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# A Clinical Practice Guideline for the Management of Patients With Acute Spinal Cord Injury: Recommendations on the Role of Baseline Magnetic Resonance Imaging in Clinical Decision Making and Outcome Prediction

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## Abstract

**Introduction:** The objective of this guideline is to outline the role of magnetic resonance imaging (MRI) in clinical decision making and outcome prediction in patients with traumatic spinal cord injury (SCI).

**Methods:** A systematic review of the literature was conducted to address key questions related to the use of MRI in patients with traumatic SCI. This review focused on longitudinal studies that controlled for baseline neurologic status. A

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multidisciplinary Guideline Development Group (GDG) used this information, their clinical expertise, and patient input to develop recommendations on the use of MRI for SCI patients. Based on GRADE (Grading of Recommendation, Assessment, Development and Evaluation), a strong recommendation is worded as “we recommend,” whereas a weaker recommendation is indicated by “we suggest.”

**Results:** Based on the limited available evidence and the clinical expertise of the GDG, our recommendations were: (1) “We suggest that MRI be performed in adult patients with acute SCI prior to surgical intervention, when feasible, to facilitate improved clinical decision-making” (quality of evidence, very low) and (2) “We suggest that MRI should be performed in adult patients in the acute period following SCI, before or after surgical intervention, to improve prediction of neurologic outcome” (quality of evidence, low).

**Conclusions:** These guidelines should be implemented into clinical practice to improve outcomes and prognostication for patients with SCI.

### Keywords

acute spinal cord injury, clinical decision making, clinical guideline, guideline, magnetic resonance imaging, outcome prediction, spinal cord injury, traumatic spinal cord injury

## Summary of Recommendations

We suggest that MRI be performed in adult patients with acute spinal cord injury prior to surgical intervention, when feasible, to facilitate improved clinical decision making.

*Quality of Evidence:* Very Low

*Strength of Recommendation:* Weak

We suggest that MRI should be performed in adult patients in the acute period following SCI, before or after surgical intervention, to improve prediction of neurologic outcome.

*Quality of Evidence:* Low

*Strength of Recommendation:* Weak

## Introduction

Imaging of the spine is an essential part of the initial management of acute spinal cord injury (SCI).<sup>1</sup> Plain X-rays or computed tomography (CT) of the spine form the basis of standard trauma protocols and can identify most fractures and ligamentous injuries. These imaging modalities, however, do not visualize the spinal cord or the surrounding soft tissues. CT myelography is an invasive procedure where a radio-opaque dye is injected into the cerebrospinal fluid (via lumbar puncture) to visualize the spinal cord; this procedure has nontrivial risk related to lumbar puncture and injection of dye (cerebrospinal fluid leak, hemorrhage, infection, injury to neural tissue, reaction to the dye) and can be cumbersome to perform in a trauma setting.

Magnetic resonance imaging (MRI) is currently the putative gold standard for imaging the spinal cord and related soft tissues<sup>1-3</sup>; however, debate remains about the appropriate use of MRI in acute SCI as it requires considerable resources to ensure 24-hour availability and may be dangerous in trauma patients with respiratory difficulties or hemodynamic instability. MRI studies are usually shortened in acute SCI to minimize risk and typically consist of sagittal and axial T2-weighted images, and potentially T1-weighted and short-tau inversion

recovery (STIR) sequences. Some surgeons have argued that MRI is essential in the acute period of SCI prior to surgical decision-making to (1) determine if there is ongoing spinal cord compression; (2) identify what structures are responsible for compression, such as disc herniation, epidural hematoma, intramedullary hematoma, and preexisting canal stenosis; and (3) detect ligamentous instability at the level of injury, or at other spinal levels, that is not apparent on X-ray or CT.<sup>2</sup> Furthermore, through the use of MR angiography (MRA), vertebral artery injury (VAI) or dissection can be identified, which can also alter initial management. Finally, certain MRI features such as hemorrhage or degree of compression may help predict neurological and functional outcomes, which could be of great value for patients that suffer SCI and their treating physicians.<sup>4-6</sup>

This guideline provides evidence-based recommendations for the use of MRI in clinical decision making and outcome prediction in acute SCI. Individual studies have variably defined the term “acute”; for the purpose of this guideline, we chose to use a relatively broad definition of within 1 week of injury. The systematic review aimed to determine (1) whether MRI influenced clinical decision making and, consequently, neurologic, functional, patient-reported and safety outcomes; and (2) the most important MRI predictors of neurologic and functional outcomes following acute SCI. The ultimate goal of this guideline is to improve outcome and reduce morbidity in patients with SCI by promoting standardization of care and encouraging clinicians to make evidence-informed decisions. An introductory article in this focus issue provides further background information on SCI and summarizes the rationale, scope, and specific aspects of care covered by this guideline. This article is titled “A Clinical Practice Guideline for the Management of Acute Spinal Cord Injury: Introduction, Rationale, and Scope.”

These guidelines are intended to be used by emergency room physicians, critical care specialists, radiologists, neurologists, and spine surgeons.

