Intensive Care Med
https://doi.org/10.1007/s00134-025-08224-1

NARRATIVE REVIEW

Disorders of consciousness diagnosis, interventions, and prognostication for the intensivist: Report of the 2025 ISICEM roundtable

Yelena G. Bodien[1,2*], Katharina M. Busl[3], Cherylee W. J. Chang[4], Jan Claassen[5], Nicolas Gaspard[6,7], Olivia Gosseries[8,9], Raimund Helbok[10,11], Marcello Massimini[12,13], Lionel Naccache[14], Virginia Newcombe[15], Chiara Robba[16,17], Benjamin Rohaut[18], Jose I. Suarez[19], Alexis F. Turgeon[20,21], Paul Vespa[22], Sarah Wahlster[23], Fabio Silvio Taccone[24] and Giuseppe Citerio[25,26]

Abstract

Disorders of consciousness (DoC) represent a spectrum of clinical conditions, including coma, unresponsive wakefulness syndrome, and the minimally conscious state, which may result from structural and non-structural brain injuries due to trauma, stroke, anoxia, infections of the brain, and other causes. Clinical management of patients with DoC is especially challenging in the critical care environment, where the level of consciousness, a key factor in determining the trajectory of recovery, may be obscured by sedation, analgesia, and other confounders. The 2025 International Symposium on Intensive Care and Emergency Medicine hosted a Roundtable of 18 expert clinicians and researchers to synthesise and discuss the latest evidence on acute DoC epidemiology, diagnosis, treatment, and prognosis. Here, we summarise the output of the Roundtable in the format of a roadmap with six steps related to identifying patients with DoC, assessing for and treating confounders, establishing a diagnosis and prognosis, selecting interventions, and effectively communicating with family. This roadmap provides practical, evidence-informed guidance to help intensivists navigate diagnosis, treatment, and prognostication in patients with acute DoC. Advances in structural and functional neuroimaging, electrophysiology, and blood-based biomarkers offer promise for refined diagnostics and prognostication, though their clinical translation remains limited.

Keywords: Acute brain injury, Disorders of consciousness, Intensive care, Coma, Cognitive motor dissociation, Neuroprognostication, Ethical decision-making, Minimally conscious state, Unresponsive wakefulness syndrome, Vegetative state

Introduction

Acute brain injury, whether due to trauma, stroke, hypoxic–ischaemic encephalopathy, infection, or other causes, can lead to a disorder of consciousness (DoC) characterised by absent, or fluctuating, wakefulness or awareness. Patients with acute DoC are admitted to the intensive care unit (ICU), where accurate assessment of a patient's level of consciousness is critical, as it informs prognostication and helps guide decisions related to the goals of care. The clinical management of patients with DoC places a high burden on the healthcare system [1] and raises complex ethical questions, particularly regarding level-of-care decisions that could lead to early withdrawal of life-sustaining treatment (WLST) [2, 3]. In a recent large study comparing rates of WLST amongst mechanically ventilated patients with and without

*Correspondence: yelena.bodien@vumc.org
[1] Critical Illness, Brain Dysfunction, and Survivorship Center, Vanderbilt University Medical Center, Nashville, USA
Full author information is available at the end of the article

Springer

acquired brain injury, the group with brain injury had significantly higher rates of WLST and shorter time to WLST. These observations suggest that the mere presence of a brain injury is associated with an increased likelihood of early WLST in the ICU [4]. The field of DoC is evolving rapidly, and expertise is required to provide care and clinical recommendations that incorporate current guidelines and cutting-edge scientific discoveries. In 2025, the International Symposium on Intensive Care and Emergency Medicine (ISICEM) hosted a Roundtable of expert clinicians and researchers to synthesise and discuss the latest evidence on acute DoC epidemiology, diagnosis, treatment, and prognosis. Unlike previous reviews of the scientific landscape and knowledge gaps [5–11], the primary aim of the Roundtable was to outline evidence-based strategies for managing critically ill patients with acute brain injury and DoC that could be rapidly implemented by intensivists across diverse healthcare settings, regardless of resource availability.

In this report, the ISICEM Roundtable participants present a stepwise evidence-informed and practical roadmap for diagnosis, treatment, and prognostication of patients with acute DoC. The six-step framework ranges from patient identification to family communication and shared decision-making (Fig. 1). In addition to these actionable recommendations, we highlight key scientific advances that support current practices and note emerging research advances that, whilst promising, remain preliminary and require replication, validation, or clinical translation. Broader theoretical debates on the nature of consciousness and a systematic review of the field are beyond the scope of this report and have been addressed elsewhere [8, 12–18].

Take-home message

The 2025 International Symposium on Intensive Care and Emergency Medicine hosted a Round Table of 18 expert clinicians and researchers to synthesise and discuss the latest evidence on acute DoC epidemiology, diagnosis, treatment, and prognosis. Experts identified a six-step roadmap that ranges from patient identification to family communication and shared decision-making. In addition to providing actionable recommendations, the manuscript highlights key scientific advances that support current practices and emerging research advances that, while promising, remain preliminary and require replication, validation, or clinical translation.

Methods

The ISICEM Roundtable dedicated to DoC brought together 18 international experts from seven countries selected for their recognised expertise across complementary fields, including neurocritical care, neurology, neuroscience, electrophysiology, clinical trial methodology, rehabilitation medicine, neuroimaging, and bioethics. Participants were identified through their track record of peer-reviewed publications, leadership in international research consortia, and contributions to the development of clinical practice guidelines, ensuring a balanced representation of disciplines and perspectives. The Roundtable opened with pre-recorded videos, provided by the Neurocritical Care Society Curing Coma Campaign [19], of perspectives from patients and families on the unmet needs of persons with DoC lived experience. These testimonies contributed to the conceptualisation of the roadmap. The video presentation was followed by sessions addressing the pathophysiology of DoC, theories of consciousness, epidemiology, taxonomy and classification, diagnostic strategies (encompassing behavioural phenotyping and advanced tools, such as

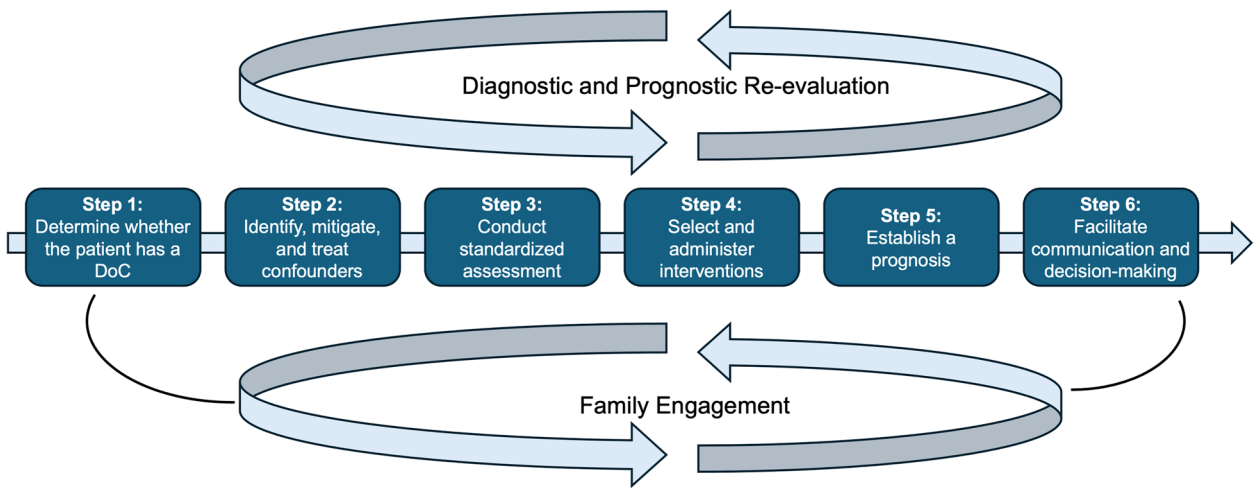

Fig. 1 A roadmap for acute disorders of consciousness (DoC) clinical care

neuroimaging, electrophysiology, and automated pupillometry), therapeutic interventions (pharmacological, neuro-modulatory, both non-invasive and invasive, and rehabilitative), prognostication (including long-term outcomes, predictive models, communication with families, and level-of-care decisions such as WLST), and ethical considerations. Presentations for each topic included a discussion of current practices, clinical guidelines, feasibility of widespread ICU application, existing evidence and gaps in knowledge, and the most recent research advances. Roundtable participants synthesised the information into six actionable and evidence-supported clinical practices that could be implemented immediately by intensivists caring for patients with acute DoC. For each step, we first presented information that has immediate clinical relevance, followed by additional considerations that frame or expand upon the clinical information. Finally, we described research advances that require further investigation prior to adoption into clinical care. Notably, we acknowledge that there are no well-defined DoC endotypes, evidence-based ICU interventions targeting DoC, or precise acute DoC prognostic markers. Therefore, rather than focussing on specific mechanisms of brain injury that could result in DoC, we designed the roadmap to emphasise challenges commonly encountered across DoC aetiologies. Where applicable, we highlight individual studies or practices that are pertinent to a specific aetiology.

A roadmap for acute DoC clinical care

Step 1: determine that a patient may have a DoC

Patients who sustain a severe brain injury but do not recover cognitive functions such as basic communication or functional object use have a DoC, traditionally defined as coma [20, 21] or vegetative state (VS; or, more recently, unresponsive wakefulness syndrome [UWS]) [5, 22, 23]. These patients may remain with their eyes closed regardless of external stimulation, or may open their eyes but not demonstrate evidence of awareness of themselves or their circumstances. In recent years, the minimally conscious state [24] (MCS) has been recognised as a distinct milestone along the DoC continuum that describes patients with emerging signs of awareness and signals the potential for further functional improvement [25, 26]. MCS is subcategorised as MCS without language function (MCS−; e.g., visual tracking, localisation to noxious stimulation) and MCS with language function (MCS+; e.g., command-following, intelligible speech) [27]. A key clinical feature of DoC is fluctuation between states of consciousness, which can occur over minutes, hours, or days, complicating diagnosis and clinical management [28, 29]. In the ICU, patients with coma, VS/UWS, and MCS require specialised care, as they are at risk for misdiagnosis and imprecise prognosis, which may result in premature WLST. The subsequent series of steps apply to patients who meet criteria for coma, VS/UWS, or MCS as defined in Table 1.

Additional considerations

The term "coma" is widely used to describe patients with DoC in the critical care setting. However, a central challenge lies in the definitional ambiguity of this term, which is often reduced to a Glasgow Coma Scale (GCS) [30] total score of 3–8 [31]. Notably, this range of scores encompasses a broad spectrum of patients, including both patients with persistently absent sleep–wake cycles [20, 21], as demonstrated by eye closure and lack of responses to external stimuli, and patients who meet criteria for MCS as evidenced by non-reflexive behaviours, such as localization to noxious stimulation, visual pursuit, and even command-following [32]. Moreover, the original intention for developing the GCS was to characterise the severity of a traumatic brain injury (TBI) and not to diagnose a state of consciousness. As a testament to the lack of consensus on the key features of "coma," a six-part expert definition provided in the Curing Coma Campaign COME TOGETHER survey achieved only 64% agreement amongst neurocritical care experts [31, 33]. The same survey also found that formal, standardised evaluation of level of consciousness (i.e., coma, VS/UWS,

Table 1 Overview of terminology and diagnostic criteria commonly used in patients with disorders of consciousness

Diagnosis	Wakefulness	Behavioural responsiveness	Key behaviours
Coma	Absent	Absent or reflexive	None
Vegetative state (VS)/unresponsive wakefulness syndrome (UWS)	Present	Absent or reflexive	Eye-opening, no purposeful responses
Minimally conscious state minus (MCS−)	Present	Present, without language function	Visual pursuit, localization to pain, automatic motor responses
Minimally conscious state plus (MCS+)	Present	Present, with language function	Command-following, intelligible expression
Emerged from MCS (eMCS)	Present	Present, with or without language function	Accurate yes/no communication, functional object use

MCS−, MCS+) assessed via tools such as the Coma Recovery Scale-Revised (CRS-R) [34], is rarely employed in routine ICU practice, precluding precise DoC diagnosis. Currently, there is no systematic approach for screening and assessing patients in the ICU for a DoC, conducting serial evaluations of consciousness, or collecting longitudinal data.

Research priorities

The epidemiology of acute DoC, defined in at least one guideline as a DoC occurring in the first 28 days after injury [35], remains poorly characterised due to the absence of structured surveillance systems, consistent definitions, and routine use of standardized diagnostic assessments [36]. Rapid recoveries and fluctuations in the level of consciousness are also common, further complicating epidemiological studies [28, 29, 37, 38], because the timing of DoC assessment could drastically affect data on DoC prevalence and incidence. Furthermore, DoC diagnoses have not been routinely documented in medical records; although, the 11th Revision of the International Classification of Diseases [39] now includes specific codes for VS/UWS, MCS−, and MCS+, which should enhance future epidemiological work [10, 40–44]. A 2022 crowdsourcing survey conducted in the United Kingdom and the United States estimated an annual coma incidence of 135/100,000 and 258/100,000, respectively, and a point prevalence of 7/100,000 and 31/100,000, respectively [45]. In this study, "coma" was broadly defined as unable to be awakened with stimulation, unable to speak or move, unable to answer questions or communicate, and unaware of the world, and the survey relied on respondents' understanding of these terms and recollection of the patients' state. Rigorous epidemiological studies are needed to understand the incidence, prevalence, and determinants of acute DoC.

