

## Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: Bone graft extenders and substitutes as an adjunct for lumbar fusion

MICHAEL G. KAISER, M.D.,<sup>1</sup> MICHAEL W. GROFF, M.D.,<sup>2</sup> WILLIAM C. WATTERS III, M.D.,<sup>3</sup> ZOHER GHOGAWALA, M.D.,<sup>4</sup> PRAVEEN V. MUMMANENI, M.D.,<sup>5</sup> ANDREW T. DAILEY, M.D.,<sup>6</sup> TANVIR F. CHOUDHRI, M.D.,<sup>7</sup> JASON C. ECK, D.O., M.S.,<sup>8</sup> ALOK SHARAN, M.D.,<sup>9</sup> JEFFREY C. WANG, M.D.,<sup>10</sup> SANJAY S. DHALL, M.D.,<sup>5</sup> AND DANIEL K. RESNICK, M.D.<sup>11</sup>

<sup>1</sup>Department of Neurosurgery, Columbia University, New York, New York; <sup>2</sup>Department of Neurosurgery, Brigham and Women's Hospital, Boston, Massachusetts; <sup>3</sup>Bone and Joint Clinic of Houston, Houston, Texas; <sup>4</sup>Alan and Jacqueline Stuart Spine Research Center, Department of Neurosurgery, Lahey Clinic, Burlington, and Tufts University School of Medicine, Boston, Massachusetts; <sup>5</sup>Department of Neurological Surgery, University of California, San Francisco, California; <sup>6</sup>Department of Neurosurgery, University of Utah, Salt Lake City, Utah; <sup>7</sup>Department of Neurosurgery, Icahn School of Medicine at Mount Sinai, New York, New York; <sup>8</sup>Center for Sports Medicine and Orthopaedics, Chattanooga, Tennessee; <sup>9</sup>Department of Orthopaedic Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York; <sup>10</sup>Department of Orthopaedic Surgery, Keck School of Medicine, University of Southern California, Los Angeles, California; and <sup>11</sup>Department of Neurosurgery, University of Wisconsin, Madison, Wisconsin

In an attempt to enhance the potential to achieve a solid arthrodesis and avoid the morbidity of harvesting autologous iliac crest bone (AICB) for a lumbar fusion, numerous alternatives have been investigated. The use of these fusion adjuncts has become routine despite a lack of convincing evidence demonstrating a benefit to justify added costs or potential harm. Potential alternatives to AICB include locally harvested autograft, calcium-phosphate salts, demineralized bone matrix (DBM), and the family of bone morphogenetic proteins (BMPs). In particular, no option has created greater controversy than the BMPs. A significant increase in the number of publications, particularly with respect to the BMPs, has taken place since the release of the original guidelines. Both DBM and the calcium-phosphate salts have demonstrated efficacy as a graft extender or as a substitute for AICB when combined with local autograft. The use of recombinant human BMP-2 (rhBMP-2) as a substitute for AICB, when performing an interbody lumbar fusion, is considered an option since similar outcomes have been observed; however, the potential for heterotopic bone formation is a concern. The use of rhBMP-2, when combined with calcium phosphates, as a substitute for AICB, or as an extender, when used with local autograft or AICB, is also considered an option as similar fusion rates and clinical outcomes have been observed. Surgeons electing to use BMPs should be aware of a growing body of literature demonstrating unique complications associated with the use of BMPs.  
(<http://thejns.org/doi/abs/10.3171/2014.4.SPINE14325>)

**KEY WORDS** • lumbar spine • bone graft • bone substitute • fusion • bone morphogenetic protein • practice guidelines

### Recommendations

There is no evidence that conflicts with the previous recommendations published in the original version of the “Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine” regarding the use of hydroxyapatite (HA), various calcium-based preparations, and recombinant human bone morphogenetic protein-2 (rhBMP-2) as bone graft extenders and substitutes for lumbar fusion.<sup>48</sup>

No prior recommendations regarding the use of rhBMP-7 for lumbar fusions were published in the original Lumbar Fusion Guidelines.

*Abbreviations used in this paper:* ACS = absorbable collagen sponge; AICB = autologous iliac crest bone; ALIF = anterior lumbar interbody fusion;  $\beta$ -TCP =  $\beta$ -tricalcium phosphate; BMA = bone marrow aspirate; CHA = coralline hydroxyapatite; CRM = compression-resistant matrix; DBM = demineralized bone matrix; FRA = femoral ring allograft; HA = hydroxyapatite; ICBG = iliac crest bone graft; IDE = investigational device exemption; mJOA = modified Japanese Orthopaedic Association; NRS = numeric rating scale; ODI = Oswestry Disability Index; OP-1 = osteogenic protein-1; PLIF = posterior lumbar interbody fusion; RCT = randomized controlled trial; rhBMP = recombinant human bone morphogenetic protein; SF-36 = 36-Item Short Form Health Survey; TLIF = transforaminal lumbar interbody fusion; VAS = visual analog scale.

## Part 16: Bone graft extenders and substitutes

### Demineralized Bone Matrix

*Grade C (Single Level III and Single Level V Studies)*

The use of demineralized bone matrix (DBM) as a bone graft extender is an option for 1- and 2-level instrumented posterolateral fusions.

### Hydroxyapatite/Calcium Extenders

*Grade C (Single Level II Study)*

The use of  $\beta$ -tricalcium phosphate ( $\beta$ -TCP)/local autograft as a substitute for autologous iliac crest bone (AICB) is an option for single-level instrumented posterolateral fusion due to comparable fusion rates and clinical outcomes.

*Grade C (Single Level II Study)*

The use of HA with local autograft/bone marrow aspirate (BMA) as a substitute for AICB is an option for instrumented posterolateral fusion due to comparable fusion rates and clinical outcomes.

*Grade C (Multiple Level V Studies)*

The use of HA can be considered an option as a graft extender when mixed with AICB for instrumented posterolateral fusions.

*Grade C (Single Level IV and Multiple Level V Studies)*

The use of calcium sulfate preparations mixed with local autograft, as a substitute for AICB, is an option for instrumented posterolateral fusions.

*Grade I (Single Level V Study)*

There is insufficient evidence to recommend for or against the use of a HA-glass/BMA composite as an autograft substitute for posterolateral fusion.

### rhBMP-2: Interbody Fusion

*Grade B (Multiple Level II Studies)*

The use of rhBMP-2 as a substitute for AICB for ALIF with threaded interbody cages is an option due to similar fusion rates and clinical outcomes.

*Grade C (Single Level II Study)*

The use of rhBMP-2 as a substitute for AICB for single-level PLIF is an option due to similar fusion rates and clinical outcomes; however, formation of heterotopic bone has been observed.

*Grade C (Single Level IV and Multiple Level V Studies)*

The use of rhBMP-2 as a bone graft extender can be considered as an option when performing a TLIF procedure with a structural interbody graft.

*Grade I (Single Level III Study)*

There is insufficient evidence to make a recommendation regarding the use of rhBMP-2 as a supplement for

stand-alone ALIF procedures using femoral ring allograft (single Level III study) or with a resorbable spacer when performing TLIF procedures (single Level V study).

### rhBMP-2: Posterolateral Fusion

*Grade B (Multiple Level II Studies)*

The use of rhBMP-2 supplemented with 15% HA/85%  $\beta$ -TCP matrix as a substitute for AICB is an option in single-level posterolateral instrumented fusions given the consistent observation of comparable fusion rate and clinical outcomes.

*Grade C (Single Level II and Single Level IV Studies)*

The use of rhBMP-2 supplemented with graft extenders as an alternative to AICB is an option for single-level, instrumented posterolateral fusions in patients older than 60 years.

*Grade C (Single Level III and Single Level V Studies)*

The use of rhBMP-2 as a graft extender with either AICB or local bone is an option in patients undergoing either instrumented or noninstrumented posterolateral fusions.

*Grade I*

There is insufficient evidence to formulate a recommendation regarding the use of rhBMP-2/local bone as a substitute for AICB when performing revision posterolateral fusions (single Level III study) or the use of rhBMP-2/calcium-based extenders for single level posterolateral fusions in patients who smoke and elect to undergo surgery for lumbar spondylosis (single Level III study).

### rhBMP-2: Complications

*Grade C (Multiple Level IV and V Studies)*

The use of rhBMP-2 as a graft option has been associated with a unique constellation of complications that the surgeon should be aware of when considering the use of this graft extender/substitute.

### rhBMP-7

*Grade C (Single Level II Study)*

The use of rhBMP-7 when combined with local autograft as an alternative to AICB/local autograft is an option for single-level instrumented fusions based on equivalent clinical and radiographic outcomes. The use of rhBMP-7 has not been approved by the FDA for spinal fusions and currently requires a humanitarian device exemption.

*Grade I (Conflicting Level II Studies)*

No recommendation regarding the use of rhBMP-7/absorbable collagen sponge (ACS) as a substitute for AICB in posterolateral fusions can be made due to conflicting evidence from studies of equal strength.

## Rationale

The objective of a lumbar fusion is to create an environment that will allow bone to form a solid osseous bridge across the involved spinal segments. Autologous iliac crest bone has been considered the gold standard because of its ideal graft characteristics, including osteoconduction, osteoinduction, and osteogenesis.<sup>4,28,39</sup> The harvesting of AICB, however, is commonly associated with increased postoperative pain, which may be underestimated by the treating surgeon.<sup>31,55</sup> Additional drawbacks of AICB include limited supply and increased operative time and blood loss.

Allograft bone, one of the original substitutes for AICB, may avoid some of these drawbacks; however, when used alone, it is commonly associated with an increased pseudarthrosis rate.<sup>28</sup> For this reason, and to avoid the morbidity of harvesting AICB, a great deal of time and expense has been dedicated to investigate and promote extenders and/or substitutes of AICB. Potential candidates include locally harvested autograft, calcium-phosphate salts, such as HA or  $\beta$ -TCP, and DBM. However, no material has received more attention and generated more controversy than the family of BMPs. There are numerous papers that demonstrate the fusion potential of BMPs;<sup>2,7,18,19</sup> however, complications associated with their use have been reported.<sup>29,47,50</sup> Whether the benefits of BMPs justify the costs remains to be determined. Possibly more alarming than the potential complications and costs have been questions related to bias and conflict of interest associated with the reporting of results from trials investigating the potential of BMPs.<sup>9</sup> This escalating controversy prompted the editors of *The Spine Journal* to dedicate the June 2011 issue to concerns regarding the use of BMPs in spinal fusion surgery.

The objective of this update is to build upon the previous recommendations formulated in the original guidelines publication.<sup>48</sup> A review of the recent medical literature was conducted to determine the utility of these materials with respect to their clinical efficacy, fusion potential, and complication risk. It is beyond the scope of the current update to comment on cost utility of these materials or the ethics of investigational reporting.

### Search Criteria

A computerized search of the National Library of Medicine MEDLINE database, utilizing the online search engine PubMed, was conducted from 2003 through December 2011 utilizing the following search terms (((“Lumbosacral Region”[MeSH] OR “Lumbar Vertebrae”[MeSH]) AND “Spinal Fusion”[MeSH]) OR “lumbar fusion”[All Fields] OR (“lumbar”[title] AND “fusion”[title])) AND (((“Bone Substitutes”[MeSH] OR “Calcium Phosphates”[MeSH]) OR “Hydroxyapatites”[MeSH]) OR “Bone Morphogenetic Proteins”[MeSH]) AND (“2003”[PDAT]: “3000”[PDAT]) AND “humans”[MeSH Terms] AND English[lang]). The search was limited to the English language and human subjects and yielded a total of 151 papers. The titles and abstracts of these articles were reviewed and those specifically investigating the fusion potential, clinical efficacy, and poten-

tial complications of bone graft substitutes and extenders were selected. Of these papers a secondary review of the bibliographies was conducted to identify any additional relevant papers. A total of 79 articles were selected and reviewed in detail. Studies supporting similar conclusions of equivalent strength were grouped together. Those providing the best evidence from these compilations were included in the evidentiary tables. A detailed description of high-level studies or a representative of lower-level studies of similar conclusions serve as the scientific foundation for this update.

## Scientific Foundation

### *Demineralized Bone Matrix*

Since the publication by Urist, the osteoinductive properties of demineralized bone matrix (DBM) have been well recognized and extensively studied as both a substitute and extender of autograft bone.<sup>57</sup> Cammisia et al. conducted a multicenter, prospective, controlled trial to investigate the potential of DBM as a graft extender for AICB when performing a posterolateral instrumented lumbar fusion (Table 1).<sup>8</sup> One hundred twenty patients with a variety of degenerative disorders were enrolled and underwent up to a 3-level lumbar fusion. An independent, blinded radiologist, utilizing static and dynamic radiographs, performed fusion assessment at 3, 6, 12, 18, and 24 months. The clinical outcome of these patients was not recorded. All patients served as his/her own control receiving AICB within one intertransverse space and an equal volume of DBM/AICB to the contralateral intertransverse space. The follow-up rate at 24 months was 68%. A comparable fusion rate was observed on both sides (52% with DBM/AICB and 54% with AICB). Seventy-five percent of patients demonstrated fusion on both sides. Based on these observations the authors concluded that DBM could serve as an effective graft extender, decreasing the amount of autograft required and potentially reducing the risk and severity of donor site morbidity. Due to the utilization of internal controls, one cannot exclude a possible interaction between the investigational and control groups that could affect the outcome. This is therefore considered a case series when determining baseline level of evidence. Additional limitations include a heterogeneous patient population with respect to presenting diagnosis and the inclusion of a variety of fusions methods, including various interbody techniques. A large percentage of patients were lost to follow-up at 24 months. In the presence of pedicle screw stabilization, assessment of fusion with plain radiographs may be compromised. Secondary to these limitations, the case series was downgraded to Level V evidence in support of DBM as a graft extender for AICB in posterolateral lumbar fusion.

Schizas et al. conducted a pilot study comparing the clinical and radiographic outcome of patients undergoing 1- and 2-level posterolateral instrumented lumbar fusion using a novel DBM as a graft extender for autograft (Table 1).<sup>51</sup> Fifty-nine consecutive patients were divided into the 2 treatment groups; 33 received DBM mixed with autograft/BMA and 26 received only autograft. Fusion assessment

**TABLE 1: Demineralized bone matrix: summary of evidence\***

Authors & Year	Level of Evidence	Description of Study	Comments
Schizas et al., 2008	III	The objective of this pilot cohort study was to compare the clinical & radiographic performance of a novel DBM as a graft extender for autograft in 1- & 2-level posterolat instrumented fusions. 59 consecutive pts were divided into the 2 treatment groups: 33 received DBM mixed w/ autograft/BMA (treatment) & 26 received only autograft (control). Fusion assessment was blinded & determined w/ plain radiographs. Validated outcome measures were used to determine clinical status. At 12 mos after surgery, the fusion rate for the interventional group was 69.7% & that for the control group was 76.9% (p = 0.57). There was no difference in the clinical outcome btwn groups. The authors concluded that DBM is a safe & effective graft extender for 1- & 2-level posterolat fusions.	This study is limited by the relatively small study population w/ varying presenting diagnoses. Inadequate baseline demographic data are provided. The authors fail to standardize the DBM/autograft composite. Due to these limitations this study provides Level III evidence regarding the efficacy of DBM to act as a graft extender.
Cammisa et al., 2004	V	The authors conducted a multicenter prospective controlled trial to determine the efficacy of DBM as a graft extender for posterolat instrumented lumbar fusions. 120 pts were enrolled w/ varying degenerative diagnoses & underwent up to 3-level lumbar fusions. Radiographic assessment of fusion was performed at 3, 6, 12, 18, & 24 mos by independent blinded radiologists using static & dynamic radiographs. No clinical outcome measures were used. Each pt served as his/her own control & received equal vols of either AICB or a DBM/AICB composite to the intertransverse spaces. The follow-up rate at 24 mos was 68%. The fusion rate for the DBM/AICB composite side was 52% & 54% on the control side, w/ a 75% agreement btwn the 2 sides. Based on these observations the authors concluded that DBM can serve as an effective graft extender, decreasing the amount of autograft required & potentially reducing the risk & severity of donor site complications.	This study benefits from a relatively large no. of pts who were followed for an extended time; however, this study is considered a case series since control & treatment cohorts were conducted w/in the same pt & therefore possible interaction btwn the investigational & control sites cannot be excluded. A significant loss to follow-up rate (32%) was encountered. A variety of diagnoses were included & the surgical technique was not standardized. The use of plain radiographs may be an inadequate means of fusion assessment in the presence of pedicle screw instrumentation. The authors failed to include clinical outcome data. Due to these limitations the study was downgraded to Level V in support of DBM as a graft extender for AICB in pts undergoing instrumented posterolat fusions.

