oxygen and nutrients to the cerebral demand and maintain the brain function. Multimodality neuromonitoring helps intensivists to assess the brain function in brain-injured patients [31]. Although the definition of hypervolemia is very complicated, it may be defined as an intravascular volume that increases the P_C and might induce to venous congestion with excessive extravascular fluid retention, resulting in alteration in oxygen diffusion to the cells.

5.4.1 Importance of Cumulative Fluid Balance

Vigilant fluid balance assessment is advised to guide fluid administration. Recent guidelines in the ABI recommend using daily and cumulative fluid balances to guide the volume status. In fact, insufficient fluid administration in the early phase of a TBI may lead to cerebral hypoperfusion. However, several studies documented that a fluid balance lower than 0.5–0.8 L during the 96 h following the TBI is independent of poor outcomes [32, 33]. In the SAH, euvolemia is recommended to prevent delayed cerebral ischemia (DCI), and aggressive fluid administration for hypervolemia was not found to have any benefit on CBF augmentation and neurologic outcome. Excessive fluid balances were instead associated with systemic complications, including congestive heart failure, pulmonary edema, and renal dysfunction. A lot of investigations of the goal-directed therapy corroborate the association between a more aggressive fluid loading and adverse outcomes in both SAH and TBI patients.

5.4.2 Renal Congestion Due to Fluid Overload

The etiology of renal dysfunction associated with congestive heart failure is interpreted as a renal perfusion impairment due to low cardiac output. The increase in both CVP and right atrial pressure is now suspected to be the independent predictive factors of glomerular filtration impairment following renal dysfunction [34–36].

For these reasons, the pathology of renal venous hypertension caused by renal congestion may play a crucial role in renal dysfunction. When renal venous pressure begins to increase, renal arterial vasoconstriction occurs in order to maintain the glomerular filtration. Given that the kidney is surrounded by a rigid capsule, the gradual volume expansion leads to an elevated tissue pressure, which is followed by capillary and renal tubular compression. Such an increase in venous pressure promotes tissue edema and results in tissue hypoxia, as the oxygen is impaired to diffuse into the cells. Renal venous hypertension induces both Na^+ and water retention by activating the renin-angiotensin-aldosterone system [37]. In this context, such cases identified with oliguria do not require fluid loading.

5.4.3 Osmotherapy

Osmotherapy with mannitol has been used as a treatment for ICP elevation and is a main component of most neurocritical care guidelines. In order to start osmotherapy, comprehensive deliberations, including a combination of neurological worsening and ICP elevation over 25 mmHg, are needed. However, although many investigations and meta-analysis related to osmotherapy were published, the beneficial evidence on outcome was not yet found to be reliable [38].

As a matter of fact, osmotherapy leads to ICP reduction; however, it has adverse effects, especially when analyzing mannitol, including a rebound increase in ICP, electrolyte disturbances, and renal failure. The pathophysiology of the rebound increase in ICP after mannitol infusion is explained as follows: (a) an osmotic fluid filtration force is generated by extravascular accumulation of mannitol following the infusion termination and (b) P_C increases following the ICP (P_{tissue}) reduction. Brain edema and expansion of the swollen brain after decompressive craniectomy are suggested to be guided by the same mechanism [39].

5.4.4 Sodium Imbalance After Acute Brain Injury

The disturbance in serum sodium concentration is frequently observed in patients with ABI. Especially, hyponatremia is associated with increased mortality [40, 41]. Both the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and the cerebral salt wasting syndrome (CSWS) were recognized as ABI-related hyponatremia. Not only persistent hyponatremia but also rapid correction of hyponatremia lead to neuronal demyelination followed by unconsciousness, seizures, and coma in severe cases.

The fluid status is a fundamental for differentiating between the SIADH and the CSWS (Table 5.2). In fact, the SIADH pathology is an inappropriate secretion of antidiuretic hormone following increased atrial and brain natriuretic peptides, whereas the CSWS presents an inappropriate urinary salt elimination accompanied

Table 5.2 Characteristics of the serum sodium abnormality in acute brain injury

	SIADH	CSWS
Cause	Oversecretion of ADH	Renal sodium transport abnormality
Serum level of sodium	Hyponatremia	Hyponatremia
Urinary osmolality	Elevated	Elevated
Urinary sodium concentration (mEq/l)	Normal or elevated(>25)	Elevated (>25)
Urine output	Decreased	Decreased
Urine specific gravity	>1.010	>1.010
Extracellular volume	Increased	Decreased
Treatment	Fluid restriction, sodium replacement	No fluid restriction, sodium replacement

by hypovolemia. The SIADH is therefore defined as a hypotonic hyponatremia with euvolemia or hypervolemia; in contrast, CSWS is referred to as a hypotonic hyponatremia with hypovolemia. Accordingly, the SIADH requires sodium supplementation with water restriction, whereas the CSWS necessitates both sodium and water supplementation instead.

5.4.5 Pitfall of Insulin Infusion

In the case of a constant unexpected fluctuation of the blood glucose concentration in neurocritically ill patients infused with insulin, the absorbance of insulin to infusion-set may be one of the important causes. Therefore, intensivists should pay attention to the fact that both the polyvinylchloride (PVC) surfaces of the fluid containers and the infusion-sets lead to a decreased amount of insulin that reaches the patients. In fact, many investigators demonstrated that insulin absorbance occurs at the surfaces of the infusion-sets, who increased the primary dosage of insulin added to the PVC infusion solutions. The selection of a polyethylene infusion-set seems to be beneficial to overcome this problem [42]. Additionally, factors such as storage temperature, concentration, and infusion rate also influence the extent of adsorption [43].

5.4.6 Fluid Strategy Recommendation in Neurocritical Care

The current best clinical practice in neurocritical care is summarized as follows:

1. Resuscitation phase.
   (a) Crystalloids are recommended as the first-line solution.
   (b) Adverse effects of balanced crystalloids may be less frequent when compared to normal saline solutions.

(c) The use of hypotonic albumin (4% albumin) is not recommended.
(d) The use of 25% albumin is not recommended.
(e) The use of synthetic colloids is not recommended.
(f) The use of hypertonic saline or synthetic colloids in patients with hypotension is not recommended.

2. Maintenance phase.

(a) Crystalloids are recommended as the maintenance fluids.
(b) The use of glucose containing hypotonic solutions, albumin, and synthetic colloids is not recommended.
(c) The target of volume management is euvolemia.
(d) Both hypervolemia and hypovolemia are not recommended.

3. Monitoring.

(a) To optimize fluid replacement, arterial blood pressure and fluid balance are recommended.
(b) The use of central venous pressure (CVP) alone for considering the hemodynamics is not recommended.
(c) CVP does not correlate to cerebral blood flow.

5.5 Advanced Monitoring Technique for Volume Status

Critically ill patients with ABI are frequently associated with hemodynamic instability due to neurogenic myocardial stunning (Takotsubo cardiomyopathy), neurogenic pulmonary edema (NPE), neurogenic shock, hemorrhagic shock with polytrauma, and pre-existing disease, including chronic heart failure and arrhythmia. In the scientific field, both hemodynamic monitoring and fluid responsiveness have been investigated vigorously in patient with ABI. In addition to arterial blood pressure and fluid balance, multimodal monitoring helps intensivists to optimize fluid replacement.

5.5.1 Noninvasive Monitoring

Transthoracic echocardiogram in patients with a trauma may lead to an increase in favorable outcome through protecting overhydration [44].

The respiratory diameter variation of both the inferior vena cava (IVC) and the superior vena cava (SVC) represents noninvasive monitoring for speculating on the fluid responsiveness. However, accurate SVC measurements require a transesophageal echocardiogram, which becomes an invasive technique. These monitoring are useful, not only for the ventilated patients but also for patients suffering from

arrhythmia. In the case of postabdominal surgery and intra-abdominal hypertension, the data are not reliable. In neurocritical care, the respiratory diameter variation of IVC may be a useful predictor of fluid responsiveness in patients with subarachnoid hemorrhage instead [45].

5.5.2 *Invasive Monitoring*

Static parameters, including the CVP or cardiac filling pressure, failed to predict the hemodynamic response to volume challenge [46].

In contrast, *dynamic* parameters of volume status relying on the transpulmonary thermodilution (TPT) technique seem feasible to guide fluid management. The recent device technology is based on a combination of the TPT and the arterial pulse contour analysis. This technology provides continuous measurements of cardiac contractility, volumetric preload, afterload status, fluid responsiveness (e.g., stroke volume variance, SVV; pulse pressure variance, PPV), and interstitial fluid balance in the lungs. This method allows both the differentiation between permeability and hydrostatic pulmonary edema and the guidance of fluid management.

The volume replacement therapy monitored by the TPT technique in patients with SAH led to an increase in favorable outcome and a decrease in complications, such as the DCI and pulmonary edema [47, 48]. TPT studies demonstrated that the euvolemic hypertension strategy may be most suitable in maintaining the CBF, without compromising brain and systemic oxygenation in patients with SAH.

Previous studies reported survivors to have a higher cardiac output (CO) after the trauma when compared to non-survivors [49, 50]. The hypotension in patients with severe TBI may be caused by either the decrease in CO following the reduction in myocardial contractility or the hypovolemia as a result of dehydration. Additionally, hypotension may be produced by the decreasing vascular tone following injury to the diencephalic region. The hemodynamic evaluation by TPT reported that 30% of patients with severe TBI had a hypodynamic state, with high systemic vascular resistance. They showed hypovolemia with a significant decrease in preload. Although the SVV can be useful for predicting the fluid responsiveness [51], the combined use of TPT and ICP monitoring in severe TBI patients may be a good method to maintain an optimal CPP and reduced hypervolemia-related complications. Additionally, the TPT may help both maintain an adequate intravascular blood volume and avoid the vasoconstrictor administration which may induce P_C elevation in both the injured BBB and the pulmonary interstitium. In case of a neurogenic pulmonary edema following severe TBI, the TPT may support the evaluation of both the systemic and pulmonary fluid status [52, 53].

A recent systematic review on advanced hemodynamic monitoring in ABI proved these monitoring to be widely applied; however, intensivists should recognize the important limitations of the SVV/PPV monitoring below mentioned.

(a) Spontaneous breathing decreases accuracy. Mechanically ventilated patients are desirable. The use of a short-acting paralytic agent to eliminate spontaneous breathing is preferable.
(b) A tidal volume over 8 ml/kg is needed.
(c) The results from patients with sustained cardiac arrhythmia or atrial fibrillation are not reliable.
(d) The results from patients with right ventricular dysfunction are not reliable.

5.5.3 Fluid Responsiveness

Hemodynamic monitoring is necessary for patients with ABI, considering that the volume status is correlated to the neurological outcome. Given that uncontrolled volume overload and strict fluid administration appeared to be harmful, intensivists are required to assess for the intravascular volume status. Recently, the topic of volume responsiveness was related to the need for fluid administration. A simple clinical technique is fluid challenge, as the change of stroke volume (SV) or CO after fluid challenge is an indicator of fluid responsiveness. The Frank-Starling curve is an important finding to understand fluid responsiveness; the increasing ventricular filling pressure through the increase in venous return leads to stroke volume augmentation.

5.5.3.1 Fluid Challenge

Fluid challenge is easy and can be performed repeatedly. Fluid challenge by 6 ml/kg (250–500 ml) of crystalloid for 15 min is generally recommended; the 15% increase in SV is determined as the fluid responder. However, this method may induce overhydration and worsen the prognosis when performed on patients repeatedly. For this reason, the mini-fluid challenge is introduced, in which a 100 ml colloid is infused in 1 min. It is yet to be defined whether the results from such a small preload are reliable.

5.5.3.2 PLR Test

The passive leg raise (PLR) test is a useful clinical bedside test that overcomes some of the limitation encountered with the TPT monitoring. As the SLR test is likely to lead to self-blood infusion, no risk of overhydration is present. In addition, this method does not have an effect on vascular resistance due to hemodilution [54, 55]. However, the effectiveness of the PLR has not been yet evaluated in the neurocritical care field. It is not clear whether a rapid change in body position might lead to an impairment of ICP in patients with compromised brain tissue compliance.

5.6 Conclusion

Considering that patients who suffered from ABI may be experiencing multiple traumas and chronic complications, including hypertension, chronic heart failure, and chronic kidney disease, fluid management is context-sensitive. During BBB disruption, avoidance of intracranial hypertension is crucial to recognize both the fluid osmolality and the pathophysiology of the transcapillary hydrostatic pressure. All intensivists are concerned about the clinical question addressing whether a patient needs fluid and vasoconstrictors. In fact, uncontrolled volume overload and excessive administration of vasoconstrictors may lead to severe complications, such as pulmonary edema. Additionally, it is hard to maintain both the euvolemia and an optimal CPP. Therefore, hemodynamic multimodal monitoring combined with neuro-monitoring may help intensivists plan the fluid management. Furthermore, appropriate fluid therapy can improve the unstable hemodynamics and avoid unnecessary vasoactive agents.

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Chapter 6
The Evaluation and Management of the Blood Glucose for the Intracranial Disease

Takashi Moriya

Abstract The usefulness of intensive insulin therapy to keep blood glucose levels tightly controlled has been reported. Since then, the usefulness of intensive insulin therapy has been studied in various serious diseases including sepsis that should be controlled in an intensive care setting. Studies in central nervous system disease have involved traumatic brain injury or subarachnoid hemorrhage with ruptured cerebral aneurysm. It is clear that hyperglycemia leads to poor prognosis; however, as to how tightly blood glucose should be controlled in an intensive care setting, some researchers have described that blood glucose control levels should be slightly higher in patients with central nervous system disease than in those with sepsis or other illnesses not complicated by central nervous system disease. It is difficult in the clinical setting to determine to what extent low blood glucose levels are acceptable without any sequelae. Monitoring of brain tissue using microdialysis shows that the institution of intensive insulin therapy appears to lead to the elevation of concentrations of extracellular glutamate, an excitatory amino acid, and lactate/pyruvate ratio, which is highly sensitive and specific to cerebral ischemia. Microdialysis has the potential to gain maximum benefit without these abnormalities in achieving blood glucose control.

Keywords Stress-induced hyperglycemia · Intracranial lesion · Intensive insulin therapy · Conventional insulin therapy · Glucose transporter protein · Microdialysis

6.1 Introduction

Hyperglycemia associated with seriously ill patients commonly exhibits insulin resistance and is well known to exacerbate prognosis regardless of the presence or absence of diabetes [1]. Its mechanism is associated with indicated oxidative stress

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[2] and increased neutrophil adhesion capacity to vascular endothelial cells [3]. On the other hand, insulin used to manage hyperglycemia promotes bacterial infection and wound healing [4], protein synthesis in muscle tissue via insulin-like growth factor-1 and growth hormone [5], and anti-inflammatory action [6] by intercellular adhesion molecule-1 production inhibition around ischemic lesions. Insulin activity may have the potential to improve prognosis in patients with hyperglycemia. However, in insulin treatment for stress-induced hyperglycemia or insulin-resistant hyperglycemia in the twentieth century, no obvious indicators with clear medical significance were observed. At the beginning of this century, Van den Berghe et al. [7] reported significant results of a 42% reduction in the mortality rate of patients entering the surgical intensive care unit (ICU) by intensive insulin therapy (IIT) and control of blood glucose levels to 80–110 mg/dL with insulin, emphasizing the necessity for blood glucose management [8]. Later, studies on various clinical settings were reported. However, approval/disapproval of the effect of IIT is still debated. In this review, we aim to provide information on the current status of blood glucose assessment of central nervous system (CNS) diseases and of IIT obtained from recent clinical research.

6.2 Glucose Metabolism and Insulin Effect on the Central Nervous System

Glucose supply from systemic circulation to the CNS is controlled by the glucose transporter protein (GLUT) [9] of vascular endothelial cells and neurons in the blood-brain barrier and glia cell membrane. Neurons have an isoform I of GLUT, and endothelial cells and neurons have isoforms I and III. GLUT-I affects glucose supply to maintain a glucose concentration slightly higher than that in the blood in systemic circulation, and the GLUT-III also accelerates glucose supply during hypoglycemia [10]. Due to glucose metabolic demand and the glucose utilization rate, expression of GLUT changes.

In traumatic brain injury, promotion of glucose transport from the blood to the extracellular space of the brain can be confirmed by an increase in the expression of GLUT-I located in vascular endothelial cells [11], and at several hours after injury, both the utilization and metabolic rate in neurons simultaneously increase and sometimes cause functional dysfunction. In the analysis using cortical surface electroencephalogram and microdialysis (MD), extracellular glucose concentration tends to be low as the depolarization record increases [12]. Low extracellular glucose values were also found in secondary brain injuries such as increased intracranial pressure. Under these circumstances, glucose supply is necessary due to an increased demand for glucose in the CNS. However, it is highly probable that adequate glucose supply to the CNS is impaired even when glucose in the systemic blood is sufficient.

In the CNS, the existence of a system in which insulin found in muscle/fat tissue promotes glucose uptake in cells by transporter translocation is suspected. Neurons themselves have insulin receptors, but insulin alone does not react to increased uptake of glucose, and most glucose uptake and metabolism are not affected by insulin [13]. In addition to the intracranial environment, insulin is also involved in decreased intracranial pressure activity [14] and the maintenance of perfusion pressure.

6.3 Blood Glucose Management for Traumatic Brain Injury

In the subgroup analysis of head injuries [7], a shorter rehabilitation period was observed in the IIT group. In response to the results of this study, comparison between an IIT group where blood glucose level is controlled to 80–120 mg/dL and a conventional insulin therapy (CIT) group managed to 220 mg/dL or less was carried out, and the advantages and dangers were considered [15]. The ITT group showed a shorter stay in the ICU (CIT group, 10 days, and IIT group, 7. 7 days), but no other significant difference was observed. Almost all cases (99.0%) in both groups showed at least one hypoglycemia episode, and the number of hypoglycemic events significantly increased (CIT group, 7 times; IIT group, 15 times). If the risk of hypoglycemia can be reduced, a sufficient neuroprotective effects can be achieved. But in the ICU, it is difficult to determine clinical symptoms of hypoglycemia due to the use of sedatives or respirators, and in many cases, low-dose corticosteroids are used, resulting in low evidence levels. In current study designs, the value is defined as a hypoglycemic event, and the optimal interval for blood glucose varies depending on the research.

Furthermore, when the usefulness of IIT (80–110 mg/dL) was compared with CIT (200 mg/dL or less) [16], the IIT group significantly showed a decrease in infection rate, a shorter ICU stay, and a favorable GOS (Glasgow Outcome Scale) after 6 months. Hypoglycemic events with blood glucose less than 40 mg/dL were observed 11 times (four cases) in the IIT group and five times (three cases) in the CIT group. There were only a total of seven cases (2.9%), which showed meaningful results not only in safety but also in prognosis. Hyperglycemia occurring in invasive stress after head trauma is usually more severe and worsens neurological prognosis. In the CIT group, 81.5% of cases showed a blood glucose level of 200 mg/dL at admission, and good prognosis was achieved for 22.4%. In the IIT group, the blood glucose level of 200 mg/dL or more at admission was close to 82.5%, but good prognosis was 29.1%, a significant increase for the IIT group. Proactive administration of insulin may result in direct and long-term effects that are not related to glucose toxicity or glycemic control.

In a study on brain MD which considered brain metabolic circulation during IIT [17], extracellular glucose concentration decreased and lactic acid/pyruvic

acid ratio increased. Introduction of IIT from the acute phase worsened glucose metabolism in the CNS and led to an increase in mortality rate. In IIT, extracellular glucose concentration decreased, but local glucose metabolism rate did not change. In addition, the extracellular glutamate and lactate/pyruvate ratio increased, extracellular glucose concentration decreased, and the oxygen uptake rate increased [18]. Ultimately, fluctuation in cerebral metabolism led to somewhat worsened conditions, and significance for good prognosis was not observed. Consequently, slightly increasing the desired value of IIT, 80–110 mg/dL, may be required [19]. Furthermore, a narrow glucose control may be developed. In a recent meta-analysis, IIT did not improve long-term neurologic outcome [20, 21], mortality [20, 22], or infection rate [20]. In the background, IIT increased the risk of hypoglycemia [21, 22]. Prompt blood glucose control should be most appropriate under these circumstances. In both Japan and the United States of America, the most appropriate glucose management for severe traumatic brain injury is still unclear.

6.4 Blood Glucose Management for Subarachnoid Hemorrhage

Hyperglycemia due to various stresses, such as cerebral aneurysmal rupture, rerupture, acute hydrocephalus, and cerebral vasospasm, is very different from that due to stress reaction occurring in the early phase.

Pasternak et al. [23] examined the relationship between increased blood glucose after direct aneurysmal surgery, its subsequent neurological symptoms, and higher cerebral dysfunction. At 3 months of follow-up, significantly higher cerebral dysfunction was observed postoperatively for cases of blood glucose above 129 mg/dL during aneurysmal surgery and deterioration of neurological symptoms at intraoperative blood glucose above 152 mg/dL. Blood glucose assessment and management were more important from the perioperative phase of surgery.

In the blood glucose assessment of subarachnoid hemorrhage due to cerebral aneurysmal rupture, hyperglycemia at hospitalization and the perioperative period exacerbates neurological prognosis. In cases where hyperglycemia at 200 mg/dL or more was observed from onset to the 14th hospital day for 2 days or more, neurological prognosis after 10 months deteriorated about seven times [24]. According to meta-analysis [25], the need for a randomized trial to clarify not only the blood glucose evaluation during the perioperative period and the need to strictly control blood glucose are indicated.

Blood glucose assessment is important not only at hospitalization and the time of early postoperative management but also during vasospasm and from the 4th to 14th hospital day [26]. Blood glucose levels at hospitalization and up to day 14 were significantly higher in the group that developed symptomatic cerebral

vasospasm. Since hyperglycemia extends ICU stay and prognosis at discharge deteriorates, blood glucose management may become a therapeutic target in the future.

Hyperglycemia at hospitalization and on subsequent days was related to the complication rate and prognosis. Daily hyperglycemia correlated with low values of extracellular glucose concentration by brain MD. Furthermore, when presented with neurological symptoms due to cerebral vasospasm, MD monitoring in the vascular region showed a decrease in extracellular glucose concentration and an increase in the lactic acid/pyruvic acid ratio and the lactic acid/glucose ratio [27]. On the other hand, glucose of the blood and cerebrospinal fluid at this time did not decrease. In the future, criteria for optimal blood glucose management in the metabolic state of the brain during IIT may be determined using MD, and predicting blood glucose target values of the CNS may be possible.

A comparative study of a CIT (80–120 mg/dL) group and an IIT (220 mg/dL or less) group was carried out in order to clarify the usefulness of strict management of cerebral aneurysmal rupture for perioperative hyperglycemia. Vasospasm (31.5% and 27.6%) and mortality rate after 6 months (18% and 15%) did not significantly vary although infection rate (42% and 27% in CIT group and IIT group) improved [28]. In this study, no advantage in glycemic control at the perioperative stage of cerebral aneurysm by IIT was observed. Recent studies have shown the importance of blood glucose control of subarachnoid hemorrhage caused by a ruptured cerebral aneurysm and that hyperglycemia exacerbates neurological prognosis. In poor-grade SAH, extracellular glucose remains low, and insulin administration is associated with a reduction in brain glucose concentration independent of serum glucose level [29]. A study based on nutritional support and brain and serum glucose levels may be necessary. Due to the large range of factors, such as disease, pathology, severity, etc., application to IIT may be less advantageous. In Japan, the usefulness of intensive insulin therapy for severe stroke patients has yet to be clarified.

6.5 Blood Glucose Management for Central Nervous System Diseases

The importance of blood glucose management in cases of neurological surgery, regardless of individual disease, has been examined. In a randomized trial [30], the usefulness of IIT (80–110 mg/dL) for 14 days after surgery was compared to a CIT group (215 mg/dL or less). In the IIT group, infection rate decreased and ICU stay was shorter. Although incidence of a hypoglycemic (less than 50 mg/dL) event and the number of hypoglycemic events per patient were significantly higher, no significant difference in GOS after 6 months was observed. Whether hypoglycemia below

80 mg/dL (especially below 40 mg/dL) causes secondary brain injury is not known, but it did not affect neurological prognosis. Although the safety of IIT cannot be proven, blood glucose control after intracranial surgery has been shown to be important.

In cases of cerebrovascular disease, brain tumor, and traumatic brain injury where the blood glucose level was 150 mg/dL for 12 h or more after hospitalization, a randomized trial to compare an IIT group where blood glucose level was controlled to 80–120 mg/dL and a CIT group below 180 mg/dL was carried out [31]. In order to investigate the clinical effect of IIT, the incidence of hypoglycemia (80 mg/dL or less), ICU stay, infection rate, convulsion, and neurological status by GOS after 3 months were compared. Even with IIT, ICU stay (IIT, 9 days; CIT, 9 days) did not change, and no significant difference was observed for all items of this survey. Insulin treatment was blinded, and a limitation in blood glucose measurement techniques with the nursing staff on research design was indicated.

6.6 Brain Dysfunction Due to Hypoglycemia

Complications due to hypoglycemia are known to greatly affect the CNS. On-site ICU doctors, who manage these complications, controlled values of hyperglycemia to 120 mg/dL or more for adults, 150 mg/dL or more for children, and hypoglycemia to 40–80 mg/dL for both [32]. Pediatric ICU doctors pay more attention to hypoglycemia than general ICU doctors. Consequently, management by IIT was higher in adults. Even in Japan, where intensive care management is performed, actual clinical surveys are expected early.

During hypoglycemic challenge, intracerebral glycogen [33] is mobilized in large amounts and increases beyond normal in the temporal course between hypothalamic blood flow and invasive hormones that detect hypoglycemia [34]. However, most studies are based on normal volunteers, and the pathology of hypoglycemia and the extent of injury in cases with complications of CNS diseases are not known. Analysis of extracellular glucose, glutamate, and lactate/pyruvate ratio by MD for hypoglycemia occurring during IIT for CNS diseases may lead to elucidation of the pathophysiology of hypoglycemic encephalopathy associated with CNS diseases.

A correlation between hyperglycemia in the early phase in CNS disease and poor prognosis was confirmed. However, whether strict glycemic control by IIT is necessary has not been determined. MD may be useful in identifying pathologies associated with hypoglycemic complications by IIT.

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Chapter 7
Nutritional Support in Neurocritical Care

Kunihiro Shirai

Abstract In patients requiring neurocritical care, stimulation of metabolism/catabolism by excessive stress can aggravate malnutrition, infections, and neurological prognosis. For this reason, it is necessary to assess the nutritional risk in these patients through nutritional evaluation and to begin early enteral nutrition if the digestive tract is functioning. The target energy dose is calculated with a predictive equation or a rule of thumb (25–30 kcal/kg/day) or an indirect calorimetry, with the protein dose target level set at 1.2 g/kg/day or higher. However, underfeeding should be undertaken in the first week if the nutritional risk is low. In cases with a high nutritional risk, feeding at the level of at least 80% of the target goal should be attempted during the first 72 h while paying close attention to the refeeding syndrome. Because acute hyperglycemia can worsen the neurological prognosis and increase the risk of complications, insulin administration should be started if the blood glucose level rises to ≧180 mg/dL. Appropriate nutritional therapy contributes to a better prognosis.

Keywords Nutritional assessment · Nutritional risk · Early enteral nutrition Underfeeding · Glycemic control

7.1 Introduction

In patients requiring neurocritical care (e.g., cases of head injury, stroke, meningitis, and encephalitis), the energy consumed is high, due to enhanced metabolism and catabolism [1, 2]. In cases of traumatic brain injury (TBI), the energy requirement increases to 87–200% of the predicted metabolic rate during the first 30 days after injury because of stress-induced catecholamine, steroid hormone, and inflammatory mediator release [1]. Patients with stroke also show an increased energy requirement as a result of enhanced metabolism, just like patients with TBI [3]. Furthermore, energy consumption levels also change under the influence of factors such as deterioration

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of the consciousness level, presence of confusion or delirium, use of analgesics or sedatives, implementation of immobilization or early mobilization, etc. For these reasons, malnutrition has been reported to occur at an incidence of 6.1–62.0% after stroke and of 68% within 2 months after TBI, and early occurrence of dysphagia has been reported in 50% of these patients [4, 5]. Malnutrition in critically ill patients contributes to poor outcomes, including prolonged hospital stay, delay in discharge from the hospital, a higher incidence of complications (infection, etc.), and a higher mortality [6–8]. It is therefore essential to begin appropriate nutritional therapy at the appropriate timing, with administration of energy and protein in amounts needed corresponding to the condition of individual cases. To date, however, few studies have been conducted in patients requiring neurocritical care. Existing guidelines such as ASPEN (American Society for Parenteral and Enteral Nutrition)/CCM (Society of Critical Care Medicine, guideline 2016 [9]) and ESPEN (European Society of Clinical Nutrition and Metabolism, guideline 2018 [10]) cover critically ill patients with traumatic brain injury (TBI), stroke, trauma, sepsis, pancreatitis, burn, and so on.

7.2 Nutritional Assessment

In patients requiring nutritional therapy, usefulness of prior evaluation of the nutritional status by means of nutritional screening, such as by Nutritional Risk Screening (NRS), Malnutrition Universal Screening Tool (MUST), subjective global assessment (SGA), and NUTRIC (Nutrition Risk in the Critically Ill) score, has been reported [8, 11, 12]. In addition, biochemical tests such as measurement of the serum albumin, nitrogen balance, and anthropological parameters are also used as nutritional indicators, although these indicators do not always reflect the precise nutritional status, because the nutritional status can vary depending on the severity/features of the disease, type of underlying disease, treatment, and complications. It is therefore necessary to conduct comprehensive nutritional assessment on the basis of nutritional screening as well as collection of data on the pre-admission nutrient intake and nutritional condition, changes in body weight, underlying disease/complications, physical findings, disease severity, gastrointestinal functions, etc.

7.3 Route of Nutrient Administration and Timing of Its Start

The route of first choice for nutrient administration is the oral route. However, in patients requiring neurocritical care, the oral route is often impossible for reasons such as consciousness disturbance, dysphagia, and need for mechanical ventilation. In critically ill patients, enteral nutrition is superior to parenteral nutrition, in that it is associated with a lower incidence of infections, shorter ICU stay periods, smaller healthcare expenditure, etc. [13–15].

Enteral nutrition should therefore be adopted preferentially in all patients having a functioning digestive tract. Furthermore, Heyland et al. [16] conducted a meta-analysis of 16 RCTs in relation to early enteral nutrition administered within 24–48 h, reporting a significant reduction in the incidence of infections. Furthermore, a meta-analysis of studies on severe injury conducted by Doing et al. [17] revealed a reduction in the mortality associated with enteral nutrition. Furthermore, early enteral nutrition after stroke [18] or TBI [19–21] has been reported to be associated with improved outcomes, in terms of improved treatment efficacy, reduced risk for mortality, improved survival rate and better scores on the Glasgow Coma Scale, improved physical/cognitive function following rehabilitation, reduced incidence of infection and hyperglycemia, etc. In the field of neurology, ESPEN [22] recommends starting enteral nutrition within 72 h after severe stroke; also, ASPEN [9] recommends starting enteral nutrition within 24–48 h after TBI. In both ASPEN [9] and ESPEN [10], continuous enteral nutrition is recommended. Therefore, continuous early enteral nutrition should be proactively applied.

7.4 Setting of the Target Energy and Protein Intake

In critically ill patients, precise measurement of the energy requirement is difficult because of differences or changes in the extent of metabolism/catabolism enhancement depending on the severity/features of stress, type of underlying disease, and the therapeutic intervention. For this reason, measurement with an indirect calorimetry [23] or calculation with an equation for estimation (Harris-Benedict equation, etc.) or a rule of thumb (25–30 kcal/kg/day) has been conducted extensively. In recent studies, a rule of thumb (25–30 kcal/kg/day) has been used particularly frequently. Stress-stimulated increase of protein catabolism promotes the degradation of body protein and synthesis of positive acute-phase proteins. Increased vascular permeability results from cytokine-induced vascular endothelial injury, leading to extravascular leakage of proteins. The skeletal muscles of critically ill patients decrease by about 18% in muscle mass over 10 days, with the rate of decrease in the muscle mass accelerating as the number of organ failures increases [24]. Therefore, from the viewpoint of enhanced protein catabolism and new protein synthesis, reduction of protein anabolism through restriction of protein intake should be avoided, even during the first week after the event. Although no reports showing the appropriate protein requirement have been published, a protein intake level of 1.2–2.0 g/kg/day has been suggested in ASPEN [9], and a protein intake level equivalent to 1.3 g/kg/day has been recommended in ESPEN [10], based on the view that a protein intake level of 1.2 g/kg/day or more is necessary, when the protein loss for improvement of nitrogen balance is taken into consideration [25]. Therefore, the protein dose level should be at least 1.2 g/kg/day.

7.5 Target Amount of Energy During the First Week of the Acute Phase

During the first week after admission to the ICU, endogenous energy is consumed by enhanced metabolism/catabolism, while nutrients are less likely to be well-utilized under the influence of stress hormones, such as catecholamines. Rice et al. [26] conducted a comparison between trophic feeding (400–500 kcal/day) and full feeding (target dose level), reporting no difference in the prognosis between the two ways of feeding. Arabi et al. [27] compared permissive underfeeding (40–60% of the target level) with standard feeding (70–100% of the target level), reporting no difference in the mortality or incidence of infection associated with the two. A meta-analysis also revealed no difference, while a subgroup analysis demonstrated a better prognosis after underfeeding (33–66%) than after 90–100% feeding [28]. Therefore, when dealing with patients not showing signs of malnutrition, the energy dose during the first week should be set lower than the target energy dose, with the dose increased to the target level after 1 week. When dealing with high nutritional risk patients (NRS ≧3, NURIC score ≧5) or severe malnutrition, it has been recommended that 80% or more of the target energy level be administered within 72 h, if judged as tolerable, while paying close attention to the monitoring of data on the refeeding syndrome [9].

7.6 Indications for Parenteral Nutrition (PN)

PN is indicated in patients in whom the digestive tract cannot be utilized for nutrition, but no study has been published concerning PN in patients requiring neurocritical care. ASPEN [9] suggests that PN should be avoided for the first 7 days in cases with a low nutritional risk and that PN should be started as soon as possible in cases with a high nutritional risk (NRS 2002 ≧5, NUTRIC score ≧5) or malnutrition. It additionally recommends that if 60% or more of the energy requirements are not met by enteral nutrition alone in 7–10 days, start of supplemental PN should be considered. ESPEN [10] recommends starting PN within 3–7 days, with the suggestion that positive PN may be started earlier in patients with severe malnutrition.

7.7 Immune-Modulating Formulations

Antioxidants, such as glutamine, arginine, omega-3 fatty acid, EPA, DHA, and selenium, are known to have effects such as preserving the host defense capacity against infections, promoting wound healing and anti-inflammatory activity, and preventing

tissue injury caused by oxidative stress. In the study by Rice et al. (OMEGA study) [29] and the study by Heyland et al. (REDOXS study) [30], immune-modulating formulations failed to manifest favorable effects and were, in fact, found to have hazardous effects, such as prolonging the duration of mechanical ventilation and increasing the mortality due to excessive glutamine. Falcao et al. [31], on the other hand, demonstrated a reduction in the incidence of infections following administration of immune-modulating formulations. ASPEN [9] proposed that in patients with TBI, immune-modulating diets containing arginine should be used or a standard enteral nutrient preparation supplemented with EPA/DHA should be administered. This proposal is, however, based on an expert consensus using data primarily derived from small-scale studies, including few reports showing effectiveness; therefore, this approach cannot be strongly recommended.

7.8 Optimal Glycemic Control

Acute hyperglycemia reflects the severity of the disease and is associated with the prognosis of patients. In patients with head injury or stroke, hyperglycemia immediately before ischemia aggravates the neurological prognosis. Van den Berghe et al. [32] applied intensive insulin therapy with the target blood glucose level set at 80–110 mg/dL, reporting that this therapy reduced the mortality during ICU stay. Subsequently, various studies have been reported, including the NICE-SUGAR trial [33], which demonstrated a higher incidence of hypoglycemia and a higher rate of mortality at 90 days in the group receiving intensive insulin therapy as compared to the conventional glycemic control group (target blood glucose, 180 mg/dL or less). Furthermore, in a meta-analysis of the data from neurocritical care patients, the incidence of hypoglycemia was higher in the intensive insulin therapy group (70–140 mg/dL; 3.9–7.8 mmol/L) than in the conventional glycemic control group (144–300 mg/dL; 8.0–16.7 mmol/L), although no difference in the mortality was found between the two groups, and the risk for a poor neurological prognosis was lower in the former group [34]. However, improved neurological prognosis was shown in people with intermediate glycemic targets (adjustment made to avoid a blood glucose level of 200 mg/dL or higher; 140–180 mg/dL; 7.8–10.0 mmol/L) among the conventional glycemic control cases. In a meta-analysis of data from TBI cases, the incidence of severe hypoglycemia was higher in the intensive control group (4.4–6.7 mmol/L; 79–120 mg/dL) than in the conventional control group (8.4–12 mmol/L; 151–216 mg/dL), although the mortality did not differ between the two groups and the risk for poor neurological prognosis was lower in the former group [35]. Taken together, these results indicate that blood glucose control should be started with an insulin dose level that would yield a blood glucose level of 180 mg/dL or higher, but not exceeding 200 mg/dL.

Table 7.1 Nutritional therapy protocol of neurocritical patients

1. Route of nutrient administration
• Enteral route for nutrient administration should be preferred, if possible
2. Estimation of energy expenditure
• Indirect calorimetry measurements or calculations using predictive equations (Harris-Benedict equation, etc.) or a rule of thumb (25–30 kcal/kg/day)
3. Optimal amount of protein administration
• Should be at least 1.2 g/kg/day
4. Amount of energy administration during the first week of the acute phase
• Low nutritional risk: 33–66% of the target amount of energy
• High nutritional risk: at least 80% of the target amount of energy and protein within 72 h
5. Optimal glycemic control
• If the glucose level is ≧180 mg/dL, a continuous intravenous insulin infusion should be started (pay attention to prevent development of refeeding syndrome)

7.9 Conclusions

Table 7.1 shows the conclusions from this study. In patients requiring neurocritical care, catabolism is markedly enhanced, and, for this reason, early enteral nutrition is useful if the nutritional assessment reveals a low nutritional risk and a functional digestive tract. Thus, nutritional therapy is a valid approach that can contribute to improving the prognosis in these patients. For nutritional therapy, administration of energy and proteins at appropriate target levels is required, and the prognosis can be worsened by overfeeding, long-term underfeeding, and poor blood glucose control. It is therefore essential that a protocol or manual for nutritional therapy, with reference to the guidelines and reflecting the status at individual facilities, be prepared and that the protocol thus prepared is followed under multidisciplinary control.

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Chapter 8
Pathology and Prevention of Secondary Brain Injury for Neurocritical Care Physicians

Kenji Dohi

Abstract The pathophysiology of brain injuries occurring due to neuroemergencies, such as stroke or head trauma, can be broadly classified into primary brain injury and secondary brain injury. The latter is a general term for brain damage caused by various pathologies that arise after the onset of injury and can be alleviated with treatment. Therefore, secondary brain injury is the primary therapeutic target in neurocritical care, and understanding its true nature is essential for neurocritical care physicians. In this section, I have explained the different pathologies that cause secondary brain injury and have commented on their relationships with current therapeutic options. The relation of systemic inflammation to neuroinflammation, a unique condition in the brain, has also been discussed.

