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## Review Article

## Clinical Neurorestorative Therapeutic Guidelines for Spinal Cord Injury (IANR/CANR version 2019)



Hongyun Huang<sup>a,b,\*\*</sup>, Wise Young<sup>c</sup>, Stephen Skaper<sup>†,d</sup>, Lin Chen<sup>e</sup>, Gustavo Moviglia<sup>f</sup>,  
Hooshang Saberi<sup>g</sup>, Ziad Al-Zoubi<sup>h</sup>, Hari Shanker Sharma<sup>i</sup>, Dafin Muresanu<sup>j</sup>, Alok Sharma<sup>k</sup>,  
Wagih El Masry<sup>l</sup>, Shiqing Feng<sup>m,\*</sup>, On behalf of The International Association of  
Neurorestoratology and The Chinese Association of Neurorestoratology

<sup>a</sup> Institute of Neurorestoratology, Third Medical Center of PLA General Hospital, Beijing, People's Republic of China

<sup>b</sup> Hongtianji Neuroscience Academy, Lingxiu Building, No.1 at Gucheng Street, Beijing, People's Republic of China

<sup>c</sup> W. M. Keck Center for Collaborative Neuroscience, Rutgers, State University of New Jersey, Piscataway, NJ, USA

<sup>d</sup> Department of Pharmaceutical and Pharmacological Sciences, University of Padua, Padua, Italy

<sup>e</sup> Department of Neurosurgery, Tsinghua University Yuquan Hospital, Beijing, People's Republic of China

<sup>f</sup> Center of Research and Engineer of Tissues and Cellular Therapy, Maimonides University, Buenos Aires, Argentina

<sup>g</sup> Department of Neurosurgery, Brain and Spinal Injury Research Center, Tehran University of Medical Sciences, Tehran, Iran

<sup>h</sup> Jordan Ortho and Spinal Centre, Al-Saif Medical Center, Amman, Jordan

<sup>i</sup> Intensive Experimental CNS Injury and Repair, University Hospital, Uppsala University, Uppsala, Sweden

<sup>j</sup> Department of Neurosciences "Iuliu Hatieganu", University of Medicine and Pharmacy, Cluj-Napoca, Romania

<sup>k</sup> Department of Neurosurgery, LTM Medical College, LTMG Hospital, Mumbai, Mumbai, India

<sup>l</sup> Spinal Injuries Unit, Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, United Kingdom

<sup>m</sup> Department of Orthopaedics, Tianjin Medical University General Hospital, Tianjin, People's Republic of China

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## ABSTRACT

Functional restoration after spinal cord injury (SCI) is one of the most challenging tasks in neurological clinical practice. With a view to exploring effective neurorestorative methods in the acute, subacute, and chronic phases of SCI, "Clinical Therapeutic Guidelines of Neurorestoration for Spinal Cord Injury (China Version 2016)" was first proposed in 2016 by the Chinese Association of Neurorestoratology (CANR). Given the rapid advances in this field in recent years, the International Association of Neurorestoratology (IANR) and CANR formed and approved the "Clinical Neurorestorative Therapeutic Guidelines for Spinal Cord Injury (IANR/CANR version 2019)". These guidelines mainly introduce restoring damaged neurological structure and functions by varying neurorestorative strategies in acute, subacute, and chronic phases of SCI. These guidelines can provide a neurorestorative therapeutic standard or reference for clinicians and researchers in clinical practice to maximally restore functions of patients with SCI and improve their quality of life.

*The translational potential of this article:* This guideline provided comprehensive management strategies for SCI, which contains the evaluation and diagnosis, pre-hospital first aid, treatments, rehabilitation training, and complications management. Nowadays, amounts of neurorestorative strategies have been demonstrated to be benefit in promoting the functional recovery and improving the quality of life for SCI patients by clinical trials. Also, the positive results of preclinical research provided lots of new neurorestorative strategies for SCI treatment. These promising neurorestorative strategies are worthy of translation in the future and can promote the advancement of SCI treatments.

\* Corresponding author. Department of orthopaedics, Tianjin Medical University General Hospital, No.154 Anshan Road, Heping District, Tianjin, 300052, China.  
\*\* Corresponding author. Institute of Neurorestoratology, Third Medical Center of PLA General Hospital, No. 69, Yongding Road, Haidian District, Beijing, People's Republic of China, 100039, China.

E-mail addresses: [hongyunh@gmail.com](mailto:hongyunh@gmail.com) (H. Huang), [sqfeng@tmu.edu.cn](mailto:sqfeng@tmu.edu.cn) (S. Feng).

† Deceased (DD, MONTH, YYYY).

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## Introduction

Spinal cord injury (SCI) refers to the insult of the spinal cord or cauda equina caused by a fracture or dislocation of the vertebrae, with or without an open wound track. There are more than one million patients with spine injury and SCI in China, and this number is still growing at the rate of 120 thousand per year in China. The worldwide prevalence of SCI is highest in the United States of America (906 per million) and lowest in Rhone-Alpes, France (250 per million) [1–7]. Approximately 14% of victims with spinal fracture suffer from SCI, most injuries being mono-segmental. SCI often occurs in people at the age of 30–40 years. The mortality of patients with SCI is higher than that of age-matched controls [8]. In recent years, the mortality of victims with spine injury and SCI has been reduced from 4.42% to 0.44% owing to progress in prehospital first aid and treatments in the acute stage and improved nursing techniques. These management advances have improved quality of life of patients with SCI and increased their life span.

