Management strategies for acute spinal cord injury: current options and future perspectives

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Purpose of review
Spinal cord injury is a devastating acute neurological condition with loss of function and poor long-term prognosis. This review summarizes current management strategies and innovative concepts on the horizon.

Recent findings
The routine use of steroids in patients with spinal cord injuries has been largely abandoned and considered a 'harmful standard of care'. Prospective trials have shown that early spine stabilization within 24 h results in decreased secondary complication rates. Neuronal plasticity and axonal regeneration in the adult spinal cord are limited due to myelin-associated inhibitory molecules, such as Nogo-A. The experimental inhibition of Nogo-A ameliorates axonal sprouting and functional recovery in animal models.

Summary
General management strategies for acute spinal cord injury consist of protection of airway, breathing, oxygenation and control of blood loss with maintenance of blood pressure. Unstable spine fractures should be stabilized early to allow unrestricted mobilization of patients with spinal cord injuries and to decrease preventable complications. Steroids are largely considered obsolete and have been abandoned in clinical guidelines. Nogo-A represents a promising new pharmacological target to promote sprouting of injured axons and restore function. Prospective clinical trials of Nogo-A inhibition in patients with spinal cord injuries are currently under way.

Keywords
axonal regeneration, Nogo-A, spinal cord injury, spine damage control

INTRODUCTION

Spinal cord injuries are devastating, life-altering events for patients and their families [1,2]. The incidence of acute spinal cord injury (SCI) is about 10 000–12 000 per year, with an estimated prevalence of about 350 000 patients in the United States [3]. Young men in their late 20s to mid-30s represent the predominant patient population, with a three-fold to four-fold increased incidence compared with the female gender [4▪]. Although spine injuries are rare as compared with the overall incidence of other skeletal injuries (around 1% of all fractures), their incidence increases in high-energy trauma mechanisms, multiply injured patients and in the presence of traumatic brain injury [5].

INJURY CLASSIFICATION

The severity of SCI is classified according to the impairment scale published by the American Spinal Injury Association (ASIA). The extent of neurological injury is stratified into 'complete' (ASIA grade A) or 'incomplete' (ASIA grades B-D), with ASIA grade E reflecting a normal neurological status (Fig. 1) (www.asia-spinalinjury.org). SCI is further stratified into paraplegia (paralysis of the lower extremities), resulting from thoracic and lumbar spine injuries, and quadriplegia (paralysis of all four extremities), which originates from cervical spine injuries [6]. With incomplete injuries, the patient has some extent of preserved neurological function below the level of injury, which is associated with a better

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Curr Opin Crit Care 2012, 18:651–660
DOI:10.1097/MCC.0b013e32835a0e54

KEY POINTS

- Basic management principles for acute spinal cord injury include adequate oxygen delivery and blood flow in conjunction with early surgical measures of spine reduction, stabilization and fixation coupled with spinal cord decompression and restoration of spinal canal dimensions.
- The adult central nervous system is inherently incapable of regeneration, and there are currently no pharmacological strategies available to heal the injured spinal cord.
- The routine use of corticosteroids has been abandoned as a 'harmful' standard of care for patients with acute spinal cord injuries.
- Promising new experimental strategies for attenuating neuroinflammation in the injured spinal cord include site-targeted complement inhibition and the administration of synthetic PPAR agonists.
- Nogo-A represents a potent endogenous inhibitor of regenerative sprouting of injured axons and a new pharmacological target which is currently under investigation in clinical trials.

outcome prediction than complete injuries, in which the prognosis is dismal [7▪].

Traumatic spinal dislocations, vertebral fractures and fracture-dislocations are classified by the comprehensive Arbeitsgemeinschaft fuer Ostesynthesefragen/Orthopaedic Trauma Association classification system [8]. In brief, the anatomic region is defined by a number (51 for cervical, 52 for thoracic, 53 for lumbar spine), whereas the injury severity is assigned an alpha-numeric grade (A,B,C and 1,2,3), which increases with injury severity (Fig. 2). 'A-type' fractures occur as a result of axial loading to the anterior spinal column and are frequently stable. The A3 subtype of burst fractures may be associated with acute SCI in the case of fragment dislocation into the spinal canal, leading to spinal cord compression [9]. The entity of 'B-type' injuries represents unstable three-column injuries secondary to flexion/distraction (B1/B2) or hyperextension (B3) mechanisms [9]. The worst extent of traumatic spinal injuries is reflected by 'C-type' fractures, which represent rotationally unstable fracture-dislocations. The incidence of SCI increases with the alpha-numeric fracture classification, from near 0% in stable A1-type compression fractures to near 100% in C3-type injuries (Fig. 2). The C3-type is representative of the most severe and unstable injury pattern of any spinal fracture, termed a 'Holdsworth' injury, a 'slice' fracture or a 'traumatic spondyloptosis' [9,10].