Keywords Intensive care · Secondary brain injury · Pathophysiology · Treatment Neuroinflammation

8.1 Pathophysiology of Neurological Emergencies

The pathophysiology of brain injuries occurring due to neuroemergencies, such as stroke or head trauma, can be broadly classified into two conditions. Brain damage that occurs at the onset or immediately after injury (primary brain damage) is simple brain damage caused by a disease or an injury [1]. In cerebral infarction, primary brain damage can be caused by ischemia, whereas in cerebral hemorrhage or head trauma, primary brain damage can be caused by the breakdown of brain tissue due to physical damage. Conversely, secondary brain damage is a general term for a variety of pathologies in which the brain tissue is damaged as a result of secondary factors brought about by primary brain damage [1]. Therefore, it is not too much to say that the suppression of secondary brain damage is the therapeutic

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objective of intensive care units. The neurocritical care treatment and management discussed in other sections of this book thus often target secondary brain damage. The final pathologies of secondary brain damage are an increase in intracranial pressure (ICP), the progression of localized ischemia and the promotion of bleeding due to a mass effect surrounding the area of brain damage, and worsening of neuroinflammation [2, 3]. In this section, we have explained the pathology, treatment, and targets of secondary brain damage from the viewpoint of preventing secondary brain damage in neurocritical care.

8.2 Approaches Toward Suppressing Secondary Brain Injury

Secondary brain damage is the main therapeutic target in neurocritical care centers. However, as previously explained, secondary brain damage is not a simple condition but is a general term for an increase in ICP, localized progression of ischemia and promotion of bleeding due to a mass effect surrounding the area of brain damage, and worsening of neuroinflammation. Neurocritical care physicians must therefore thoroughly understand the objective of treatment for secondary brain damage. An increase in ICP results in a decrease in cerebral perfusion pressure (CPP), promotes brain ischemia and hypoxia, and ultimately causes cerebral herniation and severe brain damage. Consequently, it is extremely important to control increases in ICP. However, merely controlling ICP is not adequate for treatment in neurocritical care because a localized mass effect and neuroinflammation can exist even within the normal value range for ICP. If existing areas of primary brain damage are close to eloquent areas of the brain, physicians must understand the potential for any progression of localized damage to cause motor paralysis and language and higher brain dysfunction, and they must accordingly suppress secondary brain injury to a minimum.

8.3 Pathology-Specific Factors for Secondary Brain Injury (Fig. 8.1)

8.3.1 ICP Elevation

Increases in ICP are caused by an increased intracranial capacity. In conditions such as stroke or head trauma, increases in brain tissue, blood, cerebrospinal fluid, and hematomas are specific causes of elevated ICP. Increases in brain tissue volume are the main cause of brain edema that occurs following brain damage. Brain edema is classically categorized into cytotoxic edema and vasogenic edema. Cytotoxic edema is also known as cellular or ionic edema where the blood–brain barrier (BBB) is intact. The basis of cytotoxic edema is “cellular energy failure with disrupted ionic pump with anaerobic metabolism,” which is either due to hypoxia

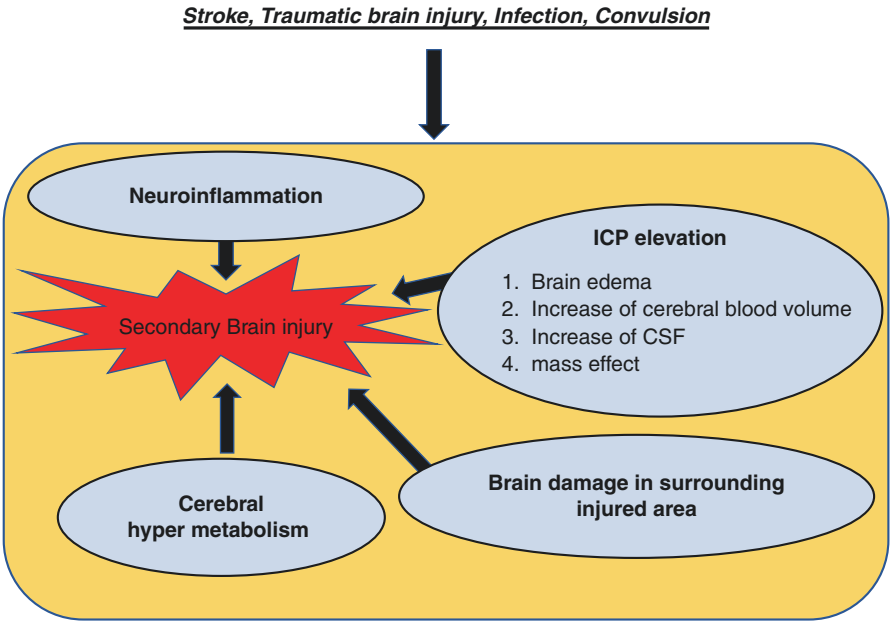

Fig. 8.1 Pathology of secondary brain injury. Secondary brain injury is a general term for secondary brain damage that occurs as a result of primary brain injury. The main pathologies of secondary brain injury include elevated ICP, brain hypermetabolism, neuroinflammation, and secondary damage to areas surrounding brain damage

or ischemia. Vasogenic edema is primarily due to the breakdown of the BBB secondary to mechanical disruption or chemical mediators. The causes of increase in intracranial blood include a marked elevation in blood pressure, autoregulation in the cerebral blood vessels, increased cerebral blood flow due to the breakdown of autoregulation, and venous reperfusion injury. An increase in cerebrospinal fluid is attributable to hydrocephalus due to the obstruction of cerebrospinal fluid circulation, overproduction of cerebrospinal fluid, and decreased cerebrospinal fluid absorption capacity.

8.3.2 Cerebral Hypermetabolism

Brain metabolism is dependent on glucose and oxygen transported by the blood. In head trauma or stroke, a decrease in endogenous energy sources in the brain tissue and an increase in lactate levels are observed. First, the levels of phosphocreatine decrease the fastest, followed by those of adenosine triphosphate, glucose, and glycogen. Brain hypermetabolism causes relative ischemia and anaerobic metabolism in which lactic acid is produced, and secondary brain damage is promoted. This condition leads to further worsening of brain damage when accompanied by convulsive seizures, systemic hypoxia, decreased CPP due to reduced blood pressure, reduced

oxygen-carrying capacity due to decreased hemoglobin, and the onset of other factors. The brain consumes 20% of the body's total oxygen supply. When the body temperature drops by 1 °C, the cerebral oxygen metabolism rate ($CMRO_2$) decreases by 7%. The depth of anesthesia, body temperature, and seizures all strongly affect the $CMRO_2$. Hyperglycemia is also known to promote secondary brain damage. Hyperglycemia promotes anaerobic glycolysis that causes lactic acid accumulation, resulting in lactic acidosis, which is considered a cause of aggravated secondary brain damage.

8.3.3 Neuroinflammation (Figs. 8.2 and 8.3)

Blood cells do not naturally occur in the brain. Cerebral blood vessels are separated from the brain by the blood–brain barrier (BBB) and are normally isolated from the systemic immune system. The BBB is not simply a physical barrier but a regulatory

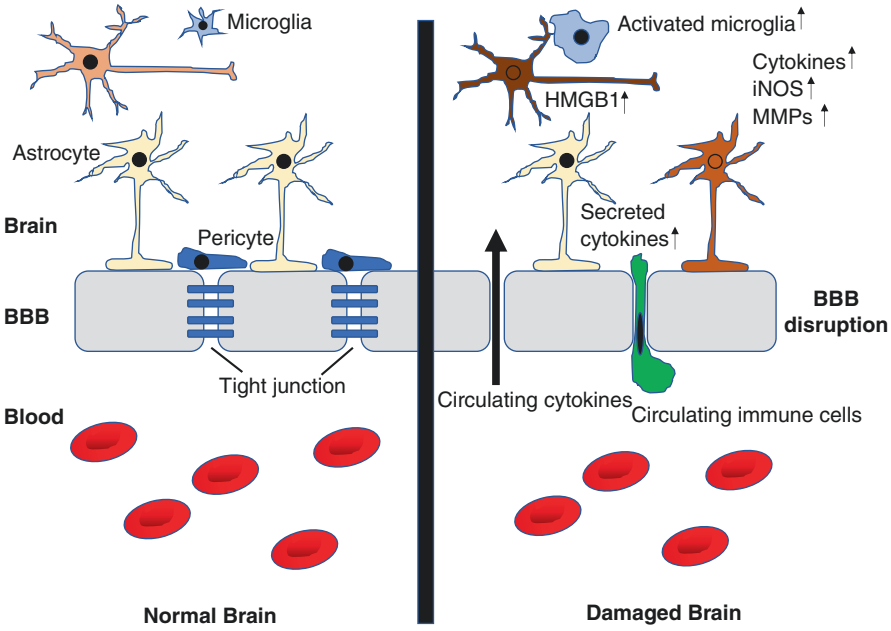

Fig. 8.2 Scheme of BBB disruption and neuroinflammation. The left panel shows the normal relationship between the blood–brain barrier (BBB) and brain cells. The tight junctions in the BBB ensure that the blood and brain tissue exist as separate, individual immune systems. The right panel shows this relationship during brain damage. The tight junctions in the BBB are disrupted, thereby allowing circulating cytokines in the blood to penetrate the BBB and move from the blood vessels to the brain. Furthermore, systemic immune cells, including macrophages, migrate into the brain via the BBB and promote local inflammation. HMGB1 is also released by nerve cells damaged by the brain injury, causing an inflammatory response. Microglia are activated to classical activated microglia and are involved in the production of inflammatory substances such as free radicals and inflammatory cytokines

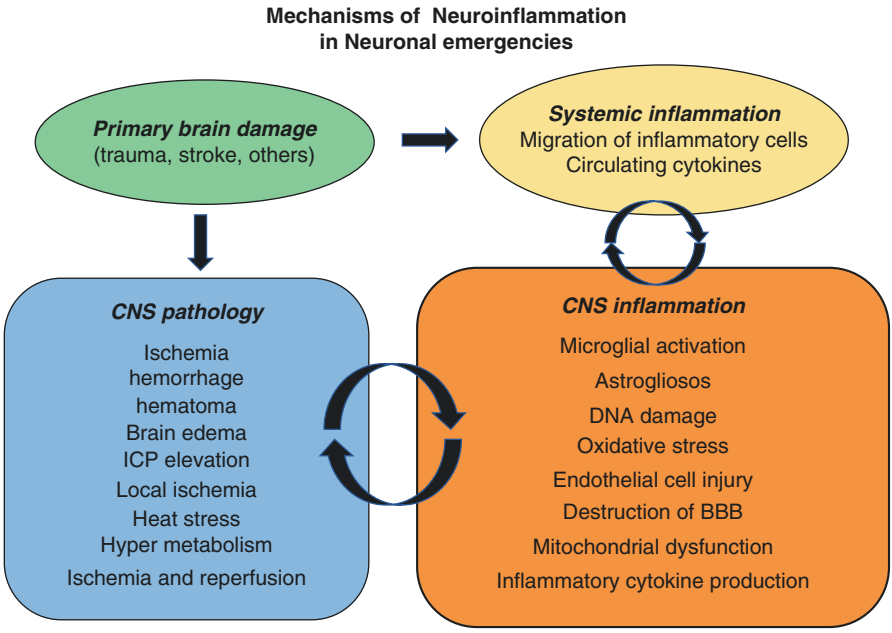

Fig. 8.3 Relationship between local inflammation and systemic inflammation in neuroinflammation. Primary brain damage induces central nervous system inflammation and systemic inflammation. Each acts on the other, creating a negative cycle

interface between the central nervous system (CNS) and immune system [2]. The BBB both affects and is affected by the immune system and connects at many levels with the CNS. Recently, disruption of the BBB has been discovered to be involved in the onset of neurodegenerative diseases such as Alzheimer's disease. In neuroemergencies such as stroke and neurotrauma, vascular endothelial dysfunction and dysfunction of nearby astrocytes in the cerebral blood vessels surrounding the site of injury cause the tight junctions of the BBB to break down, resulting in disruption of the BBB. This results in the so-called neuroinflammation, in which negative cross talk occurs between local inflammation in the brain and systemic inflammation. Microglia play an important role in local brain inflammation in neuroinflammation and exhibit a role similar to that of macrophages in the systemic immune system. Almost immediately after the occurrence of a brain injury, microglia are activated and produce active oxygen and inflammatory cytokines, which act as the so-called phagocytes, which engulf nerve cells and other cells that can cause cell death. Inflammatory responses induced by damage-associated molecular patterns (DAMPs), which are autologous tissue-derived signal molecules, are also drawing interest [3, 4]. In particular, the high-mobility group box 1 (HMGB1) protein is believed to originally execute specialized intranuclear functions, such as gene transcription regulation, chromatin structure maintenance, and DNA repair [3, 4]. However, it has been revealed that HMGB1 is briefly released into the extracellular space and exerts an action similar to that of cytokines. Anti-HMGB1 antibodies are therefore expected to be effective

therapeutic agents against cerebral infarction and traumatic brain injury. In addition to macrophages migrating to the brain and acting as inflammatory cells due to disruption of the BBB, circulating inflammatory cytokines in the body penetrating the BBB to act on the brain are one of the many important actions resulting in the spread of systemic inflammation to the brain [2, 5, 6]. This promotes an inflammatory response in the damaged part of the brain and exacerbates secondary brain injury. Hyperglycemia caused by disease-related stress can also exacerbate neuroinflammation, and hyperglycemia-induced lactic acidosis exacerbates secondary brain damage [7–9]. Furthermore, oxidative phosphorylation due to hyperglycemia produces superoxides that promote neuroinflammation. Controlling neuroinflammation is therefore the key to suppressing secondary brain injury. However, no single therapeutic option exists. The therapeutic options include the suppression of glial cell activation, prevention of BBB disruption, control of vascular endothelial dysfunction, antioxidative stress therapy, anti-inflammatory cytokine therapy, blood glucose control, and control of systemic inflammation [2–4, 8, 10–14]. Many current treatments for secondary brain injury and neuroinflammation, treatments in development, or a combination of these are currently employed as therapeutic options. For example, the main targets of molecular hydrogen therapy for brain damage, which is currently drawing attention, are hydrogen radicals and scavengers. However, molecular hydrogen therapy targets several aspects of the complex mechanism of neuroinflammation, including inflammatory cytokine production and the suppression of glial activation [14, 15].

8.3.4 Secondary Brain Damage in the Surrounding Injured Area

Secondary brain damage must be prevented even if ICP is normal. Even if it has no effect on the vital prognosis, suppressing local brain damage to a minimum may improve the functional prognosis, including that of paralysis and higher brain dysfunction. Cerebral edema caused by head trauma and stroke or compression by hematoma results in decreased local cerebral perfusion. Furthermore, neuroinflammation resulting from primary brain damage causes the area of damage to expand. In particular, penumbra area in ischemic stroke, an area of decreased blood flow, exists from the start surrounding the area of brain injury, which causes irreversible dysfunction when secondary brain damage develops in this area. Thus, acute treatment through neurocritical care is vital regardless of the severity of injury.

8.4 Treatment of Secondary Brain Injury

When reading this paper, you may want to refer to various sections of this book for further details on the treatment and management of brain injury. The relationships between different types of secondary brain injury and their treatments are listed here.

8.4.1 Control of ICP

The treatment for elevated ICP must address various factors that could be the potential cause of the elevation.

1. Brain edema.
   (a) PO_2 control.
   (b) Head-up position.
   (c) Prevention of anemia.
   (d) Control of epilepsy which involved nonconvulsive status epilepticus (NCSE).
   (e) Control of cerebral perfusion pressure (CPP).
   (f) Prevention of BBB disruption.
2. Control of cerebral blood volume.
   (a) CBF control: PO_2 control, pCO_2 control, control of blood pressure.
   (b) Prevention of venous congestion: control, head-up position, control of intrathoracic pressure, avoidance of compression of the jugular vein.
3. Control of CSF.
   (a) Drainage of CSF.
4. Control of mass effect.
   (a) Control of brain edema.
   (b) Control of coagulopathy.
   (c) Operation (internal decompression, external decompression).

8.4.2 Control of Cerebral Hypermetabolism

1. Hypothermia (temperature management).
2. Prevention of epilepsy which involved nonconvulsive status epilepticus (NCSE).
3. Avoidance of hyperoxygenation.
4. Sedation.
5. Anti-neuroinflammatory therapy.

8.4.3 Prevention of Neuroinflammation

1. Hypothermia (temperature management).
2. Prevention of BBB disruption.
3. Prevention of endothelial cell injury.
4. Suppression of glial activation.

5. Suppression of inflammatory agent production (free radicals, HMGB1, inflammatory cytokines).
6. Antioxidant therapy.
7. Prevention of hyperglycemia.
8. Control of secondary systemic inflammatory response (infection, others).

8.4.4 Prevention of Secondary Brain Damage in Surrounding Injured Area

1. The basic views on secondary brain injury localized to the area of brain injury correspond to the aforementioned points (1–3).

8.5 Conclusion

This section explains the pathologies and treatments of secondary brain injury. Secondary brain injury is caused by brain damage resulting from primary brain injury. Neurocritical care physicians must understand these pathologies to provide patients with interdisciplinary systemic management and treatment for brain damage. Currently, the treatments for secondary brain injury remain inadequate, and new therapeutic options targeted at suppressing neuroinflammation are urgently required.

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Chapter 9
Coagulopathy and Brain Injury

Ryuta Nakae, Shoji Yokobori, and Hiroyuki Yokota

Abstract Traumatic brain injury (TBI) is often associated with coagulopathy, which is linked to higher rates of morbidity and mortality. Coagulopathy following TBI involves hypercoagulable and hypocoagulable states that can lead to secondary injury due to either microthrombi or hemorrhage. In particular, hemorrhagic lesions as a result of hypocoagulability are a critical and often fatal complication of TBI. Several mechanisms have been proposed to explain the underlying pathophysiology of TBI-induced coagulopathy, including tissue factor activation, thrombocytopenia, platelet dysfunction, protein C activation, and hyperfibrinolysis. In clinical practice, coagulopathy following TBI is primarily identified by examining coagulation and fibrinolytic test parameters such as the prothrombin time-international normalized ratio, activated partial thromboplastin time, platelet count, and D-dimer. These parameters undergo dynamic changes during the acute phase of TBI, and a deeper understanding of these values is needed. Routine assessment of coagulation and fibrinolytic parameters is warranted to predict the occurrence of coagulopathy and the associated outcome.

Keywords Traumatic brain injury · Coagulopathy · Coagulation · Fibrinolysis Outcome

9.1 Introduction

Coagulopathy is a frequent occurrence in patients with traumatic brain injury (TBI) and is linked to high morbidity and mortality [1–3]. Coagulopathy following TBI leads to hyper- and hypocoagulability [4]. Hypercoagulability is characterized by a higher predisposition to thrombosis and hypocoagulability by prolonged bleeding and hemorrhagic progression. Notably, hemorrhagic lesions arising as a result of hypocoagulability represent serious and potentially fatal complications of TBI [5]. Therefore, it is pertinent that strategies for managing TBI are centered on hypocoagulability.

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In this chapter, we review what is currently known about the incidence and mechanisms of coagulopathy in TBI and discuss the associated clinical tests and management procedures.

9.2 Definition of Coagulopathy

Coagulopathy is primarily identified by examining coagulation test parameters such as the prothrombin time-international normalized ratio (PT-INR), activated partial thromboplastin time (aPTT), and platelet count. While there are no standard criteria for defining coagulopathy, the disorder is typically diagnosed when PT-INR > 1.1–1.5 and/or aPTT >35–60 s and/or platelet count <100–120 × 10^9 L^{-1}.

9.3 Epidemiology of Coagulopathy Following TBI

9.3.1 Incidence of Coagulopathy

Coagulopathy in isolated TBI (head Abbreviated Injury Scale (AIS) score ≥3 with an extracranial AIS score <3) is observed in 12.5–45.7% of patients with TBI at hospital admission [3, 6–11]. This broad range is likely associated with differences in the definition of coagulopathy, blood sampling time, and the type and severity of TBI [12, 13]. In a large German trauma registry study [3], 22.7% of patients with isolated TBI in the emergency department exhibited acute coagulopathy, and this was correlated with increased rates of morbidity and mortality. Coagulopathy is more likely to be observed in severe TBI, TBI with additional trauma, and penetrating injuries compared to mild TBI, isolated TBI, and blunt trauma, respectively [11, 14, 15].

9.3.2 Relationship Between Coagulopathy and Hemorrhagic Progression

Coagulopathy in TBI is highly correlated with hemorrhagic progression [5]. About 50% of TBI patients with coagulopathy exhibit hemorrhagic progression of initial brain contusions and continued intracerebral hematoma (ICH) within 2 days of developing TBI [16, 17]. Hemorrhagic progression of brain contusions is evidenced by the enlargement of existing contusions as well as the delayed development of non-contiguous hemorrhagic lesions [18, 19]. Hemorrhagic progression of intraparenchymal contusions is more prevalent in elderly patients with coagulopathy on admission compared to younger patients [20].

9.3.3 Relationship Between Coagulopathy and Outcome

The presence of coagulopathy is a strong indicator of the outcome and overall prognosis of TBI, being associated with mortality rates between 21.7% and 66.7% [3, 6–11]. Progressive ICH is a primary cause of mortality associated with TBI [5].

9.4 Mechanism of Coagulopathy Following TBI

Several mechanisms have been proposed to explain the underlying pathophysiology of TBI-induced coagulopathy. Some of these include tissue factor (TF) activation, thrombocytopenia, platelet dysfunction, protein C activation, and hyperfibrinolysis.

9.4.1 TF Activation

Keimowitz et al. [21] and Goodnight et al. [22] were the first to propose that brain tissue when damaged released TF into the systemic circulation, which in turn caused coagulopathy. TF is highly expressed in the central nervous system (CNS) [23] but is also found in perivascular smooth muscle cells, pericytes, and fibroblasts [24]. TF in the CNS is cut off from the systemic circulation by the blood-brain barrier (BBB) and is not directly in contact with coagulation factors. Intravascular release of TF due to direct vessel injury or defragmentation from microvascular failure can activate the extrinsic coagulation pathway. This leads to the formation of thrombin in the initiation phase of the coagulation process, followed by platelet dysfunction and exhaustion [25, 26]. Subsequently, coagulopathy causes fibrin deposition and intravascular microthrombosis and possibly post-traumatic cerebral infarction [27, 28]. This may further raise consumption of coagulation factors and platelets, which can potentially cause more bleeding.

9.4.2 Thrombocytopenia and Platelet Dysfunction

TBI has been linked to reduced platelet count [29, 30] and/or function [31, 32]. Microvasculature injury and BBB disruption induce interactions between platelets and the perturbed endothelium or exposed subendothelial matrix. Such an interaction results in direct or von Willebrand factor-mediated platelet adhesion, platelet activation, and development of a platelet plug at the injury site [12, 19, 33]. Platelet hyperactivity can additionally cause secondary platelet depletion and, at subsequent stages, platelet exhaustion with a higher risk of bleeding [25]. Platelet dysfunction occurs when the agonists adenosine diphosphate (ADP) or arachidonic acid (AA) have a decreased ability to activate platelets due to inhibition of ADP and AA receptors [25].

9.4.3 Protein C Activation

Injury and hypoperfusion lead to surplus thrombomodulin expression in the endothelial cell wall. After a thrombin burst, thrombin binds to thrombomodulin to form a complex that can activate protein C. Activated protein C is presumed to be important due to its inhibition of factors Va and VIIIa and plasminogen activator inhibitor 1, leading to hypocoagulability and hyperfibrinolysis [12, 34].

9.4.4 Hyperfibrinolysis

Hyperfibrinolysis is a suggested cause of coagulopathy after TBI. A constantly active fibrinolytic system acts to stop improper thrombus formation and can be induced by the hemostatic cascade as part of a negative feedback loop. Plasmin, the cleaved product of circulating plasminogen, is the primary effector of fibrinolysis. In a more upstream pathway, tissue plasminogen activator and urokinase plasminogen activator are the primary activators of plasminogen. Plasmin is quickly inactivated by α2 plasmin inhibitor (α2-PI) to form a plasmin-α2-PI complex (PIC). Therefore, the presence of PIC in plasma is a direct indicator of the level of fibrinolytic activation [35]. Kushimoto et al. [36] suggested that depletion of α2-PI and the associated rise in plasmin may contribute to hyperfibrinolysis and cause bleeding diathesis as a result of its broad activation or by the dissolving of a newly developed local fibrin clot in the damaged brain. Fibrinogen/fibrin degradation products (FDP) and D-dimer also signal fibrinolysis. FDP arises following the degradation of fibrinogen (primary fibrinogenolysis) and fibrin (fibrinolysis). On the other hand, D-dimer detects degraded products formed by the actions of plasmin on stabilized fibrin (fibrinolysis) [37].

9.5 Clinical Tests for Coagulopathy Following TBI

The International Mission on Prognosis and Analysis of Clinical Trials in TBI (IMPACT) study [38] findings indicate that changes in coagulation parameters, including increased PT and reduced platelet count, may constitute reliable markers of TBI outcome. However, other studies suggest that fibrinolytic parameters such as D-dimer may be more reliable markers than coagulation parameters [13, 16, 35, 39, 40]. Understanding the time course of these parameters is critical given that coagulation and fibrinolytic parameters undergo active changes in the acute phase of TBI.

9.5.1 Time Course of Coagulation/Fibrinolytic Parameters

Nakae et al. [13] examined the timeline of changes to coagulation and fibrinolytic parameters during the acute phase of isolated TBI (head AIS score ≥3 with an extracranial AIS score <3) on admission and at 3, 6, and 12 h after injury (Fig. 9.1). Platelet

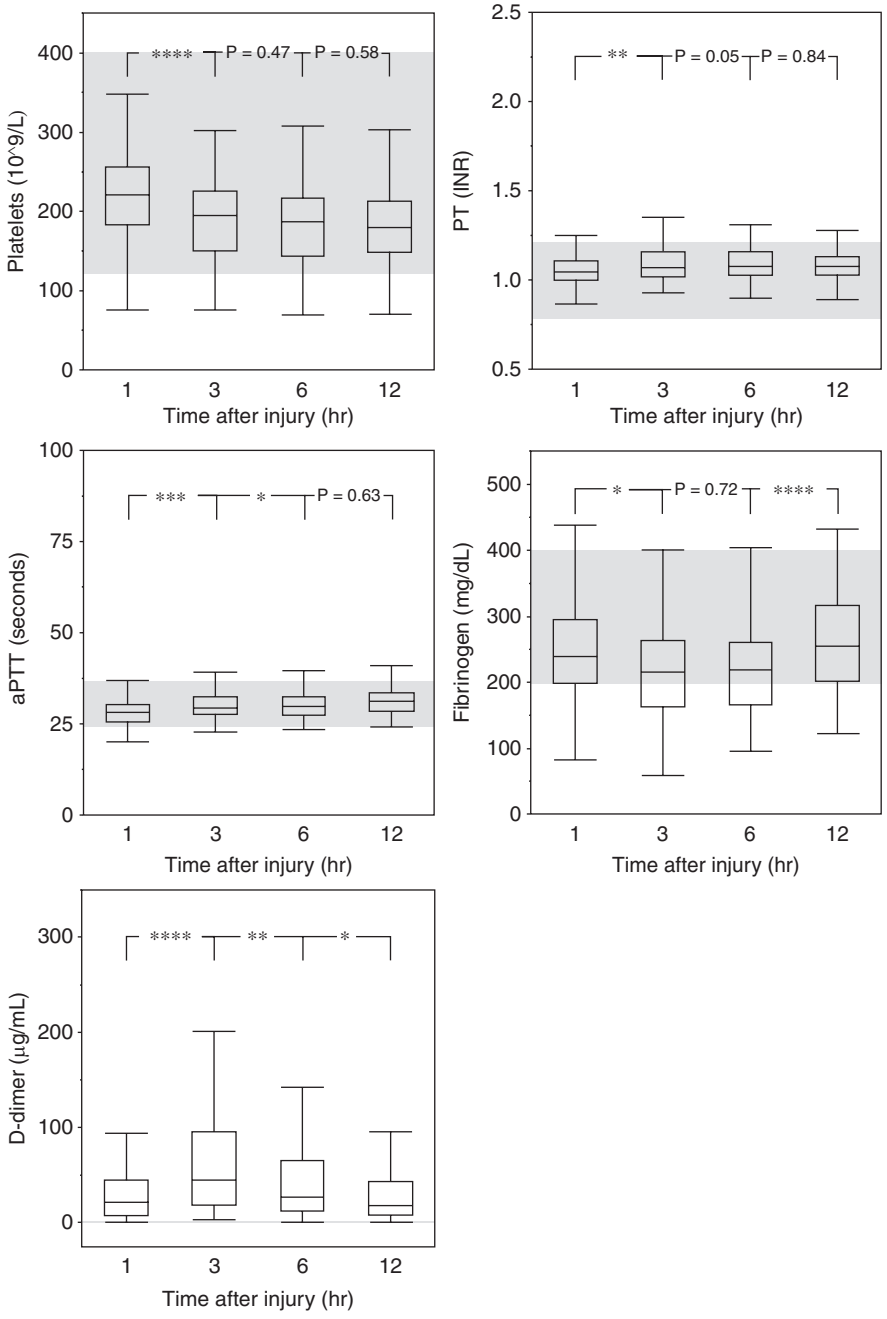


Fig. 9.1 Platelet count, PT, aPTT, and plasma levels of fibrinogen and D-dimer of all patients on admission and at 3, 6, and 12 h after TBI. The gray areas indicate the normal ranges for each parameter. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. Figure is reproduced from ref. [13]

count was significantly reduced from admission to 3 h after injury ($p < 0.0001$) and continued to drop, albeit not in a significant manner, from 3 to 12 h after injury. PT and aPTT levels rose significantly from admission to 3 h after injury ($p < 0.01$ and $p < 0.001$, respectively). After 3 h, median PT and aPTT values stayed within the normal range with some fluctuations outside this range. Plasma fibrinogen concentration was significantly reduced from admission to 3 h after injury ($p < 0.05$) but rose, albeit not in a significant manner, from 3 to 6 h after injury, and continued to rise significantly from 6 to 12 h after injury ($p < 0.0001$). D-dimer plasma levels exhibited the most dramatic fluctuations: the median plasma level of D-dimer, which was already above the normal range on admission, rose further from admission to 3 h after injury ($p < 0.0001$) before decreasing significantly. In severe TBI, 98.7% of patients exhibited abnormal D-dimer levels on admission.

9.5.2 *Relationship Between Coagulation/Fibrinolytic Parameters and Outcome*

To assess the relationship between coagulation/fibrinolytic parameters and outcome, Nakae et al. [13] examined differences in these parameters in the acute phase of isolated TBI between a good outcome group (Glasgow Outcome Scale: good recovery or moderate disability at 3 months post-injury) and a poor outcome group (Glasgow Outcome Scale: severe disability, vegetative state, or death at 3 months post-injury) (Fig. 9.2). PT, aPTT, and D-dimer levels in the poor outcome group, except for the aPTT level at 12 h after injury, were significantly increased compared

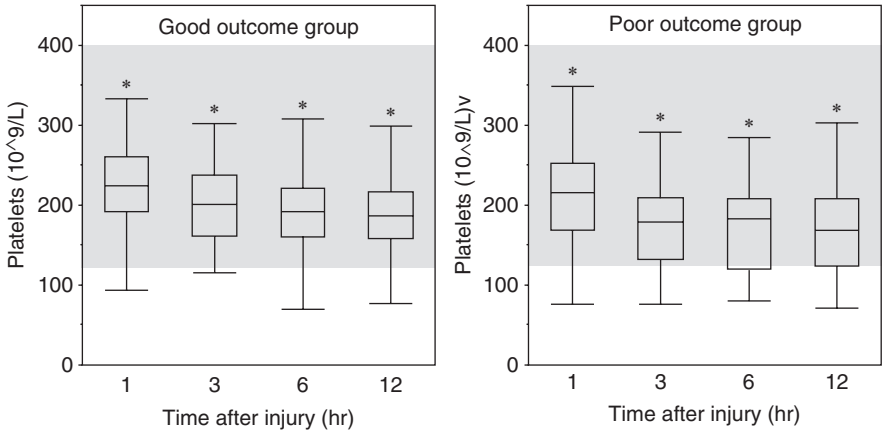
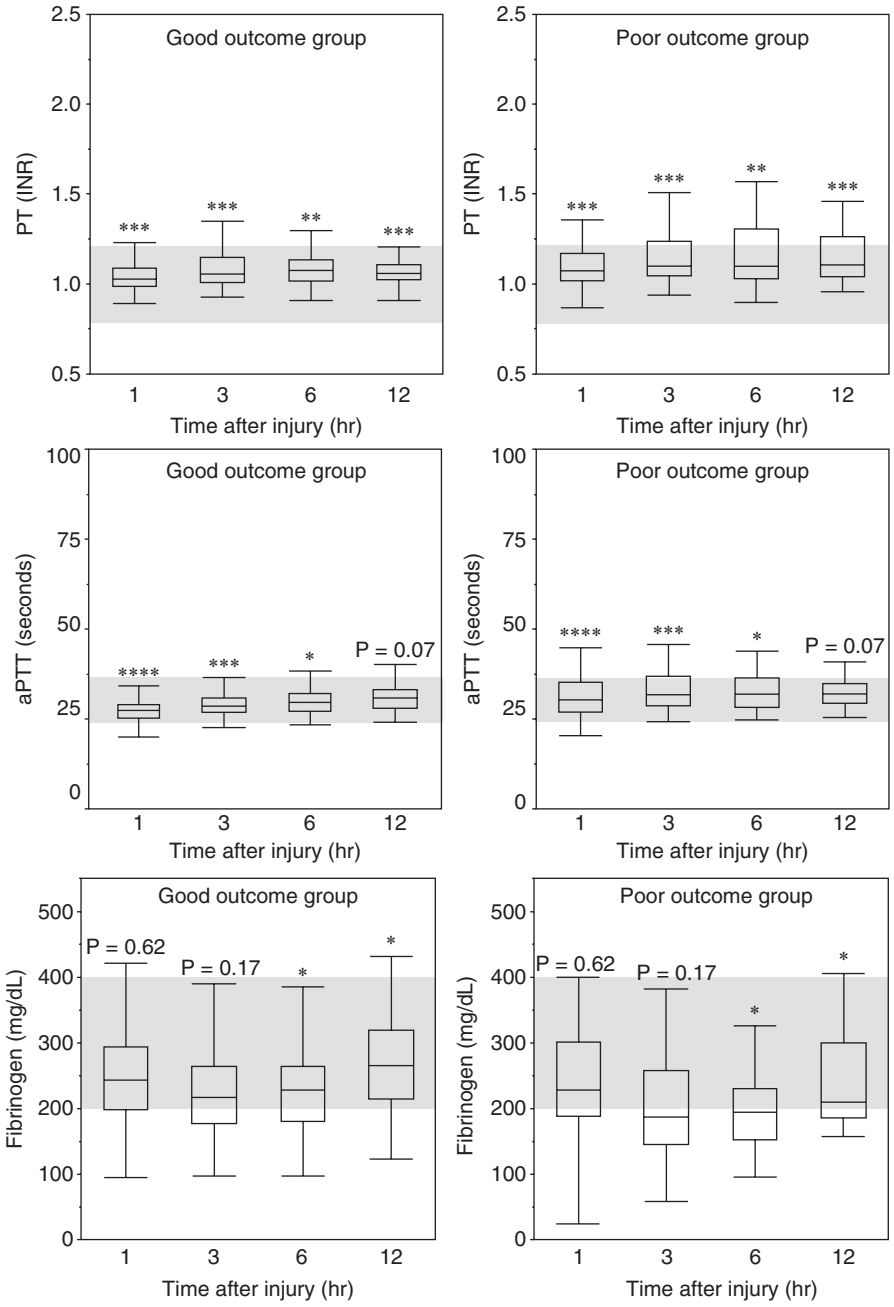


Fig. 9.2 Platelet count, PT, aPTT, and plasma levels of fibrinogen and D-dimer of patients with good outcome or poor outcome on admission and at 3, 6, and 12 h after TBI. The gray areas indicate the normal ranges for each parameter. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. Figure is reproduced from ref. [13]



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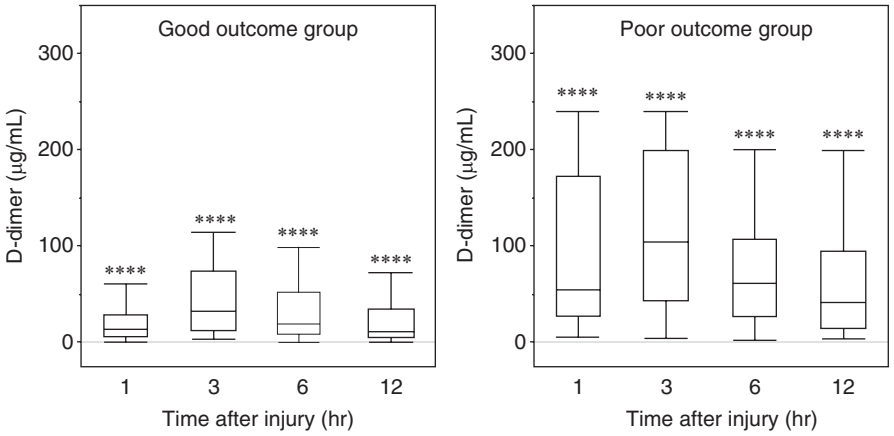

Fig. 9.2 (continued)

to the good outcome group from admission to 12 h after injury. In contrast, platelet count and plasma fibrinogen concentrations were significantly reduced in the poor outcome group compared to the good outcome group at all time points, except for the fibrinogen levels at admission and 3 h after injury. Plasma D-dimer levels were the most dramatically different between the groups at all time points from admission to 12 h after injury ($p < 0.0001$ at all time points).

Unlike D-dimer, FDP arises following the breakdown of both fibrin (fibrinolysis) and fibrinogen (fibrinogenolysis), and patients with hyperfibrinolysis show dramatic increases in fibrinogenolysis products [37]. The FDP/D-dimer ratio is thus used as a surrogate marker of hyperfibrinolysis [41]. In practice, concurrent measurements of both FDP and D-dimer can produce more accurate estimations of the severity of hyperfibrinolysis.

9.5.3 Age-Related Differences in Fibrinolytic Parameters

Nakae et al. also compared fibrinolytic parameters in older (>55 years) and non-older groups (16–55 years) matched for head AIS scores. They showed that platelet counts were significantly reduced in the older group compared to the non-older group at all time points from admission to 12 h after injury, except for that at 12 h after injury in patients with AIS scores of 3 and 4. PT, aPTT, and plasma fibrinogen concentrations were comparable between the two groups at each head AIS score of 3–5. Plasma D-dimer levels were the most dramatically different between older and non-older patients, being significantly higher in older than non-older patients when matched for head AIS score (Figs. 9.3, 9.4, and 9.5). Fibrinolytic abnormalities, such as increased plasma D-dimer levels, are more severe in older acute-phase TBI patients, suggesting that patient age may constitute a factor for poor prognosis.

