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What's New in Spine Surgery.

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SPECIALTY UPDATE

What's New in Spine Surgery

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What's New in the Treatment of the Cervical Spine

Clinical spinal research has excelled in the past year, and the results will aid in decision making for our patients. A large observational trial and a series of systematic reviews on cervical myelopathy provide much-needed evidence regarding treatment decisions. The measurement and understanding of cervical spinal alignment as part of the overall spinal balance and its correlation to pain and neurologic dysfunction is being critically evaluated. Three new cervical artificial discs have been approved, and long-term outcomes of already approved devices show maintenance of good and excellent outcomes.

Cervical Myelopathy

Fehlings et al. reported on the one-year results of a multicenter observational study of 222 patients with cervical myelopathy. Significant improvement was seen in pain reduction, function, gait, and quality of life after surgery. Three patients had neurologic deterioration perioperatively, and two recovered to their baseline status. The outcomes with regard to anterior or posterior approach, after adjusting for baseline differences, showed no statistical differences. In a multivariate analysis, predictors of poor outcome were longer duration of symptoms, poorer baseline function, the presence of psychological comorbidities, severe gait disorder, and older age.

The journal *Spine* recently published a focus issue on cervical myelopathy. The authors used systematic reviews and, when appropriate, made recommendations in accordance with currently accepted standards. Those reviews indicated that 20% to 60% of patients with symptomatic cervical myelopathy had subsequent neurologic deterioration if the myelopathy was not treated surgically. Chronic spinal cord compression can result in chronic inflammation, cellular apoptosis, and microvascular

compromise, which are believed to be the biologic basis for neural deterioration. Unfortunately, no effective nonoperative treatment was identified.

In asymptomatic patients who had spinal cord compression, there was strong evidence that 8% at one year and 23% of patients at a median follow-up time of forty-four months will develop symptomatic cervical myelopathy. There were conflicting results with regard to the prediction of outcome based on the effect of cord signal changes. Asymptomatic patients with clinical or electrophysiological evidence of radicular dysfunction or central conduction deficits have an increased risk of the development of symptomatic cervical myelopathy. Imaging predictors of deterioration and surgical outcome remain enigmatic. Only weak associations can be found between the development of symptomatic cervical myelopathy and high signal on T2-weighted magnetic resonance imaging (MRI), the number of levels compressed, the presence of signal changes on T1-weighted and T2-weighted MRI, and spinal cord compression ratios that exceed 50%. If T2-weighted signal changes are to be used clinically, they should be used in combination with other imaging parameters, such as compression ratio and the number of levels involved.

Sagittal Balance of the Cervical Spine

Sagittal balance of the cervical spine and its relation to overall spinal alignment and neurologic syndromes is increasingly being evaluated. It is known that scoliotic patients with thoracic hypokyphosis have compensatory cervical kyphosis. Newer thinking is that cervical malalignment should be assessed in conjunction with thoracolumbar sacral pelvic alignment. Kyphosis can be evaluated with use of the C2-C7 Cobb angle or its variants or by evaluation of sagittal alignment. The latter is best performed with use of the C2-C7 sagittal vertical axis, measured as the horizontal distance between a plumb line from the center of C2 and the posterior aspect of the C7 superior end

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plate. Sagittal cervical malalignment can also be associated with pain and myelopathy. In a study of fifty-six patients with cervical myelopathy, sagittal alignment (as documented by C2-C7 sagittal vertical axis but not kyphotic angle) correlated with myelopathic symptoms. Further, increased C2-C7 sagittal vertical axis was correlated with decreased cord volume and cross-sectional area, while the opposite was true for lordotic alignment.

Disc Arthroplasty

In the last year, two additional total cervical disc replacement devices have been approved by the U.S. Food and Drug Administration (FDA) for single-level radiculopathy or myelopathy while another was approved by the FDA for both single level and two levels. These devices had similar outcomes and safety profiles as the other already approved discs. Long-term outcomes of currently approved devices at seven to nine years after implantation show maintenance of good to excellent clinical outcomes and, in general, lower reoperation rates at adjacent levels as compared with the reoperation rates of control patients who were managed with fusion. Explant analyses of cervical discs have consistently shown pathologic wear patterns secondary to edge impingement. However, substantial inflammatory reactions, such as those seen in patients with metal-on-metal arthroplasty devices, are rare. Cost analyses made with use of insurance databases show lower costs after arthroplasty than after fusion, largely because of lower reoperation rates and lower postoperative cost of care.

