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State-of-the-Art Evaluation of Acute Adult Disorders of Consciousness for the General Intensivist

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OBJECTIVES: To provide a concise review of knowledge and practice pertaining to the diagnosis and initial management of unanticipated adult patient disorders of consciousness (DoC) by the general intensivist.

DATA SOURCES: Detailed search strategy using PubMed and OVID Medline for English language articles describing adult patient acute DoC diagnostic evaluation and initial management strategies including indications for transfer.

STUDY SELECTION: Descriptive and interventional studies that address acute adult DoC, their evaluation and initial management, indications for transfer, as well as outcome prognostication.

DATA EXTRACTION: Relevant descriptions or studies were reviewed, and the following aspects of each manuscript were identified, abstracted, and analyzed: setting, study population, aims, methods, results, and relevant implications for adult critical care practice.

DATA SYNTHESIS: Acute adult DoC may be categorized by etiology including structural, functional, infectious, inflammatory, and pharmacologic, the understanding of which drives diagnostic investigation, monitoring, acute therapy, and subsequent specialist care decisions including team-based local care as well as intra- and inter-facility transfer.

CONCLUSIONS: Acute adult DoC may be initially comprehensively addressed by the general intensivist using an etiology-driven and team-based approach. Certain clinical conditions, procedural expertise needs, or resource limitations inform transfer decision-making within a complex care facility or to one with greater complexity. Emerging collaborative science helps improve our current knowledge of acute DoC to better align therapies with underpinning etiologies.

KEY WORDS: coma; diagnosis; disorder of consciousness; imaging; neurocritical care; neurology; transfer

Every intensivist and multi-professional team member—regardless of parent discipline or setting—evaluates and manages patients with disorders of consciousness (DoC). Pathobiological changes in the brain result in acute encephalopathy that clinically manifests as DoC (1). DoC includes rapidly (< 4 wk) developing disturbances in attention, awareness and cognition that present along a continuum ranging from delirium to severely depressed responsiveness (1). DoCs previously regarded as static conditions are increasingly characterized by potentially recruitable brain function (2). National campaigns such as the Curing Coma Campaign have been launched to raise awareness of coma's potential malleability (3). It is therefore essential that the critical care team understands and can deploy a framework within which to safely and

DOI: 10.1097/CCM.0000000000005893

KEY POINTS

Question: Are acute, unanticipated adult disorders of consciousness (DoC) evaluable in a fashion that aligns diagnosis and initial therapy?

Findings: Unanticipated acute adult DoC are reliably evaluated by the general intensivist using a structural, functional, infectious, inflammatory, and pharmacologic framework. Rescue care and initial therapy benefits from a team-based approach. Collaborative data science further aligns therapies with underpinning etiologies. Specific clinical conditions, procedural needs, or monitoring requirements inform intra- or inter-facility transfer.

Meaning: Most patients with unanticipated acute adult DoC may be managed using team-based care including a neurologist and/or neurosurgeon. Select patients benefit from transfer for specialty neurocritical care.

effectively discover the root cause of an acute DoC and initiate therapy (4). This concise definitive review presents a structured approach to evaluation, consultation, initial intervention, and consider patient transfer for management by a neurocritical care (NCC) team.

METHODS

This narrative review presents practical aspects of the evaluation and management of an adult patient with an unanticipated acute DoC focused on the general intensivist. It will not address pediatric, neonatal or chronic DoC (i.e., minimally conscious state, unresponsive wakefulness syndrome [aka. persistent vegetative state]), traumatic brain injury, rare or orphan diseases, dementia, prognostication, or management within a NCC ICU. English-language manuscripts were identified across PubMed and OVID using relevant search terms (**Supplemental Table 1**, http://links.lww.com/CCM/H338); selections were limited to the last 15 years (January 2008 to January 2023) to ensure current practice relevance.

Epidemiology of Adult DoC

Acute DoCs widely vary with regard to onset and duration depending on patient population and clinical condition. Therefore, precise epidemiology is challenging to characterize. Moreover, DoCs are generally not reported across different ICUs within a healthcare facility or within a single ICU and are inaccurately captured by billing codes. There is more focused DoC data during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic onset (March 2020 to July 2020). In a tertiary care facility, nearly 33% of critically ill COVID-19 patients were comatose by hospital day 2 from hypoxia, opioids, sedatives, and neuromuscular blockade (5). This study underscores the interplay of index hospitalization etiology with rendered care and their combined impact on DoCs. Thus, it is difficult for intensivists to provide a landscape view of unanticipated DoC for decision-makers.

Anatomy of Consciousness

While attractive to ascribe consciousness to activity at a specific location, a network-based approach offers mechanistic explanations for alertness and DoC. DoCs have been considered related to bilateral hemispheric dysfunction, brainstem, or thalamic injury involving the reticular activating system. There are interconnected structural and functional networks that are identifiable using electroencephalography mapping and functional MRI (fMRI) (6, 7). Patients with sensory stimulation failure also demonstrate basal forebrain atrophy (8). These data may provide clues to rescue therapies designed to stimulate atrophied domains. Furthermore, the "default mode network" (DMN), active during rest and quiescent during tasks or seizure activity, interfaces with other networks and is partly responsible for cognition and perceptual alertness (9). Therefore, disruption of the DMN may result in DoC.

Framework of Etiologies

Potential DoC drivers may be grouped into a practical framework of five categories (structural, functional, infection, inflammation, and pharmacologic) to inform evaluation, diagnosis, and treatment (**Fig. 1**).

Structural Etiologies. A focal neurological deficit suggests a structural etiology that one must rapidly identify (**Fig. 2**). Nontraumatic structural etiologies include global or focal ischemia (e.g., cardiac arrest or stroke), intracranial hemorrhage (ICH), tumor, abscess, and hydrocephalus. "Stroke" is categorized as ischemic or hemorrhagic and may be suggested by history, examination, and medications. Since acute ischemic stroke (AIS) and

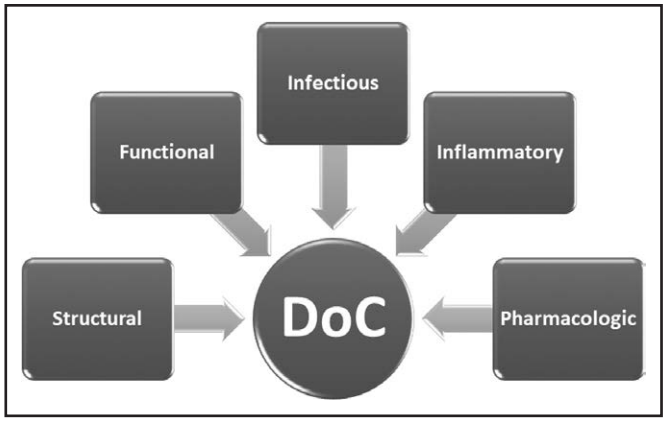

Figure 1. A framework for etiology evaluation. This graphic presents a framework of etiologies from which to explore an acute unanticipated disorder of consciousness (DoC) in an adult patient.

ICH are time-sensitive conditions, rapid recognition and evaluation is critical (10). Impaired or absent flow leads to rapid neuronal death as well as injury to penumbral cells and neurons (11). AIS is serially assessed using the National Institutes of Health Stroke Scale (NIHSS), which trends progress and guides decision-making. Prehospital stroke scales can detect an increased likelihood of large vessel occlusion and indicate the need for care by an endovascular capable team (12). Neurosurgical or neurovascular intervention is driven by conditions including vascular anomalies and complications such as intracranial hypertension (13, 14).

"Aneurysmal subarachnoid hemorrhage (aSAH)" is often associated with acute hypertension that requires