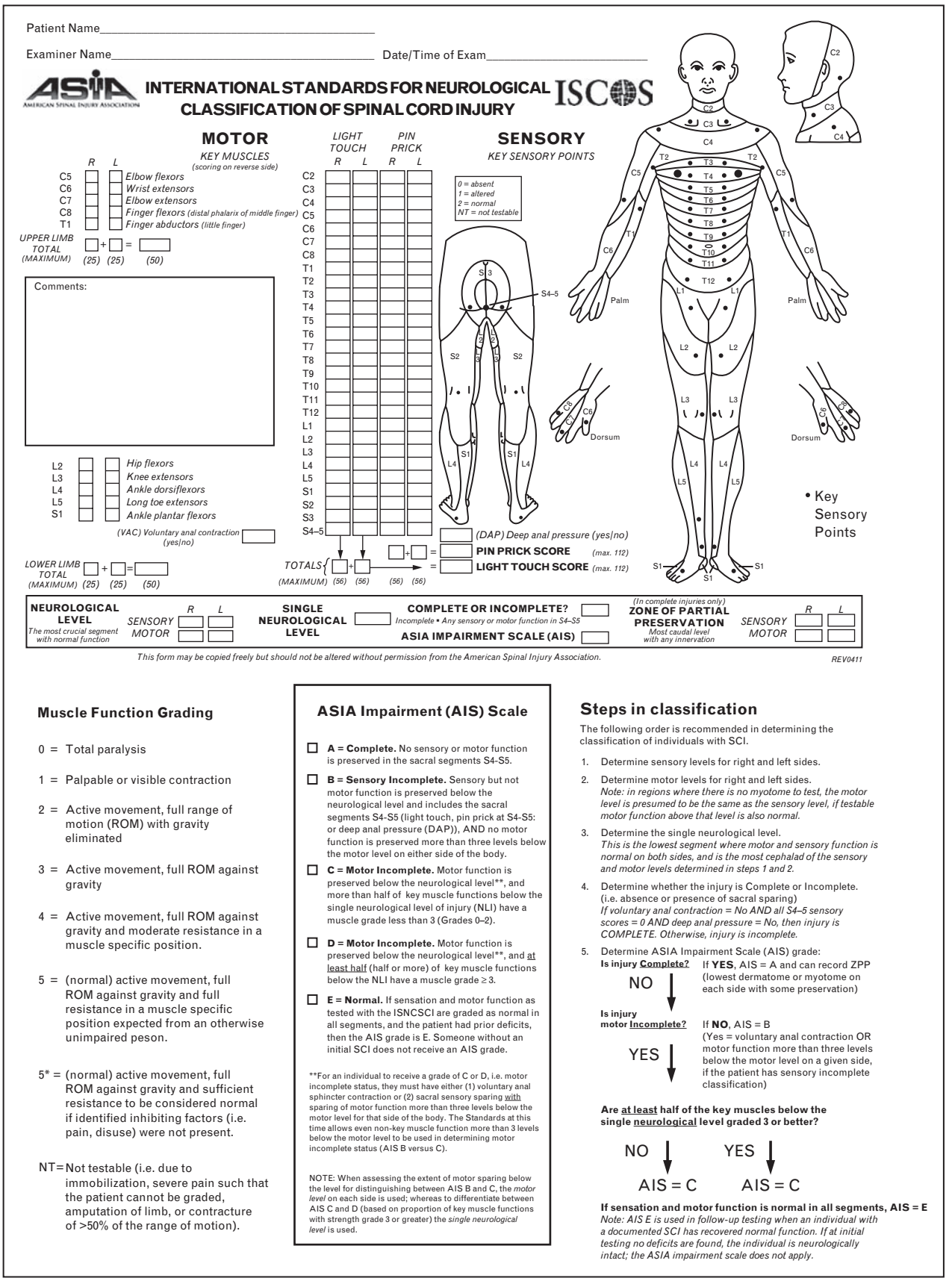
NEUROINFLAMMATION AND SECONDARY SPINAL CORD INJURY

The primary traumatic injury to the spinal cord occurs as a result of the mechanical impact to the spine, leading to acute compression of the spinal canal from displaced bone or interverterbral disk, or from acute kinking of the spinal cord at the time of injury [3]. A complete transection of the spinal cord is rare but may occur from high-energy rotational/translational forces, as, for example, in the case of C3-type 'slice' fractures (Fig. 3). In contrast, spinal contusions and diffuse shearing injuries from stretching of axons occur more frequently as a consequence of the direct primary injury to nerve cells [11]. This primary trauma induces the so-called 'secondary' injuries, which evolve over time and lead to a delayed deterioration of the initial extent of injury [12,13▪]. The ensuing host-mediated immunological response mediates neuroinflammation and perpetuates neurodegeneration and cytotoxicity within the injured spinal cord [11,14–18].

Resident cells in the injured central nervous system (CNS) are activated in response to the traumatic impact and initiate an orchestrated neuroinflammatory response, mediated by pro-inflammatory cytokines, chemokines and complement activation products [18,19▪,20–23]. Chemotaxis by chemokines and complement anaphylatoxins leads to transmigration of haematogenous inflammatory cells, such as neutrophils, macrophages and lymphocytes, into the injured CNS [24,25▪▪,26▪,27]. These infiltrating leukocytes perpetuate the neuroinflammatory response by the local release of neurotoxic molecules, including reactive oxygen species, nitrogen-derived free radicals, proteases and other neurotoxic enzymes [28,29▪,30–32]. These secondary pathophysiological events ultimately lead to breakdown of the blood–spinal cord barrier (BSCB), which allows for an uncontrolled leakage of systemic toxic molecules, such as matrix metalloproteases and other inflammatory mediators, into the subarachnoid space in the injured spinal cord [14,33,34▪,35–37]. This 'vicious cycle' of self-perpetuating exacerbated neuroinflammation leads to spinal oedema, expansion of the primary traumatic lesion and delayed neuronal cell death [12]. Until present, there is not a single pharmacological agent available on the market that would prevent the development of secondary SCI and induce regenerative processes aimed at healing the spinal cord and restoring neurological function [38,39▪].