Step 2: identify, mitigate, and treat confounders that may mask consciousness

Maintaining homeostasis and physiologic targets, ensuring adequate oxygenation, ventilation, and haemodynamic stability, and vigilant monitoring to detect medical (e.g., infections, venous thromboembolism, ulcers) or iatrogenic complications (e.g., related to sedation or drug–drug interactions) are essential pillars of ICU care and, by extension, DoC care [46–52]. Concomitant injuries, pain, acute hydrocephalus, seizures, paroxysmal sympathetic hyperactivity, infections, and toxic/metabolic derangements are amongst the potentially treatable/reversible medical situations that patients with DoC frequently encounter [5, 53–58], potentially leading to secondary brain injury, and masking intact consciousness in unresponsive patients. Sedation and language impairments [59] should also be considered, as both could also mask intact consciousness. Before determining whether a patient has a DoC, these factors should be considered and mitigated or treated whenever possible.

Seizures are particularly common following acute brain injury and represent a potentially reversible cause of DoC. Their frequency varies considerably depending on the underlying aetiology, with high rates reported in patients with infection, cardiac arrest, haemorrhagic stroke, and TBI. Importantly, a substantial proportion of these seizures are electrographic and subclinical, detectable only with electroencephalography (EEG) [60]. This underscores the need for EEG monitoring in patients with DoC and for treatment decisions to follow strict management protocols [61].

Additional considerations

Sedation, analgesics, and fever are frequent confounders that may transiently mask awareness, leading to diagnostic uncertainty if not carefully accounted for. Beyond organ-specific considerations, the cumulative impact of polypharmacy in critically ill patients should not be underestimated, as drug interactions or improper dosing may cloud the clinical picture, especially when medication clearance is impaired (e.g., due to renal or hepatic dysfunction). In addition, clinicians should remain alert to less obvious but equally relevant contributors to secondary brain injury and fluctuations in arousal. Disturbances of glycaemic control, electrolyte imbalances, renal or hepatic dysfunction, and endocrine abnormalities (e.g., thyroid, adrenal, and pituitary) may all exacerbate impaired consciousness if unrecognised. Nutritional deficits and impaired gastrointestinal function can further complicate recovery trajectories, whilst immobility-related complications, including contractures and pressure injuries, can limit rehabilitation potential. Finally, environmental and iatrogenic factors, such as noise, light, sleep disruption, and the absence of structured stimulation, can interfere with arousal and hinder accurate diagnostic assessment. Taken together, these aspects highlight the need for broad expertise that may require a multidisciplinary approach integrating intensivists, neurologists, rehabilitation specialists, nurses, and allied health professionals.

Research priorities

One especially challenging confounder to DoC management in the ICU is the influence of sedation on patient arousal and unresponsiveness. There are no well-defined approaches to determine whether sedation is affecting daily clinical assessments, nor guidelines on the optimal timing for a clinical exam after sedation is weaned

to minimise its residual effects. In addition, prospective assessment and validation of which ICU factors, hospital events, and complications are most likely contributing to DoC may guide timely preventive interventions that optimise recovery [62].

Step 3: conduct standardised, serial assessments to determine level of consciousness

Behavioural assessment remains the cornerstone of DoC diagnosis [5]. Table 2 provides comparative characteristics of behavioural scales used for the assessment of DoC. The GCS [30] has been adopted nearly universally in the ICU setting. However, the GCS lacks the sensitivity required to detect subtle signs of awareness [32, 63]. The Full Outline of UnResponsiveness (FOUR) Score [64] is more comprehensive but has similar limitations [65]. In contrast, the CRS-R [34] is a standardised behavioural assessment designed specifically to detect subtle signs of awareness and diagnose DoC. Its use reduces misdiagnosis when compared to a clinical consensus [66] or GCS assessment [63]. The CRS-R comprehensively assesses six domains: auditory function, visual function, motor function, oromotor/verbal function, communication and arousal. DoC diagnosis is based on the presence of specific behaviours within these domains. In patients with prolonged DoC (i.e., DoC lasting ≥ 28 days) [35], the most prevalent behaviours that denote MCS are a reproducible response to a command, localisation to nociceptive stimulation, visual pursuit and fixation, and automatic motor responses (e.g., scratching nose, grabbing bedrail) [37, 67]. Notably, visual pursuit and fixation, and automatic motor responses are not assessed on the GCS. The CRS-R is a National Institute of Neurological Disorders and Stroke Common Data Element [68], recommended for DoC diagnosis by professional organisations in the United States, Europe, and the United Kingdom [5, 69–71] and translated into multiple languages [72, 73]. However, CRS-R administration requires 25–35 min, making it infeasible for serial assessment of medically unstable patients in the ICU [74]. Adaptations of the CRS-R, such as the abbreviated CRS-R For Accelerated Standardized Testing (CRSR-FAST) [75] and the Simplified Evaluation of CONsciousness Disorders (SECONDs) [76], have been developed to facilitate rapid (i.e., < 10 min) assessment of level of consciousness in the ICU. Serial assessments are crucial because, as demonstrated in patients with prolonged DoC, fluctuations in arousal and responsiveness may lead to misdiagnosis when the diagnosis relies on a single assessment [28, 37].

Optimising the conditions under which behavioural assessment is conducted is essential. Patients should be assessed in a quiet setting with minimal distractions from screens, conversation, or other co-occurring assessments or interventions (e.g., application of EEG). If present, sedation should be weaned in advance of the examination. If sedation cannot be safely weaned, the evaluation should be considered as being potentially confounded. Examiners should ensure that sensory aids used pre-injury (e.g., hearing aids, glasses) are utilised during assessment. In the case of reduced arousal (e.g., evidenced by eye closure and/or unresponsiveness), the patient should be maximally stimulated using a standard protocol such as the CRS-R Arousal Facilitation Protocol. If present and safe to do so, consider removing restraints and boosting the patient to a seated position.

Accurate assessment of a patient's level of consciousness in the ICU is critical, as it informs prognosis and helps guide decisions, related to the goals of care, including continuing life-sustaining treatment, withholding life-sustaining treatment, or WLST (see Step 5) [2, 3]. Yet, the detection of consciousness in this setting is frequently hindered by confounding factors [87, 88]. Notably, WLST rates vary significantly within and between countries [77–82] and 30–80% of WLST decisions are made within the first 72 h following the acute event [4, 77, 80, 83–86].

Additional considerations

Approximately 15–25% of persons who do not follow commands behaviourally (i.e., coma, UWS, MCS−) demonstrate covert brain responses to verbal commands that are detected by advanced neuroimaging and electrophysiological techniques, such as functional magnetic resonance imaging (fMRI) and EEG [10, 41, 43, 44]. This state is known as cognitive motor dissociation (CMD) [89]. Interestingly, many individuals who do follow commands behaviourally (e.g., MCS+ level of consciousness) do not appear to follow commands when assessed with task-based fMRI and EEG, highlighting the low sensitivity of these approaches [44, 59]. To date, CMD detection has been largely confined to research settings, because the expertise required to analyse and interpret the fMRI and EEG data is not available in most medical centres around the world [90]. These techniques have not yet been standardised or validated for routine clinical application, limiting their current utility in bedside diagnosis. Given that CMD, by definition, cannot be detected on routine clinical examination, it is important to remember that it is a relatively common phenomenon in patients with DoC.

Research priorities

Recent studies have focussed on validating newly proposed behavioural indicators of consciousness [91]. These include resistance to passive eye-opening, habituation of the auditory startle reflex, auditory localisation, spontaneous eye blink rate, olfactory responses,

Table 2 Comparative characteristics of behavioural scales for disorders of consciousness

Feature/Domain	GCS	FOUR Score	SECONDs	CRSR-FAST
Total score range	3–15	0–16	0–8	Binary (consciousness present vs absent)
Eye/visual responses	Spontaneous; to speech; to pain; none	Open/track or blink to command; open but no tracking; to voice; to pain; none	Eye-opening, visual pursuit, fixation	Visual pursuit and fixation
Motor responses	Obeys commands; localises pain; withdraws from pain; abnormal flexion; extension; none	Follows commands; localises pain; flexion; none	Command-following; pain localisation; oriented behaviours	Follows commands; automatic motor responses; localisation to pain; functional object use
Verbal/communication	Oriented; confused; inappropriate words; incomprehensible sounds; none	Not assessed	Yes/no communication	Intelligible speech; Yes/no communication
Brainstem reflexes	Not assessed	Pupil, corneal, cough reflexes	Not assessed	Not assessed
Respiration	Not assessed	Regular; Cheyne-Stokes; Irregular; Above ventilator; Apnoea/ventilator	Not assessed	Not assessed
Sensitive to transitions between DoC states	No	No	Yes	Yes
Administration and scoring manual available	No	No	Yes	Yes
Time required to administer	1–2 min	2–4 min	~7 min	~6 min
Clinical intent	TBI severity grading	Neurologic function, especially in intubated patients	DoC diagnostic classification; research; clinical follow-up	DoC diagnostic classification; research; clinical follow-up
Strengths	Widely validated; global use; simple	Assesses brainstem and respiration; works for intubated patients	Differentiates states of DoC	Differentiates states of DoC
Limitations	Insensitive to DoC transitions; poor for intubated patients	Less intuitive than GCS; limited DoC granularity	Requires prognostic validation; needs translation	Requires prognostic validation; needs translation

Comparison of four bedside tools for assessing the level of consciousness in the ICU: the Glasgow Coma Scale (GCS), Full Outline of UnResponsiveness (FOUR) Score, Simplified Evaluation of CONsciousness Disorders (SECONDs), and the Coma Recovery Scale-Revised For Accelerated Standardized Testing (CRSR-FAST). The table summarises their scoring range, domains assessed, diagnostic sensitivity, administration time, training requirements, clinical applications, strengths, and limitations

swallowing, and spontaneous leg crossing. Moreover, several additional advanced techniques have been developed to detect and probe residual brain function in patients with DoC, though none alone can establish a definitive diagnosis of consciousness. EEG event-related potentials, including the P300 component, offer insights into residual cognitive processing but also show low sensitivity [92, 93]. Characterising resting-state EEG dynamics with power spectral analysis [94], including the ABCD model [95], can offer relevant information for patient stratification, but does not provide a DoC diagnosis. Multimodal analysis of EEG through power spectrum, complexity, and connectivity using artificial intelligence also showed promising results [12, 96, 97]. Concurrent transcranial magnetic stimulation and EEG (TMS-EEG) [2, 88, 95, 98] can assess complex brain interactions independent of sensory processing, motor responsiveness, and executive functioning. TMS-evoked metrics like the perturbational complexity index show high sensitivity for detecting patients in MCS [99, 100], even in the presence of abnormal resting-state EEG patterns [100] and may detect the brain's capacity for consciousness in unresponsive patients. Automated pupillometry measures pupillary responses to light and cognitive stimuli, offering a non-invasive, bedside method to assess subtle changes in arousal and cognitive processing [101]. Many of these techniques may have prognostic value as well (Step 5). As is the case for assessment for CMD, access to these techniques is limited to a few centres, and their application has been generally restricted to research, rather than clinical, settings. A key priority for future research is to ensure rigorous validation and to develop techniques and analysis pipelines that are practical for widespread use, thereby facilitating clinical translation.

Step 4: selecting therapeutic interventions

Currently, no intervention has been proven to initiate or accelerate recovery from acute DoC [7]. Although several pharmacologic and neuro-modulatory treatments show promise in prolonged DoC, none have sufficient evidence to support routine use in the acute ICU setting [102]. These approaches should therefore be considered experimental and limited to research protocols or highly selected cases in specialised centres.

Currently, best practice focuses on meticulous supportive care, prevention of secondary injuries, and early rehabilitation, whilst ongoing trials assess whether targeted therapies can be safely and effectively translated into clinical practice [103]. Beyond brain-directed care, patients with acute DoC require comprehensive general ICU management to maintain systemic homeostasis and prevent complications that may impede neurological recovery [104, 105]. Patient management is intended to prevent secondary physiological insults that could aggravate neuronal injury. As with all patients who may have a prolonged ICU admission, patients with DoC are at high risk for medical and iatrogenic complications, such as infections, venous thromboembolism, pressure ulcers, and nutritional deficits. Key priorities include prevention of contractures and orthostatic hypotension, timely detection and treatment of paroxysmal sympathetic hyperactivity [107], prevention of heterotopic ossification, early and safe mobilisation, and appropriate tracheostomy [106] and gastrostomy management, when these procedures are performed. In addition to following principles and best practices of critical care management, unique considerations in the care of patients with DoC (e.g., related to intracranial pressures, cerebral perfusion, and metabolic demands) may be necessary to mitigate secondary brain injury. Failure to address these issues may compromise long-term recovery and quality of life. A structured, multidisciplinary approach that integrates general ICU goals with DoC-specific needs should be implemented early to optimise functional outcomes and preserve recovery potential.

Additional considerations

Several studies of pharmacological treatments have demonstrated efficacy in patients with prolonged DoC. In patients with TBI and a DoC 1–4 months post-injury, one large randomised, placebo-controlled pharmacological trial successfully demonstrated that behavioural recovery was accelerated when amantadine hydrochloride was administered for 4 weeks [108]. Zolpidem, a sedative-hypnotic agent that acts on GABA receptors, paradoxically enhances responsiveness in approximately 5–10% of patients with prolonged DoC [109–111]. Although its effects are transient and inconsistent, the phenomenon suggests that modulation of inhibitory neurotransmission may play a role in restoring consciousness in select cases. Other agents, including apomorphine [112, 113, 115], methylphenidate [114, 115], saxagliptin [116], and emerging psychedelic compounds [117–119], are under investigation. However, clinical responses remain variable [120], underscoring the need for understanding individual phenotypes and targeting treatment towards specific neurobiological profiles [121–123].

A cornerstone of care for patients with DoC is not only treating the brain injury itself but also safeguarding against the cascade of secondary insults and medical complications that can follow. These patients are highly susceptible to cardiorespiratory compromise, infections, thromboembolism, skin breakdown, contractures, and nutritional deficits. Monitoring and anticipating these risks and addressing them through structured preventive

strategies is essential to preserve the patient's potential for recovery.