## Methods

This guideline was developed under the auspices of AOSpine North America, AOSpine International, and the American Association and Congress of Neurological Surgeons. A multidisciplinary Guideline Development Group (GDG) was formed and consisted of clinicians from a broad range of specialties as well as patient representation. The GDG was solely responsible for guideline development and was editorially independent from all funding sources. Members were required to disclose financial and intellectual conflicts of interest (see Appendix, Chapter 2, available in the online version of the article). A guideline development protocol, based on the Conference on Guideline Standardization (COGS) checklist,<sup>7,8</sup> was created to outline the rationale and scope of the guideline and to direct its development. Systematic reviews were conducted based on accepted methodological standards to summarize the evidence informing the recommendations. Details of specific methods used for each topic are outlined in the individual reviews included in this focus issue. Methods outlined by the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group were used to assess the overall quality (strength) of evidence for critical outcomes.<sup>9,10</sup> The GRADE Guideline Development Tool was used to document the guideline development process, rank the importance of outcomes, weigh the benefits and harms of various options, and determine the strength of recommendations.<sup>11-14</sup> Methodologists with no financial or intellectual conflicts of interest worked closely with clinical authors to conduct the systematic reviews and provided methodological expertise on the guideline development process. Guideline development methods are provided in another article included in this focus issue: "Guidelines for the Management of Degenerative Cervical Myelopathy and Acute Spinal Cord Injury: Development Process and Methodology."

## Clinical Recommendations

### Part I. The Role of Baseline Magnetic Resonance Imaging in Clinical Decision Making

*Population Description:* Patients with acute SCI

*Key Question:* Should baseline MRI be performed to facilitate clinical management decisions in adult patients with acute spinal cord injury?

*Recommendation 1:* We suggest that MRI be performed in adult patients with acute spinal cord injury prior to surgical intervention, when feasible, to facilitate improved clinical decision making.

*Quality of Evidence:* Very Low

*Strength of Recommendation:* Weak

### Evidence Summary

A systematic review of the literature was conducted to address the following key questions: In adult patients with acute traumatic SCI, (1) How does the acquisition of a baseline MRI

influence management strategies compared with no MRI (or another comparator), and consequently, what changes does it effect in neurologic, functional, patient-reported, and safety outcomes? (2) Do spinal cord lesion characteristics, pattern, and length identified on baseline MRI predict neurologic, functional, patient-reported, and safety outcomes? (3) Do spinal cord characteristics identified on diffusion tensor imaging predict neurologic, functional, patient-reported, and safety outcomes? (4) Is there evidence to suggest that baseline MRI is cost-effective in patients with acute SCI. The systematic review is published separately as part of this focus issue and focused on longitudinal studies that adjusted for baseline neurological status and other potential confounding factors.

The systematic review identified a single prospective study by Papadopoulos et al (2002) that evaluated the effect of pretreatment MRI on neurological outcomes.<sup>15</sup> A MRI-treatment protocol was applied to 66/91 patients and led to emergency surgery in 34 patients (54%). Outcomes in this group were compared to a reference group of 25 patients that had contraindications to MRI, required a non-spinal emergency procedure, or had a "specific surgeon bias regarding the futility of emergent treatment." Patients in the MRI-protocol group improved, on average, an additional 7/10 of a Frankel grade compared to the reference group ( $P < .006$ ). Furthermore, 50% of patients in the MRI-protocol group exhibited an improvement in Frankel grade, whereas only 24% of the reference group changed grades. Finally, 8 MRI-protocol patients (12%) improved from a motor-complete injury to independent ambulation, whereas none of the patients in the reference group achieved this improvement. Unfortunately, this study did not specifically evaluate the impact of baseline MRI on treatment strategies (surgical rates in the reference group were not reported and no details of clinical decision making were provided in the MRI group); however, the authors stated that "emergency MRI provided an essential tool for the accurate diagnosis of spinal cord compression and directly influenced our initial clinical management in the majority of protocol patients." Finally, the MRI-protocol group had decreased length of stay. The overall strength of evidence for the impact of MRI on clinical decision making was assessed as very low.

### Rationale for Recommendation

The outcomes ranked as critical for decision making were improved neurological and functional outcomes, decreased length of intensive care unit and hospital stay, and the need for emergency stabilization. The strength of evidence for findings related to these outcomes was rated as very low (very low = 16; low = 4). The study by Papadopoulos et al had serious risk of bias as the control group was selected based on MRI exclusion criteria or "specific surgeon bias regarding the futility of emergent treatment"<sup>15</sup>; these differences in patient selection may explain the differences in neurological outcomes and length of stay between the MRI-protocol and control groups. Furthermore, this study did not directly report how the acquisition of or findings on MRI altered management decisions and provided

limited detail in terms of adverse outcomes (“no patient suffered neurological deterioration during transport to/from MRI suite”). Finally, it is unclear whether an average improvement of 0.7 on the Frankel Grade is clinically important as the minimal clinically important difference has not been established for this scale. The findings related to neurological and functional outcomes and length of stay were also imprecise with unknown consistency.

