Traumatic spinal cord injury

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Abstract

Traumatic spinal cord injury (SCI) has devastating consequences for patients' physical, social, and vocational wellbeing. The demographic of SCIs is shifting such that an increasing proportion of older individuals are being affected. Pathophysiologically, the initial mechanical trauma (the primary injury) permeabilizes neurons and glia and initiates a secondary injury cascade that leads to progressive cell death and spinal cord damage over the subsequent weeks. Over time, the lesion remodels and is composed of cystic cavitations and a glial scar, both of which potently inhibit regeneration. Several animal models and complementary behavioural tests of SCI have been developed to mimic this pathological process and form the basis for development of preclinical and translational neuroprotective and neuroregenerative strategies. Diagnosis requires a thorough patient history, standardized neurological physical examination and radiographic imaging of the spinal cord. Following diagnosis, several interventions need to be rapidly applied, including haemodynamic monitoring in the intensive care unit, early surgical decompression, blood pressure augmentation and, potentially, the administration of methylprednisolone. Managing the complications of SCI, such as bowel and bladder dysfunction, the formation of pressure sores and infections, is key to address all facets of the patient's injury experience.

[H1] Introduction

Spinal cord injury (SCI) is defined as damage to the spinal cord (Figure 1) that temporarily or permanently causes changes in its function. SCI is divided into traumatic and non-traumatic aetiologies.[1] Traumatic SCI occurs when an external physical impact (for example, motor vehicle injuries (MVI) , fall, sports-related injury and violence) acutely damages the spinal cord, whereas non-traumatic SCI occurs when an acute or chronic disease process, most commonly tumours, but also infection or degenerative disc disease, generates the primary injury.

In traumatic SCI, the primary insult damages cells and initiates a complex secondary injury cascade, which cyclically produces the death of neurons and glial cells, ischaemia and inflammation. This cascade is followed by changes in the organisation and structural architecture of the spinal cord, including the formation of a glial scar and cystic cavities. The glial scar and cystic cavities, in combination with poor endogenous remyelination and axonal regrowth mean the spinal cord has a poor intrinsic recovery potential, such that SCI causes permanent neurological deficits.

SCIs have devastating physical, social and vocational consequences for patients and their families and a loss of independence and persistently elevated lifelong mortality rates are the hallmarks of SCI. Furthermore, the direct costs for the care of patients with SCI are staggering at US $1.1-4.6 million per patient over their lifetime, which underscores the role of prevention as the most important intervention we can deliver. For SCI that cannot be prevented, the development of effective treatments becomes critically important[2].

The past three decades have marked an exciting time for the field, as numerous neuroprotective and neuroregenerative therapies have been translated from preclinical studies

into clinical trials. Although undoubtedly impressive, further progress will require a concerted effort to better understand the pathophysiological cascade of SCI, limitations in translating data obtained from animal models and how to apply combinatorial treatments to this complex, multifaceted disease process.

This Primer provides new researchers with a succinct, up-to-date foundation on SCI. Discussed herein are key aspects of epidemiology, pathophysiology and patient presentation, relevant to both translational researchers and basic scientists. The Primer also provides an overview of important in-practice and upcoming therapeutic strategies including medical, surgical and cell-based treatments and concludes with the current outlook for patients and future directions of the field.

[H1] Epidemiology

[H2] Incidence and prevalence

Epidemiological data on SCI are often divided into traumatic and non-traumatic aetiologies, suggesting important epidemiological distinctions.[1] However, data are most often reported by individual national or provincial databases making generalizations between countries difficult. In addition, data are often retrospective and based on treatment codes or surgical procedures, which fail to capture the true incidence and prevalence of SCI.

The incidence of SCI varies worldwide (Figure 2).[3] Among developed regions, the incidence of traumatic SCI is higher in North America (39 cases per million individuals) than in Australia (16 cases per million individuals) or Western Europe (15 cases per million individuals), due to higher rates of violent crime and self-harm.[4] By comparison, the prevalence of non-traumatic

SCI has been estimated as 1,227 cases per million individuals in Canada and 364 cases per million individuals in Australia; reliable data from other countries are not available.[5,6]

Traumatic SCI occurs more commonly in males (79.8 %) than females (20.2 %)[7]. The age profile of individuals with a traumatic SCI has a bimodal distribution; one peak is between 15–29 years of age and the second, smaller but growing peak, is in those >50 years of age.[8,9] In the USA, the proportion of patients with traumatic SCI >60 years of age increased from 4.6% in 1970 to 13.2% in 2008.[10,11] This trend is continuing in parallel with the aging population of the world[7].

Traffic accidents are the primary cause of all traumatic SCIs in North America, and accounted for 38% of injuries between 2010–2014, although this number is gradually declining[7]. Falls are typically the second most common cause of traumatic SCIs, and accounted for 31% of injuries between 2010–2014, followed by sports-related injuries, which account for 10-17% of traumatic SCIs.[9,11] High-energy impacts, such as traffic accidents and sport-related injuries are more common in younger persons, whereas low-energy impacts, such as falls, disproportionately occur in persons >60 years of age, in whom underlying spinal degenerative changes, such as degenerative cervical myelopathy, are common.[9,11] Indeed, the incidence of cervical SCI for the general population (0.13 per thousand-years)[12] is much lower than for patients with degenerative cervical myelopathy is (12.33 per thousand-years)[13]. Overall in the general population, traumatic SCI occurs most frequently at the level of the cervical spine (~60%), followed by thoracic (32%) and lumbosacral (9%)[7].

[H2] Mortality

Although the survival of patients with traumatic SCI has improved over time, patients continue to have mortality rates that exceed those of age-matched controls [14]. Estimates for acute in-hospital mortality range from 4-17%, then after hospital discharge, annual mortality rates remain persistently high, with 3.8% of patients dying in the first year after injury, 1.6% in the second year and then 1.2% for every year thereafter. The risk of mortality increases with more severe injuries, higher injury levels (that is, cervical SCIs are associated with higher mortality than lumbar SCIs), increasing patient age, the presence of multi-system trauma and higher energy injury mechanisms. Despite modern medical care, patients with traumatic SCI have a significantly reduced lifespan. For example, a 40 year old's life expectancy after SCI is lowered to 23 years after C5-8 injury, 20 years after C1-4 injury and 8.5 years if they are ventilator-dependent[2].

[H1] Mechanisms/pathophysiology

[H2] Acute injury phase

Traumatic SCI is pathophysiologically divided into primary and secondary injuries and can be temporally divided into the acute (<48 hours), subacute (48hours – 14 days), intermediate (14 days – 6 months) and chronic (>6 months) phases (Figure 3). The initial traumatic event (that is, the primary injury) produces immediate mechanical disruption and dislocation of the vertebral column, which causes compression or transection of the spinal cord. This focal region of damage injures neurons and oligodendrocytes (that is, the myelinating cell type of the CNS), disrupts the vasculature, and compromises the blood-spinal cord barrier. Together, these

events immediately initiate a sustained secondary injury cascade, which leads to further damage to the spinal cord and neurological dysfunction. This damage can often be in excess to that caused by the primary injury.

Secondary cellular changes during the acute phase of injury, such as cell dysfunction and death are caused by cell permeabilization, pro-apoptotic signalling and ischaemic injury due to the destruction of the microvascular supply of the spinal cord within minutes of injury.[15,16] In addition, blood vessel injury can cause severe haemorrhages, which can expose the cord to an influx of inflammatory cells, cytokines and vasoactive peptides. Indeed, elevations in proinflammatory cytokines, such as tumour necrosis factor (TNF-α) and IL-1β, are evident in the spinal cord within minutes of injury [17]. This parallels the arrival of inflammatory cells (such as macrophages, neutrophils and lymphocytes) into the spinal cord, which remain in the cord well beyond the subacute phase. The subsequent overwhelming inflammatory response in the acute and subacute phases of injury, combined with the disrupted blood-spinal cord barrier, progressively add to spinal cord swelling. Swelling can lead to further mechanical compression of the cord, which can extend for multiple spinal segments and worsen the injury.

[H2] Subacute injury phase

In the acute to subacute period, ischaemia and excitotoxicity contribute to a loss of intra- and extra-cellular ionic homeostasis occurs due to ischaemia and excitotoxicity, with a key mediator of cell death being intracellular calcium dysregulation in both neurons and glia. Data from animal models suggests that high intracellular calcium concentration activate calpains, which can cause mitochondrial dysfunction and cell death[18,19]. Furthermore, ongoing

necrosis of neurons and glia due to ischemia, inflammation, and excitotoxicity releases ATP, DNA and potassium, which can activate microglial cells. Activated microglia, in addition to other inflammatory cells such as activated macrophages, polymorphonuclear cells and lymphocytes, infiltrate the injury site, where they propagate the inflammatory response and contribute to ongoing apoptosis of neurons and oligodendrocytes. Phagocytic inflammatory cells can clear myelin debris at the injury site, but can also induce further damage to the spinal cord through the release of cytotoxic by-products, including free radicals (for example, $O2^-$, hydrogen peroxide and peroxynitrite). These reactive oxygen species cause lipid peroxidation, DNA oxidative damage and protein oxidation, which causes additional necrotic and delayed apoptotic cell death, contributing to the harsh post-injury microenvironment[20,21].

High levels of the neurotransmitter glutamate are released from dying neurons and astrocytes and are poorly reabsorbed by surviving astrocytes[22,23]. This causes methyl-D-aspartate (NMDA), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), and kainate receptor overactivation, which, combined with loss of ATP-dependent ion pump functions and subsequent resultant sodium dysregulation, can lead to excitotoxic cell death[24,25]. Neuron death due to excitotoxicity, as well as the other insults discussed above, cyclically propagates the secondary injury cascade[19].

The impaired autoregulatory capacity of the injured cord vasculature, in addition to the systemic effects of SCI (such as hypotension and respiratory failure; see later), can contribute to ongoing ischaemia that persists for days to weeks after injury. Prolonged ischaemia contributes to further neuronal and glial (predominantly oligodendrocyte) cell death and the propagation of the injury. The multiple causes of cell death that occur during the acute and subacute phases of

SCI can produce greater damage than the original primary injury and form the basis for the neuroprotective interventions (see below).

[H2] Intermediate-chronic phase

As the acute inflammatory response subsides, the spinal cord lesion evolves through dynamic intermediate through chronic phases that are marked by attempts at remyelination, vascular reorganization, alterations in the composition of the extracellular matrix (ECM) and remodelling of neural circuits [19].

[H3] Cystic cavitations. In humans, the overwhelming cell death and degeneration in the acute phase of injury promotes the *ex vacuo* (i.e. loss of tissue volume) formation of cystic, which contain extracellular fluid, thin bands of connective tissue and macrophages[26]. The cystic cavities coalesce to become a formidable barrier to directed axonal regrowth and are a poor substrate for cell migration[27,28].

[H3] Glial scar. Studies using animal models have shown a perilesional zone around the cystic cavities, in which reactive astrocytes proliferate and tightly interweave their processes, creating an inhibitory mesh-like array. In the acute phase, signalling from activated microglia, astrocytes and macrophages causes the secretion of ECM proteins that are inhibitory to axonal growth, such as chondroitin sulfate proteoglycans (CSPGs), tenascin and NG2 proteoglycan, which condense with astrocytes to form the glial scar. The glial scar potently restricts axon

regeneration (that is, the repair or regrowth of existing neural pathways, or the development of *de novo* pathways) and anatomical plasticity by inhibiting neurite outgrowth [29,30].

Oligodendrocyte progenitor cells that express NG2 proteoglycan migrate to the lesion site and associate with dystrophic axons (that is, swollen, injured axons that can be found in the damaged CNS). Pericytes also proliferate after SCI, giving rise to stromal cells that might deposit numerous ECM proteins [31]. Furthermore, fibroblasts can infiltrate the perilesional region, particularly after breaks in the glial layer that separates neural tissue from the meninges[26], to replace the ECM with fibrous connective tissue and dense collagen deposits. Together, these ECM and cellular changes represent a significant physical and biochemical barrier to regeneration. However, not all aspects of the scar pose an inhibitory barrier[32]; complete attenuation of astrocytes in the glial scar results in impaired regeneration, as astrogliosis in the acute-subacute phases is responsible for isolating the injury site, to reduce the spread of cytotoxic molecules and inflammatory cells into adjacent, uninjured parenchyma[33,34]. Furthermore, perilesional astrocytes might provide local trophic support and promote neovascularization [35]. This dual role of the glial scar continues to be investigated.

[H3] Adult CNS myelin. Even if regenerative efforts are able to overcome spinal cord lesions, properties of the adult mammalian CNS can still limit neurite regrowth. For example, molecules present in myelin are potent inhibitors of axon regeneration and several molecules released by degenerating oligodendrocytes can contribute to the failure of regeneration. These molecules include neurite outgrowth inhibitor A (Nogo-A), oligodendrocyte-myelin glycoprotein (OMgp) and myelin-associated glycoprotein (MAG), which can all bind to the Nogo receptor and p75

neurotrophin receptor (p75NTR) to activate RhoA and Rho-associate protein kinase (ROCK), which causes growth cone collapse, neurite retraction and increases the risk of apoptosis[36]. CSPGs in the glial scar can also activate the Nogo receptor, in addition to the membrane-bound protein tyrosine phosphatase θ (PTPθ) to trigger growth cone collapse via the Rho-ROCK pathway[37]. Interestingly, individual knockout of Nogo, MAG and OMgp showed limited effects on axon regeneration *in vivo*, potentially due to synergistic inhibitory activity of myelin-associated proteins and CSPGs on axonal regeneration [38,39]. This continues to be an area of active investigation.

[H3] Attempts at remyelination. Although severe SCI can destroy substantial portions of the spinal cord white matter, a surviving subpial rim of demyelinated axons can persist in a rodent model of injury[40]. These neurons are susceptible to subsequent injury and progressive Wallerian degeneration (that is, an ordered process of axonal death)[41,42]. In theory, Oligodendrocyte precursor cells can differentiate into mature oligodendrocytes and remyelinate these axons. However, remyelination requires a coordinated inflammatory response by macrophages, lymphocytes and astrocytes, and is inhibited by the presence of EphrinB3 in myelin debris[43,44], as well as molecules within the glial scar [36,45,46]. This could lead to poor remyelination post-injury, which in turn impairs functional recovery[47].

[H2] Endogenous attempts at repair

Contrary to historical dogma, endogenous mechanisms exist for at least partial regeneration of the injured spinal cord. CNS neurons exhibit both anatomical and synaptic plasticity, which might contribute to ongoing functional recovery for years after injury[48,49]. Furthermore, neural precursor cell pools, which are mostly found in the ependymal layers of the central canal, as well as widely-distributed oligodendrocyte precursor cells, can generate neurons, oligodendrocytes and astrocytes (including reactive astrocytes)[50,51]. These cells might have both helpful and detrimental roles throughout the post-injury regenerative process. Exploiting these endogenous mechanisms by increasing the recruitment of pro-regenerative cells[52], producing a microenvironment more conducive to cell migration and neurite outgrowth[53], and/or shifting the balance towards pro-regenerative cell phenotypes[54] are some of the exciting areas of ongoing research. These and other mechanisms can be supplemented by the neuroprotective and neuroregenerative strategies discussed later, but barriers to regeneration still exist, meaning additional therapies to remove or overcome these barriers are necessary.

[H2] Animal models

Animal models have contributed to our understanding of the pathophysiology of SCI and have been useful for the preclinical testing of new therapies. The ideal animal model should anatomically and pathophysiologically resemble human SCI, require minimal training, be inexpensive and produce consistent results. Rat models are the most commonly used for SCI research and are well-established, inexpensive and the injury response is similar to that observed in humans (including the production of cystic cavities, glial scar formation and changes in the ECM) (Box 1). However, differences in size, molecular signalling, anatomy and

the recovery potential following SCI have made direct translation challenging[55]. Numerous therapies in SCI and other CNS fields (such as stroke) have, unfortunately, been ineffective when translated to humans from small animals, due to their inherent biological differences. Large animal models, such as nonhuman primates, overcome some of these barriers but substantial differences in cost and unique housing requirements makes their use less common and even they are unable to exactly mimic human SCI[56]. However, larger animal models can form an important intermediary model to confirm results from rodents by providing relevant safety, bio-distribution, and technical feasibility data[57,58]. Furthermore, testing novel therapies in multiple species is important approach to bolster preclinical evidence prior to commencing clinical trials, as is now recommended for stroke therapies[59].

