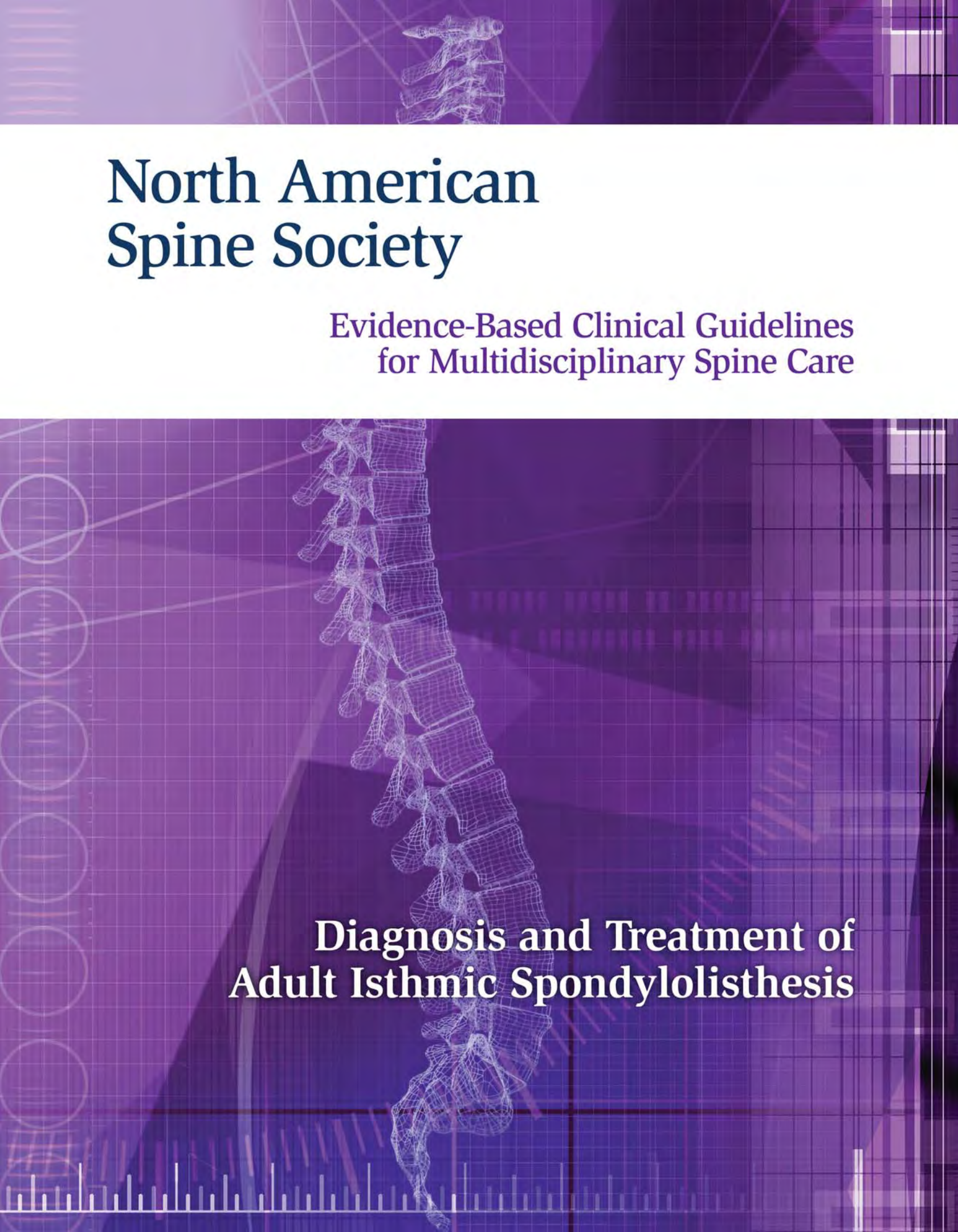
North American Spine Society

Evidence-Based Clinical Guidelines for Multidisciplinary Spine Care



Diagnosis and Treatment of Adult Isthmic Spondylolisthesis

Evidence-Based Clinical Guidelines for Multidisciplinary Spine Care

Diagnosis and Treatment of Adult Isthmic Spondylolisthesis

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Clinical Guidelines for Multidisciplinary Spine Care
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Range Key:

Level A. $100 to $1,000
Level B. $1,001 to $10,000
Level C. $10,001 to $25,000
Level D. $25,001 to $50,000
Level E. $50,001 to $100,000
Level F. $100,001 to $500,000
Level G. $500,001 to $1M
Level H. $1,000,001 to $2.5M
Level I. Greater than $2.5M

Comments

Comments regarding the guideline may be submitted to the North American Spine Society and will be considered in development of future revisions of the work.

Table of Contents

I. Introduction 4

II. Guideline Development Methodology 5

III. Summary of Recommendations. 8

IV. Definition and Indicence of Adult Isthmic Spondylolisthesis 13

V. Recommendations for Diagnosis and Treatment of Adult Isthmic Spondylolisthesis. 15
- A. Natural History 15
- B. Diagnosis/Imaging 22
- C. Outcome Measures for Medical/Interventional and Surgical Treatment 34
- D. Medical/Interventional Treatment 35
- E. Surgical Treatment 41
- F. Value of Spine Care 67

VI. Appendices. 69
- A. Acronyms. 69
- B. Levels of Evidence for Primary Research Questions 70
- C. Grades of Recommendations for Summaries or Reviews of Studies. 71
- D. Linking Levels of Evidence to Grades of Recommendation 72
- E. NASS Literature Search Protocol 73

VII. References 74

A technical report, including the literature search parameters and evidentiary tables developed by the authors, can be accessed at https://www.spine.org/Documents/ResearchClinicalCare/Guidelines/AdultIsthmicSpondyGuidelineTechReport.pdf.

I. Introduction

Objective

The objective of the North American Spine Society (NASS) *Clinical Guideline for the Diagnosis and Treatment of Adult Isthmic Spondylolisthesis* is to provide evidence-based recommendations to address key clinical questions surrounding the diagnosis and treatment of adult patients with isthmic spondylolisthesis. This guideline is based upon a systematic review of the evidence and reflects contemporary treatment concepts for symptomatic isthmic spondylolisthesis as reflected in the highest quality clinical literature available on this subject as of June 2013. The goals of the guideline recommendations are to assist in delivering optimum, efficacious treatment and functional recovery from this spinal disorder.

Scope, Purpose and Intended User

This document was developed by the North American Spine Society Evidence-based Guideline Development Committee as an educational tool to assist practitioners who treat adult patients with isthmic spondylolisthesis. The goal is to provide a tool that assists practitioners in improving the quality and efficiency of care delivered to these patients. The NASS *Clinical Guideline for the Diagnosis and Treatment of Adult Isthmic Spondylolisthesis* provides a definition of this disorder, outlines a reasonable evaluation of patients suspected to have isthmic spondylolisthesis and outlines treatment options for adult patients with this diagnosis.

THIS GUIDELINE DOES NOT REPRESENT A "STANDARD OF CARE," nor is it intended as a fixed treatment protocol. It is anticipated that there will be patients who will require less or more treatment than the average. It is also acknowledged that in atypical cases, treatment falling outside this guideline will sometimes be necessary. This guideline should not be seen as prescribing the type, frequency or duration of intervention. Treatment should be based on the individual patient's need and doctor's professional judgment and experience. This document is designed to function as a guideline and should not be used as the sole reason for denial of treatment and services. This guideline is not intended to expand or restrict a health care provider's scope of practice or to supersede applicable ethical standards or provisions of law.

Patient Population

The patient population for this guideline encompasses adults (18 years or older) with variable back, lower extremity pain and/or neurologic deficit related to isthmic spondylolisthesis.

II. Guideline Development Methodology

Through objective evaluation of the evidence and transparency in the process of making recommendations, it is NASS' goal to develop evidence-based clinical practice guidelines for the diagnosis and treatment of adult patients with various spinal conditions. These guidelines are developed for educational purposes to assist practitioners in their clinical decision-making processes. It is anticipated that where evidence is very strong in support of recommendations, these recommendations will be operationalized into performance measures.

Multidisciplinary Collaboration

With the goal of ensuring the best possible care for adult patients suffering with spinal disorders, NASS is committed to multidisciplinary involvement in the process of guideline and performance measure development. To this end, NASS has ensured that representatives from both operative and non-operative, medical, interventional and surgical spine specialties have participated in the development and review of NASS guidelines. To ensure broad-based representation, NASS welcomes input from other societies and specialties.

Evidence Analysis Training of All NASS Guideline Developers

All Evidence-Based Guideline Development Committee Members have completed NASS' Fundamentals of Evidence-Based Medicine Training. Members have the option to attend a one-day course or complete training via an online program. In conjunction with Qwogo Inc., a University of Alberta affiliated enterprise, NASS offers an online training program geared toward educating guideline developers about evidence analysis and guideline development. All participants in guideline development for NASS have completed the live or online training prior to participating in the guideline development program at NASS. Both trainings include a series of readings and exercises, or interactivities, to prepare guideline developers for systematically evaluating literature and developing evidence-based guidelines. The live course takes approximately 8-9 hours to complete and the online course takes approximately 15-30 hours to complete. Participants are awarded CME credit upon completion of the course.

Disclosure of Potential Conflicts of Interest

All participants involved in guideline development have disclosed potential conflicts of interest to their colleagues in accordance with NASS' Disclosure Policy for committee members (https://www.spine.org/Documents/WhoWeAre/DisclosurePolicy.pdf) and their potential conflicts have been documented in this guideline. NASS does not restrict involvement in guidelines based on conflicts as long as members provide full disclosure. Individuals with a conflict relevant to the subject matter were asked to recuse themselves from deliberation. Participants have been asked to update their disclosures regularly throughout the guideline development process.

Levels of Evidence and Grades of Recommendation

NASS has adopted standardized levels of evidence (Appendix B) and grades of recommendation (Appendix C) to assist practitioners in easily understanding the strength of the evidence and recommendations within the guidelines. The levels of evidence range from Level I (high quality randomized controlled trial) to Level V (expert consensus). Grades of recommendation indicate the strength of the recommendations made in the guideline based on the quality of the literature.

Grades of Recommendation:

A: Good evidence (Level I studies with consistent findings) for or against recommending intervention.

B: Fair evidence (Level II or III studies with consistent findings) for or against recommending intervention.

C: Poor quality evidence (Level IV or V studies) for or against recommending intervention.

I: Insufficient or conflicting evidence not allowing a recommendation for or against intervention.

Levels of evidence have very specific criteria and are assigned to studies prior to developing recommendations. Recommendations are then graded based upon the level of evidence. To better understand how levels of evidence inform the grades of recommendation and the standard nomenclature used within the recommendations see Appendix D.

Guideline recommendations are written utilizing a standard language that indicates the strength of the recommendation. "A" recommendations indicate a test or intervention is "recommended"; "B" recommendations "suggest" a test or intervention and "C" recommendations indicate a test or intervention "may be considered" or "is an option." "I" or "Insufficient Evidence" statements clearly indicate that "there is insufficient evidence to make a recommendation for or against" a test or intervention. Work group consensus statements clearly state that "in the absence of reliable evidence, it is the work group's opinion that" a test or intervention may be appropriate.

The levels of evidence and grades of recommendation implemented in this guideline have also been adopted by the Journal of Bone and Joint Surgery, the American Academy of Orthopaedic Surgeons, Clinical Orthopaedics and Related Research, the journal Spine and the Pediatric Orthopaedic Society of North America.

In evaluating studies as to levels of evidence for this guideline, the study design was interpreted as establishing only a potential level of evidence. As an example, a therapeutic study designed as a randomized controlled trial would be considered a potential Level I study. The study would then be further analyzed as to how well the study design was implemented and significant shortcomings in the execution of the study would be used to downgrade the levels of evidence for the study's conclusions. In the example cited previously, reasons to downgrade the results of a potential Level I randomized controlled trial to a Level II study

would include, among other possibilities: an underpowered study (patient sample too small, variance too high), inadequate randomization or masking of the group assignments and lack of validated outcome measures.

In addition, a number of studies were reviewed several times in answering different questions within this guideline. How a given question was asked might influence how a study was evaluated and interpreted as to its level of evidence in answering that particular question. For example, a randomized controlled trial reviewed to evaluate the differences between the outcomes of surgically treated versus untreated patients with lumbar disc herniation with radiculopathy might be a well designed and implemented Level I therapeutic study. This same study, however, might be classified as providing Level II prognostic evidence if the data for the untreated controls were extracted and evaluated prognostically.

Guideline Development Process

Step 1: Identification of Clinical Questions

Trained guideline participants were asked to submit a list of clinical questions that the guideline should address. The proposed questions were compiled into a master list, which was then circulated to each member for review and comment. A conference call was held to review comments and condense and refine the draft clinical question list. The draft clinical question list was then submitted to the NASS Health Policy and Research Councils for review. The councils submitted additional questions that may be useful for health policy or research purposes and approved the master list.

Step 2: Identification of Work Groups

Multidisciplinary teams were assigned to work groups and assigned specific clinical questions to address. Because NASS is comprised of surgical, medical and interventional specialists, it is imperative to the guideline development process that a cross-section of NASS membership is represented on the work group. This also helps to ensure that the potential for inadvertent biases in evaluating the literature and formulating recommendations is minimized.

Step 3: Identification of Search Terms and Parameters

One of the most crucial elements of evidence analysis is the comprehensive literature search. Thorough assessment of the literature is the basis for the review of existing evidence and the formulation of evidence-based recommendations. In order to ensure a thorough literature search, NASS has instituted a Literature Search Protocol (Appendix E) which has been followed to identify literature for evaluation in guideline development. In keeping with the Literature Search Protocol, work group members have identified appropriate search terms and parameters to direct the literature search. Specific search strategies, including search terms, parameters and databases searched, are documented in the technical report that accompanies this guideline.

Step 4: Completion of the Literature Search

Once each work group identified search terms/parameters, the literature search was implemented by a medical/research librarian at InfoNOW at the University of Minnesota, consistent with the Literature Search Protocol. Following these protocols ensures that NASS recommendations (1) are based on a thorough review of relevant literature; (2) are truly based on a uniform, comprehensive search strategy; and (3) represent the current best research evidence available. NASS maintains a search history in Endnote, for future use or reference.

Step 5: Review of Search Results/Identification of Literature to Review

Work group members reviewed all abstracts yielded from the literature search and identified the literature they will review in order to address the clinical questions, in accordance with the Literature Search Protocol. Members have identified the best research evidence available to answer the targeted clinical questions. That is, if Level I, II and or III literature is available to answer specific questions, the work group was not required to review Level IV or V studies.

Step 6: Evidence Analysis

Members have independently developed evidentiary tables summarizing study conclusions, identifying strengths and weaknesses and assigning levels of evidence. In order to systematically control for potential biases, at least two work group members have reviewed each article selected and independently assigned levels of evidence to the literature using the NASS levels of evidence. Any discrepancies in scoring have been addressed by two or more reviewers. Final ratings are completed at a final meeting or webconference of all section workgroup members including the section chair and the guideline chair. The consensus level was then assigned to the article. Multi-diagnosis studies that did not include sub-group anlaysis of isthmic spondylolisthesis patients failed to meet inclusion criteria and were excluded from the guideline.

As a final step in the evidence analysis process, members have identified and documented gaps in the evidence to educate guideline readers about where evidence is lacking and help guide further needed research by NASS and other societies.

Step 7: Formulation of Evidence-Based Recommendations and Incorporation of Expert Consensus

Work groups held web-conferences and face-to-face meetings to discuss the evidence-based answers to the clinical questions, the grades of recommendations and the incorporation of expert consensus. Expert consensus was incorporated only where Level I-IV evidence is insufficient and the work group has deemed that a recommendation is warranted. Transparency in the incorporation of consensus is crucial, and all consensus-based recommendations made in this guideline very clearly indicate that Level I-IV evidence is insufficient to support a recommendation and that the recommendation is based only on expert consensus.

Consensus Development Process

Voting on guideline recommendations was conducted using a modification of the nominal group technique in which each work group member independently and anonymously ranked

a recommendation on a scale ranging from 1 ("extremely inappropriate") to 9 ("extremely appropriate"). Consensus was obtained when at least 80% of work group members ranked the recommendation as 7, 8 or 9. When the 80% threshold was not attained, up to three rounds of discussion and voting were held to resolve disagreements. If disagreements were not resolved after these rounds, no recommendation was adopted.

After the recommendations were established, work group members developed the guideline content, addressing the literature supporting the recommendations.

Step 8: Submission of the Draft Guidelines for Review/ Comment

Guidelines were submitted to the full Evidence-Based Guideline Development Committee and the Research Council for review and comment. Revisions to recommendations were considered for incorporation only when substantiated by a preponderance of appropriate level evidence.

Step 9: Submission for Board Approval

Once any evidence-based revisions were incorporated, the drafts were prepared for NASS Board review and approval. Edits and revisions to recommendations and any other content were considered for incorporation only when substantiated by a preponderance of appropriate level evidence.

