Critical Care Management of Acute Spinal Cord Injury—Part II: Intensive Care to Rehabilitation

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Abstract

Spinal cord injury is devastating to those affected due to the loss of motor and sensory function, and, in some cases, cardiovascular collapse, ventilatory failure, and bowel and bladder dysfunction. Primary trauma to the spinal cord is exacerbated by secondary insult from the inflammatory response to injury. Specialized intensive care of patients with acute spinal cord injury involves the management of multiple systems and incorporates evidence-based practices to reduce secondary injury to the spinal cord. Patients greatly benefit from early multidisciplinary rehabilitation for neurologic and functional recovery. Treatment of acute spinal cord injury may soon incorporate novel molecular agents currently undergoing clinical investigation to assist in neuroprotection and neuroregeneration.

Keywords
- autonomic dysreflexia
- blunt cerebrovascular injury
- hemodynamic monitoring
- neurogenic shock
- neuropathic pain therapy
- neuroprotection
- neuroregeneration
- spinal cord injury
- spinal cord rehabilitation
- tracheostomy

Introduction

In part I of this review, we first highlighted trends in the global epidemiology of acute spinal cord injury (SCI). We then summarized the mechanisms of primary injury and illustrated the cascade of biomolecular changes, called "secondary injury," linked to the body's inflammatory response to the initial trauma. We next summarized best practices for early assessment and resuscitation of SCI patients during initial presentation using the ABCDE (Airway, Breathing, Circulation, Disability, Exposure) approach as well as evidence-based recommendations for the timing of surgical decompression. We concluded with suggestions for anesthesia management during surgery for SCI to help mitigate secondary injury and optimize surgical outcomes. In this second part, we provide a systems-based review of critical care management, beginning with cardiovascular concerns. We then discuss recovery and rehabilitation efforts initiated in the intensive care unit (ICU) and conclude by reviewing promising neuroprotective approaches and neuroregenerative therapies.

Intensive Care Unit Management of Neurologic Injury and Its Sequelae

Cardiovascular

Acute SCI is associated with life-threatening cardiovascular complications that require heightened vigilance and preventive management in the ICU. Patients are at risk of neurogenic shock, unstable arrhythmias, and autonomic dysreflexia (AD) for weeks to months after injury (►**Table 1**).[1-3]

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Table 1 Suggested intensive care unit guidelines for the detection, prevention, and management of critical care concerns in acute spinal cord injury

Problem	Monitoring[a]	Finding	Prevention/Management
Neurologic			
Secondary injury	Spinal cord assessment[b]	Often none Worsening of neurologic deficits	Spinal precautions Surgical decompression and stabilization Avoidance of hypotension, hypoxemia, and anemia Consider MAP augmentation to 85–90 mm Hg using fluids to achieve euvolemia, then vasopressors if needed
Pain	Pain assessments using NRS-V or BPAT[c]	Self-reported pain or behavioral symptoms of pain	Multimodal analgesia Neuropathic pain therapies Physical, occupational, speech, and psychiatric therapy
Cardiovascular			
Neurogenic shock	Invasive hemodynamic monitoring TTE POCUS	Hypotension Bradycardia Peripheral vasodilation	Volume resuscitation Inotropic vasopressors
Cardiac arrhythmia	Telemetry	Sinus bradycardia (most common) Atrioventricular blocks Supraventricular tachycardia	Atropine Vasopressors with inotropic and chronotropic effects Temporary transcutaneous or transvenous pacing Fluid bolus therapy Abdominal binders Permanent pacemaker
Autonomic dysreflexia	Telemetry Arterial pressure monitoring	Sudden rise in BP Headache Pupillary constriction, blurred vision Nasal congestion Anxiety Diaphoresis, flushing above the lesion Piloerection, pale, cool skin below the lesion	Remove inciting stimulus Analgesia IV nitroglycerin
Respiratory			
Respiratory insufficiency and atelectasis	Capnography Cough assessment[d] ABG Chest XR	Mild hypoxemia Diminished breath sounds Tachypnea Weak cough Pulmonary atelectasis or edema on imaging	Chest physiotherapy and pulmonary hygiene[e] Cautious nasotracheal suctioning Noninvasive positive pressure ventilation
Ventilatory failure	Capnography Cough assessment Vital capacity assessment every 12 h ABG Chest XR	Hypoxemia Hypercarbia Dyspnea Audible pooling of secretions Ineffective cough Paradoxical inward depression of ribs Vital capacity < 10–15 mL/kg IBW Pulmonary atelectasis or edema on imaging	Chest physiotherapy and pulmonary hygiene Video laryngoscopy and endotracheal intubation with MILS Awake fiberoptic bronchoscope intubation with topicalization of the airway in cooperative patients and nonemergent scenarios Mechanical ventilation

(continued)