What's New in Biologic Topics for the Spine

Much of the 2013 focus on biologics in the spine was centered on the safety of recombinant human bone morphogenetic proteins (rhBMPs). In addition, there were continued efforts to find biologic treatments for disc degeneration.

Recombinant Osteoinductive Proteins

In 2013, there was a continued focus on the potential local adverse events associated with rhBMP-2. Since 2011, questions have been raised with regard to the association of INFUSE bone graft (Medtronic) with retrograde ejaculation and cancer. In June of 2013, the Yale University Open Data Access (YODA) effort reported two independent assessments of raw data from the Medtronic clinical trial database on INFUSE. One study confirmed that fusion success was comparable with that achieved with autograft, and the other study showed a slight increase in fusion rates for the INFUSE group. Neither study found a significant increase in retrograde ejaculation. One study showed an increased risk of cancer at twenty-four but not forty-eight months, while the authors of the other study believed that the small number of cancer events precluded firm conclusions. Review of the FDA investigational device exemption data regarding posterolateral higher dose (40 mg) rhBMP-2 showed that there was a higher prevalence of cancer in patients who received rhBMP-2 than there was in control patients, raising the possibility of a dose effect. Since the time of publication of those

studies, a review of 146,000 Medicare patients (average 4.7-year follow-up; 15.4% rhBMP patients versus 17.0% control patients with detected new cancer) demonstrated no association of rhBMP with cancer risk. While any actual association with cancer remains unclear, the most likely potential mechanism of tumor enhancement may be via induction of vascular endothelial growth factor or other factors that promote tumor survival, since rhBMP-2 biologically typically slows growth in the majority of cancer cell lines.

The relative benefit and potential local side effects of INFUSE are best reviewed with regard to the specific application. Use of INFUSE in anterior cervical spine fusion has been associated with increased seromas and dysphagia. Recent work has confirmed that these local side effects are dose-related. Use of INFUSE in multilevel anterior cervical arthrodesis resulted in higher fusion rates without complications when the dose did not exceed 1.1 mg/level.

Anterior lumbar interbody fusion, the only "on-label" indication, has been associated with vertebral resorption and graft subsidence. Recent studies suggest that these side effects are related to dose (>6 mg/level) and possibly to aggressive end-plate decortication.

Posterior or transforaminal lumbar interbody fusion with INFUSE is associated with an increased prevalence of postoperative radiculitis in some reports. Other reports demonstrate consistently high fusion rates (>90%) with low rates of seroma (<0.4%) and ectopic bone (0.6%). This dichotomy suggests that these local side effects are avoidable with proper dosing and surgical technique.

Posterolateral spine fusion is the application that likely affords the greatest opportunity for improvement of fusion rates with use of iliac crest bone graft. The four-year follow-up results of a Canadian study showed that fusion rates were higher in the rhBMP-2 group (94%) than they were in the group with autograft (69%). Another study added INFUSE to local bone graft and demonstrated high (>95%) fusion rates. The complication rate related to rhBMP-2 does not appear to be any higher in patients who are sixty-five years or older than it is in younger patients.

Spinal deformity in adults is another area in which the use of INFUSE can result in a major improvement in fusion success. In the first report of the use of a high-dose (40 to 351 mg) of INFUSE in adult multilevel posterolateral and interbody fusions, the cancer prevalence rate was 3.4% and there was no correlation to increased dose. There was also no dose correlation with radiculopathy (1%) or seroma (0.6%). A prospective international study also reported no correlation between rhBMP-2 use and complications in adult patients with spinal deformity. In another report of long fusions to the sacrum, the use of rhBMP reduced the nonunion rate from 28.1% to 6.4%, and to 0% when >5 mg/level rhBMP-2 was used. Use of 20 mg rhBMP-2 posterolaterally at the L5-S1 level can provide a comparable fusion rate at a lower cost than a combined interbody fusion at that level.