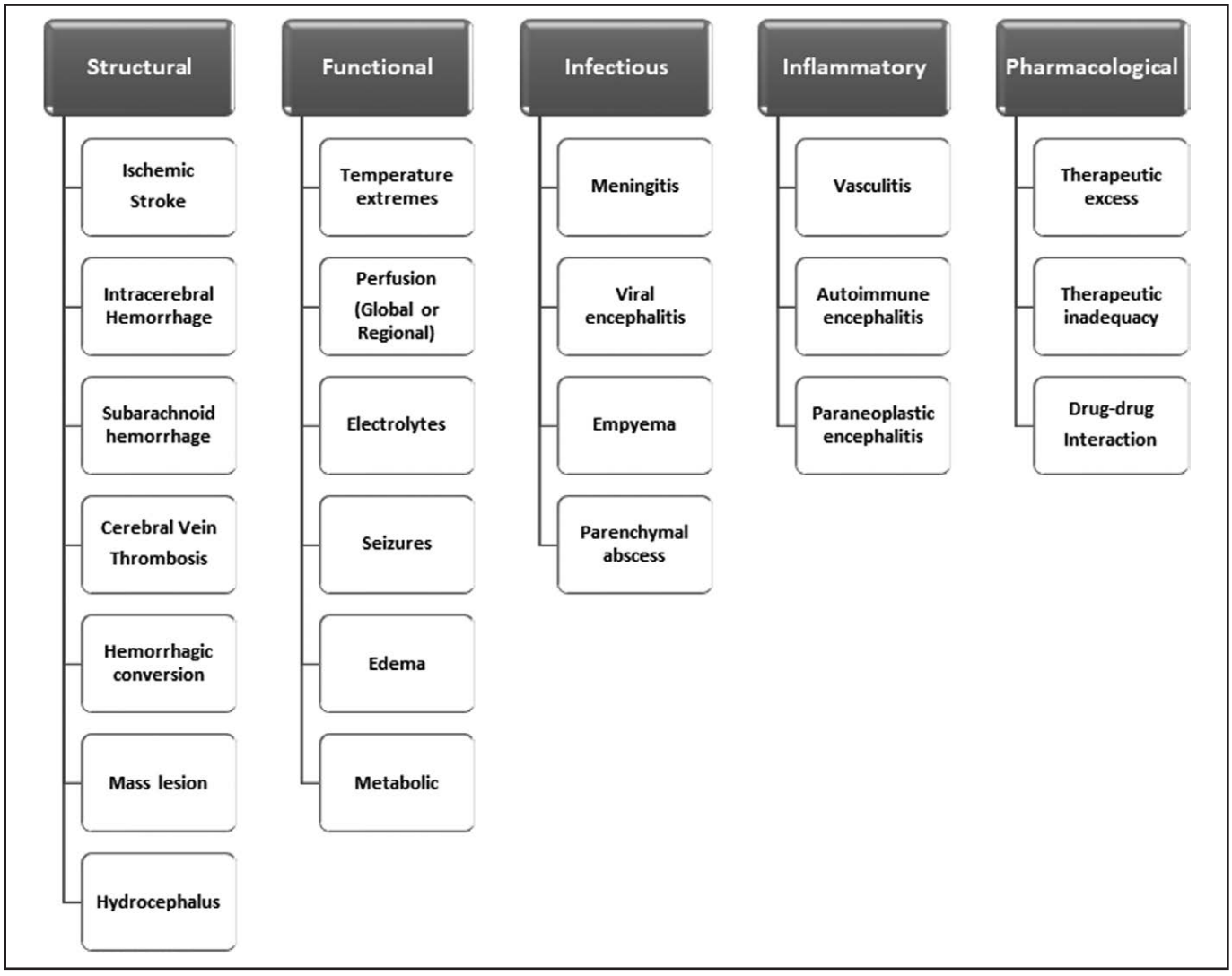

Figure 2. Specific framework etiologies. Individual diagnoses commonly responsible for disordered consciousness are presented underneath their framework etiology heading.

control to reduce rebleeding risk (15). Vessel disruption that accompanies ICH and SAH threatens distal cerebral parenchyma due to loss of oxygenated flow, as well as parenchymal compression from extravasated blood. Activation of complex immune and inflammatory cascades causes secondary brain injury (16). Complications following aSAH include intraventricular hemorrhage extension, obstructive hydrocephalus, seizures, vasospasm, and delayed neurological deficits (17). "Hemorrhagic stroke conversion" may present similarly and benefits from similar diagnostic and therapeutic pursuits (18). Cerebral venous thrombosis more commonly occurs with dehydration or a prothrombotic state, presents with DoC, seizures, intracranial hypertension, or cerebral edema and requires a high index of clinical suspicion to pursue venous flow focused imaging (19).

"Space occupying entities" are most commonly tumors but may also arise from acute hemorrhage volume, abscess, or hydrocephalus (20). Mass lesions principally compromise parenchymal viability by intrinsic, extrinsic, or vascular compression. "Hydrocephalus" is characterized as communicating or noncommunicating as well as congenital or acquired. Acquired etiologies include meningitis, tumor, or as a complication of SAH or intracranial hypertension (21). Rapidly developing hydrocephalus is an emergency.

Functional Etiologies. Functional DoC causes include extremes of temperature, abnormal perfusion, electrolyte derangements, seizures, intracranial hypertension, and metabolic derangements (Fig. 2). "Extremes of temperature" are typically encountered in a seasonally specific or geographically driven fashion. "Hyperthermia" may lead to hypovolemia, acidosis, hypernatremia, and worsened neuronal injury due to metabolic acceleration, O_2 radical generation, increased blood-brain-barrier (BBB) permeability, increased calcium-dependent phosphorylation, DNA fragmentation, apoptosis, and surface adhesion molecule expression (22). Extreme hypothermia may sufficiently decrease cerebral metabolism to induce DoC and must be resolved prior to a brain death/death by neurologic criteria (BD/DNC) assessment (23). Compared to aggressive avoidance of hyperthermia, controlled hypothermia has not demonstrated reproducible clinical benefit but remains within care guidelines for the post-cardiac arrest patient with coma (24). Putative hypothermia benefit mechanisms include decreased O_2 demand, excitotoxicity, edema, apoptosis, calcium influx, and beneficial inflammo- and immuno-modulation (25).

"Abnormal perfusion," both macrovascular and microvascular, merits correction to preserve cerebral O_2 delivery (Do_2) and utilization. Cerebral blood flow (CBF; normal = ~ 50 mL/100 g of tissue/min) is related to the cerebral perfusion pressure (CPP), which is the difference between mean arterial pressure and intracranial pressure (ICP). The normal brain uses 20% of delivered O_2 (26). Importantly, metabolic acidosis may impede RBC deformation through capillary beds, impeding O_2 delivery (27). Pressures (intra-thoracic and intra-abdominal) that raise central venous pressure (CVP) can impede cerebral venous drainage due to the absence of valves between the brain and right atrium. Decreasing such pressures improves CBF by increasing the CPP to CVP gradient. While augmented RBC mass may increase the arteriolar O_2 content, undesirable increases in viscosity may not improve cerebral Do_2 (28).

"Electrolyte derangements" influence consciousness principally by their impact on transmembrane voltage potential and chemo-mechanical coupling (29). Chief abnormalities include hypernatremia and hyponatremia, hypermagnesemia, and hypercalcemia. Exploring pathways that generate these derangements is beyond the scope of this review. Nonetheless, note is made of obtundation due to hypermagnesemia during attempted tocolysis and hypercalcemia from any cause (30). Acute hypernatremia generally reflects a water deficit rather than sodium excess and may trigger DoC through reduced perfusion. Excessively rapid hypernatremia correction may induce cerebral edema and DoC. Acute hyponatremia (< 125 mEq/L) is associated with DoC and seizure threshold reduction (31).

Prolonged "seizure" activity, both convulsive and nonconvulsive status epilepticus (NCSE), injures neurons, degrades outcomes, and increases long-term mortality (32, 33). Occult nonconvulsive seizures (NCSz) occur with an increased frequency in patients with sepsis in the absence of known risk factors (34). Seizure activity may stem from infection, injury, perfusion abnormalities, space occupying lesions, and increased ICP.

"Intracranial hypertension" disorders consciousness by: 1) decreased perfusion and 2) cerebral parenchymal compression against fixed structures. Regardless of cause, unmitigated elevated ICP leads

to cerebral herniation and DoC with abnormal neurologic and hemodynamic profiles (e.g., refractory hypertension) (35). Herniation syndromes include subfalcine, typically manifesting as DoC alone; transtentorial with unilateral or bilateral unreactive pupillary dilation; and central, which can include a progression from posturing to no movement, irregular breathing followed by apnea, and irregular followed by unreactive midposition or dilated pupils. Compression impedes cerebrospinal fluid (CSF) flow leading to hydrocephalus and stretching (Duret hemorrhages) or impingement of blood vessels (e.g., posterior cerebral artery infarcts). These insults further increase ICP, decrease CPP, decrease O_2 delivery, and worsen ischemia and edema. Rostral brainstem displacement and herniation through the foramen magnum results in BD/DNC (23).

The tight coupling of CBF over a broad range of CPPs (50–150 mm Hg) is termed "cerebral autoregulation." Ischemia occurs when CPP falls below the lower threshold; edema ensues with breach of the upper threshold. When there is discordance between CBF and metabolic demand, cellular and neuronal dysfunction ensues. Clinically expressed as DoC, this condition is termed hypoxic-ischemic brain injury. Normal CBF restoration may trigger reperfusion injury characterized by neuron damage from toxic oxygen metabolites, disordered calcium metabolism, deranged intracellular signaling, neuromediator elaboration, glial activation, neutrophil trafficking, as well as autophagy and accelerated apoptosis (36). Recently, the notion of PANoptosis—pyroptosis, apoptosis, and necroptosis—has emerged as a unifying concept underpinning regulated cell death that involves inflammatory pathway activation and signaling (37).

Infectious Etiologies. Infectious etiologies include meningitis, encephalitides (the majority of which are viral), peridural abscesses, and intra-parenchymal abscess (Fig. 2). "Meningitis," whether bacterial, viral, fungal, or parasitic results in meningeal inflammation and launches a host response that involves neutrophil recruitment and cytokine elaboration (38). Epidemiology is linked to geography with decreasing rates noted in Western nations (38). DoC, fever, and sometimes seizures result; survivors are at risk of permanent brain damage. Fungal infection occurs more commonly in immune incompetent individuals. Parasitic etiologies are usually related to geographic abundance of environmental parasites; specific note of amebic meningitis following freshwater recreation is made due to its' high lethality.