Nowadays, a number of neurorestorative strategies have been brought to clinical practice, resulting in benefit to patients and improvement of their quality of life [9–21]. Given the rapid advances in the field, the International Association of Neurorestoratology (IANR) and the Chinese Association of Neurorestoratology (CANR) are working together to propose the improved vision of the “Clinical Neurorestorative Therapeutic Guidelines for Spinal Cord Injury (IANR/CANR version 2019)” based on the released guidelines [22]. This document was approved by the IANR council board members and CANR committee members. The scientific and professional information in the guidelines is based on clinical reasonable therapeutic evidence in acute, subacute, and chronic SCI before June 30, 2019. Described and listed interventions for restorations after acute, subacute, and chronic SCI mainly are management accepted for treatment practice or management under investigation to be applied to clinical practice. Positive results of neurorestorative experimental studies on nonhuman models and preclinical research should be encouraged to be translated into clinical studies earlier. These guidelines are recommended as a reference standard for global medical and scientific communities for SCI clinical neurorestorative treatment. Although the methods in guidelines can restore function to some extent in patients with SCI, much remains to be achieved before full functional restoration after SCI.

## Acute and subacute phases of SCI

### Evaluation and diagnosis

#### Evaluation

**Physical examinations.** Comprehensive neurological examinations should be performed three days after SCI to assess the severity and estimate the possible outcomes of treatment. It should be emphasised that about one-fourth of patients with cervical injury and SCI may also suffer from head injury, whereas thoracolumbar SCI may also be accompanied by chest, abdomen, pelvic, and limb injuries. As such, a complete physical examination is necessary to avoid mistakes in diagnosis [3,23,24]. The most commonly used quantitative diagnostic method for neurological functional assessment is the American Spinal Injury Association (ASIA) neurological score [25] (Figure 2). The International Association of Neurorestoratology Spinal Cord Injury Functional Rating Scale (Table 1) is recommended for assessing daily life or quality of life of patients with SCI [26] (Figure 1).

#### Additional investigations

**X-ray plain film.** The film includes anterior–posterior and lateral images; however, the lateral film should be examined first to limit movement of the patient. In some cases, a double oblique image should be examined. The main aspects of observation should include alignment of

**Table 1**

International association of Neurorestoratology Spinal Cord Injury Functional Rating Scale (IANR-SCIFRS).

<b>1. UPPER LIMB MOVEMENT</b>	<b>(10) Dressing</b>
<b>(1) Eating and Drinking</b>	3 Normal
3 Normal	2 Finish independently with difficulty
2 Finish independently with difficulty	1 Some assistance
1 Some assistance	0 Total dependence
0 Total dependence	<b>5. SPHINCTER CONTROL</b>
<b>(2) Grooming</b>	<b>(11) Bladder Control</b>
3 Normal	3 Normal
2 Finish independently with difficulty	2 Reflex voiding with partial sensation or control
1 Some assistance	1 Reflex voiding without sensation or control
0 Total dependence	0 Total incontinence or urethral catheterization/cystostomy needed
<b>(3) Writing</b>	<b>(12) Bowel Control</b>
3 Normal	3 Normal
2 Slow or sloppy; most words legible	2 Partial control with sensation
1 Many words not legible	1 Partial control without sensation OR no control with partial sensation
0 Unable to grip pen	0 Total incontinence
<b>2. LOWER LIMB MOVEMENT</b>	<b>6. (13)MUSCULAR TENSION</b>
<b>(4) Standing without brace</b>	(refers to the amount of tension or resistance to movement in a muscle.)
3 Normal	3 Normal
2 Stand independently but unsteady	2 Slight increase/decrease or mild spasm
1 Some assistance	1 Large increase/decrease or significant spasm
0 Cannot do	0 Extreme stiffness or spasticity
<b>(5) Walking without brace</b>	<b>7. (14)SWEATING</b>
3 Normal	3 Normal
2 Walk independently but slow or unsteady	2 Slight decrease
1 Some assistance	1 Significant decrease
0 Cannot do	0 Absent sweating
<b>3. TRUNK MOVEMENT</b>	<b>8. (15)SKIN CONDITION</b>
<b>(6) Sitting</b>	3 Normal
3 Normal	2 Partial breakdown
2 Stable when still, but unstable when moving	1 Significant breakdown, often associated with oedema
1 Unstable when still	0 Enduring bedsore or skin damage; severe oedema
0 Cannot do	<b>9. (16)PAIN</b>
<b>(7) Turning body over</b>	3 No pain
3 Normal	2 Mild pain, ordinary pain killer effective
2 Finish independently with difficulty	1 Severe pain, narcotics required
1 Some assistance	0 Extreme pain, uncontrolled
0 Total dependence	<b>10. (17)SEXUAL FUNCTION</b>
<b>4. GENERALMOVEMENT</b>	(Rate for males only; do not include in overall score)
<b>(8) Transfers: bed to chair/ wheelchair</b>	3 Normal
3 Normal	2 Can achieve erection and sexual penetration, but problems with sensation or ejaculation
2 Finish independently with difficulty	1 Can achieve erection, but no sexual penetration, sensation or ejaculation
1 Some assistance	0 Unable to achieve erection
0 Total dependence	
<b>(9) Bathing</b>	
3 Normal	
2 Finish independently with difficulty	
1 Some assistance	
0 Total dependence	

This scale includes 9 categories with 16 items in total (plus one optional category). The maximum possible score is 48; the lowest possible score is 0. Explanation of the functional rating scale scores: 48, normal functioning across all categories; 35–47, slight degree of functional handicap (mostly independent); 18–34, medium degree of functional handicap (some dependency indicated); 0–17, severe degree of functional handicap (significant impact on daily life).

the vertebrae, types of fracture or dislocation, appendixes of vertebra fracture and intervertebral space narrowing or broadening, and so on.