[H1] Diagnosis, screening and prevention

[H2] Clinical manifestations

Fractures of the spinal column are often described by their vertebral level, but the neurological injury is described by the spinal cord level at which the nerve roots emerge. The discrepancy between the two becomes increasingly apparent in the mid-low regions of the thoracic spinal cord, where a fracture at thoracic level 8 (T8) might cause a neurological SCI at T12 and a fracture at T12 might cause a SCI at sacral level 1 (S1).

The clinical manifestations of SCI depend on the level of neurological injury and the amount of preserved spinal cord tissue. SCI can result in the partial or complete loss of sensorimotor function below the level of the injury. Depending on the level of the injury, this can lead to compromised respiratory function (including hypercapnia, hypoxemia and poor

secretion clearance[60,61]); for example, injuries above C5 cause disrupted innervation of the diaphragm, injuries above T11 disrupt innervation to the intercostal chest muscles and injuries above L1 can disrupt innervation to the abdominal muscles (Figure 1C).

In addition to disruption of sensorimotor function, SCI can affect the sympathetic nervous system, as preganglionic sympathetic neurons originate in the spinal cord, between T1 and L2. SCI can reduce sympathetic outflow from the spinal cord, resulting in a loss of basal vascular tone below the level of injury (Figure 4). In addition, high thoracic or cervical injuries can lead to severe hypotension and bradycardia (that is, neurogenic shock, see below) [62,63]. The loss of innervation to secondary lymphatic organs (such as the spleen) can induce secondary immunodeficiency (also known as immune paralysis), which can increase the susceptibility to infections (for example, urinary tract infections and pneumonia)[64]. These systemic manifestations of CNS injury are the leading causes of early mortality in patients with SCI.

[H3] Spinal shock. Spinal shock is defined as a temporary clinical state of flaccid paralysis post SCI, including the loss of motor, sensory, autonomic, and reflex function at or below the level of injury. Spinal shock is commonly confused with neurogenic shock (which is a hypotensive state caused by loss of sympathetic outflow). Spinal shock can affect the performance of an accurate neurological examination, which is used to define the severity of SCI. However, understanding when a patient no longer has spinal shock is problematic and has been the subject of controversy[65]. However, the theory to which most individuals subscribe describes spinal shock as a four phase progression, from an initial stage of areflexia or hyporeflexia, to the later stage of the return of deep tendon reflexes and hyperreflexia.

[H3] Neurogenic shock. Hypotension post SCI has several causes, including hypovolaemia secondary to blood loss, the distributive pooling of venous blood within paralysed atonic musculature and bradycardia. Hypotension can also be caused by vasodilatation secondary to loss of sympathetic tone[66,67], which produces neurogenic shock and is also typified by hypotension, bradycardia, wide pulse pressure and warm pink extremities. Neurogenic shock is most clinically relevant with a neurological level of injury above T6, as these injuries prevent central impulses reaching the mid-thoracic spinal cord, which is where the sympathetic splanchnic nerves (that provide an important role in maintaining vascular tone) arise. Importantly, in injuries above T6 the sympathetic outflow to the cardiac pacemaker can also be affected. Neurogenic shock is estimated to occur in up to 20% of patients with cervical level injuries and bradycardia occurs in nearly all patients with severe cervical injuries during the acute phase[67,68].

[H2] Diagnosis

After any traumatic injury, first-responders rapidly assess patients in the field and attempt resuscitation, en route to the hospital. During this period, the advanced trauma life support (ATLS) protocols dictate initial care, which includes airway, breathing, and circulation support, along with the immobilization of the potentially injured and unstable spinal column using a rigid cervical collar and backboard. Although individual hospital approaches vary, most patients with trauma will undergo a gross neurological examination (which includes a voluntary motor and sensory exam of each limb and a rectal exam) and spinal imaging (using, for example, X-ray or

CT imaging) if a SCI is suspected. Concerns on clinical examination or early radiographic imaging are followed by advanced imaging and detail neurological examinations (see below).

[H3] Imaging. Plain X-Ray, CT and MRI are the most commonly used radiological tools when investigating damage to the spine and SCI. Anterior-posterior (AP) and lateral cervical spine X ray, AP Chest and AP Pelvis X-rays are performed in the trauma room. Although not particularly sensitive for identification of subtle fractures involving the cervical spine, X-rays are useful to detect gross fracture dislocation injuries that are often associated with SCI. It is essential to ensure the adequacy of any X-rays with visualization of the rostral half of the T1 vertebrae.

CT has largely supplanted X-ray for diagnosis of bone injuries in patients with trauma[69,70]. With respect to the spine, some authors (namely, M.G.F.) currently perform, and recommends, a high resolution fine cut CT of the cervical to lumbar. CT angiography can also be performed to evaluate the bilateral vertebral arteries in certain cervical injuries. AOSpine has also developed subaxial cervical[71] (C3-7) and thoracolumbar[72] (T1-L5) classification systems to standardize nomenclature of bony and ligamentous spinal injuries. These systems convey key information on the fracture pattern (e.g. compression injury, translational injury, etc.) including adjacent structure involvement (e.g. facets, ligaments, vertebral artery, etc.) with modifiers for neurological status (e.g. incomplete SCI, complete SCI, etc.)

Although extremely sensitive for diagnosing a fracture or dislocation of the spine, CT is less effective at evaluating the integrity of soft tissue structures such intervertebral discs, ligaments, the spinal cord and nerve roots, but MRI is well suited for assessing these

structures[73]. Specifically, when evaluating for ligament or vertebral disc injury, the T2-weighted Short-Tau Inversion Recovery (STIR) sequence enables the identification of injury related oedema and tissue disruption. MRI can identify spinal cord transection and can evaluate for the presence of oedema and/or haemorrhage[74].

The timing of MRI can be critical with respect to the treatment of patients with SCI and cervical facet dislocation. MRI before closed reduction (that is, correcting the dislocation with the use of traction) enables the detection of disc herniation, which, if present, can lead to a deterioration in neurological status, although this has been disputed[75,76]. However, MRI can, depending on the institution, substantially delay time to decompression of the spinal cord and, involves the additional transfer of a patient with a highly unstable spine. Based on the existing evidence, the most recent iteration of the American Association of Neurological Surgeons and Congress of Neurological Surgeons (AANS/CNS) guidelines for the management of cervical SCI recommends MRI before performance of open reduction (that is, realignment of the broken bones following surgery to exposure the bones) or closed reduction in an unconscious or uncooperative patient; if a disc herniation is identified, the guidelines recommend an anterior approach to remove the disc prior to reduction[77].

The role of MRI is rapidly evolving and advanced microstructural techniques that can quantify physiological changes at a cellular level and assess axon integrity (for example, diffusion tensor imaging), myelination (for example, myelin water transfer) and the presence of key metabolites related to ischaemia, cell loss, or gliosis (for example, MR spectroscopy)[30,78] are likely to see increased integration in the care of patients with SCI.

[H3] Electrophysiology. A number of electrophysiological studies have been evaluated for predicting outcome and for tracking and monitoring recovery over time after traumatic SCI. Electrophysiology is an attractive tool as it does not require the patient to be conscious or communicative. Several parameters have been studied (Box 2), which can be used to derive measures of physiological and anatomical function, such as conduction time to motor neurons, cortical and spinal inhibition, spinal cord excitability (such as the H-reflex), sensory impairment , among others. Although interesting as a research tool, electrophysiological measurements have not consistently demonstrated added value in predicting outcome in awake and alert patients with SCI[79]. However, electrophysiological measurements might provide insight into the mechanisms underlying a patient's functional recovery (for example regeneration, plasticity or adaptation), which could be of benefit as the field develops, such as for patient selection for clinical trials[80].

[H3] Classification of spinal cord injury. Perhaps the most significant advancement related to our ability to diagnose and classify SCI over the last few decades has been the development of the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)[81]. The ISNCSCI has been uniformly adopted by SCI clinical communities[82] and serves as the main measure of neurological outcome in clinical trials.

The ISNCSCI consists of three central neurological summary scores: American Spinal Injury Association (ASIA) motor score (which grades muscle power from each myotome (that is, a group of muscles innervated by one spinal nerve root), ASIA Sensory Score (which assesses

light touch and pinprick sensation in 28 dermatomes (that is, an area of skin innervated by one spinal nerve root) from cervical level 2-sacral levels 4/5) and ASIA Impairment Scale grade (which is used to determine the grade of SCI and encompasses the extent of remaining sensorimotor function; Box 3) [81]. We recommended that ISNCSCI examination is performed at the time of acute hospital admission as soon as reasonably possible to serve as a baseline for comparison throughout follow-up.

The ISNCSCI has substantial evidence of both intra- and inter-rater reliability[83,84] and correlates with other clinical, radiological and electrophysiological proxies for injury severity. Going forward, work is needed to better define the clinical relevance of sensorimotor changes on the ISNCSCI to establish how many points of gain are to be considered 'clinically important'.

[H2] Spinal cord injury syndromes

SCI patterns can broadly be defined as either complete or incomplete. A third category, discomplete, describes those with clinically complete injuries but persistent evidence of subclinical (for example, electrophysiological) brain-muscle connectivity[85]. For incomplete injuries, several patterns of neurological deficit are associated with SCI syndromes, including central cord syndrome, Brown-Séquard syndrome, anterior cord syndrome and posterior cord syndrome (Figure 5).

Central cord syndrome (CCS) is the most common incomplete SCI syndrome and accounts for 15-25% of traumatic SCIs [86]. Most commonly, central cord syndrome is diagnosed in elderly patients with pre-existing cervical spondylosis and stenosis who present after a fall resulting in cervical hyperextension[87]. Central cord syndrome is characterized by a disproportionate motor

impairment of the upper limbs, than the lower limbs, in addition to bladder dysfunction and varying degrees of sensory loss[86].

Brown-Séquard, or hemi-cord syndrome, is most commonly observed in penetrating traumatic SCI, secondary to gunshot and knife wounds. Deficits in patients with Brown-Séquard syndrome include loss of motor function, light touch, proprioception and vibration sensation ipsilateral to the injury, and loss of pain and temperature sensation contralateral to the injury[88].
Anterior and posterior cord syndromes are rarely observed in isolation in the context of traumatic SCI, but are more frequent in patients with non-traumatic SCI of vascular aetiology[88].

[H2] Prognosis

[H3] Neurological recovery. Neurological recovery in patients with SCI is typically observed within the first 6 months after injury, but continued improvements can be seen up to 5 years later[89,90]. The prognosis for neurological recovery is variable and depends primarily on the initial severity of neurological injury; a more severe degree of initial injury portends a worsened prognosis at 1 year[91,92]. The neurological level of injury can also determine neurological recovery; in general, thoracic injuries (particularly complete injuries), are associated with reduced potential for motor recovery than injuries in the cervical or lumbar spinal cord. This is thought to exist because neurological recovery is more difficult to clinically detect in the thoracic region [93,94].

Functional outcomes, in particular the ability to walk is of interest to patients. In general, patients with ASIA Impairment Scale grade A injuries are generally predicted to have

<5% chance of walking 1 year post-injury, regardless of the neurological level of injury[95]. Ambulatory rates are substantially higher for patients with incomplete injuries, but are variable and depend on the initial level of neurological injury[95].

[H3] Predicting neurological recovery. Several tools have been developed to predict neurological recovery in patients with SCI. One rule by Van Middendorp *et al*., relies primarily on acute clinical examination features, and can accurately predict long-term walking potential [96]. Other tools, such as that developed by Wilson et al. [97] use age, neurological examination and MRI features, can accurately predict the likelihood of long-term functional independence and Pavese *et al*. [98] have generated two simple models to predict urinary continence and complete bladder emptying at 1 year after injury using motor, sensory and spinal cord independent measures (SCIM) subscale scores. Each of these might serve as useful tools in the future to help clinicians estimate long-term prognosis in the acute setting.

[H1] Management

'Time is spine' has emerged as a central concept in the management of any patient with SCI. Similar to other acute CNS insults, functional neural tissue is progressively lost during the hours after SCI, making it critically important to rapidly diagnose patients and implement neuroprotective interventions during the acute injury phase. These treatments have the potential to substantially alter the long-term functional recovery of patients and provide meaningful improvements in quality of life (QOL). The management of patients with SCI is complex and involves multiple stages of care, often continuing for years after the initial injury.

[H2] Prehospital transport and hospital care setting

For any patient with suspected spinal trauma and/or traumatic SCI, complete immobilization of the cranio-spinal axis should be maintained. In the prehospital setting this should involve transport with the use of a rigid spine board and application of a cervical collar. After rapid transport to hospital, precautions, including flat bedrest with a cervical collar, should be maintained until confirmation or restitution of spinal stability.

Current AANS/CNS SCI guidelines state that management of acute patients with SCI, particularly those with complete cervical injuries, should be performed in an intensive care unit (ICU) with continuous cardiac, haemodynamic and respiratory monitoring[77]. Indeed, the existing low quality (that is, from non-randomized, retrospective observational studies) clinical evidence suggests that admission to an ICU, with the early identification and management of systemic complications of SCI (including hypoxia, hypotension, pulmonary dysfunction and cardiovascular instability) has a role in reducing secondary injury and facilitating improved recovery[30,41]. Care in the ICU is more important when considering concomitant injuries that can accompany SCI including traumatic brain injury, intra-abdominal injury, thoracic injuries, pelvic/long bone fractures and facial trauma. In all cases, transfers of care should be expedited to reduce diagnosis and intervention times and the transfer of patients to a specialized SCI care centre is recommended by AANS/CNS guidelines[77].

[H2] Medical management

[H3] Haemodynamics. In the ICU, one of the most essential components of acute SCI management is the maintenance of adequate spinal cord perfusion, through the avoidance of systemic hypotension and support of mean arterial pressure (MAP). Hypotension is common post SCI; based on findings from predominately retrospective clinical studies, the 2013 AANS/CNS SCI guidelines, recommend avoiding systemic hypotension (keeping systolic blood pressure <90mmHg) and maintaining MAP between 85-90mmHg for the first 7 days post injury [77,99]. In addition, oxygen saturation should be maintained at ≥90% and prophylaxis to prevent deep venous thrombosis should be administered as soon as possible.

[H3] Methylprednisolone sodium succinate. Historically, the most contentious issue surrounding the medical management of SCI is the suitability of the administration of high-dose intravenous methylprednisolone sodium succinate (MPSS) in the acute phase of injury. In preclinical evaluations, MPSS showed substantial promise as a neuroprotective agent[100-102]. Subsequent clinical evaluation of MPSS led to the completion of three large randomized clinical trials (that is, the National Acute Spinal Cord Injury Studies (NASCIS)). The second NASCIS study likely had the largest impact on clinical practice[103-105], and compared a high-dose 24-hour infusion of MPSS to placebo, or to naloxone. In the primary analysis, no significant difference in neurological recovery was observed between patients treated with MPSS or those that received placebo. However, in a secondary analysis (involving patients treated ≤ 8 hours post SCI), MPSS administration resulted in a 5 point increase in ASIA motor scores at 6 months follow-up, compared with placebo administration[104]. In a 2012 Cochrane review, data from two other

confirmatory randomized studies using the same dose of MPSS dose were collated with the data from the second NASCIS ; overall, administration of a high-dose 24 hour infusion of MPSS results in a 4 point increase in ASIA motor scores at long-term follow-up, compared with no treatment or placebo[106]. Regarding adverse effects, weak trends towards an increased incidence of gastrointestinal haemorrhage and wound infection were noted with MPSS, but this did not achieve significance. In line with these findings, a large proportion of the spine surgery community began the routine administration of high-dose MPPS for patients with SCI arriving to hospital within 8 hours of injury[107]. However, numerous criticisms of this practice, and of the supporting body of literature, have emerged over the years[108]. Namely, critics have pointed to the potential for increased complications, the use of subgroup analyses in the second NASCIS to prove effect, small positive effect sizes and methodological limitations in the two NASCIS II confirmatory trials, as arguments against the routine use of MPSS within 8 hours.