Step 10: Submission for Publication and National Guideline Clearinghouse (NGC) Inclusion

Following NASS Board approval, the guidelines have been slated for publication and submitted for inclusion in the National Guidelines Clearinghouse (NGC). No revisions were made after submission to NGC, but comments have been and will be saved for the next iteration.

Step 11: Review and Revision Process

The guideline recommendations will be reviewed every three to five years by an EBM-trained multidisciplinary team and revised as appropriate based on a thorough review and assessment of relevant literature published since the development of this version of the guideline.

Use of Acronyms

Throughout the guideline, readers will see many acronyms with which they may not be familiar. A glossary of acronyms is available in *Appendix A*.

Nomenclature for Medical/Interventional Treatment

Throughout the guideline, readers will see that what has traditionally been referred to as "nonoperative," "nonsurgical" or "conservative" care is now referred to as "medical/interventional care." The term medical/interventional is meant to encompass pharmacological treatment, physical therapy, exercise therapy, manipulative therapy, modalities, various types of external stimulators and injections.

III. Summary of Recommendations

Clinical Question	Guideline Reccomendation *See recommendation sections for supporting text A= Recommended; B=Suggested; C=May be considered; I=Insufficient or Conflicting Evidence
Definition and Natural History	
What is the best working definition of isthmic spondylolisthesis	Isthmic spondylolisthesis is the anterior translation of one lumbar vertebra relative to the next caudal segment as a result of an abnormality in the pars interarticularis. When symptomatic, this causes a variable clinical syndrome of back and/or lower extremity pain, and may include varying degrees of neurologic deficits at or below the level of the injury. **Work Group Consensus Statement**
What is the likelihood that spondylolysis (unilateral and/or bilateral, identified in adolescence or adulthood) will progress to become a symptomatic spondylolisthesis?	Spondylolisthesis occurs in 40% to 66% of patients with bilateral spondylolysis. Spondylolisthesis is unlikely to occur in patients with unilateral spondylolysis. **Grade of Recommendation: B**
Diagnosis and Imaging	
What are the most appropriate physical examination findings consistent with the diagnosis of isthmic spondylolisthesis in adult patients?	There is insufficient evidence to make a recommendation for or against the use of palpation in the physical exam diagnosis of adult patients with isthmic spondylolisthesis. **Grade of Recommendation: I (Insufficient Evidence)** Approximately half of adult patients with symptomatic isthmic spondylolisthesis will have a positive straight leg test on examination. **Grade of Recommendation: B**
In adult patients, what symptoms or clinical presentation are associated with the diagnosis of isthmic spondylolisthesis?	In adult patients with symptomatic isthmic spondylolisthesis, most patients present with low back pain and at least half present radicular lower extremity pain. **Grade of Recommendation: B**
What are the most appropriate diagnostic tests for adult isthmic spondylolisthesis?	There is a relative paucity of high quality studies on imaging in adult patients with isthmic spondylolisthesis. It is the opinion of the work group that in adult patients with history and physical examination findings consistent with isthmic spondylolisthesis, standing plain radiographs, with or without oblique views or dynamic radiographs, be considered as the most appropriate, noninvasive test to confirm the presence of isthmic spondylolisthesis. In the absence of a reliable diagnosis on plain radiographs, CT scan is considered the most reliable diagnostic test to diagnose a defect of the pars interarticularis. In adult patients with radiculopathy, MRI should be considered. **Work Group Consensus Statement** MRI is suggested to identify neuroforaminal stenosis in adult patients with isthmic spondylolisthesis. **Grade of Recommendation: B** There is insufficient evidence to make a recommendation for or against the use of MRI to differentiate isthmic versus degenerative spondylolisthesis in adult patients. **Grade of Recommendation: I (Insufficient Evidence)** There is insufficient evidence to make a recommendation for or against the use of discography to evaluate adult patients with isthmic spondylolisthesis. **Grade of Recommendation: I (Insufficient Evidence)** CT may be considered as an option to diagnose isthmic spondylolisthesis in adult patients. **Grade of Recommendation: C** There is insufficient evidence to make a recommendation for or against the use of SPECT in evaluating isthmic spondylolisthesis in adult patients. **Grade of Recommendation: I (Insufficient Evidence)**

Clinical Question	Guideline Reccomendation **See recommendation sections for supporting text* *A= Recommended; B=Suggested; C=May be considered; I=Insufficient or Conflicting Evidence*
In adult patients, what is the relationship between the radiological grade of isthmic spondylolisthesis and expected clinical presentation?	A systematic review of the literature yielded no studies to adequately address this question.
How frequently do adult patients with isthmic spondylolisthesis have abnormal findings of their sagittal spinopelvic alignment, sacral alignment and spinopelvic parameters?	Adult patients with a diagnosis of isthmic spondylolisthesis have a higher pelvic incidence, sacral slope, pelvic tilt and lumbar lordosis compared to patients without isthmic spondylolisthesis. **Grade of Recommendation: B**
Outcome Measures for Medical/Interventional and Surgical Treatment	
What are the appropriate outcome measures for the treatment of adult isthmic spondylolisthesis?	For information on outcome measures for spinal disorders, the North American Spine Society has a publication entitled *Compendium of Outcome Instruments for Assessment and Research of Spinal Disorders*. To purchase a copy of the Compendium, visit https://webportal.spine.org/Purchase/ProductDetail.aspx?Product_code=68cdd1f4-c4ac-db11-95b2-001143edb1c1. For additional information about the Compendium, please contact the NASS Research Department at nassresearch@spine.org.
Medical and Interventional Treatment	
What is the role of pharmacological treatment in the management of isthmic spondylolisthesis?	There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.
What is the role of manipulation in the treatment of isthmic spondylolisthesis?	There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.
What is the role of steroid injections for the treatment of isthmic spondylolisthesis?	There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.
What is the role of ancillary treatments such as bracing, traction, electrical stimulation and transcutaneous electrical stimulation (TENS) in the treatment of isthmic spondylolisthesis?	There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.
What is the role of physical therapy/exercise in the treatment of isthmic spondylolisthesis?	There is insufficient evidence to make a recommendation for or against the use of physical therapy/exercise for the treatment of isthmic spondylolisthesis. **Grade of Recommendation: I (Insufficient Evidence)**

Clinical Question	Guideline Reccomendation *See recommendation sections for supporting text A= Recommended; B=Suggested; C=May be considered; I=Insufficient or Conflicting Evidence
Does the degree of radiological grade, sagittal spinopelvic alignment, sacral and spinopelvic parameters, or the presence of dynamic instability in patients with isthmic spondylolisthesis affect the outcomes of patients treated with medical or interventional treatment?	There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.
What is the long-term result of medical/interventional management of isthmic spondylolisthesis?	There is insufficient evidence to make a recommendation for or against the use of medical/interventional treatment for the long-term management of patients with isthmic spondylolisthesis. **Grade of Recommendation: I (Insufficient Evidence)**
Surgical Treatment	
In adult patients, is surgical treatment more effective than medical/interventional treatment alone for the treatment of isthmic spondylolisthesis?	There is insufficient evidence to make a recommendation for or against the efficacy of surgical treatment as compared to medical/interventional alone for the management of adult patients with isthmic spondylolisthesis. **Grade of Recommendation: I (Insufficient Evidence)**
Does the addition of lumbar fusion, with or without instrumentation, to surgical decompression improve surgical outcomes in the treatment of adult patients with isthmic spondylolisthesis compared to treatment by decompression alone?	There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.
Does the addition of instrumentation to decompression and fusion for adult patients with isthmic spondylolisthesis improve surgical outcomes compared with decompression and fusion alone?	In patients with low-grade isthmic spondylolisthesis, the addition of instrumentation may not improve outcomes in the setting of posterolateral fusion, with or without decompression. **Grade of Recommendation: B**
How do outcomes of decompression with posterolateral fusion compare with those for 360° fusion in the treatment of adult patients with isthmic spondylolisthesis?	Posterolateral fusion and 360° fusion surgeries are recommended to improve the clinical outcomes in adult patients with low grade isthmic spondylolisthesis. **Grade of Recommendation: A** 360° fusion is recommended to provide higher radiographic fusion rates compared to posterolateral fusion in adult patients with low grade isthmic spondylolisthesis. **Grade of Recommendation: A** There is conflicting evidence whether 360° fusion provides better clinical outcomes than posterolateral fusion alone. **Grade of Recommendation: I (Insufficient/Conflicting Evidence)**

Clinical Question	Guideline Reccomendation **See recommendation sections for supporting text* *A= Recommended; B=Suggested; C=May be considered; I=Insufficient or Conflicting Evidence*
Does reduction with fusion result in better outcomes than fusion in situ in adult patients with isthmic spondylolisthesis?	There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.
What is the role of stand-alone interbody fusion, for the purpose of indirect decompression, in the treatment of adult patients with isthmic spondylolisthesis?	Anterior lumbar interbody fusion (ALIF) may be considered as an option to indirectly decompress foraminal stenosis in adult patients with low grade isthmic spondylolisthesis. **Grade of Recommendation: C**
How do outcomes from minimally invasive spinal surgery (for decompression and/or fusion) for the management of adult patients with isthmic spondylolisthesis compare with traditional/open techniques?	In adult patients undergoing ALIF, supplemental posterior percutaneous pedicle screws lead to shorter hospital stays, less operation room time and less blood loss compared to open posterior instrumentation. **Grade of Recommendation: B** There is conflicting evidence whether in adult patients undergoing ALIF, supplemental posterior percutaneous pedicle screws lead to comparable clinical outcomes to those undergoing open posterior instrumentation. **Grade of Recommendation: I (Insufficient/Conflicting Evidence)**
How do outcomes of dynamic stabilization compare with fusion for the treatment of isthmic spondylolisthesis in adult patients?	There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.
Does the degree of radiological grade, sagittal spinopelvic alignment, sacral and spinopelvic parameters, or the presence of dynamic instability in adult patients with isthmic spondylolisthesis affect the outcomes of patients treated with surgery?	There is insufficient evidence to make a recommendation regarding the degree of radiological grade, sagittal spinopelvic alignment, sacral and spinopelvic parameters, or the presence of dynamic instability on the outcomes of adult patients undergoing surgical treatment for isthmic spondylolisthesis. **Grade of Recommendation: I (Insufficient Evidence)**
Does the addition of fusion levels (cephalad, caudal or iliac) in the setting of a high grade isthmic spondylolisthesis in adult patients improve outcomes?	There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.

Clinical Question	Guideline Reccomendation *See recommendation sections for supporting text A= Recommended; B=Suggested; C=May be considered; I=Insufficient or Conflicting Evidence
What is the long-term result (four+ years) of surgical management of adult patients with isthmic spondylolisthesis?	In adult patients undergoing surgical treatment for isthmic spondylolisthesis, fusion is suggested to provide long term clinical improvements. **Grade of Recommendation: B** There is insufficient evidence to indicate that fusion leads to improved long term outcomes as compared with a directed exercise program. **Grade of Recommendation: I (Insufficient Evidence)** There is insufficient evidence to recommend one surgical fusion technique over another to improve long term outcomes in adult patients undergoing surgical treatment for isthmic spondylolisthesis. **Grade of Recommendation: I (Insufficient Evidence)** There is insufficient evidence to determine the clinical significance of adjacent segment degeneration on the long term outcomes of fusion. **Grade of Recommendation: I (Insufficient Evidence)**
Are the results of surgical management for adult patients with isthmic spondylolisthesis affected by the presence of scoliosis or concurrent deformity?	There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.
Which prognostic factors have been associated with good or poor outcomes in the surgical management of adult patients with isthmic spondylolisthesis?	There is insufficient evidence to make a recommendation regarding which prognostic factors have been associated with good or poor outcomes. **Grade of Recommendation: I (Insufficient Evidence)**
Value of Spine Care	
Which medical or interventional treatment method of isthmic spondylolisthesis is the most cost-effective?	There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.
Is the surgical treatment of isthmic spondylolisthesis cost-effective compared to the medical and interventional therapies?	There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.
Which surgical treatment method of isthmic spondylolisthesis is the most cost-effective?	There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.

IV. Definition and Incidence of Adult Isthmic Spondylolisthesis

What is the best working definition of isthmic spondylolisthesis?

Isthmic spondylolisthesis is the anterior translation of one lumbar vertebra relative to the next caudal segment as a result of an abnormality in the pars interarticularis. When symptomatic, this causes a variable clinical syndrome of back and/or lower extremity pain, and may include varying degrees of neurologic deficits at or below the level of the injury.

Work Group Consensus Statement

What is incidence of radiographic isthmic spondylolisthesis in adults?

In the general adult population, the incidence of isthmic spondylolisthesis ranges between 3.7% and 8%.

In 1954, Fredrickson[1] et al enrolled 500 first grade children to evaluate the progression of the natural history of spondyloysis and spondylolisthesis to adulthood. At enrollment, supine anteroposterior, lateral and oblique roentgenograms of the lumbar spine were taken for each child. Twenty-two patients, or 4.4%, were determined to have a lytic defect of the pars interarticularis. Repeat roentgenograms were taken at ages 10-12, 15-16 and 18 years or older. At age 18 years or older, films were available for 170 subjects (34%). By age 18 years or older, the rate of lytic defects to the pars interarticularis had risen to 6%. In 1999, at 45-year follow-up, Beutler et al[2] evaluated MRI and radiograph data for 30 patients with unilateral or bilateral pars defects. Of the 8 patients with unilateral defects, none showed progression to spondylolisthesis. Of the 22 patients with bilateral pars defects, 18 (82%) developed spondylolisthesis.

Kalichman et al[3] conducted a cross-sectional study to determine prevalance rates of spondylolysis, isthmic spondylolisthesis and degenerative spondylolithesis in patients who were originally enrolled in the Framingham Heart Study to assess aortic calcification. As part of their ancillary project to assess the aforementioned spinal conditions, 188 pariticipants were consecutively enrolled to assess the association between CT scan observed characterstics of the lumbosacral spine and low back pain. Spondylolisthesis was identified in 39 subjects (20.7%) and the prevalance of isthmic spondylolisthesis was found to be 8.2% in this study population. The highest prevalence of isthmic spondylolisthesis was found at the L5-S1 level.

Sakai et al[4] investigated the true incidene of lumbar spondylolysis in the Japanese general population. Investigators reviewed the CT scans of 2,000 subjects who had undergone abdominal and pelvic CT on a single multidetector CT scanner for reasons unrelated to low back pain. Scans were reviewed for spondylolysis, isthmic spondylolisthesis and spina bifida occulta. Of the 124 vertebrae with spondylolysis, 75 (60.5%) showed grade I or II spondylolisthesis, whereas none showed high grade. Spondylolisthesis was found in 74.5% of the vertebrae with bilateral spondylolysis and in 7.7% of the vertebrae with unilateral spondylolysis. Isthmic spondylolisthesis was found in 3.7% of study patients.

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V. Recommendations for the Diagnosis and Treatment of Adult Isthmic Spondylolisthesis

A. Natural History

What is the likelihood that spondylolysis (unilateral and/or bilateral, identified in adolescence or adulthood) will progress to become a symptomatic spondylolisthesis?

Spondylolisthesis occurs in 40% to 66% of patients with bilateral spondylolysis. Spondylolisthesis is unlikely to occur in patients with unilateral spondylolysis.

Grade of Recommendation: B

In 1954, Fredrickson[1] et al enrolled 500 first grade children to evaluate the progression of the natural history of spondyloysis and spondylolisthesis to adulthood. At enrollment, supine anteroposterior, lateral and oblique roentgenograms of the lumbar spine were taken for each child. Spondylolysis and isthmic spondylolisthesis were diagnosed according to the American Academy of Orthopeadic Surgeons' A Glossary on Spinal Terminology. Twenty-two patients, or 4.4%, were determined to have a unilateral or bilateral lytic defect of the pars interarticularis. Repeat roentgenograms were taken at ages 10-12, 15-16 and 18 years or older. At age 18 years or older, films were available for 170 subjects (34%). Between the ages of 12 to 25, eight additional patients developed unilateral or bilateral pars interarticular defects of the lumbar spine, increasing the rate to 6%. Of the 30 total patients with the defect, 22 had bilateral L5 pars defects and 8 had unilateral defects.

In 1999, at 45-year follow-up of the above patients, Beutler et al[2] evaluated MRI and radiograph data for the 30 patients with unilateral or bilateral pars defects. Of the 8 patients with unilateral defects, none showed progression to spondylolisthesis. Of the 22 patients with bilateral pars defects, 18 (82%) developed spondylolisthesis. Slip at the lumbosacral level was seen in 10 of 16 bilateral L5 defects at the initial screening. The average slip for patients with initial spondylolisthesis was 11% in 1954 and progressed to an average of 18% in 1999. There were 10 patients with early segmental laxity. These patients presented with bilateral pars defects and initial spondylolisthesis at 6 years old. Initial slip in this group ranged from 7-17%. Over the next 45 years, 5 of these patients had no slip progression and the other 5 patients had progression of slip from 7-20% of the initial slip. Three patients, who initially presented with bilateral pars defects, but no documented spondylolisthesis at 6 years old, had late segmental laxity at 45 years follow-up. Slip progression was found to be greatest early in life regardless of whether the patient had early or late defects or segmental laxity. The average slip progression was 7% in the first decade for those who did progress, 4% in the second and third decades and 2% in the fourth decade of follow-up. The Beautler study offers Level I prognostic evidence that the slippage progression is more rapid at a younger age and the progression of spondylolisthesis tends to slow with each decade.