**Computed tomography.** Computed tomography (CT) is a common technique to diagnose fracture or dislocation of the spine in patients with SCI [27,28]. Axial and three-dimensional CT scans could reveal the shape of the spinal canal and vertebral facet joints. A CT scan is strongly recommended in cases with combined injuries.



Figure 1. Clinical neurorestorative therapeutic guidelines in the acute and subacute phases of SCI. SCI = spinal cord injury.

**ASIA** INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY (ISNCSCI) **ISCSO**

Patient Name \_\_\_\_\_ Date/Time of Exam \_\_\_\_\_  
 Examiner Name \_\_\_\_\_ Signature \_\_\_\_\_

**RIGHT**

**MOTOR KEY MUSCLES**

Elbow flexors C5  
 Wrist extensors C6  
 Elbow extensors C7  
 Finger flexors C8  
 Finger abductors (ring finger) T1

Hip flexors L2  
 Knee extensors L3  
 Ankle dorsiflexors L4  
 Long toe extensors L5  
 Ankle plantar flexors S1

(VAC) Voluntary anal contraction (Yes/No)

**RIGHT TOTALS** (MAXIMUM) (50) (50) (50)

**MOTOR SUBSCORES**

UER  + UEL  = UEMS TOTAL  (MAX (25) (25) (50))  
 LER  + LEL  = LEMS TOTAL  (MAX (25) (25) (50))

Key Sensory Points

**SENSORY KEY SENSORY POINTS**

Light Touch (LTR) Pin Prick (PPR)

C2  
C3  
C4  
T2  
T3  
T4  
T5  
T6  
T7  
T8  
T9  
T10  
T11  
T12  
L1

S2  
S3  
S4-5

**SENSORY SUBSCORES**

LTR  + LTL  = LT TOTAL  (MAX (50) (50) (112))  
 PPR  + PPL  = PP TOTAL  (MAX (50) (50) (112))

**LEFT**

**MOTOR KEY MUSCLES**

Elbow flexors C5  
 Wrist extensors C6  
 Elbow extensors C7  
 Finger flexors C8  
 Finger abductors (ring finger) T1

Hip flexors L2  
 Knee extensors L3  
 Ankle dorsiflexors L4  
 Long toe extensors L5  
 Ankle plantar flexors S1

(DAP) Deep anal pressure (Yes/No)

**LEFT TOTALS** (MAXIMUM) (50) (50) (50)

**MOTOR SUBSCORES**

UES  + UEL  = UEMS TOTAL  (MAX (25) (25) (50))  
 LES  + LEL  = LEMS TOTAL  (MAX (25) (25) (50))

**NEUROLOGICAL LEVELS** Steps 1-5 for classification as on reverse

1. SENSORY  R  L

2. MOTOR  R  L

3. NEUROLOGICAL LEVEL OF INJURY (NLI)

4. COMPLETE OR INCOMPLETE? Incomplete = Any sensory or motor function in S4-5

5. ASIA IMPAIRMENT SCALE (AIS)

(In complete injuries only) ZONE OF PARTIAL PRESERVATION

SENSORY  R  L

MOTOR  R  L

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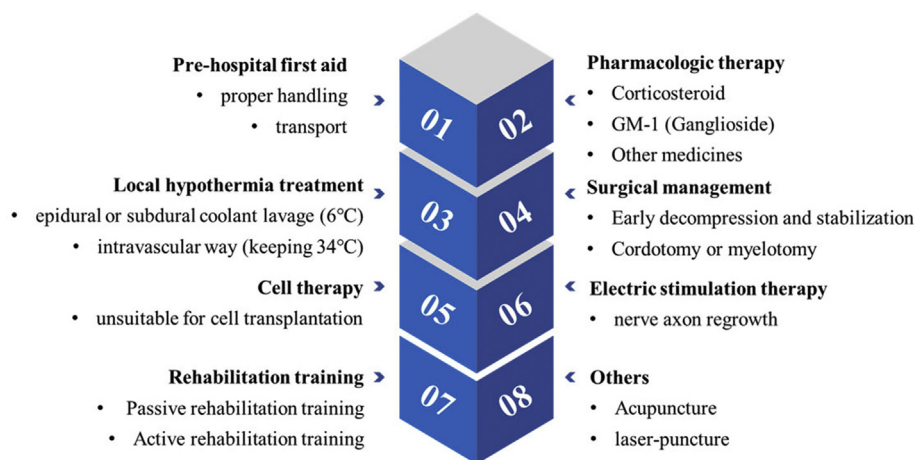
Figure 2. American Spinal Injury Association (ASIA) neurological scores.

**Magnetic resonance imaging.** Magnetic resonance imaging (MRI) is the preferred examination for patients with SCI for assessing the integrity or injury location, severity and the extent of the intervertebral discs, ligaments, the spinal cord, and nerve roots [29]. MRI can also show displaced debris of a damaged disc and ligament in the spinal canal, as well as oedema and/or haemorrhage [30].

**Somatosensory evoked potential.** Somatosensory evoked potential (SSEP) examination is a reliable method [31,32] to check sensory function and integrity of the injured spinal cord. Failure to detect SSEP 24 h after injury and during several weeks of repeated examination is indicative of complete sensory function loss. Otherwise, the injury is judged as incomplete.