Early and intensive rehabilitation, initiated during the ICU stay when feasible, has been associated with improved functional outcomes and reduced incidence of ICU-acquired weakness [124–126]. Multidisciplinary rehabilitation protocols, encompassing physical therapy, occupational therapy, and speech therapy, may promote neuroplasticity and enhance recovery [127, 128] but require further evidence, especially in the ICU setting. Family involvement in the rehabilitation process may also improve patient outcomes and support the emotional well-being of caregivers [129] but has not been systematically studied across settings. In one Curing Coma Campaign video, the wife of a stroke survivor said: "While the main purpose of the ICU is survival,…the focus of recovery should start in the ICU itself…, if we could have had more hours of therapy, recognising it was passive movement, it might have generated better outcomes. I think whilst we were in the ICU for 4 weeks, we got 15–30 min of therapy a week." Even after ICU discharge, depending on the healthcare system and model, patients may not have access to intensive inpatient rehabilitation, and the implementation of standardised rehabilitation protocols remains inconsistent across institutions and healthcare systems. Future research should focus on evaluating the potential benefits of rehabilitation for patients with DoC as well as defining the optimal timing, intensity, and modalities of rehabilitation [130–132].

Research priorities

Neuromodulation Non-invasive and invasive neuromodulation have gained increasing attention as therapeutic approaches for DoC. Repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), transcranial low-intensity focussed ultrasound (tFUS), and transauricular vagus nerve stimulation (taVNS) have reasonable safety profiles in the outpatient or general care hospital settings [102], but have not been broadly tested or used in the ICU. rTMS applies magnetic pulses to the cortex, thereby modulating neural activity in targeted regions. Studies have reported improvements in arousal and functional outcomes following rTMS in patients with prolonged DoC, although responses are heterogeneous [133, 134]. Similarly, tDCS, which delivers a low-intensity electrical current through scalp electrodes, has shown potential for facilitating recovery of awareness, although more commonly in patients with TBI and a behavioural diagnosis of MCS [135–137]. tFUS can target deeper regions of the brain and has similarly shown some promise in promoting recovery of consciousness [138, 139]. taVNS [77, 78, 140, 141], which stimulates the cortex via electrical pulses delivered to the outer ear that are transmitted to the vagus nerve, and median nerve stimulation [142], has also been studied to promote recovery of consciousness. Though promising, studies using these techniques have been limited by small convenience samples, lack of robust blinding, and the absence of sham conditions.

Invasive neuromodulation, specifically, deep brain stimulation (DBS), targets individual brain regions with direct electrical stimulation. Early phase trials have investigated DBS of the central thalamic nuclei [143] or the centromedian–parafascicular complex [144] showing promise in single cases or small case series. In conscious patients with chronic TBI-related disability, DBS may improve executive control [145]. Nevertheless, the invasiveness of the procedure, along with risks such as infection, haemorrhage, and suboptimal evidence, currently limits its use to highly selected cases. Thus, as with non-invasive techniques, the level of evidence for DBS remains low. Precise patient selection, stimulation parameters, and neuroanatomical targets will be key to maximising the potential benefits of these neuro-modulatory techniques.

Neuroregeneration The field of neuroregeneration offers promising, albeit experimental, avenues for treating DoC. Mesenchymal stem/stromal cell implantation has emerged as a potential therapeutic approach, because mesenchymal stem/stromal cells secrete neurotrophic factors, modulate inflammation, and promote endogenous neurogenesis. Preclinical studies have shown that mesenchymal stem/stromal cell implantation therapy may improve motor and cognitive outcomes following severe brain injury by creating a pro-regenerative microenvironment [146]. Early phase clinical trials, whilst promising, require further validation in larger cohorts to establish optimal cell sources, dosages, and delivery methods, and effectiveness in the clinical setting through well-designed multicentre trials [147].

Step 5: establishing a prognosis

Prognostication in patients with acute DoC is particularly challenging due to the heterogeneity of brain injuries and longitudinal data that may be confounded by WLST [11, 148]. Consequently, neuro-prognostication guidelines emphasise the absence of optimal prognostic models and tools, and a high level of uncertainty surrounding DoC outcome prediction, sometimes suggesting delaying prognostic evaluations for several weeks [5, 149]. Nevertheless, families seek information in the ICU and prognostic uncertainty, including the limited accuracy of most prediction models [150–152], and potential clinical confounders should be acknowledged and integrated into these discussions, promoting transparency whilst

avoiding premature conclusions. Yet, expressing uncertainty may not always be part of clinical training and therefore may not be practised regularly, leading to use of communication strategies that may not meet surrogate or patient needs [153]. As the husband of a basilar artery stroke survivor said in the Curing Coma Campaign video: "a doctor [*at a major academic medical center*] told me, in no uncertain terms, that you [*speaking to the wife on video*] would have locked-in syndrome, that you would never walk again, or eat my delicious cuisine again….and obviously you are speaking and eating again" …. "it makes one start to make plans based on that [information]…".

There are no published guidelines that provide recommendations regarding the optimal timing to initiate level-of-care discussions or the conditions under which these discussions should take place. Multiple factors contribute to this gap, including the absence of accurate tools for predicting neurologic recovery and the inability to account for pre-injury comorbidities or extracerebral complications that may arise during the patient's ICU stay, which can further diminish the likelihood of meaningful recovery.

Two perspectives should be considered. First, although it is recommended that level-of-care discussions be separated from those related to prognosis for neurological recovery [154], level-of-care decisions, including those related to early WLST, are often made in the context of a presumed unfavourable clinical prognosis [2, 3, 77]. As a result, it can be argued that WLST [80, 84, 155] may perpetuate a self-fulfilling prophecy, such that the prediction of an unfavourable outcome results in an unfavourable outcome (i.e., death) [156–159]. Statistical modelling suggests that, across various DoC aetiologies, some patients who died after WLST may have achieved a wide range of recovery milestones, had life-sustaining treatment been prolonged [83, 85, 86]. Amongst survivors of traumatic [160, 161] and non-traumatic [162, 163] brain injury resulting in acute DoC, recovery of consciousness, independence, and higher levels of function has been demonstrated in multiple studies, but may take several years [162–167]. Although these observations are subject to survivor and referral biases [162, 164, 166, 168], several professional guidelines caution against early WLST, especially when that decision is based solely on the prognosis [5, 149, 151, 152, 154].

A second perspective is that delaying level-of-care decisions may lead to patients surviving, and even regaining some function, but having an unacceptable quality of life. Some patients may have previously expressed that survival in an unconscious state or even with minimal impairments is personally unacceptable. Delaying WLST decisions may be incompatible with these perspectives and may place substantial strain on healthcare systems, both in terms of resource utilisation and financial burden, due to the potential increase in the number of patients in DoC requiring long-term care [148, 169, 170]. Moreover, caregivers' quality of life may be affected when life-sustaining treatments are prolonged after brain injury and result in a substantial long-term burden on families [171]. These considerations, and the potential for perspectives to change over time, have not been well studied and should not singularly drive level-of-care decisions, limit interventions, or affect access to care [172].

Establishing prognosis in patients with acute DoC requires a careful balance between recognising uncertainty and minimising the potential for long-term suffering. Improving the accuracy of prognostication requires greater awareness of DoC-related challenges in clinical practice, incorporating the perspectives of multiple team members [173], conducting systematic long-term follow-up, and developing a multimodal approach that integrates diverse sources of data across various post-admission time-points [174]. In research studies, attributing an unfavourable outcome to participants with WLST may overestimate the incidence of that outcome, especially if the neurologic prognosis was inaccurate or the WLST decision was based on other factors [175]. On the other hand, censoring patients with WLST from analyses could underestimate unfavourable outcomes [175] potentially biassing findings [176]. Therefore, application of research findings to clinical care requires caution and a nuanced interpretation of results, especially for studies conducted in countries with high rates of WLST.

Additional considerations

Although several individual clinical, radiological, electrophysiological, laboratory, and blood biomarker indicators have been associated with outcomes following DoC [11], none of these indicators alone provides sufficient accuracy. Prognostic models combining multiple metrics are therefore needed. The most robust prediction models are specific to DoC resulting from hypoxic/ischaemic brain injury after cardiac arrest, although prognostication remains uncertain in many circumstances. Individual predictors have weak-to-moderate evidence supporting their use, and a multimodal approach to prognostication is recommended [151, 154, 177]. Multimodal TBI prognostic models were intended primarily for risk adjustment in clinical trials rather than to guide clinical decision-making [178–181]. Importantly, current models use data available at admission, thereby failing to account for the impact of secondary cerebral injuries that may occur in the early phase of care, factors that could confound initial assessment (e.g., positive toxicology), and the impact of interventions (e.g., dramatic improvement immediately after emergent treatment of hydrocephalus).

Research priorities

In addition to the known prognostic indicators, serial behavioural assessments using a standardised behavioural measure provide the foundation for evaluating recovery trajectories. Combining behavioural assessments with advanced neuroimaging and electrophysiological data may enhance predictive accuracy [42, 182–186], although these findings are inconsistent [187]. There is evidence that the presence of CMD [42, 182], responses to passive language stimuli [185, 188], event-related potentials [186], somatosensory-evoked potentials [87], resting-state EEG metrics such as Synek scores [183, 184], ABCD classification [95, 183, 184], the TMS-EEG evoked perturbation complexity index [99], well-formed sleep spindles preceding observation of CMD [189], and resting-state network connectivity assessed with fMRI [184, 190] may be associated with outcome to varying degrees and at varying time-points. Increasing the number of assessments also appears to increase the likelihood of achieving an accurate prognosis [186]. However, at least two studies have shown that CMD and responses to passive language stimuli are not associated with outcome after acute TBI [40, 187]. Importantly, most of these advanced techniques are not available in clinical practice and require specialised expertise for data analysis and interpretation, making their standard ICU use infeasible in the immediate future. Moreover, whether patients with CMD or other signs of capacity for consciousness can show clinical improvement that is compatible with an acceptable quality of life has not been demonstrated.

Blood-based biomarkers are showing increasing promise for contributing to prognostic models, are feasible to acquire in the ICU, and can be analysed at the point of care. Neuron-specific enolase (NSE) levels in cardiac arrest have been integrated into prognostic guidelines [151] and large multicentre TBI studies have found that glial fibrillary acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase L1, neurofilament light, S100 calcium-binding protein beta (S100B), and total tau levels increase prognostic accuracy when compared to the GCS alone in the acute phase of care [191, 192]. A key consideration in the use of blood-based biomarkers is the timing of their measurement, because values can fluctuate over hours and days [193]. Systematic reviews with meta-analyses have consistently shown an association between S100B, GFAP, and NSE levels measured in the early phase of care and long-term prognosis [194–198]. These biomarkers are rarely included in models with other predictors to create an optimal multimodal prognostic algorithm, and their added value in a multimodal evaluation is not well known.

A key consideration in DoC outcome prediction is selecting the appropriate outcome measure. Traditional measures use a limited number of categories to characterise long-term outcomes (i.e., death to full recovery) and do not differentiate between deaths with WLST, deaths without WLST, and deaths that result from non-neurologic factors [176, 199]. The Cerebral Performance Category for post-hypoxic brain injury [200]; the original and extended Glasgow Outcome Scale for TBI [201–203]; and the modified Rankin Scale for cerebral vascular accidents [204] rate broad levels of outcome and are often dichotomised into a favourable and unfavourable recovery based on a variety of cut-points [205]. To consider the whole spectrum of these ordinal scales, methods such as the sliding dichotomy or proportional odds analyses are used to provide additional precision [206–209]. However, the sliding dichotomy approach still requires a validated prognostic model at baseline, which is not available for many brain injury conditions. Moreover, the recovery milestones assessed by these measures (i.e., independence) do not reflect subtle, potentially meaningful improvements for patients with DoC [205, 210–213], and are not selected by patients or caregivers [214–216]. It is important to note that a substantial proportion of patients with "unfavourable" outcome report average or above-average quality of life [217–221], suggesting that functional recovery may need to be considered in the context of an individual's life satisfaction. Moreover, in some studies, outcomes considered to be "unfavourable" (e.g., partial in-home independence, basic communication) are considered acceptable endpoints by persons with lived experience [170, 215, 222]. The development of person-centred outcomes that are meaningful to patients and families, and used consistently across studies, is needed.

Step 6: facilitating family communication and supported decision-making

The ICU team has the responsibility of conveying complex clinical information in an empathic, compassionate, and understandable manner to promote effective communication with families. A cohesive and consistent message, delivered with appropriate humility, is needed to ensure shared decision-making, promote goal-concordant care, and reduce caregiver strain [223, 224]. Inconsistent information from the different care team members can be confusing, making decision-making more difficult, and increasing the emotional burden for families [225, 226]. Structured family meetings [227], guided by standardised communication protocols, decision aids [228], and cultural and religious considerations, may help align clinical recommendations with the patient's and family's values and expectations. In practice, the implementation

of a time-limited trial of continued therapy may provide an approach for balancing the need to comprehensively assess for spontaneous recovery whilst avoiding indefinite life-sustaining therapies [229].

Shared decision-making in the ICU refers to the process by which family surrogates, clinicians, and, when possible, patients, make health care decisions together, with consideration of scientific evidence, as well as the patient's values and goals [230, 231]. However, how shared decision-making is operationalised varies by circumstance and cultural norms [155, 232–234]. Surrogates express a range of perspectives regarding their preferred approach to decision-making and the role of the clinical team in this process [230, 235]. These perspectives should be evaluated early in the course of recovery and re-evaluated over time. Consultation with bioethics and palliative care experts, where available, can provide guidance in complex situations where there is discord between families and the clinical team.