Fuji et al[3] retrospectively reviewed clinical and radiographic data for 134 adolescent patients who had been treated conservatively for lumbar spondylolysis to investigate prognostic variables for successful bony union. Patients with ages ranging from 7 to 17 years were evaluated by CT scan and followed for one to 9 years (average 3.4 years). Pars defects at L4 were present in 20 patients and at L5 in 114 patients. Bilateral defects were observed in 105 patients and unilateral defects were observed in 29 patients. For the purposes of reviewing CT images, pars defects were classified into early, progressive or terminal stages and the maturity of the lumbar spine was classified into cartilaginous, apophyseal and epiphyseal stages. A total of 52 of 134 (39%) patients were initially diagnosed with or developed spondylolisthesis during the study period. Results indicated that pars defects at L4 achieving union were significantly higher than that for defects at L5 ($p<0.0001$). Defects without contralateral defects or with contralateral early stage defects achieved union at significantly higher rates than those with contralateral progressive or terminal stage defects ($p < 0.001$). Six of 13 defects without contralateral defects and 8 of 15 defects with contralateral early or progressive stage defects showed union, but the 3 early stage defects with contralateral terminal stage defects at L5 did not. Union occurred less often in the presence of spondylolisthesis greater than 5% at initial presentation compared to those without spondylolisthesis ($p<0.01$). The percentage of vertebra

without spondylolisthesis at the time of follow-up increased in relation to skeletal age at initial presentation; hence, the risk of development of or increase in the degree of spondylolisthesis was greater in the immature spine. Eight cases of nonprogressive spondylolisthesis were seen at the cartilaginous stage, 15 at the apophyseal stage and 6 at the epiphyseal stage. Nine patients developed spondylolisthesis at the cartilaginous stage, 10 at the apophyseal stage and none at the epiphyseal stage. One patient experienced progression of spondylolisthesis at the cartilaginous stage, 3 at the apophyseal stage and none at the epiphyseal stage. This study offers Level II prognostic evidence that the progression of spondylolysis to spondylolisthesis is more common in the immature spine.

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B. Diagnosis and Imaging

What are the most appropriate physical examination findings consistent with the diagnosis of isthmic spondylolisthesis in adult patients?

There is insufficient evidence to make a recommendation for or against the use of palpation in the physical exam diagnosis of adult patients with isthmic spondylolisthesis.

Grade of Recommendation: I (Insufficient Evidence)

Collaer et al[1] assessed the diagnostic utility of lumbar spinous palpation in detecting isthmic spondylolisthesis. Consecutive patients were enrolled in the study if they had low back pain and/or radiculopathy, were aged 16 years or older, had no history of thoracic, lumbar or sacral surgery, and had a same-day standing lateral lumbar radiograph, which was evaluated according to the Meyerding method for grading. Three physical therapists carried out the lumbar spinous process palpation to determine the inter-rater reliability of this test. The palpation procedure consisted of applying and maintaining firm contact on the lumbosacral spinous process while sliding the examining fingertips from the upper lumbar region to the sacrum. A total of 44 patients, including 21 men and 23 women with an average age of 40 years old, were included in the analysis. Isthmic spondylolisthesis was found in 11.3% of patients based on radiograph findings. Validity of the palpation test was confirmed by comparing palpation findings to the radiograph findings. Results suggested that the sensitivity of identifying an isthmic spondylolisthesis by way of step palpation was 60% (95% CI: 72.6-95.7) and the specificity was 87.2% (95% CI: 72.6-95.7). The post-test probability for a spondylolisthesis with a positive palpation test result was 32% and 5% with a negative test result based on the established prevalence of isthmic spondylolisthesis in the patient group. In critique of this study, the sample size was small, but the work group did not find this sufficient reason to downgrade the study. This study provides Level II diagnostic evidence that palpation is not an effective test to rule out isthmic spondylolisthesis. However, the high specificity suggests that there is a high likelihood for presence of the condition in the event that a step off is detected.

Approximately half of adult patients with symptomatic isthmic spondylolisthesis will have a positive straight leg test on examination.

Grade of Recommendation: B

Markwalder et al[2] conducted a prospective study to analyze the clinical and radiological presentation in relation to the intra-operative findings and surgical results of patients with isthmic spondylolisthesis. A total of 72 patients were included in the study, including 34 females and 38 males with an average age of 40 years old. Conventional x-rays of the lumbar spine and oblique views were taken on all patients in order to characterize the spondylolytic gap in the isthmus. Isthmic spondylolisthesis was located at the L4/L5 in 14% of patients and L5/S1 in 86% of patients. According to Meyerding classification, isthmic spondylolisthesis was Grade I in 65% of patients, Grade II in 33%, and Grade III in 2% of patients. For the analysis, the patients were separated into two groups; group 1 consisted of 35 patients in whom back pain and pain in the lower limb(s) was present for a mean of 10 years, and group 2 consisted of 37 patients in whom isthmic spondylolisthesis became symptomatic within a shorter period of time (mean 3 years). During assessment, patients usually complained of low back pain, which was restricted or was diffuse, often associated with burning sensations. For both groups, radiating pain in the lower limb(s) was radicular, pseudoradicular or combined in 53%, 21%, and 14%, respectively. Neurological examination showed that 40% of patients in Group 1 and 70% in Group 2 had radicular syptoms. Radicular symptoms were predominant (64%) in patients with Grade I isthmic spondylolisthesis. The L4/L5 level was more frequently associated with radicular signs compared to the L5/S1 level (70% vs 50%). Intra-operative findings revealed that root compression due to spondylolysis tissue, bony spurs or Gill nodes was found in half of all patients, including in 22 patients in Group 1 and 16 patients in Group 2. Root compression was mostly present in comparable amounts on both sides, although radicular symptoms were unilateral (55%), absent (13%) combined with pseudoradicular symptoms (14%) or present with pseudoradicular signs alone (19%). Positive straight leg raising tests were found in 49% of patients, including positive results in 23% of patients in group 1 and 73% of patients in Group 2. This study provides level II diagnostic evidence that a positive straight leg test may be consistent with radiculitis resulting from isthmic spondylolisthesis, though it is not specific in relation to the cause of radiculitis.

Rijk et al[3] evaluated the results of patients treated with chemonucleolysis by comparing MRI findings before and after treatment. Fifteen patients, including 6 women and 9 men with a mean age of 35, were included in the analysis. According to Mey-

erding classification, 13 patients had a Grade I slip and 2 patients had a Grade II slip. The mean slip was 20% (range 10%-38%). All but one patient had low back pain for an average of 51 months and all had unilateral sciatica for an average of 33 months. On physical examination, 11 patients had restricted mobility of the lumbar spine, 8 patients had positive results for the straight leg raising test, 3 patients had positive results for the crossed straight leg raising test, and one patient had a weakness of the extensor halluces longus muscle. In critique, the sample size for this study is small and investigators did not utilize statistical methods to analyze results. Due to these reasons, the work group decided to downgrade the level of evidence. This potential level II study provides level III diagnostic evidence that a positive straight leg test was present in about half of the patients and can be consistent with a diagnosis of radiculopathy associated with isthmic spondylolisthesis.

Future Directions For Research

The work group recommends the undertaking of prospective studies evaluating specific clinical physical examination findings that may be consistent with the diagnosis of isthmic spondylolisthesis.

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In adult patients, what symptoms or clinical presentation are associated with the diagnosis of isthmic spondylolisthesis?

In adult patients with symptomatic isthmic spondylolisthesis, most patients present with low back pain and at least half present radicular lower extremity pain.

Grade of Recommendation: B

Markwalder et al[1] conducted a prospective study to analyze the clinical and radiological presentation in relation to the intra-operative findings and surgical results of patients with isthmic spondylolisthesis. A total of 72 patients were included in the study, including 34 females and 38 males with an average age of 40 years old. Isthmic spondylolisthesis was located at the L4/L5 in 14% of patients and L5/S1 in 86% of patients. According to Meyerding classification, isthmic spondylolisthesis was Grade I in 65%, Grade II in 33%, and Grade III in 2% of patients. For the analysis, the patients were separated in two groups; Group 1 consisted of 35 patients in whom back pain and pain in the lower limb(s) was present for a mean of 10 years and Group 2 consisted of 37 patients in whom isthmic spondylolisthesis became symptomatic within a mean of 3 years. During assessment, patients usually complained of low back pain, which was restricted or was diffuse, often associated with burning sensations. For both groups, radiating pain in the lower limb(s) was of the radicular, pseudoradicular and combined type in 53%, 21% and 14%, respectively. Neurological examination showed that 40% of patients in Group 1 and 70% in Group 2 had radicular syptoms. Radicular symptoms were predominant (64%) in patients with Grade I isthmic spondylolisthesis. The L4/L5 level was more frequently associated with radicular signs compared to the L5/S1 level (70% vs 50%). Intra-operative findings revealed that root compression due to spondylotic tissue, bony spurs or Gill nodes was found in 36 patients. Root compression was mostly present in comparable amounts on both sides although radicular symptoms were unilateral (55%), absent (13%) combined with pseu-

doradicular symptoms (14%) or present with pseudoradicular signs alone (19%). This study provides Level II prognostic evidence that patients with isthmic spondylolisthesis present most often with back and leg pain.

Moller et al[2] conducted a retrospective case-control study to determine whether there are any specific symptoms, signs and functional disability associated with a diagnosis of adult isthmic spondylolisthesis. A total of 111 isthmic spondylolisthesis patients were included in this analysis, including 54 women and 57 men with a mean age of 39. Standardized physical and neurologic exams were conducted on all patients. Functional disability was measured by the Disability Rating Index (DRI), which is composed of 12 functional visual analog scales (VAS). Pain was quantified on a scale of 0 to 100 for intolerable pain and by pain drawings. Isthmic spondylolisthesis patient findings were compared to the records of 39 patients with nonspecific back pain. The majority of isthmic spondylolisthesis patients had a level of slippage at L5 (n=94). Spondylolisthesis was radiographically verified and patients with sciatica were examined with MRI or myelography. Sixty-two percent of patients had low back pain and sciatica, 31% had low back pain only and 7% had sciatica only. No symptom free periods were reported by 92% patients and sleeping disturbances, back stiffness, and worsening of pain when walking and sitting were reported by 80% of patients. This study provides Level III prognostic evidence that patients with isthmic spondylolisthesis present with low back pain with or without sciatica.

Future Directions For Research

The work group recommends the undertaking of population-based observational studies, such as multi-center registry data studies, examining the clinical characteristics associated with isthmic spondylolisthesis.

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What are the most appropriate diagnostic tests for adult isthmic spondylolisthesis?

There is a relative paucity of high quality studies on imaging in adult patients with isthmic spondylolisthesis. It is the opinion of the work group that in adult patients with history and physical examination findings consistent with isthmic spondylolisthesis, standing plain radiographs, with or without oblique views or dynamic radiographs, be considered as the most appropriate, noninvasive test to confirm the presence of isthmic spondylolisthesis. In the absence of a reliable diagnosis on plain radiographs, CT scan is considered the most reliable diagnostic test to diagnose a defect of the pars interarticularis. In adult patients with radiculopathy, MRI should be considered.

Work Group Consensus Statement

MRI is suggested to identify neuroforaminal stenosis in adult patients with isthmic spondylolisthesis.

Grade of Recommendation: B

There is insufficient evidence to make a recommendation for or against the use of MRI to differentiate isthmic versus degenerative spondylolisthesis in adult patients.

Grade of Recommendation: I (Insufficient Evidence)

Annertz et al[1] conducted a radiographic study to evaluate the usefulness of MRI and myelogram in adult patients with isthmic spondylolisthesis and sciatica. Seventeen patients, including 9 men and 8 women with a mean age of 41, underwent conventional radiography and MRI of the lumbar spine. Thirteen patients also received myelogram. Vertebral displacement, reactive changes within the vertebrae, intervertebral disc, and thecal sac were studied. On conventional radiography, reduction of the intervertebral disc space was a constant finding at the level of olisthesis. In 9 of the 17 patients, it was estimated to exceed 50%. The vertebral slipping varied from 5 to 25 mm. In 9 patients, there was no evident bone reaction. There was a correlation between the degree of vertebral displacement and occurrence of reactive bone changes. In 5 of the 13 patients in whom myelography was performed, waist-like deformation of the dural sac and bilateral shortening of the root sleeves at the level of the spondylolisthesis was seen. In 4 patients, the myelogram was normal except for the spondylolisthesis, and in several of the pathological cases, the influence on the nerve roots seen on myelography was minimal despite severe olisthesis. On MRI examination, reactive changes within one or both vertebrae adjacent to the olisthesis were seen in eight cases. The degree of disc space reduction correlated well with radiograph readings. At the level of the pars defect, 2 patients had a complete disc space reduction without any protrusion. In 14 patients, a posterolateral bulge extending towards the foramina was found. At the level above the pars defect, four patients had a symmetric disc protrusion not exceeding 5 mm. All foramina had an altered shape with the long axis horizontal instead of vertical at the affected level bilaterally. In addition, the following was found in the 33 foramina evaluated: normal nerve (n=8); compressed nerve (n=16); disappearance of fat and nerve not possible to identify (n=9). The authors suggest that since the site of nerve compression was often peripheral to the root sleeves, myelography was of limited value. In critique, the study's sample size was small and it is unclear whether the patients were enrolled consecutively. This study offers Level III diagnostic evidence that MR imaging provides superior imaging of the nerve root compared to myelography. It should be noted that post myleogram CT was not performed in any study patients.

Jinkins et al[2] conducted a prospective radiographic analysis using MRI to examine the relationship between evidence of impingement of a nerve root and clinical evidence of radiculopathy in 15 consecutive patients with isthmic spondylolisthesis. The analysis was conducted by a neuroradiologist blinded to the patient's clinical history. Parasagittal T1-weighted images were reviewed to identify whether the nerve root was impinged within the neural foramen at the level of spondylolisthesis. Impingement was considered to be present if MRI demonstrated circumferential or pincer-like entrapment of the nerve root and obliteration of the perineural fat. A diagnosis of radiculopathy was based on electromyographic data or the presence of pain that radiated into the lower extremity in a dermatomal pattern. The neuroradiologists found that 17 out of 30 nerve roots appeared

to be impinged on at the level of the spondylolisthesis. Thirteen out of these 17 nerve roots were associated with clinical evidence or radiculopathy on the side of root impingements. Nine patients had symptoms of a unilateral radiculopathy of the fifth lumbar nerve root, 2 had pain that radiated into both lower extremities, which suggested bilateral radiculopathy of the fifth lumbar nerve root, and 4 patients had diffuse low-back pain, but no signs of radiculopathy. Results suggested that the association between the clinical findings of radiculopathy and the evidence of impingement on MRI was highly significant ($p<0.001$). In critique, this study had a small sample size and a narrow subgroup of patients with either Grade I or II isthmic spondylolisthesis. Due to these reasons, this potential Level II study has been downgraded and provides Level III diagnostic evidence that MRI is useful to correlate clinical radiculopathy to neuroforaminal stenosis in patients with isthmic spondylolisthesis.

Ulmer et al[3] evaluated MR images to determine whether a visually apparent increase in the anteroposterior diameter of the spinal canal (wide canal sign) is a reliable indicator in differentiating degenerative from isthmic spondylolisthesis on midline sagittal images. The investigators hypothesized that the wide canal sign would be present only in patients with isthmic spondylolisthesis. To establish the normal range of sagittal canal diameters at the various lumbar levels, the investigators reviewed the midline sagittal MR images of 100 control patients without spondylolysis or spondylolisthesis. These images were compared to 53 patients with a diagnosis of either isthmic (n=35) or degenerative (n=18) spondylolisthesis, which were confirmed by conventional radiography and/or CT. The sagittal canal ratio (SCR) for each level was calculated and defined as the maximum anteroposterior diameter of the canal at that level divided by the diameter of the canal at L1. Per analysis of the control MR images, an SCR of 1.25 or more was considered to represent abnormal widening of the spinal canal, and the wide canal sign was considered to be present whenever the SCR was 1.25 or greater at any level. Results of the evaluation by two blinded neuroradiologists indicated that the SCR did not exceed 1.25 in the 100 patients without spondylolisthesis and 18 patients with degenerative spondylolisthesis. An SCR of 1.25 or higher was found in 97% (34/35) of the isthmic spondylolisthesis patients. The investigators conclude that the presence of the wide canal sign is a useful indicator in the diagnosis of isthmic spondylolisthesis. This study provides Level II diagnostic evidence that on MR imaging, the wide canal sign is a reliable predictor of the presence of defects of the pars interarticularis at the level of the spondylolisthesis.

There is insufficient evidence to make a recommendation for or against the use of discography to evaluate adult patients with isthmic spondylolisthesis.