**Diagnosis**

The diagnosis of SCI should include the injured level and severity, the level and type of fracture and/or dislocation of the injured vertebrae, and stability of the spinal column. The severity of SCI is classified according to the ASIA Impairment Scale [25]. A patient is ASIA Grade A if both perianal sensation and voluntary anal sphincter contraction are absent. ASIA Grade B indicates that some sensation is preserved but the motor score is zero below the injury level. ASIA Grade C indicates that some motor function is present, but the motor scores below the injury level add up to less than 50% of normal. ASIA Grade D indicates that motor scores below the injury level add up to 50% or greater than normal.



**Figure 3.** Neurorestorative therapeutic strategies in acute and subacute phases of SCI. SCI = spinal cord injury.

### Treatments

Secondary injury was the main cause for the microenvironment imbalance after SCI [26], and therapies should focus on alleviating secondary injury in acute or subacute phases of SCI. The principles of management for acute SCI include restricting active and passive movement, early fixation, combined extramedullary and intramedullary decompression, suitable cell therapies, early rehabilitation treatment, and preventing complications [3,23,24,33,34]. (Figure 3)

#### Prehospital first aid

After traumatic injury, a first-aider should rapidly evaluate the patient and perform resuscitation during transport of the patient to the hospital. Life support (airway, breathing, and circulation) must be on hand if needed. Handling should be limited to avoid excessive movement of the head and entire spinal column. The best way to handle a patient with SCI is to lift/shift the patient horizontally with the help of three or more people to a flat board or special stretcher for transport to a specialised hospital by an ambulance or helicopter [3].

#### Pharmacologic therapy

Neuroprotection, one of the most important neurorestorative strategies, is essential in acute and subacute phases of SCI. The aim is to minimise and/or prevent secondary medullary lesion extension, thereby decreasing cellular apoptosis or necrosis and promoting neuronal cells and axonal survival.

**Corticosteroids.** High-dose methylprednisolone (MP) therapy at an early stage was once considered positive for neurological restoration in the acute phase of SCI [35–38]. Clinical results carried out by the National SCI Study (NASCIS I and II) showed modest efficacy but with possible severe complications. So far, there has been no unequivocal evidence to support its routine application. It is not recommended in the guidelines of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (since 2013). The most recent studies revealed insufficient evidence for the use of high-dose MP therapy in acute SCI in terms of neurological restoration [41] owing to complications such as infection, respiratory impairment, gastrointestinal bleeding, and even death. High-dose MP therapy is no longer used routinely in acute SCI, but remains an optional therapeutic approach in certain conditions [19,39–42].

MP can still be used in the case of incomplete cervical medullary lesions, especially in patients with cervical spondylitis myelopathy that requires a decompression. Should MP be used, caution is advised for the following:

(a) The time window (<8 h): Correct infusion speed should be controlled strictly in the application of high-dose MP with accurate measurement of body weight and dose [42]. For the first 3 h after SCI, MP should be given as a bolus dose of 30 mg/kg over 15 min, followed by a 23 h continuous infusion at 5.6 mg/kg/hour; for the time interval of three–eight hours after SCI, MP should be given as a bolus dose of 30 mg/kg over 15 min, followed by a 23 h continuous infusion of 5.4 mg/kg/hour.

(b) For patients whose prior neurologic symptoms have been resolved, administration of MP should be stopped as soon as possible to reduce deleterious side effects.

(c) Contraindications for high-dose MP treatment: spinal injury without neurological deficits; penetrating and gunshot injury of the spinal cord, and more than 8 h after injury; gastrointestinal bleeding; diabetes; older patients with higher risk of pneumonia.

**Ganglioside GM1.** A randomised and controlled study demonstrated that ganglioside GM1 did not show any significant neurological recovery, although there was a consistent beneficial trend [43]. A recent study combining GM1 (100 mg/day) with MP for early acute SCI showed recovery of neurological function and improved prognosis [44]. Another randomised and placebo-controlled study indicated that GM1 at a dose of 100 mg/day (intravenous, 30 days) improved sensory but not motor function [49]. Until additional trials with larger patient cohorts are performed to determine whether GM1 can restore neurological function and reduce mortality and morbidity in acute SCI, GM1 is not recommended for routine therapy in acute SCI [40,45–47].

The intervention listed previously is accepted in majority of clinical practice for acute SCI.

**Other medicines.** Erythropoietin has glioprotective and neuroprotective properties, which reduce medullary cavitation, cellular infiltration, and neuronal cell apoptosis. However, it was unable to improve functional outcome of patients with traumatic complete or incomplete cervical SCI [48]. Clinical trials with minocycline, naloxone, and tirilazad showed limited therapeutic effects on patients with SCI. Mannitol could alleviate secondary spinal cord oedema, indicating early application in the absence of contraindications [49].

#### Hypothermia treatment

Hypothermia includes systemic and local hypothermia treatment, which can decrease metabolism of injured tissues and reduce oxygen consumption. Modest hypothermia (32–34 °C) appeared to be the most effective range for systemic treatment [50–54]. Local hypothermia is also effective [55] and could be performed by an open or closed technique

with epidural or subdural coolant lavage (6 °C) [56].

Hypothermia therapies are still in an exploring phase; so far, there has been no accepted indication or contraindications for acute SCI. Therapeutic suggestion is that both local hypothermia and systemic hypothermia therapy should be performed if medical and patient conditions permit [57–59].