"Infectious encephalitides" are characterized by inflammation of the cerebral parenchyma and principally occur from viral infection, leading to an array of symptoms, some of which may be mild and therefore underreported (39). Most U.S. cases are related to herpes simplex virus 1, arboviruses, or enteroviruses. Common U.S. mosquito-transmitted encephalitis viruses include equine, LaCrosse, St. Louis, and West Nile encephalitis. Also, mosquito-transmitted, Japanese encephalitis is common outside of the United States. Infectious encephalitides may cause NCSE manifesting as DoC (40).

Inflammatory Etiologies. Inflammation is characterized by vasculitis (i.e., vessels) and encephalitis (i.e., parenchyma) (Fig. 2). Primary angiitis of the CNS is rare. Infection-related vasculitis is commonly related to angiotropic organisms including varicella zoster virus, syphilis, and *Aspergillus* (41). Cerebral vasculitis has been reported with acute SARS-CoV-2 infection and autoimmune diseases (42, 43).

"Autoimmune or antibody-mediated encephalitis" is more prevalent than infectious encephalitis and is associated with inflammation and demyelination (44). Classification may occur by affected anatomic areas (e.g., limbic), serologic targets (e.g., intracellular or surface antigens), or etiology (e.g., post-infectious, paraneoplastic, idiopathic) (45). For example, a relatively recently identified anti–N-methyl-D-aspartate receptor encephalitis is associated with an ovarian teratoma and prominent behavioral symptoms; a variety of other paraneoplastic encephalitidies have been previously identified including but not limited to encephalomyelitis, limbic or brainstem encephalitis, and Lambert-Eaton myasthenic syndrome (46). Autoimmune encephalitis may also cause NCSE.

Metabolic Etiologies. DoC may be a presenting sign of acute endocrinopathies including those of the thyroid, adrenal, pancreas, and pituitary as well as organ failures including critical illness-related corticoadrenal insufficiency, adrenal hemorrhage, acute kidney injury (AKI), or acute hepatic failure (47–49) (Fig. 2). Hepatic encephalopathy generates false neurotransmitters involving the gamma-aminobutyric acid system, inflammatory cytokines, excitotoxicity from urea permeable

glial cells, astrocytosis, and cerebral edema; a spectrum of neuronal changes occurs in those with cirrhosis (50). Uremia may lead to DoC (e.g., uremic encephalopathy) through solute retention, hormone metabolism shifts, water and electrolyte derangements, and altered vascular permeability and reactivity (51). Organ cross-talk, especially within the hepato-renal systems driven by organic anions, may exacerbate DoC related to metabolic byproduct clearance failure (52). Disorders of glycemic control with hyperosmolar states may also create a DoC and are often related to infection.

Pharmacologic Etiologies. Medication-related causes include therapeutic excess, drug-drug interactions (DDIs), therapeutic inadequacy, intoxication, or withdrawal syndromes (Fig. 2). "Therapeutic excess" occurs with inappropriately large dosage, inappropriately short dosing interval, reduced metabolism or clearance, or iatrogenic error (53, 54). Common medications related to DoC include opioids, sedative-hypnotics, and antipsychotics (55). Given the genetic polymorphisms that impact drug metabolism, up to half of all inappropriate medication responses may reflect inter-individual variations. Conditions such as obesity, acute organ injury, or chronic organ failure may reduce the metabolism of appropriately dosed agents and lead to agent accumulation; opioids present a particular risk that is magnified when delivered by continuous infusion (56). The clinical pharmacist helps avoid medication-induced organ injury that increases the risk of therapeutic excess from reduced clearance (57). Approaches that minimize analgesics and sedatives, such as the ICU Liberation bundle, help reduce therapeutic excess (58). Cytotoxic medications such as those used after organ transplantation may cause the Posterior Reversible Encephalopathy Syndrome, that is, also associated with infection, organ injury, AKI, and hypertensive or obstetric emergencies (59).

Inapparent genetic variation in enzyme function may be uncovered by coadministration of an agent that further reduces the enzyme-based metabolism of another agent (60). Such DDIs warrant surveillance and benefit from clinical pharmacist participation within the critical care team to identify unique pharmacokinetics and pharmacodynamics. As the number of therapeutic agents expand, the risk of DDIs intensifies and are likely underrecognized. Machine learning techniques may help identify DDIs (61). "Therapeutic inadequacy" may occur with compliance failure or failure to continue or resume therapeutic agents following hospital admission—a particular risk with medical tourism—but may be systematically addressed using medication reconciliation (62, 63).

Acute DoCs may be related to acute "intoxications" or "withdrawal syndromes" (64). Alcohol, heroin, cocaine, fentanyl, phencyclidine, lysergic acid diethylamide, benzodiazepines, and veterinary agents such as xylazine complicate acute DoC assessment, especially in those rescued outside of the acute care facility. Opioids laced with xylazine lead to obtundation or respiratory arrest that does not respond to naloxone (65). Chronic nonfatal opioid overdosing is associated with persistent neurologic, cognitive, and behavioral consequences that may be mistaken for an acute DoC (66).

Evaluation Techniques

History and a neurologically focused examination provide the foundations for evaluation and are supplemented by laboratory profiling; relevant data including a skin examination from the complete physical examination may complement one that is neurologically focused. Physical examination, including mental status, cranial nerves, and peripheral motor and sensory examinations, should search for localizing signs as well as asymmetry. The examination should incorporate a Glasgow Coma Scale (GCS) to complement the NIHSS, especially in awake but aphasic patients. The Full Outline of UnResponsiveness score may offer benefit in identifying "locked-in" syndrome as well as stages of cerebral herniation (67). Standard scoring metrics help maintain information transfer fidelity and provide a baseline against which to assess subsequent evaluations. DoC evaluation incorporates neuroimaging modalities and/or neuromonitoring tools to establish a diagnosis (68). Commonly utilized modalities and tools are presented in **Table 1**, along with detected abnormalities.

Modalities and tools may be grouped into those that require transport or are bedside-capable. Neurodiagnostic undertakings generally occur in the Radiology suite and include CT scanning with/without contrast, CT angiography (CTA), CT perfusion (CTP), MRI with/without diffusion weighting or CBF determination, MR angiography, and fMRI (69). Bedside assessments including CT or MRI scanning, lumbar puncture (LP), somatosensory evoked

TABLE 1.
Neuroimaging and Neuromonitoring Modalities

Neuroimaging Modality	Sequence	Etiology	Detects
CT scan	Noncontrast	Structural	Acute hemorrhage, ventriculomegaly
			Edema with mass effect
			Encephalomalacia and asymmetry
	Contrast	Structural	Tumor, Abscess
	Angiogram	Structural	Aneurysm, vascular malformation, dissection, active bleeding or extravasation (spot sign)
	Perfusion	Functional	Delayed (penumbra) or decreased CBF (ischemia)
MRI	T1	Structural	Asymmetry, ventriculomegaly
	T2	Structural	Asymmetry, ventriculomegaly, edema
	FLuid-Attenuated Inversion Recovery	Structural	Edema
	Diffusion-weighted imaging/apparent diffusion coefficient	Structural and functional	Ischemia, abscess
	Gradient recalled echo or susceptibility weighted imaging	Structural	Hemorrhage, hematoma, cavernoma, abscess rim
	Angiography	Structural	Vascular abnormalities
	Perfusion	Functional	Delayed (penumbra) or decreased CBF
	Functional	Functional	Eloquent cortex abnormality (e.g., language, motor, sensory function)
Cerebral angiography		Structural	Vascular abnormalities
Neuromonitoring Modality	**Options**	**Etiology**	**Detects**
Electroencephalography	Conventional montage	Functional	Seizures, asymmetry (structural lesion); slowing (metabolic disarray)
	Limited (hairline) montage	Functional	Seizures, asymmetry, slowing
	Processed	Pharmacological	Depth of sedation, medication effect
Cerebral tissue oximetry	Invasive: partial pressure of brain tissue oxygenation	Functional	CBF and tissue oxygen saturation
	Noninvasive: near-infrared spectroscopy		

(*Continued*)

TABLE 1. (*Continued*)
Neuroimaging and Neuromonitoring Modalities

Neuroimaging Modality	Sequence	Etiology	Detects
ICP	Fluid-coupled-external ventricular drain	Structural	Intracranial hypertension (therapeutic indication: drain cerebrospinal fluid)
		Functional	
	Fiberoptic intraparenchymal	Functional	Intracranial hypertension
Automated pupillometry	Infrared	Structural (functional and pharmacological artifact)	Asymmetry may indicate intracranial hypertension (i.e., CN III palsy due to uncal herniation/brainstem torsion) and brainstem dysfunction (CN II and III)
Somatosensory evoked potential monitoring		Structural	Integrity of nerves, posterior columns through spinal cord and brain stem and parietal cortex (e.g., loss of cortical waveforms may indicate severe global hypoxic ischemic brain injury)
		Functional	
Ocular ultrasound	Optic nerve sheathe diameter	Structural	Papilledema, intracranial hypertension
Transcranial Doppler		Structural	CBF (limited to proximal vessels), autoregulation, cerebral emboli
		Functional	

CBF = cerebral blood flow, CN = cranial nerve.

potential monitoring, transcranial Doppler scanning, electroencephalography, ocular ultrasound, and infrared pupillometry (70–76). Other monitors are more aligned with guiding therapy.

