Spinal Cord Injury - The Search For A Proven Treatment

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Since 1988, 45 percent of all SCI have been complete injuries; 55 percent have been incomplete injuries.

* Fifty-two percent of SCIs result in paraplegia; 47 percent result in tetraplegia (quadriplegia).

* Half of all SCI cases have other injuries associated with the SCI.

* Most people with neurologically complete lesions above the C-3 level die before receiving medical treatment. Those who survive are usually dependent on mechanical respirators to breathe.
Each year, approximately one-third to one-half of all people with SCI are readmitted to the hospital due to secondary complications.

* Eighty-five percent of SCI patients who survive the first 24 hours after injury are still alive 10 years later, compared with 98 percent of the non-SCI population given similar age and sex.

* The average length of stay in a rehabilitation unit is 44 days.

* Average first year expenses for a SCI (includes both quadriplegics and paraplegics) totals approximately $300,000.

* The most common cause of death for people with SCI is respiratory ailment.
<table>
<thead>
<tr>
<th>Severity of Injury</th>
<th>Average Yearly Expenses (in 2002 dollars)</th>
<th>Estimated Lifetime Costs by Age At Injury (discounted at 2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First Year</td>
<td>Each Subsequent Year</td>
</tr>
<tr>
<td>High Tetraplegia (C1-C4)</td>
<td>$626,588</td>
<td>$112,237</td>
</tr>
<tr>
<td>Low Tetraplegia (C5-C8)</td>
<td>$404,623</td>
<td>$45,975</td>
</tr>
<tr>
<td>Paraplegia</td>
<td>$228,955</td>
<td>$23,297</td>
</tr>
<tr>
<td>Incomplete Motor Functional at Any Level</td>
<td>$184,662</td>
<td>$12,941</td>
</tr>
<tr>
<td>Age at Injury</td>
<td>No SCI</td>
<td>Motor Functional at Any Level</td>
</tr>
<tr>
<td>--------------</td>
<td>-------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>20</td>
<td>57.8</td>
<td>52.9</td>
</tr>
<tr>
<td>40</td>
<td>38.9</td>
<td>34.4</td>
</tr>
<tr>
<td>60</td>
<td>21.6</td>
<td>17.8</td>
</tr>
</tbody>
</table>

Cause of death: In years past, the leading cause of death among persons with SCI was renal failure. Today, however, significant advances in urologic management have resulted in dramatic shifts in the leading causes of death. Persons enrolled in the National SCI Database since its inception in 1973 have now been followed for 30 years after injury. During that time, the causes of death that appear to have the greatest impact on reduced life expectancy for this population are pneumonia, pulmonary emboli and septicemia.
Figure 57-6  Symptoms, degree of paralysis, and potential for rehabilitation depend on the level of the lesion.

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A Complete; no sensory or motor function preserved in S4-S5

B Incomplete; sensory but not motor function preserved below neurological level and extending through S4-S5

C Incomplete; motor function preserved below neurological level. Most key muscles have < grade 3 power

D Incomplete: motor function preserved below neurological level. Most key muscles have > grade 3 power

E Normal motor and sensory function
complete cord lesion at 72 h: 10-15% improve. Only 3% improve to attain class D
* class B at 72 h: 54% will improve to a lesser degree of weakness
* class C and D at 72 h: 86% will achieve useful motor function below the level of the lesion
Figure 57-5  Mechanisms of spinal injury.

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Primary Injury

• Neurons that pass through injury site are physically disrupted and exhibit diminished myelin thickness.

• Nerve transmission may be further disrupted by microhemorrhages or edema near the injury site.

• Gray matter is irreversibly damaged within the first hour after injury whereas white matter within 72 hours after injury.
Spinal Cord Contusion
Dark Field Time Course

A. Naive
B. 1d
C. 3d
D. 7d
Blood Vessel Time Course

A. Naive
B. 1d
C. 3d
D. 7d
Neutrophil Infiltration

A

B
B  
**Presymptomatic**
- Caspase 1 activation in neurons with no cell death detected

C  
**Early symptomatic**
- Neuronal cell death
- Activation of caspase 1 and caspase 3
- Cytochrome c release
- Proapoptotic changes in Bcl-2 family
- Detection of reactive astrocytes and reactive microglia

D  
**Late symptomatic**
- Progressive neuronal cell death
- Progressive astroglial and microglial reaction
Spared Spinal Tissue