*Surgical management*

*Early decompression and stabilisation.* Laminoplasty or laminectomy can restore stability of the spinal column by reduction and fixation of the vertebrae to restore spinal canal volume. Acute SCI with spine alignment restoration and stabilisation (within 24 h) can be performed safely and is associated with improved neurological outcome, a shorter hospitalisation time, and fewer complications. Spinal cord decompression after acute SCI attenuates secondary injury, preserves neurological functions of the surviving axons, and prevents further destruction of spinal cord tissue.

*Time window of surgery.* Current evidence indicates that decompression and internal fixation should be performed as early as possible (< 24 h) in the absence of life-threatening situations for patients with obvious neurologic deficits, irrespective of whether the injury is complete (ASIA Grade A) or incomplete (ASIA Grade B–D) [60–65]. However, few patients undergo the operation within 24 h owing to transportation, preoperative examinations, and preparation issues. A clinical study of almost 5000 patients with SCI who underwent early surgical interventions (< 3 d) showed that the earlier the surgical treatment, the greater the benefit [3,66,67].

*Cordotomy or myelotomy.* Decompression of the extradural elements is the primary focus in the management of patients with acute SCI. Little attention has been paid to the potential deleterious secondary injury from spinal cord necrosis and haemorrhage currently. SCI-related cord swelling and any sustained external pressure may block normal cerebrospinal fluid (CSF) flow and further increase spinal cord oedema. Myelotomy and early debridement of necrosis could be beneficial in preventing complete paralysis by stopping further expansion of secondary injury, reducing the

pressure of spared tissue and CSF, preserving surviving axons and spared spinal cord tissue, and delaying glial cell death in white matter, thereby providing for more neurological recovery.

Decompression of the dura may restrict the level of secondary injury in human and animal SCI. Clinical studies reported neurological improvement in patients with acute SCI by myelotomy [3,22,66–69]. However, prospective randomised controlled clinical trials are still lacking.

*Injury type and decompression procedure.* Because complete transection of the spinal cord is quite rare in the clinic, intramedullary decompression should be performed under a microscope, combined with information from CT and MRI, to preserve surviving axons in neurologically impaired patients. The following are the four types of injured spinal cord with their corresponding surgical interventions and effects (Figure 4):

Type one: It showed arachnoid adhesion, the disappearance of spinal cord pulsation, obstruction of CSF, and pale and swollen spinal cord. Releasing adhesion of the arachnoid and restoring CSF flow and cord pulsation are the intervention.

Type two: It showed intramedullary hematoma, bony fragments, or foreign matter. Removing hematoma, bony fragments, or foreign matter and exploring the cord are the intervention.

Type three: Spinal cord was partly disrupted. Liquefied tissues might gush out as soon as the dura mater is opened. Exploring the injury site, removing the necrotic tissues, and washing the region gently with normal saline are the intervention.

Type four: It showed intramedullary softening. Making a 0.3– to 0.5-cm longitudinal incision at the softening region, removing softening tissue, and washing the cavity gently with normal saline are the intervention.

Because the border between the contusion and normal spinal cord is not clear at an early stage, care should be taken not to overly extend the range of the intramedullary decompression.

*Neurophysiological assessment.* Intraoperative neurophysiological evaluation of patients with acute or subacute SCI can provide

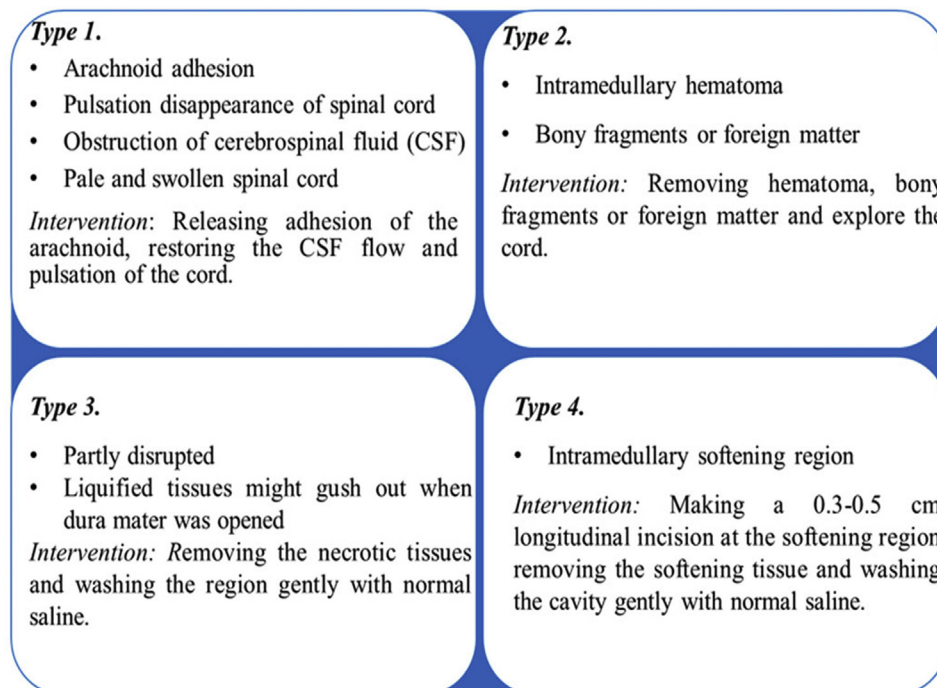


Figure 4. Injury type and decompression procedure in acute and subacute phases of SCI. SCI = spinal cord injury.

information about spinal cord function not obtainable by other methods and that can correctly predict the neurological outcome.

Those neurorestorative surgical interventions are well developed more or less for the last one hundred years. Moreover, these destructive surgical interventions or cordotomy (myelotomy) is under investigation for development of protocols for acute and subacute SCI.