\* AICB = autologous iliac bone graft; BMA = bone marrow aspirate; DBM = demineralized bone matrix; pt = patient.

was performed 12 months after surgery by a blinded independent observer utilizing plain radiographs. Validated outcome measures, including the Oswestry Disability Index (ODI) and visual analog scale (VAS) pain score, were used to determine clinical status. The fusion rate for the interventional group was 69.7% and the control group 76.9% ( $p = 0.57$ ). There was no difference in the clinical outcome between the 2 groups. The authors concluded that DBM is a safe and effective graft extender for single- and 2-level posterolateral fusions. The relatively small number of patients, varying diagnoses, inadequate baseline demographic data, and short clinical follow-up all limit the conclusions of this study. The authors failed to standardized the volume and type of autograft used, whether AICB or locally harvested autograft. Due to these limitations the study is considered to provide only Level III evidence in support of DBM as a graft extender.

#### Calcium Phosphate Salts

This class of graft extenders and substitutes consists of calcium phosphate salts of varying composition that provide a lattice framework for in growth of new bone. These materials provide an osteoconductive matrix, having little if any osteoinductive or osteogenic properties. Examples include  $\beta$ -TCP, HA, and coral-based materials (Table 2).

*$\beta$ -Tricalcium Phosphate.* Dai and Jiang performed a prospective, randomized, controlled trial to determine the efficacy of  $\beta$ -TCP as a bone graft substitute for AICB in single-level posterolateral instrumented fusions for degenerative spinal stenosis (Table 2).<sup>16</sup> Sixty-two patients were randomized to one of 2 cohorts, receiving either  $\beta$ -TCP ( $n = 32$ ) or AICB ( $n = 30$ ), both supplemented with local autograft. An independent observer assessed clinical outcome with validated outcomes measures, including mJOA, 36-Item Short Form Health Survey (SF-36), and VAS for donor site pain, at 6 weeks and 3, 6, 12, 24 and 36 months after surgery. Two independent observers evaluated plain radiographs to assess fusion status at 3, 6, 12, 24, and 36 months after surgery. No patients were lost to follow-up at 36 months. The reported fusion rate for all study participants at 36 months was reported to be 100%, and significant improvement in the clinical outcome was observed in all patients. No significant differences were observed between the treatment cohort and control group with respect to fusion rate or clinical outcome. A postoperative hematoma was reported in 3 patients undergoing harvest of AICB. All patients from the AICB group reported donor site pain after surgery, and only 20% reported no pain at 6 weeks after the operation. In some patients (data not provided) pain was still present 36 months after surgery. The authors concluded that  $\beta$ -TCP, supplemented with local autograft, could serve as an effective substitute for AICB when local bone is insufficient. This was a well-designed and executed trial of a homogeneous group of patients with excellent clinical follow-up over an extended time. There were several limitations, however, including a failure to describe the randomization process and failure to use a disease-specific outcome measure. The utilization of plain radiographs to determine fusion status may also be considered suboptimal, particularly in the presence of an instrumented fusion.

Due to these limitations the study is downgraded to Level II evidence in support of utilizing  $\beta$ -TCP/local autograft as a substitute for AICB.

*Hydroxyapatite.* In 2005, Korovessis et al. conducted a prospective randomized controlled trial (RCT) to determine the fusion potential of coralline hydroxyapatite (CH) in multilevel, instrumented posterolateral lumbar fusions (Table 2).<sup>38</sup> Sixty patients were randomized to one of 3 cohorts: bilateral application of AICB, AICB on the left and CH/local bone/BMA on the right, and CH/local bone/BMA bilaterally. Validated outcome measures, including the ODI, VAS, Roland-Morris score, and SF-36, were obtained preoperatively and at 6, 12, 24, and 48 months after surgery. Two blinded, independent radiologists evaluated plain radiographs at 3, 6, 12, 24, and 48 months after surgery, supplemented with CT imaging at 12 and 24 months, to assess fusion status. Ninety-five percent of patients were available for follow-up at a minimum of 3 years. The fusion rate was 100% for all 3 groups at 1 year after surgery, based on CT and plain radiographs; however, in the CH/local bone/BMA cohort the fusion was limited to the facet joint and lamina. Reliability of radiographic assessment was adequate with an intraobserver and interobserver correlation coefficient ( $r$ ) of 0.71 and 0.69, respectively. Improvement in all clinical outcome parameters was observed; however, no statistical analysis was performed to determine if any intergroup differences existed. The authors concluded that CH when combined with local bone/BMA is an appropriate AICB substitute when placed over the lamina and facet; however, this is inappropriate for intertransverse fusion. This was a comprehensive study of adequate design; however, the authors fail to provide adequate baseline demographic data to determine if pretreatment differences existed in the study groups. The authors avoided any limitations of utilizing an internal control by creating 2 additional study cohorts, those receiving only AICB and those receiving CH/local bone/BMA. Differences in clinical outcome are difficult to determine since no statistical analysis was performed. Due to these limitations the study is considered to provide Level II evidence in support of the authors' conclusions.

The objective of the single-center prospective cohort study conducted by Lee et al. was to determine the efficacy of a HA as a graft extender in instrumented posterolateral fusion (Table 2).<sup>41</sup> Thirty-three patients with varying diagnoses underwent either 1- or 2-level circumferential fusion with an HA/AICB mixture or AICB randomly applied to either the right or left intertransverse space. Equal volumes of graft material were used with the control arm receiving twice as much AICB as the investigational side, 6 versus 3 ml, respectively. Radiographs, obtained at 3, 6, and 12 months after surgery, and 3D thin-cut CT scans, obtained at 12 months, were independently reviewed to determine fusion status. Clinical outcome was not objectively recorded. The fusion status at 12 months was 86.7% in the investigational group and 88.9% in the control group. The volume of fusion was measured with CT and considered significantly greater on the investigational intertransverse space. The authors concluded that HA is a safe and effective graft extender for posterolateral lumbar fusion. A

TABLE 2: Calcium phosphate salts: summary of evidence\*

Authors & Year	Level of Evidence	Description of Study	Comments
Dai & Jiang, 2008	II	The objective of this single-center prospective RCT was to determine the efficacy of $\beta$ -TCP as a bone graft substitute for AICB in single-level posterolateral instrumented fusions for degenerative spinal stenosis. 62 pts were randomized to one of 2 cohorts, receiving either $\beta$ -TCP (n = 32) or AICB (n = 30), both supplemented w/ local autograft. Clinical data were collected by an independent observer at 6 wks & 3, 6, 12, 24, & 36 mos. Validated outcomes measures were utilized (mJOA, SF-36, & VAS for donor site pain). Fusion status was assessed by 2 independent observers evaluating plain radiographs at 3, 6, 12, 24, & 36 mos. The 36-mo follow-up rate was 100%. All study pts were considered to have achieved a solid arthrodesis & demonstrate significant improvement compared w/ their preoperative clinical status. There was no difference in clinical outcome btwn the 2 cohorts. 3 complications (postop hematomas) were associated w/ AICB harvesting, & donor site pain was still recorded in some pts at the 36-mo follow-up. The authors concluded that $\beta$ -TCP can be used as an effective substitute for AICB when local bone is insufficient.	This is a relatively homogeneous, small group of pts w/ adequate information regarding baseline demographics. The follow-up interval is adequate w/ an excellent rate of follow-up. However, the randomization process was not described. Although validated outcome measures were used, the authors failed to utilize a disease-specific instrument to measure response to surgery. The method of fusion assessment, particularly in the presence of an instrumented spine, is suboptimal. It is not clear if the assessors of clinical & radiographic data were blinded to treatment. Due to these limitations, the study is downgraded to Level II evidence in support of $\beta$ -TCP/local bone as a substitute for AICB/local bone in 1-level instrumented posterolateral fusions.
Korovessis et al., 2005	II	This purpose of this prospective RCT was to determine the fusion potential of CHA in multilevel instrumented posterolateral fusions. 60 pts were randomized into one of 3 groups: receiving AICB bilaterally, receiving AICB on the left & CHA/local bone/BMA on the right, & CHA/local bone/BMA bilaterally. Validated outcomes instruments (ODI, VAS, Roland-Morris, & SF-36) were obtained preoperatively & at 6, 12, 24, & 48 mos after surgery. Fusion assessment was performed w/ plain radiographs at 3, 6, 12, 24, & 48 mos postoperatively, supplemented w/ CT imaging at 12 & 24 mos. Images were evaluated by 2 independent radiologists blinded to the intervention. The follow-up rate was 95% at a minimum of 3 yrs. Reliability of radiographic assessment of plain radiographs was performed by repeating the evaluation after 3 wks. The fusion rate was 100% for all 3 groups at 1 yr after surgery, based on CT & plain radiographs; however, the fusion observed w/ application of CHA/local bone/BMA was limited to the facet joint & lamina w/o bridging bone in the intertransverse space. The intra- & interobserver coefficient values (r) for fusion assessment were 0.71 & 0.69, respectively. Improvement in all clinical outcome parameters was observed; however, no statistical analysis was performed to determine if any intergroup differences in clinical outcome occurred. The authors concluded that CHA when combined w/ local bone/BMA is an appropriate AICB substitute when placed over the lamina & facet but is inappropriate for intertransverse fusion.	This is a relatively small, heterogeneous population of pts w/ respect to preop diagnosis & no. of levels fused. The process of randomization was not adequately described. Although the authors state that the treatment groups were similar, adequate preop demographic data are not provided, & they failed to demonstrate equipoise btwn the treatment groups. The use of an internal control is suboptimal, since one cannot rule out interaction btwn the 2 intertransverse spaces; however, the authors controlled for this limitation by creating an isolated AICB & CHA/local bone/BMA groups. The authors failed to perform adequate statistical analysis of the clinical results. Due to these limitations the study was downgraded to Level II evidence supporting the efficacy of CHA combined w/ local bone/BMA as an AICB substitute.
Chang et al., 2008	IV	The authors performed a retrospective review of results from pts undergoing single-segment posterolateral lumbar fusion using either local autograft expanded w/ calcium sulfate or iliac crest autograft. 115 pts were divided into treatment groups & evaluated over 1 yr. Similar fusion rates were observed, 92.3% for the treatment group (n = 66) & 92.9% in the control (n = 49), as well as clinical outcome, as determined by VAS score & ODI. The authors concluded that local autograft supplemented w/ calcium sulfate is a safe & effective alternative to autogenous iliac crest autograft.	The investigators failed to describe how pts were allocated into treatment groups, whether the evaluation of pts was blinded, performed an inadequate description of the results, inadequately described the statistical analysis of the data, & made statements w/in the conclusion that cannot be accounted for by their observations. This study provides Level IV evidence in support of local autograft w/ calcium sulfate as a substitute for AICB in single-segment posterolateral fusions.

(continued)

**TABLE 2: Calcium phosphate salts: summary of evidence\* (continued)**

Authors & Year	Level of Evidence	Description of Study	Comments
Lee et al., 2009	V	The objective of this single-center prospective controlled cohort study was to determine the efficacy of a commercially available HA as a graft extender in instrumented posterolateral fusion. 33 pts w/ varying diagnoses underwent either 1- or 2-level circumferential fusion w/ an HA/AICB mixture or AICB randomly applied to either the right or left posterolateral space. Radiographs, performed at 3, 6, & 12 mos after surgery, & 3D thin-cut CT at 12 mos, were independently reviewed to determine fusion status. Clinical outcome was not objectively recorded. The fusion status of the posterolateral space at 12 mos was 86.7% in the investigational group & 88.9% in the control group. The volume of fusion, measured w/ CT, was considered significantly greater in the investigational group. The authors concluded that HA granules are a safe & effective graft extender for posterolateral fusion.	This study is considered a case series since control & treatment cohorts were conducted w/in the same pt, at the same level, & therefore cannot be considered independent variables. It is possible that an interaction occurred btwn the investigational & control sites that could have an impact on the outcome. The outcomes of the posterolateral fusions may also be altered by the placement of the interbody graft; therefore, it is difficult to determine the true efficacy of HA as a graft extender w/in the posterolateral space. The authors failed to include an objective measure of clinical outcome. The study population was small & heterogeneous w/ respect to presenting diagnosis. This case series is therefore downgraded to Level V evidence in support of HA as a graft extender.
Acharya et al., 2008	V	The aim of this study was to determine the efficacy of an HA-bioactive glass ceramic composite as a graft substitute for autologous bone in lumbar posterolateral fusions. 24 consecutive pts undergoing posterolateral instrumented lumbar fusion were entered into the study. The left intertransverse space received a standard mixture of BMA/HA-glass ceramic composite & the right side received an equal volume of locally harvested autograft. The primary outcome measure was graft consolidation as demonstrated on anteroposterior radiographs at 12 mos after surgery, evaluated by an independent orthopedic surgeon. At 1 yr after surgery, 22/24 pts were available for evaluation. The control side demonstrated a fusion rate of 73%; however, no definitive fusion was observed on the HA-glass/BMA composite side in any pt, w/ 77% of pts demonstrating complete graft resorption. The study was terminated at the request of the principal investigator. The authors concluded that there was no role for this HA-glass composite/BMA as a stand-alone graft substitute in posterolateral fusion of the lumbar spine.	Although this study attempts to compare 2 treatment alternatives, a major limitation is the potential interaction btwn the control & interventional groups since both occurred in the same pt & therefore were not independent of each other. For this reason this study is considered a case series & not a comparative cohort study. This is a heterogeneous cohort, w/ respect to preop diagnosis & no. of levels fused. A suboptimal assessment of fusion was performed. The follow-up interval may be considered brief; however, 91% of enrolled pts were available. The dramatic difference in fusion outcome is noted. Due to these limitations the study is downgraded to Level V evidence against the use of HA-glass/BMA composite as a fusion substitute; however, it is included due to the dramatic difference in fusion rates.
Hsu et al., 2005	V	The purpose of this prospective controlled cohort study was to determine the effectiveness of local harvested autograft & CHA as graft extenders/substitutes for AICB w/ instrumented posterolateral fusions. 58 pts were divided into 3 groups receiving different graft mixture in the right intertransverse space, AICB/local bone (n = 20), AICB/CHA (n = 19), & CHA/local bone (n = 19). All pts received AICB in the left intertransverse space. Fusion assessment using radiographs was independently performed by 2 reviewers at 4, 6, & 12 mos after surgery. If uncertainty existed a CT was performed. The fusion rates between the investigational & control groups at 12 mos were 90% for AICB/local bone vs 95% control, 78.9% for AICB/CHA vs 84.2% control, & 57.9% for CHA/local bone vs 89.5% control. The only statistically significant difference in reported fusion rate was btwn AICB/local & CHA/local. The authors concluded that either local bone or CHA can serve as a graft extender w/ AICB; however, CHA/local bone was not an acceptable substitute for AICB w/ instrumented posterolateral fusions.	There were a relatively small no. of pts w/in each study subgroup. Heterogeneity existed btwn study groups w/ respect to diagnosis & surgery & incomplete demographic data are provided. Use of the contralateral intertransverse space as a control is suboptimal since one cannot rule out an interaction btwn the control & investigational sides w/in the same pt. The authors failed to perform statistical analysis btwn the investigational & control arms w/ in each study subgroup. Due to these limitations the study was downgraded to Level V evidence in support of CHA as a graft extender.

(continued)

TABLE 2: Calcium phosphate salts: summary of evidence\* (continued)

Authors & Year	Level of Evidence	Description of Study	Comments
Chen et al., 2005	V	The authors performed a prospective controlled cohort study to determine the effectiveness of artificial calcium sulfate mixed w/ local autograft vs AICB for fusion formation in 1- or 2-level instrumented posterolat fusions. Btwn September 2000 & September 2001, 74 consecutive pts were enrolled w/ a mean follow-up of 32.5 mos. 39 pts underwent a 1-level fusion & 35 a 2-level fusion. Each pt received AICB to one side & a mixture of calcium sulfate/local autograft to the other posterolat gutter. 2 independent blinded orthopedic surgeons evaluated radiographs for bridging intertransverse bone at 3-mo intervals for the 1st year & then on an annual basis. The protocol for clinical evaluation was not well defined, but it appears that ODIs were obtained in a retrospective fashion. The fusion rate for 1-level procedures was 87.2% on the investigational side & 89.7% on the control side (p = 1.0). For 2-level procedures the fusion rate was 82.9% for the investigational side & 85.7% for the control side (p = 1.0). Clinical outcome was judged as excellent or good in 78.3%. The authors concluded that calcium sulfate/local bone is as effective as AICB in achieving a solid fusion for instrumented posterolat fusions.	This is a heterogeneous study population w/ respect to presenting diagnosis & the authors fail to provide adequate baseline demographic data. Since each pt acted as his/her own control, it is impossible to rule out a possible interaction btwn the investigational & control sides. Application of graft was not randomized; therefore bias cannot be excluded w/ respect to fusion bed preparation. The method of fusion assessment was subjective. This study is downgraded to Level IV evidence in support of calcium sulfate/local autograft as a graft substitute for AICB.