- In animal models, motor function can recover to normal levels after spinal cord injury if as few as 4-6% of cortical motor neurons regain physiologic connection through injured cord segment.
- An increase in axonal survival at injury site of from <3% to >6% allows function to return through the site and converts paralyzed muscles to those with normal function.
- Sparing 5-10% of fibers at lesion center can drive segmental circuits in production of locomotion.
Photomicrograph showing the traumatized spinal cord at the C-4 level 5 days after an incomplete cord injury due to a C4--5 fracture dislocation. Multiple hemorrhages are confined to the gray matter. The white matter adjacent to the hemorrhagic gray matter shows decreased staining, whereas the subpial peripheral white matter of the lateral and posterior columns is preserved. H & E and luxol fast blue, original magnification X 7
Figure 7: Conus medullaris syndrome. A burst fracture of T12 is depicted with posterior dislocation of bone fragments from the vertebral body into the spinal canal resulting in compression of the conus medullaris. Almost all the lumbar cord segments are opposite the T12 vertebral body, so that a severe compression injury at this level could affect all lumbar and sacral segments of the cord. Reprinted with permission from Tator.23
Figure 8: Cauda equina syndrome. The drawing shows an acute central disc herniation of L4-5 with major compression of the central aspect of the cauda equina. The medially placed sacral roots from S2 downward sustain the maximal compression, whereas the more laterally located L5 and S1 roots are completely or partially spared. Reprinted with permission from Tator.²³
SCIWORA

Occurs most often in pediatric population; accounts for up to 2/3 of severe cervical injuries in children < 8 years of age;

- Inherent elasticity in pediatric cervical spine can allow severe spinal cord injury to occur in absence of x-ray findings;

Causes - - unrecognized interspinous ligamentous injury: MRI may give a more anatomic diagnosis by showing hemorrhage or edema of the spinal cord; - pseudosubluxation: anterior displacement may be up to 4 mm; - Treatment: spine is immobilized for one to three weeks;
SCIWORA

Standards: There is insufficient evidence to support diagnostic standards.

Guidelines: There is insufficient evidence to support diagnostic guidelines.

Options: • Plain spinal radiographs of the region of injury and CT scan with attention to the suspected level of neurological injury to exclude occult fractures are recommended.

• MR of the region of suspected neurological injury may provide useful diagnostic information. • Plain radiographs of the entire spinal column may be considered.
The C-Spine Rule War and Other Controversies in SCI Management
Which is not a Nexus Criteria

• A - No altered level of consciousness
• B- No midline tenderness
• C- No fall > 5 stairs
• D- No distracting injury
• E- No focal neurological deficit
Which is not a Nexus Criteria

- A - No altered level of consciousness
- B - No midline tenderness
- C - No fall > 5 stairs
- D - No distracting injury
- E - No focal neurological deficit
QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.
NEXUS TRIAL

• Prospective study at 21 centers across U.S.
• No midline cervical tenderness, no focal neurologic deficit, normal alertness, no intoxication and no painful distracting injury.
• 34,069 patients. 818 with C-Spine injury.
• Negative predictive value 99.8 percent.
**Table 3. Performance of the Clinical Criteria in Ruling Out Cervical-Spine Injuries in Patients with Blunt Trauma.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>99.0 (98.0–99.6)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>99.8 (99.6–100)</td>
</tr>
<tr>
<td>Specificity</td>
<td>12.9 (12.8–13.0)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>2.7 (2.6–2.8)</td>
</tr>
<tr>
<td>Patients with clinically significant injuries</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>99.6 (98.6–100)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>99.9 (99.8–100)</td>
</tr>
<tr>
<td>Specificity</td>
<td>12.9 (12.8–13.0)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>1.9 (1.8–2.0)</td>
</tr>
</tbody>
</table>

*CI denotes confidence interval.
Figure 1. The Canadian C-Spine Rule.
For patients with trauma who are alert (as indicated by a score of 15 on the Glasgow Coma Scale) and in stable condition and in whom cervical-spine injury is a concern, the determination of risk factors guides the use of cervical-spine radiography. A dangerous mechanism is considered to be a fall from an elevation $\geq 3$ ft or 5 stairs; an axial load to the head (e.g., diving); a motor vehicle collision at high speed ($\geq 100$ km/hr) or with rollover or ejection; a collision involving a motorized recreational vehicle; or a bicycle collision. A simple rear-end motor vehicle collision excludes being pushed into oncoming traffic, being hit by a bus or a large truck, a rollover, and being hit by a high-speed vehicle.
Table 4. Sensitivity, Specificity, and Negative Predictive Value of the Two Rules for 162 Cases of “Clinically Important” Injury among 7438 Patients.*