GENERAL MANAGEMENT

The basic management principles for patients with acute SCI consist of protection of airway and



Muscle Function Grading

0 = Total paralysis

1 = Palpable or visible contraction

2 = Active movement, full range of motion (ROM) with gravity eliminated

3 = Active movement, full ROM against gravity

4 = Active movement, full ROM against gravity and moderate resistance in a muscle specific position.

5 = (normal) active movement, full ROM against gravity and full resistance in a muscle specific position expected from an otherwise unimpaired peson.

5* = (normal) active movement, full ROM against gravity and sufficient resistance to be considered normal if identified inhibiting factors (i.e. pain, disuse) were not present.

NT = Not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of >50% of the range of motion).

ASIA Impairment (AIS) Scale

☐ **A = Complete.** No sensory or motor function is preserved in the sacral segments S4-S5.

☐ **B = Sensory Incomplete.** Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5 (light touch, pin prick at S4-S5: or deep anal pressure (DAP)), AND no motor function is preserved more than three levels below the motor level on either side of the body.

☐ **C = Motor Incomplete.** Motor function is preserved below the neurological level**, and more than half of key muscle functions below the single neurological level of injury (NLI) have a muscle grade less than 3 (Grades 0–2).

☐ **D = Motor Incomplete.** Motor function is preserved below the neurological level**, and at least half (half or more) of key muscle functions below the NLI have a muscle grade ≥ 3.

☐ **E = Normal.** If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

**For an individual to receive a grade of C or D, i.e. motor incomplete status, they must have either (1) voluntary anal sphincter contraction or (2) sacral sensory sparing with sparing of motor function more than three levels below the motor level for that side of the body. The Standards at this time allows even non-key muscle function more than 3 levels below the motor level to be used in determining motor incomplete status (AIS B versus C).