Grade of Recommendation: I (Insufficient Evidence)

Cohen et al[4] conducted a preoperative evaluation of patients with isthmic spondylolisthesis to determine the usefulness of discography in evaluating the disc adjacent to the spondylolisthesis. Fourteen consecutive patients with Grade I or II spondylolisthesis underwent 4-level provocative discography using fluoroscopy. The L2-L3, L3-L4, L4-L5, and L5-S1 were studied. All patients were subsequently treated with AP spinal fusion. A level was considered positive only if provocation of high-intensity low back pain occurred with disc pressurization. Half of the patients (7/14) had a concordant pain response at a level adjacent to the spondylolisthesis and 2 patients had no pain at the slip level. The level of the spondylolisthesis was positive in 12 out of 14 patients. No patients had provocation of symptoms at the L2-L3 and L3-L4 levels. Of the 11 patients with L5-S1 slips, 4 had a single positive level at L5-S1, one had a positive level limited to L4-L5, and 6 had positive levels at L4-L5 and L5-S1. The investigators suggested that the disc adjacent to an isthmic slip is predisposed to symptomatic degeneration in patients with low-grade isthmic spondylolisthesis and discography may be helpful in selecting fusion levels in these patients. In critique, this study contains a very small sample size and does not contain statistical methods to analyze findings. Due to these reasons, this potential Level III study has been downgraded to Level IV. This study provides Level IV diagnostic evidence that spondylolisthesis may or may not be the sole cause of back pain as diagnosed by discography in workers compensation patients planned for surgery.

CT may be considered as an option to diagnose isthmic spondylolisthesis in adult patients.

Grade of Recommendation: C

Kalichman et al[5] conducted a community-based, cross-sectional study to determine the prevalence of spondylolysis, isthmic and degenerative spondylolisthesis and the relationship of these conditions with low back pain. The analysis was an ancillary project to the Framingham Heart study, which included 3,529 total patients aged 40 to 80 years old. All of the patients underwent multi-detector CT imaging to assess aortic calcification, and 188 patients were enrolled in this study to assess radiographic features associated with low back pain. In addition, these patients were asked to complete the modified Nordic Low Back Questionnaire. CT scans were reviewed by blinded musculoskeletal radiologists and multiple logistic regression analysis was used to examine the association between low back pain and spondylolysis and spondylolisthesis. The results suggested that there was no significant association found between the occurrence of low back pain and spondylolysis, isthmic and degenerative spondylolisthesis. In this sample, 15 (8.2%) patients had isthmic spondylolisthesis. The highest prevalence of isthmic spondylolisthesis was found at the L5-S1 level. In critique, this study was not constructed with the intention to validate diagnostic criteria. This study provides Level IV diagnostic evidence that CT scans can be used to diagnose isthmic spondylolisthesis.

Sakai et al[6] conducted a community-based, cross-sectional analysis to investigate the true incidence of spondylolysis in the general population in Japan. The CT scans of 2,000 Japanese subjects, who had undergone abdominal and pelvic CT for reasons unrelated to low back pain, were reviewed for signs of spondylolysis, isthmic spondylolisthesis, and spine bifida occulta. All images were reviewed by a certified spine surgeon and certified

radiologist and the diagnosis was achieved by consensus. Of the 2,000 subjects, 117 patients (5.9%), including 124 vertebrae, were found to have lumbar spondylolysis. Of the 124 vertebrae with spondylolysis, 75 (60.5%) showed Grade I or II spondylolisthesis, whereas none showed high grade. Spondylolisthesis was found in 74.5% of the vertebrae with bilateral spondylolysis and in 7.7% of the vertebrae with unilateral spondylolysis. In critique, this study does not include a gold standard and was not constructed with the intention to validate diagnostic criteria. This study provides Level IV diagnostic evidence that isthmic spondylolisthesis may be identified on abdominal or pelvic CT.

There is insufficient evidence to make a recommendation for or against the use of SPECT in evaluating isthmic spondylolisthesis in adult patients.

Grade of Recommendation: I (Insufficient Evidence)

Lusins et al[7] evaluated 50 cases of spondylolysis using a lumbar SPECT scan. Initial diagnosis was confirmed through CT scan and patients were divided into 3 groups for evaluation. Group 1 had only spondylolysis (n=16), Group 2 had spondyloysis and Grade I spondylolisthesis (n=18) and Group 3 had spondylolysis and Grade II or greater spondylolisthesis (n=16). Spondylolysis was confirmed when disruption of the posterior arch, in the area of the pars interarticularis, was present. The degree of spondylolisthesis was determined by taking measurements on the lateral roentogenogram or sagittal MRI of the lumbar spine. Grade I spondylolisthesis was defined as a slippage less than 30%, Grade II was 30-50% and Grade III was defined as a slippage of 51% or more. Results of SPECT scanning indicated that in Group 1, 4 patients had increased activity on the SPECT scan in the area of the pars interarticularis and twelve patients had negative SPECT scans. In Group 2, 4 patients had positive SPECT scans and increased activity in the posterior and anterior arch. Fourteen patients had negative results. In Group 3, 14 out of 16 patients had positive SPECT scans. The increased activity was more intense anteriorly, rather than being concentrated in either the pars or posterior neural arch. The investigators suggest that SPECT may be useful in evaluating the mechanical stresses occurring at any given level and time at the site of the spondylolysis. This study provides Level III diagnostic evidence that while SPECT scanning may confirm the location of the physiologic stress, it is not helpful in the diagnosis of isthmic spondylolisthesis.

Future Directions for Research

The work group identified the following potential studies that would generate meaningful evidence to assist in identifying the most useful diagnostic methods and tests for isthmic spondylolisthesis:

Recommendation #1:

Prospective study comparing the accuracy of supine to standing x-rays in diagnosing isthmic spondylolisthesis.

Recommendation #2:

An additional prospective study evaulating the canal diameter to differentiate the diagnosis of isthmic versus degenerative spondylolisthesis.

Recommendation #3:

Prospective study comparing CT myleography to MRI in diagnosing isthmic spondylolisthesis.

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In adult patients, what is the relationship between the radiological grade of isthmic spondylolisthesis and expected clinical presentation?

A systematic review of the literature yielded no studies to adequately address this question.

Future Directions For Research

The work group identified the following potential studies that would generate meaningful evidence to assist in the understanding of the relationship between radiological grade of isthmic spondylolisthesis and clinical presentation:

Recommendation #1:

Observational study examining the relationship between the presence and radiological grade of isthmic spondylolisthesis and expected clinical presentation.

Recommendation #2:

Population-based observational studies, such as multi-center registry data studies, examining the relationship between the presence and radiological grade of isthmic spondylolisthesis and expected clinical presentation.

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How frequently do adult patients with isthmic spondylolisthesis have abnormal findings of their sagittal spinopelvic alignment, sacral alignment and spinopelvic parameters?

Adult patients with a diagnosis of isthmic spondylolisthesis have a higher pelvic incidence, sacral slope, pelvic tilt and lumbar lordosis compared to patients without isthmic spondylolisthesis.

Grade of Recommendation: B

Inoue et al[1] conducted a radiographic study to investigate low-grade spondylolisthesis in patients with pre-existing isthmic spondylolisthesis of L5. Investigators sought to radioghically distinguish between vertebral slips before and after skeletal maturity as determined by deformities of the sacral endplate. The study included 367 patients, aged 20 to 59 years, presenting with bilateral pars defects of L5, including 213 without slippage and 154 with Grade I or II spondylolisthesis. Standing lumbar radiographs were taken of these patients to confirm the presence of pars defects and included anteroposterior, lateral, and bilateral oblique views. On the lateral radiographs, the following variables were examined: vertebral slippage, sacral table index, the sacral table angle, the relative thickness of the L5 transverse process and the iliac crest height. These findings were compared to a random sample of 310 control patients, aged 20 to 59 years, with low back pain who received the same radiographs, but had normal results. For analysis purposes, the patients were divided into three groups and included control patients (n=310), patients with pars defects without significant slippage (n=213) and patients with pars defects with significant slippage (n=154). Results indicated that there was a significant difference in the sacral table index between the control, nonslip and slip groups (94.4% vs 96.6% vs 102.5%, p<0.0001). The sacral table angle was signficantly smaller in the slip group (mean 91.6o) compared to the other groups (p<0.0001). Statiscally significant differences were found in the lumbar indexes when comparing groups, 89% in the control group, 82.6% in the nonslip group and 80.3% in the slip group (p<0.0001). The relative thickness of the transverse process was signifcantly greater in the nonslip group compared to controls (p<0.0001). No signficant differences were found between groups for the iliac crest measurements. When analyzing the association between age and slippage, investigators found that the prevelance of patients without slippage decreased gradually with age and elderly patients had relatively broader transverse processes and a higher iliac crest line. In critique of this study, the control patients were not consecutive and the process for random sampling was not discussed. This study provides Level II prognostic evidence that the lumbar index and sacral table angle are different in spondylolisthesis patients compared to low back pain patients without spondylolisthesis.

Jackson et al[2] conducted a radiographic study to determine the most reliable methods for measuring lumbopelvic lordosis and to define significant spinopelvic compensations for sagittal balance. Lateral radiograph findings of 50 control patients were compared to 50 patients with symptomatic degenerative disc disease, 30 patients with low grade (L5-S1) isthmic spondylolisthesis and 30 patients with idiopathic or degenerative scoliosis. Measurements for standing spinopelvic balance, angulations, and associated compensations around the pelvic hip axis were compared among the groups. Patients with spondylolisthesis and scoliosis showed less thoracic kyphosis while standing compared to controls; however, this was only signicant in patients with degenerative disorders. When compared to controls, standing patients who had spondylolisthesis showed more total lordosis, more lower lumbar segmental lordosis at L4-L5 and a significant increase in sacropelvic angle. The S1-C7 balance correlated with lower lumbar segmental lordosis at L5-S1 in patients with spondylolisthesis (r=0.36, p<0.05). In all patient groups, there were significant angular correlations between the lumbar spinal alignment and the sacropelvis. By the S1 endplate technique, total lordosis correlated with sacral incliniation in patients with spondylolisthesis (r=0.48, p<0.01). To ensure reliability of measurements, 20 percent of each group was randomly selected and remeasured. No statistically significant differences were found between initial and remeasurements. This study provides Level II prognostic evidence that patients who have spondylolisthesis have increased lumbar lordosis, increased L4-L5 segmental lordosis and increased sacral pelvic angle.

Labelle et al[3] conducted a retrospective radiographic analysis to investigate the role of pelvic anatomy and its effect on the global balance of the trunk in developmental spondylolisthesis. The lateral standing radiographs of 214 patients with developmental L5-S1 spondylolisthesis were analyzed and compared to films of 160 asymptomatic patients with no history of spine, hip or pelvic disorders. The following measurements were analyzed: pelvic incidence (PI), sacral slope (SS), pelvic tilt (PT), lumbar lordosis (LL), thoracic kypothosis (TK), and grade of spondylolisthesis. Statistically significant differences were found when comparing the spondylolisthesis patients to control patients for the measurements of PI (71.6 vs 51.8, p<0.01), SS (49.4 vs 39.7, p<0.01), PT (22.2 vs 12.1, p<0.01), LL (66 vs 42.7, p<0.01) and TK (38.9 vs 47.5, p<0.01). The differences in the spinal and pelvic parameters in the spondylolisthesis group increased progressively between Newman Grades I and IV for PI, SS, PT and

LL and decreased progressively between Grades I and IV for TK. This study provides Level II prognostic evidence that pelvic anatomy may have a direct influence on the development of spondylolisthesis.

Lee et al[4] conducted a retrospective radiographic analysis of 211 patients with various spinal disorders to define the relationship between pelvic parameters and lumbar spinal disorders. Lateral radiographs were taken on patients with spinal steonisis (n=57), degenerative spondylolisthesis (n=78), isthmic spondylolisthesis (n=34), Takemitsu Type 1 lumbar degenerative kyphosis (LDK) (n=20) and Takemitsue Type 2 LDK (n=22) and spinal analysis software was used to calculate pelvic incidence (PI), sacral slope (SS), pelvic tilt (PT), lumbar lordosis (LL), thoracic kyphosis (TK) and sagittal vertical axis. Results indicated that the mean pelvic incidence was much higher in patients with degenerative spondylolisthesis (58.8°), isthmic spondylolisthesis (56.7°) and Takemitsu Type 1 LDK (65.8°) compared to spinal stenosis (48.7°) and Takemitsue Type 2 (50.9°) patients. In critique of this study, it is unclear whether the patients studied were consecutive and the sample sizes were small. This study provides Level II prognostic evidence that patients with isthmic spondylolisthesis have increased pelvic incidence compared to those with spinal stenosis; however, pelvic incidence in isthmic spondylolisthesis patients was not found to be higher than in patients with degenerative spondylolisthesis.

Using digitzed lateral radiographs and orthopedics softoware, Rajnics et al[5] investigated the sagittal spinal shape and postion of the pelvis in patients with isthmic spondylolisthesis compared to controls. Investigators examined the radiographs of 48 patients with isthmic spondylolisthesis and 30 control patients to assess the sacrofemoral anatomic constant (SFAC), thickness of the pelvis, sacral slope, sacrofemoral tilting and overhang. According to Meyerding classification, in the isthmic sponodylolisthesis patient group, 5% had no slippage, 31% had Grade I, 58% had Grade II and 6% had Grade III. Analysis indicated that the SFAC, sacral slope and degree of L1-L5 lorsosis were greater in isthmic spondylolisthesis patients compared to controls. However, the analysis revealed no signiificant difference between groups in pelvis thickness, lumbar angle, degree of T4-T12 kyphosis, sagittal tilting angle, amplitude of curvatures or inclinination of the spine. This study provides Level II prognostic evidence that the degree of lordosis in the lumbar spine and sacral slope are increased in patients with isthmic spondylolisthesis.

Vialle et al[6] compared the angular parameters of the sagittal balance of the spine in patients with developmental L5-S1 spondylolisthesis to control patients. Standing lateral radiographs of 244 isthmic spondylolisthesis and 300 healthy/control patients were analyzed and measurements for sacral slope (SS), pelvic tilt (PT), pelvic incidence, lumbar lordosis, thoracic kyphosis (TK), T9 sagittal offset (T9SO) and degree of L5 anterior slip (L5S) were computed through digital spine software. Among the spondylolisthesis patients, 27 were classified as Meyerding's Grade I, 43 as Grade II, 98 as Grade III, 59 as Grade IV and 17 as Grade V. Investigators found significant correlation between lumbar lordosis, pelvic tilt and the severity of L5 anterior slipping and between lumbosacral angle and severity of L5 anterior slipping. PI was significantly higher in spondylolisthesis patients when compared to controls (73.05 vs 54.67, p<0.001); however, PI was not correlated with the degree of slippage. SS, PT, LL measurements were also found to be significantly higher (46.57 vs 41.86; 26.53 vs 13.21; -70.22 vs -43.13; p<0.0001, respectively). SS was found to gradually increase with Grade I, II and III slip and decrease in Grade IV and V slip. This study provides Level II prognostic evidence that patients with a diagnosis of isthmic spondylolisthesis have a higher pelvic incidence, sacral slope, pelvic tilt and lumbar lordosis compared to controls.

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C. Outcome Measures for Medical/Interventional and Surgical Treatment

What are the appropriate outcome measures for the treatment of adult isthmic spondylolisthesis?

For information on outcome measures for spinal disorders, the North American Spine Society has a publication entitled *Compendium of Outcome Instruments for Assessment and Research of Spinal Disorders*. To purchase a copy of the Compendium, visit https://webportal.spine.org/Purchase/ProductDetail.aspx?Product_code=68cdd1f4-c4ac-db11-95b2-001143edb1c1.

For additional information about the Compendium, please contact the NASS Research Department at nassresearch@spine.org.

D. Medical and Interventional Treatment

A systematic review of the literature yielded no studies to adequately address any of the following medical/interventional treatment questions:

What is the role of pharmacological treatment in the management of isthmic spondylolisthesis?

What is the role of manipulation in the treatment of isthmic spondylolisthesis?

What is the role of steroid injections for the treatment of isthmic spondylolisthesis?

What is the role of ancillary treatments such as bracing, traction, electrical stimulation and transcutaneous electrical stimulation (TENS) in the treatment of isthmic spondylolisthesis?

Relevant literature was found to address the clinical questions that follow; however, due to the paucity of evidence, no recommendations could be made.

What is the role of physical therapy/exercise in the treatment of isthmic spondylolisthesis?

There is insufficient evidence to make a recommendation for or against the use of physical therapy/exercise for the treatment of isthmic spondylolisthesis.