The surrogate decision-makers are often asked to make decisions on behalf of patients based on what they believe the patients would have wanted, even though they may have never expressed their wishes before injury. Surrogate decision-making has two key components: (1) Substituted Judgement—where the surrogate must try to determine what the patient would have decided for themselves based on their (i.e., the patient's) known values and preference; and (2) Best Interests—when the patient's values and preference are unknown, the surrogate must base their decision on the patient's best interests, considering the pain and suffering of treatments versus the potential benefits, and the resulting impairments [8, 85, 86, 164, 166, 221, 236, 237]. In either case, the patients' values and their best interests are central to the decision-making, and surrogates must be supported in making decisions based on their perception of the patient's values and beliefs, and not their own. It is therefore imperative that clinicians inquire about previously voiced wishes and values and engage in honest, sensitive multidisciplinary discussions about prognosis and treatment options. This involves balancing the limitations of our ability to accurately prognosticate in the early phase of care and obtaining informed consent for care. It is important to consider that what is in the "best interests" of the patient may vary based on cultural norms. Furthermore, the definition of an "acceptable outcome" is not for the clinicians, but for the patient and their surrogate decision-makers to determine, as this definition is not always aligned and may change over time [215, 222]. There is an ethical imperative to promote person-centred care and avoid nihilism and ableism [217] whilst considering the potential for survival with a quality of life that would be unacceptable to the patient.

Additional considerations

Families of patients with acute DoC experience a high level of emotional distress during the ICU stay, resulting from prognostic uncertainty, potentially augmented by inconsistent clinical team communication [238]. There may be discordance between families and clinical teams related to the perception of the potential for recovery [224, 239] resulting in mistrust. The clinical team can also experience significant distress when facing uncertainty in DoC patient management that can lead to reasoning pitfalls (e.g., cognitive biases) affecting neuro-prognostication, decision-making, and communication [240, 241].

It is also important to provide families with an accurate depiction of the post-acute journey, offer resources for post-acute care, and maintain avenues for long-term follow-up. Importantly, evaluating patients in follow-up clinics after they have been discharged from the hospital may help improve understanding of DoC outcomes. For families leaving the structure of the ICU environment, the journey ahead is marked by unknowns. A cardiac arrest survivor who is also a healthcare professional told us: "We had a really great team [*in the ICU*], but nobody warned us about what we should expect…not even some guidance on what to do afterwards." Some patients may be offered a period of intensive inpatient rehabilitation, but many will be discharged to long-term care facilities without the ability to provide specialised brain injury care, or home, where the burden of care will fall largely on the family. After discharge, there are minimal opportunities for accessing novel therapeutic interventions or rehabilitative services, even if there is a change in the level of function. Most outpatient clinics are not equipped to provide care for persons with DoC and ICU physicians rarely provide long-term care for patients they treated during the acute phase of recovery. Families take on the role of nurses, social workers, and case managers in coordinating the appropriate support and care. The long-term burden of providing care for a family member with severe disability is high [242, 243] and few resources are available to alleviate that burden. Families report low quality of life, high levels of distress and mental health symptoms, and the need for health information as well as support from professionals and the community when caring for their loved ones [244]. Ultimately, the transition from intensive care to rehabilitation is most effective when it is viewed as a continuum of care, sustained by close collaboration amongst intensivists, rehabilitation physicians, therapists, nurses, and families.

Research priorities

Caring for patients with DoC poses a range of ethical challenges that have received increasing attention in the last two decades [9, 63, 65, 169, 245–248]. Central to

these challenges is the high likelihood of misdiagnosing a conscious patient as being unconscious [63, 65, 66], the difficulty of establishing a prognosis in the setting of high prognostic uncertainty [148, 157], and that both of these factors critically influence decisions regarding early WLST. Maintaining the balance between doing good (beneficence) whilst avoiding harm (non-maleficence), central tenets of bioethics, is complex, especially when perspectives on acceptable outcomes change over time.

The ethical challenges inherent in DoC clinical care call for further research into effective communication [223] and decision-making strategies. Studies should focus on the development of optimal communication and decision aids to facilitate evidence-informed decision-making processes [171]. Family support interventions to help mitigate the emotional burden on surrogate decision-makers across the spectrum of the recovery journey are also needed. Additionally, research on the quality of surrogate decision-making related to WLST in the early phase of care is also needed as well as the development of outcomes that capture subtle changes in function that are meaningful to patients and families.

The need for a research roadmap

The field of DoC lags behind other areas in medicine, because distinct DoC endotypes are poorly defined (i.e., diagnosis relies on phenotypic classifications rather than pathobiological mechanisms) [19, 154, 155, 249], there are no acute interventions targeting recovery of consciousness [14], and accurate prognostic models in the acute phase are not available [250]. The lack of standardisation in diagnosing and managing DoC is a major barrier to advancing the field. The adoption of Common Data Elements by initiatives such as the Curing Coma Campaign [251] is an example of how data collection could be harmonised across institutions. Coordinated multicentre studies and global surveillance, using standardised definitions and behavioural assessments, will be essential to obtain reliable prevalence and incidence data, and to better inform neuro-prognostication, resource allocation, and long-term planning [36, 252–254]. A summary of current knowledge, immediate ICU actions, and remaining gaps in knowledge are provided in Table 3.

Future studies may focus on optimising study designs to include large samples enrolled across global sites, comprehensively characterising the level of consciousness using multiple modalities, and following participants long-term. Integrating clinical data with advanced neuroimaging, electrophysiology, and blood-based biomarkers may enable the development of personalised interventions and more accurate prognostic models, facilitating a precision medicine approach to DoC management. This approach has the potential to enhance prognostic accuracy and optimise patient selection to test interventions aiming at improving recovery. Of note, special DoC populations, such as paediatric patients [253, 255, 256] and resource-limited areas including those from low- and middle-income countries [103, 257], are especially understudied and generalizability must be considered when designing trials and developing clinical guidelines. Considering that most patients with acute brain injury, especially TBI, are from lower-income countries, low-cost and broadly available tools must be favoured over costly technology when possible. Educational programmes for ICU personnel working in neurocritical care are also needed to ensure specialised teaching in the field.

Given the multifactorial, heterogeneous nature of DoC, it is unlikely that any single intervention will suffice to improve outcomes. An integrative, multimodal approach that combines pharmacological treatments, neuromodulation, regenerative therapies, and structured rehabilitation holds the greatest promise. This strategy involves tailoring interventions based on individual patient characteristics, including clinical presentation, neuroimaging findings, electrophysiological markers, and biochemical profiles. Given the heterogeneity of DoC, adaptive platform trial designs may be the optimal approach to simultaneously and efficiently evaluate multiple interventions. Such designs allow for dynamic patient stratification based on real-time data and enable modifications to trial protocols as new evidence emerges. Future trials should incorporate patient-centred functional outcomes, such as quality of life and other measures of independence, in addition to neurologic functional outcome measures.

Artificial intelligence and machine learning techniques offer unprecedented opportunities to integrate multimodal data. By leveraging these advanced computational methods, researchers may improve predictive models that enhance prognostic accuracy, help guide personalised treatment strategies [258, 259], and develop brain–computer interfaces that support communication [260]. However, successful integration of artificial intelligence into clinical practice will require rigorous validation, transparency in algorithm design, mitigation of the potential for amplifying existing self-fulfilling prophesies, and close collaboration between clinicians and data scientists [261–264].

Conclusions

One of the most complex challenges in contemporary intensive care medicine is managing patients with impaired levels of consciousness because methods for prolonging life are becoming more effective, whilst interventions to improve recovery remain limited and prognostication is often uncertain. The 2025 ISICEM Roundtable provided a roadmap for intensivists seeking

Table 3 Synthesis of current knowledge, immediate actions, and remaining gaps in the diagnosis, intervention, and prognosis of patients with disorders of consciousness

What is known	What can be done now	Gaps
Diagnosis		
-Routine bedside exams (e.g., GCS or FOUR scores) are insufficient to detect subtle signs of consciousness -Standardised behavioural assessments increase diagnostic and prognostic precision -Advanced technologies (e.g., task-based fMRI/EEG) can detect cognitive motor dissociation (CMD)	-Identify and avoid confounders (e.g., sedation, infection, seizure) that may mask consciousness -Identify reversible causes of DoC (via imaging, electrophysiology, laboratory tests, etc.) -Maximise arousal prior to behavioural assessment -Use standardised behavioural assessments (e.g., CRSR-FAST, SECONDs) to assess consciousness -Repeat assessments during the ICU admission to track recovery trajectory	-No well-defined endotypes exist for DoC -The term "coma" is used imprecisely to describe the full spectrum of DoC -Current behavioural assessment approaches lack standardisation -Subtle signs of consciousness may be missed without comprehensive evaluations -Advanced diagnostic tools require more validation -Access to these advanced tools is limited -The absence of systematic, precise surveillance of acute DoC admissions and outcomes limits the understanding of epidemiology
Intervention		
-No treatment has been proven to enhance recovery from acute DoC -Existing ICU guidelines are largely consensus-based and have limited evidence for use in DoC -Multiple pharmacological and neuro-modulatory interventions are under development	-Optimise overall ICU medical management and prevent complications -Initiate early rehabilitation, including family involvement, when there are no contraindications	-Evidence for ICU interventions targeting DoC is limited -Lack of patient stratification approaches to optimise clinical trial responsiveness -Intervention targets remain imprecise -Limited access to experimental interventions
Prognosis		
-Outcomes range from death and prolonged DoC to full recovery -WLST may affect study outcomes and interpretations if not well-informed or if mainly based on criteria unrelated to the neurological prognosis in accordance with patient wishes -Self-fulfilling prophecies in prognostication are a concern -Existing prediction models lack the accuracy to inform clinical decision-making at an individual patient level	-Employ a cautious, multifaceted approach to prognostication -Utilise multiple sources of information to improve prognostic accuracy -Communicate the range of outcomes and degree of uncertainty -Engage in shared decision-making and provide consistent information on the current situation and post-acute journey -Regularly reevaluate prognosis during and after the ICU course -Document level-of-care discussions	-Prognostic precision for individual acute DoC patients is limited -WLST rates and decision-making processes are underreported -Absence of decision-aids to help surrogate decision-makers with level-of-care decisions -Existing outcome assessment tools are not person-centred and may not measure outcomes that are meaningful to individuals with lived experience

to navigate these complexities in a wide range of settings and with access to varying levels of resources. To summarise, consciousness can be masked by a wide range of factors that should be considered and if possible, treated, before conducting standardised, serial behavioural assessment, which is the foundation for precise phenotyping. There are no interventions proven to promote the recovery of consciousness in acute DoC. In the context of prognostic uncertainty and our suboptimal ability to prognosticate, caution is required when information about the recovery trajectory is provided at the bedside. Clear and consistent communication with surrogate decision-makers is paramount for optimising goal-concordant care for patients and providing support for their families. Progress in the management of DoC depends on the close collaboration of multiple disciplines. Intensivists, neurologists, neurosurgeons, radiologists, rehabilitation specialists, ethicists, and scientists must work together to advance our understanding of DoC and develop integrated treatment paradigms. International networks, collaborative research consortia, and professional organisation partnerships will be instrumental in driving innovation, disseminating best practices, and fostering the development of globally applicable research. Continuous reappraisal of current practices and innovation in diagnostic, therapeutic, and prognostic strategies, by this multidisciplinary team, is paramount. The ultimate goal is to improve both survival and quality of life for these vulnerable patients, ensuring that decisions in the ICU are guided by rigorous science and a deep commitment to patient-centred care.

The stepwise roadmap outlines six key domains of ICU care: (1) recognition of DoC after acute brain injury, (2) identification, mitigation, and treatment of confounding factors that may obscure consciousness, (3) standardised and serial behavioural assessments, (4) therapeutic interventions focussed on prevention of secondary injury and early rehabilitation, (5) multimodal approaches to prognostication whilst acknowledging uncertainty, and (6) structured family communication and supported decision-making.

Abbreviations

taVNS: Transauricular vagus nerve stimulation; CDE: Common data elements; CMD: Cognitive motor dissociation; CRS-R: Coma Recovery Scale-Revised; DBS: Deep brain stimulation; DoC: Disorders of consciousness; EEG: Electroencephalography; eMCS: Emerged from minimally conscious state; fMRI: Functional magnetic resonance imaging; FOUR: Full Outline of UnResponsiveness score; GCS: Glasgow Coma Scale; ICU: Intensive care unit; ISICEM: International Symposium on Intensive Care and Emergency Medicine; MCS: Minimally conscious state; MRI: Magnetic resonance imaging; rTMS: Repetitive transcranial magnetic stimulation; SECONDs: Simplified Evaluation of CONsciousness Disorders; TBI: Traumatic brain injury; tDCS: Transcranial direct current stimulation; TMS-EEG: Transcranial magnetic stimulation-electroencephalography; UWS: Unresponsive wakefulness syndrome; VS: Vegetative state; WLST: Withdrawal of life-sustaining treatment.