Acute Evaluation Approaches

An integrated evaluation approach may be grouped into elements that are common to nearly all patients compared to those more individually applied based on the suspected underlying condition. This approach assumes that the DoC is not an anticipated evolution of an identified condition and is designed to streamline diagnosis by the general intensivist prior to involving a neurologic specialist.

Common Elements. History, vital signs, a neurologically focused examination, and laboratory profile with either a venous or arterial blood gas is ideally accompanied by a portable chest radiograph and a noncontrast brain CT scan. A point-of-care ultrasound (POCUS) or other objective device should evaluate intravascular volume as well as cardiac performance, especially in those with reduced blood pressure (**Fig. 3**).

Structural Abnormality. While the examination may suggest a structural abnormality, a noncontrast CT scan is the most rapid neurodiagnostic modality and will help direct subsequent evaluations (**Fig. 4**). When stroke is considered, a CTA and CTP is also useful to help define etiology, provide precise localization, and evaluate potential interventions. Unless there is ICH, an abnormal noncontrast brain CT may prompt a specialty MRI/A. Depending on findings, neurological expertise (on-site or virtual) helps guide subsequent imaging and therapy.

Specialty MRI includes diffusion-weighted imaging (DWI)/apparent diffusion coefficient (ADC) imaging, gradient recalled echo (GRE) imaging, and susceptibility weighted imaging (SWI). DW/ADC imaging relies on the movement and impedance of water molecules relative to tissue cellularity and intact cell membranes, while ADC mapping reflects the magnitude of water movement through tissues. This technique is indispensable in identifying inapparent cerebral infarction (77). Both GRE and DWI detect blood components including hemosiderin. GRE relies on T2 weighted signals acquired during relaxation using a multigradient echo approach to detect small hemorrhagic lesions (78). SWI is sensitive to elements that distort the applied magnetic field such as iron and

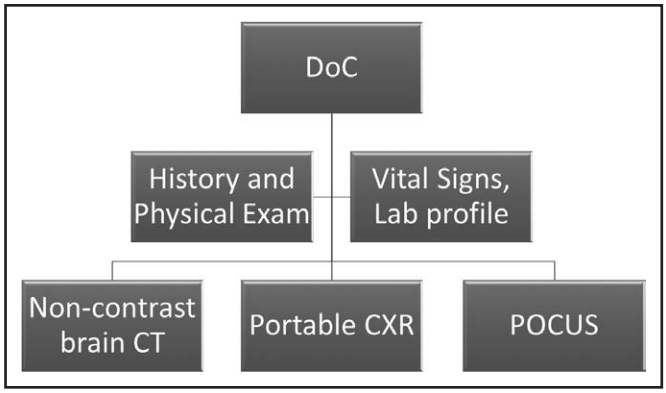

Figure 3. Common elements of a disorder of consciousness (DoC) evaluation approach. Common elements that launch an investigation into a DoC are presented in a tiered fashion. CXR = chest radiograph, POCUS = point of care ultrasound to assess fluid status and cardiac performance; alternate methods may be similarly utilized.

calcium, that highlight microscopic hemorrhage (79). SWI may detect abnormalities not visible on standard T2-weighed images including an abscess peripheral rim, thrombosis-related loss of arterial flow, stroke-related venous asymmetry, and unique aspects of mass lesions (79).

Functional Abnormality. Functional abnormalities should be repaired and the DoC reassessed (Fig. 4). If the DoC is from hypercarbia, noninvasive or invasive mechanical ventilation should provide rescue. Correction of hyponatremia or hypernatremia is common, as is the correction of stage 3 AKI using either continuous renal replacement therapy (CRRT) or acute intermittent hemodialysis (IHD) depending on hemodynamic profile. If the DoC fails to resolve, then a standard electroencephalogram is appropriate to evaluate for NCSE, especially in those with sepsis. A 2-hour electroencephalogram appears sufficient to detect most epileptiform activity, but 24-hour or continuous assessment seems prudent in those with DoC or known seizures (80). Standard electroencephalogram as opposed to a qualitative, spectral analysis driven electroencephalogram remains the standard, although limited montage electroencephalography may effectively detect seizures (81).

Infection/Inflammatory. Since there is overlap in infectious and inflammatory etiology evaluation, they are addressed together (**Fig. 5**). In addition to a routine laboratory profile, obtaining blood, sputum, and urine cultures is ideal. An examination of wounds, surgical sites, and device access points is ideal given the prevalence of device-associated infection in hospitalized patients. Obvious sites of infection require source control and adequate empiric antibiotic therapy (82). A LP is indicated in patients with DoC when there is an inapparent source of infection but signs of infection are present, and there is immune incompetence, recent CNS instrumentation, or meningeal irritation; obesity remains the major barrier to successful LP (83). LP remain contraindicated in

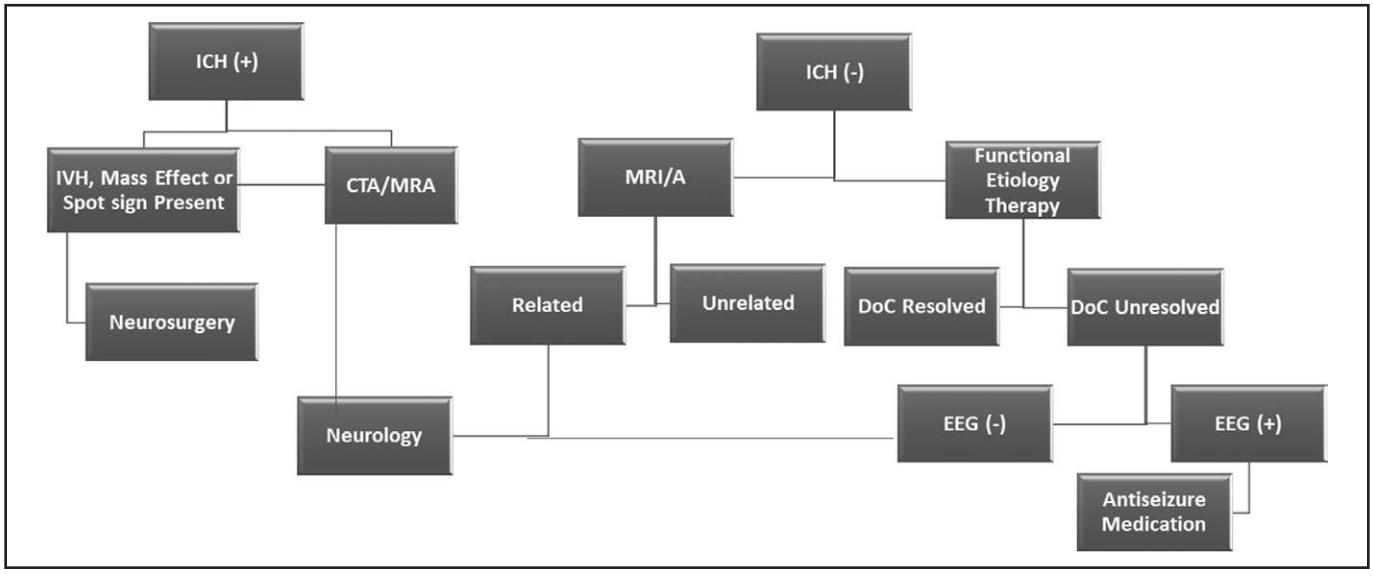

Figure 4. Subsequent evaluations (structural/functional). A step-wise approach to investigating structural and functional causes of an acute adult disorder of consciousness (DoC) are presented. (–) = absent, (+) = present, CTA = CT angiogram, EEG = electroencephalography, ICH = intracranial hemorrhage, IVH = intraventricular hemorrhage, MRA = MR angiogram, MRI/A = MRI with or without MR angiography.