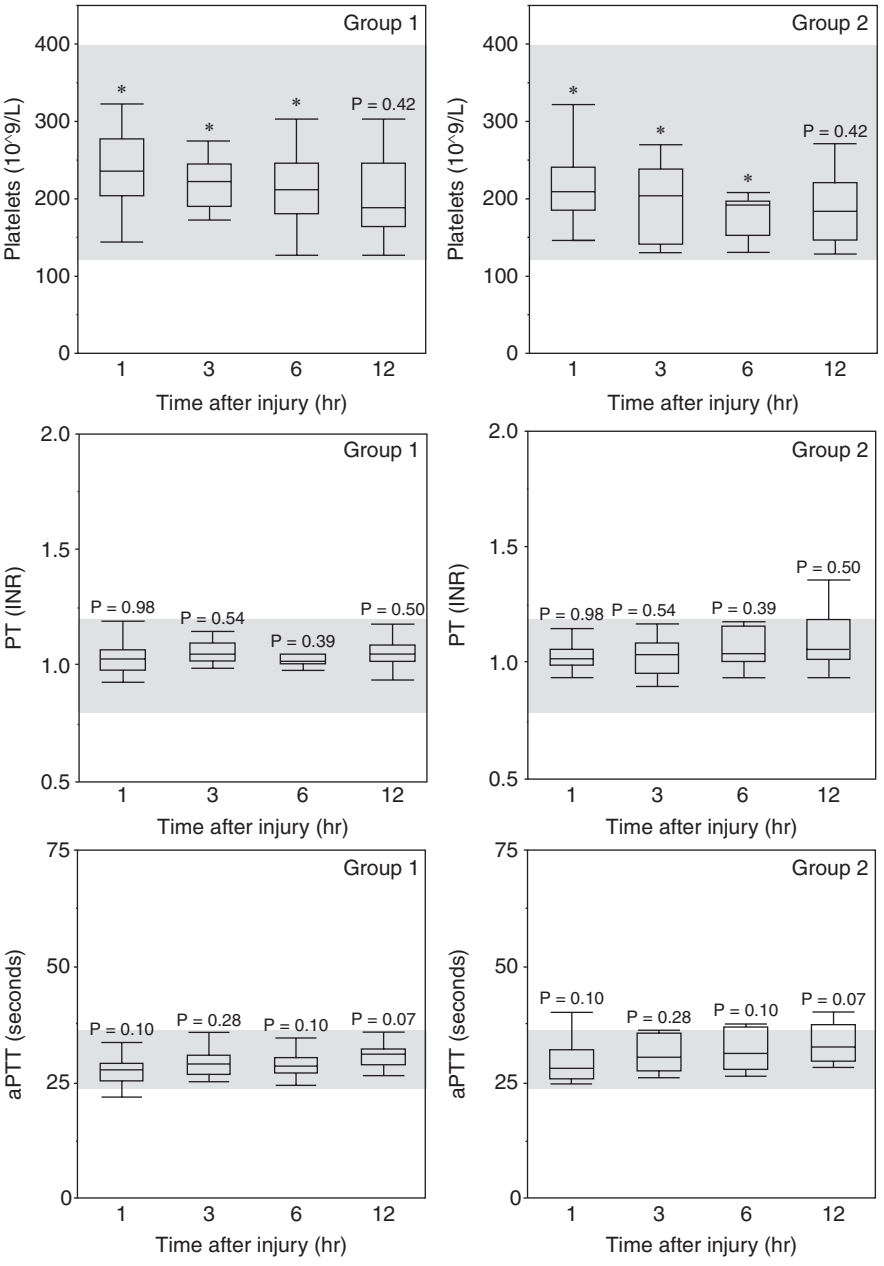

Fig. 9.3 Platelet count, PT, aPTT, and plasma levels of fibrinogen and D-dimer of patients aged 16–55 years (Group 1) or older than 55 years (Group 2) with a head AIS score of 3 on admission and at 3, 6, and 12 h after TBI. The gray areas indicate the normal ranges for each parameter. *$p < 0.05$, **$p < 0.01$. Figure is reproduced from ref. [20], and permission to reuse was obtained from Wolters Kluwer India Private Limited (#W/17-18/ADV00037)

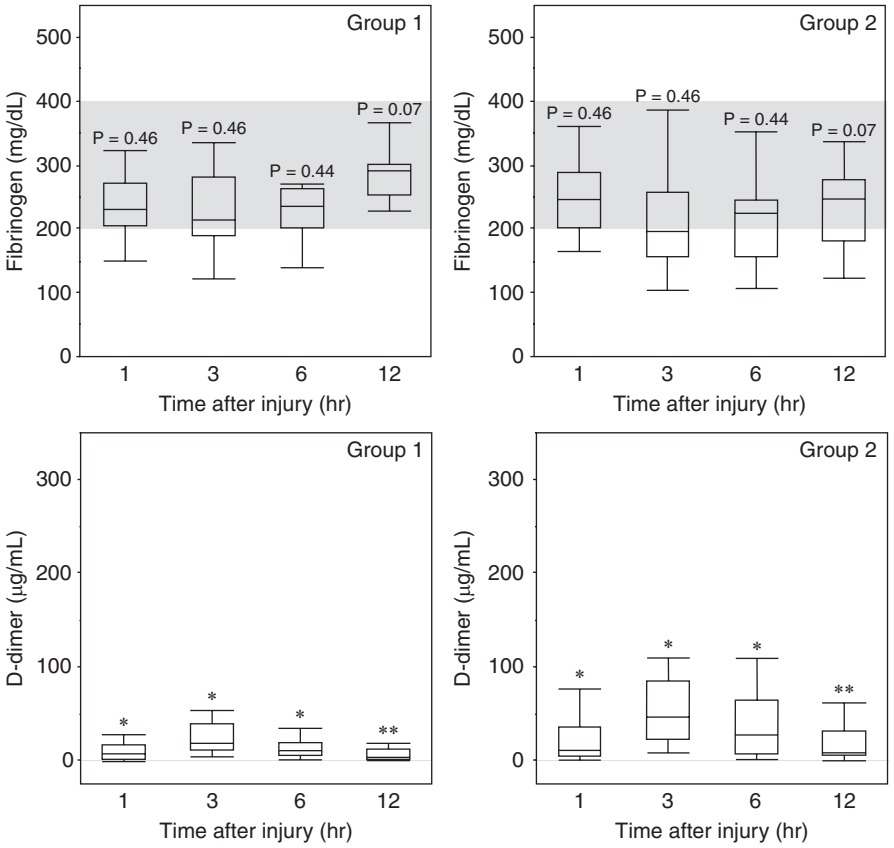

Fig. 9.3 (continued)

9.5.4 Interpretation of the Time Course of Coagulation/ Fibrinolytic Parameters

Increased PT and aPTT result from the activated coagulation pathway and depletion and/or dysfunction of plasma coagulation factors due to TBI [4, 42, 43]. Increased D-dimer levels cause high fibrinolytic activity and high subsequent plasmin activity, which stimulates fibrin degradation [4, 42, 43]; that is, the combination of increased PT and aPTT and elevated D-dimer levels in the early phase of TBI can be regarded as simultaneous hypercoagulability and hyperfibrinolysis. The reduced plasma fibrinogen concentration from admission to 3 h after injury may occur as a result of its consumption to form a fibrin clot or direct destruction [44]. The rising trend of the fibrinogen concentration after 6 h suggests a hemostatic shift, characterized by inhibition of fibrinolysis. This is in line with the reduction in plasma D-dimer levels from 3 h after injury. The reduced platelet count from admission to 3 h after injury

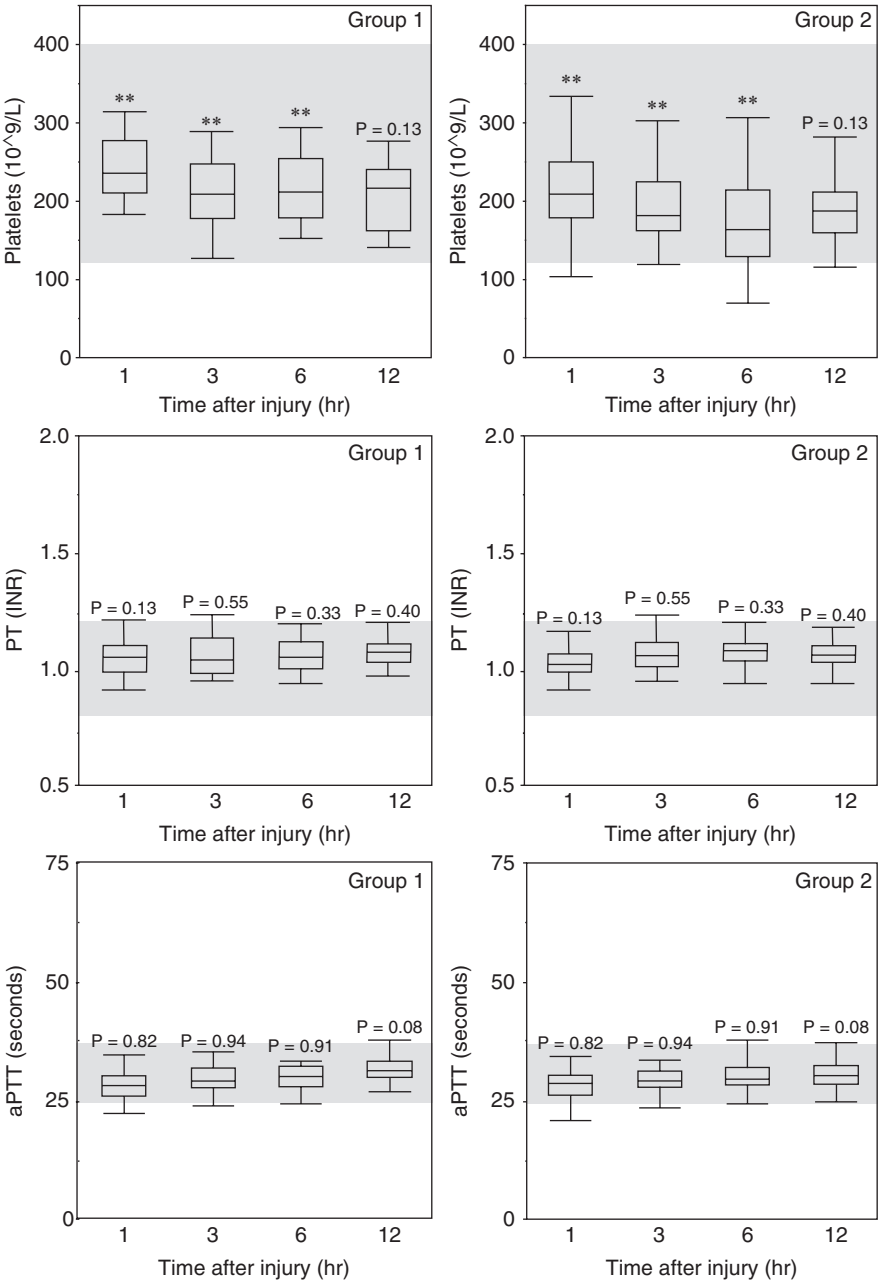

Fig. 9.4 Platelet count, PT, aPTT, and plasma levels of fibrinogen and D-dimer of patients aged 16–55 years (Group 1) or older than 55 years (Group 2) with a head AIS score of 4 on admission and at 3, 6, and 12 h after TBI. The gray areas indicate the normal ranges for each parameter. *$p < 0.05$, **$p < 0.01$. Figure is reproduced from ref. [20], and permission to reuse was obtained from Wolters Kluwer India Private Limited (#W/17-18/ADV00037)

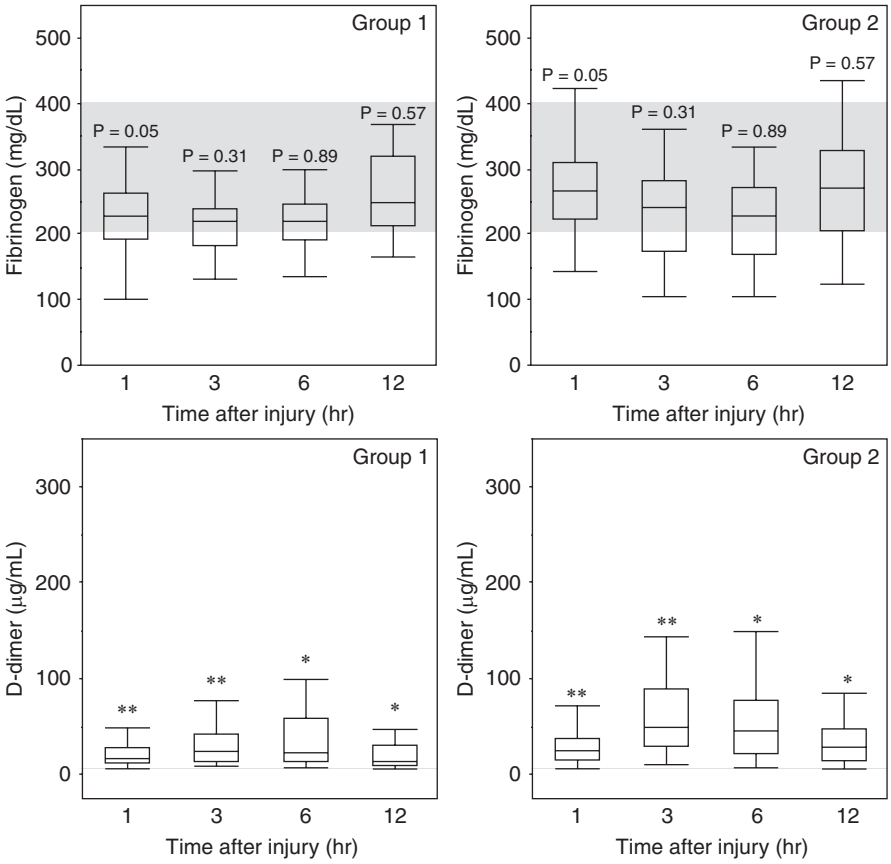

Fig. 9.4 (continued)

may occur as a result of its consumption to form a crosslink-stabilized platelet-fibrin clot immediately following TBI [4].

The fibrinolytic parameter D-dimer increases gradually between admission and 3 h after injury and remains high for at least 12 h after injury. These results suggest that patients presenting within 12 h after injury, and in particular within 3 h after injury, are at increased risk of hemorrhage enlargement resulting from hyperfibrinolysis. Hyperfibrinolysis can cause hemorrhage expansion by degradation of coagulation factors, breakdown of formed fibrin clot, and impaired clot formation due to excess generation of fibrin degradation products [13]. Patients who "talk and deteriorate" (T&D) are typically defined as those who develop rapidly progressive consciousness disturbances (Glasgow Coma Scale (GCS) score of 8 or less) within 2 days of injury [45–47]. In the majority of cases, the patient's GCS score drops within a few hours following injury [48]. Patients who subsequently develop T&D can be readily identified on admission by testing for fibrinolytic parameters such as PIC and D-dimer [35]. Hyperfibrinolysis in the acute phase of TBI is likely to result in T&D through hematoma progression [13].

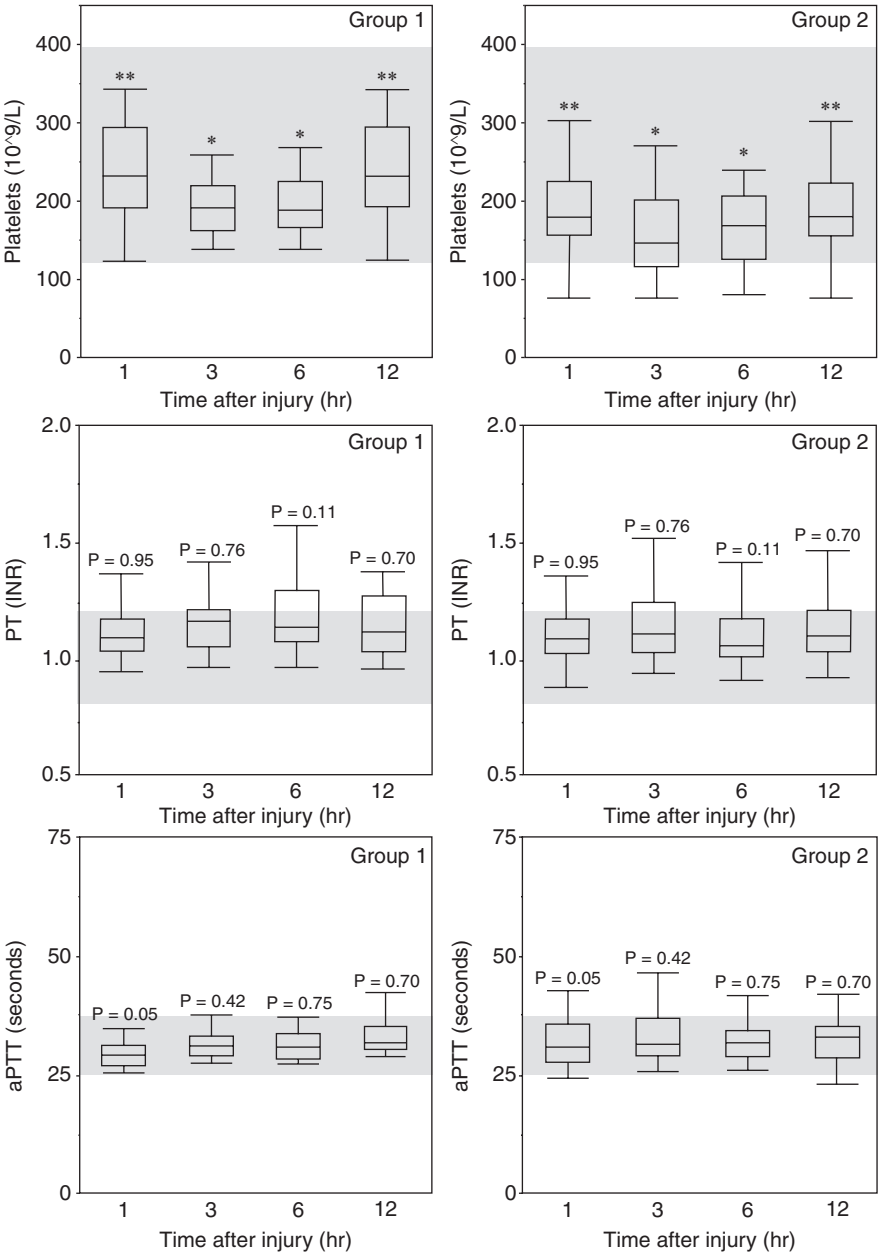

Fig. 9.5 Platelet count, PT, aPTT, and plasma levels of fibrinogen and D-dimer of patients aged 16–55 years (Group 1) or older than 55 years (Group 2) with a head AIS score of 5 on admission and at 3, 6, and 12 h after TBI. The gray areas indicate the normal ranges for each parameter. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. Figure is reproduced from ref. [20], and permission to reuse was obtained from Wolters Kluwer India Private Limited (#W/17-18/ADV00037)

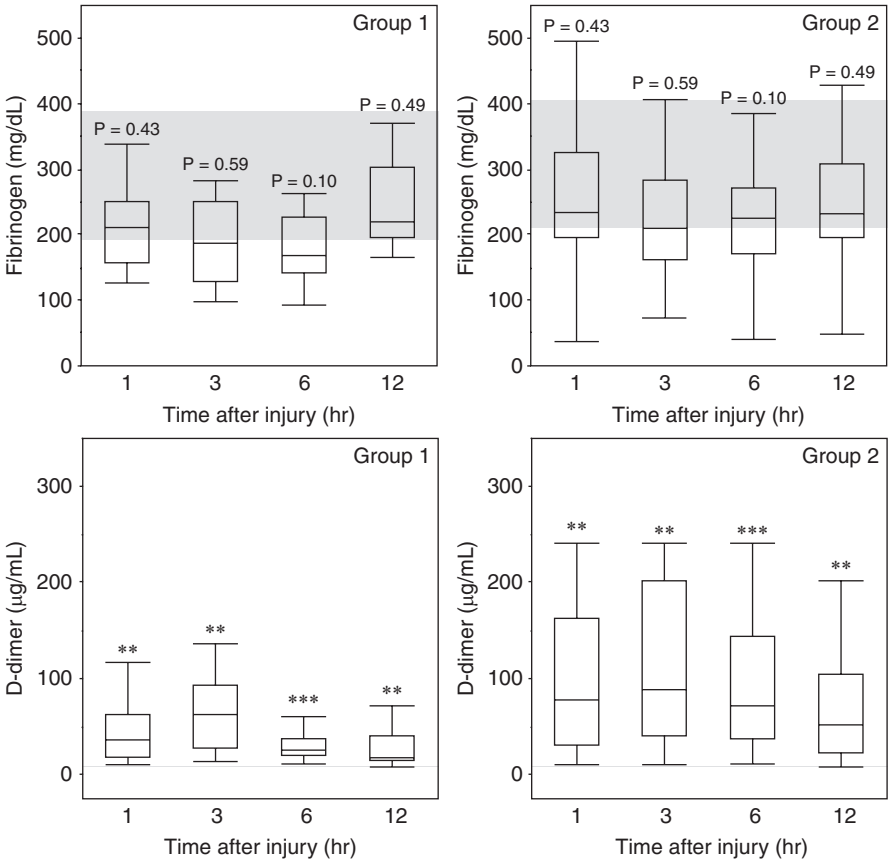

Fig. 9.5 (continued)

9.6 Treatment of Coagulopathy Following TBI

The primary treatment options for TBI-associated coagulopathy are transfusion of blood components, including platelet concentrates, fresh frozen plasma (FFP), fibrinogen, recombinant factor, and antifibrinolytic agents such as tranexamic acid (TXA).

9.6.1 Platelet Concentrates

Platelet concentrate transfusions following TBI are complex. Platelet transfusion is predominantly required in two main situations: thrombocytopenia and platelet dysfunction.

9.6.1.1 Platelet Concentrates for Thrombocytopenia

Thrombocytopenia, secondary to the occurrence of consumptive coagulopathy, is a reported independent indicator of poor outcome in TBI [29]. Patients with platelet count $<175 \times 10^9$ L^{-1} are at increased risk of hematoma enlargement, requiring craniotomy, and death [30]. However, there is no definitive value for starting platelet concentrate transfusions for TBI patients, and $< 100 \times 10^9$ L^{-1} platelets is recommended for patients undergoing elective neurosurgical procedures [49]. This value is also associated with a ninefold adjusted risk of patient death [30]. Although platelet concentrate transfusion is often considered for patients with TBI, current evidence does not indicate that it sufficiently prevents worsening intracranial bleeding [12].

9.6.1.2 Platelet Concentrates for Platelet Dysfunction

Antiplatelet therapy is frequently prescribed for prophylaxis in cardiovascular, cerebrovascular, and peripheral vascular disorders, and one-third of Americans aged ≥40 years report taking preventative aspirin and/or other antiplatelet medications [50]. A systematic review [32] reported that there was a lack of evidence to substantiate the regular use of platelet concentrate transfusions in patients with traumatic ICH and preinjury antiplatelet drugs. In contrast, a prospective study [31] reported that platelet concentrate transfusions improved aspirin-induced, but not trauma-induced, platelet dysfunction in TBI patients. Therefore, while platelet concentrate transfusion is often considered for patients with TBI with preinjury intake of antiplatelet therapy, current evidence on its effectiveness remains conflicting and inconclusive [12].

9.6.2 FFP

Treatments for hyperfibrinolysis in TBI should aim to target coagulation, reverse hyperfibrinolysis, and replenish coagulation factors using FFP. May et al. [51] supports the administration of FFP as an empiric treatment for coagulopathy in patients with a GCS score ≤6. Ivascu et al. [52] reported that 2 U of FFP used for anticoagulant reversal improved mortality. However, several studies [53–55] have reported a lack of improvement in outcome with FFP. Zhang et al. [55] demonstrated that increased perioperative FFP infusion was independently correlated with mortality or worse outcomes across a spectrum of surgical risk profiles. Moreover, overall complications, acute respiratory distress syndrome, and pneumonia rate were significantly increased in patients given FFP transfusions. FFP may also compound the inordinate coagulation trend. Therefore, it is important that clinicians calculate the timing, thresholds, and volume of FFP transfusion in patients with TBI.

9.6.3 Fibrinogen

Fibrinogen, also called coagulation factor I, is the substrate for clot formation. Fibrinogen is reduced in injured patients on admission and is linked to poor outcomes [56]; however, few studies have examined the effects of fibrinogen in TBI patients. Fibrinogen concentrations can be maintained within the range of 150–200 mg/dL by administration of FFP, fibrinogen concentrates, or cryoprecipitate [57].

9.6.4 Recombinant Factor VIIa (rFVIIa)

Treatment using rFVIIa within 4 h after the onset of intracerebral hemorrhage halts hematoma growth, decreases mortality, and improves functional outcomes at 90 days [58]. rFVIIa also enables fast and successful improvement of coagulopathy in TBI patients who were previously refractory to FFP transfusion, indicating its potential as an alternative therapeutic strategy for treating coagulopathy in TBI [59]. Interestingly, patients with TBI who were treated with rFVIIa had reduced hematoma progression compared to those who received placebo [60]. However, the use of rFVIIa is also linked to a higher risk of thromboembolic complications [58]. Recently, a Cochrane review reported that there was a lack of sufficient evidence from randomized clinical trials of rFVIIa in TBI [61] to substantiate the usefulness of hemostatic drugs in improving mortality or disability in patients with TBI. At present, evidence on the effectiveness of rFVIIa is inconclusive, making general recommendations about management using this therapy difficult [12].

9.6.5 TXA

TXA is a synthetic derivative of amino acid lysine that prevents fibrinolysis by inhibiting lysine binding sites on plasminogen [62]. The Clinical Randomisation of Antifibrinolytic in Significant Hemorrhage (CRASH-2) trial [63] was a large international multicenter randomized placebo-controlled trial that examined the effects of the antifibrinolytic agent TXA on death and the transfusion needs of adult trauma patients with significant hemorrhage. While this trial increased knowledge of the use of antifibrinolytic agents in trauma patients, it was unable to confirm that TXA improved the progression of lesions or outcome after TBI [64]. A recent meta-analysis of TXA in patients with acute severe bleeding with trauma and postpartum hemorrhage showed that TXA increased overall survival with no heterogeneity by site of bleeding [65]. The CRASH-3 trial [66] is an international, multicenter, randomized, double-blind, placebo-controlled trial that aims to quantify the effects of early TXA administration on death and disability in patients with TBI. Findings from this trial are expected to shine more light on the effects of TXA on mortality and disability in patients with TBI.

9.7 Summary

Coagulation and fibrinolytic parameters actively fluctuate throughout the acute phase of TBI. Routine assessment of these parameters is required to predict the occurrence of coagulopathy and the associated outcome. Early detection of coagulopathy may contribute to the prevention of bleeding disorders.

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Chapter 10
Stroke

Hitoshi Kobata

Abstract Stroke is a medical emergency which may cause devastating neurological sequelae and death. Rapid assessment and timely intervention are essential for achieving better outcomes. Airway management and ventilatory support for optimizing oxygenation, close neurological evaluation, optimizing fluid and electrolyte levels, maintaining adequate cerebral circulation, fever management, and glucose control are common fundamentals regardless of the stroke subtypes. Target blood pressure varies depending on the stroke subtypes and stage of illness. Moreover, specific attention to detection and mitigation of delayed cerebral ischemia in subarachnoid hemorrhage is essential. Recently there have been substantial reports indicating the beneficial effects of neurocritical care in the managements of stroke patients.

Keywords Subarachnoid hemorrhage · Intracerebral hemorrhage · Acute ischemic stroke

10.1 Introduction

Stroke has been historically identified as a major Japanese national disease ranking as the leading cause of death until 1981 in Japan [1]. More recently with advances in treatment, in 2015, stroke dropped to the fourth leading cause of death [2] and yet has remained as the leading cause of elderly disability requiring nursing care [3]. According to the Japanese Stroke Databank 2015, acute ischemic stroke (AIS) represents 76% of total stroke, while intracerebral hematoma (ICH) accounts for 18%, and subarachnoid hemorrhage (SAH) represents 6% of the total stroke [4]. Severity of stroke can vary depending both on the stroke subtypes and the individual patients.

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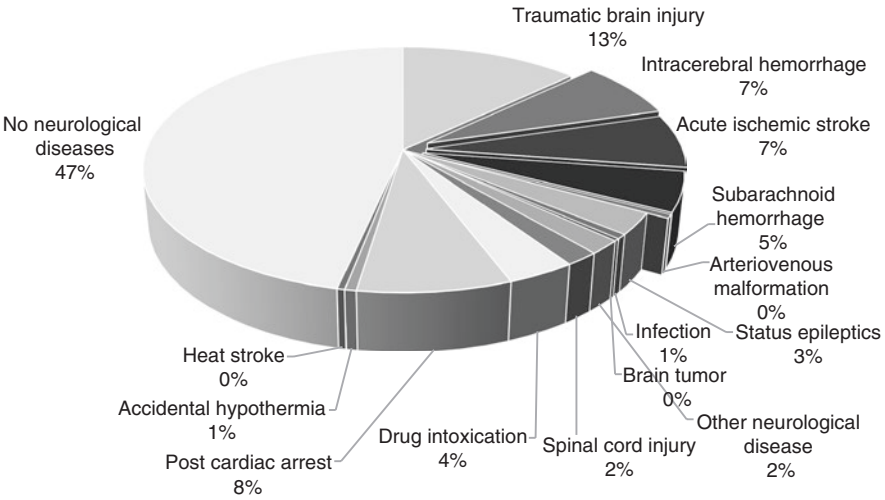

Fig. 10.1 Diagnosis of patients admitted to the ICU in Osaka Mishima Emergency Critical Care Center in 2009

In one tertiary critical care center with devoted neurointensivists, a considerable proportion of stroke patients were initially treated in the ICU: 7% were diagnosed with ICH, 7% AIS, and 5% SAH (Fig. 10.1) [5]. A systematic literature review demonstrated that establishment of a specialized neurologic critical care unit significantly contributed to decreasing mortality and increasing favorable neurological outcomes in critically ill neurological patients including those with stroke [6]. Thus, neurocritical care management is considered to be indispensable in the majority of stoke patients for obtaining better clinical outcomes. A detailed description of each stroke subtype is beyond the scope of this article, and the basic elements of neurocritical care managements such as sedation, fever and glucose control, nutritional support, treatment for epilepsy, and prevention of nosocomial infection will be discussed elsewhere. This article focuses on the essential issues surrounding neurocritical stroke care with an emphasis on recent updates.

10.2 Subarachnoid Hemorrhage

Aneurysmal SAH is a devastating cerebrovascular event associated with profound systemic effects [7–9]. Up to 90% of SAH is caused by a spontaneous rupture of an intracranial aneurysm, which leads to extravasation of high-pressure arterial blood into the subarachnoid space. When the intracranial pressure (ICP) reaches to levels approximating the mean arterial pressure (MAP), intracranial circulatory arrest occurs. This phenomenon was demonstrated clinically by means of ICP monitoring

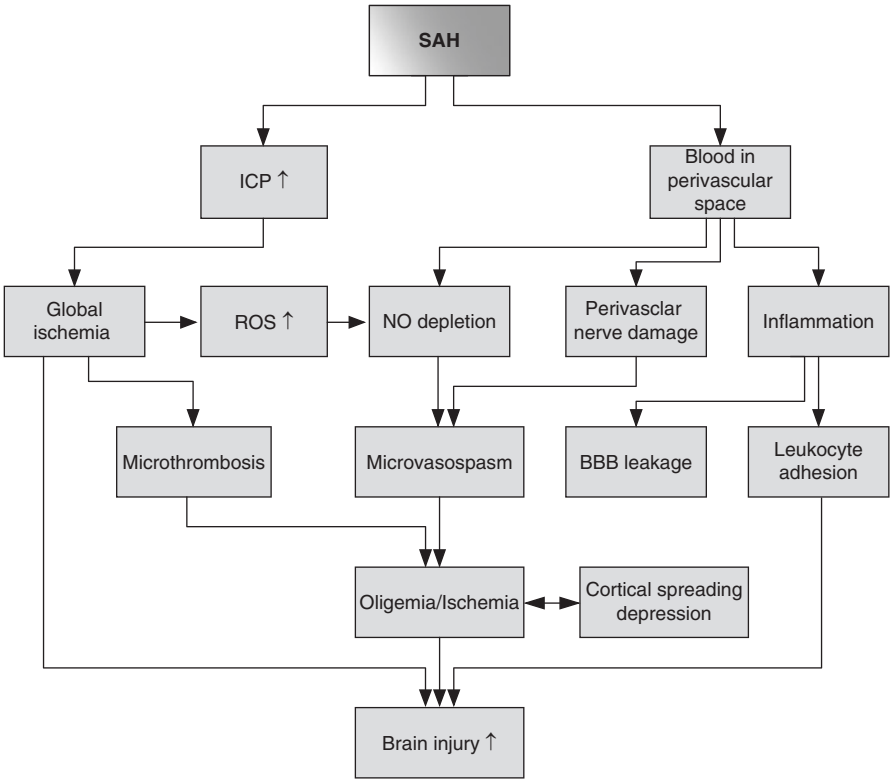

Fig. 10.2 Mechanisms of early brain injury after subarachnoid hemorrhage (SAH). BBB indicates blood-brain barrier; ICP, intracranial pressure; ROS, reactive oxygen species; and NO, nitric oxide (cited from Terpolilli et al., Stroke. 2015)

[10] and transcranial Doppler sonography observation [11]. When the pressure gradient across the aneurysm wall reaches an equilibrium, hemostasis may be facilitated by thrombus formation. At this point, there is a critical reduction in cerebral blood flow (CBF), and the patient falls into a comatose state. Following global cerebral ischemia that occurs immediately after the onset of SAH, the blood in the perivascular space produces early brain injury (EBI), which involves mechanisms of microcirculatory dysfunction, microthrombosis, damage to the blood-brain barrier, and cortical spreading depolarization (Fig. 10.2) [12]. Although aneurysmal rebleeding and infarction from vasospasm may have been traditionally attributed as the leading causes of mortality and morbidity previously, the initial direct effects of severe hemorrhage are by far the leading cause of death in the modern era [13]. Therefore, early and aggressive neurological and cardiopulmonary support is essential, especially for rescue of poor-grade SAH patients. If early repair of the ruptured aneurysm is successfully completed, SAH patients should be intensively monitored

and evaluated for early detection and treatment of delayed cerebral ischemia (DCI) typically arising 4–14 days after onset of SAH.

10.2.1 Initial Evaluation and Treatment

10.2.1.1 Emergent Resuscitation of Poor-Grade SAH

Patients who are comatose or who present with repeated vomiting may need initial airway control by endotracheal intubation immediately after focused neurological evaluation [13]. The majority of these patients have high blood pressure (BP), but some arrive in hemodynamic shock status. Because aneurysmal rerupture is more frequent in poor-grade patients during the ultra-acute period after ictus, and because rerupture is associated with devastating brain injury, endotracheal intubation should be performed after adequate analgesia and anesthesia using muscle relaxants to avoid extra irritation and sympathetic stimulation. The preferred agents are propofol and/or midazolam for anesthesia and fentanyl or remifentanil for analgesia. Currently there is no systematic data addressing recommended BP levels for patients with unsecured aneurysms. Systolic BP >160 mmHg was reported to be a possible risk factor for rebleeding [14]. In Japan, a more aggressive approach for controlling systolic BP as low as 120 mmHg have been adopted in some institutions [15]. Intravenous titration of nicardipine is a preferred option. In contrast, hypotension in the acute stage of SAH is frequently related to cardiogenic shock and may require vasopressor administration. In the absence of invasive ICP monitoring, MAP should be regulated between 70 and 90 mmHg to maintain adequate cerebral perfusion pressure (CPP).

ICP control and CPP optimization are essential in poor-grade SAH. If ICP remains elevated after maximal sedation, osmotherapy (0.5–1.5 g/kg of 20% mannitol solution) and short-term hyperventilation (target $PaCO_2$ level 30–35 mmHg) may be indicated.

Cardiopulmonary complications are common during the acute phase, especially in poor-grade SAH patients. Takotsubo cardiomyopathy is a wall-motion abnormality characterized by apical ballooning and basal hypercontraction. Because other types of wall-motion abnormality, e.g., reverse takotsubo, focal asymmetry, and diffuse hypokinesis, are not uncommon, neurogenic stunned myocardium implies the pathogenesis and may be a more appropriate term for describing this unique stress-induced cardiac dysfunction [16]. Abnormal ST-segment elevation is seen on ECG, and cardiac troponin elevations are frequently encountered. Although the abnormal wall motion is typically transient, in severe cases profound cardiogenic shock coupled with pulmonary edema may occur. Furthermore, neurogenic pulmonary edema may develop with or without neurogenic stunned myocardium. Aggressive cardiopulmonary support is crucial for maintaining optimal oxygen-

ation and CBF: high inspired oxygen fraction, positive end-expiratory pressure to levels of 5–15 cm H_2O, careful diuresis for optimizing volume status, and cardiac output monitoring combined with administration of inotropes may be useful for improving the clinical course.

10.2.1.2 Neurological Evaluation

The severity of neurological impairment at presentation has been considered one of the strongest predictors of outcome. While the Hunt and Hess score relies on some subjective elements [17], the World Federation of Neurological Surgeons (WNFS) scoring system based on the Glasgow Coma Scale (GCS) [18] is simple with less interobserver variability. According to the Hunt and Hess or the WFNS scale, Grade 4 or 5 is classified as poor-grade. Recently, the modified WFNS scoring system was proposed based on the results from a multicenter prospective observational study conducted in Japan [19]. Both the Hunt and Hess and the original WFNS grading system have included scoring for the presence or absence of neurological focal signs, whereas the modified WFNS system is simply graded only by the GCS score. Results from the modified WFNS showed statistically significant relationship to Glasgow Outcome Scale and the modified Rankin score at 3 months (Table 10.1).

In addition, acute pupillary dilatation immediately after onset has been shown to be associated with decreased brain stem blood flow rather than mechanical compression of the oculomotor nerve [20]. Therefore, it can be postulated if CBF can be rapidly restored and recovery of pupillary response is observed during a short period of time, the prognosis may be not always poor.

Table 10.1 Clinical grading scales for patients presenting with aneurysmal subarachnoid hemorrhage

Grade	Hunt and Hess grading system	WFNS grading system	Modified WFNS grading system
I	Asymptomatic, or minimal headache and slight nuchal regidity	GCS sum score 15 without hemiparesis	GCS sum score 15
II	Moderate to severe headache, nuchal rigidity, no focal deficit other than cranial nerve palsy	GCS sum score 14–13 without hemiparesis	GCS sum score 14
III	Drowsiness, confusion, lethargy, or mild focal deficit	GCS sum score 14–13 with hemiparesis	GCS sum score 13
IV	Stupor or moderate to severe hemiparesis, possibly early decebrate rigidity and vegetative disturbances	GCS sum score 12–7 with or without hemiparesis	GCS sum score 12–7
V	Deep coma, decerebrate rigidity, moribund appearance	GCS sum score 6–3 with or without hemiparesis	GCS sum score 6–3

WFNS World Federation of Neurological Surgeons, *GCS* Glasgow Coma Scale

10.2.1.3 Radiological Findings

Diagnosis of SAH is usually confirmed by non-enhanced brain CT scan. CT scanning has a high sensitivity for the detection of subarachnoid blood and offers valuable information for estimating the risk of delayed vasospasm: the classic Fisher group classification [21] and the modified Fisher grading scale [22] are shown (Table 10.2). Superior predictive value for DCI was reported using the modified Fisher scale compared with the original Fisher scale. In poor-grade patients, noncontrast brain CT often demonstrates a distinctive pattern of global brain edema characterized by effacement of the convexity sulci and disruption of the normal gray-white junction, with "finger-like" projections of lucency extending from the white matter to the cortical surface (Fig. 10.3) [23].