NOTE: When assessing the extent of motor sparing below the level for distinguishing between AIS B and C, the *motor level* on each side is used; whereas to differentiate between AIS C and D (based on proportion of key muscle functions with strength grade 3 or greater) the *single neurological level* is used.

Steps in classification

The following order is recommended in determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
2. Determine motor levels for right and left sides.
   Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.
3. Determine the single neurological level.
   This is the lowest segment where motor and sensory function is normal on both sides, and is the most cephalad of the sensory and motor levels determined in steps 1 and 2.
4. Determine whether the injury is Complete or Incomplete. (i.e. absence or presence of sacral sparing)
   If voluntary anal contraction = No AND all S4–5 sensory scores = 0 AND deep anal pressure = No, then injury is COMPLETE. Otherwise, injury is incomplete.
5. Determine ASIA Impairment Scale (AIS) grade:
   Is injury Complete? If **YES**, AIS = A and can record ZPP (lowest dermatome or myotome on each side with some preservation)
   NO ↓
   Is injury motor Incomplete? If **NO**, AIS = B (Yes = voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)
   YES ↓
   Are at least half of the key muscles below the single neurological level graded 3 or better?
   NO ↓ AIS = C
   YES ↓ AIS = C

If sensation and motor function is normal in all segments, AIS = E
Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA impairment scale does not apply.

FIGURE 1. Neurological impairment scale by the American Spinal Injury Association (ASIA) for grading the level and extent of spinal cord injury. Reproduced with permission by ASIA (www.asia-spinalinjury.org).