The GDG also discussed several additional sources of very low level evidence that examined MRI features that may influence surgical/medical decision making (based on expert opinion). These features include the presence of ongoing spinal cord compression, ligamentous injury, disc herniation, and VAI, all of which could lead to changes in surgical/medical management decisions. Several of these factors were summarized in a systematic review by Bozzo et al<sup>2</sup>; this review was rated as having poor to moderate quality (AMSTAR rating 5/11) by our methodological team because many of the articles were case series, the timing of MRI relative to injury and intervention was variable (or not reported), and the authors did not fully describe their process of data selection, synthesis or determining overall quality of evidence. Furthermore, none of the studies identified in the Bozzo et al review directly compared clinical decision making with and without MRI (or another imaging modality), nor did they relate the use of MRI with clinical outcomes. There was general consensus (informal, no vote was performed) among members of the GDG that the following clinical entities are important for decision making:

**Ongoing Spinal Cord Compression.** The review by Bozzo et al briefly mentioned that ongoing spinal cord compression is a feature that may alter management.<sup>2</sup> The rationale for this is based on the concept that spinal cord compression causes tissue ischemia, resulting in damage and cell loss in the spinal cord. Selden et al stated that the identification of ongoing cord compression resulted in the decision to perform decompressive surgery with greater urgency and that the identification of anterior or posterior cord compression strongly influenced surgical approach.<sup>16</sup> In recent years, several clinical trials, including STASCIS,<sup>17</sup> have used the presence of ongoing spinal cord compression on MRI as a key inclusion criterion. STASCIS also helped establish that, in the context of ongoing spinal cord compression, timely decompression leads to improved outcomes, confirming that ongoing cord compression is clinically important. Thus, based primarily on expert opinion and supported by indirect evidence, ongoing spinal cord compression was considered important for clinical decision making, although the evidence is insufficient.

**Ligamentous Injury.** Partial or complete injuries to spinal ligaments can cause mechanical instability, which is the abnormal movement of one bone relative to another. The clinical implication of mechanical instability is that the spinal cord can suffer additional (possibly repetitive) injury if there is abnormal movement. The sensitivity of MRI to detect ligamentous injury varies across studies and by the specific sequences used:

anterior longitudinal ligament (ALL), 46% to 71%; disk, 93%; posterior longitudinal ligament (PLL), 43% to 93%; ligamentum flavum (LF), 67%; interspinous ligament (ISL), 36% to 100%; and supraspinous ligament (SSL), 89%.<sup>18-23</sup> Certain ligamentous injuries may cause significant instability of the spinal column and require surgical stabilization or external bracing, whereas other injury patterns suggest the possibility of mechanical instability. However, even in the latter case, the knowledge of potential instability could affect decisions on the extent of surgical stabilization and also the clearance of spinal precautions (and removal of a rigid collar). Thus, based on expert opinion and supported by indirect evidence, the detection of ligamentous injury was considered important for clinical decision making.

**Disk Herniation and Injury.** Within the studies describing patients with injuries to the cervical spine in Bozzo et al,<sup>2</sup> there was a high rate of disk herniation or injury (36%) on initial MRI. There is some debate among surgeons as to how important small or moderate disc herniations are, as many surgeons are willing to perform a closed reduction maneuver in acute SCI patients without a prerelief MRI.<sup>24</sup> Furthermore, the rate of permanent neurological decline in these cases is less than 1%.<sup>24-26</sup> However, the presence of a large disc herniation is highly likely to influence the surgeon to perform anterior surgical decompression instead of, or in addition to, posterior decompression. Thus, based on expert opinion and supported by indirect evidence, it was concluded that the detection of large disc herniation is important for clinical decision making.

**Vertebral Artery Injury.** VAI can be detected through the use of MRA, usually using gadolinium contrast.<sup>2</sup> In the Bozzo et al review, 8 studies included a total of 942 patients considered to be at high risk of a VAI due to the mechanism of trauma and/or their bony or spinal cord pathology.<sup>2</sup> A unilateral VAI was found in 140 patients (15%), and bilateral injuries/occlusions in 7 patients (0.7%). The detection of VAI often leads to the initiation of immediate antiplatelet or anticoagulation therapy, except in specific circumstances where it is contraindicated (usually due to concomitant injuries such as intracranial hemorrhage). The evidence supporting the use of antiplatelet or anticoagulation therapy, however, is low and there are documented risks of hemorrhage, concluding that no treatment may be comparable to antiplatelet treatment. Furthermore, no studies have directly compared MRA versus CT angiography (CTA) in the modern era of 64-detector CT, which may have similar or superior diagnostic accuracy compared with MRA. However, at a minimum it can be said, based on expert opinion, that the detection of VAI is important for clinical decision making and that MRI is currently an accepted method for detecting VAI.

After consideration of these sources of evidence, the majority of GDG members felt that the certainty of the evidence was very low. Four members of the GDG felt that the evidence was low; discussions revealed that this difference was due to the fact that

several MRI studies in acute SCI with clinically useful information were excluded and that our systematic review focus may have been excessively narrow. Many of the reviewed studies, however, were primarily excluded because they were not longitudinal and/or did not adjust for baseline clinical factors such as neurologic status. Most of the evidence pertinent to this recommendation was indirect and derived from sources outside the systematic review, and involved intermediate outcomes (eg, identification of ongoing cord compression, disc herniation, epidural hematoma, ligamentous injury) that were deemed clinically important by expert opinion. The GDG reaffirmed the need to comply with the GRADE approach to assess the evidence in a rigorous manner. This process identified critical knowledge gaps; future studies are needed to better identify how pretreatment MRI in acute SCI directly alters clinical decision making and the downstream effects on neurological and functional outcomes.