Author details

[1] Critical Illness, Brain Dysfunction, and Survivorship Center, Vanderbilt University Medical Center, Nashville, USA. [2] Division of Acute Care Surgery, Department of Surgery, Department of Neurological Surgery, Department of Physical Medicine and Rehabilitation, Vanderbilt University Medical Center, Nashville, TN, USA. [3] Division of Neurocritical Care, Departments of Neurology and Neurosurgery, College of Medicine, University of Florida, Gainesville, FL, USA. [4] Division of Neurocritical Care, Departments of Neurology, Neurosurgery, Medicine, Duke University, Durham, NC, USA. [5] Division of Critical Care and Hospitalist Neurology, Department of Neurology, Columbia University Irving Medical Center, New York-Presbyterian Hospital, New York, NY, USA. [6] Service de Neurologie, Hôpital Universitaire de Bruxelles—Université Libre de Bruxelles, Brussels, Belgium. [7] Neurology Department, Yale University School of Medicine, New Haven, CT, USA. [8] Coma Science Group, GIGA-Consciousness, GIGA Institute, University of Liège, Liège, Belgium. [9] NeuroRehab and Consciousness Clinic, Neurology Department, University Hospital of Liège, Liège, Belgium. [10] Department of Neurology, Kepler University Hospital, Johannes Kepler University, Linz, Austria. [11] Clinical Research Institute of Neuroscience, Kepler University Hospital, Johannes Kepler University, Linz, Austria. [12] Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy. [13] Istituto Di Ricovero E Cura a Carattere Scientifico, Fondazione Don Carlo Gnocchi, Milan, Italy. [14] DMU Neurosciences—Clinical Neurophysiology, Paris Brain Institute—ICM, Inserm, CNRS, PICNIC-Lab, Sorbonne Université, APHP, Hôpital de La Pitié Salpêtrière, Paris, France. [15] Department of Medicine, University of Cambridge, Cambridge, UK. [16] IRCCS Policlinico San Martino, Genoa, Italy. [17] Dipartimento di Scienze Chirurgiche Diagnostiche e Integrated, University of Genova, Genova, Italy. [18] DMU Neurosciences—Neuro ICU, Inserm, CNRS, PICNIC-Lab, Paris Brain Institute—ICM, Sorbonne Université, APHP, Hôpital de La Pitié Salpêtrière, Paris, France. [19] Division of Neurosciences Critical Care, Departments of Neurology, Neurosurgery, and Anesthesiology and Critical Care Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD, USA. [20] Population Health and Optimal Health Practices Research Unit, Trauma-Emergency-Critical Care Medicine, CHU de Québec—Université Laval Research Center, Université Laval, Québec City, QC, Canada. [21] Department of Anesthesiology and Critical Care Medicine, Division of Critical Care Medicine, Université Laval, Québec City, QC, Canada. [22] Departments of Neurosurgery and Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA. [23] Departments of Neurology, Neurosurgery, and Anesthesiology, Harborview Medical Center, University of Washington, Washington, USA. [24] Department of Intensive Care, Hôpital Universitaire de Bruxelles (HUB), Université Libre de Bruxelles (ULB), Brussels, Belgium. [25] School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy. [26] NeuroIntensive Care Unit, Department Neuroscience, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy.

Acknowledgements

The authors thank the Neurocritical Care Society's Curing Coma Campaign for providing patient and family video perspectives used to frame the discussion.

Author contributions

The topics of the Roundtable were defined by Y.G.B., G.C., and F.S.T. Y.G.B. and G.C. prepared the initial draft and supervised the entire process. All authors participated in the discussion and contributed substantially to the Roundtable, providing critical revisions for important intellectual content. All authors revised the text and approved the final version.

Funding

The Roundtable was supported by an unrestricted educational grant from NeurOptics. The Neurocritical Care Society provided travel funds for two participants (J.I.S. and P.V.). O.G. is a research associate at FRS-FNRS. A.F.T. is the chairholder of the Canada Research Chair in critical care neurology and trauma. The funders had no role in the conception, content, or review of this manuscript.

Data availability

Not applicable—no primary data were collected or analysed.

Declarations

Conflicts of interest

Marcello Massimini is co-founder and shareholder of Intrinc Powers. Jan Claassen is a minority shareholder at iCE Neurosystems. Virginia Newcombe holds investigator-led grants with Abbott and Roche Pharmaceuticals. All other authors declare no conflicts of interest related to this work. Chiara Robba is a Deputy Editor for Intensive Care Medicine. She has not taken part in the review or selection process of this article.

Ethical approval

Ethics approval was not required, because this manuscript reports the results of an expert Roundtable discussion and does not involve human subjects or identifiable patient data.

Publisher's Note

Received: 9 July 2025 Accepted: 12 November 2025
Published online: 15 December 2025

References

1. Vasilevskis EE, Chandrasekhar R, Holtze CH et al (2018) The cost of ICU delirium and coma in the intensive care unit patient. Med Care 56:890–897
2. Turgeon AF, Lauzier F, Burns KE et al (2013) Determination of neurologic prognosis and clinical decision making in adult patients with severe traumatic brain injury: A survey of Canadian intensivists, neurosurgeons, and neurologists. Crit Care Med 41:1086–1093
3. Turgeon AF, Dorrance K, Archambault P et al (2019) Factors influencing decisions by critical care physicians to withdraw life-sustaining treatments in critically ill adult patients with severe traumatic brain injury. CMAJ 191:E652-e663
4. Taran S, Liu K, McCredie VA et al (2025) Decisions to withdraw or withhold life-sustaining therapies in patients with and without acute brain injury: A secondary analysis of two prospective cohort studies. Lancet Respir Med 13:338–347
5. Giacino JT, Katz DI, Schiff ND et al (2018) Practice guideline update recommendations summary: Disorders of consciousness. Neurology 91:450–460
6. Comanducci A, Boly M, Claassen J et al (2020) Clinical and advanced neurophysiology in the prognostic and diagnostic evaluation of disorders of consciousness: Review of an IFCN-endorsed expert group. Clin Neurophysiol 131:2736–2765
7. Edlow BL, Sanz LRD, Polizzotto L et al (2021) Therapies to restore consciousness in patients with severe brain injuries: a gap analysis and future directions. Neurocrit Care 35:68–85
8. Edlow BL, Claassen J, Schiff ND, Greer DM (2021) Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies. Nat Rev Neurol 17:135–156
9. Young MJ, Bodien YG, Giacino JT et al (2021) The neuroethics of disorders of consciousness: a brief history of evolving ideas. Brain 144:3291–3310
10. Claassen J, Kondziella D, Alkhachroum A et al (2024) Cognitive motor dissociation: gap analysis and future directions. Neurocrit Care 40:81–98
11. Fischer D, Edlow BL (2024) Coma prognostication after acute brain injury: A review. JAMA Neurol 81:405–415
12. Sitt JD, King JR, El Karoui I et al (2014) Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. Brain 137:2258–2270
13. Giacino JT, Katz DI, Schiff ND et al (2018) Comprehensive systematic review update summary: disorders of consciousness: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. Arch Phys Med Rehabil 99:1710–1719
14. Seth AK, Bayne T (2022) Theories of consciousness. Nat Rev Neurosci 23:439–452
15. Chang C, Provencio J, Pascual J et al (2023) State-of-the-art evaluation of acute adult disorders of consciousness for the general intensivist. Crit Care Med 51(7):948–963
16. Ferrante O, Gorska-Klimowska U, Henin S et al (2025) Adversarial testing of global neuronal workspace and integrated information theories of consciousness. Nature 642(8066):133–142
17. Mudrik L, Boly M, Dehaene S et al (2025) Unpacking the complexities of consciousness: theories and reflections. Neurosci Biobehav Rev 170:106053
18. Naccache L (2018) Minimally conscious state or cortically mediated state? Brain 141(4):949–960
19. Provencio JJ, Hemphill JC, Claassen J et al (2020) The Curing Coma Campaign: framing initial scientific challenges—proceedings of the first curing coma campaign scientific advisory council meeting. Neurocrit Care 33:1–12
20. Plum F, Posner JB (1972) The diagnosis of stupor and coma. Contemp Neurol Ser 10:1–286
21. Posner JB, Saper CB, Schiff ND, Claassen J (2019) Plum and Posner's diagnosis and treatment of stupor and coma. Oxford University Press, Plum and Posner's Diagnosis and Treatment of Stupor and Coma
22. Jennett B, Plum F (1972) Persistent vegetative state after brain damage: A syndrome in search of a name. Lancet 1:734–737
23. Laureys S, Celesia GG, Cohadon F et al (2010) Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med 8:68
24. Fins JJ, Master MG, Gerber LM, Giacino JT (2007) The minimally conscious state: A diagnosis in search of an epidemiology. Arch Neurol 64:1400–1405
25. Giacino TJ, Kalmar TK (1997) The vegetative and minimally conscious states: A comparison of clinical features and functional outcome. J Head Trauma Rehabil 12:36–51
26. Giacino JT, Ashwal S, Childs N et al (2002) The minimally conscious state: Definition and diagnostic criteria. Neurology 59:1473–1474
27. Thibaut A, Bodien YG, Laureys S, Giacino JT (2020) Minimally conscious state "plus": Diagnostic criteria and relation to functional recovery. J Neurol 267:1245–1254
28. Papadimitriou C, Weaver JA, Guernon A, Walsh E, Mallinson T, Pape TLB (2022) "Fluctuation is the norm": Rehabilitation practitioner perspectives on ambiguity and uncertainty in their work with persons in disordered states of consciousness after traumatic brain injury. PLoS ONE 17:e0267194
29. Barra A, Bodien YG, Tan CO, Martens G, Malone C, Giacino JT (2025) Behavioral fluctuation in disorders of consciousness: A retrospective analysis. Arch Phys Med Rehabil 106(10):1505–1513
30. Teasdale G, Jennett B (1974) Assessment of coma and impaired consciousness. Pract Scale Lancet 2:81–84
31. Helbok R, Rass V, Beghi E et al (2022) The curing coma campaign international survey on coma epidemiology, evaluation, and therapy (COME TOGETHER). Neurocrit Care 37:47–59
32. Bodien Y, Barra A, Temkin N et al (2021) Diagnosing level of consciousness: the limits of the Glasgow Coma Scale total score. J Neurotrauma 38:3295–3305

33. Mahajan C, Prabhakar H, Rass V et al (2024) A national survey on coma epidemiology, evaluation, and therapy in India: revisiting the curing coma campaign come together survey. Neurocrit Care 40:941–952
34. Giacino JT, Kalmar K, Whyte J (2004) The JFK coma recovery scale-revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 85:2020–2029
35. Giacino JT, Katz DI, Schiff ND et al (2018) Comprehensive systematic review update summary: Disorders of consciousness. Neurology 91:461
36. Tinti L, Lawson T, Molteni E et al (2024) Research considerations for prospective studies of patients with coma and disorders of consciousness. Brain Commun 6:fcae022
37. Wannez S, Heine L, Thonnard M, Gosseries O, Laureys S, Group CS (2017) The repetition of behavioral assessments in diagnosis of disorders of consciousness. Ann Neurol 81:883–889
38. Schucht JE, Rakhit S, Smith MC et al (2025) Beyond Glasgow Coma Scale: Prehospital prediction of traumatic brain injury. Surgery 179:108893
39. ICD-11 for Mortality and Morbidity Statistics [online]. Available at: https://icd.who.int/browse/2025-01/mms/en#1049761831. Accessed May 4, 2025.
40. Edlow BL, Chatelle C, Spencer CA et al (2017) Early detection of consciousness in patients with acute severe traumatic brain injury. Brain 140:2399–2414
41. Kondziella D, Friberg CK, Frokjaer VG, Fabricius M, Møller K (2016) Preserved consciousness in vegetative and minimal conscious states: Systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 87:485–492
42. Claassen J, Doyle K, Matory A et al (2019) Detection of brain activation in unresponsive patients with acute brain injury. N Engl J Med 380:2497–2505
43. Schnakers C, Hirsch M, Noé E et al (2020) Covert cognition in disorders of consciousness: A meta-analysis. Brain Sci 10(12):930
44. Bodien YG, Allanson J, Cardone P et al (2024) Cognitive motor dissociation in disorders of consciousness. N Engl J Med 391:598–608
45. Kondziella D, Amiri M, Othman MH et al (2022) Incidence and prevalence of coma in the UK and the USA. Brain Commun 4:fcac188
46. Davis DP, Idris AH, Sise MJ et al (2006) Early ventilation and outcome in patients with moderate to severe traumatic brain injury. Crit Care Med 34:1202–1208
47. McHugh GS, Engel DC, Butcher I et al (2007) Prognostic value of secondary insults in traumatic brain injury: Results from the IMPACT study. J Neurotrauma 24:287–293
48. Davis DP, Meade W, Sise MJ et al (2009) Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury. J Neurotrauma 26:2217–2223
49. Kilgannon JH, Jones AE, Shapiro NI et al (2010) Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA 303:2165–2171
50. Helmerhorst HJ, Schultz MJ, van der Voort PH, de Jonge E, van Westerloo DJ (2015) Bench-to-bedside review: the effects of hyperoxia during critical illness. Crit Care 19:284
51. Alali AS, Temkin N, Vavilala MS et al (2020) Matching early arterial oxygenation to long-term outcome in severe traumatic brain injury: Target values. J Neurosurg 132:537–544
52. Robba C, Poole D, McNett M et al (2020) Mechanical ventilation in patients with acute brain injury: Recommendations of the European Society of Intensive Care Medicine consensus. Intensiv Care Med 46:2397–2410
53. Zhang B, Huang K, Karri J, O'Brien K, Ditommaso C, Li S (2021) Many faces of the hidden souls: Medical and neurological complications and comorbidities in disorders of consciousness. Brain Sci 11(5):608
54. Muehlschlegel S, Carandang R, Ouillette C, Hall W, Anderson F, Goldberg R (2013) Frequency and impact of intensive care unit complications on moderate-severe traumatic brain injury: Early results of the Outcome Prognostication in Traumatic Brain Injury (OPTIMISM) Study. Neurocrit Care 18:318–331
55. Whyte J, Nordenbo AM, Kalmar K et al (2013) Medical complications during inpatient rehabilitation among patients with traumatic disorders of consciousness. Arch Phys Med Rehabil 94:1877–1883
56. Estraneo A, Loreto V, Masotta O, Pascarella A, Trojano L (2018) Do medical complications impact long-term outcomes in prolonged disorders of consciousness? Arch Phys Med Rehabil 99:2523-2531.e2523
57. Pistoia F, Carolei A, Bodien YG et al (2019) The comorbidities coma scale (CoCoS): psychometric properties and clinical usefulness in patients with disorders of consciousness. Front Neurol 10:1042
58. Murtaugh B, Olson DM, Badjatia N et al (2025) Caring for coma after severe brain injury: Clinical practices and challenges to improve outcomes: an initiative by the curing coma campaign. Neurocrit Care 42:325–333
59. Jacobson SD, Kansara V, Assuras S et al (2025) Impact of aphasia on brain activation to motor commands in patients with acute intracerebral hemorrhage. Neurocrit Care 42:587–594
60. Snider SB, Fong MWK, Nolan NM et al (2023) Clinical and electroencephalographic predictors of seizures and status epilepticus in 12,450 critically ill adults: A retrospective cohort study. Crit Care Med 51:1001–1011
61. Rossetti AO, Claassen J, Gaspard N (2024) Status epilepticus in the ICU. Intensive Care Med 50:1–16
62. Shah VA, Thompson RE, Yenokyan G et al (2022) One-year outcome trajectories and factors associated with functional recovery among survivors of intracerebral and intraventricular hemorrhage with initial severe disability. JAMA Neurol 79:856–868
63. Schnakers C, Giacino J, Kalmar K et al (2007) Does the Glasgow Coma Scale correctly diagnose the vegetative and minimally conscious states? Crit Care 11:P488–P488
64. Iyer VN, Mandrekar JN, Danielson RD, Zubkov AY, Elmer JL, Wijdicks EF (2009) Validity of the FOUR score coma scale in the medical intensive care unit. Mayo Clin Proc 84:694–701
65. Schnakers C, Giacino J, Kalmar K et al (2006) Does the FOUR score correctly diagnose the vegetative and minimally conscious states? Ann Neurol 60:744–745
66. Schnakers C, Vanhaudenhuyse A, Giacino J et al (2009) Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol 9:35
67. Martens G, Bodien Y, Sheau K, Christoforou A, Giacino JT (2020) Which behaviours are first to emerge during recovery of consciousness after severe brain injury? Ann Phys Rehabil Med 63:263–269
68. Hicks R, Giacino J, Harrison-Felix C, Manley G, Valadka A, Wilde EA (2013) Progress in developing common data elements for traumatic brain injury research: Version two–the end of the beginning. J Neurotrauma 30:1852–1861
69. Kondziella D, Bender A, Diserens K et al (2020) European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness. Eur J Neurol 27:741–756
70. Royal College of Physicians. Prolonged disorders of consciousness following sudden onset brain injury: National clinical guidelines. 2020; London: RCP. Access at: https://www.rcp.ac.uk/media/ptcoggi5/pdoc-guidelines_final_online_0_0.pdf
71. Noé E, Navarro MD, Moliner B et al (2025) Guideline: neurorehabilitation in patients with disorder of consciousness. Recommendations from the Spanish society of neurorehabilitation. Neurologia 40:92–117
72. Shirley Ryan Ability Lab Coma Reovery Scale-Revised [online]. Available at: https://www.sralab.org/rehabilitation-measures/coma-recovery-scale-revised. Accessed December 20, 2022.
73. Bodien YG, Chatelle C, Taubert A, Uchani S, Giacino JT, Ehrlich-Jones L (2021) Updated measurement characteristics and clinical utility of the Coma Recovery Scale-Revised among individuals with acquired brain injury. Arch Phys Med Rehabil 102:169–171
74. Woodward MR, Wells CL, Arnold S et al (2024) Behavioral assessment with the Coma Recovery Scale-Revised is safe and feasible in critically Ill patients with disorders of consciousness. Crit Care Explor 6:e1101
75. Bodien YG, Vora I, Barra A et al (2023) Feasibility and validity of the Coma Recovery Scale-Revised For Accelerated Standardized Testing: A practical assessment tool for detecting consciousness in the intensive care unit. Ann Neurol 94:919–924
76. Aubinet C, Cassol H, Bodart O et al (2021) Simplified evaluation of CONsciousness Disorders (SECONDs) in individuals with severe brain injury: A validation study. Ann Phys Rehabil Med 64:101432
77. Turgeon AF, Lauzier F, Simard JF et al (2011) Mortality associated with withdrawal of life-sustaining therapy for patients with severe