\* AICB = autologous iliac bone graft;  $\beta$ -TCP =  $\beta$ -tricalcium phosphate; BMA = bone marrow aspirate; CHA = coralline hydroxyapatite; HA = hydroxyapatite; mJOA = modified Japanese Orthopaedic Association; ODI = Oswestry Disability Index; RCT = randomized controlled trial; SF-36 = 36-Item Short Form Health Survey; VAS = visual analog score.

major limitation of the study is the use of the contralateral intertransverse space as the control arm in the study subjects. Interaction between treatment and control groups cannot be excluded; therefore, this is considered equivalent to a case series. Additional limitations include the small, heterogeneous population of patients and failure to include an objective assessment of clinical outcome. The study is considered to provide Level V evidence in support of HA acting as a graft extender for AICB.

Chang et al. performed a retrospective comparative study to determine if calcium sulfate mixed with local autograft could serve as an alternative to AICB for single-segment posterolateral fusions (Table 2).<sup>12</sup> One hundred fifteen patients were divided between treatment and control groups and were observed for longer than 1 year. Fusion was assessed through static and dynamic radiographs as well as reformatted CT images. Outcome was assessed utilizing VAS scores and ODIs. Similar fusion rates (92.3% for the treatment cohort [n = 66] and 92.9% for the control group [n = 49]) and clinical scores were observed between groups. This study benefitted from an accurate assessment of fusion and use of objective outcome measures, but it is limited by the investigators' failure to describe how patients were allocated to study cohorts, whether the evaluations were blinded, and an inadequate description of the statistical analysis. Because of these limitations, the study was downgraded to Level IV evidence in support of using a mixture of calcium sulfate and local autograft as a substitute for AICB.

Acharya et al. conducted a prospective cohort study to determine the efficacy of an HA-bioactive glass ceramic composite as a substitute for autologous bone (Table 2).<sup>1</sup> Twenty-four consecutive patients undergoing posterolateral instrumented lumbar fusion were entered into the study. Each patient served as his or her own control, with the left intertransverse space receiving a standard mixture of BMA and HA-glass ceramic composite and the right side receiving an equal volume of locally harvested autograft. Anteroposterior radiographs obtained 12 months after surgery were evaluated by an independent orthopedic surgeon and were used to assess fusion status. The follow-up rate at 1 year after surgery was 91%. A definitive fusion was demonstrated on the control side in 73% of patients; however, there was no clear evidence of a fusion on HA/BMA side for any patient, with 77% of patients demonstrating complete resorption of the HA-bioactive glass/BMA graft. Given the dramatic difference in outcome, the principal investigator terminated the study and the authors concluded that this HA-glass composite/BMA was ineffective as a graft substitute in posterolateral lumbar fusion. Although this study suffers from a relatively small, heterogeneous patient cohort, the outcome assessment was performed in an objective manner with an adequate follow-up rate at the end point of the study. However, the use of an internal control is considered inadequate, as one cannot exclude an interaction between the control and treatment sides. Such an interaction would likely bias in favor of the treatment arm. Despite this inference, this study was considered equivalent to a case series and not a comparative cohort study. Although the observed results demonstrate a significant difference in fusion potential, the study design and



limitations necessitate an assignment of Level V evidence that HA-bioactive glass when combined with BMA cannot serve as a substitute for autologous bone.

A number of lower-quality studies and case series, providing Level IV and V evidence, have also been published investigating the utility of various calcium-based graft extenders<sup>21,22,32</sup> or substitutes for AICB.<sup>11,13,15,33,45</sup> These materials were generally mixed with either local autograft or BMA (Table 2). Given the nature of the study design, control groups were poorly designed, historical, or absent; therefore, direct comparisons to AICB are difficult and lack appropriate validity. When compared with previous published results, investigators considered the fusion rates acceptable; however, many of these studies are unable to provide data with respect to the actual clinical benefit since baseline demographic data are not provided. Due to these limitations, these studies only demonstrate the feasibility of utilizing these calcium-based materials as graft extenders or substitutes.

#### *Bone Morphogenetic Proteins*

Since the introduction of BMPs by Marshall Urist in 1965,<sup>57</sup> the application of these fusion agents, intended to induce bone formation from surrounding tissue, has dramatically increased. In 2002, the US FDA granted premarket approval for the use of InFUSE (rhBMP-2, Medtronic Sofamor Danek) for single-level ALIF procedures from L-4 to S-1 when used in conjunction with the LT-CAGE Lumbar Tapered Fusion Device (Medtronic Sofamor Danek).<sup>58</sup> Under a humanitarian device exemption, the FDA subsequently approved osteogenic protein-1 (OP-1; rhBMP-7, Stryker) for revision posterolateral lumbar spine fusion, where harvesting of autograft was not possible or not expected to achieve solid arthrodesis.<sup>60</sup> Although the FDA had granted a similar approval for InFUSE/MAS-TERGRAFT (rhBMP-2, Medtronic Sofamor Danek) for revision of symptomatic, posterolateral lumbar pseudarthrosis, at the request of the sponsor, this device was withdrawn in 2010.<sup>59</sup> The use of these agents extends well beyond the FDA-approved applications, with approximately 85% of primary spine procedures utilizing BMP considered off label.<sup>46</sup> Although the off-label use of BMP for spine has met with radiographic and clinical success, concern has been raised due to reports of rare but significant neurological or structural complications following the use of BMPs, particularly with interbody fusions.<sup>42,50</sup> In addition, whether the routine use of BMPs is cost-effective has yet to be demonstrated. This uncertainty requires a careful evaluation of the literature investigating the various applications of the available BMPs.

*rhBMP-2: Interbody Fusion.* The utilization of rhBMP-2 as a substitute for AICB with threaded interbody cages for single-level ALIF procedures has been investigated in 2 randomized control trials.<sup>5,6</sup>

The larger of the 2 trials was previously evaluated in the original Lumbar Fusion Guidelines and was designated as a Level I study.<sup>48</sup> These higher-level studies were reevaluated for the purposes of this update since different criteria were used to determine levels of evidence and different recommendation grades formulated from the evi-

dence. After reviewing the paper by Burkus et al.,<sup>6</sup> several limitations were identified including a failure to perform a power calculation to determine sample size, incomplete description of presenting demographic data (specifically no mention of comorbid medical conditions), and failure to perform an appropriate statistical analysis regarding outcomes between study cohorts (Table 3).

Burkus et al. also performed a prospective RCT in 42 patients to determine fusion progression of rhBMP-2 in a threaded titanium cage compared with AICB for single-level ALIF procedures.<sup>5</sup> The investigational cohort (n = 22) received rhBMP-2 and the control arm received AICB (n = 20). Fusion status was determined by 2 independent blinded radiologists evaluating both radiographs and CT images at 2 days and 6, 12, and 24 months after surgery. The fusion rate was 100% in the investigational cohort and 95% in the control group. The patients receiving rhBMP-2 demonstrated a greater average increase in bone density as demonstrated by Hounsfield units. The authors concluded that use of rhBMP-2 is associated with a high fusion rate and is a promising method to facilitate fusion in ALIF procedures. Given the dates of recruitment, these patients may have been included in a previous publication presented by the same authors and reviewed in the original Lumbar Fusion Guidelines.<sup>6</sup> This study focuses solely on the radiographic outcome of these patients without any inclusion of clinical data. The number of patients in each cohort is relatively small and varies with respect to presenting diagnosis. Although this is an RCT, inadequate baseline demographic data are included and the authors failed to determine appropriate sample size prior to initiating the study. This study therefore provides Level II evidence in support of rhBMP-2 as a substitute for AICB for single-level ALIF procedures with threaded interbody cages (Table 3).

Haid et al. conducted a multicenter prospective randomized controlled study to investigate the clinical and radiographic outcomes of patients undergoing single-level PLIF utilizing either iliac crest bone graft (ICBG) or rhBMP-2/ACS.<sup>29</sup> Sixty-seven patients with single-level degenerative disc disease were randomized. Clinical outcome was assessed utilizing validated outcome measures at 6 weeks and at 3, 6, 12, and 24 months after surgery. Radiographs and CT scans were obtained at 6, 12, and 24 months after surgery. The follow-up rate at all time points was at least 89.6%. At 24 months after surgery the investigational group demonstrated a 92.3% fusion rate while only 77.8% were considered fused in the control group; this difference did not prove to be statistically significant. Significant clinical improvement was observed in both cohorts, with the investigational group demonstrating superior improvement in the back pain score at 24 months. Although considered to be clinically irrelevant, a significantly greater percentage of patients in the investigational group (71% vs 12%), had heterotopic bone formation posterior to the interbody cage. Sixty percent of controls continued to complain of donor site pain at 24 months. Due to concern regarding the significant increase in heterotopic bone formation, the authors terminated the study but concluded that these results were encouraging. Despite the lack of an observed consequence of this excessive bone formation, the authors elected not to con-

**TABLE 3: rhBMP-2 in interbody fusion: summary of evidence\***

Authors & Year	Level of Evidence	Description of Study	Comments
Haid et al., 2004	II	This multicenter prospective randomized nonblinded study was intended to evaluate the clinical & radiographic outcomes at 24 mos of pts undergoing 1-level PLIF using either ICBG or rhBMP-2/ACS. 67 pts w/ 1-level degenerative disc disease were randomized to study cohorts. Clinical outcome was assessed using validated outcome measures at 6 wks & 3, 6, 12, & 24 mos after surgery. Radiographs & CT scans were obtained at 6, 12, & 24 mos after surgery. The follow-up rate at all time points was at least 89.6%. The fusion rates at 24 mos were 92.3% & 77.8% in the investigational & control groups, respectively; the difference was not statistically significant. A significantly greater percentage of pts in the investigational group (71% vs 12%) had heterotopic bone formation posterior to the interbody cage. All clinical parameters improved significantly in both study cohorts compared w/ preop status. The improvement in back pain score was significantly greater in the treatment cohort vs controls at 24 mos. 60% of controls continued to complain of donor site pain at 24 mos. The authors concluded that the results were encouraging regarding the use of rhBMP-2 through the posterior interbody approach; however, further studies incorporating more refined surgical technique are required.	This study is limited by the nonblinded assessment of clinical outcome & relatively small pt cohorts. The process of randomization is not adequately described. The study was terminated due to concern regarding heterotopic bone formation posterior to the interbody cages. Although this proved to be clinically insignificant, the study was not restarted since the use of stand-alone PLIF cages had fallen out of favor. This study did provide Level II evidence in support of rhBMP-2 as a substitute for AICB in single-level PLIF w/ threaded cages.
Burkus et al., 2003	II	The authors conducted a prospective randomized controlled trial to determine fusion potential of rhBMP-2 in a threaded titanium cage compared w/ AICB for 1-level ALIF procedures. Btwn August 1998 & March 1999, 45 pts were randomized, w/ 42 (93%) available for follow-up at 24 mos after surgery. There were 22 pts in the investigational cohort & 20 in the control arm. 2 independent blinded radiologists evaluated both radiographs & CT images at 2 days & 6, 12, & 24 mos after surgery. Based on radiograph & CT criteria, the fusion rate was 100% in the investigational cohort & 95% in the control group. The pts receiving rhBMP-2 demonstrated a greater average increase in bone density as demonstrated by Hounsfield units; however, the rate of follow-up w/ respect to these data is not consistent w/ the overall follow-up rate. The authors concluded that use of rhBMP-2 is associated w/ a high fusion rate & is a promising method to facilitate fusion in ALIF procedures.	This study is limited by the relatively small pt population that varies w/ respect to presenting diagnosis. The authors fail to provide adequate baseline demographic data. The description of statistical analysis is limited & no power calculations were performed to determine sample size. Due to these limitations this study was downgraded to Level II evidence that rhBMP-2 can serve as a substitute for AICB for 1-level stand-alone ALIF procedure w/ threaded cages.
Burkus et al., 2002	II	The objective of this multicenter prospective randomized trial was to compare the efficacy of rhBMP-2 vs AICB for 1-level ALIF procedures using tapered cylindrical cages. 279 pts w/ symptomatic 1-level degenerative disc disease were enrolled, randomized in a 1:1 fashion to either receive rhBMP-2 (n = 143) or AICB (n = 136). Radiographic outcome was independently assessed using static & dynamic radiographs & CT scans at 6, 12, & 24 mos. Clinical assessment was conducted at 6 wks & 3, 6, 12, & 24 mos & included work status, neurological outcome, pain questionnaires, & ODIs. At 24 mos, the follow-up rate for both groups was >90%. Clinical outcome was comparable btwn groups. The rhBMP-2 group demonstrated a fusion rate of 94.5% at 24 mos while the fusion rate was for 88.7% of the control group. Donor site pain was reported in 32% of controls at 24 mos. The rate of secondary procedures was similar btwn groups. Based on these results the authors concluded that rhBMP-2 when used w/ a tapered cage is an effective technique for ALIF procedures & avoids the adverse effects of harvesting AICB.	This is a well-designed clinical trial & benefits from a large sample size, validated outcomes instruments, standardized surgical technique, comprehensive outcome analysis, & excellent follow-up rate. There are numerous limitations including a failure to perform power calculation to determine sample size, incomplete description of presenting demographics (no mention of comorbid medical factors), failure to describe inclusion/exclusion criteria, & failure to independently collect clinical data. The authors do not completely describe the distribution of complications btwn treatment & control groups. No statistics were performed to compare outcome btwn treatment & control groups. Due to the numerous minor limitations the study was downgraded to Level II evidence in support of rhBMP-2 as a substitute for AICB w/ 1-level ALIF procedures.

(continued)

**TABLE 3: rhBMP-2 in interbody fusion: summary of evidence\* (continued)**

Authors & Year	Level of Evidence	Description of Study	Comments
Slosar et al., 2007	III	The objective of this prospective cohort study was to determine if rhBMP-2 can safely accelerate allograft interbody fusions & reduce the no. of nonunions when compared w/ allograft alone. 75 pts w/ varying diagnoses & undergoing 1-3 level fusions were enrolled; 30 received an FRA w/ allograft (control) & 45 received an FRA supplemented w/ rhBMP-2 (investigational); both groups received posterior pedicle stabilization w/o fusion. Fusion assessment, performed at 6, 12, & 24 mos, was blinded & performed using radiographs & CT images. Objective outcome instruments were used to determine clinical outcome; however, assessment was not blinded. At 24 mos after surgery, the control group follow-up rate was 97% & the investigational group rate was 96%. Statistically significant increase in fusion rate was observed at all time points for the investigational group (94%, 100%, & 100%) compared w/ controls (66%, 84%, & 89%). The investigational group demonstrated significantly better outcomes at 6 mos, but both groups demonstrated significant improvement at 12 & 24 mos compared w/ baseline. The authors concluded that allograft interbody fusion supplemented w/ rhBMP-2 significantly improved the fusion rate compared w/ allograft alone & the more rapid fusion observed w/ rhBMP-2 led to more rapid clinical improvement.	The study population includes pts w/ varying diagnoses & the authors fail to describe the distribution of these diagnoses btwn the 2 treatment groups. The potential impact of differences in the baseline demographic data & no. of levels operated btwn the cohorts cannot be determined since the authors failed to perform statistical analysis of these data. Although radiographic data were independently reviewed, it is not clear if the clinical assessment was blinded. Due to these limitations this study was downgraded to Level III w/ respect to rhBMP-2 as a supplement to anterior interbody fusion using femoral ring allograft & pedicle screw stabilization.
Mummaneni et al., 2004	IV	This retrospective cohort study was intended to compare the efficacy of rhBMP-2 w/ AICB when placed in an interbody spacer during a TLIF procedure. 44 pts underwent the TLIF procedure btwn September 2002 & December 2003. Follow-up data were available for 40 pts (90%). 19 pts received AICB in the interbody space, & 21 pts received rhBMP-2 supplemented w/ either AICB (n = 12) or local autograft (n = 9). Radiographic evaluation was performed w/ static & dynamic radiographs at 6-wk & 3-mo intervals. Clinical outcome was assessed at 3-mo intervals using the Prolo scale & VAS for donor site morbidity. The mean follow-up was 9 mos. The fusion rate in the AICB group was 95%. A 100% fusion rate was observed in pts receiving rhBMP-2 w/ at least 6 mos of follow-up; however, only 76% of pts from this cohort were available. At 6 mos after surgery, 58% of pts continued to complain of donor site pain. The authors concluded that the use of rhBMP-2 & local autograft is an excellent option when performing a TLIF procedure & avoids AICB donor site morbidity.	This is a heterogeneous, small cohort of pts that varied w/ respect to diagnosis & surgery. It is not clear how many pts underwent a supplemental posterolat fusion. The no. of pts is too small to perform any meaningful statistical analysis to determine differences w/in the treatment groups. The radiographic assessment of fusion was not clearly defined. Clinical outcome w/ respect to treatment efficacy was not conducted w/ validated outcomes measures. The follow-up interval was relatively short w/ a significant no. of rhBMP-2 pts not available. The evaluation of both clinical outcome & radiographs was not blinded. Due to these limitations the study is downgraded to Level IV evidence, supporting the role of rhBMP-2 as a supplement to interbody fusions when performing a TLIF.
Geibel et al., 2009	V	This case series describes the clinical & radiographic outcome of 48 pts undergoing 1- & 2-level PLIF & posterolat instrumented fusions w/ rhBMP-2. 37 (77.1%) underwent a 1-level procedure & 11 (22.9%) underwent a 2-level procedure. ODis were obtained after surgery & CT images were obtained to assess fusion. The average follow-up was 17 mos. 2 independent radiologists evaluated the CT images & determined a fusion rate of 100%. Pt satisfaction, recorded as a willingness to repeat surgery, was observed in 89%. The authors concluded that rhBMP-2 can serve as a substitute for AICB & effectively & safely accomplish fusion through the PLIF approach.	This is a heterogeneous population of pts w/ respect to diagnosis & surgical procedure. No preop clinical data were recorded; therefore, the treatment effect of surgery cannot be determined. Due to these limitations the case series was downgraded to Level V evidence regarding the efficacy & safety of rhBMP-2 as a substitute for AICB w/ a PLIF.