The GDG agreed that there was no or probably no important uncertainty about how much key stakeholders value the main outcomes (important uncertainty or variability = 1; probably no important uncertainty or variability = 6; no important uncertainty or variability = 7; no known undesirable outcomes = 8). Clinicians, patients, and payers would likely similarly value improvement in neurological and functional outcomes and reduced length of stay.

The anticipated desirable effects were improved clinical decision making, functional status and neurological outcomes, decreased hospital stay, and reduced risk of additional SCI. The GDG agreed that the benefits of MRI to improve immediate clinical decision making could be profound for certain patients, especially those with ongoing cord compression, disc herniation, epidural hematoma, or ligamentous injury. More specifically, MRI is very effective at identifying the specific location(s) and cause(s) of ongoing spinal cord compression that, if present, should be decompressed emergently through closed reduction or surgery (based on data from STASCIS and other surgical trials). Cord compression may occur at multiple levels, from bony fragments, dislocation, intervertebral disc herniation, epidural hematoma, or other causes; MRI is able to accurately identify each of these, which allows surgeons to select an appropriate surgical strategy, including which levels to decompress and which approach to use (anterior versus posterior versus both). MRI also has moderate to good sensitivity/specificity for detecting ligamentous injury,<sup>2</sup> which can influence the decision on whether to use surgical instrumentation and/or external bracing, and also help enable immediate clearance of spinal precautions in patients without injury. MRI may also be of value in identifying VAI, which may prompt antiplatelet or anticoagulation therapy and increased neurological monitoring of patients. Failure to get an MRI may result in a surgeon incorrectly ascribing a patient's poor neurological status to the primary injury when, in fact, the patient may have transient neurological impairment due to cord compression that may be largely reversible through emergency decompression. Similarly, missing a ligamentous injury or a VAI could have catastrophic consequences, due to subsequent traumatic injury

or posterior circulation stroke, respectively. Although the evidence base for these conclusions is severely limited, the GDG agreed that, based on expert opinion, the anticipated desirable effects of MRI are probably large (no = 1; probably no = 1; probably yes = 1 2; yes = 11).

The anticipated undesirable effects were the risks associated with obtaining an MRI in the acute phase of SCI. These risks depend on many factors such as concomitant injuries, neurogenic shock, autonomic dysreflexia, and pain, and include (1) keeping a patient supine for approximately 30 minutes, especially in critically ill patients with hemodynamic instability or concomitant head/chest injuries; and (2) delaying the time to spinal cord decompression. The GDG unanimously agreed that the undesirable effects of obtaining an MRI are probably small and that the desirable effects are probably large relative to the undesirable effects. Clinical judgement, however, is required to assess whether a patient is able to tolerate MRI.

The GDG unanimously agreed that the resources required to implement MRI in the setting of acute SCI are not small. MRI can be very costly and include both capital expenses (approximately US\$1-2 million) and operating costs (eg, facilities and trained technicians). No studies were identified that evaluated the cost-effectiveness of MRI; however, such a study would likely require assumptions and methods that may limit its validity/applicability across centers and countries. In addition, no studies quantifying the benefits of MRI compared with other strategies were identified. As a result, the GDG determined that it is uncertain whether the incremental cost of MRI in an acute SCI setting is small relative to the net benefits.

Ten members of the GDG agreed that a recommendation for MRI would probably reduce health inequities if policy makers fund initiatives to ensure patients with SCI have better access to MRI (probably reduced = 9; reduced = 1). Eleven individuals were uncertain whether this recommendation would affect health inequities. The GDG unanimously agreed that this option would probably be acceptable to key stakeholders; this selection was driven by the assessment of the potential benefits compared with the risks described above. Furthermore, the majority of the GDG selected that providing MRI for acute SCI patients is probably feasible to implement (probably no = 1; uncertain = 2; probably yes = 15; yes = 3, varies = 1). Potential barriers include costs and MRI availability, especially in developing countries and smaller centers.

Considering all these factors, the GDG voted that the desirable consequences probably outweigh the undesirable consequences in most settings (n = 16/23); this led to the formation of a weak recommendation that MRI be performed in adult patients with acute SCI, when feasible, to improve clinical decision making (n = 15/20). In making this recommendation, we strongly considered that MRI can identify specific features (including ongoing spinal cord compression, ligamentous injury, large disc herniations, and vertebral artery injuries) that, if present, would alter clinical management and, in turn, have a beneficial effect on outcomes. The GDG agreed not to make a strong recommendation due to the lack of direct evidence that MRI influences clinical decision

making and the fact that a proportion of spine surgeons currently rely only on CT scans. It was also acknowledged that the GDG included several individuals who have published research in the area of MRI in acute SCI and that a strong recommendation for MRI based solely on expert opinion could be perceived as biased and not representative of the range of expert opinions in the larger community.