traumatic brain injury: A Canadian multicentre cohort study. CMAJ 183:1581–1588
78. Williamson T, Ryser MD, Ubel PA et al (2020) Withdrawal of life-supporting treatment in severe traumatic brain injury. JAMA Surg 155:723–731
79. Steinberg A, Abella BS, Gilmore EJ et al (2021) Frequency of withdrawal of life-sustaining therapy for perceived poor neurologic prognosis. Crit Care Explor 3:e0487
80. van Veen E, van der Jagt M, Citerio G et al (2021) Occurrence and timing of withdrawal of life-sustaining measures in traumatic brain injury patients: A CENTER-TBI study. Intensive Care Med 47:1115–1129
81. Pokrzywa CJ, Holena DN, Murphy PB et al (2022) The variation in timing of withdrawal of life-sustaining therapy in older adults with traumatic brain injury due to hospital factors. J Am Coll Surg 235(5):s106–s107
82. Vlachos S, Rubenfeld G, Menon D, Harrison D, Rowan K, Maharaj R (2023) Early and late withdrawal of life-sustaining treatment after out-of-hospital cardiac arrest in the United Kingdom: Institutional variation and association with hospital mortality. Resuscitation 193:109956
83. Elmer J, Torres C, Aufderheide TP et al (2016) Association of early withdrawal of life-sustaining therapy for perceived neurological prognosis with mortality after cardiac arrest. Resuscitation 102:127–135
84. van Veen E, van der Jagt M, Citerio G et al (2020) End-of-life practices in traumatic brain injury patients: report of a questionnaire from the CENTER-TBI study. J Crit Care 58:78–88
85. Sanders WR, Barber JK, Temkin NR et al (2024) Recovery potential in patients who died after withdrawal of life-sustaining treatment: a TRACK-TBI propensity score analysis. J Neurotrauma 41(19-20):2336-2348
86. Elmer J, Coppler PJ, Ratay C et al (2025) Recovery potential in patients after cardiac arrest who die after limitations or withdrawal of life support. JAMA Netw Open 8:e251714–e251714
87. Bodien YG, Katz D, Schiff N, Giacino JT (2022) Behavioral assessment of patients with disorders of consciousness. Semin Neurol 42:249–258
88. Edlow BL, Fecchio M, Bodien YG et al (2023) Measuring consciousness in the intensive care unit. Neurocrit Care 38:584–590
89. Schiff ND (2015) Cognitive motor dissociation following severe brain injuries. JAMA Neurol 72:1413–1415
90. Bodien YG, Fecchio M, Freeman HJ, Sanders WR, Meydan A, Lawrence P, Kirsch J, Fischer D, Cohen J, Rubin E, He J, Schaefer PW, Hochberg LR, Rapalino O, Cash S, Young M, Edlow BL (2025) Clinical implementation of functional MRI and EEG to detect cognitive motor dissociation: Lessons learned in an acute care hospital. Neurol Clin Pract 15:1
91. Mat B, Sanz LRD, Arzi A, Boly M, Laureys S, Gosseries O (2022) New behavioral signs of consciousness in patients with severe brain injuries. Semin Neurol 42:259–272
92. Gott PS, Rabinowicz AL, DeGiorgio CM (1991) P300 auditory event-related potentials in nontraumatic coma: Association with Glasgow Coma Score and awakening. Arch Neurol 48:1267–1270
93. Faugeras F, Rohaut B, Weiss N et al (2011) Probing consciousness with event-related potentials in the vegetative state. Neurology 77:264–268
94. Qing KY, Forgacs PB, Schiff ND (2024) EEG pattern with spectral analysis can prognosticate good and poor neurologic outcomes after cardiac arrest. J Clin Neurophysiol Off Publ Am Electroencephalogr Soc 41:236–244
95. Curley WH, Bodien YG, Zhou DW et al (2022) Electrophysiological correlates of thalamocortical function in acute severe traumatic brain injury. Cortex 152:136–152
96. Chennu S, Annen J, Wannez S et al (2017) Brain networks predict metabolism, diagnosis and prognosis at the bedside in disorders of consciousness. Brain 140:2120–2132
97. Engemann DA, Raimondo F, King JR et al (2018) Robust EEG-based cross-site and cross-protocol classification of states of consciousness. Brain 141:3179–3192
98. Massimini M, Boly M, Casali A, Rosanova M, Tononi G (2009) A perturbational approach for evaluating the brain's capacity for consciousness. Prog Brain Res 177:201–214
99. Casarotto S, Comanducci A, Rosanova M et al (2016) Stratification of unresponsive patients by an independently validated index of brain complexity. Ann Neurol 80:718–729
100. Casarotto S, Hassan G, Rosanova M et al (2024) Dissociations between spontaneous electroencephalographic features and the perturbational complexity index in the minimally conscious state. Eur J Neurosci 59:934–947
101. Othman MH, Olsen MH, Hansen KIT et al (2024) Covert consciousness in acute brain injury revealed by automated pupillometry and cognitive paradigms. Neurocrit Care 41:218–227
102. Thibaut A, Schiff N, Giacino J, Laureys S, Gosseries O (2019) Therapeutic interventions in patients with prolonged disorders of consciousness. Lancet Neurol 18:600–614
103. Maas AIR, Menon DK, Manley GT et al (2022) Traumatic brain injury: Progress and challenges in prevention, clinical care, and research. Lancet Neurol 21(11):1004–1060
104. Meyfroidt G, Bouzat P, Casaer MP et al (2022) Management of moderate to severe traumatic brain injury: an update for the intensivist. Intensive Care Med 48:649–666
105. Robba C, McCredie V, Chesnut RM et al (2025) Traumatic brain injury management in the intensive care unit: Standard of care and knowledge gaps. Intensive Care Med 51:1112–1127
106. Robba C, Galimberti S, Graziano F et al (2020) Tracheostomy practice and timing in traumatic brain-injured patients: A CENTER-TBI study. Intensive Care Med 46:983–994
107. Meyfroidt G, Baguley IJ, Menon DK (2017) Paroxysmal sympathetic hyperactivity: The storm after acute brain injury. Lancet Neurol 16:721–729
108. Giacino JT, Whyte J, Bagiella E et al (2012) Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med 366:819–826
109. Whyte J, Myers R (2009) Incidence of clinically significant responses to zolpidem among patients with disorders of consciousness: a preliminary placebo controlled trial. Am J Phys Med Rehabil 88:410–418
110. Whyte J, Rajan R, Rosenbaum A et al (2014) Zolpidem and restoration of consciousness. Am J Phys Med Rehabil 93:101–113
111. Zhang B, O'Brien K, Won W, Li S (2021) A retrospective analysis on clinical practice-based approaches using zolpidem and lorazepam in disorders of consciousness. Brain Sci 11:726
112. Fridman EA, Krimchansky BZ, Bonetto M et al (2010) Continuous subcutaneous apomorphine for severe disorders of consciousness after traumatic brain injury. Brain Inj 24:636–641
113. Sanz LRD, Lejeune N, Szymkowicz E et al (2024) Apomorphine for prolonged disorders of consciousness: A multimodal open-label study. EClinicalMedicine 78:102925
114. Kim Y, Shin JC, An YS (2009) Effects of methylphenidate on cerebral glucose metabolism in patients with impaired consciousness after acquired brain injury. Clin Neuropharmacol 32:335–339
115. Othman MH, Toury-Puel AG, Hansen KIT, Amiri M, Zarifkar P, Peinkhofer C, Stückler SG, Olsen MH, Bjerregaard J, Smitt M, Magnussen AS, Forsse A, Møller J, Nielsen MKK, Jessen CH, Hassager C, Hyttel-Sørensen S, Perner A, Møller MH, Møller-Sørensen PH, Hauerberg J, Birkeland P, Sigurdsson ST, Wamberg CA, Itenov TS, Meyhoff CS, Møller K, Andersen TS, Kjaergaard J, Kondziella D (2025) Stimulants for disorders of consciousness in the intensive care unit: A randomized, placebo-controlled trial. Brain 148(10):3523–3536
116. Toker D, Chiang JN, Vespa PM, Schnakers C, Monti MM (2025) The Dipeptidyl Peptidase-4 Inhibitor Saxagliptin as a Candidate Treatment for Disorders of Consciousness: A Deep Learning and Retrospective Clinical Analysis. Neurocrit Care 43(1):101–118
117. Cardone P, Alnagger N, Annen J, Bicego A, Gosseries O, Martial C (2024) Psychedelics and disorders of consciousness: The current landscape and the path forward. Neurosci Conscious 2024(1):niae025
118. Cardone P, Núñez P, Alnagger NLN et al (2025) Psilocybin for disorders of consciousness: A case-report study. Clin Neurophysiol 173:181–189
119. Cardone P, Bonhomme A, Bonhomme V et al (2025) A pilot human study using ketamine to treat disorders of consciousness. iScience 28:111639
120. Martin RT, Whyte J (2007) The effects of methylphenidate on command following and yes/no communication in persons with severe disorders of consciousness: A meta-analysis of n-of-1 studies. Am J Phys Med Rehabil 86:613–620
121. Barra ME, Solt K, Yu X, Edlow BL (2024) Restoring consciousness with pharmacologic therapy: Mechanisms, targets, and future directions. Neurotherapeutics 21:e00374