Table 1 *(continued)*

Problem	Monitoring[a]	Finding	Prevention/Management
Hematologic			
Blunt cerebrovascular injury	Neurologic assessments[d] aPTT (if heparin therapy)	Arterial hemorrhage/epistaxis Cervical bruit in patients < 50 year of age Expanding cervical hematoma Focal neurologic deficit not explained by head CT Cerebral infarction on secondary CT/MRI Cervical spine fracture of C1–C3, subluxation, or extending into the transverse foramen	Antiplatelet or anticoagulation: unfractionated heparin without bolus and a low aPTT target ASA 81 or 325 mg Endovascular intervention with stent, coil embolization, or lytic therapy Operative management with primary repair, patch angioplasty, interposition graft, arterial bypass, or vessel sacrifice
DVT	Extremity inspection[a] Doppler ultrasound aPTT (if heparin therapy)	Unilateral edema or swelling with difference in calf or thigh diameters Unilateral warmth, erythema	Thromboprophylaxis: Intermittent pneumatic compression devices ± graduated compression stockings; LMWH Therapeutic unfractionated heparin
Pulmonary embolism	ABG Temperature CT angiogram Perfusion scan Doppler ultrasound TTE Telemetry aPTT (if heparin therapy)	Tachycardia Fever Hypoxemia Widened alveolar–arterial O_2 gradient Respiratory alkalosis	Respiratory and hemodynamic support Unfractionated heparin If anticoagulation is contraindicated, consider inferior or superior vena cava filter or suprarenal filter based on DVT location
Gastrointestinal			
Paralytic ileus	Auscultation of bowel sounds Abdominal XR CT abdomen with oral contrast	Absence of flatus or stool Hypoactive bowel sounds Abdominal distention Nausea or vomiting High gastric residuals Dilated loops of bowel on plain film	NPO Naso- or orogastric catheter connected to low continuous suction Manual fecal disimpaction Stool softeners Prokinetics
Gastroduodenal ulcer or bleeding	CBC Upper endoscopy Electrolytes	Abdominal distention Hematemesis Melena Anemia	Nutritional support H2-receptor antagonist PPI
Pancreatitis	Temperature Liver function tests Amylase Lipase BUN Electrolytes CBC Strict monitoring of urine output CT abdomen with IV contrast Serial bladder pressures	Abdominal distention Hypoactive bowel sounds Fever Hypoxemia Hypotension Scleral icterus Leukocytosis Elevated HCT Elevated BUN Hypocalcemia Hyperglycemia Abdominal compartment syndrome	Aggressive fluid resuscitation Correction of electrolytes Nasojejunal enteral nutrition Treatment of underlying condition
Acute calculous cholecystitis	Temperature Abdominal ultrasound Liver function tests Amylase	Leukocytosis with left shift Mild elevation in serum aminotransferases and amylase Hyperbilirubinemia Jaundice Fever	Supportive care with IV hydration, pain control, NPO, antibiotics, correction of electrolytes Percutaneous cholecystotomy or endoscopic gall bladder drainage Cholecystectomy if complicated cholecystitis or with disease progression despite 3 d of biliary drainage

(continued)

Table 1 *(continued)*

Problem	Monitoring[a]	Finding	Prevention/Management
Genitourinary			
Urinary retention	Spinal assessment (rectal tone) Portable bladder ultrasound Urinalysis Serum BUN/CRT, electrolytes Urine electrolytes, specific gravity Renal ultrasound	Oliguria Bilateral hydronephrosis Large postvoid residual urine volumes (>500 mL)	Early placement of an indwelling catheter Suprapubic catheter if urethral trauma precludes transurethral placement Clean intermittent catheterization every 4–6 h may be initiated once resuscitation endpoints are no longer needed Oral anticholinergic
Infectious disease			
UTI	Urinalysis Temperature CBC	Fever Leukocytosis Metabolic acidosis Respiratory alkalosis Foul-smelling urine Hematuria Bacteriuria or funguria	Urine culture obtained by removing the existing indwelling catheter and sampling from a new catheter Begin empiric antimicrobial treatment immediately after culture is sampled from a new catheter if high suspicion Tailor treatment to the pathogen's susceptibility pattern once identified
Pressure ulcers	Skin integrity examination with repositioning (every 2–3 h), noting down length, width, and depth of any areas of skin damage	Subdermal injury to areas of bony prominences: occiput, shoulder blades, sacrum, coccyx, ankles, heels, chin, ears, and clavicles under cervical collar Warmth, erythema, local tenderness, purulent discharge, foul odor with infection of pressure ulcer	Removal of unnecessary immobilization devices Frequent liberation of areas at risk through pressure redistribution with proper positioning and support surfaces Local wound care with debridement of necrotic tissue if necessary Negative-pressure wound therapy Pain therapy
Pneumonia	Temperature CBC ABG Chest XR Chest CT	Hypoxemia Increased or purulent secretions Rhonchi, crackles, reduced breath sounds Leukocytosis/leukopenia New or progressive infiltrate on imaging Nonintubated patients: dyspnea, tachypnea Intubated patients: increased inspiratory pressures	Pneumococcal and influenza vaccination Sputum or endotracheal aspirate and peripheral blood sample for culture prior to initiating antibiotics Empiric antimicrobial therapy tailored to pathogen's susceptibility pattern once identified Chest physiotherapy Pulmonary hygiene Therapeutic bronchoscopy

Abbreviations: ABG, arterial blood gas; aPTT, activated partial thromboplastin time; ASA, aspirin; BP, blood pressure; BPAT, Behavioral Pain Assessment Tool; BUN, blood urea nitrogen; CBC, complete blood count; CRT, creatinine; CT, computed tomography; DVT, deep vein thrombosis; HCT, hematocrit; IBW, ideal body weight; IV, intravenous; LMWH, low molecular weight heparin; MAP, mean arterial pressure; MILS, manual in-line stabilization; MRI, magnetic resonance imaging; NPO, nil per os; NRS-V, visually enlarged Numeric Rating Scale; POCUS, point-of-care ultrasound; PPI, proton-pump inhibitor; TTE, transthoracic echocardiogram; UTI, urinary tract infection; XR, radiograph.

[a]List of suggested monitoring in addition to routine intensive care unit (ICU) measurements of continuous pulse oximetry (SaO2), heart rate (HR), respiratory rate (RR), and cardiac rhythm. BP monitoring is assumed to be noninvasive and, therefore, not continuously measured unless listed otherwise. BP may be measured upon admission of a patient with acute spinal cord injury every 15 minutes × 4, every 30 minutes × 2, every 1 hour × 8, then every 2 hours. Auscultation of heart, lung, and abdomen, palpation of pulses, and inspection of extremities may be performed every 4 hours.

[b]Comprehensive neurologic examination of spinal cord function may be performed upon admission to the ICU and then at least every 12 hours (once each nursing shift) or with a suspected change in examination. Gross motor/sensory spinal cord examination may be performed every 2 hours.