Acute diffuse ischemic injury may occur in poor-grade SAH patients and can reflect a form of early brain injury. These lesions, called ictal infarctions, are typically shown on diffusion-weighted MRI in acute phase (Fig. 10.4). Ictal infarctions are typically observed bilaterally as patchy foci and laminar lesions along the cortical gyrus and are not associated with the location of aneurysm rupture [24, 25]. Appearance of ictal infarction is a predictor of poor outcome.

Catheter cerebral angiography remains the gold standard for definitive identification of the aneurysm and can be followed immediately by interventional aneurysm treatment. CT angiography (CTA) is less invasive and can be performed promptly following the initial brain CT. However, extravasation of contrast media from the ruptured aneurysm may be seen during CTA resulting in extremely poor outcome (Fig. 10.5) [26].

Table 10.2 Comparison of the original Fisher radiological grading scale and a proposed modified grading scale

	Fisher scale	Modified Fisher scale
0	…	No SAH or IVH
1	No blood detected	Minimum or thin SAH, no IVH in either lateral ventricle
2	Diffuse deposision or thin layer with all vertical layers of blood < 1 mm thick	Minimum or thin SAH with IVH in both lateral ventricles
3	Localized clots and/or vertical layers of blood ≥ 1mm in thickness	Thick SAH, no IVH in either lateral ventricle
4	Diffuse or no subsrachnoid blood, but with intracerebral or intraventricular clot	Thick SAH with IVH in both lateral ventricles

The modified Fisher scale incorporates the effect of IVH on the risk of vasospasm and delayed ischemic damage

Delayed cerebral ischemia can be predicted by the appearance of the initial CT scan of the brain. *SAH* subarachnoid hemorrhage, *IVH* intraventricular hemorrhage

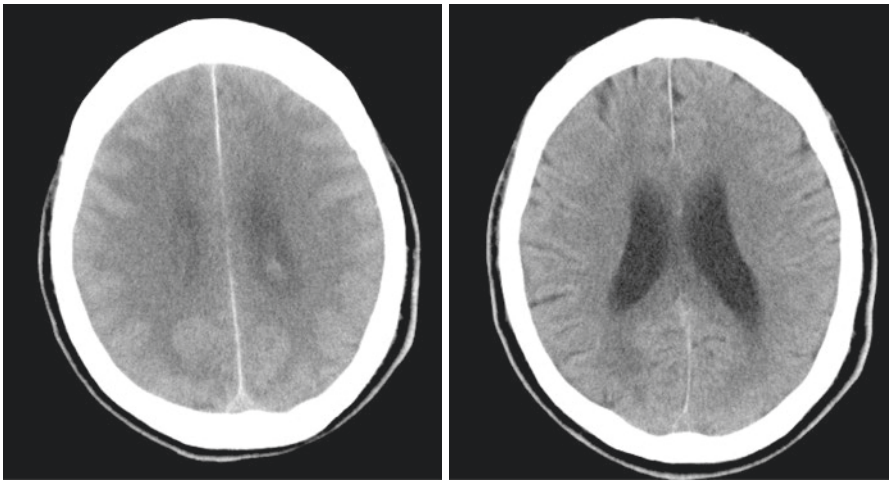

Fig. 10.3 Global edema on the admission CT scan (SAH day 0) in a 57-year-old man with a Hunt-Hess grade 5 SAH due to rupture of a left posterior cerebral artery aneurysm that was clipped. A follow-up CT scan on SAH day 23 showed normalization of the CT findings. The patient survived with moderate cognitive disability at 6 months

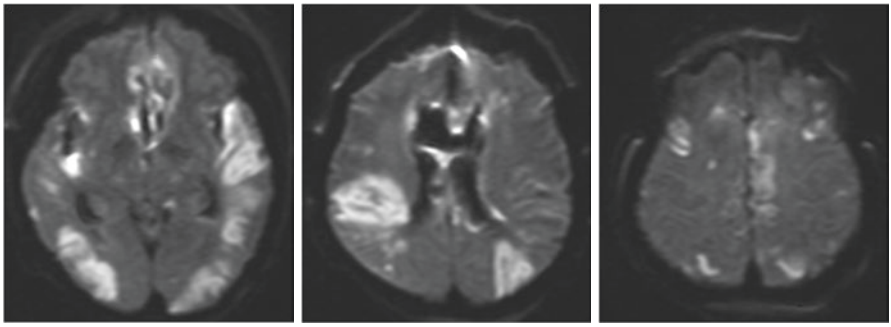

Fig. 10.4 Diffusion-weighted image demonstrating ictal infarction. A 75-year-old woman with a ruptured left anterior cerebral artery aneurysm

10.2.1.4 Laboratory Findings

Routine laboratory data can provide useful information for prognostication. Elevations in variable such as stress-induced hyperglycemia [27], the serum glucose/potassium ratio [28], and plasma d-dimer levels [29] on admission have been reported to be correlated with poor outcome. Combinations of individual laboratory parameters and physiological measures such as the physiologic derangement score

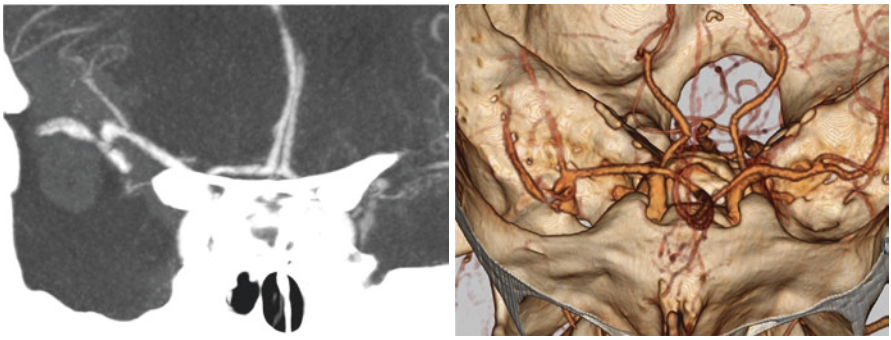

Fig. 10.5 A 69-year-old man arrived with Hunt and Hess grade 5 caused by a ruptured right middle cerebral artery aneurysm. Extravasation of contrast media was demonstrated from the ruptured aneurysm. The patient underwent emergency decompressive craniectomy and clipping of the aneurysm but subsequently died

Table 10.3 Management of poor-grade subarachnoid hemorrhage in acute phase

Secure airway
Analgesia and anesthesia
Control systolic BP at least <160 mmHg (preferred <120 mmHg)
Optimize oxygenation
Evaluate WFNS and Hunt-Hess grade
Assess patient for cardiopulmonary neurogenic injury
ECG, echocardiography, chest X-ray, hemodynamic monitoring
ICP and CPP control
CBC, blood chemistry, hemostatic test
Antiepileptics for seizing patients
Brain CT and CT angiography (MRI and MR angiography)

BP blood pressure, *ECG* electrocardiogram, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, *CBC* complete blood count, *CTA* CT angiography

[30] and the simplified acute physiology score [31] have been shown to reflect SAH severity and may be valuable prognostic indicators. Table 10.3 summarizes management of poor-grade SAH in acute phase before aneurysm repair.

10.2.1.5 Ruptured Aneurysm Repair

Surgical clipping or endovascular coiling for the ruptured aneurysm should be performed as early as possible when indicated [7, 8, 32]. In addition, emergency external ventricular drainage may be indicated for comatose patients due to acute hydrocephalus [6].

10.2.2 Prevention of Delayed Cerebral Ischemia Following Aneurysm Repair

10.2.2.1 General Management

For patients who survive the initial bleeding event of a ruptured aneurysm and have received successful aneurysm repair, DCI is one of the most important causes of mortality and poor neurological outcome. Although large-vessel narrowing with subsequent low flow may be one of the multiple mechanisms of DCI, causal framework now also includes EBI, microcirculatory dysfunction with loss of autoregulation, cortical spreading depolarization, and microthrombosis [33]. The measure aimed at prevention, early detection, and treatment of DCI should be emphasized for better outcomes.

Prophylactic triple-H therapy (hypertension, hypervolemia, hemodilution), which has been a mainstay for prevention of DCI, is no longer recommended [7, 8, 32]. There is evidence for harm from aggressive administration of fluid aimed at achieving hypervolemia. Intravascular volume management should target euvolemia and avoid prophylactic hypervolemic therapy [8].

Nimodipine is the only pharmacologic intervention to date associated with better outcomes in SAH patients; however, its use is not approved in Japan. Instead, fasudil hydrochloride and ozagrel sodium have been recommended as pharmacotherapy for DCI prevention [32].

Hyponatremia and hypovolemia frequently occur after SAH and are associated with impending DCI and poor outcome [33]. Hyponatremia is caused by either cerebral salt wasting (CSW) or the syndrome of inappropriate antidiuretic hormone (SIADH). In CSW, patients are hyponatremic due to active urinary sodium excretion and not because of water retention. Patients with CSW are hypovolemic; consequently fluid restriction, the typical treatment for SIADH, can be deleterious and increases the risk of DCI. Patients with CSW should be managed by salt supplementation and normal saline, with fludrocortisone in refractory cases [8, 33].

Fever is common in SAH and is independently associated with poor outcome, and cerebral infarction is more common in febrile patients [8]. Fever appears to be part of a systemic inflammation that is frequently noninfectious in origin. Advanced fever control with surface or intravascular cooling is effective in lowering the fever burden and has been associated with improved outcomes [34].

Abnormalities in glucose metabolism occurring after SAH may exacerbate the initial brain injury. Serum glucose should be maintained below 200 mg/dL with avoidance of hypoglycemia (<80 mg/dL) [8]. Regarding anemia, patients should receive packed RBC transfusions to maintain hemoglobin concentration above 8–10 g/dL [8].

Early detection of DCI is crucial for initiating timely intervention. Clinical examination is the most reliable method for detecting DCI in awake patients; however, in poor-grade patients remaining in persistent coma or undergoing deep sedation, clinicians must rely on available monitoring technology (Table 10.4). For

Table 10.4 Methods for detection of delayed cerebral ischemia

Clinical examination	Not available for comatose or sedated patients
Transcranial Doppler sonography	Noninvasive. Indirect detection of large-vessel narrowing. Velocities <120 cm/s in the MCA show high negative predictive value and >180 cm/s indicate high positive predictive value
Vascular imaging	Conventional angiography is the gold standard; intervention is available as needed. CT angiography and MR angiography are less invasive and readily available, useful for screening methods
Brain perfusion imaging	CT perfusion and MR perfusion allow CBF assessment
Continuous electroencephalography	Reductions in the alpha/delta ratio or in alpha variability are most sensitive and specific for predicting DCI
Multimodality monitoring	ICP, $PbtO_2$, microdialysis

MCA middle cerebral artery, *CBF* cerebral blood flow, *DCI* delayed cerebral ischemia, *ICP* intracranial pressure, *$PbtO_2$* brain tissue oxygenation

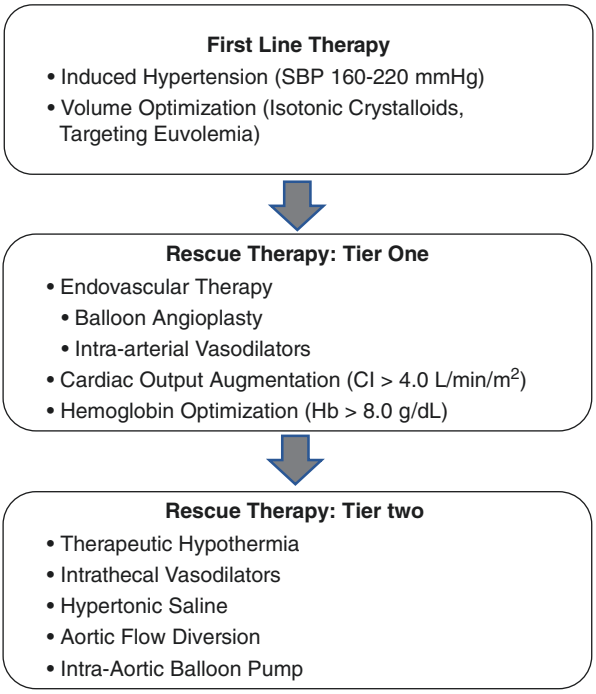

Fig. 10.6 Stepwise approach to the treatment of active DCI from vasospasm. The order or the intensity of therapy should be adapted to each individual situation. *CI* cardiac index, *Hb* hemoglobin, *SBP* systolic blood pressure (cited form Francoeur and Mayer, Critical Care. 2016)

new-onset DCI patients, hemodynamic augmentation is indicated, including induced hypertension with use of vasopressors and normal saline bolus administration. Endovascular treatment using intra-arterial vasodilators and/or angioplasty may be considered for vasospasm-related DCI (Fig. 10.6).

Routine use of anticonvulsant is not recommended. However, because nonconvulsive seizures are common in poor-grade SAH, use of continuous EEG monitoring should be considered, especially in cases of with poor-grade SAH who fail to regain consciousness or who demonstrate neurological deterioration of undetermined etiology [8].

10.3 Intracerebral Hemorrhage

Spontaneous intracerebral hemorrhage (ICH) is a medical emergency and remains a significant cause of morbidity and mortality. Rapid diagnosis and attentive management is crucial, because early deterioration is common in the first few hours after ICH onset [35]. Timely treatment is necessary for maximizing functional outcome. Basic treatment principals during the acute phase are shown in Table 10.5.

10.3.1 Predicting ICH Expansion on CT Scan

Expansion of ICH tends to occur early after onset and has been shown to increase the risk of poor outcomes. Among patients undergoing brain CT within 3 h of ICH onset, 28–38% have hematoma expansion of greater than one third of the initial

Table 10.5 Summary of treatment principals for ICH in acute phase

Diagnostic studies	CT/MRI/angiography to detect spot sign and rule out secondary ICH (i.e., aneurysm or AVM rupture)
Airway/respiration	Ensure adequate airway protection, ventilation, and oxygenation: intubation and mechanical ventilation if necessary
Anticoagulation	Reversal of any antithrombotic/antiplatelet therapy as rapidly as possible
Intracranial pressure	Control of ICP by head up 30°, drip injection of glycerol or mannitol, and/or placement of an external ventricular drain
Hemodynamic management	Acute reduction of SBP targeting 140–180 mmHg
Anticonvulsant medication	Treat clinical seizures with antiepileptic medications, the prophylactic use of anticonvulsants is not recommended, and continuous EEG monitoring is recommended to detect NCSE
Blood glucose	Monitor blood glucose and avoid hyperglycemia (<180 mg/dL), avoid hypoglycemia
Temperature	Avoid hyperthermia. Fever is associated with poor outcome
Deep vein thrombosis prophylaxis	Utilize pneumatic compression devices
Rehabilitation	As early as feasible when vital signs become stable

ICH intracerebral hemorrhage, *AVM* arteriovenous malformation, *ICP* intracranial pressure, *SBP* systolic blood pressure, *EEG* electroencephalogram, *NCSE* nonconvulsive status epilepticus

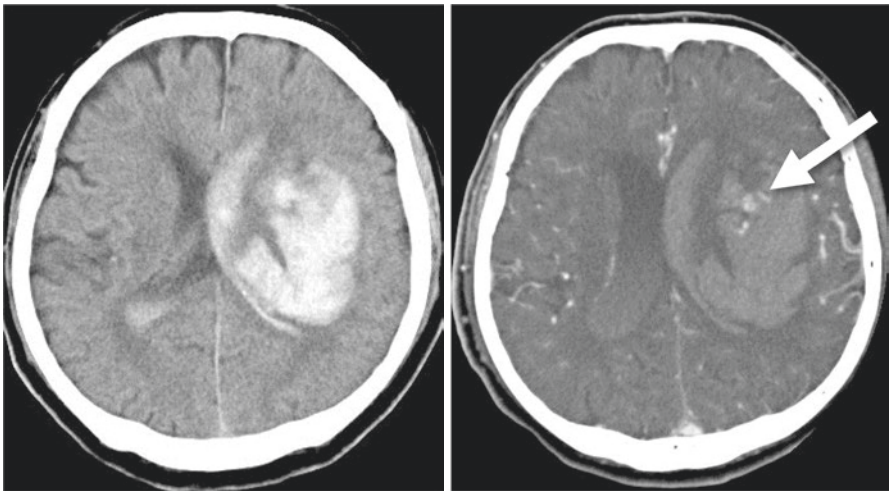

Fig. 10.7 Left combined putaminal-thalamic hemorrhage on admission CT. CT angiography source image demonstrates tiny contrast enhancement "spot sign" (arrow)

hematoma volume on follow-up CT [35]. Thus, identifying ICH patients at high risk of hematoma growth is clinically important.

Several patterns of CT findings have been reported in association with hematoma expansion. The spot sign is defined as tiny unifocal or multifocal contrast enhancement within an acute region of ICH visible on CTA source imaging (Fig. 10.7). This finding corresponds with a site of active, dynamic hemorrhage [36]. The blend sign [37] and the black hole sign [38] on non-contrast brain CT are also indicators of early hematoma expansion. CTA is also useful for early diagnosis of other underlying vascular abnormalities.

10.3.2 Blood Pressure Control

Elevated BP has been associated with hematoma growth, mortality, and disability after ICH. Recent clinical trials have evaluated the role of intensive BP reduction after ICH (Table 10.6) [39]. The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) study showed a trend toward lower relative and absolute hematoma growth from baseline onset to 24 h in the intensive treatment group [40]. The INTERACT II concluded that intensive lowering of BP did not result in a significant reduction in the rate of the primary outcome of death or severe disability; however, an ordinal analysis of modified Rankin scores indicated improved functional outcomes with intensive lowering of BP [41]. The Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) trial confirmed the feasibility and safety of early rapid BP reduction in ICH [42]. The

Table 10.6 Prospective clinical trials of blood pressure management in ICH

Trial	Study design	SBP target	Onset to randomization time	Medical intervention used	End point
INTERACT	*n* = 404, RCT, PROBE, phase II	Standard: <140	<6 h	Variable	24 h hematoma growth
		Intensive: <140			
INTERACT II	*n* = 2839, RCT, phase III	Standard: <140	<6 h	Variable	mRS at 90 days
		Intensive: <140			
ATACH	*n* = 60, RCT, phase II	Tier 1: <170–200	<6 h	Nicardipine	Treatment feasibility and safety
		Tier 2: <140–170			
		Tier 3: <110–140			
ATACH-II	*n* = 1200, RCT, PROBE, phase III	Standard: <180	<4.5 h	Nicardipine	mRS at 90 days
		Intensive: <140			
ICH ADAPT	*n* = 75, RCT, PROBE, phase II	Standard: <180	<24 h	Labetalol	Perihematoma CBF
		Intensive: <150		Hydralazine	
				Enalapril	
ICH ADAPT II	RCT, PROBE, phase III	Standard: <180	<6 h	Labetalol	DWI lesion frequency at 42 h
		Intensive: <140		Hydralazine	
				Enalapril	

ICH intracerebral hematoma, *RCT* randomized control trial, *PROBE* prospective randomized open blinded end point, *CBF* cerebral blood flow, *mRS* modified Rankin Scale, *SBP* systolic blood pressure, *DWI* diffusion-weighted image
Cited from Lim-Hing and Rincon, Frontiers of Neurology 2017 [39]

recently completed ATACH-II study concluded that the treatment measures aimed at achieving a target SBP of 110–139 mmHg did not result in a lower rate of death or disability compared with standard SBP reductions targeted at 140–179 mmHg [43]. In the Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial (ICH ADAPT), rapid BP lowering did not reduce perihematoma CBF indicating that acute BP reduction does not precipitate cerebral ischemia in ICH patients [44]. The follow-up ICH ADAPT II uses MRI and DWI for assessing the hypothesis that aggressive antihypertensive therapy will alter the natural history of hematoma growth and improving ICH primary outcomes [45]. Based on findings from these new clinical trials, it is reasonable to strive for a target SBP between 140 and 180 mmHg with modifications of individual tailored therapy based on patient comorbidities and the original level of chronic hypertension.

10.3.3 Reversal of Coagulopathy

Antithrombotic medications are a risk factor for the occurrence of ICH, as well as for hematoma expansion, if an ICH occurs. After diagnosis of acute ICH, patients taking a vitamin K antagonist should emergently receive agents to normalize the INR to 1.4 or below. For rapid reversal of warfarin, use of prothrombin complex concentrate (PCC) agents is suggested over fresh frozen plasma (FFP). The four-factor PCC, containing factors II, VII, IX, and X together with the endogenous inhibitor proteins S and C, was recently approved in Japan. It may be superior to FFP with respect to normalizing the INR and was associated with less hematoma expansion than FFP in warfarin-associated ICH patients [46]. Current guidelines [47] recommend the use of vitamin K 10 mg administered intravenously by slow push, in conjunction with another more rapidly acting agent (e.g., PCC). Idarucizumab is a new reversal agent which binds dabigatran to neutralize its anticoagulant effects within minutes of administration. Because there are no specific agents to reverse factor Xa inhibitors now, administration of a four-factor PCC may be considered for reversal of life-threatening bleeds in patients taking factor Xa inhibitors (apixaban, rivaroxaban, edoxaban) [35, 47].

Presently, the influence of antiplatelet agents on ICH expansion or neurologic outcome is controversial. Platelet transfusions are not recommended for most patients with antiplatelet-related ICH except for those who are undergoing an emergent neurosurgical procedure [47].

10.3.4 Surgical Treatment of ICH

Patients with cerebellar hemorrhage with maximum hematoma diameter ≥3 cm who are deteriorating neurologically or who have brain stem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of

the hemorrhage as soon as possible. For most patients with supratentorial ICH, the usefulness of surgery is not well established. Surgery may be considered for deteriorating patients with putaminal hematoma ≥31 ml and subcortical hematoma located ≤1 cm from brain surface [32, 35].

In addition to conventional microsurgical approaches, minimally invasive techniques, including endoscopic hematoma aspiration or instillation of a thrombolytics such as urokinase into the hematoma with aspiration of contents, are also indicated [32, 35].

10.4 Acute Ischemic Stroke

Reperfusion therapy with intravenous tissue plasminogen activator (tPA) and/or endovascular thrombectomy has become a mainstay of acute ischemic stroke (AIS) management. Intensive care management of AIS is focused on reducing complications of reperfusion, such as hemorrhagic transformation, and minimizing secondary brain injury, including brain edema and progressive stroke. For detailed information on reperfusion therapy, refer to the latest Stroke Guideline [32, 48].

10.4.1 Basic Management

A sample protocol for the basic management of AIS patients is shown in Table 10.7. Severe stroke patients frequently need ventilatory or hemodynamic support provided in an ICU setting. Close neurological evaluation is the fundamentals to the

Table 10.7 Sample of basic management of acute ischemic stroke

Neuro check every 15 min for 2 h, then every 30 min for 6 h, and then hourly
Supplemental oxygen to keep O_2 saturation >94%
BP check every 15 min for 2 h, then every 30 min for 6 h, and then every hour for 16 h
Keep BP after alteplase treatment <180/105 mmHg (note: this is lower than pretreatment values); if no alteplase keep BP <220/120 mmHg
Keep glucose 140–180 mg/dL; consider insulin drip if the blood glucose is persistently >200 mg/dL
Administer IV fluids, preferably isotonic saline, at 1.5 ml/kg/h initially, with a goal of euvolemia
Continue telemetry/bedside cardiac monitoring for at least 72 h after admission
Treat fever sources with appropriate antibiotics or therapies while preventing fever with antipyretics
Head-of-bead elevation to avoid aspiration
Patients should be NPO until evaluated for swallowing difficulties, bedside swallow test (30 ml water PO) before anything else PO

BP blood pressure, *NPO* nothing per os, *PO* per os
Summarized from Emergency Neurological Life Support: Acute Ischemic Stroke [49]

management of AIS patients, especially those undergoing reperfusion therapy [49]. The use of NIH Stroke Scale is recommended as an objective measure for assessing the stroke severity. Emergency brain CT scanning is crucial in cases of neurological deterioration. Although supplemental oxygen is needed to keep SpO_2 >94%, excessive oxygenation has been associated with adverse outcomes [49].

Strict blood pressure control less than 180/105 mmHg is required for at least 24 h after intravenous administration of tPA to avoid hemorrhagic complication, while permissive hypertension up to 220/120 mmHg is indicated for those treated without tPA [32, 48].

Persistent in-hospital hyperglycemia during the first 24 h after AIS is associated with worse outcomes compared with normoglycemia. It is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140–180 mg/dL and to closely monitor for the prevention of hypoglycemia. Hypoglycemia (blood glucose <60 mg/dL) should be treated. Sources of hyperthermia (temperature >38 °C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients [48].

Early decompressive craniectomy is associated with better favorable functional outcomes. Performing decompression before herniation may be the most important temporal consideration [50].

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Chapter 11
Multiple Injury

Takayuki Ebihara

Abstract It is important to manage multiple injury patients so as not to experience the lethal triad of hypothermia, metabolic acidosis, and coagulopathy. The treatment method in patients with massive exsanguination is greatly different from that of elective surgery patients, and it is necessary to implement damage control surgery (DCS), based on the patient's general condition. The strategy is divided into DCS for controlling surgical bleeding and damage control resuscitation (DCR) for non-surgical bleeding. Damage control surgery consists primarily of abbreviated lifesaving surgery, and DCR consists of maneuvers to avoid the lethal triad and administer critical care such as permissive hypotension, resuscitative fluid administration, and hemostatic resuscitation. Managing multiple trauma with traumatic brain injury (TBI) is different from managing single torso injury and takes into account factors such as avoiding hypotension and abdominal compartment syndrome, the effect of resuscitative endovascular balloon occlusion of the aorta on intracranial pressure, adverse effects of colloids on hemostasis, and indications for higher platelet administration, which are introduced in this chapter, respectively. The management of patients with multiple trauma and TBI remains mostly unknown, although evidence has been steadily accumulated.

Keywords Multiple injury · Traumatic brain injury · Damage control · Permissive hypotension · Massive transfusion protocol

11.1 Introduction

Hypothermia, metabolic acidosis, and coagulopathy constitute a pathological condition that leads to a poor outcome in the treatment and management of patients with multiple injuries and is called the lethal triad [1]. In general, hypothermia

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refers to a core body temperature <34 °C, acidosis refers to pH <7.2, and coagulation disorder refers to the manifestation of nonmechanical bleeding (described later). In severe trauma, these factors adversely affect each other and can cause a bloody vicious cycle [2]. In recent years, it has been pointed out that hemodilution due to excess fluid resuscitation during trauma management may lead to further resuscitation-associated coagulopathy (RAC). Some authors consider RAC occurring with the lethal triad as "the lethal quartet" [3, 4]. In treating patients with severe multiple trauma and hemorrhagic shock, avoiding and/or recovering from the lethal triad is very important in management. However, curative hemostasis surgery at the injured site is not simple for patients who have collapsed vital signs, and opening the abdominal and/or thoracic cavity for a long time aggravates hypothermia and the collapse of the coagulation fibrinolytic cascade associated with increased exsanguination. Furthermore, these factors can cause severe lactic acidosis, which may result in opposite effects. Two decades ago, resuscitation by a large amount of crystalloids and packed red blood cell (RBC) transfusion were widely administered to maintain tissue perfusion and sufficient oxygen delivery against traumatic hemorrhagic shock [5]. Such large volume resuscitation enabled the withdrawal of hemorrhagic shock, reduced early death due to exsanguination after severe trauma injury, and reduced the risk of acute renal failure [5, 6]. However, on the other hand, acute heart failure, pulmonary edema, and abdominal compartment syndrome (ACS) [7] due to intestinal edema (as described later) had increased following massive crystalloid resuscitation. In addition, these pathophysiological alterations increase inflammatory cytokine production, reperfusion injury, and immunity decline, which increase sepsis and late death because of multiple organ dysfunctions [8]. Based on these findings, since the mid-1980s, instead of performing curative surgery as the initial treatment of severely traumatized patients with unstable vital signs, damage control such as gauze packing to the surrounding bleeding organs to suppress the insult was introduced and has contributed to the improvement in the survival rate [5, 6, 9].

The phrase "damage control" is a naval military term [9]. Damage control in the military field refers to maintaining preliminary buoyancy and restoring power while maintaining water tightness and airtightness; especially in a ship in which fire, collision, stranding, or explosion has occurred, it refers to removing inflammable material, extinguishing a fire, and eliminating gas smoke. Moreover, by preparing emergency equipment, the spread of damage can be stopped, injured people can be treated, and failures and power supply can be restored [10, 11]. Furthermore, as for the origin of the damage control concept, it was introduced at the beginning of the Napoleonic war in the early 1800s [10]. At that time, the idea was that it was necessary to perform amputation within 24 h when the patient's general condition was sufficiently stable to prevent death from severe extremity injury, which was difficult to treat.

Damage control surgery (DCS) is incorporated as part of the damage control strategy. This chapter details the damage control strategy of multiple injury and the influence and related issues that they have on neurocritical care.

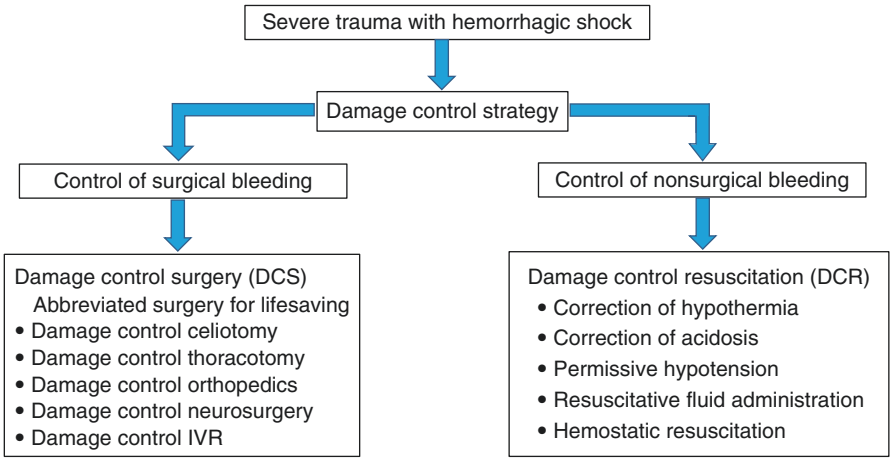

Fig. 11.1 Damage control strategy for severe trauma with hemorrhagic shock is divided into two methods. There are procedures for controlling surgical bleeding for a respective region and resuscitation for nonsurgical bleeding. *IVR* interventional radiology

11.2 Damage Control Strategy

Damage control strategy consists of two fundamental actions (Fig. 11.1). The first fundamental action is DCS, the objective of which is controlling surgical bleeding. It was initially applied to abdominal trauma; the concept has spread to celiotomy, thoracotomy, orthopedics, neurosurgery, and interventional radiology (IVR) [12–15]. The second fundamental action is trauma resuscitation, the purpose of which is controlling nonsurgical bleeding. The paradigm of management is shifting from the conventional high-volume resuscitation to low-volume resuscitation (i.e., damage control resuscitation [DCR]).

11.3 Damage Control Neurosurgery and Intracranial Pressure-Related Issues

In 2004, Rosenfeld [14] emphasized that rapid intervention of neurological treatment is equivalent to damage control of neurosurgery. They reported that the management of sustained bleeding in the torso is a priority in patients with multiple traumas accompanied by traumatic brain injury (TBI); if the patient's condition is stable, an intracranial pressure (ICP) sensor should be inserted in the emergency room or operating room in tandem with laparotomy and/or thoracotomy. The *Guidelines for the Management of Severe Traumatic Brain Injury* (third edition) published in 2007 recommended ICP should be monitored in TBI patients with Glasgow Coma

Score (GCS) of 3–8 and either an abnormal CT scan or a normal CT if two or more of the following features were noted: age >40 years, unilateral or bilateral motor posturing, or systolic blood pressure (sBP) <90 mmHg [16]. However, the latest (fourth edition) of the guidelines published in 2017 only recommends managing severe TBI patients by using information from ICP monitoring to reduce in-hospital and 2-week postinjury mortality. There was no mention of what condition of the patients for whom ICP should be monitored; however, if the value exceeds 22 mmHg, it is desirable to treat the patient because of increased mortality [17]. Also, as soon as the fourth edition of the guidelines was published, the results of the Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp) trial were reported, which could affect the recommendation. The RESCUEicp trial is a prospective randomly assigned study of 408 patients with intracranial hypertension (i.e., ICP >25 mmHg) that compared the effect of decompressive craniectomy versus that of ongoing medical care [18]. The results revealed that decompressive craniectomy patients have lower mortality, higher rate of persistent vegetative state, and severe disability. However, moderate disability and good recovery rate were similar between two groups. This finding was not contrary to the results of the 2017 guidelines. An article in which the guidelines indicated that mortality increases above ICP 22 mmHg was based on the report by Sorrentino et al. [19]. They conducted subgroup analysis of age and sex and concluded the mortality threshold did not change; however, the threshold of favorable outcome was 18 mmHg in female patients or an age >55 years. The guideline did not support subgroup analysis results of sex and age because of the small number of cases; thus, the desirable ICP may differ, depending on sex, and age is an interesting topic for the future research.

Abdominal compartment syndrome is also very important as a pathophysiological condition at a risk of elevating the ICP. The intra-abdominal pressure (IAP) is usually maintained at 0–5 mmHg, and an IAP ≥12 mmHg at rest in the supine position is defined as intra-abdominal hypertension (IAH) [20]. If the IAP rises because of abdominal trauma or intestinal edema caused by massive transfusion, the intrathoracic pressure (ITP) would also rise through the diaphragm [21]. Rising ITP decreases venous return, which increases ICP and diminishes cerebral perfusion pressure (CPP) [22]. Moreover, the worsening effect of ACS on whole body organs is substantial. The following may occur because of elevated IAP and ITP: reduced cardiac output and increased afterload in the cardiovascular system [22, 23], increased airway pressure and ventilatory failure in respiratory system [24], reduced urine volume because of hypoperfusion of the renal parenchyma and vein in the visceral organs [25], disordered mitochondrial function and energy metabolism in the liver [26], and further exacerbated edema and circulation in digestive organs [27]. Therefore, a diagnosis of ACS requires immediate intervention, and nonsurgical treatments and/or surgical management are available [20]. For primary ACS caused by abdominal trauma, decompressive laparotomy (DL) and an open abdomen are the indicated surgical treatments. For secondary ACS due to excessive volume resuscitation, nonsurgical treatment is the first-line approach [20, 28]. Nonsurgical treatment consists of five methods, as follows [20]:

1. To improve abdominal wall compliance, the use of sedatives, analgesics, muscle relaxants, and management with lowering the head to ≤30° may be considered.
2. To remove digestive tract contents, nasogastric tube insertion, colorectal drainage, and intestinal peristalsis should be administered.
3. Percutaneous drainage should be considered to remove abdominal cavity contents.
4. To control fluid balance, restricting excessive volume resuscitation and using diuretics may be considered.
5. To maintain organ function, ventilation and alveolar recruitment should be optimized.

If IAP persists at ≥20 mmHg and other organ disorders appear, despite the nonsurgical management, then it is desirable to consider DL [20, 28]. In 2018, a systematic review and meta-analysis of 286 patients with ACS who received DL was published [29]. According to the article, IAP was decreased on averate by 18.2 ± 6.5 mmHg and fell within the normal range. Moreover, heart rate, central venous pressure, pulmonary capillary wedge pressure (i.e., PCWP), and peak inspiratory pressure (i.e., PIP) were decreased; the ratio of partial pressure arterial oxygen and fraction of inspired oxygen (i.e., P/F ratio) and urinary output were increased in adult patients. Nearly similar hemodynamic beneficial effects were also observed in pediatric patients, although the reported mortality rate was as high as 49.7% for adults and 60.8% for children. Based on the aforementioned findings, it was concluded that further validation is required to determine the severity and optimal timing for which DL is effective.

11.3.1 Damage Control Resuscitation

The DCR consists of the following five components [30]: (1) recovery from hypothermia, (2) correction of metabolic acidosis, (3) permissive hypotension, (4) restrictive fluid administration, (5) and hemostatic resuscitation. Each component and related issues are described below.

11.3.2 Correction of Hypothermia and Metabolic Acidosis

Hypothermia can occur for a variety of reasons such as tissue hypoperfusion, rapid infusion, transfusions, and skin exposure during surgery in patients with severe trauma. The risk of death increases to 41-fold when the core body temperature is less than 35 °C, the platelet function and all coagulation factor activities decrease when the temperature falls below 34 °C, and the mortality rate is nearly 100% when the temperature is ≤32.8 °C [31]. The supplementation of coagulation factors is ineffective, and temperature recovery is the only treatment in hypothermia-induced coagulopathy.

It is wandering away from the main subject; many discussions exist regarding the effect and complications of induced hypothermia in TBI patients. There are two methods for inducing hypothermia. Prophylactic hypothermia is administered before ICP elevation, and therapeutic hypothermia is used for treatment-resistant ICP elevation. These treatment effects have often conflicted in previous reports. In response to a report by Clifton et al. in 2011, indicating early 33 °C prophylactic hypothermia shows no difference in mortality and outcome, compared with normothermia [32]; the Brain Trauma Foundation guidelines published in 2017 do not recommend early (i.e., within 2.5 h) short-term hypothermia to improve outcomes in patients with diffuse injury [17]. Current study subjects of the therapeutic hypothermia management have shifted to duration, depth, rewarming, and which patient populations. Clinicians also need to pay attention to metabolic acidosis at trauma resuscitation. Tissue hypoperfusion due to hemorrhagic shock causes the accumulation of lactic acid and metabolic acidosis [33]. In addition, clinicians also need to pay attention because the administration of more than 2000 mL of normal saline (0.9%) at resuscitation may cause high chloride acidosis and subsequent coagulopathy [33].

11.3.3 Permissive Hypotension and Restrictive Volume Administration

Permissive hypotension is a strategy that allows the management of blood pressure lower than normal tissue perfusion pressure with the purpose of not exacerbating bleeding until surgical bleeding is controlled [34, 35]. This concept has had much focus in this decade, although it was described in 1918 by Cannon et al. [36]. They mentioned in the article for the first time the harmfulness of administering volume resuscitation before achieving hemostasis in patients with trauma injury and advocated maintaining an sBP of 70–80 mmHg until curative hemostasis is achieved. Permissive hypotension is indicated for patients with a penetrating torso injury not accompanied by severe TBI, and low-volume resuscitation, which restricts massive crystalloid administration, is used to control the sBP to 80–90 mmHg and the mean arterial blood pressure (mAP) to 50 mmHg [34]. Restrictive volume administration may provide many advantages such as mitigation of dilutional coagulopathy (i.e., RAC), suppression of "pop" a clot phenomenon, peeling off the thrombus of hemostasis by elevated blood pressure leading to rebleeding, and avoiding resuscitation injury by massive crystalloid administration, as mentioned previously [6]. However, care should be taken in sBP and infusion management in patients with severe TBI and in patients with brain injury and multiple trauma. It has long been important to avoid hypotension to reduce secondary injury and brain swelling of TBI [37], although how to manage blood pressure and volume resuscitation in patients with severe TBI and multiple injuries has not been determined. The 2005 American Heart Association's *Guidelines for Cardiovascular Care* reported that administering rapid infusion with an sBP target value of ≥100 mmHg is recommended only for blunt trauma or for penetrating trauma to the brain or extremities alone [38].