<table>
<thead>
<tr>
<th>Result of Assessment</th>
<th>Canadian C-Spine Rule</th>
<th>NEXUS Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Injury</td>
<td>No Injury</td>
</tr>
<tr>
<td>Positive (no.)</td>
<td>161</td>
<td>3995</td>
</tr>
<tr>
<td>Negative (no.)</td>
<td>1</td>
<td>3281</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>99.4 (95% CI, 96–100)†</td>
<td>90.7 (95% CI, 85–94)†</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>45.1 (95% CI, 44–46)†</td>
<td>36.8 (95% CI, 36–38)†</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>100</td>
<td>99.4</td>
</tr>
</tbody>
</table>

* A total of 845 cases were classified as indeterminate and are therefore omitted from this analysis.
† P<0.001. CI denotes confidence interval.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Mechanism of Injury</th>
<th>CCR-Positive Criterion</th>
<th>Injury</th>
<th>Hospitalized</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>M</td>
<td>Heavy object fell on head</td>
<td>Dangerous mechanism</td>
<td>C1 arch fracture</td>
<td>No</td>
<td>Hard collar</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>M</td>
<td>Motor vehicle collision, head-on</td>
<td>Age ≥65 yr, dangerous mechanism</td>
<td>C2 odontoid fracture</td>
<td>Yes</td>
<td>Halo</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>M</td>
<td>Fall &gt;10 ft (3 m)</td>
<td>Dangerous mechanism</td>
<td>C7 body fracture</td>
<td>Yes</td>
<td>Hard collar</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>M</td>
<td>Motor vehicle collision</td>
<td>None</td>
<td>C2 odontoid fracture</td>
<td>No</td>
<td>Hard collar</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>F</td>
<td>Pedestrian struck and thrown</td>
<td>Age ≥65 yr, dangerous mechanism</td>
<td>C4 pedicle fracture</td>
<td>Yes</td>
<td>Hard collar</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>M</td>
<td>Motor vehicle collision, rollover,</td>
<td>Dangerous mechanism, paresthesias</td>
<td>C7 body or pedicle fracture</td>
<td>Yes</td>
<td>Internal fixation</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>M</td>
<td>Fall &gt;5 stairs</td>
<td>Dangerous mechanism, paresthesias</td>
<td>C5–C6 perched facet</td>
<td>Yes</td>
<td>Hard collar</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>M</td>
<td>Contact sports, axial load</td>
<td>Dangerous mechanism</td>
<td>C7 pedicle fracture</td>
<td>Yes</td>
<td>Hard collar</td>
</tr>
<tr>
<td>9</td>
<td>24</td>
<td>M</td>
<td>Fall &gt;10 ft (3 m)</td>
<td>Dangerous mechanism</td>
<td>C2 hangman’s fracture</td>
<td>Yes</td>
<td>Halo</td>
</tr>
<tr>
<td>10</td>
<td>18</td>
<td>M</td>
<td>Motor vehicle collision, rollover,</td>
<td>Dangerous mechanism</td>
<td>C7 bilateral laminar fracture</td>
<td>Yes</td>
<td>Hard collar</td>
</tr>
<tr>
<td>11</td>
<td>71</td>
<td>M</td>
<td>Fall &gt;10 ft (3 m)</td>
<td>Age ≥65 yr, dangerous mechanism</td>
<td>C6–C7 facet fracture</td>
<td>Yes</td>
<td>Hard collar</td>
</tr>
<tr>
<td>12</td>
<td>29</td>
<td>M</td>
<td>Contact sports, axial load</td>
<td>Dangerous mechanism</td>
<td>C5–C6 perched facet</td>
<td>Yes</td>
<td>Halo</td>
</tr>
<tr>
<td>13</td>
<td>31</td>
<td>M</td>
<td>All-terrain vehicle, ejected</td>
<td>Dangerous mechanism</td>
<td>C1 arch fracture</td>
<td>Yes</td>
<td>Hard collar</td>
</tr>
<tr>
<td>14</td>
<td>56</td>
<td>M</td>
<td>Motor vehicle collision, rollover</td>
<td>Dangerous mechanism</td>
<td>C7 bilateral laminar fracture</td>
<td>Yes</td>
<td>Hard collar</td>
</tr>
<tr>
<td>15</td>
<td>49</td>
<td>F</td>
<td>Fall &gt;5 stairs</td>
<td>Dangerous mechanism</td>
<td>C1 arch facet fracture</td>
<td>Yes</td>
<td>Hard collar</td>
</tr>
<tr>
<td>16</td>
<td>35</td>
<td>M</td>
<td>Motor vehicle collision, head-on</td>
<td>None —- CCR indeterminate</td>
<td>C1–C2 ligamentous instability</td>
<td>No</td>
<td>Hard collar</td>
</tr>
</tbody>
</table>
Although the present data validate the performance of the CCR, the study design has several limitations that call into question any conclusion about the superiority of one rule over the other. The NLC was tested only in patients for whom cervical radiographs were ordered, and the study population included patients 16 years of age and under and those with an altered level of consciousness. All of these patient-eligibility criteria differ from those used in the CCR study, making comparisons of the two rules in a cohort that meets CCR criteria problematic. For example, excluding patients with an altered level of consciousness effectively negates the corresponding NEXUS criterion.