Balancing the available perspectives and evidence, the latest AANS/CNS SCI guidelines (that is, the 2013 guidelines) recommend against the use of MPSS for SCI, arguing that the evidence of harm is more consistent that the evidence of potential benefit[77,109]. However, the stance adopted by the authors of this guideline has been somewhat controversial given that, in spite of any new evidence on the topic in the interval, the 2002 version of the AANS/CNS SCI guidelines recommended a 24 hour administration of MPSS, started within the first 8 hours after injury, as a treatment option[110]. As noted in recent written commentary, as well as in debate presentations at recent international neurosurgery meetings, this change in recommendation has placed the clinician in somewhat of precarious position[111,112]. An

upcoming 2017 AOSpine guideline in the Global Spine Journal will suggest a 24-hour infusion of MPSS be offered to patients within 8 hours of acute SCI as a treatment option. Ultimately, the authors of this review feel that decisions surrounding MPSS therapy should remain left to the physician involved, balancing the potential for benefit with the potential for complications, given the characteristics of the presenting patient.

[H3] Decompressive surgery. Surgical intervention is an essential cornerstone of the acute treatment for patients with spinal trauma and acute SCI (Figure 6). Overall, surgery aims to re-align the spinal column, re-establish spinal stability and decompression (that is, relief of bony or ligamentous compression) of the spinal cord. Surgery typically involves open reduction and decompression paired with an instrumented fusion (for example, using implanted metal hardware) to stabilize the spinal column in an anatomic position. The extent of surgery is tailored to the anatomical site as well as the severity and extent of injury.

From a biological perspective, ongoing compression of the spinal cord is thought to exacerbate local spinal cord ischaemia, thereby potentiating secondary injury [113,114]. Thus, decompressing the spinal cord early after SCI should help to limit the zone of injury and improve clinical outcomes. Indeed, evidence from a systematic review and a meta-analysis of preclinical studies showed that a longer duration of spinal cord compression was typically associated with worsened outcomes (including neurobehavioral recovery, blood flow disturbances and zone of injury)[115]. However, clinical, class I randomized evidence supporting the efficacy of early surgical decompression remains lacking. That being said, several prospective non-randomized studies have supported the safety and efficacy of surgical decompression, including one study noting an increased odds of a ≥2 grade improvement in

ASIA Impairment Scale grade with early (within 24 hours) decompression compared with late (>24 hours) decompressive surgery in patients with cervical SCIs. In addition, data from this study showed a trend towards a reduced incidence of acute in-hospital complications in the early surgery group, but imbalances between the treatment groups might have influenced outcomes. Other studies have shown an association between early decompressive surgery and significantly greater improvements in ASIA motor scale recovery[116]; specifically, in patients with ASIA Impairment Scale grade A injuries (Box 3), reduced length of hospital stay, complication rates and health care costs[117]. In another study very early decompression (≤8 hours) was associated with significant improvement in 1 year SCIM scores and ASIA Impairment Scale grades[118]. No international clinical guideline regarding the timing of decompressive surgery exists[119]. However, one guideline supported by AOSpine has recently been completed and will be published in the Global Spine Journal in early 2017.

[H2] Local complications

[H3] Syringomyelia. Post-traumatic syringomyelia occurs in ~3% of patients with SCI and is characterized as a longitudinal fluid-filled cavity that can span many segments of the cord and can lead to progressive myelopathy occurring months–years after SCI (Figure 7). Syringomyelia is distinct from the more common post-injury cystic cavitations, which are smaller and localized to the injury site. The pathophysiology of post-traumatic syringomyelia is not known but might involve a one-way valve that gradually leads to intraparenchymal cerebrospinal fluid and/or interstitial fluid accumulation[120]. Treatment depends on the clinical presentation and

progression of symptoms[121]; asymptomatic patients are monitored with serial clinical and MRI examinations but progressively symptomatic patients might undergo surgical decompression by connecting the fluid cavity to the intrathecal space.

[H3] Neuropathic arthropathy. Neuropathic or Charcot joint arthropathy (that is, the slow progressive destruction of a joint) can lead to deformity, overlying skin ulceration and potentially fatal infections. The loss of sensation that is common after SCI allows repeated microtraumas to go unnoticed, which promotes bone resorption[122]. Furthermore, autonomic dysregulation can cause hyperaemia of denervated joints, which promotes further bone resorption. This arthropathy can occur in any joint including the hips, knees, ankles, shoulders, elbows, spine and small joints.

Charcot arthropathy of the spine is often diagnosed 10-15 years after SCI and presents as deformity, paradoxical pain (below the sensory level of injury), a deterioration in neurological function and/or audible sounds with movement. Treatment might be conservative, such as clinical and radiographic follow-up, symptomatic (for example, treatment with analgesics or bracing), or surgical (such as vertebral fusion)[123].

[H3] Spasticity. Spasticity is the velocity-dependent increase in muscle tone with exaggerated deep tendon reflexes that results from injury to upper motor neurons. Spasticity affects 65-78% of individuals with chronic SCI (>1 year post-injury) and can substantially impact mobilization, activities of daily living and sleep. Furthermore, spasticity can contribute to other local and systemic complications of SCI including the development of pressure ulcers, contractures, fractures, and cardiorespiratory deconditioning[124]. Treatment of spasticity may

include physical therapy, systemic pharmacologic treatments (for example, clonidine or GABAergic drugs such as diazepam and baclofen), intrathecal pharmacologic treatments (for example, intrathecal baclofen pump), local botulinum toxin injections, or surgery (for example, tendon release surgery)[124].

[H2] Systemic complications

Several of chronic, systemic complications can substantially affect patients' QOL and functional independence.

[H3] Cardiovascular. Analogous to changes observed during the acute period of injury, chronic cervical or thoracic SCI compromises sympathetic outflow from the CNS, which can lead to hypotension [125] (Figure 4). As a result, ~60% of patients experience symptomatic orthostatic (or, postural) hypotension (for example, dizziness, weakness and syncope) [126]. These symptoms occur consistently initially but gradually resolve over weeks–months, although they can persist for longer in some patients[126]. Treatment includes the use of lower extremity compression stockings, abdominal binding or medical management, including volume augmentation (such as, use of hydration, salt tablets or fludrocortisone) and/or peripheral vasoconstriction (for example, with midodrine, ephedrine or droxidopa)[127].

[H3] Autonomic dysreflexia. Autonomic dysreflexia is an urgent condition that most commonly occurs in patients with injuries at or above T6 (particularly, in those with complete injuries). Autonomic dysreflexia is caused by the presence of a noxious stimulus below the level of injury

(such as bladder distension, bowel impaction or pressure sores), which causes a reflex overstimulation of spinal sympathetic neurons, leading to vasoconstriction and dangerous acute hypertension[128]. As a response, parasympathetic outflow increases above the injury level and sympathetic outflow can be inhibited, depending on the injury level, which leads to vasodilation, headache, sweating and sinus congestion. Prompt treatment requires upright positioning of the patient, removal of the triggering stimulus and pharmacological anti-hypertensives for refractory cases[129]. Episodes of life-threatening autonomic dysreflexia can occur in both the acute and chronic stages of injury, making long-term prevention key by avoiding noxious stimuli (for example, by frequent bowel and bladder care and repositioning to avoid pressure sores).

[H3] Respiratory. Paralysis of the phrenic nerve, intercostal muscles and/or abdominal muscles leads to reduced lung capacity, ineffective cough and accelerated fatigue with respiratory demand[130]. As a result, patients experience recurrent pneumonia, atelectasis (that is, alveolar collapse) and pleural effusion (fluids around the lungs) and are more likely to have sleep apnea and respiratory failure[131]. While long-term rehabilitation which promotes cardiorespiratory conditioning may be beneficial, the respiratory defects themselves restrict rehabilitation capacity and long-term independence. As a result, respiratory complications are the leading cause of mortality in patients with chronic SCI. In individuals with high cervical injuries, or those with poor respiratory reserve, lifelong ventilator dependency can also result[132,133].

[H3] Secondary immunodeficiency. As previously mentioned, the disruption of CNS input to immune organs can result in the systemic dysfunction of macrophages, T-cells, B-cells and

natural killer cells in a process termed immune paralysis. The clinical manifestation of this is an increased susceptibility to infections, such as pneumonia, urinary tract infections and wound infections[134,135]. Although the cause of immune paralysis continues to be investigated, cervical or high-thoracic injuries have been shown to cause interruption of the sympathetic innervation of lymphatic organs and are associated with rapid splenic atrophy[136]. There is no accepted management for secondary immunodeficiency.

[H3] Genitourinary and gastrointestinal. Dysfunction of the genitourinary and gastrointestinal systems increases care requirements, risk of infection and can be a source of significant social and psychological stress in patients with SCI. Injuries at or above L1–L2 interrupts innervation of the detrusor, or the bladder muscle, and urinary sphincters, which can causes an inability to empty the bladder, acontractile bladder, urinary incontinence and recurrent infections[137,138]. Management includes urethral catheterization every few hours, the surgical creation of a urinary stoma, injections of Botulinum toxin and pharmacological therapies (such as anticholinergics or alpha-blockers)[125].

The neurological level of injury can also substantially affect sexual function. For example, injuries above T11 can affect psychogenic arousal (that is, erection or vaginal lubrication as a result of arousal in the brain) with preservation of reflexive arousal (that is, erection or vaginal lubrication as a result of genital stimulation) and the ability to orgasm. Conus injuries (that is, injuries in the sacral segment) can interfere with reflexive arousal but preserve psychogenic arousal. T12-L2 injuries with sacral segment sparing can preserve all sexual functions [139].

39% of patients with SCI report that bowel dysfunction significantly reduces their QOL[125]. SCI can interrupt the voluntary control the anal sphincter (causing faecal retention) and/or the parasympathetic innervation of the bowel (in patients with lumbosacral injury). Both cases lead to constipation, increased risk of infection and stress for patients. Treatments can range from dietary fibre intake, digital rectal stimulation or disimpaction and use of suppositories, to implantation of an electrical stimulator or colostomy[140,141].

[H3] Pressure sores. Pressure sores cause pain, increased care requirements and can be life-threatening if not promptly treated. Sores most commonly occur on the buttocks (31%), lateral thighs (26%), sacrum (18%), feet (7%) and ankles (4%)[125]. Prevention of pressure sores requires daily inspection and cleaning of the skin, but also a relief of the pressure on each region every few hours. Once a sore develops, diligent aseptic technique, debridement, dressing and nutritional support are vital to halt progression to life- and limb-threatening infections[142].

[H3] Neurogenic heterotopic ossification. 10-53% of patients with chronic SCI form ectopic bone in the connective tissue around joints, in a process called neurogenic heterotopic ossification. This ossification occurs most commonly in the large joints (for example the hips, knees, elbows or shoulders), tends to develop within months of SCI and presents with localized pain, redness, low-grade fever and increased spasticity[143]. The exact cause of neurogenic heterotopic ossification is not known but it might involve a combination of local, humoral and neuro-immunological factors. Management can include physical therapy, pharmacological

therapy (such as bisphosphonates and/or non-steroidal anti-inflammatories), radiation therapy, or surgical resection of the ossification[144].

[H3] Neuropathic pain. Neuropathic pain is experienced by up to 40% of patients with chronic SCI, has a mean onset of 1.2 years after injury and can have a substantial effect on patients' psychological wellbeing and QOL. The mechanism underlying injury-level pain is thought to be sprouting of spinal cord fibres around damaged nerve roots, leading to inappropriate activation of primary afferent fibres and the initiation of pain by normally non-noxious stimuli (that is, allodynia). Below-injury-level pain is hypothesized to occur due to a loss of spinal and supraspinal inhibitory signalling combined with potentiation of brain pain-responsive areas. Neuropathic pain can be treated pharmacologically (for example, using antidepressants, anticonvulsants and/or opioids), surgically (such as implanted spinal cord stimulators, deep brain stimulators, dorsal root entry zone lesioning), or through non-allopathic treatments (such as acupuncture, massage, cognitive behavioural therapy)[145].

[H2] Rehabilitation

Rehabilitation requires an interdisciplinary approach involving nurses, physicians, dieticians, psychologists, physiotherapists, social workers, recreation therapists, speech therapists, orthotists and child life specialists. Rehabilitation can have significant effects on long-term health by helping patients recover as much function as possible, prevent secondary complications, understand the extent of their injuries, cope with loss of independence, and address other practical challenges such as vocational and financial concerns.

Physical rehabilitation is focused on regaining function, enhancing any remaining function and preventing complications. Key components of rehabilitation are strength training, cardiovascular-focused exercise, respiratory conditioning, transfer/mobility training and stretching to prevent muscle contractures (that is, the permanent shortening of muscle). The patient's progress helps to dictate the level of ongoing care needed in the community and the use of assistive devices for daily living. Further high-quality (that is, level 1-2) trials of physical rehabilitation are required to validate the intuitive efficacy and compare specific treatment modalities[146]. Interestingly, physical rehabilitation can induce significant changes in cellular signalling and growth factor expression[147]. Early mobilization increases endogenous growth factor levels (such as insulin-like growth factor 1) and axon regeneration in animal models[147]. However, in clinical practice, ventilator dependence, poor vascular tone, neuropathic and somatic pain, psychosocial challenges, and resource limitations in acute care institutions can make early mobilization challenging.[30] These important clinical barriers are often overlooked but represent formidable overarching challenges to recovery.

Weight-supported locomotor training (WSLT) uses assists devices (such as, Hocoma's Lokomat, HealthSouth's AutoAmbulator) and therapists to dynamically support the patient's weight while they attempt locomotion on a treadmill or open ground. The therapy looks to enhance the remaining connectivity between regions above the SCI and the locomotor central pattern generator (that is, a region of neurons that when activated, can initiate locomotion in the absence of sensory input, or input from the brain) with the spinal cord. WSLT has been shown to improve assisted mobility, cardiorespiratory status and to prevent pressure sores and joint-related complications of SCI. A randomized, single-blind trial (*n*=146) comparing 12 weeks

of WSLT versus similar intensity physical rehabilitation found no significant difference in outcomes, but both groups had improvements in locomotion at 6 months, highlighting the importance of intensive rehabilitation[148].

Occupational therapy focuses on integrating adaptive devices into people's daily lives to maximize functional independence at home and at work. Devices might include wheelchairs, lifts, braces, orthoses, environmental control units (such as lights, television or phones), bathroom equipment (such as showering or toileting), vehicle modifications for driving and others[149]. The US Department of Health and Human Services maintains a database (AbleData.com) of accessibility devices to help inform patients[150].

[H2] Functional electrical stimulation

Functional electrical stimulation (FES) utilizes small pulses of currents to activate muscles and has been successfully used in the upper extremities for eating, gripping and writing. In the lower extremities, FES has been connected to a wheeled walker for ambulation (for example, the Parastep by Sigmedics Inc.) and to stationary bicycles (for example, ERGYS 3 by Therapeutic Alliances Inc. and RT300 by Restorative Therapies) FES can also be surgically implanted with electrodes on the anterior sacral nerve roots to provide patients with controllable bowel or bladder function. Typically the implanted sacral nerve stimulator, such as the Vocare Bladder System (Finetech Medical), requires surgical lesioning of dorsal sensory roots to improve continence, but an open-label pilot study is underway to assess the system in patients with SCI without nerve sacrifice with results expected by 2018 (NCT02978638).

Importantly, FES can also enhance neuroplasticity and decrease the systemic complications of chronic SCI in patients[151]. In addition, FES-based exercises can double oxygen uptake, triple the ventilation rate, and improve the overall muscle to fat ratio in the body[152,153]. FES is an actively researched field with the next generation of devices integrating more advanced closed loop feedback systems, greater MRI compatibility, and novel stimulation programs to reduce adverse effects and improve efficacy[154].

[H1] Quality of life

QOL in patients with SCI is most often defined by the ability of patients to be independent of assisted-care and hold meaningful employment.[155] The most frequently used subjective measure of QOL is the Satisfaction with Life Scale (SWLS) and the most commonly used objective measure is the Short-form 36 (SF-36).[156] A new scale to assess QOL in patients with SCI is the SCI-QOL, a patient-reported outcome measure consisting of 18 domains, including metrics for physical, emotional and social aspects[157].