[c]Pain assessments may be performed no less frequently than every 4 hours or as clinically indicated using valid and reliable tools such as the NRS-V in patients who can communicate and the BPAT in patients who cannot communicate. Increases in BP, HR, and RR are not valid indicators for pain but may be used as cues to initiate pain assessment.[137–139]

[d]Neurologic examination with level of consciousness (using the Glasgow Coma Scale) and cranial nerve assessments may be performed upon admission to the ICU and every 1 hour for 8 hours, then every 2 hours for 16 hours, and every 4 hours thereafter.

[e]Examples of chest physiotherapy and pulmonary hygiene (formerly referred to as pulmonary toilet) include manual cough assist (quad cough), mechanical insufflation–exsufflation, intrapulmonary percussive ventilation, mucolytics, warm moist air, and intermittent positive-pressure breathing.

Following insult, the spinal cord enters a state of spinal shock, affecting all functions of the cord below the injury, which can last from a few days up to 4 to 12 weeks, depending on how one defines its resolution.[4,5] Neurogenic shock is the autonomic manifestation of the spinal shock syndrome.[5]Supraspinal control of sympathetic output travels in preganglionic neurons from the medulla to the intermediolateral column of the first thoracic to the second lumbar spinal cord segments, with cardioaccelerator fibers located in the first four thoracic segments.[6] While the feared triad of neurogenic shock—bradycardia, hypotension, and peripheral vasodilation—is more commonly seen with complete lesions of the upper thoracic and cervical cord than in incomplete SCI or thoracolumbar lesions, the entire length of the sympathetic cord supplies innervation to the vasculature, and therefore interruption of descending signals at any level has the capacity to induce vasoplegic shock.[7,8] Disruption of sympathetic activity reduces vascular resistance in large vascular beds and decreases venous return to the heart. In neurogenic shock, interruption of the positive chronotropic, inotropic, and dromotropic effects on the heart from cardiac sympathetic preganglionic nerves in the upper thoracic segments leaves parasympathetic activity unopposed, resulting in circulatory collapse.[9] Early judicious fluid bolus therapy restores intravascular volume and cardiac preload, which stimulates atrial stretch receptors to signal the medullary control centers to decrease parasympathetic tone through the vagus nerve to the heart, resulting in an increased heart rate.[10] Inotropic vasopressors are frequently required to supplement fluid therapy for hemodynamic stabilization in neurogenic shock and to mitigate ischemia and secondary neuronal injury to the vulnerable spinal cord. There is currently no consensus regarding the preferred pharmacological agent; dopamine, norepinephrine, and epinephrine are commonly used vasopressors to treat neurogenic shock.[11,12] While recent evidence suggests that norepinephrine may be superior to dopamine in increasing spinal cord perfusion pressure with less increases in intrathecal pressure, high-quality data to guide therapeutic endpoints are lacking.[13]

The spinal cord autoregulates its blood flow, maintaining a constant blood supply to support its metabolic demands despite changes in arterial pressure.[14] At blood pressure values outside the limits of autoregulation, spinal cord perfusion becomes passive to changes in arterial pressure. Trauma to the cord and the ensuing secondary inflammatory response may abolish autoregulatory capacity, with spinal cord perfusion passive at all values of blood pressure.[15] Experimental data indicate that cord hypoperfusion perpetuates secondary injury. Several investigators have provided class III evidence that mean arterial pressure (MAP) augmentation to 85 to 90 mm Hg for the first 5 to 7 days after injury may improve clinical outcome.[16-20] Based on data from six uncontrolled case series of SCI patients in the 1970s to 1990s, the 2002 guidelines from the American Association of Neurological Surgeons and the Congress of Neurological Surgeons (AANS/CNS) recommend maintaining a MAP goal of 85 to 90 mm Hg for 7 days postinjury.[21] The investigators chose the duration of MAP augmentation based on experiments in animals.[16-18] The 2013 AANS/CNS hemodynamic guidelines were essentially unchanged.[22] Despite the potential harmful consequences of aggressive fluid therapy and vasopressor administration, and the high cost associated with intensive care management during prolonged MAP augmentation, there is unlikely to be prospective controlled data to support these recommendations due to the ethical concerns of lower target comparison groups.[23] Future study will likely involve controlled trials examining the duration of therapy and mechanism of MAP augmentation (i.e., type of vasopressor, colloid vs. crystalloid, type of crystalloid) to help individualize therapy.

For now, a reasonable hemodynamic management strategy involves the following steps. First, consider all potential causes of hemodynamic instability, including neurogenic shock, myocardial injury, pericardial tamponade, bleeding, tension pneumothorax, and sepsis. Neurogenic shock may coexist alongside hemorrhagic shock from unappreciated bleeding, such as a retroperitoneal hematoma, under-resuscitation preoperatively, or ongoing blood loss postoperatively. Second, expeditiously expand volume with fluid followed by vasopressors to avoid hypotension and optimize cord perfusion. The addition of blood products can be led by blood counts and coagulation profiles. Ideally, fluid and pressor administration should be guided by invasive hemodynamic monitoring, such as pulmonary artery catheterization or pulse contour cardiac output, or by bedside sonography with transthoracic echocardiography or point-of-care ultrasound. Attention should be paid to changes in cardiac output and filling pressures to avoid congestive heart failure. Third, if euvolemia has been approximately achieved with fluids, MAP augmentation to 85 mm Hg may be briefly initiated so long as additional fluid or pharmacological interventions do not unfavorably impact other organ systems.