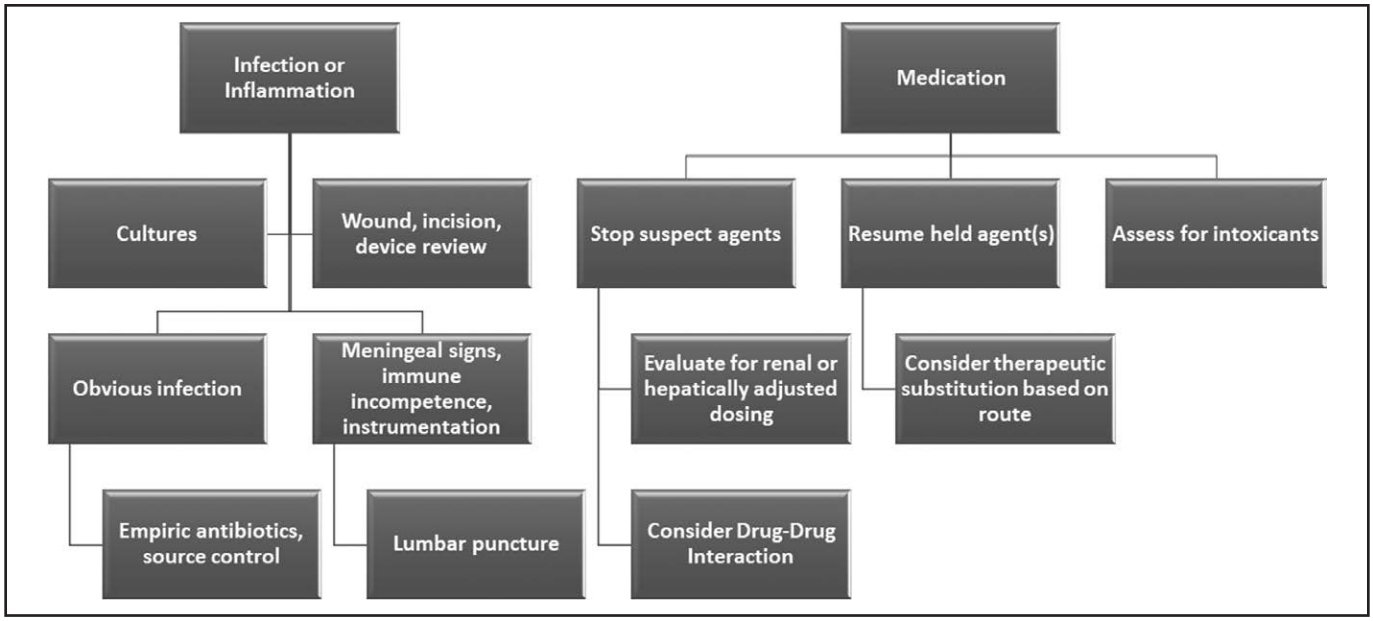

Figure 5. Subsequent evaluations (infectious/inflammatory or pharmacologic). A tiered approach to infectious, inflammatory, or pharmacologic causes of an acute unanticipated disorder of consciousness is presented.

those with space occupying lesions (herniation risk) and in those with cervical spinal stenosis with myelopathy (spinal coning). Besides routine CSF assessments, fluid should be sent for cytology and autoantibodies. A recent review explores the range of testable autoantibodies as well as indices that suggest a specific disorder (84).

Pharmacologic Abnormalities. Likely causative medications should be stopped, and rescue agents (if available) administered; opioid re-release from adipose tissue should be considered in those receiving opioid analgesia (Fig. 5). Some centers use processed electroencephalography devices to help guide sedation administration to avoid over- and under-sedation, especially with concomitant neuromuscular blockade (85). If the underlying cause is driven by DDI, both agents should be stopped, and a decision made as to whether either should be resumed or replaced. DDI are more likely with agents started in the acute care facility than with those chronically administered. Changes in organ function may drive therapeutic excess and should be met with agent cessation to allow clearance, with subsequent dosing adjusted for organ function. Medications held on admission should be resumed if their absence is potentially causative. A search for intoxicants is appropriate including a urine drug screen on initial presentation. Toxidromes may require ICU management and have been reviewed elsewhere (86).

Rescue Therapies

Rescue therapy for a DoC will depend on the underlying etiology. However, there are common approaches that enhance patient safety during diagnosis and initial therapy. Some rescue therapies may prompt intra- or more commonly inter-facility transfer to align patient needs with therapeutics (87).

Common Safety Approaches. Since airway patency, ventilation, and oxygenation adequacy are intertwined with hemodynamics, these two systems deserve rapid evaluation and management. Airway control is beneficial for patients with GCS less than or equal to 8, uncertain airway protection, and acute respiratory distress or failure in the context of an acute DoC. Invasive mechanical ventilator settings should hew to a lung protective strategy rather than a specific ventilator mode and target a normal P_{CO_2} (35–40 torr) and a safe P_{O_2} (> 60 torr) while avoiding hyperoxia or hypercarbia (cerebral vasodilation and increased ICP) (88). Hemodynamic support may require plasma volume expansion (ideally guided by POCUS or other objective data) or pressor support to correct hypotension with the specific therapeutic agent guided by suspected etiology. Blood gas analysis is imperative, and lactate may help guide perfusion assessment. Most analyzers also provide an electrolyte panel that reports key ions as well as hemoglobin concentration. Avoiding hyperthermia is essential to preserve vulnerable tissues.

Structural Etiologies With Mass Effect or Increased ICP. ICH that causes mass effect generally elevates ICP. ICP reduction measures include neutral neck alignment, 30 degree head of bed elevation, adequate analgesia and sedation, and administration of either hypertonic saline (HTS) or mannitol to reduce volume (89). In patients with impending herniation, an acute decrease in P_{CO_2} (~ 30–35 torr) to drive cerebral vasoconstriction may provide time for other therapies to work (HTS), or be initiated (external ventricular drain [EVD] insertion to drain CSF, or transfer for surgical evacuation) (90, 91). Extreme hypocapnia (P_{CO_2} < 30 torr) should be avoided as cerebral hypoperfusion may occur in vulnerable regions with excessive vasoconstriction (92). Certain goals are common including maintaining ICP less than 20–22 mm Hg, CPP greater than 60 mm Hg, and cerebral tissue oxygen saturation greater than 75%.

All ICH should trigger an assessment and correction of abnormal coagulation as part of a guideline-driven approach (93). Given the prevalence of therapeutic anticoagulation for a variety of disorders, reversal of warfarin or a direct oral anticoagulant should be anticipated (94). Compared to fresh frozen plasma, four-factor prothrombin complex offers an advantage as it reverses warfarin anticoagulation with less volume. Aspirin reversal with platelet transfusion may be harmful and is indicated only for emergency neurosurgery (93). Thromboelastography may guide coagulation component selection ahead of laboratory-based coagulation tests (95). Rapid blood pressure control with little variability to a target of 140 mm Hg may prevent hematoma expansion and improve outcome after ICH (96).

Structural Etiology Without Mass Effect or Increased ICP. The initial management of structural abnormalities devoid of mass effect broadly addresses restoration of blood flow, correction of coagulopathy, and edema reduction. Certain patients with AIS will benefit from lytic therapy or thrombectomy—a decision best established in conjunction with a neurologist after history and CT scan review (97). This approach is underpinned by widespread tele-stroke programs focused on rapid assessment and decision-making (98). If indicated, therapeutic anticoagulation with unfractionated IV heparin provides graded control of anticoagulation, has a weight-based approach that improves safety, and is readily reversed using protamine. Mass lesions without increased ICP typically require therapy due to cerebral edema. Glucocorticoids stabilize an underdeveloped BBB to decrease edema in neovascularized lesions such as tumors and abscesses but are ineffective for cytotoxic edema from ischemia or hemorrhage (99).

Flow-Based Abnormalities. Hypoperfusion should be addressed using plasma volume expansion to correct hypovolemia and pressor(s) when plasma volume is appropriate. Crystalloid therapy should use normotonic solutions to avoid inducing hyponatremia and cerebral edema. With metabolic acidosis, pH buffering to vasodilate the pulmonary artery may benefit patients with pulmonary hypertension or increased ICP to unload the right ventricle and improve cerebral drainage. Dextrose-containing fluids are avoided except with hypoglycemia to avoid delivering substrate to areas with compromised cerebral perfusion. Diuresis to correct hypervolemia is appropriate as euvolemia is optimal even with SAH (100). Specific goals will vary depending on condition, and protocol-driven management may help reduce care variation and enhance quality and safety (58).

To support perfusion of an ischemic penumbra, hypertension is permissive in those with AIS (up to 180 mm Hg following thrombolysis) (96). Post-thrombolytic therapy patients should undergo repeat examination and CT scanning to evaluate for post-lysis and reperfusion hemorrhage. Urgent assessment of whether there is a large vessel occlusion and a need for interventional therapy should not be delayed while providing lysis.

Seizures. Rapid seizure termination should be initiated using a benzodiazepine (lorazepam or midazolam) while the patient is parenterally loaded with an antiseizure medication; first-line agents include levetiracetam or sodium valproate (not for women of childbearing potential) and less frequently, fosphenytoin (32). Electroencephalography assessment is ideal to confirm seizure termination despite convulsive activity cessation. NCSz should also be urgently terminated and continuously monitored to ensure that seizure recurrence is readily identified.