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Other Bone-Graft Substitutes

Although much focus remains on rhBMPs, their relatively high cost has continued to encourage research involving other bone-graft solutions. There is continued interest in bone marrow, and studies show that the first 2 to 4 mL of aspirate from a vertebra is optimal. The clinical effectiveness of marrow remains in question.

Biologic Treatments for Disc Degeneration

Progress toward biologic treatments to prevent or retard disc degeneration continues. There is continued interest in the anabolic effect of BMP-7, link protein peptide, and platelets. Most of the studies in the past year have been in vitro proof-of-concept studies, which are difficult to translate into organ culture or the in vivo setting, making this a rewarding but challenging area.

What's New in Spinal Deformity Surgery

There were 129 papers presented from the podium and 105 posters presented at the Forty-eighth Annual Meeting of the Scoliosis Research Society (SRS), which met from September 18 through 21, 2013, in Lyon, France.

Adolescent Idiopathic Scoliosis

Studies from the SRS member database reviewed more than 17,400 cases of adolescent idiopathic scoliosis and demonstrated that, compared with the operations performed a decade previous to this writing, operations for adolescent idiopathic scoliosis are currently being performed with fewer complications and with an all-posterior approach. The decrease in complications may be attributed to the decrease in combined anterior-posterior approaches for these deformities as well as to the use of pedicle screw instrumentation, which increased from 9.5% of cases in 2002 to more than 50% in 2007.

Curve progression after treatment for adolescent idiopathic scoliosis continues to be a concern. At the time of the five-year follow-up in one study, a 22% prevalence of distal adding on was demonstrated after posterior spinal fusion for adolescent idiopathic scoliosis, although this did not affect clinical outcomes or revision surgery rates.

Dr. Stuart Weinstein reported the results of the National Institutes of Health (NIH) Bracing in Adolescent Idiopathic Scoliosis Trial (BRAIST), a prospective randomized, clinical study of the efficacy of bracing for the treatment of adolescent idiopathic scoliosis. In the short term, bracing was effective in this study, and compliance over thirteen waking hours of the day was recommended.

Adult Spinal Deformity

More than 7500 cases of surgically treated adult spinal deformity were reviewed in a study of the SRS member database. Unlike adolescent cases, these continue to have roughly equal combined anterior-posterior and all-posterior approaches for management. The combined anterior-posterior approach demonstrated higher complication rates. Nonetheless, studies from the International

Spine Study Group demonstrated that operative treatment of adult spinal deformity is cost-effective and results in superior outcomes as compared with nonoperative treatment.

Use of rhBMP-2 in long fusions for the treatment of adult scoliosis was a topic presented with much attention. In adult deformity surgery, rhBMP-2 was associated with fewer complications in the long term and lower rates of revision surgery due to implant failures at a minimum follow-up of two-years when compared with cases in which no rhBMP-2 was used. With regard to the possible risk of cancer, a study that was presented at the 2013 SRS annual meeting and in which more than 127,000 cases of rhBMP-2 use were reviewed demonstrated that age was the most important risk factor for the development of cancer, whereas use of rhBMP-2 was not definitively related to cancer prevalence.

Important prospective data from one multicenter study on adult deformity surgery demonstrated a 17% risk of neurologic complications occurring as a result of adult deformity surgery.

Proximal junctional kyphosis continues to be a clinical enigma, with three papers focused on this topic. Although prior studies have demonstrated that sagittal balance corrections to 0 cm and high lumbar lordosis were associated with good outcomes, data were presented that suggest that, for older patients having deformity surgery, the patient should be allowed to remain with a small amount of positive sagittal balance and to have a more moderate restoration of lumbar lordosis to provide a more natural global sagittal balance and possibly prevent proximal junctional kyphosis.

In a randomized controlled trial, the use of antifibrinolytic agents in adult deformity surgery resulted in lower intraoperative blood loss as compared with that in control patients.

Neuromuscular Scoliosis

Infection continues to be an important concern in the surgical management of neuromuscular scoliosis. Multiple studies demonstrated lower infection rates in patients with neuromuscular scoliosis when topical vancomycin was placed in the wound at the time of closure. No associated systemic complications were reported using this technique.