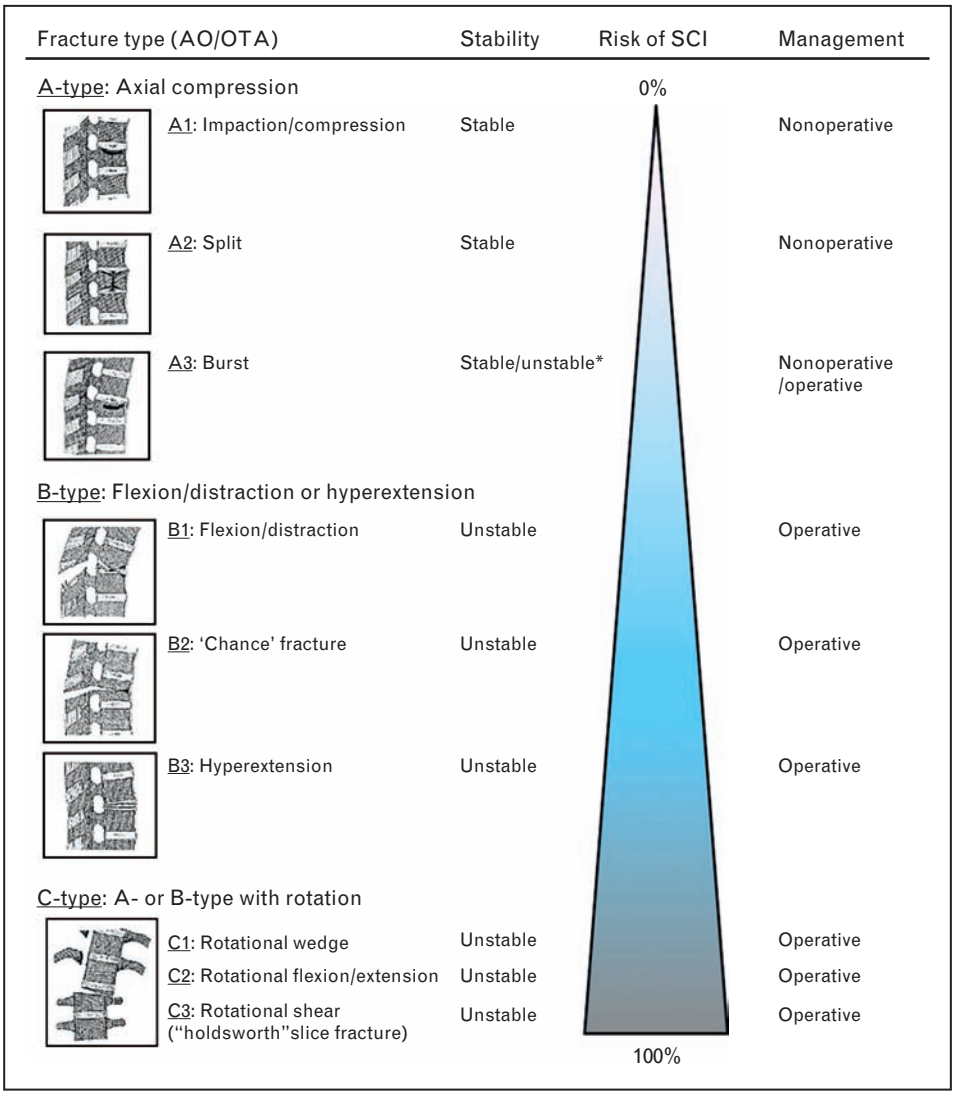


FIGURE 2. Correlation between injury severity on the basis of the standardized Arbeitsgemeinschaft fuer Ostesynthesefragen/Orthopaedic Trauma Association classification to the likelihood of an associated spinal cord injury. SCI, spinal cord injury. ∗Indication for operative intervention for A3 burst fractures depends on the extent of compression of the spinal canal, the presence of neurological injury and the extent of comminution and kyphotic deformity. Reproduced with permission [8].

breathing/ventilation, ensuring adequate oxygenation, acute control of blood loss and maintenance of adequate blood pressure through volume and vasopressors, if required [40,41]. The standardized 'Advanced Trauma Life Support' (ATLS) protocol provides guidance for the initial assessment and management of trauma patients with associated spinal injuries [42]. The presence of an unstable spinal injury must be suspected in any patient who sustained a high-energy trauma mechanism, independent of a neurological impairment [43▪]. The leading symptom of a spinal injury is pain in the back and/or neck, with tenderness to palpation [44]. In the prehospital setting, the management of patients with suspected spine injuries consists of complete immobilization, exact documentation and timing of the clinical findings, and immediate evacuation to a designated level 1 trauma centre [45,46]. Per ATLS protocol, the entire spine remains protected during the primary survey, by the use of a long spine-board and a cervical collar [42]. Hard back boards must be removed as soon as safely possible due to the high risk of developing pressure sores and decubitus ulcers after prolonged immobilization [44]. A cervical collar is kept in place until formal spine clearance, which usually requires additional radiographic workup [47,48].

Spinal injuries are identified and worked-up during the secondary survey, after successful life-saving measures [42,49]. Most spine injuries do not