[H2] Factors associated with QOL

Patients with SCI have been shown to have a lower QOL than the general population in a meta analysis[158]. Out of functional impairment (loss or abnormality of anatomic function), disability (functional limitation for specific activities), and handicap (disadvantage in acting in a certain role) handicap is most strongly associated with QOL in patients with SCI. Other studies have indicated that the severity and level of injury is significantly associated with QOL (that is, individuals with higher-level and more severe injuries showed significantly lower QOL).[159,160] However, conflicting results have been reported in other studies.[161,162] Other factors associated

with QOL include advanced age and lower QOL,[163,164] and for both functional and psychological outcome, lengthier duration of SCI is associated with a more positive assessment of QOL.[163,165]

Social support, as indicated by marriage or cohabitation, and employment have a positive effect on QOL after SCI. [166,167] A higher level of education[168] and the ability to walk without assistance[164] were associated with higher QOL scores. SCI-related morbidities, including neuropathic pain, spasticity and bladder, bowel and sexual dysfunction were all associated with a lower QOL.[169] In general, carefully designed studies are required to give us a better understanding of how we can better prognosticate and inform long-term strategies to improve QOL for those living with SCI.

[H2] Economic impact

The financial burden of SCI on patients, families, and society is substantial. Direct health care costs and living expenses vary substantially based on the geographic region and the age, survival and injury severity of individual patients. For example, in the United States, the lifetime cost for providing care to a 25 year-old patient with an ASIA Impairment Scale A injury is ~$2.3 million for thoracic injuries, ~$3.5 million for C5-8 injuries, and ~$4.7 million for C1-4 injuries over the course of the patient's life. Additionally, indirect costs (including lost wages and benefits) are estimated at ~$72,000 per year[2]. Even small improvements in function, such as mobility and manual dexterity, can substantially reduce these costs highlighting the economic importance of the 'time is spine' concept.

[H1] Outlook

[H2] Improving translation

Although numerous treatments have generated positive results in preclinical models of SCI, translation to patients has been challenging. Typically, preclinical studies use animal models with highly standardized injuries, treatment paradigms, and assessment techniques in animals that are genotypically and phenotypically similar, which is in contrast to the heterogeneity of patients. As a result, an effective therapeutic approach from a single animal model might only be translatable to a subset of individuals within a clinical trial that often assesses a wide-array of patients. This requires higher recruitment to sufficiently power the study and often necessitates controversial subgroup analyses[170]. To overcome this, one strategy is to embark on clinical trials only after a treatment has demonstrated efficacy in multiple animal models and species. Although this decreases the number of potentially translatable therapies, it might identify the highest yield treatments. Another strategy is to narrow the inclusion criteria of studies based not only on clinical factors and biomarkers, which can provide insight into the underlying pathophysiology[171]. Together, these approaches might decrease variability in clinical trials (and recruitment requirements) while increasing the statistical power of the trial.

[H2] Common data elements

The SCI field needs high-quality large-scale datasets to better understand the heterogeneity between patients, as this affects their response to treatment and our ability to predict outcomes. Generating these datasets can be logistically challenging as patients present emergently and require complex care[172], but several registries have been developed including

the North American Clinical Trials Network SCI Registry[173], International Spinal Cord Society SCI Data Sets[174] and National Spinal Cord Injury Statistical Center database[175], among others. Large clinical trials have also contributed patient records, but data elements need to be standardized to harmonize datasets and draw meaningful conclusions. Towards this goal, The National Institute of Neurological Disorders and Stroke (NINDS) within the NIH has developed a set of common data elements for SCI. The 2014 common data elements are classified along a spectrum according to their use and validation in SCI and are grouped by field including demographics, care, electrodiagnostics, functional, imaging, neurological, pain, QOL and psychological. Upcoming studies and registries should apply these elements to their data collection for the ultimate benefit of all patients.

[H2] Current clinical studies

The last several decades have seen a flurry of preclinical SCI research that has given rise to a host of promising therapeutic advances, each of which are in various stage of clinical development[61,176]. Pharmacological agents currently being investigated can broadly be classified as either neuroprotective or neuroregenerative (Table 1).

[H3] Neuroprotective treatments. Minocycline (a structural analogue of the antibiotic tetracycline) can induce neuroprotection in animal models of SCI, presumably through reducing oligodendrogcyte apoptosis and by reducing local inflammation[177,178]. A phase 2 placebo controlled randomized study showed an improvement of 6 points at the ASIA motor score in 1 year after delivery of minocycline for 7 days, compared with placebo and only one adverse

event - a transient elevation in hepatic enzymes. A larger multicentre efficacy trial is currently planned (NCT01828203).

Riluzole (a sodium channel blocker) has improved neurobehavioral and pathological outcomes in animal models of SCI and is thought to prevent continuous activation of neuronal voltage gated sodium channels, preventing cellular swelling and death, in addition, to reducing excitotoxicity. [179] Data from a phase 1 trial showed an improvement in ASIA motor scores in patients with cervical level injuries, 90 days after riluzole treatment, compared with non-treated patients matched from an historical registry cohort[180]. Three patients had temporary borderline severe elevations in liver enzymes, but no serious adverse events were attributed to the drug. Currently, a phase 2/3 multicentre randomized trial, the Riluzole in Spinal Cord Injury Study (RISCIS is enrolling patients and is supported by AOSpine (NCT01597518).

Basic fibroblast growth factor (bFGF) is an important mediator of angiogenesis, plays a key role as a morphogen in embryological development, and is used *in vitro* to maintain pluripotency of many cells types including neural stem cells[181]. In animal models, bFGF can promote neuroprotection against excitotoxicity and can reduce free radical-mediated injury[182,183]. A structural analogue to bFGF (SUN13837) has been assessed in a phase 1/2 randomized trial with results pending.

Finally, the use of systemic hypothermia as a potential neuroprotective strategy is under clinical investigation in a phase 2/3 study: the Acute Rapid Cooling for Traumatic Injuries of the Cord (ARCTIC) trial. Hypothermia can decrease the basal metabolic rate of the CNS after injury and provides an anti-inflammatory effect[184]. Systemic intravascular cooling to 33.0 °C after

acute hospital admission in patients with complete SCI, is safe and associated with increased rates of ASIA Impairment Scale grade conversion as compared to historical controls[185].

[H3] Neuroregenerative treatments. The RhoA pathway can negatively affect axonal and neurite growth and molecules that activate this pathway are upregulated following SCI [186]. A specific bacterial-derived toxin, known as VX-210 can inhibit RhoA-mediated inhibition of axonal growth leading to enhanced regeneration and improved behavioural outcomes in rodent models[187]. Cethrin, a recombinant version of VX-210, showed promise in preclinical studies and no were no serious drug related adverse events were noted in a phase 1/2a dose escalation study in patients with ASIA Impairment Scale grade A cervical and thoracic injuries [188]. Although this study was uncontrolled, ASIA motor score recovery at 12 months, was superior to historical recovery rates[188]. A phase 2b/3 study is underway.

As previously mentioned, Nogo-A is found in CNS myelin and presumably has a role in preventing the formation of new functional connections post SCI. Nogo-A antibodies have shown promise in promoting axonal regeneration in preclinical SCI studies[189] and a phase I study has been completed, with a phase 2 placebo controlled European trial underway[190].

Biomaterials are under intense investigation as they can be engineered to mimic the architecture of lost ECM in the spinal cord and can structurally support cell migration and axonal regrowth. A phase 3 trial in thoracic SCI, entitled INSPIRE is underway in the United States, with a biodegradable Neuro-Spinal Scaffold to assess the safety and improvements in ASIA Impairment Scale grade, motor scores and sensory scores (NCT02138110).

[H3] Cellular transplantation. Transplantation of various cell types to repair the injured spinal cord is an exciting therapeutic concept[191] and addresses the extensive loss of tissue caused by SCI that cannot be replaced by endogenous repair processes. In addition, transplanted cells can replace lost cells, modulate the injury environment and stimulate synergistic regenerative programmes[176]. Any specific cell type might have one or more of these actions, which remains an area of active investigation [192].

The various cell types that have been assessed in preclinical studies include neural stem or precursor cells, oligodendrocyte precursor cells, olfactory ensheathing cells, Schwann cells, umbilical cord mesenchymal stem cells, amongst others[176,193]. Cell transplantation into the transected cord has been shown to promote the recovery of motor function, including coordinated walking[194], paw use and climbing[195], in addition to improved bladder function[196] and phrenic nerve activity[197] in animal models. Importantly, neural precursor cells and adult olfactory tissue is also effective when transplanted 1 month after SCI in rats, a time point that is considered to model stable, chronic SCI in humans.

Mechanistically, transplanted cells can improve regeneration by promoting axonal growth (observed with olfactory ensheathing cells (OECs)), remyelinating denuded axons themselves (observed with Schwann cells and oligodendrocytes, among others) and supporting remyelination by endogenous oligodendrocytes[198,199] Also, factors secreted by transplanted cells can beneficially modulate the environment and promote axon regeneration[200,201].

Several trials have tested the safety and preliminary efficacy of cell transplantation in patients with SCI. The first human trial confirmed the safety of transplantation of purified OECs into the spinal cord. [202] Subsequently studies transplanted mucosal tissue, as opposed to

purified OECs, with conflicting results[203] [204] Other trials have investigated other transplanted cells, including OECs and olfactory nerve fibroblasts, Schwann cells and a combination of OECs and Schwann cells[205,206]. A systematic review of the use of OECs in SCI echoed the positive findings found in other trials [207]. More recently, data from a phase 1 trial reported motor and sensory improvements and no serious adverse events 1 year post transplantation of autologous mucosal OECs and olfactory nerve fibroblasts into the spinal cords of patients with AIS impairment grade A injuries (*n*=6) [205]. However, large sample sizes and long follow-up periods will be required to confirm safety and efficacy[203].

Further efforts at cell transplantation include the transplantation of human embryonic stem cell-derived oligodendrocyte progenitors (such as the Geron trial), but this was discontinued for financial reasons. Fortunately, renewed funding has allowed Asterias Biotherapeutics Inc. to restart the study of these cells as a phase 1/2a dose escalation study in which their product, AST-OPC1, is transplanted into the subacutely injured cervical spinal cord (NCT02302157) . Other cell types under clinical investigation include human Schwann cells and umbilical cord blood mononuclear cells, among others. One phase 1/2 trial involving umbilical cord blood mononuclear cells found that the addition of intensive locomotor training to cell-based therapy can significantly enhance functional recovery in patients with chronic injuries.

Biotech-led trials include the recently terminated testing of a human fetal neural stem cell product (HuCNS-SCs, StemCells Inc.) and Neuralstem's ongoing trial of transplanted NSI-566, stem cells derived from the human fetal spinal cord . Other possible therapies include adult autologous stem cells (RhinoCyte Inc.), although this is still at preclinical stages and human glial-restricted progenitor product (Q-cells, Q Therapeutics). A number of novel

conventional drugs, such as Anti-NogoA-antibodies are also currently being evaluated in clinical trials (Table 1).

[H3] Neuromodulation, robotics and future directions. Several neuromodulatory approaches, involving the focused delivery of electrical current to the CNS, are under study for the treatment of SCI. Specifically, spinal cord stimulation using surgically implanted electrodes in the epidural space over the conus medullaris, has improved functional and locomotion related outcomes in patients with chronic SCI [208]. This trial is no longer active. In addition, although not under investigation in the clinic, preclinical studies have shown that stimulation of deep brain centres in the region of the mesencephalic locomotor region, resulted in substantial improvement in functional deficit in rodent SCI models[209]. Finally, neuroprosthetic brain-computer interfaces have successfully restored upper limb function in a paralyzed patient; in this case, the device was implanted into the motor cortex of a patient with a complete cervical injury and stimulated specific hand and wrist muscles groups allowing functional control of motor output without transmission through the spinal cord[210]. The next steps are to reduce the movement retraining process and make this technology feasible for everyday use.

The use of robotics is also beginning to comprise a more substantive role in granting SCI patients the ability regain functionality. In 2014 the US FDA approved the first robotic exoskeleton (ReWalk; ReWalk Robotics Inc.) for use in paraplegic patients which fits around patients' legs and back to facilitate sitting, standing and walking [211,212] . Other devices include the Indego (Parker Hannifin Corp), Ekso (Ekso Bionics), REX (Rex Bionics), and Hybrid Assistive Limb (HAL; Cyberdyne Inc.)[212] As technology improves, that robotics will be used in conjunction

with the discussed biological treatments to help optimize outcomes in the long-term is anticipated.

Box 1. Animal models of SCI

The type and location of injury is a key factor in the development of a clinically-relevant and translatable animal model. The anatomical and pathophysiological differences between the cervical and thoracic spinal regions are substantial and should be considered. Furthermore, the choice of species and type of model might be useful to answer different questions. [58,213-215]

[H1] Models of traumatic SCI

- Contusion models: inflict transient, acute injuries through weight-drop or electromagnetic/pneumatic impactors
- Compression models: inflict prolonged, acute injuries through calibrated clip-compression and forceps, among others
- Transection models involving unilateral (partial) or bilateral (complete) lesions

The ideal behavioural outcome is rapidly assessable, inexpensive, requires minimal training, has good intra- and inter-rater reliability and causes minimal distress in the animal. Several established behavioural outcomes exist for mice and rats.

[H1] Locomotor function

- Open field locomotor assessment: used to assess sequential locomotor recovery of the hindlimb when used in combination with a locomotor recovery scale, such as the Basso, Beattie, and Bresnahan (BBB) scale
- Digital systems: used to quantify cadence, walk time, stride length and stride width similar to the clinical GaitRite analysis system (CIR Systems Inc.)
- Ladder, rope or wire grid test: used to assess coordinated locomotion
- Staircase test: used to measure forelimb reaching and grasping

[H1] Limb strength

- Inclined plane test: used to indirectly assess trunk stability, proprioception/sensation and unilateral limb strength
- Forelimb grip strength: used to provide quantitative readouts of the peak force of the forelimb.

[H1] Sensory deficits

- Tail flick test: used to assess nociception in response to temperature

- Von Frey filaments (thin nylon strands of varying diameter): used to assess sensory preservation and allodynia (pain sensation for normally non-painful stimuli) in response to mechanical stimuli
- The Hargreaves assay: used to assess sensory preservation and allodynia in response to temperature

Box 2. Electrophysiological recordings

Electrophysiological recordings have examined several parameters, including, motor evoked potentials (MEPs), somatosensory evoked potentials (SSEPs), dermatomal SSEPs (dSSEPs), electromyography (EMG), nerve conduction studies (NCS) and sympathetic skin response (SSR). MEPs assess the integrity of descending motor tracts, through a central impulse (usually through transcranial magnetic motor cortex stimulation), which is then detected by electrodes in peripheral muscle. The amplitude of the MEP signal, but not the signal latency, correlates with improved motor function post injury[80]. EMGs can examine subtle changes in voluntary muscle contraction to track recovery [216]. NCSs provide detailed conduction velocities of nerves to better distinguish between ventral horn/anterior root injuries and pyramidal tract injuries[217]. SSEPs assess the integrity of ascending sensory tracts, usually in the dorsal columns, through the temporal summation of electroencephalogram (EEG) signal, after the stimulation of a peripheral sensory nerve. SSEPs performed in the acute phase post injury can predict long-term neurological and functional outcomes, such as future ambulation[218]. However, SSEPs were no better than acute clinical examination in predicting ambulation[218]. In another study, in the sub-acute phase of injury the combination of lower extremity motor scores and tibial SSEPs provided the most accurate prediction of ambulation, compared with use of either variable alone. Finally, the integrity of the sympathetic system can be tested by measurement of the electrical potential generated between skin sweat glands (SSRs)[219].

Box 3. ASIA impairment scale

The ASIA Impairment Scale grade is global measure of injury severity and is based largely on the concept of sacral sparing (that is, some degree of maintained perineal sensation, voluntary anal contraction, and/or great toe flexion indicating an incomplete lesion). The scale is used to determine the grade of SCI, which ranges from ASIA Impairment Scale grade A (the most severe injury, with complete sensorimotor loss) to ASIA Impairment Scale grade E (the least severe injury with no neurological deficit).

[H1] Grade A
Sensory or motor function below the neurological level (that is, the lowest segment where sensorimotor function is normal on both sides) of injury including absent sacral function (that is, no voluntary anal contraction, no great toe flexion, no perineal, genital, anal pinprick or light touch sensation)

[H1] Grade B
Sensory, but not motor function is preserved below the neurological level of injury, including the distal sacral segments (S4-5). No motor function is present more than three levels below the neurological level, on either side of the body

[H1] Grade C
Motor function below the neurological level of injury (including the distal sacral segments) is preserved with more than half of the key muscles (that is, elbow flexors and extensors, wrist extensors, finger flexors and abductors, hip flexors, knee extensors, anxle dorsiflexors, long toe extensors and ankle plantar flexors) having a grade of less than 3 on the ASIA Motor score (against gravity without additional resistance)

[H1] Grade D
Motor function below the neurological level of injury (including the distal sacral segments) is preserved with more than half of the key muscles having a grade of 3 (antigravity) or greater

[H1]Grade E
Neurologically intact patients (that is, sensorimotor function is normal in all segments) who previously had deficits secondary to a suspected SCI.