Early Onset Scoliosis

Preliminary data on vertebral body stapling for the treatment of early onset scoliosis were reported. However, the cohort was small and the follow-up was short.

Basic Science

A number of centers continue to develop animal models for idiopathic scoliosis. One study reproduced a juvenile-type scoliosis in mice with steroid receptor deficiency in chondrocytes. However, this model seems to be more demonstrative of the skeletal dysplasia type of scoliosis rather than idiopathic scoliosis.

Vitamin D continues to draw research interest, with an animal study showing larger and more robust fusion masses in vitamin-D-replete rats as compared with vitamin-D-deficient rats.

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What's New in the Treatment of Spinal Cord Injury

Given the low prevalence of spinal cord injury and the rapid rate of recovery within the first three months after injury, any effort to demonstrate an effective intervention that improves spinal cord recovery requires an extensive data set incorporating multiple centers and investigators.

Pharmacologic Neuroprotective Intervention

Riluzole, a benzothiazole anticonvulsant sodium-channel blocking agent that has FDA approval for use in amyotrophic lateral sclerosis, has recently completed a prospective, multicenter phase-1 study looking at the efficacy, pharmacokinetics, and safety of its use in the treatment of patients with spinal cord injury.

Riluzole binds and blocks voltage-gated sodium channels, potentially mitigating against excitotoxic neural damage as well as blocking presynaptic calcium-dependent glutamate release, a mechanism known to be involved in secondary injury to the spinal cord. Data from the North American Clinical Trials Network (NACTN) spinal cord injury registry revealed that patients who were given 50 mg riluzole by mouth or via nasogastric tube twice daily for fourteen days, starting within twelve hours after cervical spinal cord injury, were noted to have a 31.2-point increase in mean motor score at ninety days after injury compared with a 15.7-point improvement in matched NACTN-registry patients who received no riluzole.

In an effort to improve neurologic outcome in patients who have sustained an acute, complete spinal cord injury, a phase-2 randomized controlled multicenter trial using site-specific injection of macrophages was performed. Autologous incubated macrophages were injected into the caudal boundary of the spinal cord injury. During the six-month follow-up period, neurologic improvement from grade A to grade B of the American Spinal Injury Association (ASIA) Impairment Scale (AIS) was experienced in only seven of twenty-six treatment patients, whereas improvement occurred in ten of seventeen control patients. Improvement from AIS grade A to grade C occurred in two treatment and two control patients. Overall, there was a trend favoring the control group for the primary outcome measure.

Pharmacologic Neuroregenerative Intervention

Results of a phase-1/2a clinical trial of BA-210 (trademarked as Cethrin by BioAxone Biosciences), a Rho pathway antagonist, were recently reported. A multicenter study enrolled forty-eight AIS grade-A cervical (C4-T1) and thoracic (T2-T12) spinal-cord-injured patients and followed them for one year after the injury. A single dose of Cethrin combined with a fibrin sealant was applied directly to the dura mater following a decompression. The dose ranged from 0.3 to 9 mg. The largest observed change in motor score occurred in the 3-mg-dose group, with 6% of the thoracic patients improving from AIS grade A to C or D as compared with 33% of cervical patients. The small number of study participants in this study renders efficacy somewhat difficult to interpret.

As recently as June 2013, minocycline was entered into a phase-3 clinical trial examining the efficacy of intravenous minocycline treatment compared with placebo in non-penetrating spinal cord injury. The phase-2 study, recently presented, demonstrated marked recovery in patients who had been managed with minocycline in the cervical spinal cord injury group, whereas the thoracic group demonstrated no benefit. Mean ASIA motor score improvement in the cervical group was 14 points over controls at the time of the final follow-up ($p = 0.05$).