The *European Guideline on Management of Major Bleeding and Coagulopathy Following Trauma* in 2016 states that the infusion volume should be limited with the aim of maintaining the mean arterial pressure (mAP) >80 mmHg in patients with severe TBI (GCS ≤8) and/or with spinal cord injury [34]. In the latest Brain Trauma Foundation guidelines in 2017, blood pressure management with TBI varies, based on age as follows: "maintaining sBP at ≥100 mmHg for patients 50–69 years old or at ≥110 mmHg or above for patients 15–49 or over 70 years old may be considered to decrease mortality and improve outcomes" [17]. As described previously, the reason the blood pressure management target cannot be set easily in patients with TBI is that it is difficult to evaluate and judge the cerebral blood flow (CBF). Monitoring the ICP is essential for accurate evaluation because CPP is included in the formula: mAP – ICP. However, in some environments it is difficult to initiate monitoring during the hyperacute phase, as well as establish high-quality research concerning blood pressure management in TBI, and comply with the research protocols. Moreover, CBF is theoretically preserved by autoregulation, even if blood pressure is reduced in a healthy person; however, this autoregulation may collapse in moderate to severe TBI, and CPP is not necessarily maintained only by blood pressure management. With regard to retaining CPP retention and decreasing ICP, attention should also be paid to the infusion fluid type for trauma patients. The use of mannitol or hypertonic saline at the time of increasing ICP is recommended [17], although hypertonic saline is recommended in DCR [39]. At present, it seems that there is no problem in choosing to administer hypertonic saline in patients with multiple trauma and TBI with the expectation that the ICP will decrease. The European guidelines in 2016 recommend avoiding hypotonic solutions such as Ringer's lactate in patients with severe head trauma to minimize fluid shift to damaged brain tissue [34]. Furthermore, caution is required for the administration of a colloid solution. Investigators in the Saline versus Albumin Fluid Evaluation (SAFE) study, which investigated in 460 patients with TBI, reported that the administration of albumin (4%) increases the mortality rate (RR, 1.62), compared with the administration of normal saline [40]. The SAFE-TBI study post hoc analysis revealed that the increase in mortality due to albumin administration in patients with severe TBI was associated with increased ICP [41]. The 2016 European *Guideline on Management of Major Bleeding and Coagulopathy Following Trauma* advocates "use of colloids be restricted because of the adverse effects on hemostasis" [34].

11.3.4 Resuscitative Endovascular Balloon Occlusion of the Aorta

Even if volume resuscitation is administered during the initial trauma management, it is possible for a crisis situation to occur in which the sBP cannot be maintained. If the uncontrolled hemorrhagic region is peripheral to the abdomen, an option is to maintain blood pressure through thoracic or abdominal aortic cross-clamping. The purpose of the procedure is to preserve blood flow and pressure in the heart and the central nervous system (CNS) by disrupting or reducing blood flow below

the clamp. Even if the method of aortic cross-clamping directly by thoracotomy or laparotomy is complete, blood flow below the clamping region is completely disrupted, and the insult caused by the procedure itself may worsen a patient's condition [42]. Resuscitative endovascular balloon occlusion of the aorta (REBOA), a method of blocking blood flow by inflating a balloon inserted in the aorta, is minimally invasive and can even be administered by a physician who is not learned in surgical procedures. Animal experiments of the REBOA procedure have data indicating that the mortality rate and lactic acid level increase when the blocking time exceeds 60 min [43]; therefore, a continuous cutoff time of 45 min or less is recommended. In direct cross-clamping, blood flow below a clamp is completely blocked, whereas REBOA can control the blood flow below the blocking region to some extent by the amount of normal saline injected into the balloon; this procedure is called partial REBOA [44]. Resuscitation is possible when the sBP is controlled to a 80–90 mmHg target as a permissive hypotension by partial REBOA in trauma patients without brain injury and is controlled to a 100 mmHg target in patients with multiple trauma and TBI. However, in actual practice, whether REBOA is beneficial or harmful for patients with TBI is inconclusive. It has been hypothesized that increased carotid artery blood flow by REBOA leads to deterioration by cerebral edema, elevation of ICP, and exacerbation of intracranial hemorrhage [45]. Some investigators report that the mortality of patients with multiple injuries and TBI requiring REBOA is as high as 50% [46, 47]. By contrast, there are animal experiments that such a supraphysiological response does not lead to hemorrhage exacerbation of brain CT. Johnson et al. [48] created hemorrhagic shock using a standardized brain trauma swine model and measured the mAP, carotid artery blood flow, and ICP and obtained brain CT imaging in the REBOA group, the partial aortic clamp group, and the control group. The mAP and carotid artery blood flow in the REBOA group was significantly high; however, the ICP was largest at the time of resuscitation due to the rapid transfusion in control group, which was contrary to expectation. There was no significant difference between the three groups in the proportion of hemorrhage exacerbations on the brain CT, and REBOA was not a factor that worsened TBI. Further study will be required for the effects and adverse effects of REBOA in patients with TBI and multiple injuries.

11.3.5 Hemostatic Resuscitation

As with other injuries, TBI was traditionally managed to maintain a high hemoglobin (Hb) level to prevent secondary brain damage due to reduced oxygen delivery [5, 49]. However, this concept has also changed in recent years. Robertson et al. [50] reported that neurological prognosis after 6 months did not change in a study of TBI patients when comparing the Hb transfusion thresholds of 7 and 10 g/dL. In a retrospective review of 1150 TBI patients, Salim et al. [49] concluded that blood transfusion is associated with high mortality (adjusted odds ratio [OR], 2.19) and high complication rate (OR, 3.67) in patients with or without anemia. Thus, it may

be that maintaining a Hb level higher than necessary is rather harmful; however, it is also a fact that there are circumstances in which massive transfusion must be administered rapidly in patients with multiple traumas. Hemostatic resuscitation in patients with multiple traumas is a strategy to minimize acute coagulopathy of trauma and shock (ACoTS) and RAC by the transfusion protocol and drug administration for massive hemorrhage [4]. Details of coagulopathy due to trauma and coagulopathy associated with massive fluid resuscitation such as ACoTS and RAC are discussed in Chap. 9 ("Coagulopathy and Brain Injury"). In this chapter, we describe the main treatment strategies for patients with multiple injuries.

11.3.5.1 Massive Transfusion Protocol

For the initial treatment of patients with severe multiple injuries and unstable vital signs, many trauma centers have adopted the massive transfusion protocol (MTP), which involves promptly administrating erythrocyte concentrate, fresh frozen plasma (FFP), and platelet concentrate (PLT) at an appropriate ratio without waiting for blood test results [4, 51]. In addition, massive transfusion is defined as the administration of more than 10 units of RBCs per 24 h, ≥150 mL/h, or 100% blood in less in 24 h; however, this definition is not evidence-based [52]. Many traumatic deaths due to exsanguination occur within 2–3 h of injury [53]. Therefore, in discussing massive transfusion in severe trauma, defining it as a transfusion volume per 24 h may not have a significant meaning [54]. Over the last decade, there have been discussions regarding whether the transfusion ratio of plasma to platelet to RBC is favorable at 1:1:1 in the MTP. Some investigators report that the survival rate increases when the proportion of plasma is increased [55–57], whereas other investigators indicate this finding is because of survival bias [58, 59]. Therefore, the appropriate ratio is of interest to researchers. Recent studies may have settled this discussion [53, 60]. The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study published by Holcomb et al. [60] in 2013 was a prospective cohort study that observed 905 trauma patients who had required at least 3 units of transfusion within 24 h of admission [60]. They elucidated a significant decrease in 6-h mortality because of the early high rate resuscitation of plasma and PLT (plasma:PLT:RBC = 1:1:1), compared with patients with a ratio less than 1:2. Furthermore, a transfusion ratio less than 1:2 was associated with a three- to fourfold mortality rate. The Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) study published in 2015 was a multicenter prospective randomized control trial in which the plasma:PLT:RBC ratios of 1:1:1 and 1:1:2 were compared in 680 patients with severe trauma [53]. The 1:1:1 transfusion group had more hemostasis (86% vs. 78%) and less exsanguination (9% vs. 15%) in the first 24 h, but the 24-h mortality and 30-day mortality were comparable. The authors suggested that the reason the mortality was not significant was that most deaths due to exsanguination often do not occur after 24 h of injury, but within 2–3 h of injury. In addition, the 1:1:2 group eventually underwent many transfusions after the intervention and frequently used cryoprecipitate (described later) with a high hemostatic

effect (22% vs. 29%). This appeared an attempt to achieve the 1:1:1 strategy. Some current guidelines recommend a 1:1:1 strategy because of the aforementioned results and similarity of complication rate associated with transfusion [61, 62]. The subject of the PROMMTT and PROPPR studies was severe trauma in general; however, neither study differentiated TBIs. In 2011, a study that differentiated TBIs was reported by Brasel et al. [54]. They retrospectively examined patients who were divided into (1) TBI^+ patients with an abbreviated injury scale of ≥3 and (2) TBI^- patients with an abbreviated injury scale <3. To prevent survival bias, patients were excluded who died within 60 min. They found that a high PLT:RBC ratio improved 30-day survival in the TBI^+ group and a high plasma:RBC ratio was associated with an improvement in the 30-day survival in the TBI^- group. The reason the authors proposed for the favorable outcome of high ratio of PLT administration in the TBI^+ group is that PLT may activate oligodendrocyte precursor cells, which differentiate into oligodendrocytes in the damaged CNS and restore demyelinated areas; they also cited an experiment of blood-brain barrier damage in a rodent model [63]. For the platelet count, it is recommended to maintain the number of platelets ongoing bleeding with TBI at 100×10^9/L or more, based on the European guidelines 2016 [34]. At present, it appears that there is no problem in using the 1:1:1 protocol in patients with multiple traumas and brain injury. However, rapid transfusion may increase ICP, based on the animal experiment of REBOA cited earlier [48]. Further research is necessary to obtain conclusions.

11.3.5.2 Fibrinogen Concentrate and Cryoprecipitate

Fibrinogen is the final component of the coagulation cascade and an essential element for stable thrombus formation [64]. It is cleaved by thrombin into fibrin, which polymerizes to form a strong thrombus resistant to fibrinolysis [64]. In a prospective study of 517 trauma patients, Rourke et al. [65] reported that a low fibrinogen level was a predictor of 24-h mortality and 28-day mortality. The importance of fibrinogen is widely recognized in the treatment of multiple trauma. However, cryoprecipitate is purified by concentrating the coagulation factors contained in plasma and contains factor VIII, factor XIII, von Willebrand factor (vWF), and fibrinogen, which have a high hemostatic effect [66]. The European guidelines in 2007 recommended supplementation at a fibrinogen level of 1 g/L or less in patients with trauma [67]. However, the 2016 guidelines recommend supplementation of fibrinogen concentrate or cryoprecipitate at 1.5–2.0 g/L or less. The initial desirable fibrinogen administration is 3–4 g, which is approximately 15–20 units for cryoprecipitate or approximately 20–25 units for FFP [34].

In 2017, Innerhofer et al. [68] announced early cancelation of the Reversal of Trauma Induced Coagulopathy Using Coagulation Factor Concentrates or Fresh Frozen Plasma (RETIC) trial because of futility and safety reasons, which was verifying the effects of FFP or coagulation factor concentrates (CFCs) for patients with severe trauma and coagulopathy (including TBI patients). The CFCs

administered in this trial consisted of fibrinogen and/or prothrombin complex concentrate and/or factor XIII. The reason for the trial cancelation was that more rescue therapy is required in the FFP group (OR, 25.3) and the necessity for massive transfusion was increased (OR, 3.0). Based on these results, they concluded that first-line CFCs outperformed FFP administration, and they emphasized the importance of early effective fibrinogen supplementation for clotting failure with severe trauma. Prospective studies are being conducted to determine whether supplementation of urgent cryoprecipitate will improve the outcome. In 2015, the CRYOSTAT pilot study [69] examined cryoprecipitate supplementation within 90 min of arrival, and, in 2018, the Early-Fibrinogen in Trauma (E-FIT 1) pilot trial [70] aimed to administer cryoprecipitate within 45 min of arrival for patients undergoing MTP for hemorrhagic shock. A prudent interpretation of E-FIT 1 trial is required because administering cryoprecipitate supplementation within 45 min is difficult. However, the early supplementation group had no significant difference in all-cause mortality at 28 days, compared with the normal administration group in either trial. It is not reasonable to administer cryoprecipitate immediately after admission. However, the accumulation of further research results is required because the efficacy for TBI is unknown.

11.3.5.3 Antifibrinolytic Agents

Tranexamic acid (TXA) has a leading role in antifibrinolytic therapy. The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) trial is a randomized controlled trial involving 20,111 injured patients with massive exsanguination, which includes TBI, within 8 h, or hypotension and/or tachycardia [71]. The TXA group, which received loading 1 g of TXA over 10 min, followed by 1 g infusion of TXA over 8 h, was compared with the placebo group (0.9% saline). The all-cause mortality (relative risk [RR], 0.91) and the risk of death from hemorrhage (RR, 0.85) decreased because of TXA administration. There were no significant differences in vascular occlusion complications and amount of transfusion. Furthermore, in an additional report in 2011, the risk of hemorrhage was significantly decreased when TXA was administered within 1 h (RR, 0.68) or 1–3 h postinjury (RR, 0.79) [72]. By contrast, the risk of hemorrhagic death was increased by administering TXA 3 h postinjury (RR, 1.44). Based on the results of the CRASH-2 trial, the 2016 European guidelines recommended TXA administration within 3 h, based on the method used in the trial [34]. In addition, the CRASH-3 trial is in progress [73]. The CRASH-3 trial is an international, multicenter, pragmatic randomized, double-blind, placebo-controlled trial for patients with intracranial hemorrhage on CT or with a GCS $\leq$12 among adults with single brain injuries within 8 h of injury and uncertainty as to whether TXA should be administered. The method of administration of TXA is similar to that in the CRASH-2 trial. The research results are pending regarding the extent an effect can be obtained for patients with single brain trauma.

11.3.5.4 Ionized Calcium (iCa)

Ionized calcium (iCa) is indispensable for the formation and stabilization of fibrin polymerization; a reduction in cytosolic iCa concentration decreases all platelet activity [74]. Giancarelli et al. [75] reported that, among 156 trauma patients who underwent massive transfusion in 2009–2013, 97% had hypocalcemia and 71% had severe hypocalcemia (iCa <0.9 mmol/L). The mortality was significantly higher among the severe hypocalcemia group than among the hypocalcemia group (49% vs. 24%), when compared with normal limit. The 2016 European guidelines recommend that iCa levels be monitored and maintained within the normal range during massive transfusion [34].

11.3.5.5 Factor VIIa

Boffard et al. [76] in their prospective study reported on the effect of factor VIIa in reducing the transfusion amount in patients with blunt trauma, even though it did not decrease mortality. Since that report, recombinant factor VIIa (rFVIIa) administration has been included in the MTP in many trauma centers [77]. The CONTROL trial in 2010 was a randomized, assignment, prospective study to verify the efficacy of rFVIIa in patients with torso or femoral trauma and refractory hemorrhage [78]. This study unfortunately resulted in less than one-half of the anticipated mortality reduction, and enrollment was censored. In 2018, Lombard et al. reported a propensity score analysis of rFVIIa administration in TBI, although it is a level III evidence [79]. This investigation covered 4284 TBI patients with GCS ≤13 who were diagnosed with brain CT and treated at 11 level 1 trauma centers. Of 129 patients were administered rFVIIa which is not involved in the risk reduction of mortality or morbidity as a result of comparison with the non-administered group. The results of prospective studies will be required to determine the effect of FVIIa administration.

11.4 Summary

As mentioned previously, some treatment strategies for patients with multiple traumas have undergone major transformations in recent decades. However, some treatment strategies also include revival of treatments that had been conducted in the past. In multiple trauma, including brain injury, there are many parts so that management is different for the torso and/or extremity injury and many factors that remain unknown. With cutting-edge treatment technology and development, we hope that the knowledge and experiences abandoned in the past will be integrated and renovate conventional trauma management, and thus many patients will be saved.

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Chapter 12
Nonconvulsive Status Epilepticus

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Abstract Nonconvulsive status epilepticus (NCSE) has rapidly expanded from classical features such as staring, repetitive blinking, chewing, swallowing, and automatism to include coma, prolonged apnea, cardiac arrest, dementia, and higher brain dysfunction, which were demonstrated mainly after the 2000s by us and other groups. This review details novel clinical features of NCSE as a manifestation of epilepsy but one that is underdiagnosed, with the best available evidence. Also, we describe the new concept of epilepsy-related organ dysfunction (Epi-ROD) and a novel electrode and headset which enables fast EEG.

12.1 Introduction

Cases requiring neurological evaluation and care account for a very high proportion—possibly 40–60%—of medical emergencies. In particular, convulsive conditions aside from acute disturbance of consciousness represent the most frequent neurological emergencies. Furthermore, in intensive care, they present the most common problem along with various encephalopathies.

Most clinicians and laypeople equate an epileptic attack with convulsive seizures. Nonconvulsive seizures and nonconvulsive status epilepticus (NCSE)—a serious condition of prolonged or recurrent nonconvulsive epileptic attacks—are often not recognized, even by specialists in the fields of intensive care, neurology, neurosurgery, and epileptology [1, 2]. In daily clinical practice, nonconvulsive seizures and

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NCSE are rarely included in differential diagnoses, even by those who recognize the underlying concepts. Even if they are included, practitioners often fail to go beyond identifying complex partial seizures or absence seizures.

This review describes NCSE especially as a manifestation of epileptic seizure that has been mainly elucidated since about 2000 but is often underdiagnosed despite its treatable nature.

12.2 Nonconvulsive Status Epilepticus and Its Causes

Epileptic seizures include overt seizures such as generalized convulsive seizures, those without convulsions involving impairment of consciousness such as complex partial seizures and those that are usually perceptible only to the patient such as sensory or psychological seizures (simple, partial seizures). NCSE is thought to arise from simple or complex partial seizures or from generalized atypical or atypical absence seizures that persist or recur for at least 30 min. However, in 2012, the Neurocritical Care Society defined status epilepticus (SE) as 5 min or more of continuous clinical and/or electrographic seizure or recurrent seizure activity without recovery between seizures [3]. In 2015, the International League Against Epilepsy (ILAE) issued a new SE classification, including a detailed semiologic axis [4]. In this classification, NCSE was classified into "NCSE with coma" and "NCSE without coma." "NCSE without coma" was subclassified into "generalized," "focal," and "unknown whether focal or generalized." Also, it should be noted that focal lesions in focal or secondarily generalized NCSE involve not only the temporal lobes but also the frontal, parietal, and occipital lobes. A separate manifestation of "NCSE in coma" has been increasingly identified since the advent of continuous EEG monitoring after cardiorespiratory arrest (CRA).

NCSE has diverse causes such as acute encephalopathy, cerebrovascular diseases (18–29% of hemorrhagic cases were reported to have caused NCSE), central nervous system (CNS) infection, brain tumor, traumatic brain injury, and postoperative complications [5]. Towne et al. investigated 19 NCSE cases admitted to the ICU and identified the following causes in order of frequency: hypoxia or anoxia (42%), cerebrovascular accident (22%), infection (5%), head trauma (5%), metabolic impairment (5%), withdrawal from alcohol or antiepileptic drugs (5%), and tumor (5%). Unidentified causes accounted for 11% of cases [6].

In 40 NCSE patients, determined by a combination of the EEG waveform changes and the corresponding clinical signs and symptoms and treated in our department (out of 1116 serial cases from May 2006 to September 2014), major underlying conditions were, in order of frequency, acute encephalopathy (eight cases), cerebrovascular diseases (eight cases), cardiac disease (six cases), CNS infection (five cases), chronic alcohol dependence (four cases), degenerative neurological diseases, traumatic CNS injury, no underlying condition, malignant disease, atrial fibrillation, and renal disease (three cases, respectively), and epilepsy (two cases) (see Table 12.1). Given that acute encephalopathy, the most frequent cause, is

Table 12.1 Clinical features of patients with nonconvulsive status epilepticus

#	Age	Sex	Major underlying disease(s)	Major clinical features	Convulsion	Type of status epilepticus	Organ dysfunction before onset	Organ dysfunction complicated	Outcome
1	53	F	Acute water intoxication, chronic alcohol dependence	Acute encephalopathy, alteration of consciousness	Yes	NCSE/ CP + GCSE	Rhabdomyolysis	None	Recovery
2	89	M	Bilateral intracranial internal carotid artery stenosis	Mimetic facial automatism	None	NCSE/CP	None	None	Recovery
3	65	M	Frontotemporal lobar degeneration	Klüver–Bucy syndrome	None	NCSE/CP	None	None	Recovery
4	79	M	Cerebrovascular dementia	Loss of consciousness attacks	None	NCSE/ absence?	Chronic renal failure, old myocardial infarction	None	Recovery
5	76	M	Acute 5-FU encephalopathy	Coma	None	NCSE/CP	Liver dysfunction	None	Recovery
6	35	F	Acute HSV encephalitis	Prolonged post-hyperventilation apnea, overeating	Yes	NCSE/CP	None	Acute respiratory failure	Refractory
7	56	M	Acute hepatic encephalopathy, alcoholic	Alteration of consciousness	Yes	NCSE/CP	None	Takotsubo cardiomyopathy	Recovery
8	83	F	Acute hyperammonemic encephalopathy, Osler's disease	Total aphasia	None	NCSE/CP	Valvular heart disease, atrial fibrillation	Renal dysfunction	Recovery
9	82	M	Old cerebral infarction, extracranial internal carotid artery stenosis	Broca's aphasia	None	NCSE/CP	Chronic pancreatitis	QT prolongation	Recovery
10	83	M	None	Alteration of consciousness	Yes	NCSE/ CP + GCSE	None	Renal dysfunction	Refractory

(continued)

Table 12.1 (continued)

#	Age	Sex	Major underlying disease(s)	Major clinical features	Convulsion	Type of status epilepticus	Organ dysfunction before onset	Organ dysfunction complicated	Outcome
11	76	F	Acute artery-to-artery cerebral embolism	Loss of consciousness attacks, alteration of consciousness	Yes	NCSE/CP	None	Cardiopulmonary arrest	Death
12	69	F	Atrial fibrillation	Staring, amnesia, alteration of consciousness	Yes	NCSE/CP	None	None	Recovery
13	79	F	Familial Parkinson's disease	Loss of consciousness attacks	None	NCSE/CP	None	None	Sudden death
14	77	F	Traumatic brain injury	Dementia, depression, staring, automatism, tremor	None	NCSE/CP	None	None	Recovery
15	57	M	Acute hepatic encephalopathy, alcoholic	Automatism at right arm	None	NCSE/CP	Hypothyroidism	None	Recovery
16	60	M	SAH and postoperative meningoencephalitis	Central alveolar hypoventilation	None	NCSE/CP	None	Central alveolar hypoventilation, pneumonia	Recovery
17	74	M	Cerebral sinus occlusion and reversible posterior leucoencephalopathy syndrome	Hallucination, abnormal behavior	None	NCSE/CP	None	None	Recovery
18	20	M	Traumatic cervical injury	Recent memory disturbance, word-finding difficulty	None	NCSE	Hyperthyroidism	None	Recovery
19	73	M	Infective endocarditis	Consciousness disturbance	None	NCSE	None	None	Recovery
20	55	M	Acute encephalopathy, chronic renal failure	Alteration of consciousness	None	NCSE	Chronic renal failure	None	Recovery

21	77	M	Acute encephalopathy, sepsis	Alteration of consciousness, Broca's aphasia	None	NCSE	Chronic hepatitis	None	Recovery
22	56	M	Acute encephalopathy	Higher brain dysfunction	None	NCSE	Chronic renal failure	None	Recovery
23	79	M	Chronic heart failure, atrial fibrillation	Consciousness disturbance	None	NCSE	None	None	Recovery
24	89	M	Chronic kidney disease, chronic heart failure	Alteration of consciousness, automatism	None	NCSE	Chronic kidney disease, heart failure	Chronic kidney disease	Refractory
25	77	M	Chronic renal failure, postoperative bladder carcinoma	Alteration of consciousness	None	NCSE	Chronic renal failure	DIC	Death
26	76	M	Chronic kidney disease, atrial fibrillation	Loss of consciousness attacks	None	NCSE	Renal dysfunction	Severe bradycardia	Recovery
27	89	F	Femoral head fracture	Alteration of consciousness	None	NCSE	None		Recovery
28	68	F	Post-traumatic epilepsy	Alteration of consciousness, auditory hallucination, delusion of persecution	Yes	NCSE/ CP + GCSE	Giant liver hemangioma	None	Recovery (recurred)
29	65	M	Alcohol dependence	Alteration of consciousness	Yes	NCSE/ CP + GCSE	None	Acute prerenal renal failure	Recovery
30	18	F	Non-HSV encephalitis sequelae	Prolonged post-hyperventilation apnea	Yes	NCSE/ CP + GCSE	None	Multiple organ failure	Death
31	56	M	Intravascular malignant lymphomatosis	Alteration of consciousness	Yes	NCSE/ CP + GCSE	None	None	Recovery
32	51	M	Postoperative SAH	Alteration of consciousness	Yes	NCSE/ CP + GCSE	None	None	Recurrent

(continued)

Table 12.1 (continued)

#	Age	Sex	Major underlying disease(s)	Major clinical features	Convulsion	Type of status epilepticus	Organ dysfunction before onset	Organ dysfunction complicated	Outcome
33	49	M	Acute disseminated encephalomyelitis	Alteration of consciousness	Yes	NCSE/ CP + GCSE	None	Renal and liver dysfunction	Recurrent
34	15	M	None	Consciousness disturbance, four extremities weakness	Yes	NCSE/ CP + GCSE	None	None	Recovery
35	45	F	Epilepsy, central nervous system lupus, lupus nephritis	Dysgraphia	Yes	NCSE/ CP + GCSE	None	None	Recovery
36	86	M	None	Difficulties in speaking, facial twitching	None	NCSE/ CP + GCSE	None	None	Recovery
37	47	M	Acute hypoglycemic encephalopathy	Consciousness disturbance	Yes	NCSE/ CP + GCSE	Liver dysfunction	Renal dysfunction	Recovery
38	34	M	Acute lymphocytic leukemia, post-irradiation basal ganglia calcification	Alteration of consciousness, irritability, perseveration	Yes	NCSE/ CP + GCSE	Hypothyroidism	None	Refractory
39	64	M	Meningoencephalitis	Alteration of consciousness	Yes	NCSE/ CP + GCSE	None	Multiple organ failure, DIC, central diabetes insipidus	Death
40	78	M	Sepsis, cerebral infarction	Consciousness disturbance	Yes	NCSE/ CP + GCSE	Chronic myeloid leukemia, liver dysfunction	DIC, renal dysfunction	Death

M male, *F* female, *5-FU* 5-fluorouracil, *CP* complex partial, *DIC* disseminated intravascular coagulation, *GCSE* generalized convulsive status epilepticus, *ICH* intracerebral hemorrhage, *HSV* herpes simplex virus, *NCSE* nonconvulsive status epilepticus, *SAH* subarachnoid hemorrhage

often accompanied by diverse and serious neurological symptoms such as impaired consciousness level, mental alteration, and SE (convulsive and nonconvulsive), it is necessary to take a careful history and physical findings to comprehend and differentiate the underlying pathology. We need to be aware that epileptic seizure can coexist with acute encephalopathy and that NCSE and convulsive seizure can coexist in a patient. For details on the causes of NCSE, please refer to the monograph edited by Kaplan and Drislane [7].

12.3 Widening the Clinical Spectrum of Nonconvulsive Status Epilepticus

It is generally understood that consciousness disturbance manifests as two types: (1) depression in level of consciousness (decreased responsiveness) and (2) alteration in type of consciousness (the content of consciousness) (see Table 12.2). Since generalized convulsive seizures are usually accompanied by type 1 consciousness problems, clinicians may dismiss the possibility of epileptic attack in type 2 patients. However, while consciousness may continue in authentic simple partial seizures and in complex partial seizures, the content of such consciousness may still be "clouded," especially in the latter. This is important for understanding NCSE.

12.3.1 Classical Clinical Features [6]

It is known that complex partial seizures in cryptogenic epilepsy may manifest, for example, as staring, repetitive blinking, chewing, swallowing, or automatism but without convulsive seizures. Most cases of SE with complex partial seizures show clouding of consciousness of temporal or frontal lobe origin and are generally characterized by alteration of mental function and consciousness with concurrent language disturbances.

Simple partial SE is accompanied not by disturbance of consciousness but by clinical symptoms linked to anatomical and functional locations of CNS foci. In temporal lobe epilepsy, amygdalar and hippocampal lesions cause epigastric discomfort and uncinate fits such as autonomic seizures, psychological seizures, and parosmia, while lateral temporal lesions cause auditory hallucinations and language disturbance. Frontal lobe epilepsy manifests as motor seizures, including not only tonic seizures and seizures with fencing postures but also those with complex gesticulation. In parietal lobe epilepsy, predominant seizures are somatosensory abnormalities such as numbness, and occipital lobe epilepsy manifests as visual seizures.

Table 12.2 Expanded spectrum of manifestations of nonconvulsive status epilepticus (NCSE)

Classical clinical features
Complex partial seizures type
Staring, repetitive blinking, chewing, swallowing, or automatism
Clouding of consciousness generally characterized by:
Alteration of mental function
Consciousness with concurrent language disturbances
Simple partial seizures type
Symptoms linked to the anatomical and functional locations of the CNS foci
Temporal lobe epilepsy, amygdalar and hippocampal lesions
Epigastric discomfort and uncinate fits
Such as autonomic seizures, psychic seizures, and parosmia
Lateral temporal lesions
Auditory hallucinations and language disturbance
Frontal lobe epilepsy
Motor seizures
Not only tonic seizures and seizures with fencing postures
But also those with complex gesticulation
Parietal lobe epilepsy
Somatosensory abnormalities such as numbness
Occipital lobe epilepsy
Visual seizures
Consciousness disturbance
Acute consciousness disturbance
Comatose state
Mental alteration
Fluctuation of consciousness level
Prolonged consciousness disturbance
Protracted coma
Fluctuation of consciousness level
Recurrent loss of consciousness attack
Transient neurological attack (TNA)
Including isolated vertigo, dizziness, and headache
Higher brain dysfunction
Wernicke's aphasia, Broca's aphasia, Klüver–Bucy syndrome
Amnesia, indifference
Confabulation, hallucinatory delusion, delirium
Body schema disturbances (e.g., abnormal proprioception and supernumerary phantom limbs)
Neglect, auditory and visual hallucinations, cortical blindness
Cognitive impairment and psychiatric manifestations
Dementia, including acute dementia

Table 12.2 (continued)

Abnormal behavior and/or speech
Persistent laughing (status gelasticus)
Automatism
Licking chops, nose wiping, facial pantomime
Abnormal eye position and movement
Conjugate deviation of eyes, spontaneous nystagmus
Myoclonus of the face and extremities
Especially interictal small myoclonus of the face and extremities
Autonomic dysfunction
Gastrointestinal or cardiovascular autonomic events
Panayiotopoulos syndrome
Acute organ dysfunction (epilepsy-related organ dysfunction [Epi-ROD])
Acute apnea, including prolonged post-hyperventilation apnea
Acute cardiac arrest, acute dysfunction of other organs
May cause sudden unexpected death in epilepsy (SUDEP)

In general, neurological deficits of an unexplained, episodic, fluctuating, or recurrent nature should arouse suspicion of NCSE. We need to consider convulsive SE and especially NCSE in the differential diagnosis of various acute organ dysfunctions, even in the absence of overt seizures
CNS central nervous system

12.3.2 Impaired Level of Consciousness (Acute and Prolonged Coma)

Since about 2000, NCSE, in particular complex partial NCSE, has been identified as a cause of coma and other neurological symptoms [6]. In a study by Towne et al., at least 30 min of EEG monitoring identified 19 cases of NCSE (8%) out of 236 convulsion-free comatose cases admitted to the general ICU [6]. This revealed, for the first time, the underdiagnosis of NCSE associated with coma. Accordingly, continuous EEG monitoring is now recommended, at least for patients with unexplained coma albeit without convulsions. Recognized practical criteria for EEG abnormalities in NCSE patients are thus urgently needed.

Since 2005, we have demonstrated novel treatable manifestations of NCSE including prolonged disturbance of consciousness [8] and prolonged post-hyperventilation apnea [9]. Prolonged disturbance of consciousness was studied in six non-traumatic patients awakened from a coma of 1 month or more and with a total Glasgow coma scale score of 7 or less. Two cases of NCSE were identified. One of these with symptomatic epilepsy was awakened after the start of phenytoin therapy, while the other, with viral encephalitis, was awakened after carbamazepine therapy. In case one, the estimated duration of NCSE was 2 weeks, and in case two it was several months [8].

12.3.3 Prolonged Post-hyperventilation Apnea

Healthy alert individuals with $PaCO_2$ reduced by short-term hyperventilation continue to breathe regularly with a lower tidal volume until $PaCO_2$ returns to normal [10]. Post-hyperventilation apnea may also rarely occur in patients with bilateral cerebral lesions [10, 11].

We examined a case of recurrent prolonged post-hyperventilation apnea following severe viral encephalitis in an 18-year-old female patient and identified nine previously reported cases [9]. These ten cases in all had the following features: year of report was 1990 or later in seven cases, and onset occurred in the second decade of life in two cases, in the third decade in three cases, in the fourth decade in one case, in the fifth decade in one case, and in the sixth decade or later in three cases. Male-to-female ratio was 1:9. Associated underlying diseases were hyperventilation syndrome in five cases, severe viral encephalitis in one case, and one case each of intellectual disability, fall-induced trauma, personality/behavioral disorder, and dental caries treatment. Hyperventilation recurred in nine cases, and severe hypoxemia (SaO_2 <80%) was observed in seven cases. The mortality rate was 30%.

A frequency histogram of positive EEG spikes in our own patient revealed marked positive spikes during hyperventilation episodes. These were interpreted as representing epileptic autonomic seizures (Fig. 12.1). Although no neurophysiological data were available for the other nine cases, given that hyperventilation attacks recurred in many of them and that involuntary movements or auras

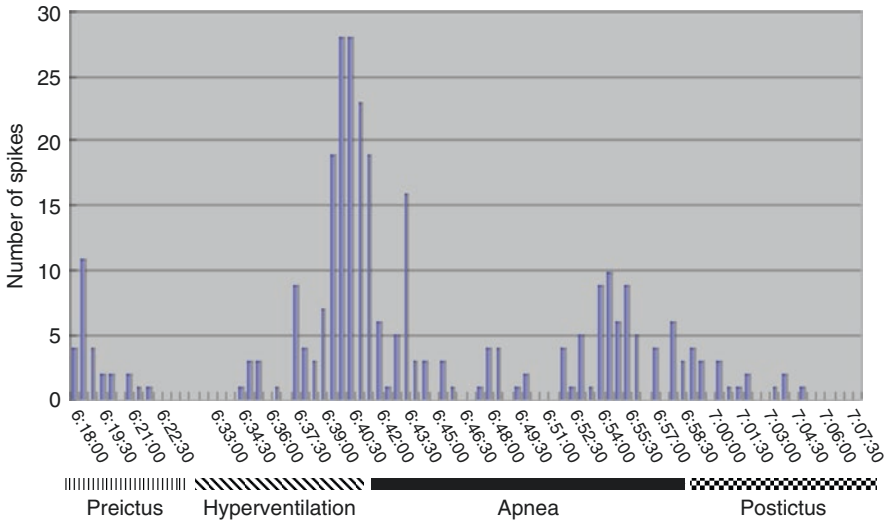

Fig. 12.1 Positive spike frequency histogram. Frequency histogram analysis of positive electroencephalographic spikes in an 18-year-old woman with recurrent, prolonged, post-hyperventilation apnea. Positive spikes were marked, in particular, during hyperventilation, which was interpreted as autonomic epileptic seizures. Quoted from Nagayama [9]

accompanied some cases, the clinical features of all cases suggested epilepsy. Therefore, we believe that prolonged post-hyperventilation apnea should properly be viewed as a novel manifestation of NCSE.

12.3.4 Higher Brain Dysfunctions and Cognitive Impairments

12.3.4.1 Klüver–Bucy Syndrome

Klüver–Bucy syndrome is a cluster of behavioral abnormalities resulting from temporal lobe lesions and was originally reported in a monkey model following bilateral temporal lobectomy involving the amygdalae, unci, and hippocampi. Effects include hyperoral tendencies (tendency to eat and smell everything), hypermetamorphosis (increased reaction to visual stimuli), placidity (calmness with a loss of aggression), increased sexual behavior, altered dietary preferences, hyperphagia, and pica. The syndrome seldom occurs in humans, and concurrence of all symptoms is very rare. Language and cognitive disturbances are foremost, and many cases are of a transient character. The following have been reported: bilateral temporal lesions (trauma, inflammation, cognitive disturbance, epilepsy, and cerebral infarction) and disconnection of the medial temporal lobes from cerebral, limbic, and other regions.

With regard to our own cases, a 65-year-old male NCSE patient recovered from prolonged Klüver–Bucy syndrome in response to antiepileptic therapy [12]. He complained chiefly of hypersexuality and gait disturbance. Aside from a history of several years of frequent nose touching resulting in skin abrasion, his presenting problems on his first visit included attacks of depressed consciousness, hypersexuality (about four episodes a day), and overeating. His past medical history was complicated and included sedative, anxiolytic and alcohol dependence, cerebral infarction, trigeminal neuralgia, dyslalia, cognitive dysfunction, homonymous hemianopia, limb rigidity, orolingual dyskinesia, and mild bilateral incoordination. MRI revealed small, bilateral infarctions in the occipital lobes and basal ganglia and bilateral hippocampal degeneration. EEG showed repetitive synchronous grouping discharges with bilateral, fronto-parieto-temporal predominance. The findings were interpreted as NCSE manifesting as Klüver–Bucy syndrome. Phenytoin therapy was initiated (we started phenytoin because we experienced harmful effects such as glossoptosis and depressed consciousness level after benzodiazepine challenge test in other patients, and phenytoin and fosphenytoin can exert their effects rapidly, although not as much as compared with benzodiazepines), whereupon the pathological sexual behavior improved and then disappeared within 2 weeks (Fig. 12.2). Overeating also disappeared but resulted in severe anorexia. A literature survey identified two previous cases. Given the almost complete disappearance of Klüver–Bucy syndrome immediately after the initiation of phenytoin therapy and the lack of morphological abnormalities in the temporal lobes and based upon the published

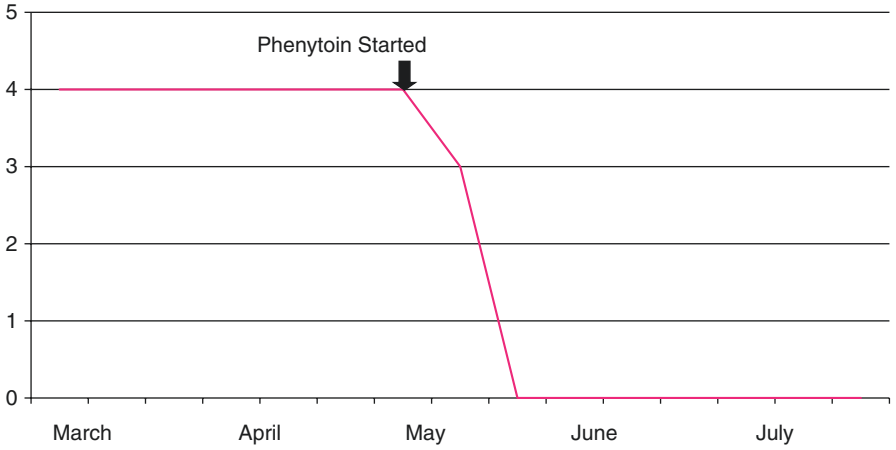

Fig. 12.2 Hypersexuality in Klüver–Bucy syndrome before/after intravenous phenytoin. Changes in overeating and sexual behaviors in a 65-year-old male NCSE patient with nonconvulsive status epilepticus manifesting as Klüver–Bucy syndrome. Hypersexuality decreased immediately after the initiation of phenytoin therapy and completely disappeared 2 weeks later. Overeating also disappeared but was followed by severe anorexia

evidence, we consider the case as one of complex partial NCSE resulting from functional abnormalities in the temporal lobes. The case is also interesting, we believe, with regard to potential treatments for higher brain dysfunction.