Grade of Recommendation: I (Insufficient Evidence)

Moller et al[1] conducted a prospective randomized trial to determine whether posterolateral fusion results in improved outcomes compared to an exercise program in adult patients undergoing treatment for isthmic spondylolisthesis. A total of 111 patients were included in the study, including 34 in the exercise group and 77 in the posterolateral fusion group. The patients were randomly allocated to their treatment group by blindly choosing one of three note cards upon enrollment in the program. Treatment allocation was kept blinded until the patient consented to participation. Of the patients who underwent posterolateral fusion, 37 received rigid pedicle screw fixation and 40 underwent fusion without instrumentation. Patients, enrolled in the exercise group, participated in the program under supervision of a physiotherapist, and the program included 12 different exercises. Four exercises included a pully and leg press machine and the other 8 exercises did not require specific equipment so that patients could easily perform at home. Patients exercised 3 times a week for 45 minutes a session during the first 6 months

and twice a week between 6 and 12 months. After one year, the patients were instructed to continue with the home exercises. After one year, patients were no longer under the supervision of the physiotherapist. Patients in both groups completed pre-treatment questionnaires and were followed-up with at one and 2 years. Functional disability was assessed using the Disability Rating Index (DRI) and pain was quantified by using the visual analogue scale (VAS). At 2 year follow-up, the surgical group reported a significantly lower DRI (p=0.004) and pain index score (p=0.002) compared to the exercise group. At 2 years, the mean DRI remained unchanged in the exercise group, which had a mean DRI of 44 before and after treatment. The mean pain index significantly improved in both groups with 63 to 37 (p<0.001) in the surgical group and 65 to 56 in the exercise group (p=0.024). Prior to the start of the program, 61% of exercise patients were not working compared to 45% at the 2 year follow-up.

In a follow-up study, Ekman et al[2] evaluated the long term outcome of exercise versus surgical treatment in the same group of patients. The 106 patients who completed the 2-year follow-up were invited by mail to take part in the long-term follow-up study. A total of 101 patients responded to the invitation resulting in a 91% long-term follow-up rate. In addition to the VAS and DRI, the Oswestry Disability Index (ODI), SF-36 and global outcome measurement were added to the patients' outcome assessments for long-term follow-up. The average long term follow up was 9 years with a range of 5 to 13 years. Results suggested that there were no significant differences in terms of functionality and pain in the exercise group at 2 and 9 years follow-up. When comparing the surgical and exercise groups, there were no significant differences in outcome measurements at long-term follow-up in any of the outcomes assessed except for the global assessment, which was found to be significantly better for surgical patients (p=0.015). In the exercise group, all scores except the ODI improved nonsignificantly between short-term and long-term follow-up. The ODI worsened from 28 to 31; however, this was not statistically significant. In the surgical group, 11 patients experienced complications, including 2 nerve root injuries, one pseudoarthrosis, one discectomy and 7 implant removals. There were no early or late deep infections reported. In critique of this study, compliance with the exercise program was not assessed after one year. Two-thirds of the exercise patients complied with the program at one year; however, it is unknown how many and to what extent the patients continued the recommended exercises beyond one year. Although this study is a randomized controlled trial, only the results from the exercise group can be directly applied to this clinical question. Therefore, this potential Level I study provides Level IV therapeutic evidence that adult isthmic spondylolisthesis patients treated with an exercise program experience short term improvements in pain, but not in functionality.

Does the degree of radiological grade, sagittal spinopelvic alignment, sacral and spinopelvic parameters, or the presence of dynamic instability in patients with isthmic spondylolisthesis affect the outcomes of patients treated with medical or interventional treatment?

There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.

What is the long-term result of medical/interventional management of isthmic spondylolisthesis?

There is insufficient evidence to make a recommendation for or against the use of medical/interventional treatment for the long-term management of patients with isthmic spondylolisthesis.

Grade of Recommendation: I (Insufficient Evidence)

As discussed earlier in this section, Ekman et al[2] evaluated the long term outcome of exercise versus surgical treatment in adult patients receiving treatment for isthmic spondylolisthesis. A total of 111 patients were initially included in the study1, including 34 in the exercise group and 77 in the posterolateral fusion group. Of the patients who underwent posterolateral fusion, 37 received rigid pedicle screw fixation and 40 underwent fusion without instrumentation. Patients enrolled in the exercise group participated in the program under supervision of a physiotherapist, and the program included 12 different exercises. Four exercises included a pully and leg press machine and the other 8 exercises did not require specific equipment so that patients could easily perform at home. Patients exercised 3 times a week for 45 minutes a session during the first 6 months and twice a week between 6 and 12 months. After one year, the patients were instructed to continue with the home exercises. After one year, patients were no longer under the supervision of the physiotherapist.

The 106 patients who completed the 2-year follow-up were invited by mail to take part in the long-term follow-up study. A total of 101 patients responded to the invitation resulting in a 91% long-term follow-up rate. Outcomes were assessed using VAS, DRI, the Oswestry Disability Index (ODI), SF-36 and global outcome measurement. The average long term follow up was 9 years with a range of 5 to 13 years. At 2 years, the mean DRI remained unchanged in the exercise group, which had a mean DRI of 44 before and after treatment. The mean pain index significantly improved in the exercise group from pretreatment to follow-up at 2 years (65 to 56, p=0.024). Results from long-term follow-up suggested that there were no significant differences in terms of functionality and pain in the exercise group at 2 and 9 years follow-up. In the exercise group, all scores except the ODI improved nonsignificantly between short-term and long-term follow-up. The ODI worsened from 28 to 31; however, this was not statistically significant. In critique of this study, compliance with the exercise program was not assessed after one year. Two-thirds of the exercise patients complied with the program at one year; however, it is unknown how many and to what extent the patients continued the recommended exercises beyond one year. Although this study is a randomized controlled trial, only the results from the exercise group can be directly applied to this clinical question. Therefore, this potential Level I study provides Level IV therapeutic evidence that adult isthmic spondylolisthesis patients treated with an exercise program experience short term improvements in pain, but not in functionality. For long term improvement, treatment of isthmic spondylolisthesis with exercise may provide little improvement compared to the natural history of the disease.

Future Directions For Research

The work group recommends the undertaking of prospective and retrospective studies, including large multi-center registry database studies with long term follow-up, evaluating the outcomes of various medical/interventional treatments for the management of adult patients with isthmic spondylolisthesis.

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E. Surgical Treatment

In adult patients, is surgical treatment more effective than medical/interventional treatment alone for the treatment of isthmic spondylolisthesis?

There is insufficient evidence to make a recommendation for or against the efficacy of surgical treatment as compared to medical/interventional alone for the management of adult patients with isthmic spondylolisthesis.

Grade of Recommendation: I (Insufficient Evidence)

In a 2 part study, Moller et al[1,2] evaluated the outcomes of 111 isthmic spondylolisthesis patients randomly treated with posterolateral fusion in situ, with or without instrumentation, versus an exercise program. For purposes of answering this clinical question, the work group included only Part 22 of the analysis, which specifically compared the outcomes of 40 patients allocated to posterolateral fusion (PLF) without instrumentation to 37 patients who received PLF with pedicle screw instrumentation. The majority of patients had a diagnosis of either Grade I or II isthmic spondylolisthesis (98%). Functional disability was assessed by the Disability Rating Index (DRI) and Global Assessment and pain was quantified using the Visual Analogue Scale (VAS). Patients were followed for 2 years and the follow-up rate was 94%. At one and 2 years follow-up, DRI and pain scores improved significantly in both the instrumented and noninstrumented groups from preoperative measurements, although there were no statistically significant differences between the groups. There was no significant difference in percentage of sick leave and disability pension at 2 years between groups with 66% of noninstrumented patients on leave prior to surgery vs 42% at follow-up ($p=0.016$) compared to 84% of instrumented patients on leave prior to surgery vs 50% at follow-up ($p=0.002$). Noninstrumented patients had a 78% solid fusion success rate while 65% of instrumented patients were categorized as fused. Mean operation time and intraoperative blood loss were significantly greater in the instrumented group compared to noninstrumented patients (298 minutes vs 201 minutes, $p<0.001$; 1517 mL vs 861mL, $p<0.0001$, respectively). Three patients experienced major postoperative complications, including 2 instrumented patients sustaining an L5 root injury with permanent sequelae and one noninstrumented patient became permanently blind in one eye.

Using the above surgical population, Ekman et al[3] evaluated the long-term outcomes of patients undergoing posterolateral fusion versus an exercise program. In addition to the 40 randomly allocated to posterolateral fusion without pedicle screw instrumentation and 37 allocated to posterolateral fusion with pedicle screw instrumentation, this analysis also included data for 34 patients randomly allocated to an exercise program. Data for 91% of the patients was available at 5 years follow-up. At long-term follow-up, the authors also collected Oswestry Disability Index (ODI) and SF-36 data. When comparing results for the surgical patients, no significant differences were found in pain index, DRI, ODI, global assessment, SF-36 or work ability scores between the instrumented and noninstrumented groups. The Moller and Ekman analyses offer Level I therapeutic evidence that there were no significant differences in clinical outcomes or fusion rates between instrumented or noninstrumented posterolateral patients.

In a randomized controlled trial, Thomsen et al[4] evaluated the effect of instrumentation on reoperation rates and functional outcome. A total of 129 patients with severe chronic low back pain were included in the study, including 35 patients with Grade I or II isthmic spondylolisthesis, 41 patients with primary degenerative instability and 53 patients with secondary degenerative instability. Upon enrollment, patients were consecutively allocated using a 20-number-per-block concealed randomization process into either fusion with or without supplementary transpedicular screw fixation. Functional outcomes were assessed by the Dallas Pain Questionnaire (DPQ) and the Low Back Pain Rating Scale (LBPR) and scored by an independent observer. At 2 years follow-up, there were no significant differences found in fusion rates between instrumented (73%) and non-instrumented groups (84%) or DPQ scores in the isthmic spondylolisthesis sub-group.

Using the above patient population, Bjarke Christensen et al[5] evaluated the long term effect of instrumentation on reoperation and functional outcome. At 5 years follow-up, 8 isthmic spondylolisthesis patients in the instrumented group underwent or were planning reoperation and 2 isthmic spondylolisthesis patients in the noninstrumented group underwent or were planning reoperation. Isthmic spondylolisthesis patients in the noninstrumented group had highly significant improvement in 3 out of 4 DPQ categories (daily activity, anxiety/depression, and social concerns) and in all 3 LPBQ questions compared to instrumented patients. Overall, among all diagnosis groups, there was no significant difference in functional outcome as measured

by the DPQ and LBPR between the instrumented and noninstrumented groups. When analyzing diagnosis subgroups, the authors found that patients with isthmic spondylolisthesis in the noninstrumented group had significantly better outcomes than patients who received instrumented fusion ($p<0.03$). In critique, due to the small sample size of the subgroup of isthmic spondylolisthesis patients, the work group decided to downgrade the study from Level I to Level II. The Thomsen and Bjarke Christensen studies offer Level II therapeutic evidence that there was no benefit found with adding instrumentation for Grade I and II isthmic spondylolisthesis patients undergoing fusion.

Future Directions For Research

The work group recommends the undertaking of a large prospective study of isthmic spondylolisthesis patients only evaluating the addition of instrumentation to fusion, including subgroup analysis, for factors potentially impacting surgical outcomes such as segmental instability, smoking and the addition of decompression.

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Does the addition of lumbar fusion, with or without instrumentation, to surgical decompression improve surgical outcomes in the treatment of adult patients with isthmic spondylolisthesis compared to treatment by decompression alone?

There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.

Although there was no literature evaluating the addition of fusion to decompression versus decompression alone in adult isthmic spondylolisthesis patients, the work group observed the presence of literature evaluating the addition of decompression to fusion versus fusion alone. Because the literature search was not specifically designed to address this topic, the work group opted not to comment on findings. A clinical question comparing the addition of decompression to fusion versus fusion alone may be considered for a future guideline on this topic.

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Does the addition of instrumentation to decompression and fusion for adult patients with isthmic spondylolisthesis improve surgical outcomes compared with decompression and fusion alone?

In patients with low-grade isthmic spondylolisthesis, the addition of instrumentation may not improve outcomes in the setting of posterolateral fusion, with or without decompression.

Grade of Recommendation: B (Suggested)

In a 2 part study, Moller et al[1,2] evaluated the outcomes of 111 isthmic spondylolisthesis patients randomly treated with posterolateral fusion in situ, with or without instrumentation, versus an exercise program. For purposes of answering this clinical question, the work group included only Part 22 of the analysis, which specifically compared the outcomes of 40 patients allocated to posterolateral fusion (PLF) without instrumentation to 37 patients who received PLF with pedicle screw instrumentation. The majority of patients had a diagnosis of either Grade I or II isthmic spondylolisthesis (98%). Functional disability was assessed by the Disability Rating Index (DRI) and Global Assessment and pain was quantified using the Visual Analogue Scale (VAS). Patients were followed for 2 years and the follow-up rate was 94%. At one and 2 years follow-up, DRI and pain scores improved significantly in both the instrumented and noninstrumented groups from preoperative measurements, although there were no statistically significant differences between the groups. There was no significant difference in percentage of sick leave and disability pension at 2 years between groups with 66% of noninstrumented patients on leave prior to surgery vs 42% at follow-up (p=0.016) compared to 84% of instrumented patients on leave prior to surgery vs 50% at follow-up (p=0.002). Noninstrumented patients had a 78% solid fusion success rate while 65% of instrumented patients were categorized as fused. Mean operation time and intraoperative blood loss were significantly greater in the instrumented group compared to noninstrumented patients (298 minutes vs 201 minutes, p<0.001; 1517 mL vs 861mL, p<0.0001, respectively). Three patients experienced major postoperative complications, including 2 instrumented patients sustaining an L5 root injury with permanent sequelae and one noninstrumented patient became permanently blind in one eye.

Using the above surgical population, Ekman et al[3] evaluated the long-term outcomes of patients undergoing posterolateral fusion versus an exercise program. In addition to the 40 randomly allocated to posterolateral fusion without pedicle screw instrumentation and 37 allocated to posterolateral fusion with pedicle screw instrumentation, this analysis also included data for 34 patients randomly allocated to an exercise program. Data for 91% of the patients was available at 5 years follow-up. At long-term follow-up, the authors also collected Oswestry Disability Index (ODI) and SF-36 data. When comparing results for the surgical patients, no significant differences were found in pain index, DRI, ODI, global assessment, SF-36 or work ability scores between the instrumented and noninstrumented groups. The Moller and Ekman analyses offer level I therapeutic evidence that there were no significant differences in clinical outcomes or fusion rates between instrumented or noninstrumented posterolateral patients.

In a randomized controlled trial, Thomsen et al[4] evaluated the effect of instrumentation on reoperation rates and functional outcome. A total of 129 patients with severe chronic low back pain were included in the study, including 35 patients with Grade I or II isthmic spondylolisthesis, 41 patients with primary degenerative instability and 53 patients with secondary degenerative instability. Upon enrollment, patients were consecutively allocated using a 20-number-per-block concealed randomization process into either fusion with or without supplementary transpedicular screw fixation. Functional outcomes were assessed by the Dallas Pain Questionnaire (DPQ) and the Low Back Pain Rating Scale (LBPR) and scored by an independent observer. At 2 years follow-up, there were no significant differences found in fusion rates between instrumented (73%) and non-instrumented groups (84%) or DPQ scores in the isthmic spondylolisthesis sub-group.

Using the above patient population, Bjarke Christensen et al[5] evaluated the long term effect of instrumentation on reoperation and functional outcome. At 5 years follow-up, 8 isthmic spondylolisthesis patients in the instrumented group underwent or were planning reoperation and 2 isthmic spondylolisthesis patients in the noninstrumented group underwent or were planning reoperation. Isthmic spondylolisthesis patients in the noninstrumented group had highly significant improvement in 3 out of 4 DPQ categories (daily activity, anxiety/depression, and social concerns) and in all 3 LPBQ questions compared to instrumented patients. Overall, among all diagnosis groups, there was no significant difference in functional outcome as measured by the DPQ and LBPR between the instrumented and noninstrumented groups. When analyzing diagnosis subgroups, the authors found that patients with isthmic spondylolisthesis in the noninstrumented group had significantly better outcomes than patients who received instrumented fusion (p<0.03). In critique,

due to the small sample size of the subgroup of isthmic spondylolisthesis patients, the work group decided to downgrade the study from level I to level II. The Thomsen and Bjarke Christensen studies offer level II therapeutic evidence that there was no benefit found with adding instrumentation for Grade I and II isthmic spondylolisthesis patients undergoing fusion.

Future Directions for Research

The work group recommends the undertaking of a large prospective study of isthmic spondylolisthesis patients only evaluating the addition of instrumentation to fusion, including subgroup analysis, for factors potentially impacting surgical outcomes such as segmental instability, smoking and the addition of decompression.

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How do outcomes of decompression with posterolateral fusion compare with those for 360° fusion in the treatment of adult patients with isthmic spondylolisthesis?

Posterolateral fusion and 360° fusion surgeries are recommended to improve the clinical outcomes in adult patients with low grade isthmic spondylolisthesis.

Grade of Recommendation: A

360° fusion is recommended to provide higher radiographic fusion rates compared to posterolateral fusion in adult patients with low grade isthmic spondylolisthesis.

Grade of Recommendation: A

There is conflicting evidence whether 360° fusion provides better clinical outcomes than posterolateral fusion alone.