Figure 1. Anatomy of the spinal column.

A| The vertebral column encircles the spinal cord in protective bone and ligament, which, in humans, is segmented into 7 cervical, 12 thoracic, 5 lumbar and 5 sacral vertebrae. Spinal nerve roots enter the spinal cord and either convey sensory information into the spinal cord (through the sensory or dorsal root) or convey motor information to the periphery (through the motor or ventral root). Blood is supplied to the spinal cord by the spinal arteries, which are located anteriorly and posteriorly and branch to perfuse the spinal cord parenchyma. The spinal cord is also surrounded by a protective layer of cerebrospinal fluid (CSF) contained within the pachymeninges. **B|** The spinal cord itself is organized into grey matter (which contains neuronal cell bodies) and white matter (which contains myelinated axons). The white matter can be further subdivided into several ascending or descending tracts, which are composed of bundles of axons that originate from and project to specific regions in the brain and periphery. These tracts convey specific information, such as sensory information (for example, temperature or itch) or motor information. **C|** Each segmental region of the spinal cord innervates a specific muscle and/or organ group. Damage to the spinal cord can result in partial or complete loss of function below the level of the injury.

Figure 2. Annual incidence of spinal cord injury across reported countries, states/provinces, and regions. The annual incidence of SCIs varies depending on geographical region. Reprinted with permission from Singh A, et al. Clin Epidemiol. 2014;6:309-331.[3]

Figure 3. Pathophysiology of traumatic spinal cord injury.
The initial mechanical trauma to the spinal cord initiates a secondary injury cascade that is characterized in the acute phase (that is, 0-48 hours after injury) by oedema, haemmorhage, ischaemia, inflammatory cell infiltration, release of cytotoxic products and cell death. This secondary injury leads to necrosis and/or apoptosis of neurons and glial cells, such as oligodendrocytes, which can lead to demyelination and the loss of neural circuits. In the subacute phase (2-4 days after injury), further ischaemia occurs due to ongoing oedema, vessel thrombosis and vasospasm. Persistent inflammatory cell infiltration causes further cell death and cystic microcavities form as cells and the extracellular architecture of the cord are damaged. In addition, astrocytes proliferate and deposit extracellular matrix molecules into the perilesional area. In the intermediate and chronic phases (that is, 2 weeks to 6 months), axons continue to degenerate and the astroglial scar matures to become a potent inhibitor of regeneration. Cystic cavities coalesce to further restrict axon regrowth and cell migration. Modified from Ahuja C, Fehlings MG. Bridging the gap: novel neuroprotective and neuroregenerative therapies for spinal cord injury. *Stem Cells Translational Medicine*. 2016;5(7):914-24[220].

Figure 4. Cervical and high thoracic spinal cord injuries disrupt the outflow of the sympathetic nervous system. Injuries in the cervical-high thoracic cord can disrupt the sympathetic outflow (green) to the heart and the peripheral vascular system, while preserving baroreceptor inputs

(orange) and parasympathetic output (blue). As a result, parasympathetic innervation to the heart dominates in patients with high injuries, which causes bradycardia and decreased cardiac output. This is further compounded by the loss of peripheral muscular and vascular tone, which promotes a redistribution of blood to the periphery with reduced venous return. Consequently, patients often experience hypotensive symptoms, particularly with exertion or upright positioning. The parasympathetic-sympathetic imbalance can also allow unchecked reflex spinal sympathetic stimulation as a consequence of noxious triggers (such as bladder distension or pressure sores), which leads to sudden peripheral vasoconstriction and acute hypertension. As a response, parasympathetic outflow above the injury level increases, leading to vasodilation, headaches, sweating and sinus congestion. This dangerous acute syndrome is known as autonomic dysreflexia. HR – heart rate; CO – cardiac output.

Figure 5. Spinal cord injury syndromes .
A | The major descending motor tracts are in yellow and the major ascending sensory tracts are in blue, as also depicted in Figure 1a. The patterns of sensorimotor loss exhibited in patients with spinal cord injury (SCI) syndromes can be explained by damage to specific spinal cord tracts with sparing of other tracts. For example, the disproportionate motor impairment of the upper limbs than the lower limbs in patients with central cord syndrome (panel b) might be explained by the complete, non-selective injury to the corticospinal tract (which is thought to transmit impulses related to fine hand and finger movements), but the preservation of the extra-pyramidal tracts (which are thought to control gross leg and proximal arm movements). In addition, the different levels of sensorimotor, pain and temperature loss in patients with Brown-Séquard syndrome (that is, the contralateral pain and temperature loss is detected several levels below that of the ipsilateral sensorimotor loss) can be explained by the decussation of the lateral spinothalamic tract over several spinal segments (panel c). Anterior cord syndrome (panel d) results in complete motor paralysis due to damage to the corticospinal tract, loss of pain and temperature sensation secondary to damage of the spinothalamic tract, but preservation of light touch sensation and proprioception (as the dorsal columns are generally preserved by this injury). Posterior cord syndrome (panel e) results in the reverse with loss of light touch and proprioception but preservation of motor function and pain/temperature sensation.

Figure 6. Surgical decompression and realignment of the injured spinal cord. A| Arrows mark the C5-6 level where the injury is centered. Pre-operative CT imaging demonstrates a severe C5-6 fracture-dislocation (arrow), with compromise of the central spinal canal. **B|**Pre-operative MRI shows on-going compression of the spinal cord (arrow) and bright T2-weighted signal in the surrounding ligaments suggesting disruption. **C|** Following surgery including cervical traction, surgical decompression and instrumented fusion anterior and posterior metal hardware can be seen on the CT, and the restoration of appropriate spinal alignment. **D|** Successful decompression of the spinal cord can be seen on the post-operative MRI.

Figure 7. Post-spinal cord injury syrinx.

T2-weighted MRI of the cervical (A) and thoracic (B) spine in sagittal (left panels) and axial (right panels) planes illustrates a post-traumatic syrinx within the spinal cord parenchyma (white arrows) and kyphosis (that is, forward bending) of the thoracic spine at the initial site of SCI (black arrows). The syrinx extends well beyond the mid-thoracic site of SCI into the high cervical spinal cord, likely causing upper limb pain.

Table 1. Selected therapies planned or currently under study in patients with SCI

Treatment	Stage	Ref
Pharmacological		
Minocycline [&]	Phase III	NCT01828203
Riluzole [&]	Phase IIb/III	NCT01597518
Granulocyte-colony Stimulating Factor [&]	Phase I/II	[221,222]
Cethrin [#]	Phase II/III	[223]
Anti-Nogo Antibody [#]	Phase II	NCT00406016
Procedural		
Systemic Hypothermia	Phase II/III	[224,225]
CSF Drainage	Phase II	NCT02495545
Blood pressure augmentation	Phase II	NCT02495545
Neuromodulation		
Spinal Cord Stimulation	Phase I	NCT02592668
Deep Brain Stimulation	Phase I	NCT02006433
Cell-based Strategies		
Oligodendroglial precursor cells	Phase I/II	NCT02302157
Schwann cells	Phase I	NCT01739023
Umbilical cord-derived stem cells	Phase III	NCT02481440
Bone-marrow derived mesenchymal stem cells	Phase II	NCT02570932
Bioengineering		
Robotic exoskeletons	Phase I	NCT02322125
Functional peripheral electrical stimulation	Phase I/II	NCT01479777
Implantable bioengineered scaffolds/matrices	Phase III	NCT02138110

*Planned for 2017; [&]denotes neuroprotective studies; [#] denotes neuroregenerative studies

Key References

Epidemiology

Singh, A., Tetreault, L., Kalsi-Ryan, S., Nouri, A. & Fehlings, M. G. Global prevalence and incidence of traumatic spinal cord injury. *Clin Epidemiol* **6**, 309-331, doi:10.2147/CLEP.S68889 (2014).
A comprehensive overview of the global epidemiology of traumatic spinal cord injury divided by available geographic regions.

Chen, Y., He, Y. & DeVivo, M. J. Changing Demographics and Injury Profile of New Traumatic Spinal Cord Injuries in the United States, 1972-2014. *Arch Phys Med Rehabil* **97**, 1610-1619, doi:10.1016/j.apmr.2016.03.017 (2016).
A cross-sectional analysis of longitudinal data highlighting key trends in the demographics of individuals with traumatic spinal cord injuries.

Mechanisms/Pathophysiology

Silver, J. & Miller, J. H. Regeneration beyond the glial scar. *Nat Rev Neurosci* **5**, 146-156, doi:10.1038/nrn1326 (2004).
An in-depth review of glial scar, extracellular matrix proteoglycans, and the behaviour of regenerating neurons in the injured CNS microenvironment.

Kwon, B. K., Oxland, T. R. & Tetzlaff, W. Animal Models Used in Spinal Cord Regeneration Research. *Spine* **27**, 1504-1510, doi:10.1097/00007632-200207150-00005 (2002).
An overview of pertinent animal models and injury paradigms to study spinal cord regeneration.

Diagnosis, screening and prevention

Kirshblum, S. C. *et al.* Reference for the 2011 revision of the International Standards for Neurological Classification of Spinal Cord Injury. *J Spinal Cord Med* **34**, 547-554, doi:10.1179/107902611X13186000420242 (2011).
The updated International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) for assessment and re-assessment of patients with traumatic SCI.

van Middendorp, J. J. *et al.* A clinical prediction rule for ambulation outcomes after traumatic spinal cord injury: a longitudinal cohort study. *Lancet* **377**, 1004-1010, doi:10.1016/S0140-6736(10)62276-3 (2011).
A clinical prediction rule for ambulation at 1 year post-SCI based on age, motor scores and sensory function in the subacute (within 15 days) injury period.

Management

Resnick, D. K. Updated Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injury. *Neurosurgery* **72 Suppl 2**, 1, doi:10.1227/NEU.0b013e318276ee7e (2013).
Widely-accepted guidelines by the American Association of Neurological Surgeon and Congress of Neurological Surgeons for the management of acute cervical spinal cord injuries.

Bracken, M. B. Steroids for acute spinal cord injury. *Cochrane Database Syst Rev* **1**, CD001046, doi:10.1002/14651858.CD001046.pub2 (2012).
A systematic review and meta-analysis of the best available randomized trials assessing steroid therapy for acute traumatic SCI.

Quality of Life

Dijkers, M. Quality of life after spinal cord injury: a meta analysis of the effects of disablement components. *Spinal Cord* **35**, 829-840 (1997).
A meta-analysis of studies to assess the relationship between quality of life and disability, impairment, and handicap.

Jain, N. B., Sullivan, M., Kazis, L. E., Tun, C. G. & Garshick, E. Factors associated with health-related quality of life in chronic spinal cord injury. *Am J Phys Med Rehabil* **86**, 387-396, doi:10.1097/PHM.0b013e31804a7d00 (2007).
A cross-sectional study investigating the health-related quality of life (HRQoL) instrument and identifying potentially modifiable factors related to quality of life in SCI.

Outlook

Ahuja, C. S. & Fehlings, M. Concise Review: Bridging the Gap: Novel Neuroregenerative and Neuroprotective Strategies in Spinal Cord Injury. *Stem Cells Translational Medicine*, doi:10.5966/sctm.2015-0381 (2016).
A review of key neuroregenerative and neuroprotective interventions for traumtic SCI along the translational pipeline.

Zorner, B. & Schwab, M. E. Anti-Nogo on the go: from animal models to a clinical trial. *Ann N Y Acad Sci* **1198 Suppl 1**, E22-34, doi:10.1111/j.1749-6632.2010.05566.x
The story of anti-Nogo therapy which provides an example of the bench to the bedside path for novel therapeutics.

Li, L. *et al.* Effects of transplantation of olfactory ensheathing cells in chronic spinal cord injury: a systematic review and meta-analysis. *Eur Spine J* **24**, 919-930, doi:10.1007/s00586-014-3416-6 (2015).
A meta-analysis pooling data from 1193 patients receving olfactory ensheathing cell transplants for chronic SCI.

References

1 Noonan, V. K., Dvorak, M. F. & Fehlings, M. G. Epidemiology of traumatic and nontraumatic spinal cord injury. 6-20, doi:10.2217/ebo.12.167 (2013).

2 Center, N. S. C. I. S. Spinal Cord Injury Facts and Figures at a Glance. *The Journal of Spinal Cord Medicine* **37**, 117-118, doi:10.1179/1079026813z.000000000249 (2014).

3 Singh, A., Tetreault, L., Kalsi-Ryan, S., Nouri, A. & Fehlings, M. G. Global prevalence and incidence of traumatic spinal cord injury. *Clin Epidemiol* **6**, 309-331, doi:10.2147/CLEP.S68889 (2014).

4 Cripps, R. A. *et al.* A global map for traumatic spinal cord injury epidemiology: towards a living data repository for injury prevention. *Spinal Cord* **49**, 493-501, doi:10.1038/sc.2010.146 (2011).

5 Noonan, V. K. *et al.* Incidence and prevalence of spinal cord injury in Canada: a national perspective. *Neuroepidemiology* **38**, 219-226, doi:10.1159/000336014 (2012).

6 New, P. W., Farry, A., Baxter, D. & Noonan, V. K. Prevalence of non-traumatic spinal cord injury in Victoria, Australia. *Spinal Cord* **51**, 99-102, doi:10.1038/sc.2012.61 (2013).

7 Chen, Y., He, Y. & DeVivo, M. J. Changing Demographics and Injury Profile of New Traumatic Spinal Cord Injuries in the United States, 1972-2014. *Arch Phys Med Rehabil* **97**, 1610-1619, doi:10.1016/j.apmr.2016.03.017 (2016).

8 van den Berg, M. E., Castellote, J. M., Mahillo-Fernandez, I. & de Pedro-Cuesta, J. Incidence of spinal cord injury worldwide: a systematic review. *Neuroepidemiology* **34**, 184-192; discussion 192, doi:10.1159/000279335 (2010).

9 Lenehan, B. *et al.* The epidemiology of traumatic spinal cord injury in British Columbia, Canada. *Spine (Phila Pa 1976)* **37**, 321-329, doi:10.1097/BRS.0b013e31822e5ff8 (2012).

10 Devivo, M. J. Epidemiology of traumatic spinal cord injury: trends and future implications. *Spinal Cord* **50**, 365-372, doi:10.1038/sc.2011.178 (2012).

11 DeVivo, M. J. & Chen, Y. Trends in new injuries, prevalent cases, and aging with spinal cord injury. *Arch Phys Med Rehabil* **92**, 332-338, doi:10.1016/j.apmr.2010.08.031 (2011).

12 Wu, J. C. *et al.* Effects of age, gender, and socio-economic status on the incidence of spinal cord injury: an assessment using the eleven-year comprehensive nationwide database of Taiwan. *J Neurotrauma* **29**, 889-897, doi:10.1089/neu.2011.1777 (2012).

13 Wu, J. C. *et al.* Epidemiology of cervical spondylotic myelopathy and its risk of causing spinal cord injury: a national cohort study. *Neurosurg Focus* **35**, E10, doi:10.3171/2013.4.FOCUS13122 (2013).

14 Krause, J., Sternberb, M., Lottes, S. & Maides, J. Mortality after Spinal Cord Injury: An 11-year prospective study. *Arch Phys Med Rehab* **78**, 815-821 (1997).

15 LaPlaca, M. C., Simon, C. M., Prado, G. R. & Cullen, D. K. CNS injury biomechanics and experimental models. *Progress in Brain Research*, 13-26, doi:10.1016/s0079-6123(06)61002-9 (2007).

16 Choo, A. M. *et al.* Contusion, dislocation, and distraction: primary hemorrhage and membrane permeability in distinct mechanisms of spinal cord injury. *Journal of Neurosurgery: Spine* **6**, 255-266, doi:10.3171/spi.2007.6.3.255 (2007).