12.3.4.2 Other Types of Higher Brain Dysfunction

Epilepsy-induced higher brain dysfunctions include aphasia, amnesia, body schema disturbances (e.g., abnormal proprioception and supernumerary phantom limbs), neglect, auditory and visual hallucinations, and cortical blindness.

Patients with simple, partial NCSE experience clinical symptoms corresponding to epileptogenic focal regions and present with aphasia if the focus is in the language areas. However, a premature diagnosis of aphasic seizure should be avoided because foci outside the language areas may also cause speech arrest [13].

As examples of higher brain dysfunctions secondary to NCSE, Midorikawa and Kawamura reported cases of anterograde amnesia [14, 15], headache, and indifference. Cases have also been reported of Wernicke's aphasia secondary to limbic encephalitis or cerebral infarction (these remitted or disappeared in response to antiepileptic medication [16, 17]). Other symptoms include confabulation, hallucinatory delusion, and delirium [13, 18]. We also treated a patient with total aphasia due to NCSE secondary to hyperammonemic encephalopathy resulting from Osler–Weber–Rendu disease and a second patient with Broca's aphasia associated with NCSE secondary to right extracranial internal carotid artery stenosis (Table 12.1). The first patient responded quickly to phenytoin: total aphasia remitted 5 min after

phenytoin administration and completely disappeared 15 min later. In the second patient, Broca's aphasia disappeared spontaneously.

Although little attention has been paid to higher brain dysfunctions in connection with epilepsy, the notion of "epileptic higher brain dysfunction" needs to be addressed further as part of diagnostic practice [19, 20].

12.3.4.3 Cognitive Impairments

Acute neurological symptoms due to NCSE also may have the appearance of acute dementia. The following cases of NCSE have been reported: normalization on the revised Hasegawa dementia scale from a score of 16 on hospitalization (due to NCSE) to 30 (full score) after antiepileptic medication in a 78-year-old woman [21], remission of fluctuating behavioral disturbance in response to antiepileptic medication [22], and disappearance of cognitive disturbance after antiepileptic medication [23]. We believe that these cases illustrate the necessity of including NCSE as a differential diagnosis in so-called treatable dementias.

Furthermore, a review of ten cases of sporadic Creutzfeldt–Jakob disease (CJD) suggested that CJD was not a cause of NCSE, but rather NCSE was a differential diagnosis [24]. However, we need to be aware that NCSE can also coexist with acute and chronic neurological diseases, as has been shown in the cases of acute encephalopathy and acute stroke as a manifestation of these neurological conditions (Table 12.1).

12.3.5 Cardiac Arrest

Sudden unexpected death in epilepsy (SUDEP) is a frequent cause of non-accidental, non-suicidal sudden death in patients with epilepsy. SUDEP most often affects patients with refractory epilepsy, and the cumulative risk is 12% over 40 years for those with uncontrolled childhood-onset epilepsy [25]. The pathology of SUDEP is not yet fully understood and is thought to be multifactorial. However, "arrhythmia" and either "hypoventilation" or "hypoxia" are thought to be involved [26]. Recently, there have been case reports of continuous ECG monitoring detecting cardiac arrest that complicated an episode of temporal lobe epilepsy, and this finding is considered a novel clinical feature of NCSE [27, 28]. Therefore, NCSE may be involved not only in prolonged post-hyperventilation apnea but also in SUDEP.

We should also note the Mortality in Epilepsy Monitoring Unit (EMU) Study (MORTEMUS) [29, 30]. Between 1 January 2008 and 29 December 2009, the authors of this study made a systematic retrospective survey of EMUs located in Europe, Israel, Australia, and New Zealand to retrieve data for all CRAs. EMUs from other regions were invited to report similar cases. There were 29 CRAs reported, including 16 SUDEP (14 at night), 9 near SUDEP, and 4 deaths from other

causes. Cardiorespiratory data, available for ten cases of SUDEP, showed a consistent and previously unrecognized pattern, whereby rapid breathing (18–50 breaths/min) developed after secondary generalized tonic–clonic seizure, followed within 3 min by transient or terminal cardiorespiratory dysfunction. Where transient, this dysfunction later recurred with terminal apnea occurring within 11 min of the end of the seizure, followed by cardiac arrest. SUDEP incidence in adult EMU was 5.1 per 1000 patient years. This study first revealed that SUDEP in EMU primarily follows an early postictal, centrally mediated, severe alteration of respiratory and cardiac function induced by generalized tonic–clonic seizure, leading to immediate death or a short period of partly restored cardiorespiratory function followed by terminal apnea and then cardiac arrest. Although small in subject number and lacking pathological data in half the cases of SUDEP as well as data on blood pressure, cerebral perfusion, oximetry, and partial pressure of CO_2, this paper is critical and a landmark study in the management and prevention not only of SUDEP but also of sudden death in general and various acute critical conditions of unknown etiology.

So cardiac arrest might possibly be a manifestation of NCSE, although it might correspond to a postictal state electrophysiologically. Conversely, physicians should include NCSE in the causative differential diagnosis of cardiac arrest, especially of the unknown cause [31, 32]. Regarding the mechanism of SUDEP, it might be plausible that it involves derangements of the central autonomic network (CAN) which include the insular cortex, amygdala, hypothalamus, periaqueductal gray matter, parabrachial complex, nucleus of the tractus solitarius, and ventrolateral medulla.

12.3.6 Autonomic Dysfunction

Autonomic function is often impaired during epileptic seizures, but many such cases are mild gastrointestinal or cardiovascular autonomic events. Thus, epilepsy or NCSE could be more likely to be overlooked if autonomic impairment is regarded as primary. In Panayiotopoulos syndrome, a common idiopathic childhood-specific seizure disorder, convulsive SE is extremely rare, and autonomic symptoms may be the only features of the seizures. Half of the seizures in this syndrome last for >30 min, thus constituting autonomic SE [33].

12.3.7 Abnormal Eye Position and Movement

Complex partial seizures can manifest as spontaneous nystagmus and conjugate deviation of eyes in addition to classical clinical features such as staring and repetitive blinking. Such manifestations can often be observed not only in patients with idiopathic epilepsy but also in critically ill patients and might suggest coexistent NCSE; however, less attention is usually paid in the latter setting. In clinical practice, we need to be aware that such findings can also be manifestations of NCSE.

12.3.8 Myoclonus of the Face and Extremities

Small amplitude myoclonus of the face and extremities is thought to be a frequently observed manifestation of NCSE. Such manifestations can also often be observed in critically ill patients and suggest coexistent NCSE; however, less attention is usually paid to this too. In clinical practice, we need to be aware that such findings can also be manifestations of NCSE.

12.3.9 Miscellaneous Signs and Symptoms

We have treated patients with mimetic facial automatism or recurrent attacks of unconsciousness, both of which were manifestations of NCSE and both of which disappeared immediately in response to antiepileptic medication (Table 12.1). In the literature, NCSE can manifest as persistent laughing (status gelasticus), vertigo, or dizziness [34, 35], which might be consistent with transient neurological attack (TNA) [32]. In general, neurological deficits of an unexplained, episodic, fluctuating, or recurrent nature should arouse suspicion of NCSE.

12.3.10 Acute Organ Dysfunction

To elucidate the relationship between SE and acute organ dysfunctions (ODs), we retrospectively investigated 30 patients with SE (from April 2006 to March 2013, 2.9% of all inpatients) for clinical features including first-ever ODs which were complicated just after ictus. Generalized convulsive SE (GCSE) was seen in 5 patients (mean 64.6 years old), NCSE was seen in 15 patients (mean 70.5 years old; complex partial SE in 14 and absence SE in one), and both GCSE and NCSE during the attack temporally apart were seen in 10 patients (mean 54.1 years old). ODs were observed in three GCSE patients (60%, multiple organ failure, arrhythmia, and liver dysfunction), six NCSE patients (40.0%, acute respiratory failure, alveolar hypoventilation, acute cardiopulmonary arrest, acute takotsubo cardiomyopathy, renal dysfunction, and QT interval prolongation), and six patients with both (60%, renal dysfunction, multiple organ failure, and disseminated intravascular coagulation with neurogenic diabetes insipidus). Underlying diseases in those patients with OD were acute encephalopathy in two, acute encephalomyelitis in two, cerebral infarction in two, acute cerebral sinus occlusion in one, and senile dementia of the Lewy body type in one; there was no underlying disease in one patient. Mortality at discharge was 33% and 9.1% in those patients with or without ODs, respectively.

One must be careful about interpreting acute ODs because some might reflect postictal secondary complications unrelated to the epileptic attack itself. However, we defined acute ODs as those first-ever ODs which were complicated just after

Table 12.3 Epilepsy-related organ dysfunction (Epi-ROD)

Features	Frequent in both convulsive and nonconvulsive status epilepticus (SE)
	Convulsive 60%, NCSE 40%, both 60%
	Life-threatening/high mortality (33.3%)
	With acute encephalopathy, stroke, and central nervous system infection and so on
	Heterogeneous in nature
Implication	Differentiate SE in acute OD, even without overt seizure

the ictus, which may eliminate the likelihood of secondary complication to a good degree. So we proposed the novel concept of epilepsy-related organ dysfunction (Epi-ROD), i.e., critical complications of convulsive and nonconvulsive SE [29, 30]. Features of Epi-ROD can be summarized as follows: (1) frequently observed in both convulsive SE and NCSE (convulsive SE 60%, NCSE 40%, and both 60%), (2) life-threatening with high mortality (33.3%), (3) can be observed in those with acute encephalopathy, stroke, CNS infection, and so on, and (4) heterogeneous in nature. The causal relationship between Epi-ROD and epileptic attack needs to be explored in larger subjects. Vice versa, most importantly, we need to consider convulsive SE and especially NCSE in the differential diagnosis of various acute ODs, even in the absence of overt seizures (Table 12.3). Also, we always need to be cautious about the relationship between cause and effect.

12.4 Ongoing Issues

Following the new definition of SE by the Neurocritical Care Society in 2012, patients with SE are increasingly recognized globally [3]. Considering the fact that NCSE is more frequent than GCSE, SE is the most frequent neurologic complication of critical medical illnesses. However, the clinical features of NCSE are not yet well recognized by most clinicians. Therefore, it is important to include NCSE in undergraduate and postgraduate medical education in related disciplines.

NCSE is a potentially treatable condition, although treatment strategies and guidelines are not firmly established yet. The underdiagnosis of NCSE is due to (1) lack of knowledge of NCSE itself, (2) lack of recognition about the diversity of NCSE and hence attribution of the impaired state to other causes (e.g., metabolic encephalopathy or postictal state), and (3) lack of an appropriate screening tool (EEG) for NCSE available anytime, anywhere, under any conditions, and to anyone.

Recently, we created a novel electrode and headset which enables fast and continuous EEG monitoring from the ER to the neuro-ICU by (1) employment of an active amplifier and disposable gel electrodes for sustainable and stable usage, (2) a wireless device by using Bluetooth technology, and (3) an easy attachment of electrode contacts by employing the headset style (Fig. 12.3a, b). This device was

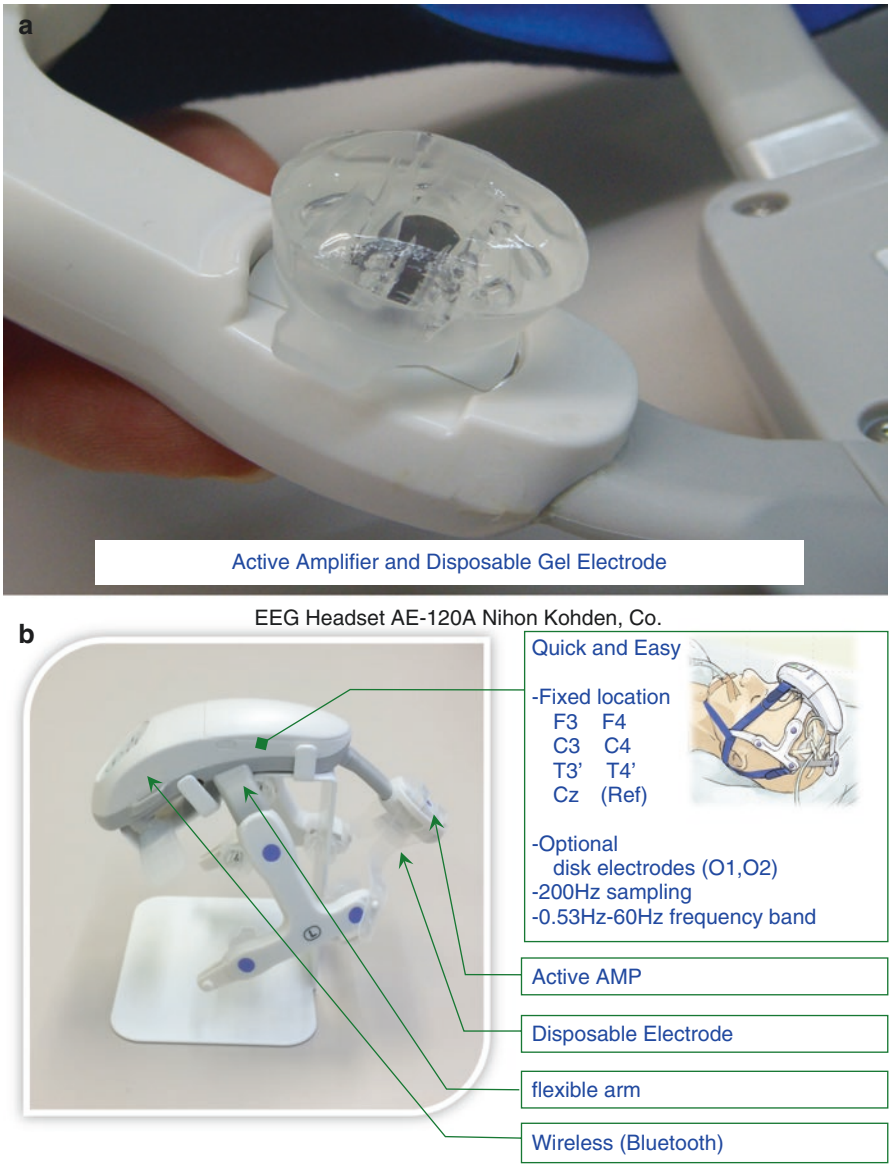

Fig. 12.3 (**a**, **b**) Novel electrodes and headset which made prompt EEG possible. Novel electrode (**a**) and headset (**b**) which enable prompt EEG by (1) employment of the active amplifier and disposable gel electrode for sustainable and stable usage, (2) wireless device by using Bluetooth technology, and (3) easy attachment by employing the headset style

Table 12.4 Indication of fast EEG neuromonitoring

Acute neurocritical condition
R/O Nonconvulsive seizure (NCS)/status epilepticus (NCSE)
From mental alteration to epilepsy-related organ dysfunction (Epi-ROD)
Convulsion
R/O coexistent NCSE
R/O postictal state
R/O cerebral ischemia
Esp. delayed cerebral ischemia (DCI)
Others
Evaluation of sedation
R/O Epileptic seizure
Outcome evaluation
Chronic neurocritical condition
Persistent/protracted consciousness disturbance
Evaluation of sequelae
Suppression of traffic accident and crime

made possible with novel industry-academia collaboration with Nihon Kohden Corporation and approved for practical use by the Ministry of Health, Labour and Welfare, Japan, at the year of 2016 [36, 37]. Fast EEG monitoring would improve the diagnosis of NCSE and might further expand the clinical spectrum of NCSE (Table 12.4). Along with this device, there is an urgent need for formal, global, and practical criteria for NCSE.

Competing Interests The authors declare that they have no competing interests.

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Chapter 13
Post-cardiac Arrest Syndrome (PCAS)

Yasuhiro Kuroda

Abstract Post-cardiac arrest syndrome (PCAS) is a pathological condition after the return of spontaneous circulation (ROSC) following cardiac arrest. PCAS involves the following four important conditions: brain injury, myocardial dysfunction, systemic ischemia and reperfusion response, and the underlying precipitating pathological process. A long interval between collapse and ROSC might be associated with poor neurological outcomes. Although the overall outcome of PCAS is severe, about half of PCAS patients with an initial shockable rhythm will survive with good neurological outcomes. Moreover, the main cause of PCAS in patients with good outcomes is cardiovascular disease, and in such patients, rescue treatment might be possible. Targeted temperature management (TTM) (32–36 °C, 24 h) involving stabilization of systemic parameters (respiration, circulation, metabolism, etc.) along with immediate coronary angiography with/without percutaneous coronary intervention is recommended; however, neuroprotective information for TTM is limited. Neurological prognostication should be performed at least 72 h after ROSC through clinical investigations and multimodal testing without sedation.

Keywords Targeted temperature management · Neurocritical care · Brain injury
Myocardial dysfunction · Prognostication

13.1 Introduction

Post-cardiac arrest syndrome (PCAS) involves the following four important conditions: brain injury, myocardial dysfunction, systemic ischemia and reperfusion response, and the underlying precipitating pathological process [1].

Neurocritical care for PCAS patients is more focused on improving survival and achieving good neurological outcomes, especially good recovery, than on prognostication or supportive care involving neurological complications.

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This chapter will focus on PCAS severity, brain injury and prognosis, treatment for myocardial dysfunction, the current concept of targeted temperature management (TTM), neurocritical care except TTM, and future directions.

13.2 PCAS Severity

The outcomes (survival and neurological outcomes) of PACS depend on the severity of ischemic insults, the cause of cardiac arrest, prehospital management, and inhospital care. In addition, a patient's prearrest health status might affect outcomes.

According to the Japanese registry data, among adults with bystander-witnessed cardiac arrest who showed return of spontaneous circulation (ROSC) before arrival at the hospital, good neurological outcomes were identified in about 50% of patients with an initial shockable rhythm and in only 15% of patients with a nonshockable rhythm [2]. In this previous analysis, the main cause of cardiac arrest was cardiovascular disease, suggesting the importance of coronary intervention.

A longtime interval between collapse and ROSC is associated with severe damage that relates to poor neurological outcomes. Regarding the termination of resuscitation, the time interval for a reduction in the proportion of patients alive at hospital discharge to under 1% was 48 min among those with an initial shockable rhythm and was 15 min among those with a nonshockable rhythm [3]. According to the US ROC-PRIMED study, 90% of patients with good neurological outcomes achieved ROSC within 20 min of collapse, and 99% of patients with good outcomes achieved ROSC within 37 min of collapse [4]. The Japanese registry data showed a similar trend [2]. Thus, a time interval between collapse and ROSC of around 50 min might be considered for not only the decision about the termination of resuscitation but also the initiation of extracorporeal cardiopulmonary resuscitation (ECPR) and neurocritical care, including TTM.

Among patients without ROSC but with good neurological indicators (shockable rhythm, short-time interval between collapse and ROSC, etc.), ECPR is an option for resuscitation. Ortega-Deballon et al. reviewed many cohort studies and reported that the overall survival rate with ECPR was 20% among patients without ROSC [5]. The survival rate is known to vary among studies. In Japan, the SAVE-J study reported that among out-of-hospital cardiac arrest patients with a shockable rhythm on initial electrocardiography, the rate of good neurological outcomes (11.2%) at 6 months after insult was higher with treatment including ECPR, therapeutic hypothermia, and intra-aortic balloon pump than with treatment not involving ECPR (2.6%) [6]. Thus, ECPR is a good approach for resuscitation in selected patients.

13.3 Brain Injury and Prognosis

Brain injury depends on the degree of ischemia and reperfusion. There is no quantified method for evaluating the degree of brain injury. Direct and indirect methods for the evaluation and prognostication of brain injury should be identified.

Coma after ROSC might be associated with brain damage and poor neurological outcomes, although there is no information on the relationship between coma duration and outcomes. A sub-analysis of the Japan hypothermia multicenter registry (J-PULSE-HYPO) showed that the Glasgow Coma Scale (GCS) motor score immediately before TTM might be associated with neurological outcomes. In this previous analysis, over 80% of patients with a GCS motor score of 4–5 had good neurological outcomes, although half of the patients had good neurological outcomes with no motor response against a painful stimulus (M1) [7]. In addition, a previous observational study in a single hospital showed a relationship between the GCS motor score and outcomes [8]. Although the evaluation of the GCS motor score in patients with coma does not contribute directly to the inclusion/exclusion criteria of TTM, it might reflect the degree of brain injury. Moreover, the FOUR score [9], which is well adapted to mechanically ventilated patients and does not depend on verbal responses, might estimate brain injury as it considers brainstem function.

Pupil diameter and/or pupil light reflex might also be associated with brain injury. In a previous study, the incidence of favorable neurological outcomes was significantly higher in patients with a pupil diameter <4 mm after ROSC than in those with a pupil diameter >4 mm [7]. Recently, quantitative assessment of the pupillary light reflex (PLR, expressed as the percentage of pupillary light response) was introduced. Heimburger et al. reported that the PLR was higher in patients with good outcomes than in those with poor outcomes at admission and 24 h after ROSC [10]. In 2017, Solari et al. reported that reduced quantitative PLR correlates with postanoxic brain injury and that the PLR at 48 h following ROSC could predict a poor prognosis in all patients [11]. Thus, the evaluation of the light reflex might be useful for the multimodal assessment of outcomes in coma patients.

Brain edema after ROSC might be associated with poor outcomes. There is limited information about intracranial pressure (ICP) after ROSC. In a previous observational study, ICP after ROSC did not increase, except in patients with electronic seizure activity, although poor neurological outcomes were observed [12]. A recent study showed a significant increase in ICP after TTM in PCAS patients with poor neurological outcomes, although good management of cerebral perfusion pressure (CPP) was achieved [13]. In this previous study, ICP was maintained within the normal range during TTM in both patients with good and those with poor outcomes, suggesting that TTM might decrease ICP. Regarding neuroimaging, a decrease in the gray/white matter ratio (<1.14) on brain CT within 2 h after ROSC was associated with poor neurological outcomes owing to brain edema [14]. The gray/white matter ratio before TTM has been shown to be an important factor for prognostication and has been included in a recently developed scoring system [15]. Thus, brain edema after ROSC, which is suppressed during TTM, might develop after TTM and might be associated with poor neurological outcomes. The early detection of brain edema using imaging modalities, such as brain CT, might be considered reasonable for determining the indication of TTM and might indicate a poor prognosis.

Regarding brain MRI, some studies have shown that multiple high intensity areas in diffusion-weighted images [16] 2–6 days after ROSC might be associated

with poor outcomes [17]. However, the MRI method has not been standardized to provide definite criteria for outcomes, because of the small number of studies and difficulties with the quantification of imaging among studies.

Continuous electroencephalography (EEG) monitoring during the early phase (within 24 h after ROSC) has been recommended for evaluating electronic seizure activity (rhythmic delta activity, spike and wave, and periodic discharge) when PCAS patients have a history of seizure activity and/or muscle relaxants are used for analgosedation during TTM. Using aEEG, several studies reported that the appearance of continuous normal voltage within 24 h after ROSC might be associated with good neurological outcomes [18, 19]. Although it is very difficult use single-point EEG to evaluate brain injury, continuous EEG might be considered as a prognostic tool.

It has been suggested that during the initial 24 h after ROSC, cerebral blood flow and metabolism change significantly, especially in patients with poor neurological outcomes. In a previous report, Buunk et al. compared jugular and mixed venous oxygen saturation and found that jugular venous oxygen saturation, which is initially lower than mixed venous oxygen saturation, increases gradually and becomes higher than mixed venous oxygen saturation 24 h after ROSC in patients with poor neurological outcomes [20]. Jugular venous oxygen saturation is correlated with the cerebral blood flow/metabolism ratio, and increased jugular venous oxygen saturation indicates high blood flow and/or low metabolism, suggesting severe brain edema. Brain oxygen saturation assessed with near-infrared spectroscopy (NIRS) originally mimicked jugular venous saturation [21] and reflected the cerebral blood flow/metabolism ratio, although there are many different evaluation points. Ahn et al. reported that extremely high brain oxygen saturation was observed in patients with poor outcomes [22]. Thus, for evaluating jugular venous oxygen saturation and brain oxygen saturation, time course is important, and an extremely high value might reflect poor outcomes. Previous studies have mentioned that if brain regional oxygen saturation is under 62%, the outcome might be poor [23, 24].

The absence of bilateral N20 in short-latency somatosensory evoked potentials 24 h after ROSC might predict poor neurological outcomes with 100% specificity but with low sensitivity [25]. The absence of the V wave in brainstem evoked potentials before the start of TTM might indicate unsuitability for TTM [26]. A neuroelectrophysiologic test might show poor neurological outcomes.

Serum NSE and tau protein levels after ROSC might be associated with poor outcomes. However, the presence of different cutoff values makes it difficult to use biomarker results in decision-making [27, 28].

Regarding the monitoring of brain metabolites, a case series involving brain microdialysis in PCAS patients showed discrepancies in glucose and lactate between brain microdialysate and plasma [13]. This previous study indicated that the brain glucose level might be associated with the blood glucose level. However, although the blood lactate level normalized after ROSC, a sustained high brain lactate level was observed in patients with poor outcomes, suggesting that the blood lactate level, but not the brain lactate level, reflects systemic circulation. Thus, it is better to monitor the brain directly after ROSC.

13.4 Treatment for Myocardial Dysfunction

The main cause of cardiac arrest is cardiovascular disease, and treatment for revascularization is necessary. If the cause of cardiac arrest is ST elevation acute myocardial infarction, immediate coronary angiography with/without percutaneous coronary intervention (PCI) is recommended. For non-ST elevation acute myocardial infarction that induces cardiac arrest, immediate coronary angiography with/without PCI is also recommended, because prehospital electrocardiography does not identify an occluded coronary artery [29] and a previous study found an occluded coronary artery in 25% of patients with non-ST elevation acute myocardial infarction [30].

Reperfusion injury, in addition to ischemic insult, is a main cause of myocardial dysfunction. Clinical research reported that TTM before PCI can decrease the volume of myocardial infarction and might improve cardiac function after ROSC.

13.5 Current Concepts of TTM

Many observational studies have reported that fever after ROSC was related with poor neurological outcomes [31, 32]. TTM to prevent fever is reasonable for neuroprotection, although information on this is limited. Regarding TTM, there is no dose-response relationship for the time interval from initiation to achievement of the target temperature, the target temperature, and the duration of hypothermia.

In 2002, a landmark study about TTM was published, and it indicated that therapeutic hypothermia (32–34 °C, 24 h) resulted in better neurological outcomes at 6 months when compared to the outcomes without fever control in patients with an initial shockable rhythm [33]. In the same year, Bernard et al. also showed that therapeutic hypothermia (33 °C, 12 h) increased the proportion of patients with an initial shockable rhythm and increased the proportion of patients who could return home or participate in rehabilitation at discharge [34]. Another landmark study on TTM (the TTM trial), published in 2013, showed that TTM (36 °C, 24 h, followed by 8 h of rewarming to 37 °C and temperature maintenance below 37.5°C until 72 h) was as effective (primary outcome, mortality) as therapeutic hypothermia (32–34 °C) and is an acceptable alternative [35]. It is important to confirm the findings of the TTM trial, in which 80% of patients had VF/VT and 20% did not have VF/VT (PEA/asystole), as the severity of brain injury might have been high. Lopez-de-Sa et al. compared temperatures of 32 and 34 °C for therapeutic hypothermia (24 h) and reported that there was no significant difference in patient independence at 6 months [36]. Regarding a nonshockable rhythm (PEA/systole), the TTM trail presented data showing that there was no significant difference in death between therapeutic hypothermia (32–34 °C) and no therapeutic hypothermia (36 °C) [35]. Regarding the optimal duration of TTM, Kirkegaard et al. reported that there was no significant difference in 6-month survival between therapeutic hypothermia at 33 °C for 24 and 48 h among patients with a combined cardiac rhythm (shockable, 90%) [37].

Thus, therapeutic hypothermia (32–34 °C, 24 h) is recommended for adult patients in a coma after ROSC, irrespective of an initial cardiac rhythm, although patients with a shockable rhythm are expected to show better outcomes. The most important notes in TTM operation are adequate neurocritical care except TTM (described below). The management of TTM at 32–34 °C is easier than that at 36 °C because shivering is severe at 36 °C. One interesting report showed that shivering control and analgosedation use are difficult with TTM at 36 °C [38]. Therefore, therapeutic hypothermia at 32–34 °C is recommended. Finally, if possible, care must be taken to control the time interval between collapse and ROSC, because the interval might determine the outcome.

13.6 Neurocritical Care Except TTM

It is important to know whether there is a difference with regard to optimization of blood pressure between PCAS and critically ill patients. For critically ill patients, systolic blood pressure >90 mmHg or mean blood pressure >65 mmHg is indicated. For PCAS patients, it is important to maintain CPP normally. There is limited data about optimization of blood pressure. In a previous study [13], ICP increased to around 10 (5–20) (median [IQR]) in patients with good outcomes. However, ICP increased to 25 (10–30) in those with poor outcomes. Considering increased ICP, it is suggested that systolic blood pressure should be maintained at about 100 mmHg (mean blood pressure, 75 mmHg).

Regarding the heart rate, the minimum heart rate during TTM is considered to be associated with outcomes. Recent study has shown that bradycardia and a low heart rate are predictors of good neurological outcomes. Recently, a relationship between the heart rate response during rewarming and outcomes has been suggested [39]. In this study, an increased heart rate during rewarming predicted good neurological outcomes. The heart rate during TTM is a key indicator of brain variability. Bradycardia without hypotension is not suitable to treat during TTM.

Antiepileptic drugs should be used to stop seizures. However, since the effects of antiepileptic drugs are not standardized and there are many side effects, such as hypotension, the prevention of seizures with antiepileptic drugs is not permitted. Continuous EEG monitoring and assessment of non-convulsive status epileptics are important [40].

Hypoxia should be avoided, and it has been suggested that hyperoxia should also be avoided. Blood glucose control in PCAS patients is similar to that in other critically ill patients. Finally, during TTM, adequate analgosedation and the control of shivering are needed. Moreover, adequate urine output and lactate clearance are considered important.

13.7 Future Directions

Preliminary information for determining the degree of brain injury is now known. Tailored neurocritical care, including TTM, should be applied to improve neurological outcomes in PCAS patients. Neurological prognostication should be performed at least 72 h after ROSC through clinical investigations and multimodal testing without sedation.

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Chapter 14
Sepsis and Sepsis-Associated Encephalopathy: Its Pathophysiology from Bench to Bed

Motoki Fujita and Ryosuke Tsuruta

Abstract Sepsis-associated encephalopathy (SAE) is characterized by diffuse cerebral dysfunction caused by a systemic inflammatory response to infection. SAE can be reversible after recovery from sepsis or can result in long-term cognitive impairments. SAE has a detrimental effect on the prognosis of septic patients. Although the exact pathophysiology of SAE remains unknown, several mechanisms have been proposed in animal and clinical studies. Animal studies suggest that neuroinflammation, oxidative stress, blood–brain barrier (BBB) disruption, impairment of cerebrovascular autoregulation, alteration of neurotransmission, mitochondrial dysfunction, and neuronal apoptosis are involved in the pathophysiology of SAE, whereas clinical studies suggest neuroinflammation, BBB disruption, oxidative stress in the brain, impairment of cerebrovascular autoregulation, and alteration of neurotransmission as underlying mechanisms. Systemic insults such as other organ dysfunction and metabolic abnormalities may also play a role in the pathophysiology of SAE, as suggested by a retrospective analysis of a large prospective multicenter database. However, there is a discrepancy in the hypothesized pathophysiology of SAE between animal and clinical studies. This discrepancy may stem from differences in the diagnosis of SAE between animals and humans. Clinically, the diagnosis of SAE is based on symptoms, whereas changes in mental status are difficult to detect in animals. Further research is necessary to clarify the pathophysiology of SAE.

Keywords Delirium · Coma · Acute brain dysfunction · Blood–brain barrier Neurotransmission · Oxidative stress · Mitochondrial dysfunction · Apoptosis Cerebrovascular autoregulation

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14.1 Introduction

Sepsis is a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection, leading to systemic inflammation and organ dysfunction [1, 2]. Patients with sepsis often show acute and reversible deterioration of mental status that matches the current criteria for delirium [3]. This disorder is termed sepsis-associated encephalopathy (SAE) and causes sepsis-induced organ dysfunction of the central nervous system (CNS) (Fig. 14.1) [4]. SAE is characterized by acute brain dysfunction in the presence of sepsis but in the absence of CNS infection or other forms of encephalopathy [5, 6].

SAE is characterized clinically by symptoms such as delirium and coma in septic patients (Fig. 14.2) [7]. However, the pathophysiology of SAE remains unclear, despite several potential mechanisms suggested by animal experiments [8–11]. The reason for this is that applying the results of animal studies to humans is difficult, and there are no animal models replicating human SAE. In addition, assessing mental status in septic animals is difficult. The present review examined the differences in the reported pathophysiology of SAE between animals and humans to clarify the mechanisms underlying SAE.

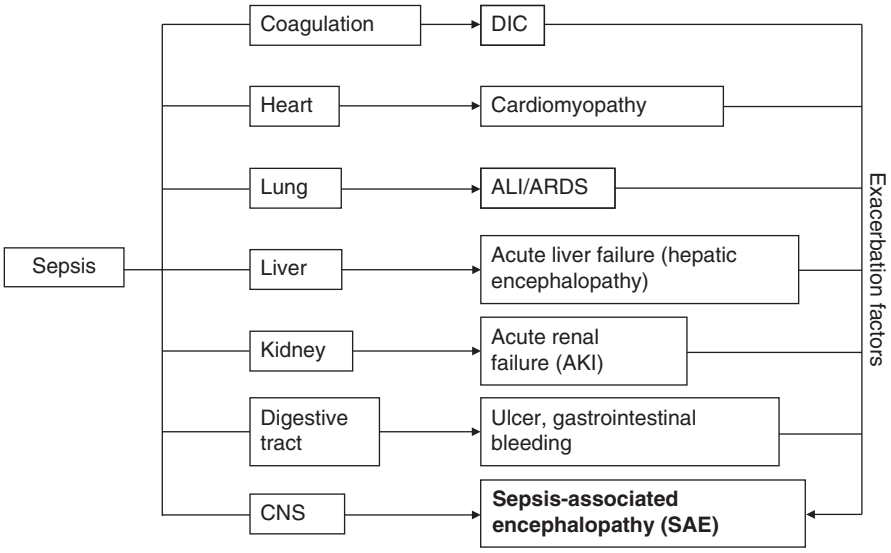

Fig. 14.1 Acute organ failure in sepsis. *DIC* disseminated intravascular coagulation, *ALI/ARDS* acute lung injury/acute respiratory distress syndrome, *CNS* central nervous system

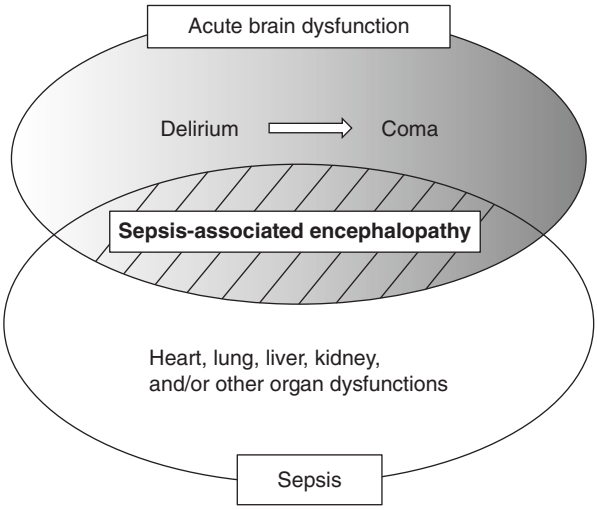

Fig. 14.2 Relationships between delirium, coma, sepsis, and sepsis-associated encephalopathy (SAE). Acute brain dysfunction includes delirium and coma. Coma is a more severe state than delirium. The shaded area indicating the overlap between acute brain dysfunction and sepsis represents SAE

14.2 Clinical Features

SAE is a common occurrence in the intensive care unit (ICU). SAE is observed in 9–71% of septic patients depending on how it is defined [12]. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) is used to assess delirium, which is diagnosed in ~50% of ICU patients with infection [13].

The clinical symptoms of SAE are delirium and coma [7]. Delirium is the symptom of SAE most commonly observed in the ICU, and coma is considered a more severe state of SAE than delirium [4]. It is important to distinguish between the concepts of SAE and delirium, because SAE is just one of the many forms of delirium (Fig. 14.2).

SAE has a negative effect on the prognosis of septic patients. The mortality from SAE is estimated as 70% when it occurs as a manifestation of multiple organ dysfunction [5]. The presence of encephalopathy along with sepsis is associated with a twofold increase in the risk of death [14]. SAE is mostly reversible after recovery from sepsis; however, it may result in long-term cognitive impairment [15]. A cohort study revealed an independent association of severe sepsis with persistent cognitive and functional limitations [16]. The risk of moderate to severe cognitive impairment triples in septic patients. The direct association between SAE and long-term cognitive impairment remains unclear, and follow-up of sepsis survivors with or without SAE is necessary to clarify this relationship.

14.3 Pathophysiology of SAE in Animal Models

The exact pathophysiology of SAE remains unknown [9]; however, several mechanisms have been proposed in animal studies. The hypothesized pathophysiology of SAE includes neuroinflammation [11, 17, 18], oxidative stress [19–22], blood–brain barrier (BBB) disruption [17, 18, 23–26], impairment of cerebrovascular autoregulation [27, 28], alteration of neurotransmission [29–35], mitochondrial dysfunction [19, 36–38], and neuronal apoptosis [39–41].