(continued)

TABLE 3: rhBMP-2 in interbody fusion: summary of evidence\* (continued)

Authors & Year	Level of Evidence	Description of Study	Comments
Burkus et al., 2009	V	This report represents an update of the clinical & radiographic outcomes of pts from 2 separate studies undergoing stand-alone 1-level ALIF w/ tapered cages & rhBMP-2. No comparison w/ the control arm (pts receiving autologous iliac crest) was performed. At 6 yrs after the index procedure, 146 pts provided clinical follow-up, & radiographic evaluation was performed on 130 pts. A solid arthrodesis was identified in 98% of pts. There was no significant difference in any of the clinical outcome measures at 6 yrs compared w/ the values observed at 2 yrs after surgery. Significant improvement compared w/ preop scores was maintained at 6 yrs after surgery. 25 revision surgeries were performed over the 6-yr follow-up period & 7 btwn the 2- & 6-yr time points. The authors concluded that this technique was an effective method of obtaining an ALIF & maintaining long-term, significant clinical improvements.	The efficacy of rhBMP-2 as a substitute for autologous bone w/ tapered cages in 1-level ALIF was previously established w/ the prior studies. The results reported in this case series are limited by the significant no. of pts lost to follow-up, 48% dropout rate for clinical data, & 55% for radiographic evaluation & therefore was downgraded to Level V evidence. This case series does not retract or contribute significantly to the prior studies.
Rihn et al., 2009 <sup>49</sup>	V	The objective of this retrospective review of a case series was to determine the clinical & radiographic outcomes of pts undergoing 1-level TLIF w/ rhBMP-2. 48 of 53 pts w/ varying diagnoses of lumbar degenerative disease were identified over a 2-yr interval. Static & dynamic radiographs were reviewed by an independent blinded spine surgeon at an average follow-up of 19.4 mos. Odom's criteria, pt satisfaction, & NRS of leg & back pain were obtained through telephone interview at an average follow-up of 27.4 mos. The fusion rate was 95.8%. 71% achieved excellent or good outcome, w/ 84% of pts satisfied w/ their outcome. Persistent back & leg pain was reported in 60.4% & 41.7%, respectively. An overall complication rate of 21.7% was reported, w/ approximately 25% attributed to the use of rhBMP-2. The authors concluded that adequate clinical & radiographic outcomes can be obtained.	This is a retrospective review of a case series of pts undergoing a 1-level TLIF. The study benefits from an independent assessment of fusion using appropriate radiographic methods. Validated outcome measures were incorporated to determine response to treatment. The heterogeneous pt population is considered a significant limitation, & therefore the study is downgraded to Level V evidence in support of rhBMP-2 used as an adjunct to interbody fusion.
Villavicencio et al., 2005	V	This retrospective case series describes the clinical & radiographic outcomes of 74 pts undergoing TLIF w/ allograft supplemented w/ rhBMP-2/ACS for a variety of degenerative disorders through a variety of surgical approaches. Pts were divided into subgroups based on the no. of levels fused & whether an open or minimally invasive approach was used. A single independent radiologist evaluated radiographs at 3, 6, 12, & 24 mos & CT images at 12 & 24 mos after surgery. Independent clinical assessment was performed at 12 mos after surgery utilizing MacNab criteria. 96% of pts were available at 12 mos after surgery. There were no adverse events directly related to the use of rhBMP-2. The fusion rate for the entire cohort was 100% by 10 mos after surgery. Improved clinical outcome was observed in all groups; however, those undergoing minimally invasive procedures tended to have a better outcome. The authors concluded that rhBMP-2 is a safe & effective bone graft extender when used in conjunction w/ allograft for the TLIF procedure.	This study suffers from significant heterogeneity w/ respect to diagnosis & surgical procedure. The no. of pts in each subgroup was relatively small, & incomplete description of demographic characteristics is provided. Nonvalidated outcome measures were used to assess clinical outcome. The study provides only Level V evidence in support of rhBMP-2 as a graft extender for allograft for TLIF procedures.
Lanman & Hopkins, 2004	V	This case series describes the clinical & radiographic results of 42 pts undergoing the TLIF procedure using rhBMP-2 & a bioresorbable interbody graft. Clinical & radiographic follow-up was conducted at 3, 6, & 12 mos after surgery using the ODI, plain radiographs, & CT images. The radiographic follow-up rate at 6 mos was 98% & at 12 mos was 26%. Preop clinical data were obtained in only 59% of pts w/ a follow-up rate of 92% at 6 mos & 36% at 12 mos. The fusion rate was 98% at 6 mos & 100% at 12 mos. Clinical improvement was observed at each study end point, although significance was not determined. There were no device-related complications. The authors conclude that these results indicate that the combination of rhBMP-2 w/ a resorbable spacer may be an appropriate alternative for interbody fusion & deserves further investigation.	This is a relatively poorly conducted case series w/ little information regarding the efficacy of rhBMP-2 used w/ a bioresorbable spacer. The study population is small & varies w/ respect to diagnosis, no. of levels fused, & op approach. An excessive no. of pts were lost during the follow-up period to make any judgments regarding clinical efficacy. It is not clear if the radiographic or clinical follow-up was blinded. The authors failed to perform any statistical analysis. This study provides only Level V evidence.

\* ACS = absorbable collagen sponge; AICB = autologous iliac crest bone; ALIF = anterior lumbar interbody fusion; FRA = femoral ring allograft; ICBG = iliac crest bone graft; NRS = numeric rating scale; ODI = Oswestry Disability Index; PLIF = posterior lumbar interbody fusion; pt = patient; rhBMP-2 = recombinant human morphogenetic protein-2; TLIF = transforaminal lumbar interbody fusion.

tinue since the use of threaded titanium cages through the PLIF approach had fallen out of favor. The relatively small number of patients (< 50) in each cohort and the lack of a blinded clinical assessment limit conclusions formulated from this study. The study provides Level II evidence in support of using rhBMP-2 with threaded cages through the PLIF approach (Table 3).

Additional studies of lesser quality have explored the potential of rhBMP-2 as a graft extender for lumbar interbody fusion. Slosar et al. performed a prospective cohort study to determine the impact of rhBMP-2 on fusion rate and clinical outcome following ALIF with femoral ring allograft (FRA).<sup>54</sup> Seventy-five patients with varying diagnoses and undergoing up to a 3-level fusion were enrolled; 30 control patients (n = 30) received an FRA with allograft croutons and an investigational group (n = 45) received an FRA supplemented with rhBMP-2/ACS. A statistically significant increase in fusion rate was observed at all time points for the investigational group compared with controls. Both groups demonstrated significant clinical improvement at 12 and 24 months over baseline, but no significant difference was observed between treatment groups. A heterogeneous patient population with respect to presenting diagnosis and number of levels fused, an inadequate statistical analysis of potentially confounding baseline demographics, and failure to perform an independent, blinded clinical assessment requires that the study be downgraded to Level III in support of rhBMP-2 as an adjunct to FRA interbody fusion (Table 3).

Several retrospective cohort studies and case series have investigated the use of rhBMP-2 as a graft extender when performing TLIF with an interbody graft. Rihn et al. performed a retrospective review of 48 patients receiving rhBMP-2 during TLIF procedures and observed a fusion rate of 95.8% at the 2-year follow-up with 71% reporting excellent or good outcomes.<sup>49</sup> The complication rate was 21.7% with one-quarter of these complications attributed to the use of rhBMP-2. Villavicencio et al. reviewed the data from 74 patients undergoing either open or minimally invasive TLIF for varying diagnoses using rhBMP-2 and allograft.<sup>67</sup> The fusion rate for the entire cohort was 100%; however, a trend toward improved clinical outcome was observed for patients undergoing less invasive procedures. Mummaneni et al. conducted a retrospective cohort study intended to compare the efficacy of rhBMP-2 with AICB for TLIF.<sup>44</sup> Forty-four patients underwent a TLIF, with 40 patients (90%) available for a mean follow-up of 9 months. The control arm (n = 19) consisted of patients receiving AICB in an interbody spacer, while the investigational group (n = 21) received rhBMP-2 supplemented with either AICB (n = 12) or local autograft (n = 9). With at least 6 months of follow-up, the fusion rate in the AICB group was 95% and 100% in patients receiving rhBMP-2; however, only 76% of patients receiving rhBMP-2 were available for follow-up. At 6 months after surgery, 58% of patients continued to complain of donor site pain. The authors concluded that rhBMP-2 and local autograft is an excellent graft option and avoids donor site morbidity when performing a TLIF procedure. The relatively small, heterogeneous population of patients with respect to diagnosis and surgery performed limits these studies. Nonvalidated clinical outcome

measures were used, and the method of fusion assessment is questionable given the presence of pedicle screw instrumentation. In the Mummaneni et al. study, neither the radiographic evaluation nor assessment of clinical outcome was performed in an independent, blinded fashion. Due to the baseline study designs and various limitations, these studies provide at best Level IV or V evidence in support of rhBMP-2 as a supplement for interbody fusion through the TLIF approach (Table 3). Additional case series have been published exploring the potential of rhBMP-2 as a graft extender or substitute.<sup>7,24,40</sup> Burkus et al. published a long-term clinical and radiographic companion study to their previous published report of patient undergoing single level ALIF procedures with stand-alone tapered cages and rhBMP-2/ACS.<sup>7</sup> No significant difference in outcome at 6 years was observed when compared with the previously published data obtained at 2 years after surgery. Geibel et al. reported a 100% fusion rate with an 89% patient satisfaction rate in 48 patients undergoing 1- and 2-level instrumented PLIF with rhBMP-2 and posterolateral fusion.<sup>24</sup> Lanman and Hopkins published the only case series investigating the use of rhBMP-2 in conjunction with a bioresorbable cage.<sup>40</sup> This study was limited by 64% of patients lost to follow-up at 12 months after surgery, compromising any attempt at a meaningful interpretation of the data. Since these studies are all case series with limitations, at best they provide only Level V evidence.

*rhBMP-2: Posterolateral Fusion.* In 2006, Dimar et al. reported the 24-month radiographic and clinical results of patients enrolled in an FDA investigational device exemption (IDE) study comparing rhBMP-2 combined with a compression-resistant matrix (CRM; bovine type I collagen carrier containing 15% HA and 85%  $\beta$ -TCP) with AICB in instrumented posterolateral fusions (Table 4).<sup>19</sup> Ninety-eight of 150 randomized patients were available for review. Clinical outcome, assessed using validated outcomes instruments (SF-36, ODI, and back/leg pain scores), was performed at 6 weeks and 3, 6, 12, and 24 months. Independent assessment of radiographs and CT images was performed at 6, 12, and 24 months. Operative parameters, including the surgical time and blood loss, were significantly less in the rhBMP-2/CRM cohort. Both groups demonstrated a significant clinical improvement compared with baseline, but not between treatment groups. The rhBMP-2/CRM cohort demonstrated a statistically higher fusion rate, 90.6% compared with 73.3%. At final follow-up, 16% of patients in the AICB cohort continued to complain of donor site pain. The authors concluded that rhBMP-2/CRM demonstrated similar clinical outcomes and improved fusion rates compared with AICB for single-level instrumented posterolateral fusions. Thirty-five percent of patients from the original cohort of randomized patients were lost to follow-up. This study included a heterogeneous patient population with respect to diagnosis. Due to these limitations the study was considered to provide level II evidence in support of rhBMP-2/CRM as a substitute for AICB.

Dimar et al. later reported the 2-year radiographic and clinical outcomes of a multicenter prospective randomized controlled IDE trial to investigate the use of rhBMP-2

**TABLE 4: rhBMP-2 in posterolateral fusion: summary of evidence\***

Authors & Year	Level of Evidence	Description of Study	Comments
Dimar et al., 2009	II	The purpose of this study was to report the 2-yr radiographic & clinical outcomes of a multicenter, prospective, randomized controlled IDE trial to investigate the use of rhBMP-2 matrix (bovine type I collagen carrier containing 15% HA & 85% $\beta$ -TCP) as a substitute for autologous iliac crest for 1-level posterolat instrumented fusions. Well-described radiographic criteria were used to assess fusion in a blinded fashion, & validated outcome measures were completed to determine clinical outcome. Clinical follow-up was performed at 6 wks & at 3, 6, 12, & 24 mos & radiographic follow-up at 6, 12, & 24 mos. 463 pts were randomized btwn the treatment cohorts, w/ a 2-year follow-up rate of 89%. The control group demonstrated significantly longer op times & blood loss. The clinical outcome measures improved significantly compared w/ preop scores in both cohorts w/ no significant difference noted btwn treatment groups. 60% of the control group continued to complain of donor site pain at the 24-mo follow-up evaluation. The fusion rate, based on CT assessment, demonstrated a statistically significant difference in fusion rates at all times points; the final fusion rate was 96% in the rhBMP-2 group & 89% in the control group. There was no significant difference in adverse events except that the control group suffered 17 graft site-related events. The authors concluded that the use of rhBMP-2 matrix improved op parameters, achieved a higher fusion rate & comparable clinical outcomes, & therefore can eliminate the need for autologous iliac crest bone for 1-level posterolat instrumented fusions.	This is a well-designed trial. The authors failed to perform a power analysis to determine sample size & failed to account for pts lost to follow-up. It is not clear if the clinical assessment was blinded; however, given that the outcome measures were pt self-assessment instruments, this fact does not detract significantly from the observations & conclusions of the study. Due to these limitations the study was downgraded to Level II evidence to support the use of rhBMP-2 as a substitute for AICB in 1-level posterolat fusions.
Dawson et al., 2009	II	The purpose of this multicenter prospective randomized controlled trial was to investigate the use of rhBMP-2 on an ACS reinforced w/ 15% HA/85% TCP ceramic granules as a replacement for iliac crest autograft in posterolat instrumented fusions. Well-described radiographic criteria were used to assess fusion in a blinded fashion, & validated outcome measures were completed to determine clinical outcome. Overall success was determined by combining the results of these measures. Clinical follow-up was performed at 3, 6, 12, & 24 mos & radiographic follow-up at 6, 12, & 24 mos. 50 pts were randomized to the cohorts w/ a 24-mo follow-up rate of 88% in the treatment group & 86% in the control group. Improvements were observed in all clinical outcome measures in both groups w/ a trend toward superior improvement in the experimental group. At each time point, there was a trend for more successful fusion in the treatment group, w/ final fusion rates of 95% in the investigational group & 70% in the control group. No difference in the radiographic or clinical follow-up proved to be statistically significant. The authors concluded that the combination of rhBMP-2 & HA/TCP may be an effective alternative to autologous bone graft for 1-level posterolat instrumented fusions.	This is a well-designed study but was downgraded to Level II evidence due to the relatively small pt cohorts (<50 pts/cohort), incomplete description of baseline pt demographic data, failure to describe if the clinical assessment was blinded, & an overall outcome measure that has not been validated.