The choice of study sites may also have affected the performance of these rules in the current study. Stiell et al. enrolled patients at the same sites where the CCR was derived. Even if many of the physicians who enrolled patients and provided data did not participate in the earlier derivation study, the potential local and regional familiarity with the CCR might have improved the performance of this rule relative to the performance of the NLC. The finding that clinicians documented the presence of the CCR risk factor “paresthesias in extremities” but failed to document the similar NEXUS criterion “fo-
Mechanism is Important
If not wearing seatbelt, stopping distance determined by nature of collision with windshield, steering column, etc.: stopping distance 0.2 ft.

- Deceleration = 4836 ft/s^2 = 1474 m/s^2 = 150 g's
- Force = 24068 lb = 107059 N = 12 tons!!
If firmly held in non-stretching seatbelt harness: Stopping distance 1 ft.

- Deceleration = 967 ft/s^2 = 294 m/s^2 = 30 g's
- Force = 4813 lb = 21412 N = 2.4 tons
Treatments
Steroid Mechanism

- Anti-inflammatory effect – inhibit cell chemotaxis, phagocytosis, synthesis of mediators, release of lysosomal enzymes.
- Reduces lipid peroxidation, protects membrane – bound enzymes like ATPase and intracellular molecular assemblies like neurofilaments and reverses increase of lactic acid.
- Dose is 1000 times amount necessary to activate glucocorticosteroid receptors.
Methylprednisolone

- Doses similar to those that inhibit lipid peroxidation and breakdown of neurofilament in animal models. The breakdown of membrane peaks within 8 hrs of injury.
- Methylprednisolone does not produce a significant decrease in neutrophil accumulation but does reduce vascular permeability and tissue edema.
- Does INCREASE leukotriene B4 synthesized by neutrophils.
- Protective effects are not neutrophil mediated.
Steroids NASCIS - I

- 330 patients
- Efficacy of high dose MP (1000 mg bolus with 1000/day) vs. Low dose (100 mg Bolus with 100mg/d x 10 d)
- No placebo control - Unethical to withhold
Data after NASCIS I

- MP has strange dose-response curve - 30mg/kg inhibits lipid peroxidation but 60 mg/kg has no effect.
- MP should be initiated as early as possible because distribution into spinal tissue decreases rapidly after injury whereas lipid peroxidation occurs rapidly.
- More frequent dosing required
NASCIS 2

• 487 patients. 3 Groups: Placebo, Naloxone, or MPS.
• Patients treated within 12 hours of injury.
• At 1 year after injury, there were no significant differences among tx groups.
NASCIS 2

- **SUBGROUP ANALYSIS:** In reanalyzing all the data – steroids were reported to be efficacious in a subgroup treated within 8 hrs. of injury.
- This subgroup consisted of less than 50% of patients
- Average increase in motor score (Max 70) for steroid and placebo groups was 17.2 and 12 points
- 5.2 pt difference (p=0.03)
NASCIS 2

• At 1 year, Pinprick and light touch sensation were 2.4 pts (p=0.251) and 3.4 pts (p=0.122) respectively.