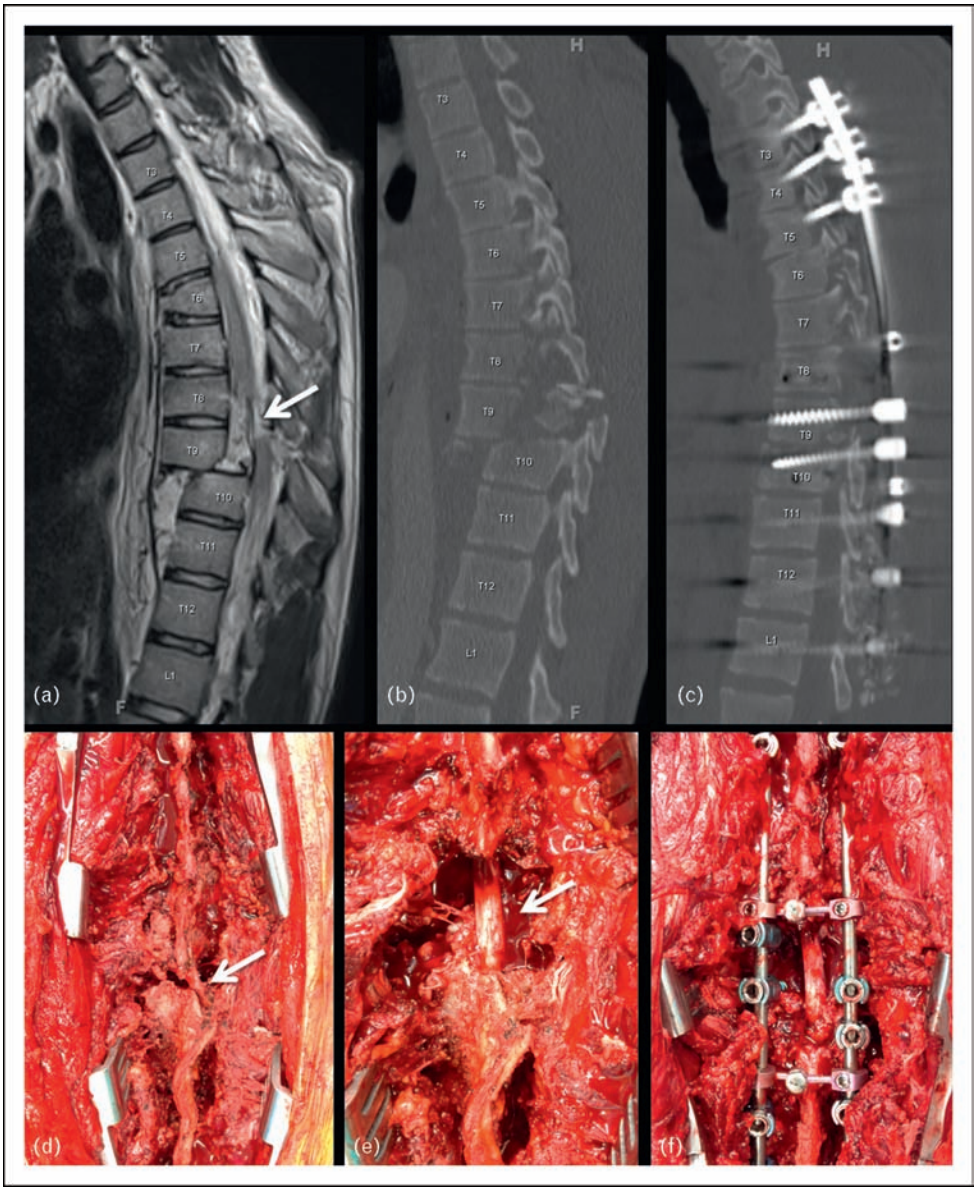


FIGURE 3. Case example of a C3-type 'Holdsworth' slice fracture-dislocation with a complete spinal cord transsection. This 27-year-old patient sustained a direct hit in conjunction with a twisting injury to the thoracic spine after a fall from a balcony, leading to a rotationally and translationally unstable fracture-dislocation. The patient was paraplegic at the accident site, with a complete spinal cord injury (American Spinal Injury Association grade A). The initial MRI shows the extent of displacement at T9/T10 and the spinal cord transsection at T8/T9 (arrow in panel A). The sagittal CT reconstruction demonstrates the amount of translational displacement at T9/T10 (panel B) and the surgical restoration of the sagittal profile with posterior instrumentation T3-L1 (panel C). The posterior ligamentous injury and laminar fracture (arrow in panel D) and the exposed spinal cord after surgical decompression (arrow in panel E) and posterior instrumentation (panel F) illustrate the early surgical management in terms of a 'spine damage control' procedure on day 1.

present with a neurological impairment [44]. If a patient has signs of numbness, tingling sensation or paralysis to any extremity, a serious injury to the spinal cord must be suspected [44]. Impairment to bladder and bowel function are frequently missed on initial evaluation, which speaks to the absolute necessity of a thorough rectal examination including motor, sensory and reflexes [44].

The diagnostic work-up of spinal injuries includes plain radiographs, computed tomography (CT) scans and MRI for visualization of soft-tissue injuries to ligaments and intervertebral discs, epidural bleeding, dural tears, spinal cord contusions and lacerations, and intramedullary lesion expansion over time [50]. However, MRI must be exclusively obtained in patients who are haemodynamically

stable due to difficult access to these patients while in the scanner [41]. The initial work-up of multiply injured patients by multislice 'whole-body' CT scans provides thin-section images of the entire spine, along with two-dimensional and three-dimensional reconstructions [49,51]. In this regard, the imaging modality has drastically changed in the past decade, whereby a full-body CT scan has largely replaced the necessity of obtaining conventional radiographs of the entire spine to prevent missing additional vertebral fractures at a different level, which occur in approximately 10% of all cases [42,52].