Disruption of autonomic homeostasis in SCI can also lead to fatal cardiac rhythm and conduction abnormalities. Most commonly experienced abnormalities in the acute phase of SCI are bradyarrhythmias due to parasympathetic predominance, which reflect the level and completeness of injury.[2] Complete SCI presents as total loss of motor, sensory, and reflex functions, reflecting an absence of communication between the nerves below the lesion and the brain. In an incomplete injury, some signals persist, which manifest in varying degrees of function below the level of injury.[24] In one series, 100% of complete cervical SCI patients had persistent resting heart rates less than 60 beats per minute (bpm) and 71% had heart rates less than 45 bpm for at least 1 day postinjury.[1] This was compared with 35% of incomplete cervical SCI patients with heart rates less than 60 bpm and 12% less than 45 bpm, and 13% of thoracolumbar SCI patients with heart rates less than 60 bpm and 4% less than 45 bpm. Notably, patients with complete SCI exhibit exquisite sensitivity to vagal stimulation, such that changes in position, increased intrathoracic pressure, suctioning, airway manipulation, and Valsalva maneuvers have all been shown to trigger episodes of severe bradycardia, with some leading to conduction block, sinus pause, and sinus arrest.[1,25,26] Treatment involves atropine, promoting cardiac preload, and temporary or permanent cardiac pacing.

Supportive measures include abdominal binders to improve venous return.

According to some authors, the autonomic expression of spinal shock is neurogenic shock, and the autonomic expression correlate of spinal hyperreflexia after recovery from spinal shock is autonomic hyperreflexia.[4,5] This is a logical comparison because autonomic hyperreflexia, or more commonly referred to as AD, is a group of symptoms typically seen in the chronic phase of SCI after recovery from neurogenic shock and presents as severe paroxysmal hypertension triggered by cutaneous or visceral stimulation below the lesion.[27] The earliest reported case of AD was 4 days after injury, but an initial or recurrent episode can present at any time during the life of an SCI patient.[28,29] AD is more common and more severe in patients with complete and upper cord lesions than in those with incomplete and lower cord lesions.

AD is thought to be mediated by an upregulation of adrenoceptor number, an increase in catecholamine sensitivity, and the loss of inhibitory descending sympathetic control.[27] Triggered by a strong sensory input below the level of the lesion, peripheral nerves carry the disturbing message to the spinal cord. Afferent signals then travel up and down the intact portion of the cord and paraspinal sympathetic ganglion, evoking a massive reflex sympathetic surge from the thoracolumbar sympathetic nerves. This causes widespread vasoconstriction, most significantly in the splanchnic vasculature, and release of epinephrine and norepinephrine into the systemic circulation through stimulation of the adrenal medulla. Aortic and carotid baroreceptors convey the message of this hypertensive crisis through cranial nerves IX and X to the nucleus of the solitary tract (NTS) in the medulla. The NTS projects to the cardioinhibitory area containing the nucleus ambiguus and dorsal motor nucleus of the vagus, which results in strong parasympathetic outflow. The NTS also relays to the caudal ventrolateral medulla (CVLM), which, when activated, inhibits the rostral ventrolateral medulla (RVLM).[6]Bulbospinal presympathetic neurons in the RVLM travel through the cord and typically release glutamatergic excitatory impulses to the sympathetic preganglionic neurons in the intermediolateral column from T1 to L2. With a functional baroreceptor reflex, the NTS and CVLM quiet this sympathoexcitatory output from the RVLM.[6] In SCI patients, however, these signals can only travel as far as the level of neurologic injury. The parasympathetic activity and descending supraspinal efforts to suppress the sympathetic activity are ineffective in reducing blood pressure. Above the level of the injury, parasympathetic activity dominates, and patients display pupillary constriction, diaphoresis, and flushing. Below the level of injury, unfettered sympathetic activity leads to piloerection and pale, cool skin.[27] Presynaptic sympathetic nerves from T5 to T9 form the greater splanchnic nerve, which, through the celiac ganglion, supplies most of the splanchnic vascular bed. AD is less commonly seen in patients with lesions below T6 (and rarely below T10) because at least some signals descend far enough to modulate splanchnic tone.[9]

A rise in systolic blood pressure greater than 20 mm Hg from baseline is used as the diagnosis of AD.[30] Treatment is to identify and relieve the patient of the offending agent. Noxious stimulus from bladder distention is more easily addressed than pain from wounds and skeletal fractures. In the ICU setting, simply providing additional analgesia may be effective for acute AD. In refractory cases, a rapid-onset short-acting vasodilator such as nitroglycerin is a preferred agent to avoid hypotension after AD resolves.[27,31]

Respiratory

Acute injury to the cervical and thoracic spinal cord affects respiratory mechanics, ventilatory control, and bronchial reactivity, all of which play a large role in early and late morbidity and mortality.[32,33] Respiratory insufficiency may be apparent immediately or develop over time, depending on the severity and anatomic level of injury and the duration of spinal shock.[34] Flaccid paralysis of the muscles below the level of the injury associated with the first phase of spinal shock may last several hours to several weeks.[4] Complete injury above C3 produces acute ventilatory failure and apneic respiratory arrest. Complete and incomplete injuries at C3 through C5 typically require airway protection and mechanical ventilation during the first few days to weeks. As the initial flaccidity of the diaphragm and inspiratory accessory muscles transitions to spasticity, and additional accessory muscles are recruited, spontaneous ventilation may be sufficient for liberation from mechanical ventilation. With lesions at C6 through C8 and paralysis of intercostal muscles, negative intrathoracic pressure during inspiration can lead to a paradoxical inward depression of the ribs. This mechanical imbalance results in increased work of breathing, distal airway collapse, atelectasis, and inefficient ventilation. Airway secretions accumulate through increased production and decreased clearance secondary to impaired cough.[33,35] Pneumonia is seen in more than 20% of SCI patients and is a common cause of mortality in this population.[34] Patients with an injury to the T12 level or lower should have no respiratory impairment; despite this, traumatic SCI patients frequently suffer from rib fractures, pulmonary contusions, hemopneumothorax, or other injuries to the thoracic cage that lead to acute respiratory failure requiring intubation and mechanical ventilation. Close respiratory monitoring and aggressive pulmonary hygiene and chest physiotherapy should be undertaken early in intubated patients.[36] Of note, even minor increases in the vagal tone that are normally counteracted by sympathetic influences, such as during bronchocarinal stimulation from suctioning, may precipitate severe bradyarrhythmias leading to sinus arrest.[1,25] Readily available intravenous atropine and preoxygenation prior to suctioning are recommended.[25]