(continued)

**TABLE 4: rhBMP-2 in posterolateral fusion: summary of evidence\* (continued)**

Authors & Year	Level of Evidence	Description of Study	Comments
Glassman et al., 2008	II	The purpose of this prospective RCT was to compare the clinical & radiographic outcomes of patients >60 yrs undergoing instrumented posterolat fusions w/ either rhBMP-2/ACS or AICB. Various bone graft extenders were applied at the discretion of the surgeon in both cohorts. Validated outcome measures (SF-36, ODI, & NRS for back & leg pain) were administered. 2-yr follow-up data were collected in 94% of the pts (49 in the rhBMP-2 cohort & 51 in the AICB group). Baseline NRS leg pain was reported w/ greater frequency in the rhBMP-2/ACS cohort (p = 0.031); however, there were no other differences in baseline demographics. There was a statistically greater no. of complications in the AICB cohort (20 vs 8, p = 0.014), although none of the complications were directly attributed to either the harvest of AICB or the use of rhBMP-2/ACS. Statistically significant improvement was observed in all clinical outcome measures in both cohorts compared w/ baseline, although none of the differences btwn the cohorts was significant. CT images were obtained in 99 pts at 24 mos after surgery (93% follow-up rate). The fusion rate in the rhBMP-2/ACS cohort was 86.3% & 70.8% in the AICB group. The average CT grade was significantly higher in the rhBMP-2/ACS group (4.3 vs 3.8 [p = 0.03]). Revision surgery for nonunion was required in 1 pt in the rhBMP-2 cohort & 5 in the AICB group. An estimation of total cost over the 2 yrs was not significantly different btwn the 2 groups (\$42,574 for the AICB cohort & \$40,131 for the rhBMP-2/ACS cohort). The authors concluded that the study provided Level I evidence supporting the use of rhBMP-2/ACS as an AICB replacement for lumbar fusion in the older pt.	This is a heterogeneous population of pts w/ respect to the presenting diagnosis, level of involvement, & no. of levels included in the surgery. No power analysis was performed to determine sample size. The surgical procedure was not standardized, w/ bone graft extenders added to both groups at the discretion of the surgeon. It is not clear if the "grading" scheme of fusion assessment has been validated. No statistics were performed w/ respect to rate of fusion. Due to these limitations the study was downgraded to Level II evidence in support of rhBMP-2 as a substitute for AICB when supplemented w/ a graft extender for posterolat instrumented fusions in pts >60 yrs.
Dimar et al., 2006	II	The purpose of this prospective randomized nonblinded report was to present the 24-mo radiographic & clinical results of pts enrolled in an FDA IDE study undergoing 1-level instrumented posterolat fusion w/ either rhBMP-2/CRM or AICB. 98 of 150 pts, a follow-up rate of 65%, were available at 24 mos after surgery. Clinical assessment w/ validated outcomes instruments (SF-36, ODI, & back/leg pain scores) was performed at 6 wks & 3, 6, 12, & 24 mos. A blinded radiologist & 2 orthopedic surgeons independently evaluated radiographs & CT images at 6, 12, & 24 mos. The surgical time & blood loss were significantly less in the rhBMP-2/CRM cohort. Significant improvements in all clinical outcome measures compared w/ baseline values were observed in both groups, but no difference existed btwn groups. A significantly higher fusion rate was observed in the rhBMP-2/CRM cohort (90.6% vs 73.3%). 16% of pts in the AICB cohort continued to complain of donor site pain at 24 mos. The authors concluded that rhBMP-2/CRM demonstrated similar clinical results & improved fusion rates as AICB for 1-level instrumented posterolat fusions.	The heterogeneous pt population w/ respect to diagnosis limits this study & the significant loss to follow-up at the 2-yr study end point. Validated clinical outcomes were utilized & an effective method of fusion assessment was performed in a blinded fashion. Due to the significant loss to follow-up the study is downgraded to Level II evidence in support of rhBMP-2/CRM as a substitute for AICB in 1-level posterolat instrumented fusions.

(continued)

**TABLE 4: rhBMP-2 in posterolateral fusion: summary of evidence\* (continued)**

Authors & Year	Level of Evidence	Description of Study	Comments
Taghavi et al., 2010	III	The objective of this retrospective comparative study was to determine the efficacy of rhBMP-2/local bone to either allograft or autograft in revision instrumented posterolat fusions. 62 pts w/ varying initial diagnoses were included w/ minimum follow-up of 2 yrs. Pts were divided into 3 groups: Group 1 (n = 24) received rhBMP-2, Group 2 (n = 18) BMA/allograft, & Group 3 (n = 20) autograft. All received supplemental local bone. Fusion assessment, through static & dynamic radiographs, was performed by 3 blinded independent reviewers w/ a diagnosis of nonunion based on either surgical exploration if revision was performed or radiographic findings. Clinical outcome was determined through VAS scores. Group 1 demonstrated a fusion rate of 100%, Group 2 demonstrated a 77.8% fusion rate, & Group 3 had a 100% fusion rate. Pts undergoing multilevel procedures w/ BMA/allograft demonstrated a statistically lower fusion rate. No difference in VAS scores was observed. The authors concluded that rhBMP-2 could be an appropriate alternative to AICB in revision posterolat fusion.	Although an adequate description of baseline demographics is provided w/ appropriate statistical analysis, there remains the possibility of selection bias due to the potential differences in presenting diagnoses that the authors do not describe. The authors included an adequate assessment of fusion w/ acceptable radiographic criteria & incorporated validated outcome measures. Due to the retrospective nature of the study design, but lack of significant limitations, the study is considered Level III evidence in support of rhBMP-2/local bone as an alternative to AICB for revision posterolat fusions.
Singh et al., 2006	III	This is a prospective case-matched cohort study to determine if rhBMP-2 enhances fusion rate w/in a shorter time interval for pts undergoing instrumented posterolat fusion using AICB. 52 pts presenting w/ stenosis & spondylolisthesis were evaluated: 41 received rhBMP-2/AICB/local bone & 11 received AICB/local bone. Fusion assessment was performed w/ reformatted CT images & evaluated in a blinded, independent manner by 2 surgeons & 1 radiologist. 2 pts were lost to follow-up at the 2-yr time point. The fusion rates in the rhBMP-2 & AICB cohorts were 97% & 77%, respectively. Pts receiving rhBMP-2 were judged to fuse faster & demonstrate more robust fusions. Fusion rate & quality of fusion proved to be statistically superior in the rhBMP-2 cohort. No complication was attributed to the use of rhBMP-2. The authors concluded that rhBMP-2 may serve as a safe & effective supplement to AICB for posterolat instrumented fusion.	Limitations of this study include the potential for selection bias since an inadequate description of baseline demographics is provided & the authors failed to evaluate these data for significant differences, e.g., it is not known if the no. of levels fused was comparable btwn treatment groups. The no. of pts w/in the control group is relatively small. It is not clear whether the surgical technique was standardized between cohorts, w/ no mention regarding the amount of AICB used. The value of the outcome parameters, in particular the subjective assessment of fusion quality, is of limited value & has not been shown to impact clinical outcome. Due to these limitations the study was downgraded to Level III evidence in support of rhBMP-2 as a graft extender for AICB in instrumented posterolat fusions.

(continued)



TABLE 4: rhBMP-2 in posterolateral fusion: summary of evidence\* (continued)

Authors & Year	Level of Evidence	Description of Study	Comments
Glassman et al., 2007 <sup>27</sup>	III	The objective of this retrospective review of data collected during a prospective, randomized, unblinded trial was to determine the influence of smoking on fusion rate & outcome of pts receiving either AICB or rhBMP-2 for single-level posterolateral fusions. All pts were evaluated at a minimum of 2 yrs after surgery. Clinical outcome was measured utilizing validated outcomes instruments (ODI, SF-36, back & leg pain scores) at 6 wks & 3, 6, 12, & 24 mos after surgery. An independent, blinded assessment of fusion status was performed w/ static & dynamic radiographs & CT imaging at 6, 12, & 24 mos after surgery. The records of 148 pts were reviewed, 42 smokers & 106 nonsmokers. The smokers were equally distributed btwn the 2 cohorts, w/ 55 nonsmokers in the rhBMP-2 cohort & 51 in the AICB group. Fusion rate at 24 mos based on radiographs was 100% in the rhBMP-2 nonsmokers, 95.2% in the rhBMP-2 smokers, 94.1% in the AICB nonsmokers, & 76.2% in the AICB smokers. A significant difference was observed btwn all smokers (85.7%) & all nonsmokers (97.2%) as well as btwn smokers & nonsmokers receiving AICB. Similar rates of fusion were determined w/ CT imaging. Clinical outcome was improved in all parameters in all 4 cohorts, w/o a significant difference in the degree of improvement btwn groups. When considered collectively, the nonsmokers consistently demonstrated better ODI & SF-36 scores. The authors concluded that rhBMP-2/CRM may enhance fusion rate in cigarette smokers undergoing single-level fusion & that smoking is detrimental to clinical outcome regardless of fusion status.	The retrospective nature of this study does limit inferences formulated from the results despite the fact that the data were collected during a prospective RCT. Since pts were not randomized w/ respect to smoking status, the benefit of the randomization process is nullified. Given the study design, this report provides Level III evidence regarding the impact of rhBMP-2/CRM on fusion rate in smokers & the impact of smoking on clinical outcome.
Lee et al., 2009	IV	The objective of this retrospective comparative study was to determine the efficacy of rhBMP-2 in pts >65 yrs undergoing an instrumented posterolateral fusion. 127 pts w/ lumbar degenerative disease were divided into 3 groups: pts >65 yrs received both rhBMP-2 & allograft (Group A, n = 34), pts <65 yrs received rhBMP-2 & allograft (Group B, n = 52), & pts >65 yrs received autograft (Group C, n = 41). Fusion assessment was performed by an independent blinded radiologist using static & dynamic radiographs, supplemented w/ CT when fusion was questionable. Kirkaldy-Willis & VAS scores were used to determine clinical outcome. The average follow-up was ~36 mos, although VAS scores were obtained up to 24 mos after surgery. The fusion rates were 82.4% in Group A, 94.2% in Group B, & 78.1% in Group C. At 2 yrs, Group B demonstrated a statistically superior VAS score compared w/ Group A. Clinical outcome was not statistically different btwn the 3 groups. The authors concluded that rhBMP-2/allograft yields equivalent outcomes to AICB in pts >65 yrs, but is not able to overcome all negative comorbidities associated w/ age.	There are limited baseline demographic data provided, w/ an inadequate description of comorbidities that would affect fusion potential. Apparent differences exist w/ respect to several of these comorbidities, e.g., no. of levels fused, & the authors fail to determine if these differences were significant. The existence of selection bias therefore cannot be excluded. The surgical technique is not described. An adequate assessment of fusion was performed, although the authors include time to fusion, which is of questionable significance. Due to these limitations the study was downgraded to Level IV evidence in support of rhBMP-2/allograft as a substitute for AICB in pts >65 yrs undergoing 1-level, instrumented, posterolateral fusions.
Hamilton et al., 2008	V	The authors performed a retrospective review of pts undergoing noninstrumented posterolateral fusion using local harvested autograft supplemented w/ rhBMP-2/ACS. 47 of 55 pts, median age 68.2 years, were evaluated. Fusion assessment was independently performed using radiographs & CT scans at various time points up to 36 mos after surgery. An independent clinical evaluation using validated instruments was performed at least 29 mos & up to 36 mos after surgery. The fusion rate was 80%. Greater than 85% of pts demonstrated an improved clinical outcome & pain relief. The authors concluded that the use of rhBMP-2 as a supplement to noninstrumented posterolateral fusions leads to improved pain & a comparable fusion rate in elderly pts.	This case series contains a heterogeneous study population w/ respect to fusion justification & no. of levels involved. Although the clinical outcome was performed by an independent assessor, pts were required to "recall" their pre- & postop pain & health status. The description of clinical results is difficult to interpret. CT evaluation was only performed in 85% of study pts. Due to these limitations, the case series is downgraded to Level V evidence that rhBMP-2 is an effective bone graft extender.

\* ACS = absorbable collagen sponge; AICB = autologous iliac crest bone;  $\beta$ -TCP =  $\beta$ -tricalcium phosphate; BMA = bone marrow aspirate; CRM = compression-resistant matrix; HA = hydroxyapatite; IDE = investigational device exemption; NRS = numeric rating scale; ODI = Oswestry Disability Index; pt = patient; RCT = randomized controlled trial; rhBMP-2 = recombinant human bone morphogenetic protein-2; SF-36 = 36-Item Short Form Health Survey; VAS = visual analog scale.

## Part 16: Bone graft extenders and substitutes

matrix as a substitute for AICB for single-level posterolateral instrumented fusion (Table 4).<sup>20</sup> Fusion assessment was performed in a blinded fashion, and clinical status was evaluated through validated outcome measures. Clinical follow-up was performed at 6 weeks and at 3, 6, 12, and 24 months and radiographic follow-up at 6, 12, and 24 months. Four hundred sixty-three patients were randomized, with a 2-year follow-up rate of 89%. Significantly longer operative times and greater blood loss was observed in the control group. There was no statistical difference in clinical outcome between groups, although both demonstrated significant improvement compared with baseline scores. Donor site pain was reported in 60% of the control group at final follow-up. Based on CT imaging, the interventional group demonstrated a statistically superior fusion rate at 6 months (79% with rhBMP-2 and 65% with AICB [ $p = 0.002$ ]) and at 24 months (96% with rhBMP-2 and 89% with AICB [ $p = 0.014$ ]). The overall rate of adverse events was statistically similar; however, 17 graft-related complications were recorded in the control group. The authors concluded that the use of rhBMP-2 matrix improved operative parameters, led to a higher fusion rate, and achieved comparable clinical outcomes to AICB and therefore can be considered an acceptable substitute for single-level posterolateral instrumented fusion. This was a well-designed and well-executed study. It is not clear if the clinical assessment was blinded; however, utilization of patient self-assessment questionnaires decreases the likelihood of bias with reporting. The authors did not perform an appropriate power analysis to determine sample size and failed to provide information regarding patients lost to follow-up. Due to these limitations the study was downgraded to Level II evidence in support of rhBMP-2 matrix as a substitute for AICB.

Dawson et al. conducted a multicenter prospective RCT to investigate if rhBMP-2/ACS supplemented with an HA/TCP extender could serve as an appropriate substitute for AICB in instrumented posterolateral fusions (Table 4).<sup>17</sup> Fifty patients were randomized; clinical follow-up was performed at 3, 6, 12, and 24 months, and radiographic follow-up at 6, 12, and 24 months. At 24 months, the follow-up rate was 88% in the treatment group and 86% in the control group. Both groups demonstrated improvements in all clinical outcome measures with the rhBMP-2 cohort demonstrating a trend toward better outcomes. The fusion rate was higher at all time points in the rhBMP-2 cohort, with final fusion rates of 95% in the investigational group and 70% in the control group. No difference in the radiographic or clinical outcome proved to be statistically significant. The authors concluded that the combination of rhBMP-2 and HA/TCP could be an effective alternative to AICB for single-level posterolateral instrumented fusions. The relatively small numbers of patients (< 50 patients per treatment arm), failure to provide adequate baseline demographic data, and utilization of a nonvalidated composite score to assess overall success are limitations of the study. The study was therefore considered to provide Level II evidence in support of rhBMP-2/ACS and HA/TCP as a graft substitute for instrumented posterolateral fusions.

Glassman et al. conducted a prospective RCT to com-

pare the clinical and radiographic outcomes of 106 patients older than 60 years of age undergoing instrumented posterolateral fusions with either rhBMP-2/ACS or AICB (Table 4).<sup>26</sup> The method of grafting was not standardized, with various graft extenders added at the discretion of the surgeon. Clinical outcome was determined with validated outcome measures, including SF-36, ODI, and numeric rating scale (NRS) for back and leg pain. Computed tomography scans were used to assess fusion. At 24 months after surgery the clinical and radiographic follow-up was 94% and 93%, respectively. At baseline, the patients in the rhBMP-2 cohort reported leg pain with greater frequency ( $p = 0.031$ ); there were no other differences in baseline demographics. The complication rate was significantly greater in the AICB cohort (20 vs 8,  $p = 0.014$ ), although none of the complications were directly attributed to either the harvest of AICB or the use of rhBMP-2/ACS. Both cohorts demonstrated a statistically significant clinical improvement over baseline; however, there was no difference in clinical outcome between treatment groups. An 86.3% fusion rate was observed in the rhBMP-2/ACS cohort, compared with 70.8% in the AICB group. The authors provided a CT “grade” for the observed fusion with the rhBMP-2 cohort demonstrating a significantly higher score (4.3 vs 3.8 [ $p = 0.03$ ]). Nonunion requiring revision was reported in 1 patient in the rhBMP-2 cohort and 5 in the AICB group. An estimation of total cost over 2 years was calculated, and the difference between the 2 groups was not significantly different (\$42,574 for the AICB cohort and \$40,131 for the rhBMP-2/ACS cohort). The authors concluded that the study provided Level I evidence supporting the use of rhBMP-2/ACS as an AICB replacement for lumbar fusion in the older patient. This study suffers from several limitations, including a heterogeneous patient cohort with respect to presenting diagnosis, failure to account for patients lost to follow-up, lack of a standard surgical protocol, questionable “grading” scheme to assess fusion, failure to determine sample size through a power analysis, and failure to perform an adequate statistical analysis. Due to these limitations the study was downgraded to Level II evidence in support of rhBMP-2 for patients older than 60 years of age undergoing posterolateral lumbar fusions.

Singh et al. published a prospective cohort study to compare outcome of patients receiving a mixture of rhBMP-2/local bone/AICB ( $n = 41$ ) to those receiving only local bone/AICB ( $n = 11$ ).<sup>53</sup> Fusion assessment was performed in an independent, blinded manner with reformatted CT images. The fusion rate with rhBMP-2 was 97% while the control cohort demonstrated a fusion rate of 77%. Those receiving rhBMP-2 were thought to achieve fusion faster and demonstrate a more robust fusion. However, this study failed to provide an adequate description of baseline demographics (for example, the number of levels fused in each group). This is a small and heterogeneous population of patients; it is not clear if the surgical procedure was standardized between cohorts, and no objective clinical outcomes were reported. The study was therefore downgraded to Level III evidence in support of utilizing rhBMP-2 as an extender.