Electrolyte and Metabolite Management. Perhaps the most essential electrolyte to manage is sodium as hyponatremia supports cerebral edema and increased ICP, while hypernatremia supports cellular dehydration and sluggish flow. Hyponatremia diagnostic and therapeutic algorithms help guide accurate diagnosis

and therapy (31). Hypernatremia nearly uniformly reflects a water deficit that is formulaically estimable. Rarely does hypernatremia reflect sodium overload, but it may represent a therapeutic condition to address high ICP and is well tolerated up to 155 mEq/L in that setting; in specific circumstances and in conjunction with a neurologist or neurosurgeon, a sodium concentration up to 160 mEq/L may provide benefit for select patients. Sodium correction following prolonged hyper/hyponatremia. should not exceed 0.5 mEq/L/hr nor 10 mEq/L per day in either direction. Untoward sequelae include cerebral edema (rapid rehydration) or osmotic demyelination syndromes (i.e., central and extra-pontine myelinolysis; rapid hyponatremia correction). There remains controversy regarding demyelination syndrome etiology and permanence (101). All other electrolyte abnormalities may be addressed as for any other critically ill or injured patient with the exceptions of uremia and hyperammonemia.

Patients with acute DoC due to uremic encephalopathy should undergo either IHD or CRRT to achieve metabolic clearance and neurologic reevaluation (51, 102). Patients taking valproic acid, or those with acute hepatic failure, may manifest hyperammonemia and benefit from gastrointestinal tract catharsis (i.e., lactulose) and luminal antibacterial therapy (i.e., rifaximin) to reduce potentially culpable metabolites (103, 104). Failure of glycemic control (hyperglycemia) as well as glycemic maintenance (hypoglycemia) adversely impacts intracellular dynamics, established osmotic gradients, and worsens brain injury.

Infection Management. Standard approaches to extracranial infection management should be utilized. Intracranial infection regardless of microbe benefits from the selection of agent(s) with a high partition coefficient for CSF or cerebral parenchyma (105). Specific engagement of an infectious disease consultant, as well as a PharmD, is prudent. Abscesses may require operative drainage, and neurosurgical consultation is required as is a search for a primary source.

Inflammation Management. A mainstay of acute inflammation reduction is glucocorticoid therapy. Dexamethasone is commonly utilized and often induces hyperglycemia. IV as opposed to subcutaneous insulin may be required for those with anasarca or hypoperfusion due to uncertain insulin uptake (106). High-dose glucocorticoid therapy should be coupled with gastric mucosal protection. Other anti-inflammatory agents such as azathioprine do not alter glucose metabolism and are suitable for long-term management.

Pharmacologic Management. Besides adjusting medications that may lead to DoC, minimizing sedative and analgesic agents to permit frequent neurologic reassessment is optimal. Intermittent, compared to continuous, sedative and analgesic dosing may be helpful. A multimodal approach to analgesia that incorporates nonpharmacologic aids, nonopioid pharmacologic agents, and then opioid agents in a tiered structure reduces opioid exposure (107).

Approaches to Care

Patients with DoCs typically require complex care that may be delivered by an acute care facility's ICU team in conjunction with a neurologist and/or neurosurgeon for many patients. The ability to do so depends on the availability and capability of the clinical staff and specialty resources. Critical access facilities may routinely transfer patients with DoCs to more complex facilities due to resource limitations. Nonetheless, even well-resourced facilities may be unable to provide the intensity of care, or the specific procedural aspects of care (intracranial vascular stenting or thrombectomy) to address an acute DoC establishing the need for inter-facility transfer. When selecting a destination NCC facility, current standards may inform facility selection (108). It is important to note that not every patient with a DoC needs to be transferred to a center with a neuroICU and a NCC team. Common indications for inter-facility transfer include: 1) EVD insertion, 2) decompressive surgery, 3) neuro-interventional therapy, and 4) aSAH, intraventricular hemorrhage, or acute hydrocephalus management. A less common indication is peri-BD/DNC management with the potential for organ donation if the referring facility is not equipped to address that management; other transfer opportunities will reflect local dynamics. Intra-facility transfer from a general ICU to a neuroICU (when one exists) also occurs to garner specialty care, and in particular, specialty nursing expertise.

Emerging Discovery Science

Recognizing that the care of patients with DoCs lacked a clear evidence base upon which to link interventions with desirable outcomes, the Neurocritical Care Society articulated an overarching goal to design and

explore DoC relevant ICU therapies (109, 110). This approach, launched in 2019, is termed the "Curing Coma Campaign" and leverages a multiprofessional approach to DoC. The collaboration classified consciousness endotypes to more precisely align investigations and therapies (111). Other inquiries address mechanisms underpinning DoC and are supported by World Coma Day advocacy and modeled after World Sepsis Day and others that support global education (112–114).

CONCLUSIONS

This review provides a structured approach to evaluating and providing initial therapy for adults with an unanticipated acute DoC by a general intensivist. Accordingly, diagnostic investigations may be aligned with commonly identified etiologies to guide diagnosis and acute therapy spanning structural, functional, infectious, inflammatory, and pharmacologic drivers of DoC. Indications for specialist consultation as well as patient transfer are framed within the context of capabilities and resources. While many patients may be well cared for at their initial facility using a team-based approach, certain conditions benefit from specialty ICU and specialist NCC. Unique approaches refine the boundaries of acute DoCs and enable outcome enhancing intervention discovery.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Dr. Chang received funding from the American Board of Internal Medicine, American Board of Psychology and Neurology Neurocritical Care, and Society of Critical Care Medicine (SCCM) for work as Associate Editor of Critical Care Medicine (2021–2023) and a past-President of the Neurocritical Care Society; she disclosed that she is employed by Duke University; and she serves as a Council member and Treasurer for SCCM and is a member of the Board of Rehabilitation Hospital of the Pacific. Dr. Provencio's institution received funding from SCCM Weil Research Grant; he received funding from Minnetronix; he disclosed that he is an SCCM Council Member and on the Scientific Advisory Board for the Neurocritical Care Society Curing Coma Campaign; and he is a member of the steering committee of the Curing Coma Campaign. Dr. Pascual received funding from multiple medicolegal firms for expert testimony; and he is the Secretary of the SCCM. Dr. Livesay received funding from Stroke Challenges/Lombardi Hill LLC; she disclosed that she is the President of Neurocritical Care Society. Dr. Kaplan received funding from SCCM as President (2020–2021). Dr. Olson is a co-chair of the Neurocritical Care Society's Neurocritical Care Research Network Subcommittee. Dr. Heavner has disclosed that she does not have any potential conflicts of interest.

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REFERENCES

1. Slooter AJC, Otte WM, Devlin JW, et al: Updated nomenclature of delirium and acute encephalopathy: Statement of ten societies. *Intensive Care Med* 2020; 46:1020–1022
2. Edlow BL, Claassen J, Schiff ND, et al: Recovery from disorders of consciousness: Mechanisms, prognosis and emerging therapies. *Nat Rev Neurol* 2021; 17:135–156
3. Provencio JJ, Hemphill JC, Claassen J, et al; Neurocritical Care Society Curing Coma Campaign: The curing coma campaign: Framing initial scientific challenges—proceedings of the first curing coma campaign scientific advisory council meeting. *Neurocrit Care* 2020; 33:1–12
4. Thibaut A, Schiff N, Giacino J, et al: Therapeutic interventions in patients with prolonged disorders of consciousness. *Lancet Neurol* 2019; 18:600–614
5. Boehme AK, Doyle K, Thakur KT, et al: Disorders of consciousness in hospitalized patients with COVID-19: The role of the systemic inflammatory response syndrome. *Neurocrit Care* 2022; 36:89–96
6. Dell'Italia J, Johnson MA, Vespa PM, et al: Network analysis in disorders of consciousness: Four problems and one proposed solution (exponential random graph models). *Front Neurol* 2018; 9:439
7. Zhuang W, Wang J, Chu C, et al: Disrupted control architecture of brain network in disorder of consciousness. *IEEE Trans Neural Syst Rehabil Eng* 2022; 30:400–409
8. Lutkenhoff ES, Chiang J, Tshibanda L, et al: Thalamic and extrathalamic mechanisms of consciousness after severe brain injury. *Ann Neurol* 2015; 78:68–76
9. Danielson NB, Guo JN, Blumenfeld H: The default mode network and altered consciousness in epilepsy. *Behav Neurol* 2011; 24:55–65
10. Scalea TM, Rubinson L, Tran Q, et al: Critical care resuscitation unit: An innovative solution to expedite transfer of patients