## Part 2. The Role of Baseline Magnetic Resonance Imaging in Predicting Neurologic and Functional Outcomes

*Population Description:* Patients with acute SCI

*Key Question:* Should baseline MRI (within 7 days of injury) be performed in adult patients with acute spinal cord injury to facilitate improved prognostication of neurologic and functional outcomes?

*Recommendation 2:* We suggest that MRI should be performed in adult patients in the acute period following SCI, before or after surgical intervention, to improve prediction of neurologic and functional outcome.

*Quality of Evidence:* Low

*Strength of Recommendation:* Weak

### Evidence Summary

As previously described, a systematic review was performed to inform the development of our clinical recommendations. Longitudinal studies that controlled for baseline clinical factors such as neurologic status were considered for inclusion. Seven studies were identified that evaluated MRI predictors of neurologic, functional, patient-reported, and safety outcomes.<sup>5,6,16,27-30</sup> Five studies investigated the association between the presence of intramedullary spinal cord hemorrhage (region of decreased signal intensity surrounded by a thin rim of high signal intensity on T2-weighted images in the acute period) and neurologic outcomes.<sup>5,16,27-29</sup> Two studies found no relationship,<sup>28,29</sup> while 3 studies reported that the presence of hemorrhage was predictive a worse neurologic recovery.<sup>5,16,27</sup> Longer rostro-caudal intramedullary hematoma length was also associated with worse neurologic recovery in 2 studies (moderate evidence).<sup>16,29</sup>

Two studies evaluated the relationship between maximum canal compromise (MCC) and neurologic recovery.<sup>5,30</sup> Of these, one reported no association,<sup>5</sup> and the other indicated that a lower MCC was associated with worse neurologic recovery.<sup>30</sup> Maximum spinal cord compression (MSCC) was not predictive of neurologic recovery across 3 studies.<sup>5,16,30</sup>

Based on 3 studies, MRI evidence of cord edema (a region of high signal intensity on T2-weighted images) was not significantly associated with neurologic outcomes.<sup>5,28,29</sup> In contrast, a longer edema lesion length was predictive of worse neurologic recovery in one study,<sup>27</sup> but not another.<sup>16</sup> In a third study, edema lesion length was associated with neurologic recovery in univariate but not multivariate analysis.<sup>29</sup>

Two studies reported no association between SCI lesion (either hemorrhage, edema, or a combination of both) length and neurologic recovery.<sup>5,30</sup> Cord swelling (increased spinal cord diameter) was marginally significantly associated with worse neurologic outcomes in one study.<sup>5</sup> Based on single studies, there was no association between neurologic recovery and soft-tissue injury,<sup>5</sup> pre-injury stenosis,<sup>5</sup> disc herniation,<sup>5</sup> cord contusion,<sup>28</sup> rostral point of edema,<sup>27</sup> and smaller diameter within swollen length of the cord.<sup>16</sup>

In summary, there is moderate evidence suggesting that a longer hemorrhage length on MRI in the acute phase of injury is predictive of a worse neurologic recovery, and that there is no association between neurologic outcomes and cord edema, MSCC, and SCI lesion length. There is low evidence indicating that a lower MCC is associated with worse FIM (Functional Independent Measure) scores, a longer SCI lesion length is related to worse manual dexterity and dysesthetic pain, and cord swelling is predictive of worse neurologic recovery. Furthermore, based on low evidence, there is no association between SCI lesion length and FIM scores, MSCC and functional recovery, and MCC and manual dexterity or dysesthetic pain. Finally, there is very low evidence suggesting that length of cord swelling and the rostral point of edema are not associated with neurologic outcomes.

### Rationale for Recommendation

The outcomes ranked as critical for decision making were improved prediction of neurological and functional outcomes. Seven studies discussed the predictive value of various MRI factors using multivariate analysis that controlled for baseline neurologic status. As presented above, the strength of evidence ranged from very low to moderate; most findings had a serious risk of imprecision and were inconsistent across studies (or had unknown consistency if only one study was available). The GDG unanimously agreed that the overall certainty of the evidence was low.

The GDG acknowledged that there is possibly important uncertainty or variability about how much stakeholders value the main outcomes. Improved prognostication is potentially valuable to patients and their families, while the benefit to other stakeholders (clinicians and payers) is uncertain.

The anticipated desirable effects are improved prediction of neurological and functional outcomes. The GDG unanimously agreed that the anticipated desirable effects are probably not large; however, knowledge of a patient's likely outcome can help appropriately manage expectations, determine the optimal treatment pathway for patients, and improve allocation of resources.

The anticipated undesirable effects were the risks associated with obtaining an MRI in the acute phase of SCI. These risks depend on many factors such as concomitant injuries, neurogenic shock, autonomic dysreflexia, and pain and include (1) keeping a patient supine for approximately 30 minutes, especially in critically ill patients with hemodynamic instability or concomitant head/chest injuries; and (2) delaying the time to spinal cord decompression. For the purpose of prediction,



however, MRI can be performed in the postoperative time period (potentially several days after injury) when most acute medical issues are no longer present. The GDG unanimously agreed that the undesirable effects of obtaining an MRI were probably small; clinicians, however, must carefully assess whether a patient can tolerate an MRI and if the benefit outweighs the risk. Based on the 2 previous responses, the GDG was uncertain whether the desirable anticipated effects were large relative to the anticipated undesirable effects.