Hamilton et al. published a retrospective case series of patients undergoing noninstrumented posterolat-

eral fusions utilizing local autograft supplemented with rhBMP-2.<sup>30</sup> An 80% fusion rate was observed; 85% of patients were felt to demonstrate clinical improvement. This study provides only Level V evidence in support of rhBMP-2 as an extender with local bone for noninstrumented fusions due to the heterogeneous patient population, failure to collect clinical outcomes in a prospective manner, and a radiographic follow-up rate of only 85%.

Taghavi et al. performed a retrospective cohort study to determine the efficacy of rhBMP-2/local bone to either allograft combined with bone marrow aspirate or autograft, in revision instrumented, posterolateral fusions. Sixty-two patients with varying diagnoses were included with a minimum follow-up of 2 years.<sup>56</sup> Patients were divided into 3 groups: Group 1 (n = 24) received rhBMP-2, Group 2 (n = 18) received BMA/allograft, and Group 3 (n = 20) received autograft. The exact source of autograft bone for Group 3 was not clearly defined. All 3 cohorts received supplemental local bone. Static and dynamic radiographs were used to assess fusion and were reviewed by 3 blinded independent reviewers with a diagnosis of nonunion based on either surgical exploration if revision performed or radiographic findings. Clinical outcome was determined through VAS scores. A fusion rate of 100% was observed for Groups 1 and 3; however, Group 2 demonstrated a 77.8% fusion rate. Patients undergoing multilevel procedures with BMA/allograft demonstrated a statistically lower fusion rate. No difference in VAS scores was observed. The authors concluded that rhBMP-2 could be an appropriate alternative to AICB in revision posterolateral fusion. Although this study was well executed with appropriate follow-up, validated outcome measures, and appropriate assessment of fusion, due to the retrospective nature of the study design it provides Level III evidence. As this was the only study identified to investigate the use of rhBMP-2 in revision surgery, evidence is insufficient to formulate a recommendation. Additional studies of similar or lesser quality, such as retrospective reviews or case series, promoting the use of rhBMP-2 for various clinical scenarios, such as in patients who use tobacco, have been published.<sup>3,25,27,36</sup> Due to an insufficient number of such studies no formal recommendations could be constructed regarding the use of rhBMP-2 under the specific clinical circumstances.

*rhBMP-2: Complications.* Between 2003 and 2007, the annual number of procedures utilizing BMPs increased by 4.3-fold (from 23,900 to 103,194 cases), with spinal fusions accounting for almost 93% of these cases.<sup>46</sup> Although it is difficult to deny a positive impact on fusion rate, surgeons must be aware of the potential risks and complications related to the use of BMPs, particularly since the majority of procedures would be considered off label.

Rihn et al. performed a single-center retrospective cohort study to specifically identify complications associated with the use of rhBMP-2 for single-level TLIF procedures and to determine if these complications differed compared with the use of AICB.<sup>50</sup> Between January of 2004 and May of 2007, 130 patients underwent a single-level TLIF using either AICB or rhBMP-2 (Table 5). One hundred nineteen patients were available for review, 33 receiving AICB and 86 receiving rhBMP-2, with an average radiographic fol-

low-up of 19.1 months and an average clinical follow-up of 27.6 months. A combination of plain radiographs and CT images were used to assess fusion status. Those patients receiving AICB demonstrated a 96.5% fusion rate, and the fusion rate in the rhBMP-2 cohort was 97% (p = 0.09). The overall complication rate was higher in the autograft cohort (45.5% vs 29.1%), but the difference was not significant. Donor site morbidity was the most common complication associated with AICB, and postoperative radiculitis was more often observed in the rhBMP-2 cohort (14% vs 3% [p = 0.08]). A significant decrease in radiculitis was observed after 2006 (20.4% to 5.4% [p = 0.047]), following the utilization of a hydrogel sealant intended to shield the exiting root. Additional complications thought to be related to the use of rhBMP-2 included osteolysis and heterotopic bone formation. The authors concluded that the TLIF procedure, regardless of graft, is associated with a relatively high complication rate (33.6% for the entire cohort). Although rhBMP-2 eliminates donor site morbidity, the surgeon should be aware of additional complications, such as radiculitis, osteolysis, and heterotopic bone formation, that may be associated with its use. The authors failed to disclose if the assessment, clinical or radiographic, was performed in a blinded fashion. No validated outcome measures were used, and the fusion criteria were not adequately described. This study provides Level IV evidence supporting the use of rhBMP-2; however, more importantly, it highlights several of the more common complications thought to be associated with the interbody application of rhBMP-2.

Pradhan et al. observed an increased rate of graft resorption, fracture, or collapse in patients undergoing stand-alone ALIF with femoral ring allograft.<sup>47</sup> Lewandrowski et al. observed osteolysis of the vertebral endplate following minimally invasive TLIF and speculated that endplate violation during interbody decortication may have been a contributing factor.<sup>42</sup> Although not specific for lumbar procedures, Vaidya et al. observed a higher incidence of graft subsidence when rhBMP-2 was used with an allograft interbody spacer.<sup>66</sup> Joseph and Rampersaud observed a greater incidence of heterotopic bone formation following the use of rhBMP-2 for minimal access interbody lumbar fusion, but no clinical sequelae associated with this excessive bone formation were identified.<sup>34</sup> Mindea et al. observed a higher incidence of postoperative radiculitis of a nonstructural cause associated with the use of rhBMP-2 during minimal access TLIF procedures.<sup>43</sup> Garrett et al. reported on the formation of painful postoperative seromas following the use of rhBMP-2 during posterolateral fusions.<sup>23</sup> Finally, Carragee et al. identified a higher incidence of retrograde ejaculation in patients receiving rhBMP-2 during ALIF procedures.<sup>10</sup> There have been a number of additional retrospective reviews and case series that have corroborated the findings from these reports.<sup>3,14,37,52</sup>

Although a direct cause and effect relationship between the use of rhBMP-2 and these complications cannot be formulated based on these studies, the potential association should not be ignored. The surgeon should carefully consider the off-label utilization of rhBMP-2, or any osteobiologic, and make sure that the patient has been adequately informed regarding these risks.

TABLE 5: Complications and the use of rhBMP-2: summary of evidence\*

Authors & Year	Level of Evidence	Description of Study	Comments
Rihn et al., 2009 <sup>50</sup>	IV	This retrospective cohort study was intended to evaluate the complications associated w/ 1-level TLIF procedures & determine if complications differed btwn pts receiving AICB or rhBMP-2. 119 of 130 pts were available for follow-up, 33 receiving autograft & 86 rhBMP-2. After 2006, a hydrogel sealant was used in 37 pts to shield the nerve root from exposure to the rhBMP-2. Fusion assessment, through a combination of radiographs & CT scans, was performed on average at 19.1 mos & clinical follow-up at 27.6 mos after surgery. The fusion rate for the autologous cohort was 96.5% & it was 97% for the rhBMP-2 cohort (p = 0.09). A higher complication rate was observed in the autograft cohort (45.5% vs 29.1%), but the difference was not significant. Donor site morbidity was the most common complication in the autologous cohort. Postop radiculitis was more commonly observed in the rhBMP-2 cohort (14% vs 3% [p = 0.08]); however, this incidence significantly decreased after the application of the hydrogel sealant (20.4% to 5.4% [p = 0.047]). Additional complications thought to be related to the use of rhBMP-2 included osteolysis & heterotopic bone formation. The authors concluded that the TLIF procedure, regardless of graft, is associated w/ a relatively high complication rate (33.6% for the entire cohort), & although rhBMP-2 eliminates donor site morbidity, additional complications such as radiculitis, osteolysis, & heterotopic bone formation are associated w/ its use.	The study is limited due to its retrospective design & failure to describe if the assessment of complications & fusion status was performed in a blinded fashion. No validated outcome instruments were used. The criteria for fusion assessment were not adequately described, & it is not clear if similar methods were performed equally for both study groups. This retrospective cohort study is downgraded from Level III to Level IV w/ respect to the complications associated w/ the use of rhBMP-2 in TLIF procedures.

\* AICB = autologous iliac crest bone; pt = patient; rhBMP-2 = recombinant human bone morphogenetic protein-2; TLIF = transforaminal lumbar interbody fusion.

*rhBMP-7: Posterolateral Fusion.* Osteogenic protein-1, also known as rhBMP-7, is another member of the transforming growth factor- $\beta$  superfamily and plays a key role in osteoblast differentiation. Compared with rhBMP-2, there have been relatively few clinical studies investigating rhBMP-7 as an agent of spinal fusion, with the majority, if not all, focusing on posterolateral fusion techniques. The FDA has not approved the use of rhBMP-7 for spinal fusions. Currently, its use requires a humanitarian device exemption. There were no recommendations pertaining to the use of rhBMP-7 in the original guidelines publication (Table 6).<sup>48</sup>

Delawi et al. published a prospective multicenter RCT comparing the efficacy of local autograft supplemented with either rhBMP-7 or AICB in single-level instrumented posterolateral fusions for isthmic or degenerative spondylolisthesis.<sup>18</sup> Clinical and fusion assessment was performed at 6 weeks, and 3, 6, and 12 months after surgery. Fusion assessment through CT imaging was performed in a blinded fashion. Validated clinical measures (ODI and VAS) were used to determine response to surgery. The follow-up rate at 12 months was 89%. There was no statistical difference in the fusion rate between the groups (63% in the rhBMP-7 group and 67% in the AICB cohort). Both groups demonstrated clinical improvement compared with baseline scores, but there was no statistical difference regarding clinical outcome between groups. At 12 months after surgery, 64% of AICB patients complained of at least “mild” donor site pain ( $2.7 \pm 2.8$  VAS). No specific adverse event was related to AICB harvesting or use of rhBMP-7. The authors concluded that rhBMP-7 is an effective alternative to AICB for supplementing local autograft for single-level posterolateral fusions. The small sample size (< 50 patients), incomplete statistical analysis, and potential impact of differences in baseline characteristics requires that the study be downgraded to Level II evidence in support of utilizing rhBMP-7/local autograft as a substitute for AICB/local autograft in single-level instrumented posterolateral fusions.

In 2008, Vaccaro et al. conducted a multicenter prospective RCT to further investigate the safety and efficacy of rhBMP-7/ACS and to demonstrate noninferiority as a replacement for AICB for noninstrumented, single-level posterolateral fusion.<sup>62</sup> Three hundred thirty-five patients were randomized in a 2:1 fashion, but only 293 were treated (208 patients received rhBMP-7/ACS and 87 received AICB). Independent blinded clinical and radiographic evaluations were performed at 6 weeks and at 3, 6, 12, 24, and longer than 36 months utilizing validated outcome measures, including ODI, SF-36, and VAS, and radiographs. Fusion assessment after 36 months was supplemented with CT scans. The primary overall success was reported as a composite measure, intended for FDA submission, and required a 20% improvement in ODI, absence of treatment-emergent adverse events related to the device, absence of a decline in neurological status, and radiographic successful fusion. At 24 months with a follow-up rate of 87%, the investigational group did not achieve statistical equivalence with respect to the overall success rate compared with controls (38.7% compared with 49.4% [p = 0.33]). The investigational group demonstrated a

**TABLE 6: rhBMP-7 in posterolateral fusion: summary of evidence\***

Authors & Year	Level of Evidence	Description	Comments
Delawi et al., 2010	II	The objective of this pilot, prospective, randomized, controlled multicenter trial was to compare the efficacy of rhBMP-7 w/ AICB, both supplemented w/ local bone, in 1-level instrumented posterolateral fusions for ischmic or degenerative spondylolisthesis. Clinical & fusion assessments were performed at 6 wks & 3, 6, & 12 mos after surgery. Fusion assessment through CT imaging was performed in a blinded fashion. Validated clinical measures (ODI & VAS) were used to determine response to surgery. The follow-up rate at 12 mos was 89%. There was no statistical difference in the fusion rate btwn the groups (63% in the rhBMP-7 group & 67% in the AICB cohort). Both groups demonstrated clinical improvement compared w/ baseline scores, but there was no statistical difference regarding clinical outcome btwn groups. At 12 mos after surgery, 64% of AICB pts complained of at least "mild" donor site pain (2.7 ± 2.8 VAS). No specific adverse event was related to AICB harvesting or use of rhBMP-7. The authors concluded that rhBMP-7 is an effective alternative to AICB when supplementing local autograft for 1-level posterolateral fusions & avoids the morbidity associated w/ AICB harvesting.	This study population is relatively small (<50 pts), but represents a homogeneous group of pts. The randomization protocol is adequately described & the treating surgeon was blinded as best as possible regarding intervention. Despite randomization there was a difference btwn groups w/ respect to the spinal segment undergoing fusion. Although statistics were adequately described, it is difficult to determine the significance due to the small sample size & no confidence intervals were applied. The small sample size, incomplete statistical analysis, & potential impact of differences in baseline characteristics require that the study be downgraded to Level II evidence in support of rhBMP-7 as a substitute for AICB to supplement local autograft in 1-level instrumented posterolateral fusions.
Vaccaro et al., 2008 <sup>62</sup>	II	The purpose of the prospective randomized controlled multicenter study was to determine the safety & efficacy of rhBMP-7/ACS & to demonstrate noninferiority as a replacement for AICB for uninstrumented, 1-level posterolateral fusion. 335 pts were randomized, but only 293 were treated. 208 pts received rhBMP-7 & 87 control pts received AICB. Independent blinded clinical & radiographic evaluations were performed at 6 wks & at 3, 6, 12, 24, & >36 mos after surgery using validated outcome measures & radiographs. Fusion assessment after 36 mos was supplemented w/ CT scans. At the 24-mo end point the investigational group did not achieve statistical equivalence w/ respect to the overall success rate compared w/ controls (38.7% vs 49.4% [p = 0.33]). The investigational group demonstrated a lower fusion rate (61.7% vs 83.1%). Noninferiority of the overall success was demonstrated after 36 mos (47.2% in the investigational group & 46.8% in the control cohort [p = 0.025]). CT evaluation demonstrated a statistically greater percentage of pts in the control arm demonstrating bridging bone across the intertransverse space (83% vs 56% [p = 0.001]). There was not a statistically significant difference in the rate of treatment-related serious adverse events btwn the investigational & control groups (85.6% & 84.7%, respectively [p = 0.863]). Donor site pain was reported in 44% of controls at 12 mos & 35% after 36 mos, w/ VAS scores of 1.6 at 12 mos & 1.1 after 36 mos. Op time & blood loss were significantly less in the investigational cohort. No significant immunological reaction related to the application of rhBMP-7 was recorded. The authors concluded that rhBMP-7/collagen composite is a safe & effective alternative to ICBG.	This is a well-designed large prospective randomized trial but several limitations exist. Although the authors performed a power calculation to determine sample size, the benefits of randomizations were compromised since 13% of pts were not treated & the authors failed to describe these pts. The follow-up rate at 24 mos was 87% of pts treated (76% of pts randomized), dropping to 69% (60% of randomized pts) after 36 mos. The assessment of overall success was modified after 36 mos compared w/ the 24-mo evaluation. Due to these limitations, this study provides Level II evidence that at 24 mos, rhBMP-7 did not achieve a noninferior outcome to AICB, as measured by the a priori overall success criteria defined by the authors, at 24 mos compared w/ AICB. The results were comparable after 36 mos; however, this conclusion is compromised due to the significant dropout rate.