Grade of Recommendation: I (Insufficient/Conflicting Evidence)

Farokhi et al[1] compared the clinical outcomes of posterolateral fusion (PLF) to posterior lumbar interbody fusion (PLIF) with posterior instrumentation for the treatment of isthmic spondylolisthesis. Patients were randomized to receive either PLF (n=40) or PLIF (n=40) using computerized random number generator software. Almost half of patients (45%) had isthmic spondylolisthesis at the L5-S1 level. Isthmic spondylolisthesis was present at the L4-L5 in 35% and at the L3-L4 in 12.5% of patients. Patients were followed for one year, although most results were only reported for 6 months after surgery. Outcomes were assessed using the Oswestry Low Back Pain Disability (OLBP) sale and Visual Analogue Scale (VAS) and by comparing radiologic results. Radiological evaluation included static and functional lumbar spine plain x-rays and CT, and MRI scans assessed foraminal stenosis and the presence of lumbar spinal stenosis. At baseline, neurogenic claudication was observed in 38 (95%) patients in the PLF group and in 36 (90%) patients in the PLIF group. At one year after surgery, complaints of neurogenic claudication were significantly higher in the PLIF patients compared to PLF patients (33.3% vs 7.3%, p=0.004). Improvement in low back pain as measured by the OLBP was significantly higher in PLF patients compared to PLIF patients (25.34+9.36 vs 17.1, p=0.001). It is important to highlight that the standard deviations for these two measurements overlap; thus, the work group questions the significance of this finding. There were no significant differences in postoperative complications at one year between the groups. In the PLF Group 4.3% experienced cerebrospinal fluid leak compared to 5% of PLIF patients. The infection rate was 2.1% for the PLF Group and 2.5% for the PLIF Group. Permanent motor impairment occurred in 4.3% of PLF patients and 5% of PLIF patients. Intraoperative blood loss was significantly greater in the PLIF Group (0.04) and surgical duration was longer for PLIF patients, although the difference was not statistically significant. At 6 months after surgery, 66.7% of PLF patients and 89.1% of PLIF patients reported good fusion results; this difference was not statistically significant. At 3 days after surgery, reports of low back pain were statistically lower in PLF patients. In PLF patients, there was no significant correlation between slip, Meyerding grade and disc height, radicular pain and low back pain. This study offers Level I therapeutic evidence that at one year, PLF is clinically superior to PLIF as measured by ODI low back pain measures; however, PLIF was found to have more successful postoperative fusion rates when compared to PLF.

Musluman et al[2] randomly allocated patients into receiving either posterolateral fusion (PLF) or posterior lumbar interbody fusion (PLIF) for the treatment of Grades I and II isthmic spondylolisthesis. Patients were only considered for surgery after undergoing at least 6 months of unsuccessful conservative treatment measures. Using a computerized random number generator, 25 patients were enrolled per group. Posterior decompression, laminectomy, medial facetectomy and foraminotomy were performed in all patients. In addition, bone fragments collected from the iliac wing during decompression were used as autografts in the PLF Group and lamina obtained during decompression, and spinous process bone autograft was used in the PLIF Group. The spondylolisthesis levels in the PLF Group were located at L4-L5 (13, 52%), L5-S1 (8, 32%) and L3-L4 (4, 16%). In the PLIF Group, spondylolisthesis levels were located at the L4-L5 (13, 52%), L5-S1 (6, 24%) and L3-L4 (5, 20%). Patients were followed for a minimum of 18 months and an aver-

age of 3.3 years. Radiologic examinations were performed via plain and dynamic radiographs, MR imaging and CT scanning. Clinical and functional evaluations were conducted via Visual Analogue Scale (VAS), Oswestry Disability Index (ODI) and SF-36. The mean operating time was 146 minutes in the PLF Group and 168 minutes in the PLIF Group. The mean amount of blood lost during operation and the first postoperative day was significantly greater in the PLF Group compared to the PLIF Group (1100 + 280ml vs 830 + 215ml, p<0.05). There were no significant differences in complications between groups. Postoperative complications in the PLF Group included one case of transient nerve palsy, 2 deep infections, 3 patients with pain in the bone graft donor site and 4 nonunions. In the PLIF Group, there was 1 case of transient nerve palsy, one deep infection and one cage dislocation. Significant decreases in both low back and leg pain were observed in both groups after surgery. When comparing pain levels between the groups, PLIF patients experienced more improvement in low back pain (p<0.05); however, there were no significant differences in leg pain improvements between groups. There was a statistically significant improvement in mean ODI scores from pre to postop in both groups, favoring the PLIF Group at early follow-up. At baseline, PLF patients scored 29.20 + 6.42 and improved to 18.2 + 3.65 at 3 months and 14.12 + 2.42 at 1.5 to 6 years (p<0.0001). PLIF patients had a mean preoperative ODI of 30.2 + 5.70, which improved to 13.60 + 1.95 at 3 months and 13.40 + 1.95 at 1.5 to 6 years (p<0.0001). In critique, the work group would like to highlight the inconsistent follow-up period for patients (ie, range 1.5 to 6 years); however, they didn't feel that this critique alone justified downgrading the study as all patients were followed for at least 1.5 years. This study offers Level I therapeutic evidence that statistically significant improvement in outcome measures occurred in both groups; however, the PLIF Group had statistical superiority in some outcome measures compared to PLF.

In a randomized controlled trial, Christensen et al[3] assessed the surgical outcomes of 148 patients undergoing either posterolateral fusion (PLF) with titanium instrumentation or circumferential fusion for the treatment of Grade I or II isthmic spondylolisthesis, primary degeneration, secondary degeneration, or accelerating degeneration. Circumferential fusion was performed via anterior lumbar interbody fusion with the use of a radiolucent cage, using a retroperitoneal approach to the lumbar discus plus posterolateral fusion. Within the isthmic spondylolisthesis subgroup, 19 patients were randomized to the PLF Group and 24 were randomized to the circumferential group. Patients were followed for two years and outcomes were assessed using the Dallas Pain Questionnaire (DPQ), Low Back Pain Rating Scale (LBPR) and radiographic measurements. For isthmic spondylolisthesis patients, no statistical differences were found between the groups for DPQ or LBPR scores at either the one or 2 year follow-up assessments, although there were significant improvements in scores for each group before and after surgery. In critique, there was no subgroup analysis of isthmic spondylolisthesis patients for radiographic measures and the subgroup sample size was small and, thus, potentially underpowered to detect any statistical differences. Due to these reasons, the work group downgraded the level of evidence from I to II. This data provides Level II therapeutic evidence that there were no significant differences in clinical outcomes as measured by DPQ and LBPR in PLF compared to 360° fusion in patients with low grade isthmic spondylolisthesis at one year and 2 years follow-up.

In a prospective comparative study, Swan et al[4] compared the early and medium treatment outcomes of patients undergoing either single-Level Instrumented posteriorlateral fusion (PLF) or PLF plus anterior interbody fusion (ALIF) for the treatment of unstable Grade I or II isthmic spondylolisthesis at L5-S1 or L4-L5. For the purposes of this study, the authors defined "unstable" spondylolisthesis as documented slip progression (3mm or one Meyerding Grade) under observation in the 2 years prior to surgery or > 3mm translation and/or > 22o of angulation seen on standing flexion-extension or prone lateral radiographs. Patient selection was conducted through sequential enrollment, with the first 50 enrolled in the PLF Group and the second group of 50 patients enrolled in the PLF ALIF Group. Follow-up assessments occurred at 6 months, 12 months and 24 months. The primary outcome measurement of success was an Oswestry Disability Index (ODI) <20 and secondary outcome measures included pain intensity as measured by the Visual Analogue Scale (VAS), medication intake and work status. Radiographic measures were evaluated via flexion-extension x-rays. Operative results indicated that operation duration for the PLF ALIF Group was one hour longer than that for the PLF Group; however, blood loss and length of hospital stay were similar between the groups. At 6 and 12 months VAS, ODI, medication and occupational outcomes were significantly better in the PLF ALIF Group compared to the PLF Group only, although differences were not statistically significant at 24 months. When comparing the percentage of patients who met the primary outcome (ODI < 20), more patients in the PLF ALIF Group achieved this outcome at 6, 12 and 24 months compared to PLF only patients (30 vs 11 patients, RR=2.67, p=0.0001; 34 vs 20 patients, RR=1.66, p<0.005; 36 vs 29 patients, RR=1.21, p=0.47, respectively). It is important to note that although that the combined group met the primary outcome at a significantly higher rate at 6 and 12 months compared to the PLF Group, this difference was no longer significant at 24 months. Improvements in preoperative anterolisthesis, disc height and slip angle measurements were maintained at a significantly greater rate at 24 months postop in combined patients compared to PLF patients (20.9 + 12.1 to 9.9 + 6.7 vs 21.2 + 9.9 to 19.5 + 7.2, p=0.001; 17.3 + 6.7 to 24.0 + 5.9 vs. 16.9 + 7.5 to 18.1 + 8.0, p=0.01; -18.1 + 11 to 125.2 + 9 vs. -19.2 + 9 to -20.2 + 12, p=0.03, respectively). The majority of complications reported were minor, but occurred more frequently after combined surgery. Regarding major infections, 2 patients in each group had to undergo reoperation and one combined and 3 PLF patients experienced nonunion. In critique, it is important to note that the authors only included patients with unstable, low-grade slips and that no direct decompression was performed in either group. This study provides Level II therapeutic data that at 6 and 12 months, there were statistically significant improvements in ODI and VAS scores in patients receiving posterolateral fusion plus anterior interbody fusion versus posterolateral fusion alone; however, at 2 year follow-up, these differences were no longer statistically significant. Radiographic measurements, including improvements in preoperative anterolisthesis, disc height and slip angle, were maintained at a significantly greater rate at 2

years after surgery in the posterolateral fusion plus anterior interbody fusion group.

In a retrospective comparative study, Suk et al[5] evaluated the advantages of adding PLIF to posterior segmental pedicle screw instrumentation and PLF for the surgical treatment of instability created by decompressive surgery in spinal stenosis caused by isthmic spondylolisthesis. The records of patients who had undergone PLF (n=40) or PLF plus PLIF (n=36) were compared. Patients were followed for a minimum of two years; PLF patients were followed for a mean of 5.4 years and PLIF patients were followed for a mean of 3.3 years. Clinical outcomes were assessed using Kirkaldy-Willis criteria and radiographic measurements were evaluated using standing and flexion-extension radiographs and CT scan or MRI. At preoperative radiographic evaluation, spinal stenosis was one Level In 22 patients (61%), two levels in 11 patients (30.5%) and three levels in 3 patients (8.5%). In the PLF Group, isthmic defects were at L4 in 25 patients (62.5%), L5 in 14 (35%) and double Level In L4-L5 in 1 patient (2.5%). According to Meyerding's Grade, 14 (35%) patients were Grade I, 24 (60%) Grade II and 2 (5%) Grade III. In the PLF plus PLIF Group, the isthmic defect was at L3 in 1 (3%) patient, L4 in 20 (55.5%) patients, L5 in 15 (41.6%) patients and double-level L4-L5 in 1 (2.5%) patient. Meyerding Grade I slippage was present in 12 (33.3%) patients, Grade II in 21 (58.3%) patients and Grade III in 3 (8.3%) patients. At follow-up, solid union was obtained in all PLF plus PLIF patients and 35 of 40 (87.5%) of PLF patients. As measured by the Taillard method, the mean preoperative slip in the PLF Group improved from 28.3 + 13.2% to 15.1 + 7.7% immediately after surgery and to 20.3 + 8.5% at final follow-up. In the PLF plus PLIF Group, the mean preoperative slip of 27.9 + 9.7% improved to 13.5 + 7.3% immediately after surgery and to 16.3 + 8.8% at final follow-up. The difference in measurements was statistically significant ($p<0.05$) favoring the PLF plus PLIF Group. There were no significant differences in total lumbar, segmental lordosis, sacral inclination or sagittal rotation between groups. As measured by Kirkaldy-Willis criteria, excellent or good results were obtained in 95% of PLF patients and 97% of PLIF plus PLIF patients. When narrowing these findings, 75% of PLIF patients reported excellent results compared to only 45% of PLF patients ($p<0.05$). When comparing postoperative complications: nonunions, instrument breakage, infections and neurological weakness were reported in 3, 2, 1 and 0 patients, respectively, in the PLF Group versus 0, 0, 1, and 1 patient, respectively, in the PLF plus PLIF Group. This study provides Level III therapeutic data that the addition of PLIF to PLF is radiographically and clinically superior when compared to PLF and pedicle screw instrumentation only.

In a retrospective comparative study, Ekman et al[6] compared the outcomes of posterior lumbar interbody fusion (PLIF) to posterolateral fusion (PLF) in adult isthmic spondylolisthesis patients. A total of 163 patients were included in the study, including 86 PLIF patients and 77 PLF patients, with (n=40) or without (n=37) pedicle screw fixation. Patients were followed for 2 years and outcomes were assessed using VAS, DRI, ODI and Global Outcome Assessment. The majority of patients in all groups had Grade I slip. There was a statistically significant distribution of Grade II slips among the groups with 23% of PLIF patients, 36% of PLF plus instrumentation patients and 11% of PLF without instrumentation patients ($p=0.0004$). However, there were no statistically significant differences in outcomes based on preoperative slip level between the groups. In both PLIF and PLF groups, VAS and DRI scores improved significantly from the preoperative period to the 2 year follow-up; however, there were no statistically significant differences in improvements between the groups. ODI scores for both groups at 2 year follow-up was 25. At baseline, there were no significant differences in the proportion of patients with sciatica between groups, but at 2 years, sciatica was present in more PLIF patients (48% vs. 37%, $p=0.18$). The percentage of patients at work increased from 36% to 52% ($p=0.0008$) at follow-up in the PLIF Group and 25% to 54% ($p<0.0001$) in the PLF Group. Return to work status was not significantly different between the groups. According to the Global Outcome Assessment, 74% of patients in both groups evaluated their surgical results as "much better" or "better." In the PLIF Group, there were 12 major complications, including 3 deep wound infections, 2 patients were permanent leg pain, 2 patients with transient leg pain, one patient with DVT, one patient with pulmonary embolism, 2 foot drops, and one patient with postoperative paraparesis. There were 4 major complications in the PLF group, including 2 permanent L5 injuries, one permanent blindness, and one transient dermatomal pain, which resolved after one month. In critique, there were statistically significant differences in Grade slip level between the groups. Due to this heterogeneity, the work group downgraded the level of evidence from III to IV. This potential Level III study offers Level IV therapeutic evidence that in patients with low grade isthmic spondylolisthesis, there are no statistically significant differences as measured by VAS, DRI and ODI between PLIF and PLF.

Future Directions For Research

The work group recommends the undertaking of a prospective study evaluating the outcomes of 360° fusion (posterolateral plus interbody fusion) versus posterolateral fusion alone in adult patients undergoing surgical treatment for isthmic spondylolisthesis.

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Does reduction with fusion result in better outcomes than fusion in situ in adult patients with isthmic spondylolisthesis?

There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation

Future Directions for Research

The work group recommends the undertaking of a prospective or retrospective study to determine if there is a clinical benefit of actively attempting a reduction prior to fusion.

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What is the role of stand-alone interbody fusion, for the purpose of indirect decompression, in the treatment of adult patients with isthmic spondylolisthesis?

Anterior lumbar interbody fusion (ALIF) may be considered as an option to indirectly decompress foraminal stenosis in adult patients with low grade isthmic spondylolisthesis.

Grade of Recommendation: C

Kim et al[1] retrospectively compared the clinical and radiographic results of isthmic spondylolisthesis patients who had undergone ALIF (n=20) to those who received posterolateral fusion (PLF) with transpedicular fixation (n=20). Patient follow-up was a minimum of one year after surgery. ALIF patients were followed for a mean of 3.6 years, and PLF patients were followed for a mean of 2.3 years. At follow-up, patients underwent radiographic assessments, measurement of the correction rate of anterior displacement using the Taillard method and evaluation of clinical results using criteria outlined in a 1991 study by one of the authors. No validated instruments or criteria were utilized in evaluating postoperative outcomes. According to Meyerding's classification, Grade I spondylolisthesis was present in 70% of ALIF patients and 75% of PLF patients. Grade II was present in 30% of ALIF patients and 25% of PLF patients. Results indicated that there were no statistically significant differences in correction rate, fusion rate and clinical results between the groups. In the ALIF Group, the preoperative anterior slippage was 16.1% compared to 10.4% after surgery. The degree of anterior slippage in PLF patients was 15.2% before surgery compared to 9.8% after surgery. The correction rate was 35% in the ALIF Group compared to 36% in the PLF Group. Complete or partial fusion was obtained in 90% of ALIF patients and 95% of PLF patients by one year after surgery. Satisfactory results were obtained in 85% of ALIF patients and 90% of PLF patients. When reviewing postoperative complications in the ALIF Group, 2 patients experienced warm sensations in lower extremities, 2 developed transient paralytic ileus, 2 experienced delayed union and one experienced urinary retention. All symptoms in these patients improved over time. In the PLF Group, loosening of a pedicle screw was reported in one patient. In critique, outcomes were not measured using validated criteria; thus, the work group downgraded the level of evidence from III to IV. This study offers Level IV therapeutic evidence that in adult patients with isthmic spondylolisthesis, ALIF provides adequate indirect decompression with similar results as direct decompression.