The GDG unanimously agreed that the resources required to implement MRI in the setting of acute SCI were not small. MRI can be very costly and include both capital expenses (approximately US\$1-2 million) and operating costs (eg, facilities and trained technicians). Unfortunately, there were no studies that evaluated the cost-effectiveness of MRI; however, such a study would likely require assumptions and methods that may limit its validity/applicability across centers and countries. As a result, the GDG agreed that it is uncertain whether the incremental cost of MRI in an acute SCI setting is small relative to the net benefits.

The GDG unanimously agreed that a recommendation for MRI would probably reduce health inequities if policy makers fund initiatives to ensure patients with SCI have better access to MRI. The GDG also agreed that this option would probably be acceptable to key stakeholders although there is some uncertainty given the lack of evidence on the cost-effectiveness of this option. Furthermore, the majority of the GDG felt that providing MRI for acute SCI patients is probably feasible to implement. Potential barriers include costs and MRI availability, especially in developing countries and smaller centers.

Considering these factors, the entire GDG voted that the desirable consequences probably outweigh the undesirable consequences in most settings; this led to the formation of a weak recommendation that MRI be performed in adult patients with acute SCI, before or after surgical intervention, to improve prediction of neurologic outcomes

## Evidence Gaps and Future Research Recommendations

Despite publication of numerous studies investigating the use of MRI in acute SCI, no studies directly link the application of MRI to changes in clinical decision making; only one low-quality study indirectly evaluated the association between obtaining an MRI and changes in neurological outcome. This study, however, primarily focused on the impact of early surgical decompression rather than MRI, which were linked together in a protocolized treatment algorithm. Furthermore, no studies compared decision making based on MRI with decision making based on other imaging modalities or no MRI. Future prospective studies are needed to better identify how pretreatment MRI in acute SCI alters clinical decision making, such as the need, timing, type, and approach of surgery, and ultimately affects neurological and functional outcomes. Such studies must follow strict protocols and document decision making and outcome assessment. Moreover, studies are also

needed that compare decision making based on MRI with other imaging modalities. Further research is also needed on the utility of MRI for later stages of care in SCI, such as assessing the quality of spinal cord decompression following surgery, and for monitoring the chronic phase for development of post-traumatic syringomyelia.

The 7 studies that investigated the association between MRI characteristics and outcomes following acute SCI used different MRI features and outcome measures, limiting our ability to synthesize results. Future methodologically sound studies with sufficient sample sizes are warranted to better characterize the relationship between MRI factors such as hemorrhage, edema, and cord compression and standard neurologic outcomes such as AIS (American Spinal Injury Association Impairment Scale) and ISNCSCI (International Standards for Neurological Classification of Spinal Cord Injury) motor score. Recently, additional studies have been published that were not included in our systematic review but should be considered for future updates of these guidelines; for example, a single study by Talbott et al<sup>31</sup> introduced a novel “Brain and Spinal Injury Score” based on axial T2-weighted images to assess the severity of acute SCI, whereas another study by Haefeli et al<sup>32</sup> employed a multivariate approach using nonlinear principle analysis to examine the prognostic value of several MRI characteristics. Future prospective longitudinal studies are needed to accurately determine the predictive value of various MRI factors, while adjusting for baseline neurological status as this is a well-established prognostic factor.

No evidence was identified that evaluated the utility of DTI for prognostication in acute SCI. Investigation into DTI and other emerging MRI techniques, such as magnetization transfer (MT), MR spectroscopy (MRS), myelin water fraction (MWF), and functional MRI (fMRI) should be pursued, as these techniques can characterize specific aspects of tissue microstructure and function that may better correlate with outcomes compared to conventional MRI.<sup>33-35</sup> These techniques are rapidly evolving and becoming increasingly available, but their utility for prognostication in acute SCI has yet to be established.

Finally, the relationship between cost and clinical utility of MRI has not been established in acute SCI. Future research that characterizes a positive cost-effectiveness ratio would help promote adoption and standardization of MRI into clinical protocols.

## Implementation Considerations

It is expected that this guideline will influence clinical practice and facilitate evidence-based decision making. Dissemination of the knowledge from this guideline is of critical importance and will be accomplished at multiple levels:

1. Presentation at international spine surgery, critical care, neurology, anesthesiology, and vascular medicine conferences
2. Scientific and educational courses in symposium format

3. Webinar dissemination of information to a broad audience in an interactive format
4. Publication of a focus issue in a peer-reviewed journal
5. Submission to the National Guideline Clearinghouse
6. AOSpine International Spinal Cord Injury Knowledge Forum

Potential barriers to implementation include the following:

1. *The availability of MRI:* Each spine trauma center would require timely access to MRI so that decision making based on MRI findings would not prevent timely surgical decompression. This does not necessarily require 24-hour per day MRI availability, which can be costly, but requires availability within a time-frame that allows for early surgical decompression ( $\leq 24$  hours of injury).
2. *Clinical uptake by physicians:* This guideline is based on very low to low level evidence and expert opinion, which may not be sufficient to drive policy changes. Thus, the decision to obtain an MRI in the acute phase of SCI will likely remain in the hands of individual surgeons. It may be difficult to change the beliefs and/or practices of these individuals without stronger evidence.
3. The recommendation to obtain MRI in patients with acute SCI does not apply to a small subset of patients, including those deemed too unstable to tolerate a supine MRI.