Several studies have investigated the timing and clinical predictors of tracheostomy in patients with acute cervical SCI.[37-40] Risk factors for tracheostomy after traumatic cervical SCI include American Spinal Injury Association (ASIA) Impairment Scale (AIS)[24] grade A and B, upper cervical SCI (C4 or higher), Glasgow Coma Scale 8, thoracic injury, and respiratory complications.[41] Tracheostomy should be performed shortly after hemodynamic stability is obtained in patients with complete injury to the high cervical spine (C3 or higher). Tracheostomy placement both prior to and immediately

after anterior cervical spine surgery has been shown to be safe and does not increase the risk of surgical wound infection.[42,43] Success in remaining without invasive airway support varies in patients with injuries from C3 to C6. Early tracheostomy (less than 7 days after injury) has a clear benefit in patients who are likely to require prolonged mechanical ventilation, such as shorter length of ICU stay and decreased laryngotracheal complications.[44] Cord swelling and bleeding within the first few days of injury may cause loss of up to one AIS level, making this period of time high risk for intubation but probably too soon to predict the need for long-term mechanical ventilation. However, retrospective studies suggest that early tracheostomy is beneficial in reducing the duration of mechanical ventilation in SCI patients irrespective of the level of injury.[44,45]

Though not yet prospectively studied in SCI patients, interest has grown in the use of ultrasound as a noninvasive, bedside approach for evaluating diaphragm function to help predict which patients will become ventilator dependent.[46,47] Diagnostic criteria for diaphragmatic paralysis include paradoxical movement and/or significantly reduced dome excursion using M mode at the subcostal windows or reduced diaphragm thickening during inspiration using a linear high-frequency transducer at the zone of apposition.[46,48] This is best assessed during maximal inspiratory maneuvers in spontaneously breathing nonintubated patients or during spontaneous breathing trials in intubated patients. More prospective studies are needed to determine the best methods for predicting extubation success, ventilatory dependency, and the appropriate timing of tracheostomy in SCI patients.

Hematological

In patients with traumatic SCI, concomitant blunt cerebrovascular injury (BCVI) is an independent risk factor for increased morbidity and mortality.[49-51] Cervical SCI is highly associated with extracranial carotid and vertebral artery injury. Forceful neck flexion, hyperextension, and rotation during motor vehicle crashes account for almost one-half of BCVI.[52,53] However, upper cervical vertebral fractures sustained during low-energy ground-level falls account for one-third of BCVI in patients aged 65 years and older.[54] Impingement of the carotid or vertebral artery against bone, stretching or twisting of the vessel, or laceration by bone fragments produces an intimal tear. Intimal defects provide a pathway for blood to enter the layers of the artery wall, which may cascade into one or more mechanisms of injury.[55] Simple exposure of subendothelial collagen initiates platelet aggregation and thrombus formation, which may lead to stenosis, occlusion, or embolization. Less commonly, a subintimal dissection may occur and advance cranially, with further risk of luminal narrowing or vessel occlusion. Similarly, traumatic pseudoaneurysm from subadventitial expansion of blood may develop, which also carries a risk of vessel compression, thrombus formation, or enlargement and rupture. Complete transection of the artery occurs rarely, resulting in intra- or extracranial hemorrhage or arteriovenous fistula.[52]

Although evidence surrounding screening protocols for BCVI is still evolving, computed tomography (CT) angiography (CTA) using a comprehensive screening criterion is currently recommended as part of the initial trauma imaging assessment.[56-59] While digital subtraction angiography is considered the gold standard modality for diagnosing BCVI, it is not without risk, and availability depends on local expertise.[60] Suggested expanded screening criteria include both signs and symptoms of BCVI (i.e., arterial bleeding, cervical bruit, expanding hematoma, focal neurologic deficit, neurologic examination incongruous with head CT findings, stroke on secondary CT or magnetic resonance imaging [MRI]), as well as high-risk injury mechanisms and fracture patterns in asymptomatic patients (i.e., cervical spine fractures, traumatic brain injury [TBI] with thoracic injury, and Le Fort II or III facial fractures, among others).[57] Fracture patterns with the greatest risk of carotid and vertebral artery injury in traumatic SCI patients include cervical spine fractures involving C1 to C3, cervical fracture subluxations, and cervical fractures extending to the foramen transversarium.[61] Patients with BCVI may present to the hospital during their initial trauma with signs of stroke and corresponding neurologic deficits already in progress or the effects of BCVI may be masked by concurrent traumatic brain, craniofacial, or cervical spine injuries.[62] More commonly, patients with BCVI experience an asymptomatic period before the onset of stroke, which typically ranges from 10 to 72 hours.[57,62-65] The hope is to identify and initiate treatment during this latent period before devastating ischemic neurologic deficits occur.

Once a diagnosis of BCVI is made, determining the grade of injury aids in clinical communication between multidisciplinary providers and helps guide treatment and prognosis.[59] In the commonly used scale proposed by Biffl et al,[66] grade I represents a mild intimal injury or dissection with less than 25% luminal narrowing. Grade II represents a dissection with a raised intimal flap or vessel thrombosis, resulting in luminal narrowing greater than 25%. Grade III is a dissecting aneurysm or a pseudoaneurysm. Grade IV represents complete vessel occlusion or thrombosis, and grade V represents vessel transection with active extravasation or hemodynamically significant arteriovenous fistula.[67] Treatment may include medical therapy with antiplatelets or anticoagulation as early as safely possible, endovascular intervention, or operative repair.[59] The treatment strategy depends on the site(s) of vessel injury, grade of injury, extent of neurologic symptoms, local expertise, and associated injuries. There have been no randomized trials conducted in BCVI patients comparing antiplatelet therapy with anticoagulation therapy, evaluating drugs within each class (i.e., unfractionated vs. low-molecular weight heparin) or assessing the safest time to begin antithrombotic therapy after multi-system trauma.[68] Unfractionated heparin infusion with a low partial thromboplastin time goal and no bolus is preferred in the acute setting as it is reversible and can be monitored easily in the ICU.[68] Several observational studies suggest that benefits of early antithrombotic treatment of BCVI may outweigh any potential harm to other traumatic injuries, including spinal cord, traumatic brain, and solid organ injury.[68-71] Studies suggest that in SCI patients with concurrent TBI and intracerebral hemorrhage, antithrombotic therapy may be safely