(continued)

**TABLE 6: rhBMP-7 in posterolateral fusion: summary of evidence\* (continued)**

Authors & Year	Level of Evidence	Description	Comments
Kanayama et al., 2006	II	The objective of this prospective RCT was to compare the clinical & radiographic outcomes of pts undergoing 1-level posterolat instrumented fusions for degenerative spondylolisthesis. 20 pts were randomized into 2 groups, rhBMP-7/collagen (n = 10) & local autograft/HA/TCP (n = 10). Static & dynamic radiographs & CT images were obtained at 3 & 6 wks as well as at 3, 6, & 12 mos to assess fusion status. Validated clinical outcome measures (ODI) were obtained at 3, 6, 9, & 12 mos after surgery. All pts who demonstrated radiographic fusion underwent removal of instrumentation, regardless of clinical status. The follow-up rate at 1 yr was 90%. Both cohorts demonstrated significant improvement in the ODI scores at 3 mos after surgery; however, no significant difference was observed btwn the groups. It is not clear if the significance of clinical improvement was maintained after this time point. The fusion rate based on radiographic assessment was 78% in the rhBMP-7 cohort & 90% in the control group. Those pts considered fused (7 in the rhBMP-7/collagen cohort & 9 controls) underwent surgical exploration at an average of 15.3 mos after the index procedure. Solid arthrodesis was identified in 57% of rhBMP-7 pts explored (calculated fusion rate for all patients receiving rhBMP-7/collagen = 44%) & in 78% of the control group (calculated fusion rate for entire control group = 70%). No statistical analysis regarding fusion rate was performed. The authors concluded that rhBMP-7 was capable of inducing new bone growth however the fusion rate was not encouraging & they suggested modifications in either surgical technique or carrier may be required.	This is a small pt population, but it benefits from the homogeneous diagnosis. The authors fail to describe the randomization scheme. It is not clear if the radiographic assessment was performed in a blinded fashion. The authors provide cursory baseline demographic data. No power calculation was performed to determine sample size & a superficial description of statistical analysis was performed. The intraop determination of fusion status is generally considered the "gold standard" for fusion assessment & a clear advantage in this study. Due to limitations this study was downgraded to Level II evidence, not supporting the use of rhBMP-7 for 1-level instrumented posterolat fusions in degenerative spondylolisthesis.
Vaccaro et al., 2004	II	The purpose of the prospective randomized controlled multicenter pilot study was to determine the safety & efficacy of rhBMP-7/ACS as a replacement for AICB for uninstrumented posterolat fusion. 36 pts w/ degenerative spondylolisthesis were randomized & followed at 6 wks & 3, 6, & 12 mos after surgery. Safety was determined by comparing the nature & frequency of adverse events. Radiographs were analyzed by independent radiologists, blinded to the intervention, & validated outcomes instruments were used to determine clinical efficacy. The follow-up rate at 12 mos was 79% for the investigational group & 83% for the controls. The rate of adverse events did not differ btwn groups & no specific adverse event was related to the rhBMP-7. The fusion rate for the rhBMP-7 cohort was 74% & for the control group 60% (p = 0.675). The clinical success rate was 86% for the rhBMP-7 cohort & 73% for the control group (p = 0.39). The authors concluded that rhBMP-7 has an acceptable safety profile, & the comparable results to AICB justify further investigation to define the efficacy of rhBMP-7 as a bone graft substitute.	This is a well-designed pilot study but is limited by the small sample size (<50 pts) & pts lost to follow-up at the study end point. No power calculation was performed to determine the sample size. The 1-yr end point may also be considered too brief for fusion procedures. The measure of overall clinical success was a nonvalidated composite score of both fusion & clinical measures. Due to these limitations the study was downgraded to Level II, finding that the use of rhBMP-7 as a bone graft substitute in uninstrumented posterolat fusions is safe & effective.
Vaccaro et al., 2005	II	The purpose of this study was to report the long-term follow-up data from the previously reported pilot study described above. Pts were followed up to 24 mos after surgery using the same clinical & radiographic outcome measures as previously reported. The clinical & radiographic rates of follow-up were 86% & 83%, respectively. The fusion rates for the control & investigational cohort were 40% & 55%, respectively. Clinical success, w/ respect to the validated outcomes instrument, was 85% in the investigational cohort & 64% in the control group. No long-term adverse events were specifically related to the use of rhBMP-7. The authors concluded that safety & efficacy of rhBMP-7 is comparable to AICB for at least 24 mos after surgery.	The initial study (from 2004) was downgraded to Level II evidence due to limitations outlined in the comments. At the 24-mo time period no additional significant limitations were identified; therefore the study maintained a Level II designation supporting rhBMP-7 as a bone graft substitute.

(continued)

**TABLE 6: rhBMP-7 in posterolateral fusion: summary of evidence\* (continued)**

Authors & Year	Level of Evidence	Description	Comments
Vaccaro et al., 2008 <sup>65</sup>	III	The purpose of this study was to report the long-term follow-up data from the previously reported pilot study described above. Pts were followed up to 48 mos after surgery using the same clinical & radiographic outcome measures as previously reported. The clinical & radiographic rates of follow-up were 69% & 61%, respectively. The fusion rates for the control & investigational cohort were 50% & 68.8%, respectively. Clinical success, w/ respect to the validated outcomes instrument, was 73.7% in the investigational cohort & 57.1% in the control group. The overall success was 62.5% in the investigational cohort & 33.3% in the control group. No long-term adverse events were specifically related to the use of rhBMP-7. The authors concluded that safety & efficacy of rhBMP-7 is comparable to AICB for at least 48 mos after surgery.	The initial study (from 2004) was downgraded to Level II evidence due to limitations outlined in the comments. Further limitations were identified during the follow-up period that significantly limit conclusions drawn from this study, in particular the large no. of pts lost to follow-up. Due to this significant limitation this follow-up report provides only Level III evidence supporting rhBMP-7 as a bone graft substitute.
Vaccaro et al., 2003	IV	The purpose of this pilot study was to determine the safety of rhBMP-7 combined w/ autograft for posterolat uninstrumented fusions in pts w/ symptomatic degenerative spondylolisthesis. 12 pts underwent a 1-level fusion receiving rhBMP-7 mixed w/ AICB. Independent radiographic assessment of dynamic radiographs was performed at 6 wks & 3, 6, 9, & 12 mos, & validated outcomes instruments, ODI scores, were used to assess clinical outcome at 6 & 12 mos. Results were compared w/ a historical cohort of pts who only received AICB. 75% of pts achieved clinical success & 55% attained a solid fusion. There were no adverse events specifically associated w/ the use of rhBMP-7. The authors concluded that rhBMP-7 demonstrated an acceptable safety profile when used as an adjunct to AICB.	The small pt population, compared w/ a historical cohort, & relatively short follow-up for a fusion procedure limit this cohort study. The study design is difficult to categorize but falls btwn a prospective case series & retrospective cohort study. It was initially considered a Level III study but due to the limitations was downgraded to Level IV evidence supporting the safety & efficacy of rhBMP-7 as a bone graft extender for uninstrumented 1-level posterolat fusions in pts w/ symptomatic spondylolisthesis.

\* ACS = absorbable collagen sponge; AICB = autologous iliac crest bone; HA = hydroxyapatite; ICBG = iliac crest bone graft; ODI = Oswestry Disability Index; pt = patient; RCT = randomized controlled trial; rhBMP-7 = recombinant human bone morphogenetic protein-7; TCP = tricalcium phosphate; VAS = visual analog scale.

## Part 16: Bone graft extenders and substitutes

lower fusion rate (61.7% vs 83.1%). Noninferiority of the overall success was demonstrated after 36 months (47.2% in the investigational group and 46.8% in the control cohort [ $p = 0.025$ ]). Computed tomography evaluation demonstrated a statistically greater percentage of patients in the control arm demonstrating bridging bone across the intertransverse space (83% vs 56% [ $p = 0.001$ ]). However, at 36 months after surgery, only 69% of the original 293 patients were available for evaluation. There was no significant difference in the rate of treatment-related serious adverse events between the investigational and control groups, 85.6% and 84.7% respectively ( $p = 0.863$ ). No significant immunological reaction related to the application of rhBMP-7 was recorded. The authors concluded that rhBMP-7/collagen composite is a safe and effective alternative to ICBG. This was a well-designed and executed trial; however, limitations exist. The randomization process was compromised as 13% of those originally randomized were not treated, and no data are provided regarding these patients or those lost at final follow-up. The method of fusion assessment was altered at the final follow-up, with the addition of CT images, and a significant number of patients not available for evaluation ( $> 30\%$ ). Due to these limitations the study was downgraded to Level II evidence that rhBMP-7/ACS is noninferior to AICB for noninstrumented posterolateral lumbar fusion.

Kanayama et al. conducted a prospective RCT to compare the clinical and radiographic outcomes in 20 patients with degenerative spondylolisthesis receiving either rhBMP-7/ACS ( $n = 10$ ) or local autograft/HA/TCP ( $n = 10$ ) for single-level posterolateral instrumented fusions.<sup>35</sup> Fusion status was assessed using plain radiographs and CT images at 3 and 6 weeks as well as at 3, 6, and 12 months after surgery. Validated clinical outcome measures (ODI) were obtained at 3, 6, 9, and 12 months after surgery. Regardless of clinical status, all patients underwent a second surgery to remove their instrumentation if a solid arthrodesis was diagnosed based on radiographic imaging, on average 15.3 months following the index procedure. At 1 year after surgery the follow-up rate was 90%. The ODI scores significantly improved at 3 months in both cohorts; however, it is difficult to determine if the significance of this improvement was maintained beyond 3 months. The fusion rate based on radiographic assessment was 78% in the rhBMP-7 cohort; however, only 57% of these patients demonstrated a solid arthrodesis during direct surgical exploration. The radiographic fusion rate of the control group was 90%, with 78% of controls demonstrating a fusion at the time of implant removal. No statistical analysis regarding fusion rate was performed. The authors concluded that utilization of rhBMP-7 was feasible, but the observed fusion rate was not encouraging, suggesting that modifications of the surgical technique or carrier were required. The study cohort was small yet homogeneous with respect to surgical procedure and presenting diagnosis. It is not clear if the radiographic assessment was performed in a blinded fashion; however, confirmation of fusion through direct operative exploration is considered the gold standard for fusion assessment. Limitations of the study design include failure to describe the randomization scheme or perform a power calculation to determine sample size. The authors failed

to perform an adequate statistical analysis; this may be a secondary consequence of the small sample size. Despite the randomized nature of this study, the study was downgraded to Level II evidence suggesting that rhBMP-7 is an inadequate substitute for AICB in instrumented posterolateral fusion.

Vaccaro et al. published 3 separate studies over a 4-year period reporting the radiographic and clinical results from a prospective randomized controlled multicenter clinical pilot study investigating the efficacy and safety of OP-1 compared with AICB in noninstrumented posterolateral lumbar fusions.<sup>61,64,65</sup> The original pilot study, published in 2004, randomized 36 patients with degenerative spondylolisthesis to receive either rhBMP-7/ACS or AICB.<sup>64</sup> The initial study followed patients at 6 weeks and at 3, 6, and 12 months after the index procedure. An independent blinded radiologist evaluated plain radiographs to assess fusion and validated outcome measures; ODI and SF-36, were used to assess clinical status. At 12 months after surgery, the follow-up rate was 79% for the rhBMP-7 cohort and 83% for the control group. No short-term adverse events directly related to the use of rhBMP-7 were reported. At 12 months after surgery, the fusion and clinical success rates were 74% and 86%, respectively, for the rhBMP-7 cohort and 60% and 73%, respectively, in the control group, with no statistically significant difference between groups. From this initial study the authors concluded that rhBMP-7 has an acceptable safety profile and comparable results to AICB to justify further investigation. This initial study was limited by the lack of a power calculation, a small sample size ( $< 50$  patients), and significant loss to follow-up within the interventional group. A nonvalidated overall clinical outcome composite score is included that is difficult to objectify. Given these limitations, and those inherent with a pilot study, the initial publication is downgraded to Level II evidence in support of an acceptable safety profile and comparable efficacy of rhBMP-7 to AICB.

The same authors published 2 follow-up studies in 2005 and 2008 to report the 2- and 4-year outcomes from the same study population.<sup>61,65</sup> As the initial report provided Level II evidence, the subsequent reports were started at this level and downgraded further if additional limitations were identified. At the 24-month follow-up end point, the follow-up rate for the investigational and control groups were 86% and 83%, respectively.<sup>61</sup> Radiographic fusion occurred in 55% of patients receiving OP-1 and 40% of AICB patients. Clinical success was recorded in 85% of OP-1 patients and 64% of control patients. No additional limitations were identified in this study; therefore, a Level II designation is maintained. However, at 48 months only 69% and 61% were available for clinical and radiographic evaluations, respectively.<sup>65</sup> The fusion and clinical success rates were reported as 68.8% and 73.7% in the rh-BMP-7 group and 50% and 57.1% in the control cohort. Due to the small number of patients available at 48 months, formal statistical analysis was not performed. The authors concluded that rhBMP-7 had an acceptable safety profile and comparable results to AICB. Due to the additional attrition of patients at the 48-month follow-up time point, this study was downgraded to Level III evidence in support of comparable efficacy between rhBMP-7 and AICB.



In 2003, Vaccaro et al. conducted a pilot study to determine the safety of rhBMP-7 combined with AICB for posterolateral uninstrumented fusions in patients with symptomatic degenerative spondylolisthesis.<sup>63</sup> Seventy-five percent of patients achieved clinical success and 55% attained a solid fusion. There were no adverse events specifically associated with the use of rhBMP-7. The authors concluded that rhBMP-7 demonstrated an acceptable safety profile when used as an adjunct to AICB. The small patient population, comparison with a historical cohort, and relatively short follow-up for a fusion procedure limit the study. Due to these limitations the study is downgraded to Level IV evidence. As this was the only study investigating this specific application of rhBMP-7, there is insufficient evidence to formulate a recommendation.

### Summary

A wide variety of bone graft extenders and substitutes are currently available. Enhanced fusion rates and the ability to avoid complications associated with iliac crest harvesting are the intended benefits of their use. Many, if not all, of these extenders and substitutes evaluated in this review have demonstrated a positive effect on fusion rate with clinical outcomes comparable to AICB. Convincing evidence exists that calcium-based composites cannot be considered substitutes for AICB due to inferior fusion rates. These materials, along with allograft-derived grafts (DBM), function primarily as extenders, requiring some form of autograft to achieve adequate fusion rates. There has been little if any risk associated with the use of these extenders.

Bone morphogenetic proteins have dramatically altered the landscape of spinal fusion surgery. These powerful osteoinductive agents have demonstrated excellent potential as substitutes for AICB with both interbody and posterolateral fusions. The vast majority of investigations have evaluated the effect of rhBMP-2. Although rhBMP-2 has shown a positive effect on fusion rate, complications have been reported related to its use. As a result, careful consideration is required when utilizing these products.

Despite the beneficial effect on fusion, the current literature has also not adequately addressed the issue of whether these improved fusion rates justify the cost, especially for treatment of routine degenerative lumbar disease. Although it is likely that certain patient populations would benefit from the addition of BMPs when performing spinal fusion surgery, the current literature has failed to adequately identify such patient populations.

### Key Issues for Future Investigation

There has already been an extensive amount of research investigating the potential impact of these graft extenders and substitutes. Further investigations should focus on improving study design to validate the conclusions formulated from previous publications and a comprehensive evaluation of risks and complications will be necessary to properly inform our patients. Identification of patient populations at risk for pseudarthrosis would also better define patient populations where the benefits of utilizing BMPs justify the risks. Potentially more rel-

evant than defining the clinical impact of these materials is to determine their cost utility. Comprehensive cost analyses, not simply a superficial quantification of upfront costs, will ultimately be required. Such an endeavor will require the concerted effort of a multidisciplinary panel of experts from the clinical, epidemiological, and administrative disciplines.

### Acknowledgments

We would like to acknowledge the AANS/CNS Joint Guidelines Committee (JGC) for their review, comments, and suggestions; Laura Mitchell, CNS Guidelines Project Manager, for her organizational assistance; and Linda O'Dwyer, medical librarian, for assistance with the literature searches. We would also like to acknowledge the following individual JGC members for their contributions throughout the review process: Timothy Ryken, M.D.; Kevin Cockroft, M.D.; Sepideh Amin-Hanjani, M.D.; Steven N. Kalkanis, M.D.; John O'Toole, M.D., M.S.; Steven Casha, M.D., Ph.D.; Aaron Filler, M.D., Ph.D., F.R.C.S.; Daniel Hoh, M.D.; Steven Hwang, M.D.; Todd McCall, M.D.; Jeffrey J. Olson, M.D.; Julie Pilitsis, M.D., Ph.D.; Joshua Rosenow, M.D.; and Christopher Winfree, M.D.

### Disclosure

Administrative costs of this project were funded by the Congress of Neurological Surgeons and the Joint Section on Disorders of the Spine and Peripheral Nerves of the American Association of Neurological Surgeons and Congress of Neurological Surgeons. No author received payment or honorarium for time devoted to this project. Dr. Ghogawala receives grants from the Patient Centered Outcomes Research Institute (PCORI) and the National Institutes of Health (NIH). Dr. Groff is a consultant for DePuy Spine and EBI Spine. Dr. Mummaneni owns stock in Spinicity and receives honoraria from DePuy Spine and Globus and royalties from DePuy Spine, Quality Medical Publishers, and Thieme Publishing. Dr. Wang owns stock in Bone Biologics, AxioMed, Amedica, CoreSpine, Expanding Orthopedics, Pioneer, Syndicom, VG Innovations, PearlDiver, Flexuspine, Axis, FzioMed, Benvenue, Promethean, Nexgen, ElectroCore, and Surgitech and holds patents with and receives royalties from Biomet, Stryker, SeaSpine, Aesculap, Osprey, Amedica, Synthes, and Alphatec. The authors report no other potential conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Kaiser. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kaiser. Study supervision: Kaiser.