Neuroinflammation has been detected in the brains of rodents with systemic inflammation [11]. Infiltration of immune cells into the brain parenchyma was shown in a mouse endotoxemia model [17]. Neutrophil infiltration into the brain and astrocytosis have been observed in the early phase after intraperitoneal (ip) lipopolysaccharide (LPS) administration in association with delayed and progressive loss of neurons in the substantia nigra [17]. Hoogland et al. reviewed systemic inflammation and microglial activation in animal experiments and reported that microglial activation was observed at 6 h after LPS challenge and remained present for at least 3 days [11]. These authors also reported that microglial activation was associated with an increase in the mRNA or protein levels of Toll-like receptor (TLR-2 and TLR-4), tumor necrosis factor alpha (TNF-α), and interleukin-1 beta (IL-1β) [11]. In endotoxemic mice induced by intravenous (iv) LPS, TNF-α levels in the brain increased rapidly and steeply and remained elevated for 10 months [18].

Cerebral oxidative stress is induced by systemic inflammation [19]. In a rat cecum ligation and puncture (CLP) model, the contents of superoxide anion radical, nitrite, and lipid peroxidation in brain capillaries increased at the subacute phase after sepsis induction [20]. Oxidative stress, as assessed by thiobarbituric acid reactive species and protein carbonyl assays, occurred early (after 6 h) in the course of sepsis development in the hippocampus, cerebellum, and cortex of CLP rats [21]. This cerebral oxidative damage was not present in the subacute phase. Another study revealed that both cerebral NAPDH oxidase activity, which is a major source of superoxide anion radical, and the levels of 8-hydroxydeoxyguanosine, an indicator of oxidative DNA damage, were increased in the brains of mice in a CLP model [22].

BBB disruption has been shown in both in vitro [23, 24] and in vivo studies [17, 18, 25, 26]. In in vitro experiments, BBB disruption was confirmed by an increase in the permeability of endothelial cells in culture and endothelial cell injury [23, 24]. Exposure of cultured bovine brain capillary endothelial cells (BBCECs) to LPS induces a large increase in the paracellular permeability of the monolayer of BBCECs [23]. Another study demonstrated BBB disruption using cultured mouse cerebrovascular endothelial cells (MCVEC) [24]. Exposure of cultured MCVECs to the plasma of mice with feces-induced peritonitis increased permeability and oxidative stress. In in vivo experiments, BBB disruption was confirmed by brain edema [17, 25, 26], infiltration of immune cells into the brain parenchyma [17], and cytokine transportation across the BBB [18]. The development of brain edema has been demonstrated in various models, including a mouse endotoxemia model induced by ip LPS [17, 18], a rat CLP model, and a pig fecal peritonitis model [25].

Impairment of cerebrovascular autoregulation was observed in a rat endotoxemia model induced by iv LPS infusion [27] and in a rat model of pneumococcal bacteremia and/or meningitis [28]. In the rat endotoxemia model, cerebrovascular autoregulation was assessed using a carotid compression technique that measures the transient hyperemic response ratio in the cortex by laser Doppler flowmetry after iv LPS administration [27]. Autoregulatory compensation for low blood pressure levels was impaired in the endotoxemia rats after iv LPS administration [27]. In the rat pneumococcal bacteremia and/or meningitis model, cerebrovascular autoregulation was assessed by laser Doppler flowmetry after iv or intracisternal inoculation of *Streptococcus pneumonia* [28]. Bacteremia without meningitis was associated with an increase in the lower limit of cerebrovascular autoregulation, whereas bacteremia with meningitis was associated with loss of autoregulation [28].

Alteration of neurotransmission was shown in a rat CLP model [29–31] and a rodent endotoxemia model induced by ip or iv LPS administration [32–35]. The alteration of neurotransmission extended to the cholinergic [32, 34, 35], β-adrenergic [33, 34], and GABAergic systems [29, 31]. In the cholinergic system, the mRNA expression of choline acetyltransferase, acetylcholinesterase, and M1 muscarinic acetylcholine receptor was downregulated in the brains of mice with endotoxemia [35], and a reduction of cholinergic innervation in the parietal cortex was reported after recovery from endotoxemia in mice [34]. In the β-adrenergic system, the cerebral concentrations of adrenaline and noradrenaline were decreased in a rat endotoxemia model and a CLP model [30], and the catabolites of noradrenaline and dopamine were increased in the brains of endotoxemia mice [33]. Septic rats induced by CLP showed increased serum gamma-aminobutyric acid (GABA) levels [31] and cerebral GABA receptor density [29]. These alterations of neuroendocrine pathways are among the factors that aggravate the state of SAE [10].

Mitochondrial dysfunction is associated with cerebral oxidative stress [19, 36], and has been proposed as a mechanism underlying SAE in a rodent CLP model [37, 38]. Mitochondrial dysfunction associated with sepsis is mediated by several mechanisms, including electron transport chain dysfunction [37], oxidative inhibition of mitochondrial dehydrogenases and adenine nucleotide transporters, and decreased cytochrome content and respiratory uncoupling [36, 38]. Mitochondrial dysfunction is associated with uncoupling proteins and opening of the permeability transition pore, which increases the permeability of the inner mitochondrial membrane leading to proton leak and loss of mitochondrial membrane potential [36, 38]. During sepsis, mitochondrial dysfunction compromises the bioenergetic efficiency of tissues, inducing cellular dysfunction and mitochondria-dependent neuronal apoptosis [42].

Neuronal apoptosis, as determined by TUNEL staining, has been observed in the cortex, striatum, hippocampus, midbrain, and cerebellum of endotoxemic rats at 4 h after ip LPS administration, reaching a maximum at 8 h in the cortex, striatum, and hippocampus and at 24 h in the midbrain and cerebellum [39]. Neuronal apoptosis in septic animals is associated with nitric oxide production [40] and is suppressed by inducible nitric oxide synthase (iNOS) inhibition [39]. Neural apoptosis also occurs through a mitochondrial-dependent pathway induced by mitochondrial dysfunction in CLP rats [41].

14.4 Pathophysiology of SAE in Clinical Studies

The pathophysiology of SAE in the clinical setting has been examined in few studies. Neuroinflammation was confirmed by an increase in cytokine levels in the cerebrospinal fluid (CSF) of septic patients with SAE [43, 44]. The concentration of IL-1β is markedly higher in the plasma and in the CSF of septic patients with SAE than in those of patients without SAE [43]. Cojocaru et al. showed that TNF-α and IL-6 are significantly elevated in the serum and CSF of septic patients with neurologic complications [44]. The occurrence of BBB disruption was suggested by an increased correlation between cytokines in serum and in CSF [44]. Vasogenic edema in white matter, suggesting increased BBB permeability, was detected in septic shock patients with neurological abnormalities by magnetic resonance imaging [45]. Regarding oxidative stress, the levels of ascorbate, an antioxidant, are decreased in the plasma and CSF of septic patients with neurological abnormalities, and the decrease in the CSF is correlated with the severity of neurologic symptoms [46]. These findings indicate that the BBB disruption and oxidative stress observed in the brain in animal studies may also be associated with clinical SAE.

Impairment of cerebrovascular autoregulation has been suggested as one of the mechanisms of SAE in clinical studies [47, 48]. Cerebrovascular autoregulation is assessed by measuring the correlation between mean arterial pressure and blood flow velocity in the middle cerebral artery using transcranial Doppler sonography [47, 48]. Cerebrovascular autoregulation is disturbed in patients with sepsis-associated delirium diagnosed by CAM-ICU, and elevated C-reactive protein is significantly correlated with disturbed autoregulation [47]. Schramm et al. examined cerebrovascular autoregulation impairment daily for 4 days after onset in patients with severe sepsis or septic shock [48]. Autoregulation was impaired in 60% of patients on day 1, 59% on day 2, 41% on day 3, and 46% on day 4. Sepsis-associated delirium diagnosed by CAM-ICU was present in 76% of patients. Impaired autoregulation on day 1 was also associated with the presence of sepsis-associated delirium on day 4. Cerebral hypoperfusion/hyperperfusion in septic patients may contribute to the role of impaired cerebrovascular autoregulation in SAE [4].

Alterations of neurotransmission have been reported in several studies. In the cholinergic system, LPS administration in healthy individuals increases plasma acetylcholinesterase (AChE) activity, which is associated with better performance in evocative memory tasks and worse performance in working memory [49]. In addition, patients that respond to LPS by suppressing the cholinergic system have a better working memory performance than those with enhanced cholinergic activity, indicating that limited cholinergic activation may be beneficial for cognition [49]. The involvement of the α-adrenergic and GABAergic systems in SAE was suggested by the protective effects of the α-adrenoceptor agonist dexmedetomidine and the harmful effects of the GABA agonist benzodiazepine on brain dysfunction in septic patients [50].

A recent retrospective analysis of a large prospective multicenter database indicated that systemic insults, including other organ dysfunction and metabolic abnormalities, may play a role in the pathophysiology of SAE [51]. In this retrospective

study, acute renal failure and common metabolic disturbances, including hypoglycemia, hyperglycemia, hypercapnia, and hypernatremia, were potentially modifiable factors associated with SAE, as diagnosed by the Glasgow Coma Scale <15 or in the presence of features of delirium [51]. These results suggest that SAE is induced not only by inflammation extending to the central nervous system but also by the patient's general condition, including other organ dysfunction excluding the brain and metabolic abnormalities.

14.5 Diagnosis

A flowchart for the diagnosis of SAE is shown in Fig. 14.3. In patients diagnosed with sepsis, it is important to determine the potential presence of SAE. Therefore, the detection of changes in mental status such as delirium and coma is important. The 2013 American College of Critical Care Medicine/Society of Critical Care Medicine clinical practice guidelines for pain, agitation, and delirium recommend that critically ill patients should undergo routine monitoring for the onset of delirium in the ICU using a validated tool [52]. The CAM-ICU [53] and the Intensive Care Delirium Screening Checklist [54] are the most valid and reliable tools for monitoring delirium in adult ICU patients [52].

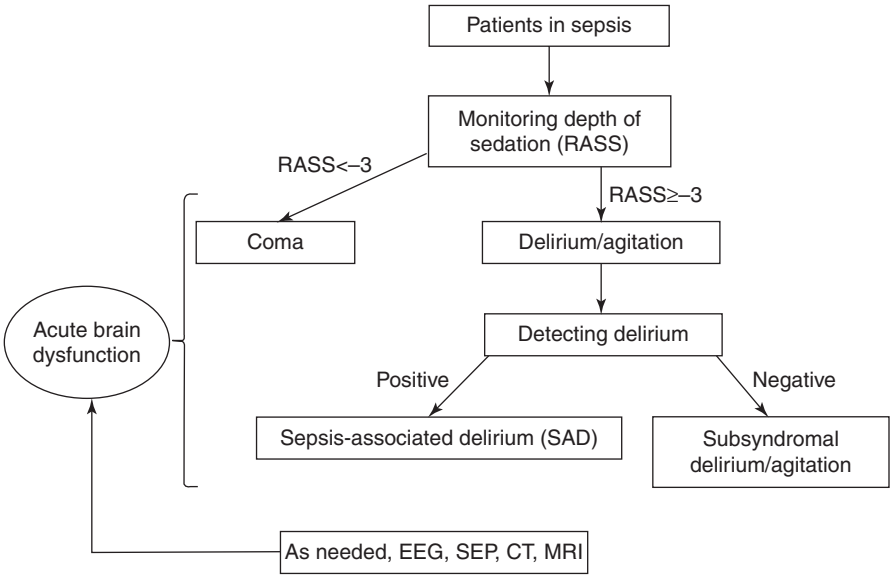

Fig. 14.3 Diagnostic decision tree for sepsis-associated encephalopathy (SAE). SAE includes acute brain dysfunction such as sepsis-associated delirium and coma in septic patients. *RASS* Richmond Agitation–Sedation Scale, *SAD* sepsis-associated delirium, *EEG* electroencephalography, *SEP* sensory evoked potential, *CT* computed tomography, *MRI* magnetic resonance imaging. Figure sourced from Ref. 4

In addition, electroencephalograms (EEGs) and neuroimaging are supportive tools for the diagnosis of SAE (Fig. 14.3). These tests should be considered in patients with persistent coma or delirium despite improvements in the function of other organs and after the effects of sedatives wear off.

14.6 Treatment

Specific treatments for SAE have not been identified to date. The treatment of SAE currently consists of treatments for sepsis, which causes SAE, and supportive therapy for organ dysfunction [8, 12]. Among these supportive therapies, the use of non-benzodiazepine sedatives [50, 52, 55, 56], early initiation of rehabilitation [57], and improvement of sleep quality may be effective for the prevention of SAE [55] based on guidelines recommending these treatments for the prevention of delirium in the ICU [52, 55].

14.7 Differences in the Pathophysiology of SAE Reported in Animals and Humans

Differences in the pathophysiology of SAE between animal and human studies could be attributed to differences in the study design (Fig. 14.4). Most animal studies use a systemic inflammation model induced by LPS administration (iv or ip) or

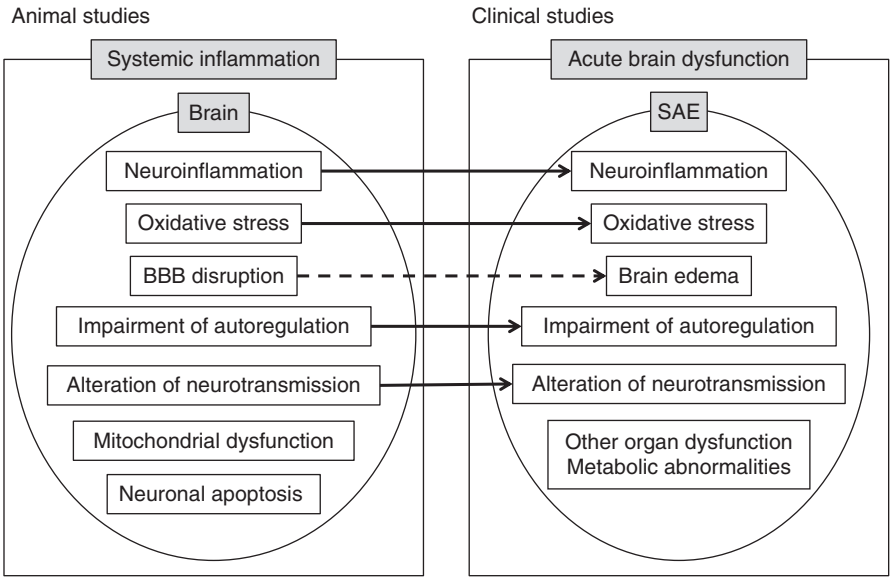

Fig. 14.4 The mechanisms of sepsis-associated encephalopathy (SAE) reported in animal and clinical studies. *SAE* sepsis-associated encephalopathy, *BBB* blood–brain barrier

CLP, except in studies using in vitro models. Hypotheses on the pathophysiology of SAE derived from animal studies are based on phenomena observed in the brain of animals with systemic inflammation. Few studies have investigated alterations in the mental status of animals during sepsis because it is difficult to assess the mental status of animals. Several rodent studies confirmed physiological changes in the brain of rats with systemic inflammation by EEG [58–62], whereas other studies have assessed behavioral changes based on tail flick time [62] or neurological reflexes such as the pinna reflex, corneal reflex, paw or tail flexion reflex, and righting reflex [63] during systemic inflammation.

In clinical studies, SAE is a type of acute brain dysfunction, and its diagnosis is symptom based. Unlike in animal studies, clinical studies of SAE are based on the clinical diagnosis. This difference of approach is an important limitation for extrapolating the results of animal studies to hypothesize the pathophysiology of clinical SAE.

14.8 Conclusions

The exact pathophysiology of SAE remains unknown. There is a discrepancy in the hypothesized pathophysiology of SAE between animal studies and clinical studies. This discrepancy may stem from differences in approach between animal and human studies. Clinical SAE is diagnosed based on symptoms, whereas changes in mental status in animals are difficult to determine. Further experiments are needed to clarify the pathophysiology of SAE.

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Chapter 15
Acute Infections of the Central Nervous System: Focus on Bacterial Meningitis and Herpes Simplex Encephalitis

Akihiko Morita and Masaki Ishihara

Abstract Acute infectious diseases of the central nervous system, particularly bacterial meningitis and herpes simplex encephalitis (HSE), are neurological emergencies. These diseases often have no definitive symptoms or signs, which makes diagnosis difficult. Delayed diagnosis or treatment of bacterial meningitis or HSE leads to a poor prognosis.

If bacterial meningitis is clinically diagnosed, optimal antimicrobial therapy should be started within 1 h after initial contact with the patient. In Japan, pneumococcal and *Haemophilus influenzae* type b (Hib) meningitis account for 75% of all community-acquired bacterial meningitis cases, and most causative pathogens of these meningitis are resistant to ampicillin and third-generation cephem antibiotics. If pneumococcal meningitis is suspected, the choice of antibiotics should be strategically determined on the assumption that the etiologic agent is penicillin-resistant *Streptococcus pneumoniae* in Japan. Hib and pneumococcal vaccines contribute to reducing the frequency of bacterial meningitis.

The etiology of acute encephalitis is often unknown. HSE is one of the major causes, and its prognosis is extremely poor without treatment. Acyclovir (ACV) is the most efficient agent for the treatment of HSE. If acute encephalitis is clinically diagnosed, treatment with intravenous ACV (10 mg/kg, every 8 h for 14–21 days in immunocompetent patients) should be immediately started. In definitive HSE patients, ACV treatment should not be stopped until confirmation of HSV-negative polymerase chain reaction results in cerebral spinal fluid samples on two separate occasions. In patients with ACV-resistant HSE, adjunctive vidarabine or foscarnet should be considered.

Keywords Pneumococcal meningitis · *Haemophilus influenzae* type b (Hib) meningitis · Herpes simplex encephalitis · Japan

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15.1 Introduction

All infectious diseases involving the central nervous system (CNS), including bacterial meningitis, acute encephalitis, tuberculous meningitis, fungal meningitis, and brain abscess, represent potentially life-threatening neurological emergencies. Half of all patients with bacterial meningitis present within 24 h of the onset of symptoms. Therefore, patients who have a hyper-acute to acute onset of headache and altered mental status should be considered as potentially having meningitis or encephalitis. Combination of fever, neck stiffness, new rash, focal neurological findings, or new seizures suggests CNS infection. In a large series of 696 adult patients with bacterial meningitis, the classic triad of fever, neck stiffness, and change in mental status was present in only 44% of patients. However, 95% of patients had at least two of the tetralogy: fever, headache, neck stiffness, and change in mental status [1]. The absence of fever, headache, neck stiffness, or altered mental status does not eliminate bacterial meningitis. In this chapter, an update on the management of CNS infection in Japan is introduced.

15.2 Bacterial Meningitis

Bacterial meningitis is strongly associated with morbidity and mortality. Early diagnosis and treatment of bacterial meningitis are essential. Any delay in the initiation of antimicrobial therapy results in poor outcomes. The incidence of meningitis in Japan, including viral, bacterial, tuberculous, and fungal meningitis, is estimated at about 32,000 cases per year [2]. In 75% of cases, the etiology of meningitis is unknown. Since many patients with meningitis recover without treatment, the infectious agent often remains unknown but is presumed to be viral. Over 90% of meningitis cases are likely attributed to viral infection, 5% of cases are attributed to bacterial infection, and less than 1% of meningitis cases are attributed to tuberculous infection. The incidence of bacterial meningitis in Japan is estimated to be 1500 cases per year. In 75% of bacterial meningitis cases, the causative agent is *Streptococcus pneumoniae* or *Haemophilus influenzae* type b (Hib). Thus, successful strategies against bacterial meningitis must include effective treatments for pneumococcal and Hib meningitis.

15.2.1 Pneumococcal Meningitis

S. pneumoniae is a major human pathogen that causes a range of community-acquired infections, including respiratory tract infections, acute otitis media, septicemia, and meningitis. *S. pneumoniae* remains a leading cause of morbidity and mortality worldwide, especially among children and the elderly. In particular,

penicillin-resistant *S. pneumoniae* (PRSP) emerged in the 1980s and rapidly spread to many countries. In Japan, pediatric meningitis caused by PRSP was first reported in 1988. The prevalence of PRSP has rapidly increased since the late 1990s, especially in young children. According to the Nationwide Surveillance for Bacterial Meningitis program in Japan between 1999 and 2002, the prevalence of PRSP was over 80% of clinical isolates. Notably, cefotaxime was not an effective agent for the clinical treatment of PRSP meningitis. Carbapenems, e.g., panipenem-betamipron or meropenem (MEPM), and vancomycin (VCM) are the antibiotics of choice for the treatment of pneumococcal meningitis caused by PRSP in Japan [3].

Vaccination is essential to reduce the number of patients with pneumococcal meningitis. Pneumococcal conjugate vaccines (PCVs) were introduced in 2010 in Japan. At the end of 2011, the vaccination rate among infants at risk throughout Japan was estimated to be 40–60%. The incidence of pneumococcal meningitis declined after PCVs were introduced. However, the occurrence of pneumococcal meningitis caused by non-vaccine serotypes has subsequently increased.

15.2.2 Haemophilus influenzae *Type b Meningitis*

Hib is a common pathogen that causes meningitis in infants and children older than 3 months of age. In Japan, the incidence of Hib infection is 10–12 per 100,000 children under 5 years of age [4]. Furthermore, beta-lactamase-nonproducing ampicillin-resistant (BLNAR) organisms have been found among Hib isolates since 1997. The proportion of BLNAR and Hib isolates from patients with meningitis rapidly increased as these strains exponentially increased in patients with respiratory tract infections. Ceftriaxone and MEPM combination therapy is recommended for Hib meningitis caused by BLNAR.

Hib vaccination of children was introduced in 2008 in Japan. Subsequently, the immunization rate for Hib in Japanese children up to 1 year of age has continued to rise each year. Over the same interval, the number of Hib meningitis patients has decreased. Hib is presently considered a rare cause of bacterial meningitis in children.

15.2.3 Diagnosis and Treatment of Bacterial Meningitis

Bacterial meningitis is suspected when a patient visits the emergency department of a hospital with headache, fever, and meningismus. First, airway, breathing, circulation, and neurological disability should be assessed. Initial laboratory examinations should include two sets of blood cultures, blood gas, complete blood count (CBC), and serum chemistry investigations, including C-reactive protein. Next, indications for lumbar puncture should be assessed. If warning signs for a space-occupying lesion, e.g., new-onset seizure, papilledema, or evolving signs of brain tissue shift,

are present or patients who have risk factors, underlying disease, and/or immunocompromised condition, lumbar puncture should not be performed. Additionally, lumbar puncture should not be performed if patients have systemic shock, coagulation abnormalities, local infection at the lumbar puncture site, and/or respiratory insufficiency. Instead, empirical antimicrobial therapy should be immediately started. These warning signs are important and useful. Head computed tomography (CT) scan is not always required before lumbar puncture. However, an emergency head CT scan is performed in most Japanese emergency departments when bacterial meningitis is suspected. Because Japan leads the world in the number of CT scanners and magnetic resonance imaging (MRI) units in use, CT scanners and MRI units are common and easily accessible tools. If warning signs of a space-occupying lesion are not present, emergency head CT should be assessed. Only when head CT scanning is estimated to take too much time, lumbar puncture should be performed without head CT. Lumbar puncture is recommended after confirmation of the absence of an intracranial space-occupying lesion or herniation. If an intracranial space-occupying lesion or herniation is present, empirical antimicrobial therapy should be immediately started. The following items should be assessed when lumbar puncture is performed. For cerebral spinal fluid (CSF) samples, opening pressure, white blood cell count with differential, glucose level, CSF/blood glucose ratio, protein level, Gram stain, culture, and *S. pneumoniae* antigen testing using a rapid immunochromatographic assay should be assessed. If possible, polymerase chain reaction (PCR) analysis should also be performed.

If bacterial meningitis is clinically diagnosed, optimal antimicrobial therapy should be immediately started. Antimicrobial therapy should be started within 1 h after initial contact with the patient. Administration of empirical antibiotics for patients with bacterial meningitis should be based on local epidemiology, patient's age, and presence of specific underlying diseases or risk factors. For instance, the incidence of meningococcal meningitis is <0.02 patients per 100,000 persons annually in Japan, although meningococcal disease is a serious problem globally [5]. *Listeria monocytogenes*, which is resistant to cephalosporins and sensitive to amoxicillin or ampicillin (ABPC), may be common in immunosuppressed patients with meningitis who are at risk of this infection, including pregnant patients and those older than 50 years of age. However, the occurrence of listeriosis is limited to approximately 200 cases per year in Japan [6]. The current Japanese clinical guideline committee recommended treatment for etiology unknown bacterial meningitis is described in reference [7].

When the CSF Gram stain is negative and a patient has recently undergone surgery, including ventriculoperitoneal shunt, infection by *Staphylococcus epidermidis*, *Staphylococcus aureus*, or Gram-negative rods, including *Pseudomonas aeruginosa*, is presumed. The combination of MEPM plus VCM is recommended as an empirical treatment.

When the patient has an underlying disease or is immunocompromised, *S. pneumoniae* or staphylococci including methicillin-resistant *S. aureus* (MRSA) can be the most frequent pathogen. Infections caused by Gram-negative rods, including extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* or *P. aeruginosa*, are also increasing. Ceftazidime, VCM, and ABPC or MEPM plus

VCM combination therapy is recommended as an empirical treatment. Among immunocompetent patients older than 50 years of age, the most frequent pathogen is *S. pneumoniae*, which is typically PRSP. *L. monocytogenes*, *S. aureus* including MRSA, Hib, group B streptococci, or *Escherichia coli* are also seen. The combination of third-generation cephalosporins, VCM, and ABPC or the combination of MEPM plus VCM is recommended as an empirical treatment. Among immunocompetent patients aged 16–49 years, the most frequent pathogen is *S. pneumoniae*, which is typically PRSP. Carbapenems alone or third-generation cephalosporins plus VCM combination therapy is recommended as an empirical treatment.

Additionally, the Japanese clinical guidelines recommend adjunctive corticosteroid treatment. Corticosteroid reduces excess production of pro-inflammatory cytokines. Blockage of this pathophysiological cascade improves outcomes in bacterial meningitis.

15.3 Acute Encephalitis

Acute encephalitis is one of several neurological emergencies that frequently cause considerable morbidity and mortality. Encephalitis is defined as inflammation of the brain parenchyma. Acute encephalitis is commonly viral in origin, with herpes simplex, varicella-zoster, rubella, and measles viruses being the most common etiologic agents in Japan. Although the term "encephalitis" is often used to indicate a viral etiology, many other infectious entities, including bacterial, tuberculous, and fungal infections and acute disseminated encephalomyelitis (ADEM), and noninfectious entities, including systemic lupus erythematosus (SLE), Hashimoto's disease, paraneoplastic neurological syndromes, and antibody-mediated diseases (especially anti-*N*-methyl-D-aspartate receptor antibody), can cause encephalitis or encephalitis-like symptoms.

In Japan, infectious disease surveillance for acute encephalitis started in 2003. This surveillance requires registration of all patients who are clinically diagnosed with acute encephalitis. The diagnosis and management of acute encephalitis are challenging for most clinicians. The differential diagnosis of acute encephalitis is wide-ranging and includes infectious etiologies (e.g., viral, bacterial, tuberculous, and fungal infections and prion disease), ADEM, autoimmune disorders (e.g., SLE and Hashimoto's disease), metabolic disorders (e.g., thiamine deficiency), toxic disorders (e.g., drug intoxication), vascular diseases, neoplastic disease, paraneoplastic neurological syndromes, antibody-mediated diseases (e.g., anti-*N*-methyl-D-aspartate receptor antibody), subclinical status epilepticus, and brain dysfunction due to systemic sepsis.

The incidence of encephalitis in Japan is estimated at about 2200 cases per year. In 60% of cases, the etiology of encephalitis is unknown, and 36% of encephalitis cases are likely attributed to viral infection. In about 60% of viral encephalitis cases, the etiology is herpes simplex virus (HSV). The incidence of herpes simplex encephalitis (HSE) in Japan is estimated at about 3.5 cases per 1,000,000 persons annually [2].

15.3.1 Herpes Simplex Encephalitis

The incidence of HSE in developed countries is estimated to be 0.5–7 cases per 1,000,000 persons annually. HSE occurs throughout the year and in patients of all ages. Both sexes are equally affected. HSE is one of the most devastating infections acquired by humans. The limbic system is mainly injured, and patients present with symptoms attributed to dysfunction of mesial temporal lobe structures. Short-term memory loss, behavioral disturbances, psychiatric problems, and recurrent seizures are seen.

In patients who receive no therapy, the mortality rate is >70%. Acyclovir (ACV), developed as a selective and specific inhibitor of viral replication, was introduced in 1984 and released in 1985 in Japan.

A randomized controlled trial comparing vidarabine and ACV revealed that ACV was significantly superior to vidarabine for treatment of biopsy-proven HSE. The mortality rate in vidarabine-treated patients was 54% compared with 28% in ACV-treated patients. Furthermore, a 6-month morbidity assessment revealed that 38% of ACV-treated patients recovered normal function [8]. ACV treatment dramatically reduced the rate of poor outcomes in HSE. Since no new antiviral drugs have been introduced in nearly three decades, much effort has focused on learning how to better use ACV and how to use existing databases to establish an earlier diagnosis. Delays in starting ACV treatment, particularly beyond 48 h after admission, are associated with a worse prognosis.

15.3.2 Diagnosis and Treatment of Acute Encephalitis

Acute encephalitis is suspected when a patient visits an emergency department with fever and disturbance of consciousness [9]. First, airway, breathing, circulation, and neurological disability should be assessed. Initial laboratory examinations should include two sets of blood cultures, blood gas, CBC, and serum chemistry investigations, including C-reactive protein. Next, the indications for lumbar puncture should be assessed. If warning signs for a space-occupying lesion are present or patients have risk factors, underlying disease, and/or immunocompromised condition, lumbar puncture should not be performed. Additionally, lumbar puncture should not be performed if patients have systemic shock, coagulation abnormalities, local infection at the lumbar puncture site, and/or respiratory insufficiency. Instead, intravenous ACV should be immediately started. If warning signs of a space-occupying lesion are not present, emergency head CT should be assessed. Only when head CT scanning is estimated to take too much time should lumbar puncture be performed without head CT. Lumbar puncture is recommended after confirmation of the absence of an intracranial space-occupying lesion or herniation. If an intracranial space-occupying lesion or herniation is present, intravenous ACV should be immediately started. MRI can detect abnormalities in approximately 90% of

patients hospitalized within 48 h. MRI also identifies alternative, often treatable, diagnoses in patients with conditions mimicking HSE. The following items should be assessed when lumbar puncture is performed. For the CSF, opening pressure, white blood cell count with differential, glucose level, CSF/blood glucose ratio, protein level, and PCR for HSV DNA using a real-time PCR or nested PCR method should be performed.

HSV PCR in the CSF between day 2 and 10 of illness has an overall sensitivity and specificity of >95% for HSE in immunocompetent adults. In approximately 5–10% of adults with proven HSE, initial CSF findings may be normal with no pleocytosis and a negative HSV PCR result. Thus, if an initial lumbar puncture is non-diagnostic, a second lumbar puncture should be performed 24–48 h later. In HSE, the CSF usually remains HSV PCR-positive for several days after starting ACV treatment. Even if a lumbar puncture is delayed, subsequent CSF sampling can still confirm the diagnosis. When HSV PCR is not performed for patients with suspected encephalitis in the acute stage, CSF and serum samples collected approximately 10–14 days after illness onset should be sent for HSV-specific IgG antibody testing.

When acute encephalitis is clinically suspected, including CSF and/or radiologically findings, intravenous ACV should be immediately started. HSE is the most commonly diagnosed viral encephalitis in industrialized countries. Once the initial CSF and/or imaging findings suggest viral encephalitis, ACV treatment should be started even without detection of HSV DNA from CSF samples. Japanese guidelines recommend that initiation of therapy should not be delayed beyond 6 h of arrival at the hospital. Delays in starting ACV treatment, particularly beyond 48 h after admission, are associated with a worse prognosis. HSV replication usually occurs about 6 h postinfection. ACV is only effective in halting viral replication. Therefore, intravenous ACV should be given early to prevent extensive replication and subsequent CNS damage. Intravenous ACV (10 mg/kg, every 8 h) should be started for any of the following: (1) initial CSF microscopy or imaging results are normal, but HSE is clinically suspected, (2) initial CSF and/or imaging findings suggest viral encephalitis, (3) there is a strong clinical suspicion of encephalitis, but CSF and/or imaging results will not be available within 6 h of hospital visit, or (4) strong clinical suspicion of encephalitis and the patient is very unwell or deteriorating. If HSE is proven, intravenous ACV treatment should be continued for 14–21 days, and lumbar puncture should be repeated a few days to a week later. After the confirmation of negative HSV PCR result in the CSF, ACV treatment can be stopped. Negative HSV PCR results in the CSF should be confirmed on two separate occasions. If HSV PCR remains positive, intravenous ACV should be continued until weekly HSV PCR in the CSF is negative. Intravenous ACV treatment for immunocompromised patients should be continued for 21 days. The dosage of initial ACV treatment for immunocompromised patients is the same as that for immunocompetent patients. In patients with ACV treatment-resistant HSE, ACV plus vidarabine (5–10 mg/kg/day) or ACV plus foscarnet (40 mg/kg, every 8 h) combination therapy may be useful.

15.4 Conclusion

A clinical management process for CNS infection in Japan is introduced. Bacterial meningitis and HSE are severe CNS infections that, if not immediately and optimally treated, lead to poor outcome. Acute CNS infection is strongly suspected when patients have the clinical tetralogy (i.e., fever, headache, neck stiffness, and change in mental status). Early and optimal treatment could change the outcome of patients with bacterial meningitis and HSE.

In Japan, the primary characteristic of bacterial meningitis has been the high antimicrobial resistance frequency of bacterial pathogens, for instance, PRSP and BLNAR. Japanese clinical guidelines recommend the administration of carbapenem as a first-line empirical treatment for PRSP and BLNAR. The introduction of PCVs and Hib vaccine is expected to reduce the frequency of bacterial meningitis.

HSE is the most frequent cause of viral encephalitis in industrialized countries. When acute encephalitis cannot be ruled out, treatment with intravenous ACV (10 mg/kg, every 8 h) should be immediately started. Differential diagnoses of acute encephalitis are wide-ranging. HSE is a devastating disease and delays in starting ACV treatment lead to a worse prognosis. Until exclusion of HSE can be verified, empiric ACV is reasonable.

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Chapter 16
Pediatric Neurocritical Care

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Abstract Pediatric neurocritical care is a multidisciplinary field of medicine. The main role of pediatric neurocritical care is improving outcomes in children with primary brain injury by various neurological diseases and limiting secondary brain injury through state-of-the-art critical care delivery and the support of integrating neuronal function. Recognition of neurological deficits in children is not easy even for an experienced clinician. The diseases such as stroke, cardiac arrest, and traumatic brain injury (TBI) have distinct clinical and pathophysiological characteristics that distinguish them from their adult features and prevent the direct translation of the adult experience to pediatric patients. In addition, the importance of the application of neuromonitoring and neuroprotective strategies in the pediatric intensive care unit has been aware in both primary neurological and primary non-neurological disease. Although much can be learned from the adult experience, there is a need for evidence-based guidelines in pediatric neurocritical care since there are differences in the circumstances that surround the emergence of neurocritical care in pediatrics.

Keywords Pediatric · Traumatic brain injury · Stroke · Cardiac arrest
Neuromonitoring

16.1 Introduction

Because the anatomy and physiology of children's central nervous systems are different from those of adults and are constantly transforming through growth, it is important to interpret pathophysiology and diagnostic imaging correctly. This is especially true of neurological diseases requiring intensive care management. Evaluation for neurological disease must include neurological examination, recognition of the signs of intracranial hypertension, and management of the systemic condition. In this chapter, we will outline and focus on practicing pediatric neurointensive care.

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16.2 Characteristics of Pediatric Head

16.2.1 Anatomy

1. Skin

   Neonates and infants' scalps are very thin, with limited ability to buffer external forces. The epidermis is especially fragile; blisters form easily, and the dermis is also prone to rupture. Extracellular fluid tends to accumulate in the subcutaneous layer, and hematoma related to birth trauma can occur due to the breakdown of microvessels. Subgaleal hematoma and cephalohematoma are formed if blood is stored under the aponeurosis and periosteum, respectively.
2. Skull

   The neonatal cranium/face ratio is the greatest. In newborns, both the anterior and posterior fontanelles are still open; the sutures are also loose and flexible. As seen in cranial deformation during passage through the birth canal, for example, it can be shaped without fracture [1]. The skull constituting the calvarium is thin, soft, abundant in bone marrow, and thick in the periosteum. The posterior fontanelle closes within 2 months of birth, and the anterior fontanelle tends to close in 12–18 months. Until then, there seems to be a buffering effect on intracranial hypertension, particularly if intracranial volume increases slowly. The periosteum and dura mater are strongly adhered to the skull, and traumatic dissection of the dura causes venous hemorrhage that can lead to hematoma formation. In pediatric skull fractures, sharp bone fragments are less likely, and periosteal continuity is often preserved even with skull fracture (ping-pong ball fracture), which is commonly treated with conservative management [2].
3. Brain/nerve fiber brain tissue

   Neonatal central nervous tissue has an underdeveloped myelin sheath and high moisture content in a certain brain tissue volume. The phospholipid ratio increases as the myelin sheath develops. Because the brain parenchyma is very pliable, brain tissue can be stretched and deformed based on external force, so rupture does not occur easily. In contrast, direct external force on immature brain tissue frequently causes brain contusion. If traction occurs in the cortical vein connecting the dura mater and the brain surface due to rotatory external force, it may rupture and cause bleeding. It may also cause intradural sinus thrombosis.
4. Neck and cervical vertebra

   The cervical muscle group is underdeveloped, impairing head stability. The head is large and heavy and is easily shaken back and forth. The ligaments/soft tissues connecting the vertebral bodies are rich in mobility but tend to cause ligament rupture. Most spine injuries occur in the cervical spine region, usually due to neurological deficits. Spinal cord injury without radiographic abnormality (SCIWORA) is particularly common in pediatric patients, reflecting a deformed cervical spine with external loading. The cervical ligaments and paraspinal mus-

cles are weaker in the pediatric spine. The intervertebral disks' water content increases, and the facet joint is shallow. The vertebral bodies are wedged anteriorly. The fulcrum of the vertebral body is in the upper cervical vertebrae in younger individuals [3, 4]. These characteristics contribute to a malleable spine, which is associated with relatively high risks of spinal cord injuries.

16.3 Systemic Factors Affecting Neurointensive Care in Children

16.3.1 Systemic Anatomical Differences

Infants are at high risk of airway obstruction. First, the tongue is larger than the soft palate tissue and intraoral volume. The epiglottis is relatively long and stiff. The larynx is located high and forward, and the airway is the narrowest at the cricoid cartilage; hence, children's airways are easily obstructed. The trachea is still short, and the bronchus is higher. The trachea is generally compressed with a small diameter, increasing the risk of atelectasis. Because the child's occiput is usually large, the neck tends to bend forward, so airway obstruction may occur when the child is in a supine position [5, 6]. The chest wall is cartilaginous and easy to deform without rib fractures. Therefore, pulmonary contusion without external injuries to the chest wall is common [7]. In general, because children have small lung volumes, they are prone to hyperventilation which can cause impaired cerebral blood flow (CBF). Because children use the abdominal diaphragm in breathing, abdominal injuries and gastric distension easily affect breathing conditions [8]. Neonates and infants have much larger body surfaces than adults, and they tend to have large heads. Heat loss is common, and hypothermia can easily occur. Injury to solid organs is common in children because they have larger organs that are closer to each other within the intraperitoneal space. Most abdominal injuries can be treated conservatively, but care should be taken because minor organ injuries and/or intestinal injuries cause delayed peritonitis [9].