#### Cell therapy

Cell therapy is a promising therapeutic option for SCI. The mechanisms of cell therapies for SCI include axonal remyelination and regeneration, neuroplasticity, neuroprotection, neuromodulation, neurorepair, antiinflammatory response or immunomodulation, neurogenesis, angiogenesis, reducing scar and cavity formation, and cell replacement [13,49,70–72]. To date, a few clinical trials for acute or subacute SCI by cell therapy have been performed, irrespective of the outcome [73–75]; there were also some encouraging observations in animal studies of acute SCI [71,72]. In an animal study, recovery of motor function was dramatically increased when transplants and neurotrophins were delayed until 2–4 weeks rather than applied immediately after transection [76], possibly due to acute inflammation and macrophage infiltration in the lesion area. For this reason, acute SCI may not be suitable for direct cell transplantation into the injured area, and currently, cell therapies need to be tested for their benefits in acute and subacute SCI.

Cell therapy can serve as a new restoring therapy which may promote recovery from acute SCI. At the same time, it needs to develop assessing and monitoring sensory motor integration mechanisms with cell therapy.

#### Electric stimulation therapy

The nervous system relies on electrical signal transmission for information transfer, and local electrical stimulation may improve and induce axon regrowth [77].

There are several categories of electrical stimulation. First, the oldest is galvanic and faradic neuromuscular stimulation, with the expectation to delay disuse of muscle effects during paralysis. The second category is about electronic control of the paralysed body [78,79]. The third category developed from functional electrical stimulation of peripheral nerve structures to spinal cord stimulation. This method is known under the name of neuromodulation and is for sure promising but still under investigation [80]. The fourth category is using advancement of motor control of SCI with multimodality interventions from physical, pharmacological, neurophysiological, and neurorestorative surgery and a variety of neurobiological stimulations. In all these modalities of electrical stimulation of the nervous system, stimulation and inhibition is used as a primary intervention or supplement to the electrical component. This is also under investigational [81].

#### Rehabilitation training

##### Physiotherapy

**Passive rehabilitation training.** Postoperative passive rehabilitation training (e.g., massage and pressure therapy) can not only reduce the incidence of pressure sores and deep venous thrombosis but also restore neurological function. Supportive nursing staff encouraging self-efficacy was shown to be important in rehabilitation [82]. In addition, patients who received intensive peer mentoring during and after rehabilitation had greater gains in self-efficacy, and the time for unplanned rehospitalisation was decreased [83].

**Active rehabilitation training.** As soon as patients' condition allows, active rehabilitation training after surgery with the assistance of a halo or vest can begin. This may include occupational training, locomotion training, and hydrotherapy. The recommended positive training method is active movement-target enhancement-neurorehabilitation therapy, which can help patients to maximise functional neurorestoration [27].

There are at least two complementary goals in physical therapy which is progressively more supported by robotics, intended to expand periods

of maintenance and recovery after SCI impaired motor control. These are certainly well-established procedures for support and recovery of motor control. There is also research in the optimization of plasticity of the nervous system for motor recovery, and for certain, this is a method of clinical practice and supplementary for guiding recovery elicited by other physical modalities [84].

#### Occupational therapy

Occupational therapy is part of comprehensive rehabilitation that solves the patient's occupations (self-care, work, and leisure issues). The purpose of this therapy includes helping patients adapt to the social life and other types of environments [85].

It is essential to emphasise that early occupational and physical therapies are very important after neurorestorative therapy. We strongly recommend taking earlier rehabilitation exercise or treatment including occupational therapy, physical therapy, intermediate-frequency electrical stimulation, low-frequency electrical stimulation and magnetic therapy, and especially active exercise after neurorestorative treatment if available [86].

#### Others

Acupuncture [87] and laser puncture [88] may promote functional recovery for patients with acute or subacute SCI with little risk. Intrathecal treatment with human anti-Nogo-A antibody was well tolerated in patients with acute complete SCI and showed some efficacy [89].

#### Complications and management

##### Circulatory complications

**Hypopnoea.** After cervical SCI, sympathetic (but not parasympathetic) nerve activity is suppressed, resulting in more sputum, a slower heart rate, and decreased blood pressure in patients. Anisodamine could be administered intravenously (20 mg added to 500 ml of normal saline) at a speed of 11–15 drops per minute for an adult, and the speed should be modified according to body surface area for a child. Drug effects usually include an increase in heart rate and mean arterial pressure and reduced sputum.

**Hyponatremia.** Various clinical trials demonstrated that this is a common and severe complication of cervical SCI with an incidence of 45–100%. Hyponatremia often occurs 6.4–8.9 days after injury, with the lowest serum sodium concentration being detected 8.7 to 17.3 days after injury, which elevated at  $21.8 \pm 10.2$  days. In general, hyponatremia disappears after  $30.4 \pm 6.0$  days. The reasons related to hyponatremia include the level of cervical SCI, infections, use of a ventilator, and medications (such as dehydrating agents and diuretics). Refined carbamide could be used (oral administration, 30 mg/day) for inappropriate antidiuretic hormone syndrome, and fludrocortisone (oral administration, 0.1–0.2 mg/day), for cerebral salt-wasting syndrome. As these two types of syndromes are difficult to be distinguished, fludrocortisone (added to normal saline) is safe and effective for agnogenic hyponatremia [90,91].