initiated for BCVI within 72 hours of injury, after head CT demonstrates improvement or stability.[68,70,71] Additional evidence indicates that if SCI patients with BCVI require surgical decompression, antithrombotic therapy may be held perioperatively and safely initiated 72 hours after surgery.[70] However, individual clinical circumstances should inevitably dictate management with all responsible providers informed and in agreement with the care plan.

Operative management is indicated for surgically accessible grade II, III, and V BCVI according to major trauma society guidelines.[58,59] Many lesions, however, are not surgically accessible, especially vertebral artery injuries, since they involve vessels at the base of the skull. Although there are no randomized trials, successful endovascular therapy for surgically inaccessible grade II, III, and V BCVI has been demonstrated in several small case series.[72-74] While endovascular treatment may prevent new or recurrent stroke, dual antiplatelet therapy required for stent patency increases the risk of hemorrhage in trauma patients.

Grade I injuries (mild intimal irregularities) typically resolve with antithrombotic therapy alone and have a low stroke risk.[75] Initiating early antithrombotic therapy with heparin is similarly recommended in grade II injuries (dissection); however, endovascular stenting may be indicated if arterial dissections progress to near-occlusion.[76] Grade III injuries (pseudoaneurysm) also benefit from early therapy with heparin. Operative repair with patch angioplasty, interposition graft, or bypass procedures or endovascular intervention with stent or coil embolization is warranted if a pseudoaneurysm is symptomatic or expanding.[77,78] Grade IV injuries (occlusion) are associated with high mortality, and antithrombotic therapy with heparin is recommended as early as possible. There are no data demonstrating benefit from surgical or endovascular therapy for grade IV injuries.[79,80] Grade V injuries (transection) are also associated with high rates of stroke and mortality. An expanding neck hematoma from active extravasation or rupture should be controlled with direct pressure until surgical control is obtained or until endovascular angioembolization if the injury is inaccessible. Repeat imaging with CTA 7 to 10 days after the injury (or sooner if new neurologic deficits manifest) is recommended for all injury grades. This repeat image is intended to confirm or repudiate the diagnosis of BCVI in cases where the initial CTA displayed vasospasm or was misinterpreted.[56]

Venous thromboembolism (VTE) is another potentially life-threatening risk in both the acute and chronic phases of SCI. Vasomotor tone is initially lost in acute SCI, and dependent extremities become edematous. Venous stasis predisposes patients to deep vein thrombosis, pulmonary embolism, stroke, and other vascular complications. While vasomotor tone may eventually improve, SCI patients remain at a high risk of VTE throughout their lives due to limited movement. A large nationwide retrospective cohort study from Taiwan revealed that SCI patients have a 2.46-fold adjusted hazard ratio of deep vein thrombosis and a 1.57-fold adjusted hazard ratio of pulmonary embolism compared with that of the general population.[81]The Consortium for Spinal Cord Medicine provides grade 1C (strong recommendation, low-quality evidence) support for mechanical thromboprophylaxis with intermittent pneumatic compression devices (with or without graduated compression stockings) as soon as feasible after acute SCI and chemical thromboprophylaxis with low molecular weight heparin once there is no evidence of bleeding.[82]

Gastrointestinal, Genitourinary, and Infectious Disease

Spinal shock after acute SCI affects intrinsic enteric nervous system control, which may result in an array of gastrointestinal (GI) maladies, such as paralytic ileus, gastroduodenal ulceration and hemorrhage, pancreatitis, and cholecystitis.[83] GI injury in acute SCI is further exacerbated by steroid administration, opioid therapy, and antibiotics. Sensory deficits in acute SCI contribute to a delay in diagnosis, and therefore routine monitoring of electrolytes, hepatic enzymes, coagulation parameters, and blood counts is warranted.[84] Early implementation of bowel care may reduce the risk of catastrophic GI injury during the acute phase of SCI and includes digital or manual evacuation of stool; H2-receptor antagonists, proton-pump inhibitors, and enteral nutrition (as soon as safely possible) for gastric ulceration prophylaxis; and nasogastric suctioning to reduce ileus.[36]Prokinetic agents such as metoclopramide and erythromycin may be necessary to overcome refractory dilatation.[85,86] Urinary retention is common and requires bladder catheterization in the acute phase of injury to avoid bladder distension injury and chronic management to avoid AD. Patients with acute SCI are also at an increased risk of infection, with the urinary tract being the most common site.[87] Patients are highly prone to decubitus ulcers, which can progress to deep infections and sepsis. Even in the acute phase of SCI, patients must be turned routinely and assessed by caregivers to avoid development, or start early treatment of ulcers. Sepsis is a leading cause of death in all ICU patients, and SCI patients are no exception. The causes of death found to have the greatest impact on reduced life expectancy over the past 45 years in patients enrolled in the United States National SCI Database were pneumonia and septicemia.[88,89]

Thermoregulatory dysfunction is common in SCI due to unbalanced autonomic homeostasis and impaired sudomotor and vasomotor responses, leading to poikilothermia. Hypothalamic regulation of sympathetically mediated vasodilation and hidrosis is disrupted after upper SCI, leading to ineffective heat dissipation in response to warm ambient temperatures and hyperthermia.[90] Conversely, large portions of insentient skin and loss of skeletal muscle activity delay or prevent hypothalamic initiation of shivering in response to cold ambient environments. Combined with impaired sympathetically mediated peripheral vasoconstriction, cervical SCI patients are highly vulnerable to hypothermia from ineffective heat conservation.[91] Accidental hypothermia is associated with multiple harmful effects, including coagulopathy, metabolic acidosis, cardiac arrhythmias, and impaired tissue oxygen delivery. Hypothermia also decreases the cardiovascular response to catecholamines and increases the risk of wound infection, pneumonia, and sepsis. Moreover, fever in response to infection may be masked in an SCI patient with subnormal baseline temperatures.[92] In some cases, euthermia may be a sign of infection.