17 Pineau, I. & Lacroix, S. Proinflammatory cytokine synthesis in the injured mouse spinal cord: multiphasic expression pattern and identification of the cell types involved. *J Comp Neurol* **500**, 267-285, doi:10.1002/cne.21149 (2007).

18 Schanne, F. A., Kane, A. B., Young, E. E. & Farber, J. L. Calcium dependence of toxic cell death: a final common pathway. *Science* **206**, 700-702 (1979).

19 Kwon, B. Pathophysiology and pharmacologic treatment of acute spinal cord injury*1. *The Spine Journal* **4**, 451-464, doi:10.1016/j.spinee.2003.07.007 (2004).

20 Dizdaroglu, M., Jaruga, P., Birincioglu, M. & Rodriguez, H. Free radical-induced damage to DNA: mechanisms and measurement1,2 1This article is part of a series of reviews on "Oxidative DNA Damage and Repair." The full list of papers may be found on the homepage of the journal. 2Guest Editor: Miral Dizdaroglu. *Free Radical Biology and Medicine* **32**, 1102-1115, doi:10.1016/s0891-5849(02)00826-2 (2002).
21 Hausmann, O. N. Post-traumatic inflammation following spinal cord injury. *Spinal Cord* **41**, 369-378, doi:10.1038/sj.sc.3101483 (2003).
22 Liu, M. *et al.* Necroptosis, a novel type of programmed cell death, contributes to early neural cells damage after spinal cord injury in adult mice. *The Journal of Spinal Cord Medicine* **38**, 745-753, doi:10.1179/2045772314y.0000000224 (2015).
23 Wang, Y. *et al.* Necroptosis inhibitor necrostatin-1 promotes cell protection and physiological function in traumatic spinal cord injury. *Neuroscience* **266**, 91-101, doi:10.1016/j.neuroscience.2014.02.007 (2014).
24 Li, S., Mealing, G. A., Morley, P. & Stys, P. K. Novel injury mechanism in anoxia and trauma of spinal cord white matter: glutamate release via reverse Na+-dependent glutamate transport. *J Neurosci* **19**, RC16 (1999).
25 Li, S. & Stys, P. K. Mechanisms of ionotropic glutamate receptor-mediated excitotoxicity in isolated spinal cord white matter. *J Neurosci* **20**, 1190-1198 (2000).
26 Norenberg, M. D., Smith, J. & Marcillo, A. The pathology of human spinal cord injury: defining the problems. *J Neurotrauma* **21**, 429-440, doi:10.1089/089771504323004575 (2004).
27 Tator, C. H. Update on the Pathophysiology and Pathology of Acute Spinal Cord Injury. *Brain Pathology* **5**, 407-413, doi:10.1111/j.1750-3639.1995.tb00619.x (1995).
28 Milhorat, T. H., Capocelli, A. L., Anzil, A. P., Kotzen, R. M. & Milhorat, R. H. Pathological basis of spinal cord cavitation in syringomyelia: analysis of 105 autopsy cases. *Journal of Neurosurgery* **82**, 802-812, doi:10.3171/jns.1995.82.5.0802 (1995).
29 McKeon, R. J., Schreiber, R. C., Rudge, J. S. & Silver, J. Reduction of neurite outgrowth in a model of glial scarring following CNS injury is correlated with the expression of inhibitory molecules on reactive astrocytes. *J Neurosci* **11**, 3398-3411 (1991).
30 Ahuja, C. S., Martin, A. R. & Fehlings, M. Recent advances in managing a spinal cord injury secondary to trauma. *F1000Res* **5**, doi:10.12688/f1000research.7586.1 (2016).
31 Cregg, J. M. *et al.* Functional regeneration beyond the glial scar. *Exp Neurol* **253**, 197-207, doi:10.1016/j.expneurol.2013.12.024 (2014).
32 Silver, J. & Miller, J. H. Regeneration beyond the glial scar. *Nat Rev Neurosci* **5**, 146-156, doi:10.1038/nrn1326 (2004).
33 Wanner, I. B. *et al.* Glial scar borders are formed by newly proliferated, elongated astrocytes that interact to corral inflammatory and fibrotic cells via STAT3-dependent mechanisms after spinal cord injury. *J Neurosci* **33**, 12870-12886, doi:10.1523/JNEUROSCI.2121-13.2013 (2013).
34 Anderson, M. A. *et al.* Astrocyte scar formation aids central nervous system axon regeneration. *Nature* **532**, 195-200, doi:10.1038/nature17623 (2016).
35 Rolls, A. S., R; Schwartz, M. The bright side of the glial scar in CNS repair. *Nat Rev Neurosci* **10**, 235, doi:10.1038/nrn2591 (2009).
36 Filbin, M. T. Myelin-associated inhibitors of axonal regeneration in the adult mammalian CNS. *Nat Rev Neurosci* **4**, 703-713, doi:10.1038/nrn1195 (2003).
37 Forgione, N. & Fehlings, M. G. Rho-ROCK Inhibition in the Treatment of Spinal Cord Injury. *World Neurosurgery* **82**, e535-e539, doi:10.1016/j.wneu.2013.01.009 (2014).

38 Lee, J. K. *et al.* Assessing spinal axon regeneration and sprouting in Nogo-, MAG-, and OMgp-deficient mice. *Neuron* **66**, 663-670, doi:10.1016/j.neuron.2010.05.002 (2010).

39 Geoffroy, C. G. & Zheng, B. Myelin-associated inhibitors in axonal growth after CNS injury. *Curr Opin Neurobiol* **27**, 31-38, doi:10.1016/j.conb.2014.02.012 (2014).

40 Fehlings, M. G. & Tator, C. H. The relationships among the severity of spinal cord injury, residual neurological function, axon counts, and counts of retrogradely labeled neurons after experimental spinal cord injury. *Exp Neurol* **132**, 220-228 (1995).

41 Tator, C. H. & Fehlings, M. G. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. *Journal of Neurosurgery* **75**, 15-26, doi:10.3171/jns.1991.75.1.0015 (1991).

42 Fehlings, M. G. & Tator, C. H. The relationships among the severity of spinal cord injury, residual neurological function, axon counts, and counts of retrogradely labeled neurons after experimental spinal cord injury. *Experimental Neurology* **132**, 220-228, doi:10.1016/0014-4886(95)90027-6 (1995).

43 Kotter, M. R., Li, W. W., Zhao, C. & Franklin, R. J. Myelin impairs CNS remyelination by inhibiting oligodendrocyte precursor cell differentiation. *J Neurosci* **26**, 328-332, doi:10.1523/JNEUROSCI.2615-05.2006 (2006).

44 Syed, Y. A. *et al.* Antibody-mediated neutralization of myelin-associated EphrinB3 accelerates CNS remyelination. *Acta Neuropathol* **131**, 281-298, doi:10.1007/s00401-015-1521-1 (2016).

45 Kotter, M. R., Setzu, A., Sim, F. J., Van Rooijen, N. & Franklin, R. J. Macrophage depletion impairs oligodendrocyte remyelination following lysolecithin-induced demyelination. *Glia* **35**, 204-212 (2001).

46 Bieber, A. J., Warrington, A., Pease, L. R. & Rodriguez, M. Humoral autoimmunity as a mediator of CNS repair. *Trends Neurosci* **24**, S39-44 (2001).

47 Jeffery, N. D. & Blakemore, W. F. Locomotor deficits induced by experimental spinal cord demyelination are abolished by spontaneous remyelination. *Brain : a journal of neurology* **120 (Pt 1)**, 27-37 (1997).

48 Lynskey, J. V., Belanger, A. & Jung, R. Activity-dependent plasticity in spinal cord injury. *J Rehabil Res Dev* **45**, 229-240 (2008).

49 Raineteau, O. & Schwab, M. E. Plasticity of motor systems after incomplete spinal cord injury. *Nat Rev Neurosci* **2**, 263-273, doi:10.1038/35067570 (2001).

50 Meletis, K. *et al.* Spinal cord injury reveals multilineage differentiation of ependymal cells. *PLoS Biol* **6**, e182, doi:10.1371/journal.pbio.0060182 (2008).

51 Barnabe-Heider, F. *et al.* Origin of new glial cells in intact and injured adult spinal cord. *Cell Stem Cell* **7**, 470-482, doi:10.1016/j.stem.2010.07.014 (2010).

52 Mao, Y., Nguyen, T., Sutherland, T. & Gorrie, C. A. Endogenous neural progenitor cells in the repair of the injured spinal cord. *Neural Regen Res* **11**, 1075-1076, doi:10.4103/1673-5374.187035 (2016).

53 Bradbury, E. J. *et al.* Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature* **416**, 636-640, doi:10.1038/416636a (2002).

54 Li, G. *et al.* Mdivi-1 Inhibits Astrocyte Activation and Astroglial Scar Formation and Enhances Axonal Regeneration after Spinal Cord Injury in Rats. *Front Cell Neurosci* **10**, 241, doi:10.3389/fncel.2016.00241 (2016).

55 Tator, C. H. REVIEW OF TREATMENT TRIALS IN HUMANSPINAL CORD INJURY. *Neurosurgery*, 957???987, doi:10.1227/01.neu.0000245591.16087.89 (2006).

56 Zhang, N., Fang, M., Chen, H., Gou, F. & Ding, M. Evaluation of spinal cord injury animal models. *Neural Regen Res* **9**, 2008-2012, doi:10.4103/1673-5374.143436 (2014).

57 Nout, Y. S. *et al.* Animal models of neurologic disorders: a nonhuman primate model of spinal cord injury. *Neurotherapeutics* **9**, 380-392, doi:10.1007/s13311-012-0114-0 (2012).
58 Kwon, B. K. *et al.* Large animal and primate models of spinal cord injury for the testing of novel therapies. *Exp Neurol* **269**, 154-168, doi:10.1016/j.expneurol.2015.04.008 (2015).
59 Fisher, M. *et al.* Update of the stroke therapy academic industry roundtable preclinical recommendations. *Stroke* **40**, 2244-2250, doi:10.1161/STROKEAHA.108.541128 (2009).
60 Tator, C. H. Acute spinal cord injury: a review of recent studies of treatment and pathophysiology. *Can Med Assoc J* **107**, 143-145 passim (1972).
61 Wilson, J. R., Forgione, N. & Fehlings, M. G. Emerging therapies for acute traumatic spinal cord injury. *CMAJ* **185**, 485-492, doi:10.1503/cmaj.121206 (2013).
62 Guha, A., Tator, C. H. & Rochon, J. Spinal cord blood flow and systemic blood pressure after experimental spinal cord injury in rats. *Stroke* **20**, 372-377, doi:10.1161/01.str.20.3.372 (1989).
63 Guha, A. B. & Tator, C. H. Acute Cardiovascular Effects of Experimental Spinal Cord Injury. *The Journal of Trauma: Injury, Infection, and Critical Care* **28**, 481-490, doi:10.1097/00005373-198804000-00011 (1988).
64 Schwab, J. M., Zhang, Y., Kopp, M. A., Brommer, B. & Popovich, P. G. The paradox of chronic neuroinflammation, systemic immune suppression, autoimmunity after traumatic chronic spinal cord injury. *Exp Neurol* **258**, 121-129, doi:10.1016/j.expneurol.2014.04.023 (2014).
65 Ko, H., Dittuno, J., Graziani, V. & Little, J. The pattern of reflex recovery during spinal shock. *Spinal Cord* **37**, 402-409 (1999).
66 Ploumis, A., Yadlapalli, N., Fehlings, M. G., Kwon, B. K. & Vaccaro, A. R. A systematic review of the evidence supporting a role for vasopressor support in acute SCI. *Spinal Cord* **48**, 356-362, doi:sc2009150 [pii]
10.1038/sc.2009.150 (2010).
67 Lehmann, K. G., Lane, J. G., Piepmeier, J. M. & Batsford, W. P. Cardiovascular abnormalities accompanying acute spinal cord injury in humans: incidence, time course and severity. *J Am Coll Cardiol* **10**, 46-52 (1987).
68 Guly, H. R., Bouamra, O., Lecky, F. E., Trauma, A. & Research, N. The incidence of neurogenic shock in patients with isolated spinal cord injury in the emergency department. *Resuscitation* **76**, 57-62, doi:10.1016/j.resuscitation.2007.06.008 (2008).
69 Acheson, M., Livingston, R., Richardson, M. & Stimac, G. High-resolution CT scanning in the evaluation of cervical spine fractures:Comparison with plain film examinations. *AJR* **148**, 1179-1185 (1987).
70 Woodring, J. & Lee, C. Limitations of cervical radiography in the evaluation of acute cervical trauma. *J Trauma* **34**, 32-39 (1993).
71 Vaccaro, A. R. *et al.* AOSpine subaxial cervical spine injury classification system. *Eur Spine J* **25**, 2173-2184, doi:10.1007/s00586-015-3831-3 (2016).
72 Vaccaro, A. R. *et al.* AOSpine thoracolumbar spine injury classification system: fracture description, neurological status, and key modifiers. *Spine (Phila Pa 1976)* **38**, 2028-2037, doi:10.1097/BRS.0b013e3182a8a381 (2013).
73 Lammertse, D. *et al.* Neuroimaging in traumatic spinal cord injury: an evidence-based review for clinical practice and research. *J Spinal Cord Med* **30**, 205-214 (2007).
74 Miyanji, F., Furlan, J., Aarabi, B., Arnold, P. & Fehlings, M. Acute Cervical Traumatic Spinal Cord Injury: MR Imaging Findings Correlated with Neurologic Outcome--Prospective Study with 100 Consecutive Patients. *Radiology* **243**, 820-827 (2007).

75 Vaccaro, A. R. *et al.* Magnetic resonance evaluation of the intervertebral disc, spinal ligaments, and spinal cord before and after closed traction reduction of cervical spine dislocations. *Spine (Phila Pa 1976)* **24**, 1210-1217 (1999).
76 Nakashima, H. *et al.* Posterior approach for cervical fracture-dislocations with traumatic disc herniation. *Eur Spine J* **20**, 387-394, doi:10.1007/s00586-010-1589-1 (2011).
77 Resnick, D. K. Updated Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injury. *Neurosurgery* **72 Suppl 2**, 1, doi:10.1227/NEU.0b013e318276ee7e (2013).
78 Cadotte, D. W. & Fehlings, M. G. Will imaging biomarkers transform spinal cord injury trials? *Lancet Neurol* **12**, 843-844, doi:10.1016/S1474-4422(13)70157-1 (2013).
79 Curt, A. & Dietz, V. Electrophysiological recordings in patients with spinal cord injury: significance for predicting outcome. *Spinal Cord* **37**, 157-165 (1999).
80 Curt, A., Van Hedel, H. J., Klaus, D., Dietz, V. & Group, E.-S. S. Recovery from a spinal cord injury: significance of compensation, neural plasticity, and repair. *J Neurotrauma* **25**, 677-685, doi:10.1089/neu.2007.0468 (2008).
81 Kirshblum, S. C. *et al.* Reference for the 2011 revision of the International Standards for Neurological Classification of Spinal Cord Injury. *J Spinal Cord Med* **34**, 547-554, doi:10.1179/107902611X13186000420242 (2011).
82 ASIA. (American Spinal Injury Association, Chicago, 2000).
83 Marino, R. J., Jones, L., Kirshblum, S., Tal, J. & Dasgupta, A. Reliability and repeatability of the motor and sensory examination of the international standards for neurological classification of spinal cord injury. *J Spinal Cord Med* **31**, 166-170 (2008).
84 Savic, G., Bergstrom, E. M., Frankel, H. L., Jamous, M. A. & Jones, P. W. Inter-rater reliability of motor and sensory examinations performed according to American Spinal Injury Association standards. *Spinal Cord* **45**, 444-451, doi:3102044 [pii]
10.1038/sj.sc.3102044 (2007).
85 Sherwood, A. M., Dimitrijevic, M. R. & McKay, W. B. Evidence of subclinical brain influence in clinically complete spinal cord injury: discomplete SCI. *J Neurol Sci* **110**, 90-98 (1992).
86 Schneider, R. C., Cherry, G. & Pantek, H. The syndrome of acute central cervical spinal cord injury; with special reference to the mechanisms involved in hyperextension injuries of cervical spine. *Journal of neurosurgery* **11**, 546-577, doi:10.3171/jns.1954.11.6.0546 (1954).
87 Fehlings, M. G. *et al.* The Aging of the Global Population: The Changing Epidemiology of Disease and Spinal Disorders. *Neurosurgery* **77 Suppl 4**, S1-5, doi:10.1227/NEU.0000000000000953
00006123-201510001-00001 [pii] (2015).
88 McKinley, W., Santos, K., Meade, M. & Brooke, K. Incidence and outcomes of spinal cord injury clinical syndromes. *J Spinal Cord Med* **30**, 215-224 (2007).
89 Burns, A. & Ditunno, J. Establishing Prognosis and Maximizing Functional Outcomes after Spinal Cord Injury. *Spine* **26**, S137-S145 (2001).
90 Kirshblum, S., Millis, S., McKinley, W. & Tulsky, D. Late neurologic recovery after traumatic spinal cord injury. *Arch Phys Med Rehabil* **85**, 1811-1817, doi:S0003999304003867 [pii] (2004).
91 Fawcett, J. *et al.* Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic trials. *Spinal Cord* **45**, 190-205 (2007).
92 Marino, R., Dittuno, J., Donovan, W. & Maynard, F. Neurologic Recovery after Traumatic Spinal Cord Injury: Data from the Model Spinal Cord Injury Systems. *Arch Phys Med Rehab* **80**, 1391-1396 (1999).
93 Waters, R., Yakura, J., Adkins, R. & Sie, I. Recovery Following Complete Paraplegia. *Arch Phys Med Rehab* **73**, 784-789 (1992).