In a retrospective review of low-grade isthmic spondylolisthesis patients, Kim et al[2] compared surgical outcomes of instrumented ALIF (n=43) to instrumented circumferential fusion (n=32). All patients had single-level, low-grade spondylolisthesis. Clinical outcomes were evaluated using the Visual Analog Scale (VAS) and functional outcomes were measured using the Oswestry Disability Index (ODI) and return to work status. The authors also compared operation time, blood loss, blood transfusions, length of hospital stay, complications and radiologic results. Independent observers evaluated the radiologic outcomes on anteroposterior, lateral and flexion-extension radiographs. Patients in the ALIF group were followed for a mean of 41.1 months and circumferential fusion patients were followed for a mean of 32.9 months. In both groups, disc height, segmental lordosis, and degree of listhesis significantly improved from pre to post-op. In ALIF patients, disc height, segmental lordosis, whole lumbar lordosis and degree of listhesis changed from 8.0, 13.9, 50.6o and 21.9, respectively to 15.9, 20.8, 56.3o and 11.3, respectively (all $p<0.001$), at postoperative follow-up. Radiologic evidence of successful arthrodesis was noted in 97.7% of ALIF patients versus 100% of circumferential fusion patients. There were no statistically significant differences in pre to postop VAS and ODI scores between the groups. The mean VAS scores for back and leg pain and ODI scores significantly improved in the ALIF group from 7.6, 7.5 and 49.3%, respectively to 2.1, 2.0 and 13.7%, respectively (all $p<0.0001$). For ALIF patients, the mean operation time, hospital stay, blood loss and return to work was 190 minutes, 7.4 days, 300mL and 3.7 months, respectively. There were no cases of life-threatening complications or wound infection in either group. In the ALIF group, there was one case of postoperative pneumonia, one case of urinary tract infection, one venous injury and one patient with a break in the pedicle screw. For the purposes of answering this clinical question, findings from the ALIF group only are applied. This study offers Level IV therapeutic data that ALIF provides significant indirect reduction leading to improved clinical scores.

In a case-series study, Riouallon et al[3] evaluated the efficacy of ALIF without using a reduction maneuver in 65 patients with isthmic spondylolisthesis. The olisthetic level was at L5-S1 in 52 patients and at L4-L5 in 13 patients. According to Meyerding classification, 32 patients presented with Grade I and 33 presented with Grade II. Patient follow-up was approximately 6.6 years (range 2.5-22 years) and outcomes were evaluated via VAS for lumbar and radicular pain and ODI and Beaujon score for functional status. Standard AP, lateral and three-quarter oblique radiographs were used to evaluate pre- and postoperative radiologic parameters. According to their findings, the overall fusion rate was 91%, 97.5% when the segment was instrumented and 80% when it was noninstrumented. The fusion rate was 77% for patients at the L4-L5 level and 96% at L5-S1. At postop, slippage decreased by 30% and disc height increased by 177%. On the sagittal plane, lordosis improved by 5o, without any changes in

pelvic parameters. Patients improved an average of 4.6 points on the VAS for lumbar pain and an average of 5 points for radicular pain. On average, there was a 38 point improvement in ODI scores from preoperative to postoperative measurement and a 7.3 point increase for Beaujon scores. The preoperative maximum walking time was 20 minutes, which improved to one hour or more in the majority of patients (84%) after surgery. The intensity of painful claudication at follow-up was reduced in 71% of patients. There were no cases of surgical site infection, vascular injury or thromboembolic complications, but one patient experienced transient retrograde ejaculation and 9 required intraoperative transfusion. This study provides Level IV therapeutic evidence that ALIF alone can provide good results clinically and radiographically.

Future Directions for Research

The work group recommends the undertaking of a randomized controlled trial comparing indirect decompression via ALIF to direct posterior decompression for the surgical treatment of isthmic spondylolisthesis.

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How do outcomes from minimally invasive spinal surgery (for decompression and/or fusion) for the management of adult patients with isthmic spondylolisthesis compare with traditional/open techniques?

For the purposes of the literature analysis, the work group defined minimally invasive surgery as a posterior muscle sparing procedure.

In adult patients undergoing ALIF, supplemental posterior percutaneous pedicle screws lead to shorter hospital stays, less operation room time and less blood loss compared to open posterior instrumentation.

Grade of Recommendation: B

There is conflicting evidence whether in adult patients undergoing ALIF, supplemental posterior percutaneous pedicle screws lead to comparable clinical outcomes to those undergoing open posterior instrumentation.

Grade of Recommendation: I (Insufficient/Conflicting Evidence)

Kim et al[1] retrospectively compared the surgical outcomes of low-grade isthmic spondylolisthesis patients who had undergone ALIF with percutaneous pedicle screw fixation (n=43) to instrumented circumferential fusion (n=32), which comprised of mini-ALIF and instrumented PLF with iliac bone graft. All patients had single-level low-grade spondylolisthesis. Clinical outcomes were evaluated using the Visual Analog Scale (VAS) and functional outcomes were measured using the Oswestry Disability Index (ODI) and return to work status. The authors also compared operation time, blood loss, blood transfusions,

length of hospital stay, complications and radiologic results. Independent observers evaluated the radiologic outcomes on anteroposterior, lateral and flexion-extension radiographs. Patients in the ALIF group were followed for a mean of 41.1 months and circumferential fusion patients were followed for a mean of 32.9 months. In both groups, disc height, segmental lordosis, and degree of listhesis significantly improved from pre to post-op. Radiologic evidence of successful arthrodesis was noted in 97.7% of ALIF patients and 100% of circumferential fusion patients. There were no statistically significant differences in pre- to postoperative VAS and ODI scores between the groups. The mean VAS scores for back and leg pain and ODI scores significantly improved in the ALIF group from 7.6, 7.5 and 49.3%, respectively to 2.1, 2.0 and 13.7%, respectively (all $p<0.0001$). In the circumferential group, VAS back and leg pain and ODI scores improved from 7.4, 6.0 and 60.8% to 1.6, 0.8 and 6.8%, respectively (all $p<0.001$). The mean hospital stay was significantly shorter in the ALIF Group compared to circumferential fusion patients (7.4 days vs 15.2 days, $p<0.05$). There were also statistically significant differences in mean operation time and mean blood loss between the ALIF and circumferential patients (190 minutes vs. 260.8 minutes, $p<0.05$; 300mL vs. 379mL, $p<0.05$, respectively). There were no cases of life-threatening complications or wound infection in either group. In the ALIF group, there was one case of postoperative pneumonia, one case of urinary tract infection, one venous injury and one patient with a break in the pedicle screw. There were 2 cases of venous injury in the circumferential fusion group. This study offers Level III therapeutic data that ALIF followed by percutaneous screw fixation leads to comparable clinical results as ALIF followed by open posterior instrumented fusion. Patients who had undergone instrumented ALIF Group had shorter length of hospital stays, shorter operation time and less blood loss when compared to instrumented circumferential fusion patients.

Shim et al[2] retrospectively compared the clinical and radiological outcomes of elderly patients (> 65 years old) with L5–S1 isthmic spondylolisthesis and foraminal stenosis who received either ALIF and instrumented posterolateral fusion (PLF) or ALIF with percutaneous pedicle screw fixation (PSF). A total of 49 patients were included, including 23 patients in the ALIF PLF group and 26 patients in the ALIF and percutaneous PSF group. Postoperative assessments occurred at 3 months, 6 months and then annually. The mean follow-up was 30.3 months and outcomes were evaluated via VAS and modified MacNab criteria. Radiological parameters were evaluated using dynamic plain radiographs and CT scans. At 6 months and 2 years follow-up, there were significant decreases in VAS low back pain scores in both groups with statistically greater improvements in the ALIF PLF Group. The mean preoperative low back pain VAS score in the ALIF PLF was 5.9 and 5.7 in the ALIF with percutaneous PSF Group and improved to 1.4 and 3.6 ($p<0.001$), respectively, at 6 months and 1.3 and 2.3 ($p=0.003$), respectively, at 2 years. There were no statistically significant differences in VAS scores for leg pain between the groups. According to the modified MacNab criteria, 91.3% of ALIF PLF patients and 69.2% of ALIF and percutaneous PSF reported excellent or good outcomes at 6 months after surgery ($p=0.01$). This difference was significant at 6 months, favoring the ALIF PLF Group; however, at 2 years postoperatively, this difference was no longer significant. Complications rates were low, occurring in one patient per group. This study offers Level III therapeutic data that both ALIF and instrumented posterolateral fusion and ALIF with percutaneous pedicle screw fixation result in significant improvement in VAS scores. In patients over 65 years of age, ALIF followed by open posterior instrumented fusion had superior VAS back pain measures compared to ALIF followed by percutaneous pedicle screw instrumentation at 6 months and 2 years follow-up. At 6 months, fusion rates were statistically better in the fusion group; however, at 2 years, there was no difference between groups. Patients in the ALIF with percutaneous pedicle screw fixation group had shorter hospital stays, less OR time, less blood loss and less need for transfusion.

Future Directions for Research

The work group recommends the undertaking of a randomized controlled trial or prospective comparative study comparing traditional open techniques to minimally invasive spine surgery for the treatment of adult patients with isthmic spondylolisthesis.

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How do outcomes of dynamic stabilization compare with fusion for the treatment of isthmic spondylolisthesis in adult patients?

There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.

Future Directions For Research

The work group recommends the undertaking of comparative studies and multi-center registry database studies comparing dynamic stabilization to fusion for the treatment of isthmic spondylolisthesis in adult patients.

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Does the degree of radiological grade, sagittal spinopelvic alignment, sacral and spinopelvic parameters, or the presence of dynamic instability in adult patients with isthmic spondylolisthesis affect the outcomes of patients treated with surgery?

There is insufficient evidence to make a recommendation regarding the degree of radiological grade, sagittal spinopelvic alignment, sacral and spinopelvic parameters, or the presence of dynamic instability on the outcomes of adult patients undergoing surgical treatment for isthmic spondylolisthesis.

Grade of Recommendation: I (Insufficient Evidence)

Ming Li et al[1] conducted a prospective study to analyze the factors affecting surgical outcomes of low-grade isthmic spondylolisthesis patients undergoing posterolateral fusion (PLF). All 125 consecutive patients received a 6-month trial of conservative therapy with no improvement before undergoing surgical treatment. Preoperative and postoperative x-rays were taken of all patients and follow-up data and measurements were collected at a minimum of two years after surgery. Five cases were ultimately excluded from the analysis due to breakage of pedicle screws and pseudarthrosis and one death due to myocardial infarction. A total of 119 patients were evaluated for potential factors affecting the surgical outcome including the following preoperative variables: gender, age at operation, spondylolisthetic position, length of disease history and Japanese Orthopaedic Association (JOA) score; and the following postoperative variables: percentage disc height, percentage slip, JOA score and recovery rate. Multifactor stepwise correlation analysis was used to evaluate the correlation between pre and postoperative variables. Results from the analysis indicated that length of disease, preoperative JOA score and postoperative percentage of slipping were significantly related to postoperative JOA score and postoperative improved JOA score. Length of disease and postoperative percentage of slipping were significantly related to postoperative recovery rate. Age, gender, spondylolisthetic position and postoperative disc height were not significant factors. In critique, the preoperative and postoperative measurements, including percentage slip, for most variables are unclear and the authors did not utilize a validated outcome assessment tool. Due to these reasons, the work group has downgraded the level of evidence. For the purposes of addressing this clinical question, this potential Level I study offers Level II prognostic data that postoperative percentage slip is significantly correlated to postoperative JOA score.

Park et al[2] investigated the relationship between adjacent-segment degeneration (ASD) and pelvic parameters in isth-

mic spondylolisthesis patients. The records of 132 consecutive Grade I isthmic spondylolisthesis patients, who had undergone one stage, single-level (L4-L5 or L5-S1) 360o fixation and had follow-up data available for 1, 3, 6 and 12 months, were considered for this retrospective case-series review. The records of 34 patients, who had both pre and postoperative lateral radiograph images depicting the femur head, met inclusion criteria and were included in the prognostic analysis. Of the 34 patients, 7 had ASD and 27 did not. The 7 patients with ASD developed this condition after undergoing fusion. Radiographic measurements for degree of spondylolisthesis, lordotic angle, segmental lordosis, sacral slope angle, pelvic tilt and pelvic incidence were compared between the groups. The authors found that all cases of ASD occurred at the adjacent rostral segment and that the pre and postoperative measurements for degree of spondylolisthesis, segmental lordosis, lordotic angle, sacral slope angle and preoperative pelvic tilt and pelvic incidence did not differ significantly between groups. The only measures that were significantly different were postoperative pelvic tilt and pelvic incidence. The authors suggest that these parameters may be related to the development of ASD. This study offers Level IV prognostic data that postoperative pelvic tilt and pelvic incidence may be related to ASD.

Future Directions for Research

The work group recommends the undertaking of prospective or retrospective observational studies assessing influence of preoperative radiographic parameters on postoperative outcomes for adult patients undergoing surgical treatment for isthmic spondylolisthesis.

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Does the addition of fusion levels (cephalad, caudal or iliac) in the setting of a high grade isthmic spondylolisthesis in adult patients improve outcomes?

There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.

Future Directions for Research

The work group recommends the undertaking of prospective or retrospective observational studies assessing the influence of the addition of fusion levels on radiographic levels and clinical outcomes in adult patients undergoing surgical treatment for high grade isthmic spondylolisthesis.

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What is the long-term result (four+ years) of surgical management of adult patients with isthmic spondylolisthesis?

In adult patients undergoing surgical treatment for isthmic spondylolisthesis, fusion is suggested to provide long term clinical improvements.
Grade of Recommendation: B

There is insufficient evidence to indicate that fusion leads to improved long term outcomes as compared with a directed exercise program.
Grade of Recommendation: I (Insufficient Evidence)

There is insufficient evidence to recommend one surgical fusion technique over another to improve long term outcomes in adult patients undergoing surgical treatment for isthmic spondylolisthesis.
Grade of Recommendation: I (Insufficient Evidence)

There is insufficient evidence to determine the clinical significance of adjacent segment degeneration on the long term outcomes of fusion.
Grade of Recommendation: I (Insufficient Evidence)

Ekman et al[1] evaluated the long-term effects of patients who were randomly allocated to either posterolateral fusion or exercise for the treatment of isthmic spondylolisthesis. A total of 111 patients initially participated in the study, including 34 randomly allocated to an exercise program and 77 randomly allocated to posterolateral fusion, with or without transpedicular fixation. Patients in the exercise program completed 12 different exercises and required approximately 45 minutes per session. Four exercises included a pully and leg press machine, while 8 did not include specific training equipment so they could be performed at home. The patients exercised 3 times a week during the first 6 months and twice a week between 6 and 12 months. Functional disability was assessed by the Disability Rating Index (DRI) and pain was quantified using the Visual Analogue Scale (VAS). In addition, the observer and patients classified their overall outcome into "much better," "better," "unchanged," or "worse." Long-term follow-up with an average of 9 years was obtained in 101 of 111 (91%) patients. Long-term follow-up of the surgical group revealed that 11 patients (14%) underwent reoperation due to 2 nerve root injuries, one case of pseudarthrosis, one discectomy and 7 removal of implants. There were no early or late deep infections. In addition to evaluation for pain and functional disability using the VAS and DRI instruments, researchers also assessed patient reported quality of life using the SF-36, work status, disability using the Oswestry Disability Index (ODI) and global assessment classifying results into "much better," "better," "unchanged," or "worse." There were statistically significant improvements in the surgical group at long term follow-up measurements for DRI (48 to 33, $p<0.001$) and pain index (63 to 40, $p<0.0001$), but no significant improvements in the conservative group for these measures. There were no statistically significant differences in VAS, DRI, ODI, SF-36 or work ability between the surgical and conservative groups. Although not a validated measurement, the global assessment was significantly better for the surgical group with 76% classifying their overall outcome as "much better" compared to 50% of conservative care patients ($p=0.015$). This study provides Level I therapeutic evidence that the surgical group had significantly better outcomes at 9 years as measured by the global outcome compared to the conservative treatment group; however, there were no statistically significant differences in VAS, DRI, ODI and SF36 scores between the groups.