For example, in children with traumatic brain injury (TBI), hypotension is associated with poor outcome and must be avoided. Hypotension may compromise cerebral perfusion of both normal brain tissue and ischemic penumbra tissue surrounding the lesion. If blood pressure decreases outside the limits of cerebrovascular autoregulation, children may be at risk of cerebral ischemic or hyperemic injury. However, the blood pressure limits of autoregulation are unclear in infants and children, and they can shift after brain injury [10]. Therefore, monitoring hemodynamic status for all pediatric patients with a potential for CBF autoregulation impairment is critical. An arterial line should be placed preoperatively, and blood pressure should be maintained in a normal physiologic range. Hypotension is defined as a BP decrease >20–30% from the baseline systolic BP in children. A recent study showed that admission systolic blood pressure (SBP) <75th percentile was associated with a

higher risk of in-hospital mortality after isolated severe TBI in children. Also, SBP targets based on the 75th percentile were higher compared to traditional ACS targets [11]. In contrast, hypertension can cause unexpected bleeding with brain swelling if autoregulation is impaired.

16.3.2 CBF

Normal CBF values vary with age. Significant changes occur in CBF in the early years of life along with cerebral development, continuous myelination, and synaptogenesis. CBF is lowest at birth, peaks between ages 3 and 7 years, and progressively decreases to adult levels [12, 13]. The most significant increase is in the first 6 months of life, and it continues over the next 3 years at a slower pace [14]. Global cerebral perfusion reaches a peak of approximately 2.5 times that of adults between 3 and 4 years old [15]. If we try to determine normal-range CBF, age-related phenomena should be considered. A greater proportion of the cardiac output goes to the brain in children, and the fraction of cardiac output to the brain is more than twice that of adults [13]. In a PET study of children, regional CBF was 140–175% of adult values for children between 3 and 7 years, although the cerebral metabolic rate of oxygen was less markedly different (100–120% adult values). Transcranial Doppler (TCD) is a noninvasive technique used to determine cerebral blood velocity in major cerebral vessels [16]. It is useful to diagnose and monitor acute cerebrovascular disorders in intensive care patients, particularly following TBI [17]. TCD is also one of the ancillary tests used to confirm the clinical diagnosis of brain death by documentation of cerebral circulatory arrest [18].

16.3.3 Intracranial Pressure

Increased intracranial pressure (ICP) can add injury to a brain by secondary mechanism through cerebral hernia and cerebral ischemia, decreasing cerebral perfusion. Conventionally, ICP 20 mmHg has been used as the threshold for abnormal values for children; however, since multiple factors increase ICP and each disease condition is quite diverse, no clinical evidence shows that a uniform treatment protocol for pediatric neurological diseases is appropriate. Carefully understanding the causes of intracranial hypertension and choosing treatment are important. All ICP therapies have adverse consequences; therefore, the risk-benefit ratio should be considered for each situation. In addition, data on the determination of age- or cause-specific recommendations for therapies are limited [19]. A prospective observational study investigated ICP/cerebral perfusion pressure (CPP) thresholds and indices of ICP and CPP burden, in connection with patient outcomes in severe TBI and accidental and abusive head trauma cohorts. This study found the duration of ICP >20 mmHg and CPP <45 mmHg best discriminated poor outcome. As the number

of hours with ICP >20 mmHg increases by 1, the odds of a poor outcome increase by 4.6% [20]. Although normal ICP values are lower for children than adults [21], and increased ICP affects pediatric central nervous systems differently, the ICP treatment threshold is determined as 20 mmHg. This is because most pediatric neurointensive care guidelines tend to divert clinical research results from adult studies [22]. Even if a certain ICP threshold is regarded as normal for children, whether it can be applied to brains that are swollen or injured by cerebral ischemia is unclear. Along with increased CBF, ICP and cerebral tissue oxygenation often increase, but the time point where the condition has exacerbated is unclear. The pathophysiology of brain injury is extremely varied by age and cause. Therefore, uniform treatment for all types of neurological diseases may be controversial. Identifying a parameter to monitor the diversity of pediatric neurological diseases in real time and select a treatment reflecting children's peculiarities is an important future task.

16.3.4 CPP

Mean arterial pressure (MAP) is a more useful measurement than SBP, and the ICP must be known to calculate CPP. In children, adequate CPP is age-based, but adult practices showed that chasing higher CPP targets increases the risk of lung injuries due to aggressive fluid and inotrope administration. The published guidelines for children suggest a CPP threshold of 50 mmHg in older children and 45 mmHg in children younger than 2 [23]. In addition, we must know that patients who are managed based on published guidelines commonly experience episodes of very low brain oxygenation despite adequate adherence to ICP and CPP targets [24]. Overall, there is an ongoing consensus that optimal CPP varies between patients. Impaired autoregulation after TBI is associated with poor prognosis. Observational data suggest that optimal neurologic outcome and survival is associated with optimal CPP defined by autoregulation monitoring.

16.3.5 Autoregulation

Cerebral autoregulation is a homeostatic process where arterioles dilate and constrict to maintain CBF constantly over a range of blood pressures. In healthy adults, MAP changes between 60 and 160 mmHg, or CPP between 50 and 150 mmHg produces little or no change in CBF [25, 26]. This homeostatic mechanism ensures that, as MAP or CPP increases, resistance increases in the small cerebral arteries and arterioles. Conversely, this mechanism maintains constant (adequate) CBF by decreasing cerebrovascular resistance or vasodilation when MAP or CPP decreases. Beyond these autoregulation limits, CBF depends on MAP or CPP; hypotension results in cerebral ischemia, and hypertension causes cerebral hyperemia. Hypotension after pediatric TBI is associated with poor outcome [27–29].

Few studies on cerebral autoregulation in normal children have been published. Vavilala et al. [28] reported no age-related differences in the lower limit of cerebral autoregulation, which shows that children aged 6 months to 2 years have a lower cerebral autoregulation limit of 6 ± 9 mmHg [27]. Therefore, lower blood pressure or hypotension should be avoided because it can cause hazardous ischemia. The mechanisms of cerebral autoregulation in children are not completely understood but may involve myogenic, neurogenic, and metabolic processes regulating cerebrovascular resistance to maintain CBF [28].

Children with severe TBI develop impaired autoregulation in the acute phase, which is associated with worse outcomes. Currently, there are no recommendations of how autoregulatory capacity should be considered when managing pediatric TBI.

16.4 Brain Oxygenation Monitoring in Children

Brain oxygen monitoring has not been extensively studied in pediatric neurointensive care. Invasive tissue monitoring and the near-infrared spectroscopy (NIRS) have some data in pediatric TBI. NIRS has been evaluated more commonly in neonates and cardiac patients. Data from the largest studies are consistent with the adult experience in terms of thresholds related to outcome. Stiefel et al. reported on six children with severe TBI, in whom $PbtO_2$ was lower if ICP was >20 mmHg and CPP was <40 mmHg [29]. Figaji et al. [24] also reported that reduced $PbtO_2$ is associated with poor outcome in severe pediatric TBI. Many patients in their study showed episodes of compromised $PbtO_2$ despite achieving acceptable treatment targets [24]. Clinical experience also confirms its value as an ancillary test in patients diagnosed with brain death and as predictors of mortality and functional outcome [30]. Whether treatment directed at maintaining $PbtO_2$ improves outcomes is yet to be determined for both adults and children.

16.5 Brain Metabolism

Children's brain metabolism changes with advancing age. It depends on progressive myelination and synaptogenesis and drives the substantial changes in CBF [14]. The cerebral metabolism of glucose starts at low rates, approximately 60% of adult values at birth, and rapidly accelerates to >200% of adult values by 5 years before slowly decreasing to adult levels through adolescence [31]. Data on imaging metabolism in children are limited. Continuous local monitoring of basic metabolism parameters is possible through microdialysis, but it is not widely used as a clinical tool [32]. Tolias et al. reported on a small series of children with severe TBI who underwent microdialysis [33, 34]; elevated lactate-pyruvate ratio was associated with mortality, poor clinical outcome, and low brain oxygen [35]. Because reduced $PbtO_2$ is independently associated with poor outcome, a better understanding of ICP and $PbtO_2$ management in pediatric TBI seems to be needed [36].

16.6 Cerebral Edema

Cerebral edema is defined as an absolute increase in the brain's water content and can arise from a variety of different causes. Cerebral edema is divided into subtypes: (1) vasogenic, (2) cytotoxic, and (3) interstitial edema. Vasogenic edema is characterized by disruption of the blood-brain barrier, leading to fluid accumulation in the extracellular space. The inflammatory response to injury results in recruitment and activation of leukocytes, generation of pro-inflammatory mediators (cytokines, eicosanoids), release of oxygen radicals, and production of nitric oxide. Vasogenic edema commonly occurs in areas with inflammatory process diseases and typically responds to osmotic agents such as mannitol and hypertonic saline. Cytotoxic edema results from the cerebral cells' failure to maintain their transmembrane ionic gradients. When sodium accumulates in the intracellular space, water follows passively, resulting in intracellular edema. Cytotoxic edema results from severe cellular dysfunction and cell death. Cytotoxic edema is characteristic of hypoxic-ischemic brain injury. Interstitial edema results from increased cerebrospinal fluid hydrostatic pressure.

16.7 General Management

Normal saline is usually used to prevent hypotonia in patients with cerebral swelling. Isotonic fluids routinely administered at maintenance are recommended, particularly for the first 24 h post-surgery. Excessive glucose in fluids must be avoided in the acute phase of brain injury. Timing for parenteral nutritional support remains unclear. Bell et al. reported that nutritional support and glucose administration varied widely, with nutritional support beginning before 96 h, and glucose administration started earlier in most centers in the trial [37].

Postoperative hyponatremia is common and should be corrected quickly. It may be caused by cerebral salt-wasting syndrome (CSWS). It may also occur secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The best way to differentiate between these two causes is to assess the intravascular volume status with central venous pressure (CVP) monitoring. A high CVP indicates fluid overload, suggesting SIADH rather than CSWS. Some children will develop diabetes insipidus. Close monitoring of urine output is critical. Lost volume should be replaced with normal saline, and a vasopressin infusion, titrated to normal urine output, is beneficial [38].

Anemia and bleeding are serious concerns in neurocritical care. Anemia is generally associated with worse outcomes, so efforts to minimize anemia are encouraged. Recently, the Pediatric Critical Care Transfusion and Anemia Expertise Initiative have reported the Consensus Recommendations for RBC Transfusion Practice in Critically Ill Children. In critically ill children with acute brain injury (e.g., trauma, stroke), RBC transfusion may be considered if the hemoglobin concentration

decreases between 7 and 10 g/dL [39]. Anemia and brain hypoxia are of great concern in critically ill children, but there is no specific recommendation regarding blood transfusion. Data on the effect of blood transfusion in pediatric neurocritical care are limited. Figaji et al. [40] investigated the influence of blood transfusion on brain tissue oxygen pressure (PbtO2) in children with severe TBI. The PbtO2 increased transiently in 79% of blood transfusions in pediatric TBI patients and decreased transiently in 21%. It also returned to baseline within 24 h [40]. They concluded that no predictive factor indicates blood transfusion but also suggested that transfusion threshold triggers be raised if children showed evidence of cerebral ischemia or tissue hypoxia. In other studies, blood transfusion for chronic anemia seemed to be associated with increased $PbtO_2$ using NIRS [41], but further studies will be needed to evaluate using noninvasive cerebral tissue oximetry.

16.8 Decompressive Craniectomy

Decompressive craniectomy (DC) is performed as a lifesaving procedure in patients with intractably increased ICP after TBI, intracerebral hemorrhage, cerebral infarction, or brain swelling from other causes. However, DC is as controversial in the pediatric population as it is in adults [42]. Although previously conducted retrospective studies described DC's benefits [43–49], studies in children with severe TBI have been single-center, observational trials. Taylor et al. conducted a randomized pilot trial in 27 pediatric patients with TBI for a 7-year period, and the surgery group seemed to have better outcomes [50]. A meta-analysis of DC in pediatric patients concluded that it is warranted in cases of refractory increased ICP from any etiology [42]. Ardissino et al.'s systematic literature review found that currently available evidence may support a beneficial role of DC in controlling ICP and improving long-term outcomes [51]. One of the problems with DC in children is the high rate of bone resorption, particularly in the infants. Rocque et al. [52] reported that 21.7% showed bone resorption significant enough to warrant repeat surgical intervention, and the most important predictor of bone resorption was age at the time of operation. They also found that, for every month of increased age, the risk of bone flap resorption decreased by 1%. Cranioplasty using foreign material is also more difficult in children because of growing skulls. This must be evaluated with other known complications such as hydrocephalus [52].

16.9 Hypothermia

Therapeutic hypothermia (TH) of 32–34°C benefits adult patients following cardiac arrest in terms of both survival and neurological outcome. Moler et al. reported no such benefit for children after out-of-hospital cardiac arrest [53]. Recently, Moler et al. again found TH did not confer a significant benefit in survival with

a favorable functional outcome at 1 year [54]. Unlike adult cardiac arrest, most pediatric cardiac arrest occurs second to respiratory failure or circulatory shock, so a preceding period of hypoxia-ischemia probably compounds the neurological insult. The presenting rhythm is most commonly asystole or pulseless electrical activity in children, and ventricular fibrillation or pulseless ventricular tachycardia is relatively rare. Most recommendations are not substantially different from the adult guidelines and are generally considered optional. Avoiding hyperthermia is widely accepted as a strategy.

The effectiveness of TH for severe TBI has been examined by numerous basic experiments and clinical observational studies. Hutchison et al. conducted a randomized controlled trial using a protocol to lower body temperature to 32°C within 8 h from injury for patients with severe pediatric TBI, but neurological outcome did not improve [55]. Adelson et al. conducted several verifications, and hypothermia for 48 h with slow rewarming does not reduce mortality or improve global functional outcome after pediatric severe TBI [56]. Currently, several systematic reviews showed the effectiveness of TH on TBI (risk ratio, 1.66; 95% confidence interval [CI], 1.06–2.59; $p = 0.03$) and a marginal deterioration of neurologic outcome (risk ratio, 0.90; 95% CI, 0.80–1.01; $p = 0.06$) [57–59]. They concluded that TH cannot be recommended in children for treatment following TBI [60].

16.10 Traumatic Brain Injury

In the critical care session, changes in the neurologic examination often indicate early signs of ICP elevation. For example, the Cushing triad (bradycardia, hypertension, and respiratory failure) is a well-known physical finding related to intracranial hypertension. Real-time, continuous monitoring of clinical parameters is essential, and an emergent CT scan should be obtained when intracranial hypertension is suspected. ICP monitoring should also be considered for all patients whose initial GCS score is <8 because a high percentage of severe TBI cases will, subsequently, have significantly increased ICP.

Although many studies have shown ICP monitoring is effective, none reported that it improved long-term outcomes in children with severe TBI. No report showed that ICP monitoring worsened the prognosis. ICP monitoring improves treatment efficiency for increased ICP, reducing the risk of secondary brain injury. Establishing standard indicators is particularly desirable for infants younger than 1 year because of the wide variations in usage of ICP monitoring [61]. Currently, there is no consensus on normal ICP values in children. Blood pressure (MAP) has been well known to change in children compared to adults by age. In contrast, because the lower limit of CPP is considered to be the same as that of adults, there are opinions that setting normal ICP values according to age is reasonable [62, 63]. Miller Ferguson et al. reported that unfavorable outcome is classified based on the sustained time of ICP ≥20 mmHg and CPP ≤45 mmHg, and an increase of 1 h increases the odds ratio by 4.6% [20]. CPP has been used to estimate blood flow to

the brain [2]. It is obvious that the low CPP value absolutely makes the prognosis worse. Therefore, paying sufficient attention to maintaining appropriate CPP value when managing severe pediatric TBI is necessary.

Sedatives, analgesics, and muscle relaxants are preferable if adequate airway management is available, such as in the pediatric intensive care unit. In severe TBI cases, sedatives reduce ICP.

External ventricular drainage (EVD) is often performed to manage severe TBI. EVD can directly measure intraventricular pressure and can also drain cerebrospinal fluid from the ventricles so that therapeutic effect can be obtained rapidly. EVD is also advantageous because it is inexpensive. In contrast, because children's ventricles are quite narrow, precautions against intraventricular or intracerebral bleeding must be taken during the procedure [64]. Baldwin and Rekate [65] and Levy et al. [66] reported lumbar drainage may be effective if intracranial hypertension persists after inserting EVD. Open cisterns also need to be confirmed via CT scan [65, 66]. Shapiro and Marmarou performed EVD for patients with refractory intracranial hypertension, and improved pressure–volume index was reported [67]. The risk of hemorrhagic complications associated with EVD insertion and/or catheter withdrawal need to be considered, however, fatal bleeding rarely occurred [68, 69].

Hyperventilation should be avoided when managing severe TBI in general, but it can be applied in a short period when patients deteriorate abruptly with signs of cerebral herniation. Because hyperventilation can reduce CBF, particularly in children, multimodal monitoring helps determine the appropriate CPP. In patients with severe TBI, CBF reactivity to $PaCO_2$ is unpredictable because CBF autoregulation is more likely to be disrupted. CBF monitoring should be considered when vulnerability of cerebrovascular tissues is suspected to maintain CPP. Figaji et al. reported that conventional CPP parameters do not reflect the extent and progress of secondary brain injury and $PbtO_2$ will be the next damage assessment index [70]. Skippen et al. [71] measured CBF and cerebral metabolism following severe TBI in children prospectively and pointed out a decrease in CBF and cerebral oxygen consumption. Although the incidence of cerebral hyperemia was infrequent, increased CBF beyond demand for cerebral metabolism was obvious. Because the correlation between hypocarbia and cerebral ischemia is clear, hyperventilation is no longer recommended [71]. Warner et al. examined adult TBI cases and reported that patients with high severity tended to have high $PaCO_2$ level and were more likely to experience complications such as hypotension, hypoxia, and acidosis. As a result, $PaCO_2$ 30–35 mmHg should be determined as a treatment target by tracheal intubation at the site [72]. Avoiding blind hyperventilation and maintaining appropriate $PaCO_2$ level under proper monitoring is important.

Few recent clinical studies investigated the efficacy of barbiturates against TBI; there is a risk of myocardial suppression and a potent risk of hypotension [73]. Hence, when a barbiturate is administered to control ICP under vulnerable CBF condition, children must be monitored closely [74, 75]. Ideally, these drugs will be administered in the ICU where multimodal monitoring is possible by experienced intensivists [76].

Posttraumatic seizure (PTS) can cause cerebral metabolic failure and subsequent poor prognosis [23]. Early PTS is common in pediatric TBI; therefore, prophylactic anticonvulsants are recommended for the first 7 posttraumatic days, particularly with radiographic evidence of cerebral contusion. Phenytoin is believed to reduce the incidence of PTS, but it is ineffective for preventing late PTS. Currently, no statistically significant difference was found in the prophylactic effect of early PTS between levetiracetam and phenytoin [77]. Liesemer et al. [78] conducted a retrospective study of 299 children with moderate-to-severe TBI, and early PTS was seen in 12% of children. Clinical parameters, such as prehospital hypoxia, young age, abusive head trauma, severe TBI, primary parenchymal injury, and subdural hematoma were selected with univariate analysis as risk factors. Multivariate analysis revealed that the incidence of early PTS posttraumatic seizure was highly associated with age younger than 2 years, GCS ≤8, and abusive head trauma. Approximately 68% of early was found within 12 h after injury [78]. Continuous electroencephalogram (cEEG) showed frequent seizure activities in moderate-to-severe TBI, particularly in children with AHT. Best practice can be applied with cEEG protocols to detect and treat PTS promptly. In the future, positive prognostic groups may be classified based on PTS characteristics [79]. There is no international consensus on cEEG implementation rate in treating pediatric TBI, selecting anticonvulsants, and treating early PTS. Levetiracetam tends to be more selected worldwide [80]. Fosphenytoin was also mostly used as a prophylaxis in the management of severe TBI in children; however, there is treatment protocol variability among facilities in terms of timing of administration and drug selection [81]. In moderate-to-severe TBI cases, early PTS will possibly occur frequently despite prophylactic administration of levetiracetam [77]. Subclinical seizures in the acute phase were markedly detected by cEEG both in children younger than 4 years and children with AHT [82].

16.11 Neuromonitoring for Nonconvulsive Seizure

Many critically ill pediatric patients require sedatives that further limit examination sensitivity. Noninvasive monitoring includes NIRS, transcranial Doppler (TCD), or continuous electroencephalography (cEEG). A recent focus of neuromonitoring in pediatrics has been on diagnosing nonconvulsive seizure (NCS) and nonconvulsive status epilepticus (NCSE). Adult population studies have included patients with TBI, sepsis, CNS infection, stroke, and intracranial hemorrhage and those undergoing induced hypothermia following cardiac arrest. Younger age has also been suggested as a risk factor. NCS has been associated with increased neurological morbidity and is an under-recognized neurological insult in critical illness. NCS incidence in these studies varies widely from 16.3% to 39%. Abend et al. [83] found NCS and NCSE in nearly half of 100 patients who underwent cEEG monitoring in accordance with predetermined clinical practice institutional guidelines. Most patients with NCS had NCS exclusively [83]. In contrast, Shahwan et al. [84] diagnosed NCS in only 7 of

100 pediatric patients. The diagnoses of NCS and NCSE are likely being missed in some critically ill pediatric patients. Most pediatric patients with NCS seem to have nonconvulsive seizures. In addition, half of NCS will not be diagnosed with routine 60-min EEG monitoring. Prospective studies are needed to better define the prevalence of NCS and NCSE and to help create practice guidelines for using cEEG monitoring in the pediatric ICU [84].

16.12 Developmental Outcomes

Better outcomes are usually expected for children compared to adults. Plasticity may aid recovery substantially in ways lost to adults [85]. Animal and human studies show greater cognitive improvements associated with dendritic arborization in stimulating environments. The youngest patients are at highest risk of poor outcomes because of the developmentally immature brain. The Pediatric Workgroup's recommendations address primary clinical research objectives, including characterizing the course of recovery from TBI, predicting later outcome, measuring treatment effects, and comparing outcomes across studies. Consistent with other Common Data Elements Workgroups, the Pediatric TBI Outcomes Workgroup adopted the standard in its selection of measures such as daily living skills, family and environment, global outcome, health-related quality of life, infant and toddler measures, language and communication, neuropsychological impairment, physical functioning, psychiatric and psychological functioning, recovery of consciousness, social role participation and social competence, social cognition, and TBI-related symptoms [86].

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Chapter 17
Post-intensive Care Syndrome

Toru Hifumi and Shigeaki Inoue

Abstract In 2010, post-intensive care syndrome (PICS) was agreed on as the recommended term to describe new or worsening physical, cognitive, or mental health status impairments that arise after a critical illness and persist beyond acute care hospitalization. One of the physical components of PICS that has been well discussed is intensive care unit-acquired weakness (ICU-AW). The diagnosis of ICU-AW is made using the Medical Research Council (MRC) scale, which ranges from 0 to 5, for grading the strength of various muscle groups in the upper and lower extremities; higher scores indicate greater muscle strength, and an MRC score of <48 is diagnostic of ICU-AW.

Keywords Post-intensive care syndrome · ICU-acquired weakness · Chronic critical illness · Early rehabilitation · ICU diary

17.1 Introduction

The mortality rate of severe sepsis has remarkably decreased from 35% to <20%, owing to the global initiatives against sepsis, including the Surviving Sepsis Campaign guidelines, during the past two decades [1–5]. However, this progress has also resulted in an increasing number of critically ill patient survivors with impaired physical, cognitive, and mental ability [6]. Secondary analyses of two international randomized clinical trials on patients with severe sepsis (i.e., ACCESS and PROWESS-SHOCK) demonstrated that one third of patients died and that among those who survived, one third were not able to return to independent living by 6 months [7]. These results suggested that sepsis trials should take into consideration both mortality and quality of life when designing new interventions and

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considering endpoints [7]. Furthermore, patients in the medical and surgical intensive care units (ICUs) are at a high risk for long-term cognitive impairment; in particular, a longer duration of delirium was reported to be independently associated with worse global cognition at 3 and 12 months after ICU admission [8].

Taken altogether, persistent impairment of those three components (impaired physical, cognitive, and mental ability) are serious problems that prevent ICU survivors from being discharged for home and from returning to usual daily life after discharge [6, 9]. Moreover, 28-day ICU survivors were found to have a very high mortality risk after only a few years of hospital discharge [10]. Therefore, we are now required to shift the focus of attention from short-term outcomes to long-term outcomes.

17.2 What Is PICS?

In 2010, the Society of Critical Care Medicine held a conference in order to inform stakeholders from the rehabilitation, outpatient, and community care settings of the long-term consequences of critical illness and to initiate improvements across the continuum of care for ICU survivors and their families. Post-intensive care syndrome (PICS) was agreed on as the recommended term to describe new or worsening physical, cognitive, or mental health status impairments that arise after a critical illness and persist beyond acute care hospitalization [11].

ICU-acquired weakness (ICU-AW) is one of the physical components of PICS that has been well discussed. Kress and Hall described that the term ICU-AW can be applied to cases in which a patient has a clinically detected weakness without a plausible cause other than the critical illness [12]. The diagnosis of ICU-AW is made using the Medical Research Council (MRC) scale, which ranges from 0 to 5, for grading the strength of various muscle groups in the upper and lower extremities; higher scores indicate greater muscle strength, and an MRC score of <48 is diagnostic of ICU-AW [12].

17.3 Epidemiology

Of the five million patients who receive critical care in the United States each year, 50–70% will acquire PICS [13]. PICS may occur as early as 2 days after a patient receives critical care and can also affect the patient's family members [14]. ICU-AW can develop in 33% of all patients who receive mechanical ventilation, in 50% of patients with sepsis, and in up to 50% of those who are admitted to the ICU for at least 1 week. Cognitive dysfunction can persist in 30–80% of patients discharged from the ICU. The mental status impairments that can arise among critical illness survivors include depression in approximately 30%, anxiety in 70%, and posttraumatic stress disorder (PTSD), which is characterized by intrusive memories that arise from a combination of true events after ICU discharge, in 10–50% [14].

Kahn et al. determined the prevalence, outcomes, and associated costs in patients who survived their initial acute illness but had persistent organ failures necessitating prolonged intensive care. A syndrome known as chronic critical illness (CCI) recategorized the eligible conditions into six simple groups, such as prolonged acute mechanical ventilation; tracheotomy; sepsis; severe wounds; stroke, including both ischemic stroke and intracerebral hemorrhage; and traumatic brain injury [15]. The true cost of CCI was reported to be closer to $35 billion or 1.4% of all healthcare spending in the United States. The prevalence of CCI rose steadily with age in persons younger than 75 years, peaked at 82.1 per 100,000 in persons 75–79 years old, and then declined in persons more than 80 years old. From these interesting results, important perspectives were discussed. Although the prevalence of CCI generally increases with age, it declines after 80 years of age due to an increased risk for mortality before day 8 in the ICU; this finding could influence the decision to withdraw or withhold life support [16].

17.4 Risk Factors

The risk factors for the development of PICS have not been universally examined and vary according to the component of PICS. De Jonghe et al. reported that female sex was an independent predictor of ICU-acquired paresis (OR 4.66; 95% CI 1.19–18.30); this was possibly due to the smaller muscle mass in women than in men [17]. Davydow et al. examined individuals with normal cognition before sepsis, survived 540 hospitalizations for severe sepsis, and completed at least one follow-up interview for assessment of cognitive function using versions of the Telephone Interview for Cognitive Status. They found that women were at risk for developing cognitive impairment (OR 2.61, 95% CI 1.48–4.60; $p < 0.001$) [18]. A systematic review by Davydow et al. showed that two of seven studies indicated female sex as the significant predictor of PTSD after ICU care [19]. Based on these studies, female sex is a risk factor for the development of all three components of PICS. Another study reported depression and anxiety, PTSD, low educational level, and alcohol abuse before ICU admission as risk factors for developing PICS [20].

17.5 Clinical Manifestations

The three major components of PICS are physical, cognitive, and mental dysfunctions. The clinical features of ICU-AW may be neuropathic, myopathic, or a combination of both [21], with the latter being known as critical illness polyneuropathy and critical illness myopathy [22]. Delirium, dementia, and depression can present with cognitive dysfunction in critically ill patients in the ICU [23]. Depression and PTSD are two major mental illness [24].

17.6 Prevention and Treatment

Early mobilization, ABCDEFGH bundles, and ICU diary are the proposed prevention and treatment strategies for PICS.

17.6.1 Early Mobilization

Fuke et al. were the first to conduct a systematic review and meta-analysis on the effect of early rehabilitation on PICS [25]. In that study, early was defined as (1) initiation of care ahead of the usual time or (2) being conducted within 7 days of ICU admission. Rehabilitation included all physiotherapy, occupational therapy, and palliative care-related support. That study concluded that early rehabilitation had a limited effect on the prevention of PICS and significantly improved the short-term outcomes of physically related variables, including the MRC scale and incidence of ICU-AW, but not the cognitive function, mental health-related outcomes, and mortality of critically ill patients.

17.6.2 ABCDEFGH Bundles

An ABCDEFGH bundle comprises the following components: (1) awaken the patient daily, sedation cessation; (2) breathing, daily interruptions of mechanical ventilation; (3) coordination, daily awakening and daily breathing and choice of sedation and analgesic exposure; (4) delirium monitoring and management; (5) early mobilization and exercise; (6) family involvement, follow-up referrals, and functional reconciliation; (7) good hand-off communication; and (8) handout materials on PICS and PICS-F [26]. The ABCDE bundle can reduce delirium, ICU-AW, and PICS. Recently, the FGH elements have been added to the ABCDE elements to facilitate shared decision-making with the patient and family, continuity of care by adequate hand-offs and referrals, and memory reconstruction with supporting documents, such as an ICU diary [27].

17.6.3 ICU Diary

Jones et al. examined 352 patients who stayed at the ICU for more than 72 h and who were randomized to receive an ICU diary or no diary at 1 month following discharge [28]. The diary was a daily record of the patients' ICU stay and was written in everyday language by the healthcare staff and/or family, with accompanying photographs. That study showed that the incidence of PTSD at 3 months

was significantly reduced in the ICU diary group than in the no diary group (5% vs. 13%, $p = 0.02$). In another study on patients in whom ICU diaries were started on the fourth day of ICU admission, the PTSD symptom scores after 12 months were significantly reduced in the surviving patients than in the non-survivors (21 vs. 34) [29]. A systematic review on the impact of ICU diaries showed that four of five randomized trials demonstrated that the rate of new-onset PTSD after 3 months was significantly reduced with the use of ICU diaries (5% vs. 13%, $p = 0.02$) [30].

17.7 Outcome and Natural History

Herridge et al. evaluated 109 survivors of ARDS at 3, 6, and 12 months and at 2, 3, 4, and 5 years after discharge from the ICU. At 5 years, the median 6-min walk distance was 436 m (76% of the predicted distance), and the physical component score on the Medical Outcomes Study 36-Item Short-Form Health Survey was 41, relative to the mean age- and sex-matched normal score of 50 [31]. Patel et al. prospectively observed 255 patients with shock and ARDS and showed that the incidence of PTSD associated with ICU admission was 12% within 1 year of discharge [32]. Therefore, prevention and early intervention for patients with PICS are critical due to the typically poor natural course of this syndrome [20].

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Chapter 18
Coping with Prognostic Uncertainty and End-of-Life Issues in Neurocritical Care

Yasuhiro Norisue

Abstract Uncertainties in neurological outcome, treatment planning, and communication with patients' family members can greatly complicate neurocritical care, especially during the acute phase of intracranial conditions such as traumatic brain injury, post-cardiac arrest, and intracranial hemorrhage with intact brainstem function. This chapter introduces concepts useful for coping with the complexities of neurocritical care.

Keywords Neurological prognostication · Uncertainly · Neurocritical care
Time-limited trial · Goal-oriented care · Self-fulfilling prophecy · Doing everything
End of life

Case

A 60-year-old woman with a past medical history of recurrent cerebral infarction secondary to Moyamoya disease presents with acute left-sided hemiparesis and altered mental status. A CT scan of the head shows right-sided subcortical intracerebral hemorrhage (ICH; estimated volume, 40 mL) and mild midline shift. She undergoes emergent surgical evacuation of the hematoma. Four days after surgery, she opens her eyes but cannot follow commands. She develops septic shock due to ventilator-associated pneumonia. Her husband indicates that she would not want to live if she were unable to communicate with him and her daughter and asks you to speculate on the probability she will regain this level of consciousness. He also states that he would want to withdraw care, including treatment for sepsis, if she is in a persistent "vegetative state."

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18.1 Uncertainty and the Self-Fulfilling Prophecy

In neurocritical care, a patient's family member's question of "Will he/she survive?" is usually followed by "Will he/she wake up?" or "Will he/she be able to talk again?" In end-of-life settings, shared decision-making with patients and their families is essential practice in neurocritical care. Because very few patients want to survive without a meaningful recovery, physicians are frequently asked to provide patients' families with detailed neurological prognostications. However, such prognostication is frequently extremely difficult, especially during the acute phase of intracranial conditions such as traumatic brain injury, post-cardiac arrest, and intracranial hemorrhage with intact brainstem function. The uncertainty and discomfort of delivering bad news to a family can be very stressful, especially for physicians without the education or training to discuss end-of-life issues. Physicians cope with this stress consciously or subconsciously in several ways. Some convey unrealistically optimistic prognoses, while others avoid discussing prognosis [1, 2]. These reactions to stress are dishonest and impede the process of timely shared patient-centered decision-making with the family. Although neurointensivists should offer a careful neurological prognosis as soon as objective findings permit, they must nevertheless be clear with the family that the prognosis remains uncertain during the acute phase and that more time may be necessary before the outcome is obvious.

When urged to provide information on neurological prognosis, based on available data, physicians must remain aware of possible self-fulfilling prophecies. Retrospective validation of findings thought to predict a "grave prognosis" is an example of such a self-fulfilling prophecy. A patient with a hematoma volume greater than 60 mL and a Glasgow Coma Scale (GCS) score less than 8 was traditionally considered to be a powerful predictor of mortality. Indeed, the prognostic value of these findings was validated in retrospective studies [3, 4]. However, in this self-fulfilling prophecy, the outcome predicted by the prognostic findings was eventuated by the findings themselves because patients with these signs frequently died after receiving palliative care because of the "grave prognosis." This phenomenon is now widely known. Becker et al. studied 20 patients identified as having poor prognoses because of ICH volumes exceeding 60 mL and an initial GCS score less than 8. Six of these patients underwent surgical evacuation of the ICH, even though they had "validated" features indicating poor prognosis. Five survived and had significantly recovered several months later, with good functional outcomes and only minor disabilities [5].

Estimation of neurological outcome is complicated and requires assessment of several factors, including comorbidities and age, and, in clinical decision-making, caution is required when using patient data believed to predict poor prognostic outcomes. This chapter will discuss time-limited trials and goal-oriented decision-making, which are practical and useful concepts for coping with uncertainty in neurocritical care in acute settings.

18.2 Time-Limited Trials

A family may want to avoid invasive treatment or life prolongation for a patient in a persistent vegetative state. However, they do not want to forgo treatment that might result in survival and subsequent neurological recovery. Because the disease process itself is one of the most important factors contributing to prognostic uncertainty, proposing a time-limited trial to the family can be very helpful. A time-limited trial is a process in which active management aims at survival and recovery for a defined period of time, after which the goal of care can be reset when the prognosis is clearer [6, 7]. Such a trial reduces uncertainty and gives the family time to prepare for the consequences of potential decisions based on a more certain prognosis.

A well-known example of a time-limited trial is the process of neurological prognostication after cardiac arrest. Because it is usually impossible to predict the extent of patient recovery immediately after return of spontaneous circulation (ROSC), it is recommended to postpone prognostication until 48–92 h after ROSC and, during this period, to proceed with all life-saving and brain-saving treatments, such as cardiac catheterization and targeted temperature management [8]. The duration of a time-limited trial depends on the disease and the patient's condition. While days to a few weeks may be sufficient for an elderly patient with severe intracranial hemorrhage to reach a plateau of neurological function, over 6 months may be necessary for a young patient with traumatic brain injury [9].

Time-limited trials require an environment in which any treatment can be withdrawn at any time, when it is in the patient's best interest. In some countries, such as Japan, terminal extubation for palliative care is rare [10], because of a limited understanding of the bioethical issues involved, the absence of consensus regarding whether treatment withdrawal is ethically permissible, and fear of prosecution for murder. In such countries, the family is frequently forced to choose either exclusively palliative care, at the beginning of treatment, or life-prolonging treatment without the possibility of subsequent withdrawal, regardless of neurological outcome or quality of life. Offering only these two options might lead to insufficient treatment of a curable condition in a patient who could have enjoyed the rest of his/her life or a decision not to withdraw life-prolonging treatment with tracheostomy and percutaneous endoscopic gastrostomy tubes until the patient's heart stops, even when such a decision was against the patient's wishes. Thus, it is essential to form a consensus within a facility that a treatment, once started, can be stopped at the point it is deemed futile or not in the patient's best interest.

Case (Continued)
After a discussion with the attending physicians, the husband agrees to a time-limited trial with a tentative duration of 2 weeks and to aggressive treatment of pneumonia and septic shock. After hemodynamic stabilization, his wife continues to be minimally responsive to stimulus. A follow-up head CT shows new

bilateral diffuse infarcts, possibly due to brain malperfusion, secondary to septic shock and Moyamoya disease. Her husband is told that it is now almost certain she will not be able to communicate again. He states that although he wants to withdraw life-prolonging treatment, as it was her stated preference, their daughter has not seen them during the past 20 years and wants "everything done" for her mother.

18.3 "Doing Everything" and Goal-Oriented Care

Families often want "everything done" for a patient. Some family members insist on continuing invasive life support despite an extremely poor long-term neurological prognosis. In fact, physicians have no other option but to do "everything" for the patient. However, the family must be made aware that the meaning of "everything" varies in relation to the goals of care [11, 12]. During a time-limited trial that continues until the prognosis becomes more certain, treatment options may include invasive measures, because the goal of care is survival and potential recovery of neurological functions. When death or irreversible neurological damage is the obvious outcome, the goal of care changes to lessening the burden of treatment and providing palliative care. In such cases, "doing everything" means giving opioids as needed, avoiding unnecessary blood draws, and stopping intravenous fluid or artificial feeding that can worsen edema and decubitus ulcers. Multiple family meetings with a medical team may be necessary before a family accepts the prognosis and is ready to respect the patient's previously stated desires or likely preference.

Case (Continued)
After several family meetings with the husband and daughter, they agree to "do everything" to respect the patient's wishes and focus on her comfort. A continuous morphine infusion is started, and all treatment that would not contribute to her comfort, such as antibiotics, artificial nutrition, intravenous fluids, and mechanical ventilation, is withdrawn. She dies on the same day, with her husband and daughter at her side.

18.4 Summary

Neurological prognosis is as important as mortality. Physicians should be prepared to guide families in careful and thoughtful shared decision-making under conditions of uncertainty. Time-limited trials and goal-oriented decision-making are useful concepts in addressing the uncertainties of neurocritical care.

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