SURGICAL STRATEGIES

Any unstable fracture and/or dislocation of the spine with acute neurological impairment must be recognized early and managed in a timely fashion [53,54▪]. The basic management principles include restoration of the coronal, sagittal and axial profiles by closed or open reduction manoeuvers, decompression of the spinal canal through posterior and/or anterior approaches and the stabilization of unstable spinal segments by surgical fusion and instrumentation [9,55]. Proactive modern protocols of 'spine damage control' have recently demonstrated that the early surgical fixation of unstable spine fractures on 'day 1' results in decreased complication rates and improved outcomes in severely injured patients with or without SCI [56▪▪,57–59]. Clearly, the optimal timing of spinal fixation will continue to depend on individual surgeons' preference and institutional capacity and logistic support [60]. Although common sense would dictate that any compression on the spinal cord should be alleviated as soon as possible, there is currently a lack of solid evidence-based recommendations regarding the 'optimal' timing of spinal decompression and fixation [61]. Future prospective studies will hopefully provide some scientific clarification for this onging debate and allow the design and implementation of standardized institutional protocols to mandate a specific time-window for early surgical management of patients with acute SCI [59].

NONINVASIVE TREATMENT OPTIONS

Healing of the injured spinal cord represents one of the remaining unresolved challenges and 'frontiers' in modern medicine [12]. Research strategies designed to interrupt the pathophysiological sequelae of secondary SCI have largely failed in translation from the 'bench to beside', and there is currently not a single pharmacological agent available to heal the injured spinal cord and restore function [62,63▪▪,64,65,66▪▪,67]. A few selected noninvasive treatment modalities of current interest and ongoing debate are presented in the following sections.

THERAPEUTIC HYPOTHERMIA – FACT OR FAD?

Systemic hypothermia has been investigated for decades as a noninvasive modality of neuroprotection for patients with head injuries, cerebrovascular stroke, cardiac arrest and SCI [39▪,68]. The underlying rationale of moderately lowering the patient's body temperature is aimed at slowing down the acute inflammatory processes in the injured CNS and to reduce the extent of traumatic and ischaemic tissue injury [69]. The recent report of a professional football player, who was apparently 'rescued' by systemic hypothermia after sustaining a C3/C4 fracture-dislocation with complete (ASIA A) SCI, raised wide public interest in this treatment option [70]. The causal role of neuroprotection by hypothermia in this prominent case was widely scrutinized on the basis of the notion that the early restoration of function may have been attributed to spontaneous recovery from an incomplete SCI, after resolution of spinal shock [71].

Unquestionably, the bulk of the peer-reviewed literature regarding the efficiency of systemic hypothermia for neuroprotection in SCI is largely derived from experimental studies in animal models [63▪▪]. In light of the current lack of scientific evidence from controlled clinical trials in humans, systemic hypothermia has to be considered a pure empirical and experimental treatment option, despite anecdotal testimonies for its clinical application [70]. Notably, the historic euphoria regarding therapeutic hypothermia for patients with severe head injuries in the 1990s [72] was revoked in further clinical validation studies, and therapeutic hypothermia is no longer recommended for this indication [73]. This example should serve as a 'red flag' reminder to exert caution regarding the unjustified enthusiasm for a therapeutic modality in absence of high quality science.

Role of steroids revisited

The challenge and limitations of extrapolating knowledge derived from animal studies to successful implementation of pharmacological treatment for patients with SCI are most explicitly outlined by the role of steroids [74–76]. The administration of high-dose steroids was a standard of care for patients with brain tumours and head injuries in the 1960s and 1970s, due to the presumed beneficial effect of lowering intracranial pressure and attenuating cerebral oedema [77]. After publication of the 2nd 'National

Acute Spinal Cord Injury Study' (NASCIS-2) in 1990, the application of high-dose methylprednisolone for patients with acute SCI became a globally accepted standard of care for more than a decade [78,79]. Over time, however, the uncritical administration of high-dose steroids came under scrutiny due to the questionable benefit and the potential for inflicting unintentional harm to patients with SCI [74]. The alleged 'experimental' nature of steroid administration [74] was later confirmed by the 'CRASH' trial (Corticosteroid randomization after significant head injury) on patients with traumatic brain injuries [80]. This large-scale, prospective, randomized, multicentre trial was aborted after enrollment of about 10 000 patients, based on the unexpected finding of a drastically increased mortality in patients treated with methylprednisolone compared with the placebo control group [80]. The negative results from the 'CRASH' trial initiated a provocative editorial in *The Lancet*, suggesting that the uncritical administration of corticosteroids in the 1980s and earlier may have been the cause of preventable postinjury mortality [81]. In absence of new prospective randomized trials on the role of steroids in SCI, current guidelines and clinical recommendations consider the routine use of steroids for patients with acute SCI obsolete [42].