94 Coleman, W. & Geisler, F. Injury severity as primary predictor of outcome in acute spinal cord injury: retrospective results from a large multicenter clinical trial. *Spine Journal* **4**, 373-378 (2004).
95 Kay, E., Deutsch, A. & Wuermser, L. Predicting Walking at Discharge From Inpatient Rehabilitation After a Traumatic Spinal Cord Injury. *Arch Phys Med Rehab* **88**, 745-750 (2007).
96 van Middendorp, J. J. *et al.* A clinical prediction rule for ambulation outcomes after traumatic spinal cord injury: a longitudinal cohort study. *Lancet* **377**, 1004-1010, doi:10.1016/S0140-6736(10)62276-3 (2011).
97 Wilson, J. R. *et al.* A clinical prediction model for long-term functional outcome after traumatic spinal cord injury based on acute clinical and imaging factors. *J Neurotrauma* **29**, 2263-2271, doi:10.1089/neu.2012.2417 (2012).
98 Pavese, C. *et al.* Prediction of Bladder Outcomes after Traumatic Spinal Cord Injury: A Longitudinal Cohort Study. *PLoS Med* **13**, e1002041, doi:10.1371/journal.pmed.1002041 (2016).
99 Ryken, T. C. *et al.* The acute cardiopulmonary management of patients with cervical spinal cord injuries. *Neurosurgery* **72 Suppl 2**, 84-92, doi:10.1227/NEU.0b013e318276ee16 (2013).
100 Braughler, J. & Hall, E. Effects of multi-dose methylprednisolone sodium succinate administration on injured cat spinal cord neurofilament degradation and energy metabolism. *J Neurosurg* **61**, 290-295 (1984).
101 Hall, E. D. & Braughler, J. M. Glucocorticoid mechanisms in acute spinal cord injury: a review and therapeutic rationale. *Surg Neurol* **18**, 320-327 (1982).
102 Hall, E. D. & Braughler, J. M. Effects of intravenous methylprednisolone on spinal cord lipid peroxidation and Na+ + K+)-ATPase activity. Dose-response analysis during 1st hour after contusion injury in the cat. *J Neurosurg* **57**, 247-253, doi:10.3171/jns.1982.57.2.0247 (1982).
103 Bracken, M. *et al.* Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. *JAMA* **277**, 1597-1604 (1997).
104 Bracken, M. B. *et al.* A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. *N Engl J Med* **322**, 1405-1411, doi:10.1056/NEJM199005173222001 (1990).
105 Bracken, M. B. *et al.* Efficacy of methylprednisolone in acute spinal cord injury. *JAMA* **251**, 45-52 (1984).
106 Bracken, M. B. Steroids for acute spinal cord injury. *Cochrane Database Syst Rev* **1**, CD001046, doi:10.1002/14651858.CD001046.pub2 (2012).
107 Eck, J. C., Nachtigall, D., Humphreys, S. C. & Hodges, S. D. Questionnaire survey of spine surgeons on the use of methylprednisolone for acute spinal cord injury. *Spine (Phila Pa 1976)* **31**, E250-253, doi:10.1097/01.brs.0000214886.21265.8c
00007632-200604200-00021 [pii] (2006).
108 Hurlbert, R. Methylprednisolone for acute spinal cord injury: an inappropriate standard of care. *J Nerosurg Spine* **93**, 1-7 (2000).
109 Hurlbert, R. J. *et al.* Pharmacological therapy for acute spinal cord injury. *Neurosurgery* **72 Suppl 2**, 93-105, doi:10.1227/NEU.0b013e31827765c6
00006123-201303002-00012 [pii] (2013).
110 Hadley, M. *et al.* Pharmacological Therapy after Acute Cervical Spinal Cord Injury. *Neurosurgery* **50**, 563-572 (2002).

111 Fehlings, M. G., Wilson, J. R. & Cho, N. Methylprednisolone for the treatment of acute spinal cord injury: counterpoint. *Neurosurgery* **61 Suppl 1**, 36-42, doi:10.1227/NEU.0000000000000412 00006123-201408001-00016 [pii] (2014).
112 Hurlbert, R. J. Methylprednisolone for the treatment of acute spinal cord injury: point. *Neurosurgery* **61 Suppl 1**, 32-35, doi:10.1227/NEU.0000000000000393 00006123-201408001-00015 [pii] (2014).
113 Carlson, G. D. *et al.* Early time-dependent decompression for spinal cord injury: vascular mechanisms of recovery. *J Neurotrauma* **14**, 951-962 (1997).
114 Dimar, J., Glassman, S., Raque, G., Zhang, Y. & Shields, C. The influence of spinal canal narrowing and timing of decompression on neurologic recovery after spinal cord contusion in a rat model. *Spine* **24**, 1623-1633 (1999).
115 Batchelor, P. E. *et al.* Meta-analysis of pre-clinical studies of early decompression in acute spinal cord injury: a battle of time and pressure. *PLoS One* **8**, e72659, doi:10.1371/journal.pone.0072659 (2013).
116 Wilson, J. R. *et al.* Early versus late surgery for traumatic spinal cord injury: the results of a prospective Canadian cohort study. *Spinal Cord*, doi:10.1038/sc.2012.59 sc201259 [pii] (2012).
117 Bourassa-Moreau, E., Mac-Thiong, J. M., Feldman, D. E., Thompson, C. & Parent, S. Non-neurological outcomes after complete traumatic spinal cord injury: the impact of surgical timing. *J Neurotrauma* **30**, 1596-1601, doi:10.1089/neu.2013.2957 (2013).
118 Grassner, L. *et al.* Early Decompression (< 8 h) after Traumatic Cervical Spinal Cord Injury Improves Functional Outcome as Assessed by Spinal Cord Independence Measure after One Year. *J Neurotrauma*, doi:10.1089/neu.2015.4325 (2016).
119 Fehlings, M., Rabin, D., Sears, W., Cadotte, D. & Aarabi, B. Current practice in the timing of surgical intervention in spinal cord injury. *Spine* **35**, 166-173 (2010).
120 Brodbelt, A. R. & Stoodley, M. A. Post-traumatic syringomyelia: a review. *J Clin Neurosci* **10**, 401-408 (2003).
121 Schurch, B., Wichmann, W. & Rossier, A. B. Post-traumatic syringomyelia (cystic myelopathy): a prospective study of 449 patients with spinal cord injury. *J Neurol Neurosurg Psychiatry* **60**, 61-67 (1996).
122 Alpert, S. W., Koval, K. J. & Zuckerman, J. D. Neuropathic Arthropathy: Review of Current Knowledge. *J Am Acad Orthop Surg* **4**, 100-108 (1996).
123 Aebli, N., Potzel, T. & Krebs, J. Characteristics and surgical management of neuropathic (Charcot) spinal arthropathy after spinal cord injury. *Spine J* **14**, 884-891, doi:10.1016/j.spinee.2013.07.441 (2014).
124 Adams, M. M. & Hicks, A. L. Spasticity after spinal cord injury. *Spinal Cord* **43**, 577-586, doi:10.1038/sj.sc.3101757 (2005).
125 Sezer, N., Akkus, S. & Ugurlu, F. G. Chronic complications of spinal cord injury. *World J Orthop* **6**, 24-33, doi:10.5312/wjo.v6.i1.24 (2015).
126 Claydon, V. E., Steeves, J. D. & Krassioukov, A. Orthostatic hypotension following spinal cord injury: understanding clinical pathophysiology. *Spinal Cord* **44**, 341-351, doi:10.1038/sj.sc.3101855 (2006).
127 Krassioukov, A., Eng, J. J., Warburton, D. E., Teasell, R. & Spinal Cord Injury Rehabilitation Evidence Research, T. A systematic review of the management of orthostatic hypotension after spinal cord injury. *Arch Phys Med Rehabil* **90**, 876-885, doi:10.1016/j.apmr.2009.01.009 (2009).

128 Krassioukov, A., Warburton, D. E., Teasell, R. & Eng, J. J. A systematic review of the management of autonomic dysreflexia after spinal cord injury. *Arch Phys Med Rehabil* **90**, 682-695, doi:10.1016/j.apmr.2008.10.017 (2009).
129 Blackmer, J. Rehabilitation medicine: 1. Autonomic dysreflexia. *CMAJ* **169**, 931-935 (2003).
130 Linn, W. S., Adkins, R. H., Gong, H., Jr. & Waters, R. L. Pulmonary function in chronic spinal cord injury: a cross-sectional survey of 222 southern California adult outpatients. *Arch Phys Med Rehabil* **81**, 757-763 (2000).
131 Brown, R., DiMarco, A. F., Hoit, J. D. & Garshick, E. Respiratory dysfunction and management in spinal cord injury. *Respir Care* **51**, 853-868;discussion 869-870 (2006).
132 Winslow, C. & Rozovsky, J. Effect of spinal cord injury on the respiratory system. *Am J Phys Med Rehabil* **82**, 803-814, doi:10.1097/01.PHM.0000078184.08835.01 (2003).
133 DeVivo, M. J., Black, K. J. & Stover, S. L. Causes of death during the first 12 years after spinal cord injury. *Arch Phys Med Rehabil* **74**, 248-254 (1993).
134 Benedikt Brommer, O. E., Marcel A. Kopp, Ralf Watzlawick, Susanne Müller, Harald Prüss, Yuying Chen, Michael J. DeVivo, Felix W. Finkenstaedt, Ulrich Dirnagl, Thomas Liebscher, Andreas Meisel, Jan M. Schwab. Spinal cord injury-induced immune deficiency syndrome enhances infection susceptibility dependent on lesion level. *Brain Behav Immun* **139**, 692 (2016).
135 Ulndreaj, A., Chio, J. C., Ahuja, C. S. & Fehlings, M. G. Modulating the immune response in spinal cord injury. *Expert Rev Neurother* **16**, 1127-1129, doi:10.1080/14737175.2016.1207532 (2016).
136 Brommer, B. *et al.* Spinal cord injury-induced immune deficiency syndrome enhances infection susceptibility dependent on lesion level. *Brain : a journal of neurology* **139**, 692-707, doi:10.1093/brain/awv375 (2016).
137 Benevento, B. T. & Sipski, M. L. Neurogenic bladder, neurogenic bowel, and sexual dysfunction in people with spinal cord injury. *Phys Ther* **82**, 601-612 (2002).
138 Taweel, W. A. & Seyam, R. Neurogenic bladder in spinal cord injury patients. *Res Rep Urol* **7**, 85-99, doi:10.2147/RRU.S29644 (2015).
139 Hess, M. J. & Hough, S. Impact of spinal cord injury on sexuality: broad-based clinical practice intervention and practical application. *J Spinal Cord Med* **35**, 211-218, doi:10.1179/2045772312Y.0000000025 (2012).
140 Coggrave, M. J. & Norton, C. The need for manual evacuation and oral laxatives in the management of neurogenic bowel dysfunction after spinal cord injury: a randomized controlled trial of a stepwise protocol. *Spinal Cord* **48**, 504-510, doi:10.1038/sc.2009.166 (2010).
141 Krassioukov, A., Eng, J. J., Claxton, G., Sakakibara, B. M. & Shum, S. Neurogenic bowel management after spinal cord injury: a systematic review of the evidence. *Spinal Cord* **48**, 718-733, doi:10.1038/sc.2010.14 (2010).
142 Consortium for Spinal Cord Medicine Clinical Practice, G. Pressure ulcer prevention and treatment following spinal cord injury: a clinical practice guideline for health-care professionals. *J Spinal Cord Med* **24 Suppl 1**, S40-101 (2001).
143 van Kuijk, A. A., Geurts, A. C. & van Kuppevelt, H. J. Neurogenic heterotopic ossification in spinal cord injury. *Spinal Cord* **40**, 313-326, doi:10.1038/sj.sc.3101309 (2002).
144 Rush, P. J. The rheumatic manifestations of traumatic spinal cord injury. *Semin Arthritis Rheum* **19**, 77-89 (1989).
145 Cardenas, D. D. & Felix, E. R. Pain after spinal cord injury: a review of classification, treatment approaches, and treatment assessment. *PM R* **1**, 1077-1090, doi:10.1016/j.pmrj.2009.07.002 (2009).

146 Gomara-Toldra, N., Sliwinski, M. & Dijkers, M. P. Physical therapy after spinal cord injury: a systematic review of treatments focused on participation. *J Spinal Cord Med* **37**, 371-379, doi:10.1179/2045772314Y.0000000194 (2014).
147 Hwang, D. H. *et al.* Survival of neural stem cell grafts in the lesioned spinal cord is enhanced by a combination of treadmill locomotor training via insulin-like growth factor-1 signaling. *J Neurosci* **34**, 12788-12800, doi:10.1523/JNEUROSCI.5359-13.2014 (2014).
148 Dobkin, B. *et al.* Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI. *Neurology* **66**, 484-493, doi:10.1212/01.wnl.0000202600.72018.39 (2006).
149 Stiens, S. A., Kirshblum, S. C., Groah, S. L., McKinley, W. O. & Gittler, M. S. Spinal cord injury medicine. 4. Optimal participation in life after spinal cord injury: physical, psychosocial, and economic reintegration into the environment. *Arch Phys Med Rehabil* **83**, S72-81, S90-78 (2002).
150 National Insitute on Disability, I. L., and Rehabilitation Research (NIDILRR). *AbleData*, <http://www.abledata.com/> (2017).
151 Ho, C. H. *et al.* Functional electrical stimulation and spinal cord injury. *Phys Med Rehabil Clin N Am* **25**, 631-654, ix, doi:10.1016/j.pmr.2014.05.001 (2014).
152 Bhambhani, Y., Tuchak, C., Burnham, R., Jeon, J. & Maikala, R. Quadriceps muscle deoxygenation during functional electrical stimulation in adults with spinal cord injury. *Spinal Cord* **38**, 630-638 (2000).
153 Kakebeeke, T. H. *et al.* Training and detraining of a tetraplegic subject: high-volume FES cycle training. *Am J Phys Med Rehabil* **87**, 56-64, doi:10.1097/PHM.0b013e31815b2738 (2008).
154 Ragnarsson, K. T. Functional electrical stimulation after spinal cord injury: current use, therapeutic effects and future directions. *Spinal Cord* **46**, 255-274, doi:10.1038/sj.sc.3102091 (2008).
155 Tate, D. & Forchheimer, M. Review of cross-cultural issues related to quality of life after spinal cord injury. *Top Spinal Cord Inj Rehabil* **20**, 181-190, doi:10.1310/sci2003-181 (2014).
156 Wilson, J. R., Hashimoto, R. E., Dettori, J. R. & Fehlings, M. G. Spinal cord injury and quality of life: a systematic review of outcome measures. *Evid Based Spine Care J* **2**, 37-44, doi:10.1055/s-0030-1267085 (2011).
157 Tulsky, D. S. *et al.* Overview of the Spinal Cord Injury--Quality of Life (SCI-QOL) measurement system. *J Spinal Cord Med* **38**, 257-269, doi:10.1179/2045772315Y.0000000023 (2015).
158 Dijkers, M. Quality of life after spinal cord injury: a meta analysis of the effects of disablement components. *Spinal Cord* **35**, 829-840 (1997).
159 Clayton, K. S. & Chubon, R. A. Factors associated with the quality of life of long-term spinal cord injured persons. *Arch Phys Med Rehabil* **75**, 633-638 (1994).
160 Evans, R. L. *et al.* Quality of life after spinal cord injury: a literature critique and meta-analysis (1983-1992). *J Am Paraplegia Soc* **17**, 60-66 (1994).
161 Fuhrer, M. J., Rintala, D. H., Hart, K. A., Clearman, R. & Young, M. E. Relationship of life satisfaction to impairment, disability, and handicap among persons with spinal cord injury living in the community. *Arch Phys Med Rehabil* **73**, 552-557 (1992).
162 Gerhart, K. A., Koziol-McLain, J., Lowenstein, S. R. & Whiteneck, G. G. Quality of life following spinal cord injury: knowledge and attitudes of emergency care providers. *Ann Emerg Med* **23**, 807-812 (1994).
163 Krause, J. S. & Crewe, N. M. Chronologic age, time since injury, and time of measurement: effect on adjustment after spinal cord injury. *Arch Phys Med Rehabil* **72**, 91-100 (1991).
164 Jain, N. B., Sullivan, M., Kazis, L. E., Tun, C. G. & Garshick, E. Factors associated with health-related quality of life in chronic spinal cord injury. *Am J Phys Med Rehabil* **86**, 387-396, doi:10.1097/PHM.0b013e31804a7d00 (2007).