Using the same patient population as above, Ekman et al[2] evaluated the long-term correlation of lumbar fusion to the development of adjacent segment disorder (ASD) in isthmic spondylolisthesis patients. A total of 80 (72%) patients, including 63 fusion patients and 17 exercise patients, whose standing A-P and lateral radiographs were available at 10-year follow-up, were included in this analysis. Using measurements taken on the radiographs, the authors used three different methods to quantify disc degeneration, including: digital radiographic measurement method, quantitative analysis software and the UCLA grading scale of disc degeneration. The prevalence of ASD at long-term follow-up was determined using four different diagnostic criteria: (1) disc height reduction > 2SD over the mean reduction as observed in the exercise group, (2) remaining mean disc height less than 20% of anterior vertebral height, (3) worsening of the UCLA score from pretreatment and (4) totally reduced poste-

rior disc height at long-term follow-up. Using the first, second, third and fourth criteria to determine the prevalence of ASD, it was found that 6%, 6%, 0% and 0% of exercise patients, respectively, versus 14%, 11%, 38% and 6% of fusion patients, respectively, were found to have ASD. In fusion patients, the use of instrumentation did not affect the prevalence of ASD using any definition. In a subgroup analysis of laminectomy versus non-laminectomy patients, 22 of 47 patients who received combined PLF and laminectomy were diagnosed with ASD using the third (UCLA) criteria compared to only 2 of 16 PLF without laminectomy patients (p=0.015). When comparing prevalence rates between these subgroups using the other criteria, however, there were not any statistically significant differences in prevalence rates. When evaluating the impact of ASD on outcomes using the first criteria, it was found that only 11% of PLF patients with ASD rated themselves as "much better" according to global outcome assessment compared to 49% of PLF patients without ASD (p<0.036). No statistically significant differences in outcomes comparing ASD versus non-ASD patients were found using the other diagnostic criteria. In general, the outcome measurements for Pain Index, DRI, ODI and global outcome were insignificantly worse for the patients defined as having ASD regardless of the criteria used. In critique, less than 80% of patient records were available at 10 years follow-up; thus, necessitating the work group to downgrade the level of evidence from I to II. Although this patient population was used in the previous study, the study objectives for this analysis are different and therefore provide different study conclusions. Thus, this potential Level I study offers Level II therapeutic data that at a mean 12 years follow-up, fusion is more likely to lead to an ASD compared to an exercise program. In addition, subgroup analysis reveals that patients with laminectomy in addition to their fusions are more likely to develop ASD when compared to patients undergoing fusion alone. There is insufficient data to make a conclusion about the long term clinical correlation of ASD on outcomes.

In a randomized controlled trial, Bjarke Christensen et al[3] evaluated the long term effect of instrumentation on reoperation and functional outcome. A total of 129 patients with severe chronic low back pain were included in the study, including 35 patients with Grade I or II isthmic spondylolisthesis, 41 patients with primary degenerative instability and 53 patients with secondary degenerative instability. Upon enrollment, patients were consecutively allocated using a 20-number-per-block concealed randomization process into either fusion with or without supplementary transpedicular screw fixation. Functional outcomes were assessed by the Dallas Pain Questionnaire (DPQ) and the Low Back Pain Rating Scale (LBPR) and scored by an independent observer. At 5 years follow-up, 8 isthmic spondylolisthesis patients in the instrumented group underwent or were planning reoperation and 2 isthmic spondylolisthesis patients in the non-instrumented group underwent or were planning reoperation. Isthmic spondylolisthesis patients in the non-instrumented group had highly significant improvement in three out of four DPQ categories (daily activity, anxiety/depression, and social concerns) and in all three LPBQ questions compared to instrumented patients. Overall, among all diagnosis groups, there were no significant differences in functional outcome as measured by the DPQ and LBPR between the instrumented and noninstrumented groups. When analyzing diagnosis subgroups, the authors found that patients with isthmic spondylolisthesis in the no instrumentation group had significantly better outcomes than patients who received instrumented fusion (p<0.03). In critique, due to the small sample size of the subgroup of isthmic spondylolisthesis patients and use of non-validated outcome instruments, the work group has downgraded this study from Level I to Level II. At the 5-year follow-up, isthmic spondylolisthesis patients who received posterolateral fusion without supplemental instrumentation had a significantly better DBQ outcomes compared to patients who received instrumented fusion (p=0.03).

Vidabeck et al[4] described the long-term outcomes of patients undergoing either posterolateral fusion (PLF) with titanium instrumentation or circumferential fusion for the treatment of Grade I or II isthmic spondylolisthesis, primary degeneration, secondary degeneration, or accelerating degeneration. Circumferential fusion was performed via anterior lumbar interbody fusion with the use of a radiolucent cage, using a retroperitoneal approach to the lumbar discus plus posterolateral fusion. Within the isthmic spondylolisthesis subgroup, 19 patients were initially randomized to the PLF Group and 24 were initially randomized to the circumferential group. A total of 125 patients completed the final follow-up at 5 to 9 years after surgery, resulting in an overall response rate of 86%. The long-term response rate for isthmic spondylolisthesis subgroup was not documented. Outcomes were assessed using the Dallas Pain Questionnaire (DPQ), Low Back Pain Rating Scale (LBPR), Oswestry Disability Index (ODI) and Short Form-36 (SF-36) and radiographic measurements; however, only DPQ scores were available for isthmic spondylolisthesis patients. As measured by the DPQ, there were no significant differences in functional outcomes between surgical groups at long term follow-up. In critique, there was no subgroup analysis of isthmic spondylolisthesis patients for most outcome measures and the subgroup sample size was small and thus potentially underpowered to detect any statistical differences. Due to these reasons, the work group downgraded the level of evidence of this study from I to II. This study provides Level II therapeutic evidence that at a minimum of 5 years follow-up, there were no significant functional differences between instrumented posterolateral fusion versus circumferential fusion in the subgroup of patients with isthmic spondylolisthesis.

Future Directions for Research

The work group recommends the undertaking of prospective or retrospective studies comparing the long term effectiveness of various surgical treatments and nonoperative treatments on clinical outcomes, radiographic outcomes and adjacent segment degeneration in adult patients with isthmic spondylolisthesis.

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Are the results of surgical management for adult patients with isthmic spondylolisthesis affected by the presence of scoliosis or concurrent deformity?

There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.

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Which prognostic factors have been associated with good or poor outcomes in the surgical management of adult patients with isthmic spondylolisthesis?

There is insufficient evidence to make a recommendation regarding which prognostic factors have been associated with good or poor outcomes.

Grade of Recommendation: I (Insufficient Evidence)

Ekman et al[1] evaluated the long term correlation of lumbar fusion to the development of adjacent segment disorder (ASD) in isthmic spondylolisthesis patients. A total of 111 patients initially participated in the study, including 34 randomly allocated to an exercise program and 77 randomly allocated to posterolateral fusion, with or without transpedicular fixation. Patients in the exercise program completed 12 different exercises and required approximately 45 minutes per session. Four exercises included a pully and leg press machine, while eight did not include specific training equipment so they could be performed at home. The patients exercised three times a week during the first 6 months and twice a week between 6 and 12 months. Functional disability was assessed by the Disability Rating Index (DRI) and pain was quantified using the Visual Analogue Scale (VAS). In addition, the observer and patients classified their overall outcome into "much better," "better," "unchanged" or "worse." For the purposes of this analysis, a total of 80 (72%) patients, including 63 fusion patients and 17 exercise patients, whose standing A-P and lateral radiographs were available at 10 year follow-up, were included. Using measurements taken on the radiographs, the authors used three different methods to quantify disc degeneration, including: digital radiographic measurement method, quantitative analysis software and the UCLA grading scale of disc degeneration. The prevalence of ASD at long-term follow-up was determined using four different diagnostic criteria: (1) disc height reduction > 2SD over the mean reduction as observed in the exercise group, (2) remaining mean disc height less than 20% of anterior vertebral height, (3) worsening of the UCLA score from pretreatment and (4) totally reduced posterior disc height at long-term follow-up.

Using the first, second, third and fourth criteria to determine the prevalence of ASD, it was found that 6%, 6%, 0% and 0% of exercise patients, respectively, versus 14%, 11%, 38% and 6% of fusion patients, respectively, were found to have ASD. In fusion patients, the use of instrumentation did not affect the prevalence of ASD using any definition. In a subgroup analysis of laminectomy versus non-laminectomy patients, 22 of 47 patients who received combined PLF and laminectomy were diagnosed with ASD using the third (UCLA) criteria compared to only 2 of 16 PLF without laminectomy patients ($p=0.015$). When comparing prevalence rates between these subgroups using the other criteria, however, there were not any statistically significant differences in prevalence rates. When evaluating the impact of ASD on outcomes using the first criteria, it was found that only 11% of PLF patients with ASD rated themselves as "much better" according to global outcome assessment compared to 49% of PLF patients without ASD ($p<0.036$). No statistically significant differences in outcomes comparing ASD versus non-ASD patients were found using the other diagnostic criteria. In general, the outcome measurements for Pain Index, DRI, ODI and global outcome were insignificantly worse for the patients defined as having ASD regardless of the criteria used. In critique, less than 80% of patient records were available at 10 years follow-up; thus, necessitating the work group to downgrade the level of evidence from I to II. Although this patient population was used in the previous study, the study objectives for this analysis are different and therefore provide different study conclusions. Thus, this potential Level I study offers Level II prognostic evidence that that fusion is more likely to lead to an ASD compared to an ex-

ercise program, but ASD does not negatively affect outcomes at two year follow-up. Subgroup analysis reveals that patients with laminectomy in addition to their fusions are more likely to develop ASD when compared to patients undergoing fusion alone.

Future Directions For Research

The work group recommends the undertaking of multi-center registry database studies assessing the clinical characteristics associated with the successful short and long-term outcomes in adult patients undergoing surgical treatment for isthmic spondylolisthesis.

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F. Value/Cost-Effectiveness

Which medical or interventional treatment method of isthmic spondylolisthesis is the most cost-effective?

There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.

Future Directions For Research

The work group recommends the undertaking of cost-analysis studies evaluating the long term cost-effectiveness of medical or interventional treatments in adult patients undergoing treatment for isthmic spondylolisthesis.

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Is the surgical treatment of isthmic spondylolisthesis cost-effective compared to the medical and interventional therapies?

There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.

Future Directions For Research

The work group recommends the undertaking of cost-analysis studies evaluating the long term cost-effectiveness of surgical treatments versus medical or interventional therapies in adult patients undergoing treatment for isthmic spondylolisthesis.

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Which surgical treatment method of isthmic spondylolisthesis is the most cost-effective?

There was no evidence to address this clinical question. Due to the paucity of literature addressing this question, the work group was unable to generate a recommendation.

Future Directions for Research

The work group recommends the undertaking of cost-analysis studies evaluating the long term cost-effectiveness of surgical treatments in adult patients undergoing treatment for isthmic spondylolisthesis.

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VI. Appendices

A. Acronyms

CI	confidence interval
CT	computed tomography
DH	disc height
DRI	Disability Rating Index
EBM	evidence-based medicine
EMG	electromyelography
JOA	Japanese Orthopaedic Association
LBPR	Low Back Pain Rating Scale
LL	lumbar lordosis
MR	magnetic resonance
MRI	magnetic resonance imaging
NASS	North American Spine Society
NCOS	Neurogenic Claudication Outcome Score
NSAIDs	nonsteroidal anti-inflammatory drugs
ODI	Oswestry Disability Index
PI	pelvic incidence
PLIF	Posterior lumbar interbody fusion
PLF	Posterolateral fusion
PT	pelvic tilt
RDQ	Roland-Morris Disability Questionnaire
RCT	randomized controlled trial
SR	sagittal rotation
SS	sacral slope
ST	sagittal translation
SEP	somatosensory evoked potentials
SNRB	selective nerve root block
TK	thoracic kyphosis
TENS	transcutaneous electrical nerve stimulation
VAS	Visual analog scale

B. Levels of Evidence for Primary Research Question[1]

	Types of Studies			
	Therapeutic Studies – Investigating the results of treatment	Prognostic Studies – Investigating the effect of a patient characteristic on the outcome of disease	Diagnostic Studies – Investigating a diagnostic test	Economic and Decision Analyses – Developing an economic or decision model
Level I	• High quality randomized trial with statistically significant difference or no statistically significant difference but narrow confidence intervals • Systematic review[2] of Level I RCTs (and study results were homogenous[3])	• High quality prospective study[4] (all patients were enrolled at the same point in their disease with ≥ 80% follow-up of enrolled patients) • Systematic review2 of Level I studies	• Testing of previously developed diagnostic criteria on consecutive patients (with universally applied reference "gold" standard) • Systematic review[2] of Level I studies	• Sensible costs and alternatives; values obtained from many studies; with multiway sensitivity analyses • Systematic review[2] of Level I studies
Level II	• Lesser quality RCT (eg, < 80% follow-up, no blinding, or improper randomization) • Prospective[4] comparative study[5] • Systematic review[2] of Level II studies or Level 1 studies with inconsistent results	• Retrospective[6] study • Untreated controls from an RCT • Lesser quality prospective study (eg, patients enrolled at different points in their disease or <80% follow-up) • Systematic review[2] of Level II studies	• Development of diagnostic criteria on consecutive patients (with universally applied reference "gold" standard) • Systematic review[2] of Level II studies	• Sensible costs and alternatives; values obtained from limited studies; with multiway sensitivity analyses • Systematic review[2] of Level II studies
Level III	• Case control study[7] • Retrospective[6] comparative study[5] • Systematic review[2] of Level III studies	Case control study[7]	• Study of non-consecutive patients; without consistently applied reference "gold" standard • Systematic review[2] of Level III studies	• Analyses based on limited alternatives and costs; and poor estimates • Systematic review[2] of Level III studies
Level IV	Case series[8]	Case series	• Case-control study • Poor reference standard	Analyses with no sensitivity analyses
Level V	Expert Opinion	Expert Opinion	Expert Opinion	Expert Opinion

1. A complete assessment of quality of individual studies requires critical appraisal of all aspects of the study design.
2. A combination of results from two or more prior studies.
3. Studies provided consistent results.
4. Study was started before the first patient enrolled.
5. Patients treated one way (eg, cemented hip arthroplasty) compared with a group of patients treated in another way (eg, uncemented hip arthroplasty) at the same institution.
6. The study was started after the first patient enrolled.
7. Patients identified for the study based on their outcome, called "cases" (eg, failed total arthroplasty) are compared to those who did not have outcome, called "controls" (eg, successful total hip arthroplasty).
8. Patients treated one way with no comparison group of patients treated in another way.

C. Grades of Recommendations for Summaries or Reviews of Studies

A: Good evidence (Level I Studies with consistent finding) for or against recommending intervention.

B: Fair evidence (Level II or III Studies with consistent findings) for or against recommending intervention.

C: Poor quality evidence (Level IV or V Studies) for or against recommending intervention.

I: Insufficient or conflicting evidence not allowing a recommendation for or against intervention.

D. Linking Levels of Evidence to Grades of Recommendation

Grade of Recommendation	Standard Language	Levels of Evidence	
A	Recommended	Two or more consistent Level I studies	
B	Suggested	One Level I study with additional supporting Level II or III studies	Two or more consistent Level II or III studies
C	May be considered; is an option	One Level I, II or III study with supporting Level IV studies	Two or more consistent Level IV studies
I (Insufficient or Conflicting Evidence)	Insufficient evidence to make recommendation for or against	A single Level I, II, III or IV study without other supporting evidence	More than one study with inconsistent findings*
*Note that in the presence of multiple consistent studies, and a single outlying, inconsistent study, the Grade of Recommendation will be based on the level of consistent studies.			

E. Protocol for NASS Literature Searches

One of the most crucial elements of evidence analysis to support development of recommendations for appropriate clinical care or use of new technologies is the comprehensive literature search. Thorough assessment of the literature is the basis for the review of existing evidence, which will be instrumental to these activities. It is important that all searches conducted at NASS employ a solid search strategy, regardless of the source of the request. To this end, this protocol has been developed and NASS-wide implementation is recommended.

NASS research staff will work with the requesting parties and the NASS-contracted medical librarian to run a comprehensive search employing at a minimum the following search techniques:

1. A comprehensive search of the evidence will be conducted using the following clearly defined search parameters (as determined by the content experts). The following parameters are to be provided to research staff to facilitate this search.

- Time frames for search
- Foreign and/or English language
- Order of results (chronological, by journal, etc.)
- Key search terms and connectors, with or without MeSH terms to be employed
- Age range
- Answers to the following questions:
    - o Should duplicates be eliminated between searches?
    - o Should searches be separated by term or as one large package?
    - o Should human studies, animal studies or cadaver studies be included?

This search will encompass, at minimum, a search of Medline/PubMed, EMBASE, and Cochrane Library. Additional databases may be searched depending upon the topic.

2. Search results with abstracts will be compiled by the medical librarian in Endnote software. The medical librarian typically responds to requests and completes the searches within two to five business days. Results will be forwarded to the research staff, who will share it with the appropriate NASS staff member or requesting party(ies). (Research staff has access to EndNote software and will maintain a database of search results for future use/documentation.)

3. NASS staff shares the search results with an appropriate content expert (NASS Committee member or other) to assess relevance of articles and identify appropriate articles to review.

4. NASS research staff will work with LoansomeDoc library to obtain requested full-text articles for review.

5. NASS members reviewing full-text articles should also review the references at the end of each article to identify additional articles which should be reviewed, but may have been missed in the search.

Following this protocol will help ensure that NASS recommendations are (1) based on a thorough review of relevant literature; (2) are truly based on a uniform, comprehensive search strategy; and (3) represent the current best research evidence available. Research staff will maintain a search history in EndNote for future use or reference.

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