**Deep venous thrombosis.** The incidence of deep venous thrombosis (DVT) with clinical symptoms after SCI is about 16–30%, whereas its incidence detected by ultrasound or venography is up to 79%. Preventive measures for DVT include limb exercise and wearing elastic stockings. Once formed, anticoagulant therapy should be given. One risk is the formation of thrombi that may lead to emboli in the heart, lung, and brain.

##### Respiratory complications

Breathing difficulty and pulmonary infection are the main respiratory system complications after spine injury and SCI. These include recurrent pneumonia, atelectasis, and pleural effusion; SCI may also result in sleep

apnoea and respiratory failure [84]. Respiratory complications are the leading cause of mortality in patients with chronic SCI [86]. Patients with cervical SCI up to the C4 level or higher may suffer from muscular paralysis of the diaphragm and a weakened or even absent cough reflex, leading to dyspnoea and lung infection. At this point, tracheotomy may be necessary, to facilitate sputum suction and ventilator support. Besides, a proper body position helps to prevent or reduce the appearance and exacerbation of respiratory infections.

In addition, timed position changes contribute to the prevention of complications, especially the emergence of pressure sores and circulation problems (DVT). Patients should be encouraged to sit up as soon as possible, or to raise the bedside for training before entering the wheelchair, thus preventing multiple respiratory-related complications. Of course, during the position change, the patient should be closely observed to prevent the occurrence of orthostatic hypotension [92–94].

**Urinary complications**

Urinary tract infection is the main urinary system complication after spine injury and SCI. Use of a urinary catheter is essential, with weekly catheter change and bladder washing at regular intervals to avoid hydronephrosis and renal failure.

**Chronic phase**

*Evaluation*

*Physical examinations*

Neurological functions can be assessed using ASIA assessment standard [25]. Daily life functions can be assessed using the International Association of Neurorestoratology Spinal Cord Injury Functional Rating Scale [27]. (Figure 5)

*Magnetic resonance imaging*

MRI can clearly show the current condition of the injured spinal cord, such as atrophy, myelomalacia, cystic cavity, or even a syringomyelia, as well as formatted scar and cord compression (if present).

*Electrophysiological examination*

Paravertebral SSEPs can assess and judge the sensory level of injured spinal cord. Electromyography is used to assess the motor level of the injured section.

*Diagnosis*

Clinical diagnosis of chronic SCI includes determining the level and severity of the injured spinal cord [25], quality of daily life [27], and whether there is still compression in the injured spinal cord or not [30]. Neurophysiological examinations and MRI may help to know exactly the

structural [31] and functional [95–98] condition of movement and sensation.

*Treatments*

For patients with chronic SCI and severe cord compression, decompression management can most likely contribute to some functional neurological recovery.

*Neurotization or nerve bridging*

Neurotization or nerve bridging by grafting nerves to a deinnervated target can restore some function for patients with complete chronic SCI as reported nearly fifty years ago [99,100], especially if accompanied by physical rehabilitation. There are three main methods as follows.

- 1). Remove a peripheral nerve above the injury site (e.g., the accessory nerve or intercostal nerve) and bridge to nerve roots or peripheral nerves for paralysed muscles below the injury site [101, 102].
- 2). Remove the ventral root from the lumbar segment five or sacral segment one above the injury site and connect to the ventral root of the sacral segment two or three that normally innervates the bladder [103,104].
- 3). Remove a peripheral nerve and insert the central stumps 4–5 mm into the ventral–lateral bundles of the thoracic cord (corticospinal tract) just above the complete cord lesion and the distal stump of the grafts connecting to the muscle nerve of the lower limb [105,106].

Several recent clinical reports describe the aforementioned therapies in restoring neurological functions to the patient with SCI [107–109].

*Neurostimulation/neuromodulation and nneuroprosthesis*

Task-specific training with epidural stimulation might reactivate previously silent spared neural circuits and promote plasticity. These interventions could be a viable clinical approach for functional recovery of patients with complete chronic SCI [17,110,111]. Transcranial direct current stimulation can be effective in the management of neuropathic pain after chronic SCI [112,113]. Functional electrical stimulation of the permanently deinnervated muscle in patients with complete chronic lower motor neuron lesions is an effective therapy, which results in rescue of muscle mass, function, and perfusion. Additional benefits include improved leg cosmetic appearance and enhanced cushioning effect for seating [114,115]. In addition, electric stimulation can improve neuroplasticity and decrease the systemic complications of patients with chronic SCI [116].

Brain–machine interfaces with neuroprosthetic limbs could help patients with long-term paralysis to perform several required activities of

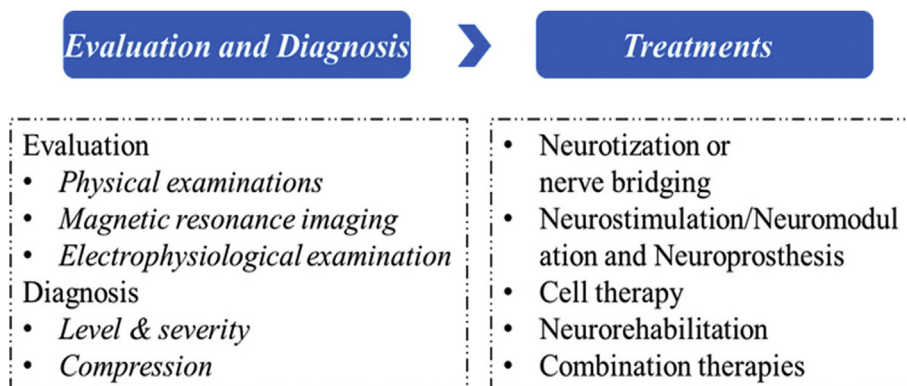


Figure 5. Clinical neurorestorative therapeutic guidelines for chronic phase of SCI. SCI = spinal cord injury.

daily living [117–119]. Sensory afferentation, feedback input, and related cerebral voluntary motor commands—the latter by electroencephalography brain–computer interface—may thus contribute to wireless informational powering of the respective robotic suit engine for bionic standing and gait assistance. Recently, a study shows that muscle activation could be controlled by using intracortically recorded signals in a paralysed human [120].