## Internal Appraisal and External Review of This Guideline

Vice-Chairs of the GDG conducted an internal appraisal of the final guideline using Appraisal of Guidelines for Research & Evaluation II (AGREE II) standards.<sup>36</sup> A multidisciplinary group of stakeholders, including patients, were invited to externally review the final draft prior to publication. Additional details of these processes and a summary of conflict of interests for external reviewers are found in the accompanying methods paper.

## Plans for Updating

The guidelines will be reviewed by the primary sponsor and the Vice-Chairs at 3 years to a maximum of 5 years following publication. The guideline will be updated when new evidence suggests the need to modify our recommendations. An earlier update will be considered if there are changes in (1) the evidence related to harms and benefits; (2) outcomes that would be considered important for decision making; (3) ranking of current critical and important outcomes; and (4) available interventions and resources.<sup>37</sup>

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Guideline Development Committee Members: Co-Chair: Michael G. Fehlings, MD, PhD, Neurosurgery; Co-Chair: James Harrop, MD,

Neurosurgery; Vice Chair: Jefferson R. Wilson, MD, PhD, Neurosurgery; Vice Chair: Anthony Burns, MD, Physical Medicine/Rehabilitation; General Member of Leadership Group: Brian Kwon, MD, PhD, Orthopedic Surgery; Systematic Review Coordinator: Lindsay Tetreault, PhD, Research.

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## Declaration of Conflicting Interests

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## Supplemental Material

The supplemental material is available in the online version of the article.