with time-sensitive critical illness. *J Am Coll Surg* 2016; 222:614–621

11. Bhurwani MM, Boutelier T, Davis A, et al: Identification of infarct core and ischemic penumbra using computed tomography perfusion and deep learning. *J Med Imaging* 2023; 10:014001
12. Ganesh A, van de Wijdeven RM, Ospel JM, et al; PRESTO Investigators: Evaluating the diagnostic performance of prehospital stroke scales across the range of deficit severity: Analysis of the prehospital triage of patients with suspected stroke study. *Stroke* 2022; 53:3605–3615
13. Mowla A, Khatibi K, Razavi SM, et al: Rescue intracranial balloon angioplasty with or without stent placement in acute strokes with intracranial atherosclerotic disease. *World Neurosurg* 2023 Jan 18. [online ahead of print]
14. Rasras S, Safari H, Zeinali M, et al: Decompressive hemicraniectomy without clot evacuation in supratentorial deep-seated intracerebral hemorrhage. *Clin Neurol Neurosurg* 2018; 174:1–6
15. Larsen CC, Astrup J: Rebleeding after aneurysmal subarachnoid hemorrhage: A literature review. *World Neurosurg* 2013; 79:307–312
16. Tschoe C, Bushnell CD, Duncan PW, et al: Neuroinflammation after intracerebral hemorrhage and potential therapeutic targets. *J Stroke* 2020; 22:29–46
17. Bederson JB, Connolly ES Jr, Batjer HH, et al; American Heart Association: Guidelines for the management of aneurysmal subarachnoid hemorrhage: A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 2009; 40:994–1025
18. Cordonnier C, Demchuk A, Ziai W, et al: Intracerebral haemorrhage: Current approaches to acute management. *Lancet* 2018; 392:1257–1268
19. Field TS, Hill MD: Cerebral vein thrombosis: We should ask the right questions to get better answers. *Stroke* 2019; 50:1598–1604
20. Ostrom QT, Price M, Neff C, et al: CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2015-2019. *Neuro Oncol* 2022; 24:v1–v95
21. Williams MA, Nagel SJ, Luciano MG, et al: The clinical spectrum of hydrocephalus in adults: Report of the first 517 patients of the adult hydrocephalus clinical research network registry. *J Neurosurg* 2019; 132:1773–1784
22. Walter EJ, Carraretto M: The neurological and cognitive consequences of hyperthermia. *Crit Care* 2016; 20:199
23. Greer DM, Shemie SD, Lewis A, et al: Determination of brain death/death by neurologic criteria: The world brain death project. *JAMA* 2020; 324:1078–1097
24. Wyckoff MH, Morley GR, et al: International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations: Summary from the Basic Life Support; Advanced Life Support; Pediatric Life Support; Neonatal Life Support; Education, Implementation, and Teams; and First Aid Task Forces. *Resuscitation* 2022; 181:208–288
25. Yenari MA, Han HS: Neuroprotective mechanisms of hypothermia in brain ischaemia. *Nat Rev Neurosci* 2012; 13:267–278
26. Cipolla MJ: Chapter 5: Control of cerebral blood flow. In: *The Cerebral Circulation*. San Rafael, CA, Morgan and Claypool Life Sciences, 2009
27. Brun JF, Varlet-Marie E, Myzia J, et al: Metabolic influences modulating erythrocyte deformability and eryptosis. *Metabolites* 2022; 12:4
28. Zimmerman R, Tsai AG, Vázquez BY, et al: Post-transfusion increase of hematocrit per se does not improve circulatory oxygen delivery due to increased blood viscosity. *Anesth Analg* 2017; 124:1547
29. Kaplan LJ, Kellum JA: Fluids, pH, ions, and electrolytes. *Curr Op Crit Care* 2010; 16:323–331
30. Maier JD, Levine SN: Hypercalcemia in the intensive care unit: A review of pathophysiology, diagnosis, and modern therapy. *J Intens Care Med* 2015; 30:235–252
31. Adrogué HJ, Tucker BM, Madias NE: Diagnosis and management of hyponatremia: A review. *JAMA* 2022; 328:280–291
32. Smith PE: Initial management of seizure in adults. *N Engl J Med* 2021; 385:251–263
33. Sculier C, Gaínza-Lein M, Sanchez Fernandez I, et al: Long-term outcomes of status epilepticus: A critical assessment. *Epilepsia* 2018; 59:155–169
34. Le Roux P, Menon DK, Citerio G, et al: The international multidisciplinary consensus conference on multimodality monitoring in neurocritical care: Evidentiary tables. *Neurocrit Care* 2014; 21:S297–S361
35. Wijdicks EF: The cushing reflex before cushing. *Neurocrit Care* 2022; 23:1–5
36. Jurcau A, Simion A: Neuroinflammation in cerebral ischemia and ischemia/reperfusion injuries: From pathophysiology to therapeutic strategies. *Internat J Molec Sci* 2022; 23:14
37. Yan WT, Yang YD, Hu XM, et al: Do pyroptosis, apoptosis, and necroptosis (PANoptosis) exist in cerebral ischemia? Evidence from cell and rodent studies. *Neural Regen Res* 2022; 17:1761–1768
38. Poplin V, Boulware DR, Bahr NC: Methods for rapid diagnosis of meningitis etiology in adults. *Biomarkers Med* 2020; 14:459–479
39. Centers for Disease Control and Prevention: Meningitis and Encephalitis Fact Sheet. 2023. Available at: https://www.ninds.nih.gov/meningitis-and-encephalitis-fact-sheet. Accessed January 26, 2023
40. Sonneville R, Mariotte E, Neuville M, et al: Early-onset status epilepticus in patients with acute encephalitis. *Medicine (Baltimore)* 2016; 95:e4092–e4097
41. Lampros A, Caumes E, Psimaras D, et al: Infection associated cerebral vasculitis. *Rev Med Interne* 2020; 42:258–268
42. Lersy F, Kremer S: Meningeal inflammation and cerebral vasculitis during acute COVID-19 with spontaneous regression. *Intensive Care Med* 2022; 48:233–235
43. Yalcin Mutlu M, Wacker J, Tascilar K, et al: Effective and safe treatment of anti-CD38 therapy in systemic lupus erythematosus–associated refractory cerebral vasculitis induces immune tolerance. *Rheumatol* 2023; 62:e21–e23
44. Graus F, Titulaer MJ, Balu R, et al: A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016; 15:391–404
45. Abboud H, Probasco JC, Irani S, et al; Autoimmune Encephalitis Alliance Clinicians Network: Autoimmune encephalitis:

Proposed best practice recommendations for diagnosis and acute management. *J Neurol Neurosurg Psychiatry* 2021; 92:757–768

46. Dalmau J, Armangué T, Planagumà J, et al: An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: Mechanisms and models. *Lancet Neurol* 2019; 18:1045–1057
47. Wartofsky L, Klubo-Gwiezdzinska J: Myxedema coma. In: *The Thyroid and Its Diseases: A Comprehensive Guide for the Clinician*. Luster M, Duntas L, Wartofsky L (Eds). Cham, Switzerland, Springer, 2019, pp 281–292
48. Hahner S, Ross RJ, Arlt W, et al: Adrenal insufficiency. *Nat Rev Dis Primers* 2021; 7:19
49. Barkhoudarian G, Kelly DF: Pituitary apoplexy. *Neurosurg Clin* 2019; 30:457–463
50. Rose CF, Amodio P, Bajaj JS, et al: Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. *J Hepatol* 2020; 73:1526–1547
51. Rosner MH, Husain-Syed F, Reis T, et al: Uremic encephalopathy. *Kidney Internat* 2022; 101:227–241
52. Lowenstein J, Nigam SK: Uremic toxins in organ crosstalk. *Front Med* 2021; 8:592602
53. Kuitunen S, Niittynen I, Airaksinen M, et al: Systemic causes of in-hospital intravenous medication errors: A systematic review. J Patient Safet*y* 2021; 17:e1660
54. Kane-Gill SL, Jacobi J, Rothschild JM: Adverse drug events in intensive care units: Risk factors, impact, and the role of team care. Crit Care Med 2010; 38:S83–S89
55. Devlin JW, Mallow-Corbett S, Riker RR: Adverse drug events associated with the use of analgesics, sedatives, and antipsychotics in the intensive care unit. *Crit Care Med* 2010; 38:S231–S243
56. Choi L, Ferrell BA, Vasilevskis EE, et al: Population pharmacokinetics of fentanyl in the critically ill. *Crit Care Med* 2016; 44:64–72
57. Polat EC, Koc A, Demirkan K: The role of the clinical pharmacist in the prevention of drug-induced acute kidney injury in the intensive care unit. *J Clin Pharm Therapeut* 2022; 47:2287–2294
58. Pun BT, Balas MC, Barnes-Daly MA, et al: Caring for critically ill patients with the ABCDEF bundle: Results of the ICU liberation collaborative in over 15,000 adults. *Crit Care Med* 2019; 47:3–14
59. Fischer M, Schmutzhard E: Posterior reversible encephalopathy syndrome. *J Neurol* 2017; 264:1608–1616
60. Forget P, de Waroux BL, Wallemacq P, et al: Life-threatening dextromethorphan intoxication associated with interaction with amitriptyline in a poor CYP2D6 metabolizer: A single case re-exposure study. *J Pain Symptom Manag* 2008; 36:92–96
61. Zhang W, Chen Y, Liu F, et al: Predicting potential drug-drug interactions by integrating chemical, biological, phenotypic and network data. *BMC Bioinf* 2017; 18:1–2
62. Dalen JE, Alpert JS: Medical tourists: Incoming and outgoing. *Am J Med* 2019; 132:9–10
63. Rungvivatjarus T, Kuelbs CL, Miller L, et al: Medication reconciliation improvement utilizing process redesign and clinical decision support. *Joint Comm J Qual Pat Safety* 2020; 46:27–36
64. De Paepe P, Lemoyne S, Buylaert W: Disorders of consciousness induced by intoxication. *Neurol Clin* 2012; 30:359–384, x–xi
65. Chhabra N, Mir M, Hua MJ, et al: Notes from the field: Xylazine-related deaths—Cook County, Illinois, 2017–2021. *MMWR* 2022; 71:503
66. Hong JS, Moran MT, Earon LA, et al: Neurologic, cognitive, and behavioral consequences or opioid overdose: A review. *Curr Phys Med Rehab Rep* 2019; 7:305–313
67. Almojuela A, Hasen M, Zeiler FA: The Full Outline of UnResponsiveness (FOUR) score and its use in outcome prediction: A scoping systematic review of the adult literature. *Neurocrit Care* 2019; 31:162–175
68. Sanz LR, Thibaut A, Edlow BL, et al: Update on neuroimaging in disorders of consciousness. *Curr Op Neurol* 2021; 34:488
69. Kondziella D, Bender A, Diserens K, et al; EAN Panel on Coma, Disorders of Consciousness: European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness. *Eur J Neurol* 2020; 27:741–756
70. Lochner P, Czosnyka M, Naldi A, et al: Optic nerve sheath diameter: Present and future perspectives for neurologists and critical care physicians. *Neurol Sci* 2019; 40:2447–2457
71. Rumboldt Z, Huda W, All JW: Review of portable CT with assessment of a dedicated head CT scanner. *Am J Neuroradiol* 2009; 30:1630–1636
72. Turpin J, Unadkat P, Thomas J, et al: Portable magnetic resonance imaging for ICU patients. *Crit Care Explor* 2020; 2:e0306
73. Jain R, Ramakrishnan AG: Electrophysiological and neuroimaging studies–during resting state and sensory stimulation in disorders of consciousness: A review. *Front Neurosci* 2020; 14:555093
74. Mecarelli O, Brienza M, Grippo A, et al: Disorders of consciousness. *Clin Electroencephalog* 2019:731–765
75. Rasulo FA, De Peri E, Lavinio A: Transcranial Doppler ultrasonography in intensive care. *Eur J Anaesthesiol* 2008; 25:167–173
76. Mathôt S: Pupillometry: Psychology, physiology, and function. *J Cognition* 2018; 1:16
77. Tsuyusaki Y, Sakakibara R, Kishi M, et al: "Invisible" brain stem infarction at the first day. *J Stroke Cerebrovasc Dis* 2014; 23:1903–1907
78. Tang MY, Chen TW, Zhang XM, et al: GRE T2*-weighted MRI: Principles and clinical applications. *BioMed Res Int* 2014; 2014:312142
79. Haller S, Haacke EM, Thurnher MM, et al: Susceptibility-weighted imaging: Technical essentials and clinical neurologic applications. *Radiology* 2021; 299:3–26
80. Oddo M, Bracard S, Cariou A, et al: Update in neurocritical care: A summary of the 2018 Paris international conference of the French Society of Intensive Care. *Ann Intens Care* 2019; 9:47
81. Vespa PM, Olson DM, John S, et al: Evaluating the clinical impact of rapid response electroencephalography: The DECIDE multicenter prospective observational clinical study. *Crit Care Med* 2020; 48:1249–1257
82. Martínez ML, Ferrer R, Torrents E, et al; Edusepsis Study Group: Impact of source control in patients with severe sepsis and septic shock. *Crit Care Med* 2017; 45:11–19