On January 23, 2013, physicians of the Miami Project to Cure Paralysis successfully performed the first Schwann-cell transplantation in a patient with new spinal cord injury. This surgery was part of an FDA-approved phase-1 clinical trial evaluating the safety and efficacy of autologous Schwann-cell transplantation into patients with spinal cord injury. The study patients will be followed for twelve months after transplantation. The olfactory mucosa comprises neurosensory cells that are continuously renewed throughout life. A prime component of the olfactory mucosa, the olfactory ensheathing cells are pluripotent stem cells exhibiting Schwann-cell-like properties that function within the olfactory mucosa to guide growth of axons from mucosal neurons to the olfactory bulb. Olfactory ensheathing cells can be obtained from either the olfactory mucosa or from cells of the olfactory bulb, which exists above the cribriform plate of the ethmoid bone at the base of the brain. Despite the fact that olfactory mucosa cells require a purification process that is unnecessary with olfactory bulb cells, on the basis of a recent risk-to-benefit analysis of the use of olfactory mucosa cells and olfactory bulb cells, the process to obtain olfactory mucosa cells is associated with much less morbidity, resulting in a much better risk-to-benefit ratio.

What's New in the Treatment of the Lumbar Spine

Pathologies leading to lumbar spinal disorders continue to be one of the most common clinical problems faced by spine practitioners. Over the past year, there have been a number of research studies that have given an update on some of these specific problems.

Reduction of Blood Loss

Authors presented a study looking at the use of antifibrinolytic agents such as tranexamic acid and aminocaproic acid in patients undergoing long posterior spinal fusion for the treatment of adult deformity. This was a prospective double-blinded study of patients receiving either tranexamic acid (nineteen patients), aminocaproic acid (nineteen patients), or placebo (fourteen patients) in the operating room (mean ages: sixty, forty-seven, and forty-five years, respectively). For patients who were fifty years or older, intraoperative blood loss in both the tranexamic acid and aminocaproic acid groups was less than that seen in the control group, although there was no significant difference for patients who were younger than fifty years. There was also a significantly lower postoperative transfusion rate between aminocaproic acid and placebo groups. One patient in each treatment arm was

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diagnosed with a pulmonary embolism. The findings support the use of these antifibrinolytic agents in adult deformity surgery in patients who are older than fifty years.

Nonoperative Management

The effect of nonoperative treatment continues to be of interest. Utilizing a prospective registry, one group of authors performed a comparative effectiveness and cost-utility analysis comparing surgical and nonsurgical medical management in elderly patients with surgical degenerative disorders. Ninety-five elderly patients (i.e., older than sixty-five years) with degenerative lumbar spondylosis conditions (stenosis, spondylolisthesis, or disc herniation) had surgery and were entered into a prospective registry. Both surgical and nonsurgical treatments were tracked at a single institution. Of the ninety-five patients, fifty had surgical treatments while forty-five had only nonsurgical medical management. Surgical management demonstrated a significant two-year improvement in all clinical validated outcome measures, while nonsurgical management failed to provide any significant improvement in any measure (visual analog scale, Oswestry Disability Index, EuroQol 5D, or quality-adjusted life years). The two-year gain in quality-adjusted life years was significantly greater after surgical management (0.67 quality-adjusted life years gained) than after nonsurgical medical management (0.18 quality-adjusted life year gained). Total cost over the two-year period was significantly greater for surgical management (\$41,500) than for nonsurgical management (\$14,000), and cost per quality-adjusted life year gained for surgical management versus nonsurgical management was \$56,437. From a value-based purchasing and patient-centered perspective, prolonged nonsurgical medical management is an inferior treatment option in the elderly population with these surgical degenerative lumbar disorders.

Low Back Pain

Low back pain remains a major clinical problem. One group of authors examined the inter-relationships between physical activity, obesity, and low back pain. This was a cross-sectional population-based study of 6796 adults from the 2003 to 2004 National Health and Nutrition Examination Survey of the National Center for Health Statistics of the U.S. Department of Health and Human Services Centers for Disease Control and Prevention. The authors found that the risk of low back pain increases in a step-wise fashion with body mass index (BMI), from 2.9% for normal weight (BMI = 20 to 25 kg/m²), to 5.2% for overweight (BMI = 26 to 30 kg/m²), to 7.7% for obese (BMI = 31 to 35 kg/m²), and 11.6% for ultra-obese (BMI = 36 kg/m² or higher). Smoking was the strongest predictor of low back pain across the BMI spectrum, while physical activity decreases all of these risks. The role of physical activity to decrease the risk of low back pain is of the highest consequence in overweight and obese populations.