• Subgroup of patients treated with MPS 8 or more hours after injury had worse neurologic outcomes than placebo group but not statistically significant (actual motor scores not reported (p=.08))
Subgroups of treatment and placebo groups might have been dissimilar – Demographic characteristics (age, gender, site of treatment etc.) have not been published.

If you stratify by time to treatment at 1 hour interval (i.e. 0-3 hrs, 2-7 hours, etc.) there would be 78 potential subgroups.

With 20 subgroups, by chance alone, 1 subgroup would be positive for a p value of 0.05
NASCIS III

- 24 vs. 48 hour MP treatment
- Tirilazad Mesylate TM (a potent nonglucocorticoid inhibitor of lipid peroxidation arm).
- No placebo control
- TM worse
- Patients receiving MP within 3 hours receive 24 hour regimen
French Study - 2000

- Age 15 to 65
- 25 placebo, 27 nimodipine, 27 steroids, 27 nimodipine plus methylprednisolone
- At 1 year no significant differences in ASIA scores.
- Small groups of patients, add 2 groups.
- French Recommendations: NO STEROIDS
Systematic Review 2000

- Medline search 1966-2000, Cochrane Database.
- Only 3 clinical trials in humans. French, Japanese, and NASCIS 2.
- 12 Large animal studies
- Small mammal experiments considered beyond evaluation.
QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.
Radiographs

• RADIOGRAPHIC ASSESSMENT OF THE CERVICAL SPINE IN ASYMPTOMATIC TRAUMA PATIENTS
• RECOMMENDATIONS Standards: Radiographic assessment of the cervical spine is not recommended in trauma patients who are awake, alert, and not intoxicated, who are without neck pain or tenderness, and who do not have significant associated injuries that detract from their general evaluation.
RADIOGRAPHIC ASSESSMENT OF THE CERVICAL SPINE IN SYMPTOMATIC TRAUMA PATIENTS

RECOMMENDATIONS
Standards: A three view cervical spine series (AP, lateral, and odontoid views) is recommended for radiographic evaluation of the cervical spine in patients who are symptomatic following traumatic injury. This should be supplemented with computed tomography to further define areas that are suspicious or not well visualized on the plain cervical x-rays.
BP Management

• RECOMMENDATIONS
  • Standards: There is insufficient evidence to support treatment standards. Guidelines: There is insufficient evidence to support treatment guidelines.
  • Options: • Hypotension (systolic blood pressure < 90 mm Hg) should be avoided if possible or corrected as soon as possible following acute SCI. • Maintenance of mean arterial blood pressure at 85 – 90 mm Hg for the first seven days following acute SCI to improve spinal cord perfusion is recommended.
Steroids

THERAPY AFTER ACUTE CERVICAL SPINAL CORD INJURY

RECOMMENDATIONS

Corticosteroids: No Standards/
No Guidelines

Options: There is insufficient evidence to support treatment standards. Methylprednisolone for either 24 or 48 hours is recommended as an option in the treatment of patients with acute spinal cord injuries that should be undertaken only with the knowledge that the evidence suggesting harmful side effects is more consistent than any suggestion of clinical benefit.

GM-1 Ganglioside:

Options: Treatment of patients with acute spinal cord injuries with GM-1 ganglioside is recommended as an option without demonstrated clinical benefit.
DVT

- Standards: Prophylactic treatment of thromboembolism in patients with severe motor deficits due to spinal cord injury is recommended.
- The use of low molecular weight heparins, rotating beds, adjusted dose heparin, or a combination of modalities is recommended as a prophylactic treatment strategy.
- Low dose heparin in combination with pneumatic compression stockings or electrical stimulation is recommended as a prophylactic treatment strategy.
Pediatric C-spine

• Guidelines: • In children who have experienced trauma and are alert, have no neurological deficit, no midline cervical tenderness, no painful distracting injury, and are not intoxicated, cervical spine radiographs are unnecessary to exclude cervical spine injury and are not recommended. • In children who have experienced trauma and who are either not alert or have neurological deficit, midline cervical tenderness, painful distracting injury, or are intoxicated, it is recommended that cervical spine radiographs be obtained.
Early Surgical Decompression

- Retrospective review of 50 patients - Improvement if surgical decompression before 24 hours.
- Shorter ICU times
- Definitive study needs to be performed but NIH will not fund it.