### References

1. Acharya NK, Kumar RJ, Varma HK, Menon VK: Hydroxyapatite-bioactive glass ceramic composite as stand-alone graft substitute for posterolateral fusion of lumbar spine: a prospective, matched, and controlled study. *J Spinal Disord Tech* **21**:106–111, 2008
2. Agarwal R, Williams K, Umscheid CA, Welch WC: Osteoinductive bone graft substitutes for lumbar fusion: a systematic review. Clinical article. *J Neurosurg Spine* **11**:729–740, 2009
3. Balseiro S, Nottmeier EW: Vertebral osteolysis originating from subchondral cyst end plate defects in transforaminal lumbar interbody fusion using rhBMP-2. Report of two cases. *Spine J* **10**:e6–e10, 2010
4. Banwart JC, Asher MA, Hassanein RS: Iliac crest bone graft harvest donor site morbidity. A statistical evaluation. *Spine (Phila Pa 1976)* **20**:1055–1060, 1995

## Part 16: Bone graft extenders and substitutes

- Burkus JK, Dorchak JD, Sanders DL: Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type 2. **Spine (Phila Pa 1976)** **28**:372–377, 2003
- Burkus JK, Gornet MF, Dickman CA, Zdeblick TA: Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. **J Spinal Disord Tech** **15**:337–349, 2002
- Burkus JK, Gornet MF, Schuler TC, Kleeman TJ, Zdeblick TA: Six-year outcomes of anterior lumbar interbody arthrodesis with use of interbody fusion cages and recombinant human bone morphogenetic protein-2. **J Bone Joint Surg Am** **91**:1181–1189, 2009
- Cammisa FP Jr, Lowery G, Garfin SR, Geisler FH, Klara PM, McGuire RA, et al: Two-year fusion rate equivalency between Grafton DBM gel and autograft in posterolateral spine fusion: a prospective controlled trial employing a side-by-side comparison in the same patient. **Spine (Phila Pa 1976)** **29**:660–666, 2004
- Carragee EJ, Ghanayem AJ, Weiner BK, Rothman DJ, Bono CM: A challenge to integrity in spine publications: years of living dangerously with the promotion of bone growth factors. **Spine J** **11**:463–468, 2011
- Carragee EJ, Mitsunaga KA, Hurwitz EL, Scuderi GJ: Retrograde ejaculation after anterior lumbar interbody fusion using rhBMP-2: a cohort controlled study. **Spine J** **11**:511–516, 2011
- Carter JD, Swearingen AB, Chaput CD, Rahm MD: Clinical and radiographic assessment of transforaminal lumbar interbody fusion using HEALOS collagen-hydroxyapatite sponge with autologous bone marrow aspirate. **Spine J** **9**:434–438, 2009
- Chang CH, Lin MZ, Chen YJ, Hsu HC, Chen HT: Local autogenous bone mixed with bone expander: an optimal option of bone graft in single-segment posterolateral lumbar fusion. **Surg Neurol** **70 Suppl 1**:S47–S49, 2008
- Chen CL, Liu CL, Sun SS, Han PY, Lee CS, Lo WH: Posterolateral lumbar spinal fusion with autogenous bone chips from laminectomy extended with OsteoSet. **J Chin Med Assoc** **69**:581–584, 2006
- Chen NF, Smith ZA, Stiner E, Armin S, Sheikh H, Khoo LT: Symptomatic ectopic bone formation after off-label use of recombinant human bone morphogenetic protein-2 in transforaminal lumbar interbody fusion. Report of 4 cases. **J Neurosurg Spine** **12**:40–46, 2010
- Chen WJ, Tsai TT, Chen LH, Niu CC, Lai PL, Fu TS, et al: The fusion rate of calcium sulfate with local autograft bone compared with autologous iliac bone graft for instrumented short-segment spinal fusion. **Spine (Phila Pa 1976)** **30**:2293–2297, 2005
- Dai LY, Jiang LS: Single-level instrumented posterolateral fusion of lumbar spine with beta-tricalcium phosphate versus autograft: a prospective, randomized study with 3-year follow-up. **Spine (Phila Pa 1976)** **33**:1299–1304, 2008
- Dawson E, Bae HW, Burkus JK, Stambough JL, Glassman SD: Recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge with an osteoconductive bulking agent in posterolateral arthrodesis with instrumentation. A prospective randomized trial. **J Bone Joint Surg Am** **91**:1604–1613, 2009
- Delawi D, Dhert WJ, Rillardon L, Gay E, Prestamburgo D, Garcia-Fernandez C, et al: A prospective, randomized, controlled, multicenter study of osteogenic protein-1 in instrumented posterolateral fusions: report on safety and feasibility. **Spine (Phila Pa 1976)** **35**:1185–1191, 2010
- Dimar JR, Glassman SD, Burkus KJ, Carreon LY: Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenetic protein-2/compression resistant matrix versus iliac crest bone graft. **Spine (Phila Pa 1976)** **31**:2534–2540, 2006
- Dimar JR II, Glassman SD, Burkus JK, Pryor PW, Hardacker JW, Carreon LY: Clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine arthrodesis. **J Bone Joint Surg Am** **91**:1377–1386, 2009
- Epstein NE: Beta tricalcium phosphate: observation of use in 100 posterolateral lumbar instrumented fusions. **Spine J** **9**:630–638, 2009
- Epstein NE: Efficacy of different bone volume expanders for augmenting lumbar fusions. **Surg Neurol** **69**:16–19, 2008
- Garrett MP, Kakarla UK, Porter RW, Sonntag VKH: Formation of painful seroma and edema after the use of recombinant human bone morphogenetic protein-2 in posterolateral lumbar spine fusions. **Neurosurgery** **66**:1044–1049, 2010
- Geibel PT, Boyd DL, Slabisak V: The use of recombinant human bone morphogenetic protein in posterior interbody fusions of the lumbar spine: a clinical series. **J Spinal Disord Tech** **22**:315–320, 2009
- Glassman SD, Carreon L, Djurasovic M, Campbell MJ, Puno RM, Johnson JR, et al: Posterolateral lumbar spine fusion with INFUSE bone graft. **Spine J** **7**:44–49, 2007
- Glassman SD, Carreon LY, Djurasovic M, Campbell MJ, Puno RM, Johnson JR, et al: RhBMP-2 versus iliac crest bone graft for lumbar spine fusion: a randomized, controlled trial in patients over sixty years of age. **Spine (Phila Pa 1976)** **33**:2843–2849, 2008
- Glassman SD, Dimar JR III, Burkus K, Hardacker JW, Pryor PW, Boden SD, et al: The efficacy of rhBMP-2 for posterolateral lumbar fusion in smokers. **Spine (Phila Pa 1976)** **32**:1693–1698, 2007
- Goldberg VM, Stevenson S: Natural history of autografts and allografts. **Clin Orthop Relat Res** (**225**):7–16, 1987
- Haid RW Jr, Branch CL Jr, Alexander JT, Burkus JK: Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages. **Spine J** **4**:527–539, 2004
- Hamilton DK, Jones-Quaidoo SM, Sansur C, Shaffrey CI, Oskoui R, Jane JA Sr: Outcomes of bone morphogenetic protein-2 in mature adults: posterolateral non-instrument-assisted lumbar decompression and fusion. **Surg Neurol** **69**:457–462, 2008
- Heary RF, Schlenk RP, Sacchieri TA, Barone D, Brotea C: Persistent iliac crest donor site pain: independent outcome assessment. **Neurosurgery** **50**:510–517, 2002
- Hsu CJ, Chou WY, Teng HP, Chang WN, Chou YJ: Coralline hydroxyapatite and laminectomy-derived bone as adjuvant graft material for lumbar posterolateral fusion. **J Neurosurg Spine** **3**:271–275, 2005
- Jenis LG, Banco RJ: Efficacy of silicate-substituted calcium phosphate ceramic in posterolateral instrumented lumbar fusion. **Spine (Phila Pa 1976)** **35**:E1058–E1063, 2010
- Joseph V, Rampersaud YR: Heterotopic bone formation with the use of rhBMP2 in posterior minimal access interbody fusion: a CT analysis. **Spine (Phila Pa 1976)** **32**:2885–2890, 2007
- Kanayama M, Hashimoto T, Shigenobu K, Yamane S, Bauer TW, Togawa D: A prospective randomized study of posterolateral lumbar fusion using osteogenic protein-1 (OP-1) versus local autograft with ceramic bone substitute: emphasis of surgical exploration and histologic assessment. **Spine (Phila Pa 1976)** **31**:1067–1074, 2006
- Katayama Y, Matsuyama Y, Yoshihara H, Sakai Y, Nakamura H, Imagama S, et al: Clinical and radiographic outcomes of posterolateral lumbar spine fusion in humans using recombinant human bone morphogenetic protein-2: an average five-year follow-up study. **Int Orthop** **33**:1061–1067, 2009
- Knox JB, Dai JM III, Orchowski J: Osteolysis in transforaminal lumbar interbody fusion with bone morphogenetic protein-2. **Spine (Phila Pa 1976)** **36**:672–676, 2011

38. Korovessis P, Koureas G, Zacharatos S, Papazisis Z, Lambiris E: Correlative radiological, self-assessment and clinical analysis of evolution in instrumented dorsal and lateral fusion for degenerative lumbar spine disease. Autograft versus coralline hydroxyapatite. *Eur Spine J* **14**:630–638, 2005
39. Kurz LT, Garfin SR, Booth RE Jr: Harvesting autogenous iliac bone grafts. A review of complications and techniques. *Spine (Phila Pa 1976)* **14**:1324–1331, 1989
40. Lanman TH, Hopkins TJ: Lumbar interbody fusion after treatment with recombinant human bone morphogenetic protein-2 added to poly(L-lactide-co-D,L-lactide) bioresorbable implants. *Neurosurg Focus* **16**(3):E9, 2004
41. Lee JH, Hwang CJ, Song BW, Koo KH, Chang BS, Lee CK: A prospective consecutive study of instrumented posterolateral lumbar fusion using synthetic hydroxyapatite (Bongros-HA) as a bone graft extender. *J Biomed Mater Res A* **90**:804–810, 2009
42. Lewandrowski KU, Nanson C, Calderon R: Vertebral osteolysis after posterior interbody lumbar fusion with recombinant human bone morphogenetic protein 2: a report of five cases. *Spine J* **7**:609–614, 2007
43. Mindea SA, Shih P, Song JK: Recombinant human bone morphogenetic protein-2-induced radiculitis in elective minimally invasive transforaminal lumbar interbody fusions: a series review. *Spine (Phila Pa 1976)* **34**:1480–1485, 2009
44. Mummaneni PV, Pan J, Haid RW, Rodts GE: Contribution of recombinant human bone morphogenetic protein-2 to the rapid creation of interbody fusion when used in transforaminal lumbar interbody fusion: a preliminary report. *J Neurosurg Spine* **1**:19–23, 2004
45. Neen D, Noyes D, Shaw M, Gwilym S, Fairlie N, Birch N: Healos and bone marrow aspirate used for lumbar spine fusion: a case controlled study comparing healos with autograft. *Spine (Phila Pa 1976)* **31**:E636–E640, 2006
46. Ong KL, Villarraga ML, Lau E, Carreon LY, Kurtz SM, Glassman SD: Off-label use of bone morphogenetic proteins in the United States using administrative data. *Spine (Phila Pa 1976)* **35**:1794–1800, 2010
47. Pradhan BB, Bae HW, Dawson EG, Patel VV, Delamarter RB: Graft resorption with the use of bone morphogenetic protein: lessons from anterior lumbar interbody fusion using femoral ring allografts and recombinant human bone morphogenetic protein-2. *Spine (Phila Pa 1976)* **31**:E277–E284, 2006
48. Resnick DK, Choudhri TF, Dailey AT, Groff MW, Khoo L, Matz PG, et al: Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes. *J Neurosurg Spine* **2**:733–736, 2005
49. Rihn JA, Makda J, Hong J, Patel R, Hilibrand AS, Anderson DG, et al: The use of RhBMP-2 in single-level transforaminal lumbar interbody fusion: a clinical and radiographic analysis. *Eur Spine J* **18**:1629–1636, 2009
50. Rihn JA, Patel R, Makda J, Hong J, Anderson DG, Vaccaro AR, et al: Complications associated with single-level transforaminal lumbar interbody fusion. *Spine J* **9**:623–629, 2009
51. Schizas C, Triantafyllopoulos D, Kosmopoulos V, Tzinieris N, Stafylas K: Posterolateral lumbar spine fusion using a novel demineralized bone matrix: a controlled case pilot study. *Arch Orthop Trauma Surg* **128**:621–625, 2008
52. Shah RK, Moncayo VM, Smitson RD, Pierre-Jerome C, Terk MR: Recombinant human bone morphogenetic protein 2-induced heterotopic ossification of the retroperitoneum, psoas muscle, pelvis and abdominal wall following lumbar spinal fusion. *Skeletal Radiol* **39**:501–504, 2010
53. Singh K, Smucker JD, Gill S, Boden SD: Use of recombinant human bone morphogenetic protein-2 as an adjunct in posterolateral lumbar spine fusion: a prospective CT-scan analysis at one and two years. *J Spinal Disord Tech* **19**:416–423, 2006 (Erratum in *J Spinal Disord Tech* **20**:185, 2007)
54. Slosar PJ, Josey R, Reynolds J: Accelerating lumbar fusions by combining rhBMP-2 with allograft bone: a prospective analysis of interbody fusion rates and clinical outcomes. *Spine J* **7**:301–307, 2007
55. Summers BN, Eisenstein SM: Donor site pain from the ilium. A complication of lumbar spine fusion. *J Bone Joint Surg Br* **71**:677–680, 1989
56. Taghavi CE, Lee KB, Keorochana G, Tzeng ST, Yoo JH, Wang JC: Bone morphogenetic protein-2 and bone marrow aspirate with allograft as alternatives to autograft in instrumented revision posterolateral lumbar spinal fusion: a minimum two-year follow-up study. *Spine (Phila Pa 1976)* **35**:1144–1150, 2010
57. Urist MR: Bone: formation by autoinduction. *Science* **150**:893–899, 1965
58. US Food and Drug Administration: **InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device - P000058**. <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm083423.htm> [Accessed April 21, 2014]
59. US Food and Drug Administration: **Listing of CDRH Humanitarian Device Exemptions**. (<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm>) [Accessed April 21, 2014]
60. US Food and Drug Administration: **OP-1 Putty - H0200008**. (<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm081181.htm>) [Accessed April 21, 2014]
61. Vaccaro AR, Anderson DG, Patel T, Fischgrund J, Truumees E, Herkowitz HN, et al: Comparison of OP-1 Putty (rhBMP-7) to iliac crest autograft for posterolateral lumbar arthrodesis: a minimum 2-year follow-up pilot study. *Spine (Phila Pa 1976)* **30**:2709–2716, 2005
62. Vaccaro AR, Lawrence JP, Patel T, Katz LD, Anderson DG, Fischgrund JS, et al: The safety and efficacy of OP-1 (rhBMP-7) as a replacement for iliac crest autograft in posterolateral lumbar arthrodesis: a long-term (>4 years) pivotal study. *Spine (Phila Pa 1976)* **33**:2850–2862, 2008
63. Vaccaro AR, Patel T, Fischgrund J, Anderson DG, Truumees E, Herkowitz H, et al: A pilot safety and efficacy study of OP-1 putty (rhBMP-7) as an adjunct to iliac crest autograft in posterolateral lumbar fusions. *Eur Spine J* **12**:495–500, 2003
64. Vaccaro AR, Patel T, Fischgrund J, Anderson DG, Truumees E, Herkowitz HN, et al: A pilot study evaluating the safety and efficacy of OP-1 Putty (rhBMP-7) as a replacement for iliac crest autograft in posterolateral lumbar arthrodesis for degenerative spondylolisthesis. *Spine (Phila Pa 1976)* **29**:1885–1892, 2004
65. Vaccaro AR, Whang PG, Patel T, Phillips FM, Anderson DG, Albert TJ, et al: The safety and efficacy of OP-1 (rhBMP-7) as a replacement for iliac crest autograft for posterolateral lumbar arthrodesis: minimum 4-year follow-up of a pilot study. *Spine J* **8**:457–465, 2008
66. Vaidya R, Weir R, Sethi A, Meisterling S, Hakeos W, Wybo CD: Interbody fusion with allograft and rhBMP-2 leads to consistent fusion but early subsidence. *J Bone Joint Surg Br* **89**:342–345, 2007
67. Villavicencio AT, Burneikiene S, Nelson EL, Bulsara KR, Favors M, Thramann J: Safety of transforaminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein-2. *J Neurosurg Spine* **3**:436–443, 2005

Manuscript submitted March 27, 2014.

Accepted April 9, 2014.

Please include this information when citing this paper: DOI: 10.3171/2014.4.SPINE14325.

Address correspondence to: Michael G. Kaiser, M.D., Columbia University, Neurological Surgery, The Neurological Institute, 710 W. 168th St., New York, NY 10032. email: mgk7@columbia.edu.