## References

1. Ryken TC, Hadley MN, Walters BC, et al. Radiographic assessment. *Neurosurgery*. 2013;72(suppl 2):54-72. doi:10.1227/NEU.0b013e318276edee.
2. Bozzo A, Marcoux J, Radhakrishna M, Pelletier J, Goulet B. The role of magnetic resonance imaging in the management of acute spinal cord injury. *J Neurotrauma*. 2011;28:1401-1411. doi:10.1089/neu.2009.1236.
3. Leypold BG, Flanders AE, Burns AS. The early evolution of spinal cord lesions on MR imaging following traumatic spinal cord injury. *AJNR Am J Neuroradiol*. 2008;29:1012-1016. doi:10.3174/ajnr.A0962.
4. Flanders AE, Spettell CM, Friedman DP, Marino RJ, Herbison GJ. The relationship between the functional abilities of patients with cervical spinal cord injury and the severity of damage revealed by MR imaging. *Am J Neuroradiol*. 1999;20:926-934.
5. Miyanji F, Furlan JC, Aarabi B, Arnold PM, Fehlings MG. Acute cervical traumatic spinal cord injury: MR imaging findings correlated with neurologic outcome—prospective study with 100 consecutive patients. *Radiology*. 2007;243:820-827. doi:10.1148/radiol.2433060583.
6. Wilson JR, Grossman RG, Frankowski RF, 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*. 2012;29:2263-2271. doi:10.1089/neu.2012.2417.
7. Shiffman RN, Michel G. Toward improved guideline quality: using the COGS statement with GEM. *Stud Health Technol Inform*. 2004;107:159-163.
  8. Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. *Ann Intern Med*. 2003;139:493-498.
  9. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64:401-406.
  10. Agency for Healthcare Research and Quality. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (AHRQ Publication No. 10(14)-EHC063-EF). Rockville, MD: Agency for Healthcare Research and Quality; 2013.
  11. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol*. 2013;66:719-725. doi:10.1016/j.jclinepi.2012.03.013.
  12. Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. *J Clin Epidemiol*. 2013;66:726-735. doi:10.1016/j.jclinepi.2013.02.003.
  13. Schunemann HJ, Oxman AD, Akl EA, et al. Moving from evidence to developing recommendations in guidelines: article 11 in integrating and coordinating efforts in COPD guideline development. An official ATS/ERS workshop report. *Proc Am Thorac Soc*. 2012;9:282-292. doi:10.1513/pats.201208-064ST.
  14. Wu JC, Ko CC, Yen YS, et al. Epidemiology of cervical spondylotic myelopathy and its risk of causing spinal cord injury: a national cohort study. *Neurosurg Focus*. 2013;35:E10. doi:10.3171/2013.4.FOCUS13122.
  15. Papadopoulos SM, Selden NR, Quint DJ, Patel N, Gillespie B, Grube S. Immediate spinal cord decompression for cervical spinal cord injury: feasibility and outcome. *J Trauma*. 2002;52:323-332.
  16. Selden NR, Quint DJ, Patel N, d'Arcy HS, Papadopoulos SM. Emergency magnetic resonance imaging of cervical spinal cord injuries: clinical correlation and prognosis. *Neurosurgery*. 1999;44:785-792.
  17. Fehlings MG, Vaccaro A, Wilson JR, et al. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). *PLoS One*. 2012;7:e32037. doi:10.1371/journal.pone.0032037.
  18. Emery SE, Pathria MN, Wilber RG, Masaryk T, Bohlman HH. Magnetic resonance imaging of posttraumatic spinal ligament injury. *J Spinal Disord*. 1989;2:229-233.
  19. Kliwer MA, Gray L, Paver J, et al. Acute spinal ligament disruption: MR imaging with anatomic correlation. *J Magn Reson Imaging*. 1993;3:855-861.
  20. Keiper MD, Zimmerman RA, Bilaniuk LT. MRI in the assessment of the supportive soft tissues of the cervical spine in acute trauma in children. *Neuroradiology*. 1998;40:359-363.
  21. Katzberg RW, Benedetti PF, Drake CM, et al. Acute cervical spine injuries: prospective MR imaging assessment at a level 1 trauma center. *Radiology*. 1999;213:203-212. doi:10.1148/radiology.213.1.r99oc40203.
  22. Haba H, Taneichi H, Kotani Y, et al. Diagnostic accuracy of magnetic resonance imaging for detecting posterior ligamentous complex injury associated with thoracic and lumbar fractures. *J Neurosurg*. 2003;99(1 suppl):20-26.
  23. Goradia D, Linnau KF, Cohen WA, Mirza S, Hallam DK, Blackmore CC. Correlation of MR imaging findings with intraoperative findings after cervical spine trauma. *AJNR Am J Neuroradiol*. 2007;28:209-215.
  24. Gelb DE, Hadley MN, Aarabi B, et al. Initial closed reduction of cervical spinal fracture-dislocation injuries. *Neurosurgery*. 2013;72(suppl 2):73-83. doi:10.1227/NEU.0b013e318276ee02.
  25. Rizzolo SJ, Vaccaro AR, Cotler JM. Cervical spine trauma. *Spine (Phila Pa 1976)*. 1994;19:2288-2298.
  26. Arnold PM, Brodke DS, Rampersaud YR, et al. Differences between neurosurgeons and orthopedic surgeons in classifying cervical dislocation injuries and making assessment and treatment decisions: a multicenter reliability study. *Am J Orthop (Belle Mead NJ)*. 2009;38:E156-E161.
  27. Flanders AE, Spettell CM, Tartaglino LM, Friedman DP, Herbigson GJ. Forecasting motor recovery after cervical spinal cord injury: value of MR imaging. *Radiology*. 1996;201:649-655. doi:10.1148/radiology.201.3.8939210.
  28. Shepard MJ, Bracken MB. Magnetic resonance imaging and neurological recovery in acute spinal cord injury: observations from the National Acute Spinal Cord Injury Study 3. *Spinal Cord*. 1999;37:833-837.
  29. Boldin C, Raith J, Fankhauser F, Haunschmid C, Schwantzer G, Schweighofer F. Predicting neurologic recovery in cervical spinal cord injury with postoperative MR imaging. *Spine (Phila Pa 1976)*. 2006;31:554-559. doi:10.1097/01.brs.0000201274.59427.a4.
  30. Aarabi B, Alexander M, Mirvis SE, et al. Predictors of outcome in acute traumatic central cord syndrome due to spinal stenosis. *J Neurosurg Spine*. 2011;14:122-130. doi:10.3171/2010.9.SPINE09922.
  31. Talbott JF, Whetstone WD, Readdy WJ, et al. The Brain and Spinal Injury Center score: a novel, simple, and reproducible method for assessing the severity of acute cervical spinal cord injury with axial T2-weighted MRI findings. *J Neurosurg Spine*. 2015;23:495-504. doi:10.3171/2015.1.SPINE141033.
  32. Haefeli J, Mabray MC, Whetstone WD, et al. Multivariate analysis of MRI biomarkers for predicting neurologic impairment in cervical spinal cord injury. *AJNR Am J Neuroradiol*. 2017;38:648-655. doi:10.3174/ajnr.A5021.
  33. Stroman PW, Wheeler-Kingshott C, Bacon M, et al. The current state-of-the-art of spinal cord imaging: methods. *Neuroimage*. 2014;84:1070-1081. doi:10.1016/j.neuroimage.2013.04.124.
  34. Wheeler-Kingshott CA, Stroman PW, Schwab JM, et al. The current state-of-the-art of spinal cord imaging: applications. *Neuroimage*. 2014;84:1082-1093. doi:10.1016/j.neuroimage.2013.07.014.
  35. Martin AR, Aleksanderek I, Cohen-Adad J, et al. Translating state-of-the-art spinal cord MRI techniques to clinical use: a systematic review of clinical studies utilizing DTI, MT, MWF, MRS, and fMRI. Paper presented at: International Society for Magnetic

- Resonance in Medicine (ISMRM) Annual Meeting; May 12, 2016; Singapore.
36. Brouwers MC, Kho ME, Browman GP, et al. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. *CMAJ*. 2010;182:E472-E478. doi:10.1503/cmaj.091716.
37. Shekelle P, Woolf S, Grimshaw JM, Schünemann HJ, Eccles MP. Developing clinical practice guidelines: reviewing, reporting, and publishing guidelines; updating guidelines; and the emerging issues of enhancing guideline implementability and accounting for comorbid conditions in guideline development. *Implement Sci*. 2012;7:62.