122. Edlow BL, Barra ME, Zhou DW et al (2020) Personalized connectome mapping to guide targeted therapy and promote recovery of consciousness in the intensive care unit. Neurocrit Care 33:364–375
123. Girard Pepin R, Seyfzadeh F, Williamson D, Gosseries O, Duclos C (2025) Pharmacological therapies for early and long-term recovery in disorders of consciousness: Current knowledge and promising avenues. Expert Rev Neurother 25:613–633
124. Giacino JT, Katz DI, Whyte J (2013) Neurorehabilitation in disorders of consciousness. Semin Neurol 33:142–156
125. Gurin L, Evangelist M, Laverty P et al (2022) Early neurorehabilitation and recovery from disorders of consciousness after severe COVID-19. Neurocrit Care 36:357–371
126. Murooka Y, Sasabuchi Y, Takazawa T, Matsui H, Yasunaga H, Saito S (2023) Long-term prognosis following early rehabilitation in the ICU: A retrospective cohort study. Crit Care Med 51(8):1054–1063
127. Giacino JT, Whyte J, Nakase-Richardson R et al (2020) Minimum competency recommendations for programs that provide rehabilitation services for persons with disorders of consciousness: A position statement of the American Congress of Rehabilitation Medicine and the National Institute on Disability, Independent Living and Rehabilitation Research Traumatic Brain Injury Model Systems. Arch Phys Med Rehabil 101:1072–1089
128. Driessen DMF, Utens CMA, Ribbers PGM, van Erp WS, Heijenbrok-Kal MH (2024) Short-term outcomes of early intensive neurorehabilitation for prolonged disorders of consciousness: a prospective cohort study. Ann Phys Rehabil Med 67:101838
129. Bogner J, Hade EM, Peng J et al (2019) Family involvement in traumatic brain injury inpatient rehabilitation: A propensity score analysis of effects on outcomes during the first year after discharge. Arch Phys Med Rehabil 100:1801–1809
130. Dijkers MP, Hart T, Tsaousides T, Whyte J, Zanca JM (2014) Treatment taxonomy for rehabilitation: Past, present, and prospects. Arch Phys Med Rehabil 95:S6-16
131. Horn SD, Corrigan JD, Beaulieu CL et al (2015) Traumatic brain injury patient, injury, therapy, and ancillary treatments associated with outcomes at discharge and 9 months postdischarge. Arch Phys Med Rehabil 96:S304-329
132. Hart T, Dijkers MP, Whyte J et al (2019) A theory-driven system for the specification of rehabilitation treatments. Arch Phys Med Rehabil 100:172–180
133. Fan J, Zhong Y, Wang H, Aierken N, He R (2022) Repetitive transcranial magnetic stimulation improves consciousness in some patients with disorders of consciousness. Clin Rehabil 36:916–925
134. Yang Z, Yue T, Zschorlich VR, Li D, Wang D, Qi F (2023) Behavioral effects of repetitive transcranial magnetic stimulation in disorders of consciousness: A systematic review and meta-analysis. Brain Sci 13:1362
135. Thibaut A, Bruno MA, Ledoux D, Demertzi A, Laureys S (2014) tDCS in patients with disorders of consciousness: Sham-controlled randomized double-blind study. Neurology 82:1112–1118
136. Thibaut A, Di Perri C, Chatelle C et al (2015) Clinical response to tDCS depends on residual brain metabolism and grey matter integrity in patients with minimally conscious state. Brain Stimul 8:1116–1123
137. Cavaliere C, Aiello M, Di Perri C et al (2016) Functional connectivity substrates for tDCS response in minimally conscious state patients. Front Cell Neurosci 10:257–257
138. Monti MM, Schnakers C, Korb AS, Bystritsky A, Vespa PM (2016) Non-invasive ultrasonic thalamic stimulation in disorders of consciousness after severe brain injury: A first-in-man report. Brain Stimul 9:940–941
139. Cain JA, Spivak NM, Coetzee JP et al (2022) Ultrasonic deep brain neuromodulation in acute disorders of consciousness: A proof-of-concept. Brain Sci 12(4):428
140. Yu Y, Yang Y, Gan S et al (2021) Cerebral hemodynamic correlates of transcutaneous auricular vagal nerve stimulation in consciousness restoration: An open-label pilot study. Front Neurol 12:684791
141. Jang SH, Cho MJ (2022) Transcutaneous auricular vagus nerve stimulation in disorders of consciousness: A mini-narrative review. Medicine 101(50):e31808
142. Wu X, Xie L, Lei J et al (2023) Acute traumatic coma awakening by right median nerve electrical stimulation: A randomised controlled trial. Intensive Care Med 49:633–644
143. Schiff ND, Giacino JT, Kalmar K et al (2007) Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature 448:600–603
144. Chudy D, Deletis V, Paradžik V et al (2023) Deep brain stimulation in disorders of consciousness: 10 years of a single center experience. Sci Rep 13:19491
145. Schiff ND, Giacino JT, Butson CR et al (2023) Thalamic deep brain stimulation in traumatic brain injury: A phase 1, randomized feasibility study. Nat Med 29:3162–3174
146. Pischiutta F, Caruso E, Lugo A et al (2021) Systematic review and meta-analysis of preclinical studies testing mesenchymal stromal cells for traumatic brain injury. NPJ Regen Med 6:71
147. Zanier ER, Pischiutta F, Rulli E et al (2023) Mesenchymall stromal cells for traumatic brain injury (MATRIx): A study protocol for a multicenter, double-blind, randomised, placebo-controlled phase II trial. Intensive Care Med Exp 11:56
148. Graham M (2020) Burying our mistakes: dealing with prognostic uncertainty after severe brain injury. Bioethics 34:612–619
149. ACS Trauma Quality Programs (TQP) Best Practices Guidelines for the Management of Traumatic Brain Injury [online]. Available at: facs.org/media/vgfgjpfk/best-practices-guidelines-traumatic-brain-injury[dot]pdf. Accessed August 25, 2025.
150. Hwang DY, Kim KS, Muehlschlegel S et al (2023) Guidelines for neuroprognostication in critically Ill adults with intracerebral hemorrhage. Neurocrit Care 40(2):395–414
151. Rajajee V, Muehlschlegel S, Wartenberg KE et al (2023) Guidelines for neuroprognostication in comatose adult survivors of cardiac arrest. Neurocrit Care 38:533–563
152. Muehlschlegel S, Rajajee V, Wartenberg KE et al (2024) Guidelines for neuroprognostication in critically Ill adults with moderate-severe traumatic brain injury. Neurocrit Care 40:448–476
153. Jones K, Quinn T, Mazor KM, Muehlschlegel S (2021) Prognostic uncertainty in critically ill patients with traumatic brain injury: A multicenter qualitative study. Neurocrit Care 35:311–321
154. Nolan JP, Sandroni C, Böttiger BW et al (2021) European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: Post-resuscitation care. Intensive Care Med 47:369–421
155. Morgan J (2015) How do you decide when to withdraw life support? Lancet Respir Med 3:430–431
156. Becker KJ, Baxter AB, Cohen WA et al (2001) Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. Neurology 56:766–772
157. Hemphill JC 3rd, White DB (2009) Clinical nihilism in neuroemergencies. Emerg Med Clin North Am 27:27–37
158. Izzy S, Compton R, Carandang R, Hall W, Muehlschlegel S (2013) Self-fulfilling prophecies through withdrawal of care: Do they exist in traumatic brain injury, too? Neurocrit Care 19:347–363
159. Elmer J, Kurz MC, Coppler PJ et al (2023) Time to awakening and self-fulfilling prophecies after cardiac arrest. Crit Care Med 51:503–512
160. McCrea MA, Giacino JT, Barber J et al (2021) Functional outcomes over the first year after moderate to severe traumatic brain injury in the prospective, longitudinal TRACK-TBI study. JAMA Neurol 78:982–992
161. Kowalski RG, Hammond FM, Weintraub AH et al (2021) Recovery of consciousness and functional outcome in moderate and severe traumatic brain injury. JAMA Neurol 78:548–557
162. Estraneo A, Fiorenza S, Magliacano A et al (2020) Multicenter prospective study on predictors of short-term outcome in disorders of consciousness. Neurology 95:e1488–e1499
163. Magliacano A, De Bellis F, Panico F et al (2023) Long-term clinical evolution of patients with prolonged disorders of consciousness due to severe anoxic brain injury: A meta-analytic study. Eur J Neurol 30:3913–3927
164. Estraneo A, Moretta P, Loreto V, Lanzillo B, Santoro L, Trojano L (2010) Late recovery after traumatic, anoxic, or hemorrhagic long-lasting vegetative state. Neurology 75:239–245
165. Whyte J, Nakase-Richardson R, Hammond FM et al (2013) Functional outcomes in traumatic disorders of consciousness: 5-year outcomes from the National Institute on Disability and Rehabilitation Research Traumatic Brain Injury Model Systems. Arch Phys Med Rehabil 94:1855–1860

166. Hammond FM, Giacino JT, Nakase Richardson R et al (2019) Disorders of consciousness due to traumatic brain injury: functional status ten years post-injury. J Neurotrauma 36:1136–1146
167. Hakiki B, Liuzzi P, Romoli AM et al (2025) Predictors of recovering full consciousness: Results from a prospective multisite Italian study. Eur J Neurol 32:e70138
168. Pavlov YG, Spiegelsberger F, Kotchoubey B (2024) Predicting outcome in disorders of consciousness: A mega-analysis. Ann Clin Transl Neurol 11:1465–1477
169. Fins JJ (2015) Rights Come to Mind: Brain Injury, Ethics, and the Struggle for Consciousness. Cambridge University Press, New York, NY
170. Rutz Voumard R, Kiker WA, Dugger KM et al (2021) Adapting to a new normal after severe acute brain injury: An observational cohort using a sequential explanatory design. Crit Care Med 49:1322–1332
171. Muehlschlegel S, Goostrey K, Flahive J, Zhang Q, Pach JJ, Hwang DY (2022) Pilot randomized clinical trial of a goals-of-care decision aid for surrogates of patients with severe acute brain injury. Neurology 99:e1446–e1455
172. Giacino JT, Bodien YG, Zuckerman D, Henderson J, Schiff ND, Fins JJ (2021) Empiricism and rights justify the allocation of health care resources to persons with disorders of consciousness. AJOB Neurosci 12:169–171
173. Hermann B, Goudard G, Courcoux K et al (2019) Wisdom of the caregivers: Pooling individual subjective reports to diagnose states of consciousness in brain-injured patients, a monocentric prospective study. BMJ Open 9:e026211
174. Retel Helmrich IRA, Lingsma HF, Turgeon AF, Yamal JM, Steyerberg EW (2021) Prognostic research in traumatic brain injury: Markers, modeling, and methodological principles. J Neurotrauma 38:2502–2513
175. Healy BC, Edlow BL, Bodien YG (2025) Accounting for withdrawal of life sustaining treatment in the analysis of traumatic brain injury studies. Neurotrauma Rep 6(1):435–441
176. Leblanc G, Boutin A, Shemilt M et al (2018) Incidence and impact of withdrawal of life-sustaining therapies in clinical trials of severe traumatic brain injury: A systematic review. Clin Trials 15:398–412
177. van Diepen S, Le May MR, Alfaro P et al (2024) Canadian Cardiovascular Society/Canadian Cardiovascular Critical Care Society/Canadian Association of Interventional Cardiology clinical practice update on optimal post cardiac arrest and refractory cardiac arrest patient care. Can J Cardiol 40:524–539
178. CRASH MRC Trial Collaborators (2008) Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. BMJ 336:425–429
179. Steyerberg EW, Mushkudiani N, Perel P et al (2008) Predicting outcome after traumatic brain injury: Development and international validation of prognostic scores based on admission characteristics. PLoS Medic 5:e165
180. Steyerberg EW, Vickers AJ, Cook NR et al (2010) Assessing the performance of prediction models: A framework for traditional and novel measures. Epidemiology 21:128–138
181. Dijkland SA, Foks KA, Polinder S et al (2020) Prognosis in moderate and severe traumatic brain injury: A systematic review of contemporary models and validation studies. J Neurotrauma 37:1–13
182. Egbebike J, Shen Q, Doyle K et al (2022) Cognitive-motor dissociation and time to functional recovery in patients with acute brain injury in the USA: A prospective observational cohort study. Lancet Neurol 21:704–713
183. Amiri M, Fisher PM, Raimondo F et al (2023) Multimodal prediction of residual consciousness in the intensive care unit: The CONNECT-ME study. Brain 146:50–64
184. Amiri M, Raimondo F, Fisher PM et al (2024) Multimodal prediction of 3- and 12-month outcomes in ICU patients with acute disorders of consciousness. Neurocrit Care 40:718–733
185. Sokoliuk R, Degano G, Banellis L et al (2021) Covert speech comprehension predicts recovery from acute unresponsive states. Ann Neurol 89:646–656
186. Rohaut B, Calligaris C, Hermann B et al (2024) Multimodal assessment improves neuroprognosis performance in clinically unresponsive critical-care patients with brain injury. Nat Med 30:2349–2355
187. Bodien YG, Fecchio M, Gilmore N et al (2025) Multimodal biomarkers of consciousness in acute severe traumatic brain injury. J Neurotrauma. https://doi.org/10.1177/08977151251377469
188. Young MJ, Fecchio M, Bodien YG, Edlow BL (2024) Covert cortical processing: A diagnosis in search of a definition. Neurosci Conscious 2024:niad26
189. Carroll EE, Shen Q, Kansara V et al (2025) Sleep spindles as a predictor of cognitive motor dissociation and recovery of consciousness after acute brain injury. Nat Med 31:1578–1585
190. Threlkeld ZD, Bodien YG, Rosenthal ES et al (2018) Functional networks reemerge during recovery of consciousness after acute severe traumatic brain injury. Cortex 106:299–308
191. Korley FK, Jain S, Sun X et al (2022) Prognostic value of day-of-injury plasma GFAP and UCH-L1 concentrations for predicting functional recovery after traumatic brain injury in patients from the US TRACK-TBI cohort: An observational cohort study. Lancet Neurol 21:803–813
192. Helmrich I, Czeiter E, Amrein K et al (2022) Incremental prognostic value of acute serum biomarkers for functional outcome after traumatic brain injury (CENTER-TBI): An observational cohort study. Lancet Neurol 21:792–802
193. Newcombe VFJ, Ashton NJ, Posti JP et al (2022) Post-acute blood biomarkers and disease progression in traumatic brain injury. Brain 145:2064–2076
194. Mercier E, Boutin A, Lauzier F et al (2013) Predictive value of S-100β protein for prognosis in patients with moderate and severe traumatic brain injury: Systematic review and meta-analysis. BMJ 346:f1757
195. Mercier E, Boutin A, Shemilt M et al (2016) Predictive value of neuron-specific enolase for prognosis in patients with moderate or severe traumatic brain injury: A systematic review and meta-analysis. CMAJ Open 4:E371–E382
196. Wang C-H, Chang W-T, Su K-I et al (2020) Neuroprognostic accuracy of blood biomarkers for post-cardiac arrest patients: A systematic review and meta-analysis. Resuscitation 148:108–117
197. Shemilt M, Boutin A, Lauzier F et al (2019) Prognostic value of glial fibrillary acidic protein in patients with moderate and severe traumatic brain injury: A systematic review and meta-analysis. Crit Care Med 47:e522–e529
198. Mondello S, Amrein K, Czeiter E et al (2025) Prognostic value of blood-based protein biomarkers in traumatic brain injury: A living systematic review and meta-analysis. J Neurotrauma 42:1256–1286
199. Taccone FS, Horn J, Storm C et al (2019) Death after awakening from post-anoxic coma: the "Best CPC" project. Crit Care 23:107
200. P. S. Resuscitation after brain ischemia. New York, NY: Churchill Livingstone, 1981.
201. Wilson JT, Pettigrew LE, Teasdale GM (1998) Structured interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: Guidelines for their use. J Neurotrauma 15:573–585
202. McMillan T, Wilson L, Ponsford J, Levin H, Teasdale G, Bond M (2016) The Glasgow Outcome Scale—40 years of application and refinement. Nat Rev Neurol 12:477–485
203. Wilson L, Boase K, Nelson LD et al (2021) A manual for the Glasgow Outcome Scale-Extended interview. J Neurotrauma 38:2435–2446
204. Rankin J (1957) Cerebral vascular accidents in patients over the age of 60. II Prognosis Scott Med J 2:200–215
205. Zuckerman DA, Giacino JT, Bodien YG (2022) Traumatic brain injury: What is a favorable outcome? J Neurotrauma 39:1010–1012
206. Murray GD, Barer D, Choi S et al (2005) Design and analysis of phase III trials with ordered outcome scales: The concept of the sliding dichotomy. J Neurotrauma 22:511–517
207. Skolnick BE, Maas AI, Narayan RK et al (2014) A clinical trial of progesterone for severe traumatic brain injury. N Engl J Med 371:2467–2476
208. Hutchinson PJ, Kolias AG, Timofeev IS et al (2016) Trial of decompressive craniectomy for traumatic intracranial hypertension. N Engl J Med 375:1119–1130
209. Turgeon AF, Fergusson DA, Clayton L et al (2024) Liberal or restrictive transfusion strategy in patients with traumatic brain injury. N Engl J Med 391:722–735
210. Ranson J, Magnus BE, Temkin N et al (2019) Diagnosing the GOSE: Structural and psychometric properties using item response theory, a TRACK-TBI pilot study. J Neurotrauma 36:2493–2505