Is Nogo the way to go?

Neuronal plasticity and axonal regeneration are limited in the adult spinal cord due to the presence of inhibitory molecules, the most potent of which has been designated as Nogo-A [82]. Nogo-A is mainly expressed by oligodendrocytes and inhibits regenerative sprouting of injured axons [83]. The pharmacological inhibition of Nogo-A has been identified as a promising new therapeutic approach for ameliorating functional recovery in patients with SCIs [84,85▪▪].

Experimental studies in genetically engineered Nogo 'knock-out' mice showed that the absence of Nogo leads to extensive postinjury sprouting of corticospinal axons and recovery of locomotor function compared with wild-type littermates [86,87]. The extrapolation to therapeutic approaches in experimental SCI models revealed that the application of neutralizing anti-Nogo-A antibodies restores long-distance axonal regeneration and functional recovery in rodents and nonhuman primates [88,89]. These encouraging data prompted the launch of a prospective clinical multicentre trial, designed to determine the effect of the intrathecal infusion of an antihuman Nogo-A antibody [ATI 355; Novartis (US headquarters: East Hanover, New Jersey. Global headquarters: Basel, Switzerland)] on the functional recovery of patients with complete and incomplete SCI [84]. This promising trial is currently underway and raises significant hope for approaching the 'holy grail' in medicine – the therapeutic healing of the injured spinal cord.

Future perspectives

The underlying mechanisms responsible for limited functional regeneration in the injured spinal cord have been extensively investigated in recent years. Mesenchymal stem cell transplantation is being thoroughly investigated as a new regenerative treatment option aimed at restoring the injured spinal cord [90]. This intriguing therapeutic modality is currently under investigation in animal research, but its applicability in humans remains in question [91–95]. Promising new opportunities for pharmacological modulation of the posttraumatic inflammatory response include a novel generation of complement therapeutics with the capacity of being 'targeted' to sites of complement activation, such as complement receptor type-2 (CR-2)-based chimeric compounds that exert a potent anti-inflammatory activity at the local site of tissue injury [12,96,97▪,98].

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated, membrane-associated transcription factors belonging to the nuclear hormone receptor family, which have been identified as 'key' regulators of neuroinflammation after CNS injury [99]. Three subtypes of PPAR have been described (PPARα, PPARβ/δ and PPARγ) which exhibit differential tissue distribution and ligand specificity [100]. These PPAR ligands represent promising new pharmacological agents to attenuate the postinjury inflammatory response [101–103]. A wide range of synthetic compounds functioning as PPAR ligands have been recently developed, of which the most prominent classes are represented by fibrates (PPARα agonists) and glitazones (PPARγ agonists) [104]. These pharmacological compounds are currently under investigation in multiple experimental animal models of SCI, with promising early results [105▪,106–111].

These promising experimental treatment modalities still await successful extrapolation to clinical trials in the future.

CONCLUSION

Acute SCI is a detrimental condition, which still lacks a pharmacological therapy capable of healing the injured spinal cord and restoring function. At present, the standard management principles

consist of ensuring adequate oxygenation and blood flow, in conjunction with early decompression of the spinal cord and restoration of spinal anatomy and spinal stability by surgical measures. The pharmacological blockade of Nogo-A, which is currently investigated in prospective clinical trials, represents the most promising modality for regeneration of the injured spinal cord. Future progress unequivocally relies on extensive basic research with the hope for successful translation into clinical treatment strategies.

Acknowledgements

None.

Conflicts of interest

Written informed consent was obtained from the patient depicted in Fig. 3 for publication of the radiographs and intraoperative pictures. Dr Stahel's basic research studies are supported by a grant from the Colorado Traumatic Brain Injury Trust Fund (COTBITF). Dr Stahel received occasional speaker's honoraria from Stryker Spine in the past 5 years. The authors declare no further conflicts of interest related to this manuscript.

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