165 Brillhart, B. & Johnson, K. Motivation and the coping process of adults with disabilities: a qualitative study. *Rehabil Nurs* **22**, 249-252, 255-246 (1997).
166 Siosteen, A., Lundqvist, C., Blomstrand, C., Sullivan, L. & Sullivan, M. The quality of life of three functional spinal cord injury subgroups in a Swedish community. *Paraplegia* **28**, 476-488, doi:10.1038/sc.1990.64 (1990).
167 DeVivo, M. J. & Richards, J. S. Community reintegration and quality of life following spinal cord injury. *Paraplegia* **30**, 108-112, doi:10.1038/sc.1992.35 (1992).
168 Saadat, S. *et al.* Health-related quality of life among individuals with long-standing spinal cord injury: a comparative study of veterans and non-veterans. *BMC Public Health* **10**, 6, doi:10.1186/1471-2458-10-6 (2010).
169 Westgren, N. & Levi, R. Quality of life and traumatic spinal cord injury. *Arch Phys Med Rehabil* **79**, 1433-1439 (1998).
170 Bracken, M. B. *et al.* Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. *JAMA* **277**, 1597-1604 (1997).
171 Kwon, B. K. *et al.* Cerebrospinal fluid inflammatory cytokines and biomarkers of injury severity in acute human spinal cord injury. *J Neurotrauma* **27**, 669-682, doi:10.1089/neu.2009.1080 (2010).
172 Siddiqui, A. M., Khazaei, M. & Fehlings, M. G. Translating mechanisms of neuroprotection, regeneration, and repair to treatment of spinal cord injury. *Prog Brain Res* **218**, 15-54, doi:10.1016/bs.pbr.2014.12.007 (2015).
173 Grossman, R. G., Toups, E. G., Frankowski, R. F., Burau, K. D. & Howley, S. North American Clinical Trials Network for the Treatment of Spinal Cord Injury: goals and progress. *J Neurosurg Spine* **17**, 6-10, doi:10.3171/2012.4.AOSPINE1294 (2012).
174 DeVivo, M. *et al.* International Spinal Cord Injury Core Data Set. *Spinal Cord* **44**, 535-540, doi:10.1038/sj.sc.3101958 (2006).
175 DeVivo, M. J., Go, B. K. & Jackson, A. B. Overview of the national spinal cord injury statistical center database. *J Spinal Cord Med* **25**, 335-338 (2002).
176 Ahuja, C. S. & Fehlings, M. Concise Review: Bridging the Gap: Novel Neuroregenerative and Neuroprotective Strategies in Spinal Cord Injury. *Stem Cells Translational Medicine*, doi:10.5966/sctm.2015-0381 (2016).
177 Wells, J., Hurlbert, R., Fehlings, M. & Yong, V. Neuroprotection by minocycline facilitates significant recovery from spinal cord injury in mice. *Brain* **126**, 1628-1637 (2003).
178 Lee, S. M. *et al.* Minocycline reduces cell death and improves functional recovery after traumatic spinal cord injury in the rat. *J Neurotrauma* **20**, 1017-1027, doi:10.1089/089771503770195867 (2003).
179 Wilson, J. R. & Fehlings, M. G. Riluzole for Acute Traumatic Spinal Cord Injury: A Promising Neuroprotective Treatment Strategy. *World Neurosurg*, doi:S1878-8750(13)00008-9 [pii] 10.1016/j.wneu.2013.01.001 (2013).
180 Grossman, R. G. *et al.* A prospective, multicenter, phase I matched-comparison group trial of safety, pharmacokinetics, and preliminary efficacy of riluzole in patients with traumatic spinal cord injury. *J Neurotrauma* **31**, 239-255, doi:10.1089/neu.2013.2969 (2014).
181 Santa-Olalla, J. & Covarrubias, L. Basic fibroblast growth factor promotes epidermal growth factor responsiveness and survival of mesencephalic neural precursor cells. *J Neurobiol* **40**, 14-27 (1999).

182 Teng, Y. D., Mocchetti, I., Taveira-DaSilva, A. M., Gillis, R. A. & Wrathall, J. R. Basic fibroblast growth factor increases long-term survival of spinal motor neurons and improves respiratory function after experimental spinal cord injury. *J Neurosci* **19**, 7037-7047 (1999).
183 Rabchevsky, A. G. *et al.* Basic fibroblast growth factor (bFGF) enhances functional recovery following severe spinal cord injury to the rat. *Exp Neurol* **164**, 280-291, doi:10.1006/exnr.2000.7399 (2000).
184 Batchelor, P. E. *et al.* Hypothermia prior to decompression: buying time for treatment of acute spinal cord injury. *J Neurotrauma* **27**, 1357-1368, doi:10.1089/neu.2010.1360 (2010).
185 Levi, A. D. *et al.* Clinical outcomes using modest intravascular hypothermia after acute cervical spinal cord injury. *Neurosurgery* **66**, 670-677, doi:10.1227/01.NEU.0000367557.77973.5F (2010).
186 Dergham, P., Ellezam, B. & Essagian, C. Rho signalling pathway targeted to promote spinal cord repair. *J Neuroscience* **22**, 6570-6577 (2002).
187 Kwon, B. K., Sekhon, L. H. & Fehlings, M. G. Emerging repair, regeneration, and translational research advances for spinal cord injury. *Spine (Phila Pa 1976)* **35**, S263-270, doi:10.1097/BRS.0b013e3181f3286d (2010).
188 Fehlings, M. G. *et al.* A phase I/IIa clinical trial of a recombinant Rho protein antagonist in acute spinal cord injury. *J Neurotrauma* **28**, 787-796, doi:10.1089/neu.2011.1765 (2011).
189 Freund, P. *et al.* Anti-Nogo-A antibody treatment enhances sprouting of corticospinal axons rostral to a unilateral cervical spinal cord lesion in adult macaque monkey. *J Comp Neurol* **502**, 644-659, doi:10.1002/cne.21321 (2007).
190 Zorner, B. & Schwab, M. E. Anti-Nogo on the go: from animal models to a clinical trial. *Ann N Y Acad Sci* **1198 Suppl 1**, E22-34, doi:10.1111/j.1749-6632.2010.05566.x
NYAS5566 [pii] (2010).
191 Harrop, J. S. *et al.* Evaluation of clinical experience using cell-based therapies in patients with spinal cord injury: a systematic review. *J Neurosurg Spine* **17**, 230-246, doi:10.3171/2012.5.AOSPINE12115 (2012).
192 Tetzlaff, W. *et al.* A systematic review of cellular transplantation therapies for spinal cord injury. *J Neurotrauma* **28**, 1611-1682, doi:10.1089/neu.2009.1177 (2011).
193 Khazaei M, A. C., Fehlings MG. Induced Pluripotent Stem Cells for Traumatic Spinal Cord Injury. *Front. Cell Dev. Biol.* **4**, doi:10.3389/fcell.2016.00152 (2017).
194 Ramon-Cueto, A., Cordero, M. I., Santos-Benito, F. F. & Avila, J. Functional recovery of paraplegic rats and motor axon regeneration in their spinal cords by olfactory ensheathing glia. *Neuron* **25**, 425-435 (2000).
195 Keyvan-Fouladi, N., Raisman, G. & Li, Y. Functional repair of the corticospinal tract by delayed transplantation of olfactory ensheathing cells in adult rats. *J Neurosci* **23**, 9428-9434 (2003).
196 Pascual, J. I., Gudino-Cabrera, G., Insausti, R. & Nieto-Sampedro, M. Spinal implants of olfactory ensheathing cells promote axon regeneration and bladder activity after bilateral lumbosacral dorsal rhizotomy in the adult rat. *J Urol* **167**, 1522-1526 (2002).
197 Li, Y., Decherchi, P. & Raisman, G. Transplantation of olfactory ensheathing cells into spinal cord lesions restores breathing and climbing. *J Neurosci* **23**, 727-731 (2003).
198 Boyd, J. G., Lee, J., Skihar, V., Doucette, R. & Kawaja, M. D. LacZ-expressing olfactory ensheathing cells do not associate with myelinated axons after implantation into the compressed spinal cord. *Proc Natl Acad Sci U S A* **101**, 2162-2166, doi:10.1073/pnas.0303842101 (2004).
199 Li, J. & Lepski, G. Cell transplantation for spinal cord injury: a systematic review. *Biomed Res Int* **2013**, 786475, doi:10.1155/2013/786475 (2013).

200 Pastrana, E. *et al.* Genes associated with adult axon regeneration promoted by olfactory ensheathing cells: a new role for matrix metalloproteinase 2. *J Neurosci* **26**, 5347-5359, doi:10.1523/JNEUROSCI.1111-06.2006 (2006).
201 Guo, J. S. *et al.* Cotransplant of neural stem cells and NT-3 gene modified Schwann cells promote the recovery of transected spinal cord injury. *Spinal Cord* **45**, 15-24, doi:10.1038/sj.sc.3101943 (2007).
202 Mackay-Sim, A. *et al.* Autologous olfactory ensheathing cell transplantation in human paraplegia: a 3-year clinical trial. *Brain : a journal of neurology* **131**, 2376-2386, doi:10.1093/brain/awn173 (2008).
203 Dlouhy, B. J., Awe, O., Rao, R. C., Kirby, P. A. & Hitchon, P. W. Autograft-derived spinal cord mass following olfactory mucosal cell transplantation in a spinal cord injury patient: Case report. *Journal of neurosurgery. Spine* **21**, 618-622, doi:10.3171/2014.5.SPINE13992 (2014).
204 Chhabra, H. S. *et al.* Autologous olfactory [corrected] mucosal transplant in chronic spinal cord injury: an Indian Pilot Study. *Spinal Cord* **47**, 887-895, doi:10.1038/sc.2009.54 (2009).
205 Tabakow, P. *et al.* Transplantation of autologous olfactory ensheathing cells in complete human spinal cord injury. *Cell Transplant* **22**, 1591-1612, doi:10.3727/096368912X663532 (2013).
206 Hill, C. E., Moon, L. D., Wood, P. M. & Bunge, M. B. Labeled Schwann cell transplantation: cell loss, host Schwann cell replacement, and strategies to enhance survival. *Glia* **53**, 338-343, doi:10.1002/glia.20287 (2006).
207 Li, L. *et al.* Effects of transplantation of olfactory ensheathing cells in chronic spinal cord injury: a systematic review and meta-analysis. *Eur Spine J* **24**, 919-930, doi:10.1007/s00586-014-3416-6 (2015).
208 Harkema, S. *et al.* Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. *Lancet* **377**, 1938-1947, doi:10.1016/S0140-6736(11)60547-3 (2011).
209 Bachmann, L. C. *et al.* Deep brain stimulation of the midbrain locomotor region improves paretic hindlimb function after spinal cord injury in rats. *Sci Transl Med* **5**, 208ra146, doi:10.1126/scitranslmed.3005972
5/208/208ra146 [pii] (2013).
210 Bouton, C. E. *et al.* Restoring cortical control of functional movement in a human with quadriplegia. *Nature* **533**, 247-250, doi:10.1038/nature17435 (2016).
211 Zeilig, G. *et al.* Safety and tolerance of the ReWalk exoskeleton suit for ambulation by people with complete spinal cord injury: a pilot study. *J Spinal Cord Med* **35**, 96-101, doi:10.1179/2045772312Y.0000000003 (2012).
212 Miller, L. E., Zimmermann, A. K. & Herbert, W. G. Clinical effectiveness and safety of powered exoskeleton-assisted walking in patients with spinal cord injury: systematic review with meta-analysis. *Med Devices (Auckl)* **9**, 455-466, doi:10.2147/MDER.S103102 (2016).
213 Akhtar, A. Z., Pippin, J. J. & Sandusky, C. B. Animal Models in Spinal Cord Injury: A Review. *Reviews in the Neurosciences* **19**, doi:10.1515/revneuro.2008.19.1.47 (2008).
214 Basso, D. M. Behavioral testing after spinal cord injury: congruities, complexities, and controversies. *J Neurotrauma* **21**, 395-404, doi:10.1089/089771504323004548 (2004).
215 Kwon, B. K., Oxland, T. R. & Tetzlaff, W. Animal Models Used in Spinal Cord Regeneration Research. *Spine* **27**, 1504-1510, doi:10.1097/00007632-200207150-00005 (2002).
216 Calancie, B., Molano, M. R. & Broton, J. G. EMG for assessing the recovery of voluntary movement after acute spinal cord injury in man. *Clin Neurophysiol* **115**, 1748-1759, doi:10.1016/j.clinph.2004.03.002 (2004).

217 Curt, A. & Dietz, V. Nerve conduction study in cervical spinal cord injury: significance for hand function. *NeuroRehabilitation* **7**, 165-173, doi:10.3233/NRE-1996-7302 (1996).
218 Jacobs, S. R., Yeaney, N. K., Herbison, G. J. & Ditunno, J. F., Jr. Future ambulation prognosis as predicted by somatosensory evoked potentials in motor complete and incomplete quadriplegia. *Arch Phys Med Rehabil* **76**, 635-641, doi:S0003-9993(95)80632-6 [pii] (1995).
219 Ogura, T. *et al.* Sympathetic skin response in patients with spinal cord injury. *J Orthop Surg (Hong Kong)* **12**, 35-39 (2004).
220 Pathania, S., Bagler, G. & Ahuja, P. S. Differential Network Analysis Reveals Evolutionary Complexity in Secondary Metabolism of Rauvolfia serpentina over Catharanthus roseus. *Front Plant Sci* **7**, 1229, doi:10.3389/fpls.2016.01229 (2016).
221 Takahashi, H. *et al.* Neuroprotective therapy using granulocyte colony-stimulating factor for acute spinal cord injury: a phase I/IIa clinical trial. *Eur Spine J* **21**, 2580-2587, doi:10.1007/s00586-012-2213-3 (2012).
222 Kamiya, K. *et al.* Neuroprotective therapy with granulocyte colony-stimulating factor in acute spinal cord injury: a comparison with high-dose methylprednisolone as a historical control. *Eur Spine J* **24**, 963-967, doi:10.1007/s00586-014-3373-0 (2015).
223 Fehlings, M. G. *et al.* A phase I/IIa clinical trial of a recombinant Rho protein antagonist in acute spinal cord injury. *J Neurotrauma* **28**, 787-796, doi:10.1089/neu.2011.1765
10.1089/neu.2011.1765. (2011).
224 Lo, T. P., Jr. *et al.* Systemic hypothermia improves histological and functional outcome after cervical spinal cord contusion in rats. *J Comp Neurol* **514**, 433-448, doi:10.1002/cne.22014 (2009).
225 Levi, A. D. *et al.* Clinical application of modest hypothermia after spinal cord injury. *J Neurotrauma* **26**, 407-415, doi:10.1089/neu.2008.0745
10.1089/neu.2008.0745. (2009).