Close temperature monitoring is warranted, with adjustment of room temperature, cooling with ice packs, or use of forced-air warming devices, as needed, to maintain normothermia.

Use of Steroids in Medical Management

The use of corticosteroids to potentially attenuate the inflammatory cascade contributing to secondary injury in SCI continues to be of great debate. The National Acute Spinal Cord Injury Study (NASCIS) trials were a series of large randomized controlled experiments assessing the utility of methylprednisolone (MP) therapy.[93-96] Results of these trials suggested that when initiated within 3 hours of injury, MP therapy for 24 hours (bolus followed by continuous infusion) improved motor function. When initiated between 3 and 8 hours of injury, MP therapy for 48 hours was associated with a greater improvement in outcomes than the 24-hour duration, however with greater risk of infection and significantly increased rates of severe sepsis. Moreover, these trials were criticized for multiple methodological flaws.[97] Since these trials, investigators have mostly demonstrated no significant long-term benefit and instead found an increased risk of GI bleeding and other adverse events.[98,99] For these reasons, in 2013, the AANS/CNS released a level 1 (standard) recommendation against using MP for acute management of SCI.[100]

Neuroprotection

Multiple neuroprotective agents are currently being evaluated as adjunctive medical treatment in patients with acute SCI. Riluzole is an oral glutamate antagonist first approved by the U.S. Food and Drug Administration as a disease-modifying agent in patients with amyotrophic lateral sclerosis.[101]Riluzole's anti-glutaminergic actions are postulated to blunt excitotoxicity at neuronal sites of injury. A phase I trial showed significant motor improvement at 90 days postinjury in patients with cervical SCI who received 14 days of riluzole beginning within 12 hours of injury.[102] The Riluzole in Acute Spinal Cord Injury Study (RISCIS) is an ongoing multicenter phase IIb/III randomized, placebo-controlled trial to assess its efficacy and safety in acute cervical SCI.[103,104] Minocycline is a second-generation tetracycline antibiotic that has anti-inflammatory properties and has been shown to reduce apoptosis and minimize lesion size in animal models.[105] A phase II single-center, randomized, placebo-controlled trial of patients with acute SCI treated with intravenous minocycline for 7 days demonstrated safety and a tendency toward improved motor recovery at 1 year in patients with cervical lesions.[106] The results of the phase III trial, Minocycline in Acute Spinal Cord Injury (MASC), have yet to be published.[107] Hypothermia has also been found to facilitate neurologic improvement in both animal models and human studies

Table 2 Recommended neuropathic pain therapies for spinal cord injury and their mechanism of action

First[a]	High-quality evidence and a strong recommendation
Gabapentinoids (pregabalin, gabapentin)	G-protein coupled receptor antagonist leading to inhibition of glutamate release
Tricyclic antidepressants (amitriptyline)	Increase 5HT and NE at axon terminal through uptake inhibition; block ACH, adrenergic, and histamine receptors
Second	**High- or moderate-quality evidence and a strong recommendation**
Tramadol	Mu-opioid receptor agonist and weakly increases 5HT and NE through reuptake inhibition
Lamotrigine	Na-channel antagonist leading to inhibition of glutamate release
Third	**High- or moderate-quality evidence and a weak recommendation**
Transcranial direct current stimulation ± visual illusion	Modulates cortical excitability from aberrant nociceptive impulses generated by the injured spinal somatosensory circuity and misinterpreted by the brain as pain Correction of the incongruence between motor output and sensory feedback, and normalization of cortical somatosensory representation maps, induced by the visual input of movements of the paralyzed limbs
Fourth	**Moderate- or low-quality evidence and a weak recommendation**
Transcutaneous electric nerve stimulation	Afferent input to the periaqueductal gray, rostral ventromedial medulla, and spinal cord by stimulation of large diameter Aβ fibers using electrical current activates descending inhibitory systems to reduce hyperalgesia
Oxycodone	Potent μ -opiate receptor agonist mediates analgesia through changes in the perception of pain at the spinal cord (μ2-, delta-, kappa-receptors) and higher levels in the CNS (μ1- and kappa 3-receptors). Opioids modulate channel activity resulting in hyperpolarization and reduced neuronal excitability. Opioid receptors are also coupled with G-protein receptors. Opioid binding inhibits adenylate cyclase, which decreases intracellular cAMP that modulates the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine, and norepinephrine
Dorsal root entry zone lesioning	Selectively destroys the nociceptive fibers grouped in the lateral bundle of the dorsal rootlet, the excitatory medial part of the Lissauer tract, and the deafferented hyperactive neurons of the dorsal horn

Abbreviations: 5HT, 5-hydroxytryptamine (serotonin); ACH, acetylcholine; cAMP, cyclic adenosine monophosphate; CNS, central nervous system; GABA, gaba-aminobutyric acid; Na, sodium; NE, norepinephrine.