211. Erler KS, Wu R, DiCarlo JA et al (2022) Association of Modified Rankin Scale with recovery phenotypes in patients with upper extremity weakness after stroke. Neurology 98:e1877–e1885
212. Snider SB, Kowalski RG, Hammond FM et al (2022) Comparison of common outcome measures for assessing independence in patients diagnosed with disorders of consciousness: A Traumatic Brain Injury Model Systems study. J Neurotrauma 39:1222–1230
213. Bodien YG, Beaulieu CL, Giacino JT, Weintraub A, Whyte J, Williams MW (2023) How severe is severe disability after traumatic brain injury? Response to Sarigul B et al., J Neurotrauma 40:2449–2451
214. Lou W, Granstein JH, Wabl R, Singh A, Wahlster S, Creutzfeldt CJ (2022) Taking a chance to recover: Families look back on the decision to pursue tracheostomy after severe acute brain injury. Neurocrit Care 36:504–510
215. Heinonen GA, Carmona JC, Grobois L et al (2024) A survey of surrogates and health care professionals indicates support of cognitive motor dissociation-assisted prognostication. Neurocrit Care 42:786–793
216. Andersen CR, Presseau J, Shea B et al (2025) What to measure in aneurysmal subarachnoid haemorrhage research-an international Delphi survey. Transl Stroke Res 16:49–78
217. Albrecht GL, Devlieger PJ (1999) The disability paradox: High quality of life against all odds. Soc Sci Med 48:977–988
218. Retel Helmrich IRA, van Klaveren D, Andelic N et al (2022) Discrepancy between disability and reported well-being after traumatic brain injury. J Neurol Neurosurg Psychiatry 93:785–796
219. Yonis H, Sørensen KK, Bøggild H et al (2023) Long-term quality of life after out-of-hospital cardiac arrest. JAMA Cardiology 8:1022–1030
220. Golden K, Ketchum J, Gary KW et al (2025) Association between disability and life satisfaction, participation, and psychological health: A Traumatic Brain Injury Model Systems study. Neurology 105(6):e214072
221. Gilmore N, Murtaugh BM, Bogdanova Y, et al. Quality of life and psychological health after recovery from disorders of consciousness: A TBI Model Systems study. J Neurotrauma 2025 (In Press).
222. Bodien YG, Borsi L, Pier E et al (2025) Perspectives of persons with lived experience on acceptable outcome after traumatic brain injury. Response Under Rev. https://doi.org/10.1101/2025.02.21.25322625
223. Quinn T, Moskowitz J, Khan MW et al (2017) What families need and physicians deliver: Contrasting communication preferences between surrogate decision-makers and physicians during outcome prognostication in critically Ill TBI patients. Neurocrit Care 27:154–162
224. Fleming V, Prasad A, Ge C et al (2023) Prevalence and predictors of shared decision-making in goals-of-care clinician-family meetings for critically ill neurologic patients: A multi-center mixed-methods study. Crit Care 27:403
225. Hwang DY, Yagoda D, Perrey HM et al (2014) Assessment of satisfaction with care among family members of survivors in a neuroscience intensive care unit. J Neurosci Nurs 46:106–116
226. Hwang DY, Yagoda D, Perrey HM et al (2014) Consistency of communication among intensive care unit staff as perceived by family members of patients surviving to discharge. J Crit Care 29:134–138
227. Nelson JE, Walker AS, Luhrs CA, Cortez TB, Pronovost PJ (2009) Family meetings made simpler: a toolkit for the intensive care unit. J Crit Care 24(626):e627–e614
228. Goostrey KJ, Lee C, Jones K et al (2021) Adapting a traumatic brain injury goals-of-care decision aid for critically ill patients to intracerebral hemorrhage and hemispheric acute ischemic stroke. Crit Care Explor 3:e0357
229. Kruser JM, Nadig NR, Viglianti EM, Clapp JT, Secunda KE, Halpern SD (2024) Time-limited trials for patients with critical illness: A review of the literature. Chest 165:881–891
230. Kon AA, Davidson JE, Morrison W, Danis M, White DB (2016) Shared decision making in ICUs: An American college of critical care medicine and American thoracic society policy statement. Crit Care Med 44:188–201
231. Scheunemann LP, Ernecoff NC, Buddadhumaruk P et al (2019) Clinician-family communication about patients' values and preferences in intensive care units. JAMA Intern Med 179:676–684
232. Sprung CL, Cohen SL, Sjokvist P et al (2003) End-of-life practices in European intensive care units the ethicus study. JAMA 290:790–797
233. Cohen S, Sprung C, Sjokvist P et al (2005) Communication of end-of-life decisions in European intensive care units. Intensive Care Med 31:1215–1221
234. Curtis JR, Vincent JL (2010) Ethics and end-of-life care for adults in the intensive care unit. Lancet 376:1347–1353
235. Cai X, Robinson J, Muehlschlegel S et al (2015) Patient preferences and surrogate decision making in neuroscience intensive care units. Neurocrit Care 23:131–141
236. Meisel A, Cerminara KL (2004) The right to die: The law of end-of-life decisionmaking, 3rd edn. Aspen Publishers, New York
237. Lo B. Resolving Ethical Dilemmas: A Guide for Clinicians, 6e: Lippincott Williams & Wilkins, a Wolters Kluwer business, 2020.
238. Hayes K, Harding S, Buckley K, Blackwood B, Latour JM (2023) Exploring the experiences of family members when a patient is admitted to the ICU with a severe traumatic brain injury: A scoping review. J Clin Med 12(13):4197
239. Kiker WA, Rutz Voumard R, Andrews LIB et al (2021) Assessment of discordance between physicians and family members regarding prognosis in patients with severe acute brain injury. JAMA Netw Open 4:e2128991
240. Lakhlifi C, Rohaut B (2023) Heuristics and biases in medical decision-making under uncertainty: The case of neuropronostication for consciousness disorders. Presse Med 52:104181
241. Lissak IA, Young MJ (2024) Limitation of life sustaining therapy in disorders of consciousness: Ethics and practice. Brain 147:2274–2288
242. Wendlandt B, Olm-Shipman C, Ceppe A et al (2022) Surrogates of patients with severe acute brain injury experience persistent anxiety and depression over the 6 months after ICU admission. J Pain Symptom Manage 63:e633–e639
243. Smith NL, James A, Matin N et al (2025) Long-term outcomes after severe acute brain injury requiring mechanical ventilation: Recovery trajectories among patients and mental health symptoms of their surrogate decision makers. Neurocrit Care 42:896–910
244. Gosseries O, Schnakers C, Vanhaudenhuyse A et al (2023) Needs and quality of life of caregivers of patients with prolonged disorders of consciousness. Brain Sci 13(2):308
245. Fins JJ (2003) Constructing an ethical stereotaxy for severe brain injury: Balancing risks, benefits and access. Nat Rev Neurosci 4:323–327
246. Fins J, Wright M, Bagenstos S (2020) Disorders of consciousness and disability law. Mayo Clin Proc 95:1732–1739
247. Lewis A, Claassen J, Illes J et al (2022) Ethics priorities of the Curing Coma Campaign: An empirical survey. Neurocrit Care 37:12–21
248. Peterson A, Young MJ, Fins JJ (2022) Ethics and the 2018 practice guideline on disorders of consciousness: A framework for responsible implementation. Neurology 98:712–718
249. Kondziella D, Menon DK, Helbok R et al (2021) A precision medicine framework for classifying patients with disorders of consciousness: Advanced Classification of Consciousness Endotypes (ACCESS). Neurocrit Care 35:27–36
250. Hammond FM, Katta-Charles S, Russell MB et al (2021) Research needs for prognostic modeling and trajectory analysis in patients with disorders of consciousness. Neurocrit Care 35:55–67
251. Edlow BL, Claassen J, Suarez JI (2024) Common data elements for disorders of consciousness. Neurocrit Care 40:715–717
252. Bodien YG, Venkatasubba CR, Lavrijsen J, Giacino JG (2023) Models and systems of care for patients with disorders of consciousness. In: Schnakers C, Laureys S (eds) Coma and Disorders of Consciousness, 3rd edn. Springer, Cham, Switzerland, pp 243–262
253. Molteni E, Canas LDS, Briand MM et al (2023) Scoping review on the diagnosis, prognosis, and treatment of pediatric disorders of consciousness. Neurology 101:e581–e593
254. Boerwinkle VL, Appavu B, Cediel EG et al (2024) Common data elements for disorders of consciousness: Recommendations from the working group in the pediatric population. Neurocrit Care 40:65–73
255. Irzan H, Pozzi M, Chikhladze N et al (2022) Emerging treatments for disorders of consciousness in paediatric age. Brain Sci 12(2):198
256. Boerwinkle VL, Schor NF, Slomine BS et al (2023) Proceedings of the first Pediatric Coma and Disorders of Consciousness symposium by the Curing Coma Campaign, Pediatric Neurocritical Care Research

Group, and NINDS: Gearing for success in coma advancements for children and neonates. Neurocrit Care 38:447–469
257. Allen BC, Cummer E, Sarma AK (2023) Traumatic brain injury in select low- and middle-income countries: A narrative review of the literature. J Neurotrauma 40:602–619
258. Dai W, Adeli E, Luo Z et al (2025) Developing ICU clinical behavioral atlas using ambient intelligence and computer vision. NEJM AI 2(2):AIoa2400590
259. Fischer D, Edlow BL, Freeman HJ et al (2025) Reconstructing covert consciousness: Neural decoding as a novel consciousness assessment. Neurology 104(4):e210208
260. Schiff ND, Diringer M, Diserens K et al (2024) Brain-computer interfaces for communication in patients with disorders of consciousness: A gap analysis and scientific roadmap. Neurocrit Care 41(1):129–145
261. Soulier T, Colliot O, Ayache N, Rohaut B (2023) How will tomorrow's algorithms fuse multimodal data? The example of the neuroprognosis in intensive care. Anaesth Critl Care Pain Med 42:101301
262. Collins GS, Moons KGM, Dhiman P et al (2024) TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. BMJ 385:e078378
263. Feng J, Xia F, Singh K, Pirracchio R (2025) Not all clinical AI monitoring systems are created equal: Review and recommendations. NEJM AI 2(2):AIra2400657
264. Tripathi S, Alkhulaifat D, Doo F et al (2025) Development, evaluation, and assessment of large language models (DEAL) checklist: A technical report. NEJM AI 2(6):Alp2401106