83. Costerus JM, Brouwer MC, van de Beek D: Technological advances and changing indications for lumbar puncture in neurological disorders. *Lancet Neurol* 2018; 17:268–278
84. Prüss H: Autoantibodies in neurological disease. *Nat Rev Immunol* 2021; 21:798–813
85. Rasulo FA, Hopkins P, Lobo FA, et al: Processed electroencephalogram-based monitoring to guide sedation in critically ill adult patients: Recommendations from an international expert panel-based consensus. *Neurocrit Care* 2022 Jul 27. [online ahead of print]
86. Rasimas JJ, Sinclair CM: Assessment and management of toxidromes in the critical care unit. *Crit Care Clin* 2017; 33:521–541
87. Wilcox SR, Wax RS, Meyer MT, et al: Interfacility transport of critically ill patients. *Crit Care Med* 2022; 50:1461–1476
88. Goligher EC, Dres M, Patel BK, et al: Lung-and diaphragm-protective ventilation. *Am J Respir Crit Care Med* 2020; 202:950–961
89. Carney N, Totten AM, O'Reilly C, et al: Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurg* 2017; 80:6–15
90. Yekula A, Mittal A, Sagi V, et al: External ventricular drains: An overview of indications, technique, and complications. *Acta Sci Neurol* 2020; 3:16–22
91. Cook AM, Morgan Jones G, Hawryluk GW, et al: Guidelines for the acute treatment of cerebral edema in neurocritical care patients. *Neurocrit Care* 2020; 32:647–666
92. Bogossian G, Peluso E, Creteur L, et al: Hyperventilation in adult TBI patients: How to approach it? *Front Neurol* 2021; 11:580859
93. Frontera JA, Lewin IJ III, Rabinstein AA, et al: Guideline for reversal of antithrombotics in intracranial hemorrhage: A statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care* 2016; 24:6–46
94. Cheng Y, Wang Y, Song Q, et al: Use of anticoagulant therapy and cerebral microbleeds: A systematic review and meta-analysis. *J Neurol* 2021; 268:1666–1679
95. Cannon JW, Dias JD, Kumar MA, et al: Use of thromboelastography in the evaluation and management of patients with traumatic brain injury: A systematic review and meta-analysis. *Crit Care Explor* 2021; 3:e0526
96. Greenberg SM, Ziai WC, Cordonnier C, et al: Guideline for the management of patients with spontaneous intracerebral hemorrhage: A guideline from the American Heart Association/American Stroke Association. *Stroke* 2022; 53:e282–e361
97. Faizy TD, Mlynash M, Marks MP, et al: Intravenous tPA (tissue-type plasminogen activator) correlates with favorable venous outflow profiles in acute ischemic stroke. *Stroke* 2022; 53:3145–3152
98. Tumma A, Berzou S, Jaques K, et al: Considerations for the implementation of a telestroke network: A systematic review. *J Stroke Cerebrovasc Dis* 2022; 31:106171
99. Wong ET, Swanson KD: Dexamethasone-friend or foe for patients with glioblastoma? *JAMA Neurol* 2019; 76:247–248
100. Lawton MT, Vates GE: Subarachnoid hemorrhage. *N Engl J Med* 2017; 377:257–266
101. Fitts W, Vogel A Mateen F: The changing face of osmotic demyelination syndrome. *Neurology* 2021; 11:304–310
102. Menez Silva PH, Unwin R, Hoorn EJ, et al: Acidosis, cognitive dysfunction and motor impairments in patients with kidney disease. *Nephrol Dial Transplant* 2021; 37(Suppl 2):ii4–ii12
103. Hudson M, Schuchmann M: Long-term management of hepatic encephalopathy with lactulose and/or rifaximin: A review of the evidence. *Eur J Gastroenterol Hepatol* 2019; 31:434–450
104. Tseng YL, Huang CR, Lin CH, et al: Risk factors of hyperammonemia in patients with epilepsy under valproic acid therapy. *Medicine (Baltimore)* 2014; 93:e66–e73
105. LaPenna PA, Roos KL: Bacterial infections of the central nervous system. *Seminars Neurol* 2019; 39:334–342
106. Shuford R, Miller-Ocuin JL: Hyperglycemia in the perioperative period. *Clin Colon Rectal Surg* 2023 Jan 25. [online ahead of print]
107. Nicholas TA, Robinson R: Multimodal analgesia in the era of the opioid epidemic. *Surg Clin* 2022; 102:105–115
108. Moheet AM, Livesay SL, Abdelhak T, et al: Standards for neurologic critical care units: A statement for healthcare professionals from the Neurocritical Care Society. *Neurocrit Care* 2018; 29:145–160
109. Olson DM, Hemphill JC 3rd; Curing Coma Campaign and its Executive Committe: The curing coma campaign: Challenging the paradigm for disorders of consciousness. *Neurocrit Care* 2021; 35(Suppl 1):1–3
110. Helbok R, Rass V, Beghi E, et al: The curing coma campaign international survey on coma epidemiology, evaluation, and therapy (COME TOGETHER). *Neurocrit Care* 2022
111. Kondziella D, Menon DK, Helbok R, et al; contributing collaborators of the Curing Coma Campaign: A precision medicine framework for classifying patients with disorders of consciousness: Advanced Classification of Consciousness Endotypes (ACCESS). *Neurocrit Care* 2021; 35(Suppl 1):27–36
112. Mainali S, Aiyagari V, Alexander S, et al: Proceedings of the second curing coma campaign NIH symposium: Challenging the future of research for coma and disorders of consciousness. *Neurocrit Care* 2022; 37:326–350
113. Olson DM, Hemphill JC, Provencio JJ, et al; Curing Coma Campaign Collaborators: The curing coma campaign and the future of coma research. *Semin Neurol* 2022; 42:393–402
114. Savelkoel J, Claushuis TA, van Engelen TS, et al: Global impact of World Sepsis Day on digital awareness of sepsis: An evaluation using Google Trends. *Crit Care* 2018; 22:61