[a]Treatment categorization determined by an expert panel based on the quality of scientific evidence and strength of recommendations, with consideration of clinical experience, side-effect profile, and effectiveness in other neuropathic pain populations.[140]

through a variety of mechanisms such as reducing inflammation and metabolism and preservation of the blood–spinal cord barrier.[108] A multicenter, randomized, case-controlled study called Acute Rapid Cooling for Traumatic Injuries of the Cord (ARCTIC) is underway to determine the safety profile and efficacy of modest (33.5°C) intravascular hypothermia within 6 hours of cervical SCI for a duration of 48 hours followed by 24 hours of controlled rewarming compared with maintenance of normothermia (37°C) for 72 hours.[109]

Recovery and Rehabilitation

Rehabilitation therapy: After definitive treatment of the SCI and the management of associated conditions in the hospital, patients greatly benefit from transfer to a rehabilitation unit for continued neurologic recovery. Here they learn techniques for mobilization and self-care to help improve functional status. In high-resource settings, rehabilitation typically begins early within the ICU and involves physical, occupational, and respiratory therapists; speech and language pathologists; dietitians; and rehabilitation psychologists.[110,111]

Pain therapy: Neuropathic pain negatively impacts quality of life, mood, and ability to participate in rehabilitation and recovery efforts in the ICU and beyond. Unfortunately, despite multiple pain therapies (►**Table 2**), approximately 50 to 60% of SCI patients experience persistent, significant pain after injury.[112,113] As a consequence of pain and disability, approximately 22% of SCI patients suffer from depression.[114,115] This can be managed with physical and psychological therapy, antidepressants, and pain control.[116,117] Additionally, patients suffer from spasticity, which also results in pain.[118] Baclofen is the primary spasmolytic used in management, which may be administered orally or through an intrathecal pump. Early oral baclofen administration (1 day after SCI) has been reported; however, further study is warranted to determine the efficacy and appropriate timing of its use in the ICU.[119]Tizanidine and benzodiazepines are also commonly used agents to treat spasticity, with the latter more commonly used in acute settings. For focal areas of spasticity, botulinum toxin injections have been used, with some success after SCI.[120] Lastly, physical treatments, such as stretching, passive cycling, static weight bearing, and electrical stimulation have been shown to both reduce spasticity and improve motor function.[121]

Prognostication of recovery: Prognostication for patients with SCI involves estimates of both neurologic and functional recovery. Neurologic recovery is inversely proportional to the severity of injury. According to a systematic review of 51 articles on clinical predictors of neurologic outcome, functional status, and survival after SCI, approximately 10 to 15% of patients with complete SCI eventually regained some neurologic function and converted to incomplete status.[122] Among those with AIS grade B, one-third did not recover any additional function, one-third moved to AIS C, and another third moved to AIS D or E over the course of follow-up. For AIS C patients, approximately 70% converted to AIS D or E. Patients with a better initial AIS grade and those with lower lesions typically have better long-term functional recovery.

Neuroregeneration: An active area of investigation in SCI is neuroregeneration to augment recovery strategies.[123] Fibroblast growth factor (FGF) has shown to have neuroprotective and neuroregenerative properties through stimulation of axonal growth, inflammation reduction, and astrocyte activation. Due to its size, FGF has limited penetration through intact blood–spinal cord barrier. SUN13837 is a small molecule that acts as an FGF mimetic and works as an agonist at FGF receptors. The phase I/II randomized controlled ASCENT-ASCI (Asubio Spinal Cord Early Neurorecovery Treatment for Acute Spinal Cord Injury) study to determine the safety, efficacy, and pharmacokinetics of giving intravenous SUN13837 within 12 hours of acute cervical SCI for no less than 7 and no more than 28 days showed promising results with nonsignificant trends in functional improvement at 16 weeks.[124]

As a result of inflammation, myelin debris, and glial scar formation, several growth inhibitory proteins are released during acute SCI. These act to impede axon regeneration partly through the activation of Rho, a family of small intracellular GTPases that regulate the formation of focal adhesion, stress fibers, and cytoskeleton organization.[125] Upon activation, Rho signals a cascade of events, leading to apoptosis, collapse of axonal growth cones, and failure of axon regeneration. Inactivation of Rho and of Rho kinases promotes axon regeneration and functional recovery after SCI in rats and mice.[125]VX-210, also referred to as BA-210 or Cethrin, is a derivative of C3 transferase, a toxin produced by *Clostridium botulinum* that inhibits Rho proteins by ADP-ribosylation in the effector binding domain of the GTPase.[126] A phase I/IIa open-label, unblinded trial of dural application ranging from 0.3 to 9 mg of Cethrin during surgery in complete (AIS A) SCI patients performed within the first 7 days after injury observed conversions to AIS C or D in 31% of cervical patients and in 6% of thoracic patients at 1-year follow-up. Of cervical SCI patients receiving a 3 mg dose of intradural Cethrin, 66% improved to AIS C or better. There were no drug-related serious adverse events.[126]VX-210 is now under investigation in the multicenter, phase IIb/III randomized, placebo-controlled Spinal Cord Injury Rho Inhibition Investigation (SPRING) trial to evaluate its efficacy and safety in acute cervical SCI and its effect on functional recovery at 6 months postinjury using an upper extremity motor score.[127]

Ongoing studies assessing the utility of cell-based therapies to promote neuronal regeneration include trials of autologous Schwann cell[128,129] and oligodendrocyte progenitor cell[130] transplantation for remyelination, clinical trials of olfactory ensheathing cell transplantation for regeneration and functional reconnection,[131] a phase II trial of allogeneic human CNS stem cell intramedullary transplantation,[132] and a phase II/III trial of autologous bone marrow derived mesenchymal stem cell transplantation.[133] Studies investigating biomaterials such as spinal scaffolds to guide axonal growth, and techniques such as cerebrospinal fluid drainage to reduce pressure, improve cord perfusion, and reduce ischemia are also underway.[134-136]

Conclusion

Patients require comprehensive, interdisciplinary care in the ICU to combat the potentially catastrophic multisystem sequelae of SCI. Patients who survive the initial hospitalization greatly benefit from early rehabilitation but need continuous care. There is an ongoing development of molecular agents to assist in neuroprotection and neuroregeneration to help recover function postinjury. Management of SCI will continue to evolve to individualize care and help improve long-term outcomes.

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Conflict of Interest

None declared.

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