Another group of authors examined the prevalence of first-time low back pain and correlated this with MRI findings. This was a prospective radiographic and clinical study of 248

asymptomatic patients with no previous history of low back pain. All these subjects underwent MRI studies of the lumbar spine. These patients were followed for a minimum of two years and were clinically assessed for the development of symptoms, which were then correlated to baseline MRI findings. The overall presence of disc degeneration, disc-space narrowing, and disc bulging and/or extrusions were noted in 60.5%, 19.0%, and 34.3% of the population, respectively. The mean clinical follow-up period was 4.3 years. The prevalence rate of first-time low back pain episodes on clinical follow-up was 34.7%, and the mean age of the patients at the time of a first-time low back pain episode was 44.8 years. The presence of disc bulging and/or extrusion and increasing degenerative disc disease score (particularly in the mid lumbar spine) were significant predictors for the development of a first-time low back pain episode. Degenerative disc disease severity and disc bulging and/or extrusion were predictive of the severity of low back pain, greater functional disability, and increased frequency of future episodes of low back pain.

Return to Driving

A group of authors examined the return of driver reaction time to assess when patients could return to driving following lumbar and cervical surgery. This was a prospective study of thirty-seven patients with use of a computer software program to mimic driving a car. Patients were tested prior to surgery and retested postoperatively to see when they returned to their baseline score. The authors concluded that these patients could consider resuming driving two to three weeks following spinal surgery, provided that they were not taking narcotics and they had no other impairments that would deter them from driving.

Appendix: Evidence-Based Orthopaedics

The editorial staff of *The Journal* reviewed a large number of recently published research studies related to the musculoskeletal system that received a Level of Evidence grade of I or II. More than 100 medical journals were reviewed to identify these articles, which all have high-quality study design. In addition to articles published previously in this journal or cited already in the Update, fifty-one additional Level-I and II studies were identified that were relevant to spine surgery. A list of those titles is available with the online version of this article as a data supplement at jbjs.org. We have provided a brief commentary about each of the articles to help to guide your further reading, in an evidence-based fashion, in this subspecialty area.

Upcoming Meetings and Events Related to Spine Surgery

- The Scoliosis Research Society (SRS) Forty-ninth Annual Meeting will be held September 10 through 13, 2014, in Anchorage, Alaska. Web site: www.srs.org

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- EUROSPINE Annual Meeting will be held October 1 through 3, 2014, in Lyon, France. Web site: www.eurospine.org
- The North American Spine Society (NASS) Twenty-ninth Annual Meeting will be held November 12 through 15, 2014, in San Francisco, California. Web site: www.spine.org
- The Cervical Spine Research Society (CSRS) Forty-second Annual Meeting will be held December 4 through 6, 2014, in Orlando, Florida. Web site: www.csr.org
- The AANS/CNS (American Association of Neurological Surgeons/Congress of Neurological Surgeons) Section on Disorders of the Spine and Peripheral Nerves Annual Meeting will be held March 4 through 7, 2015, in Phoenix, Arizona. Web site: <http://spinesection.org>
- The Federation of Spine Associations will present the spine program at Specialty Day at the Annual Meeting of the American Academy of Orthopaedic Surgeons (AAOS) on March 28, 2015, in Las Vegas, Nevada. Web site: www.aaos.org
- The International Society for the Advancement of Spine Surgery (ISASS) Fifteenth Annual Meeting will be held April 14 through 17, 2015, in San Diego, California. Web site: www.isass.org
- The American Spinal Injury Association (ASIA) Forty-second Annual Meeting will be held on May 14 and 15, 2015, in Montreal, Quebec, Canada. Web site: www.asia-spinalinjury.org
- The International Society for the Study of the Lumbar Spine (ISSLS) Forty-second Annual Meeting will be held June 8 through 12, 2015, in San Francisco, California. Web site: www.issls.org
- The International Meeting on Advanced Spine Techniques (IMAST) Twenty-second Annual Meeting will be held July 8 through 11, 2015, in Kuala Lumpur, Malaysia. Web site: www.srs.org/meetings

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