### Cell therapy

Cell therapy has become an important treatment option for patients with chronic SCI [70]. Increasing clinical evidence indicates that cell therapy is a safe and feasible treatment. Several types of cells have been found suitable for patients undergoing transplantation, such as olfactory ensheathing cells, Schwann cells [121,122], mesenchymal stromal cells, peripheral blood mononuclear cells, bone marrow haematopoietic stem cells [123], umbilical cord blood mononuclear cells, bone marrow mononuclear cells, and embryonic stem cells [124]. Partial functions and quality of life have been improved after transplantation of cells into the cord parenchyma, administration of cells intrathecally (lesion area or lumbar subarachnoid space), infusion of cells intravascularly, or multiple routes of administration [22,125–135].

### Surgical techniques for cell transplantation

Most cell transplantations for SCI are carried out directly at the site of injury or adjacent to it by injecting less than 25  $\mu$ L of cell suspension using fine needles or glass capillaries [136]. Several attempts have been made to deliver substrates to the injured cord via intrathecal injection. Intramedullary delivery seems to be the optimal site for cell transplantation, which can directly interact with the host environment to activate or trigger dysfunctional neurons or axons, help axons regenerate and sprout, remyelinate axons, and replace some types of lost cells. However, inappropriate cellular injections can be damaging to the spinal cord, inducing technical failure with false results and conclusions. Risks of intraparenchymal injections include additional injury due to needle penetration, spinal cord motion during injection, the creation of intraparenchymal pressure gradients and hydrodynamic dissection, and possible cord ischaemia. Understanding these variables can maximise the safety of injections and avoid injury to the spared structure [49,137].

### Clinical requirements

(a) Decreasing needle trauma by minimising the number of injections, especially for the SCI in the cervical and T11–L1 segment and incomplete SCI. (b) Decreasing time of operation, ideally. (c) It takes 2 h from cell collection in laboratory, cell transportation to cell transplantation. (d) A minimally invasive intervention (decreasing size of incision) can shorten time of recovery after surgery. (e) Decreasing total volume of injection, with limited thin needle for the higher concentration of cells [49,137].

### Neurorehabilitation

Intensive exercise and biofeedback training can improve motor functions for patients with chronic incomplete SCI [138–140]. Intensive training refers to 6 h per day for 6–7 days in a week over ground locomotion. Although the beneficial effects of intensive exercise alone are limited in people with chronic SCI, such exercise may be essential for motor recovery in patients who have received restorative therapies [27], which can help patients improve more neurological functions and quality of life. A phenomenon called “learned non-use” occurs after central nervous system injuries, and intensive, repetitive exercise can reverse atrophy of the muscle and nervous tissues. Substantial recovery of function (two ASIA grades) was achieved in a patient with severe C-2 ASIA Grade A injury by “activity-based recovery” [141]. Multimodal intensive exercise can significantly improve motor function in patients with chronic complete SCI, which might have therapeutic value as an adjunct to other restorative therapies. An individual with chronic SCI

ASIA Grade A injury showed improved overground walking ability after intensive physical therapy and robotic locomotor training [142]. However, these studies were performed with small sample sizes, so more studies are necessary.

### Pharmaceutical neurorestorative therapies

Treatment with acidic fibroblast growth factor and granulocyte colony-stimulating factor may be beneficial for chronic SCI, but these therapies need higher level evidence to be confirmed [143–145].

### Combination therapies

The degree of neurological recovery by a single neurorestorative therapy is still limited. Preliminary results of combination therapies for complete chronic SCI hold promise for higher functional recovery, which include identical cell transplantation by two or more routes, two or three appropriate kinds of cells being transplanted in synergy, cell therapy with neurorehabilitation, cell therapy with laser puncture, and neurorehabilitation [27,88,146,147]. In addition, neurorehabilitation combined with functional electrical stimulation [148] or a brain–machine interface–based gait protocol was shown to recover partial walking ability [149]. Implanted electrodes for electrical stimulation with intensive neurorehabilitation could partially restore standing and walking abilities in patients with complete chronic SCI [150,151] and improved qualities of daily life [152–156].

It is to be noted that a report that used combined application of the NeuroRegen scaffold and human umbilical cord blood mesenchymal stromal cells treated patients with chronic SCI by totally resecting the whole injured spinal cord [157]. Currently, the procedure of resecting the whole injured spinal cord should be forbidden because patients with chronic complete SCI still have the chance to recover some functions by neurorestorative therapies, which include cell therapy, neuromodulation, nerve bridging, neurorehabilitation, and so on as introduced previously.

Combination therapy studies pose major challenges regarding logistics and design.

### Summary

Clinical neurorestorative treatments for patients with SCI have made enormous strides in recent years [20,2,158]. This guideline definitely can provide new knowledge and information to physicians in treating patients with SCI. After further therapeutic improvement that restores more neurological functions and improves quality of life for patients with SCI, the guideline will be further revised and improved.

### Conflict of interest

The authors have no conflicts of interest to disclose in relation to this article.

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