

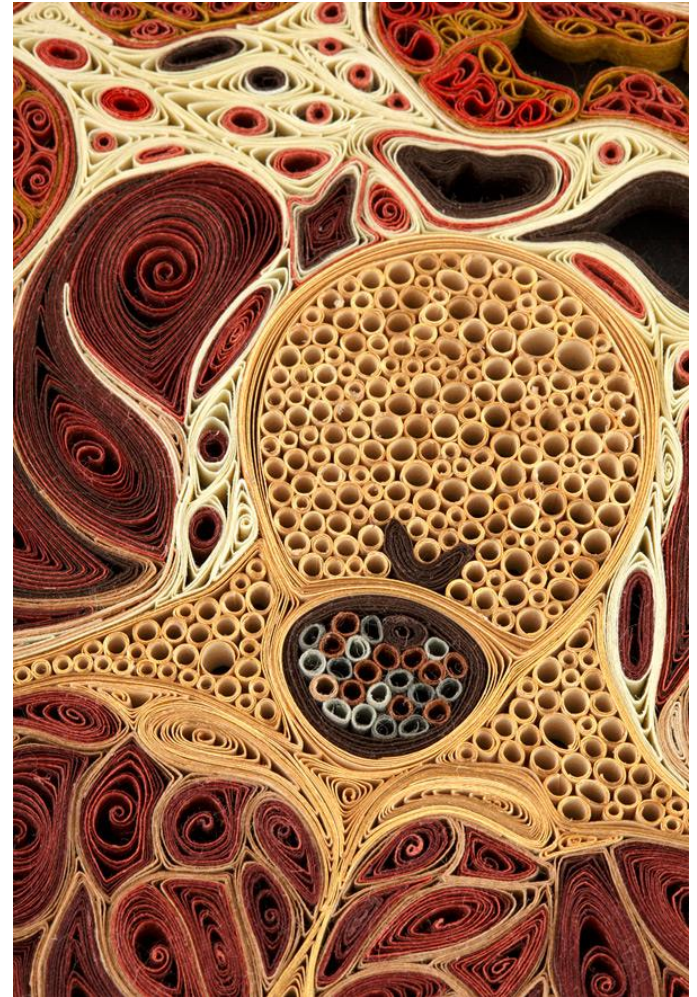
Fusion in MISS.

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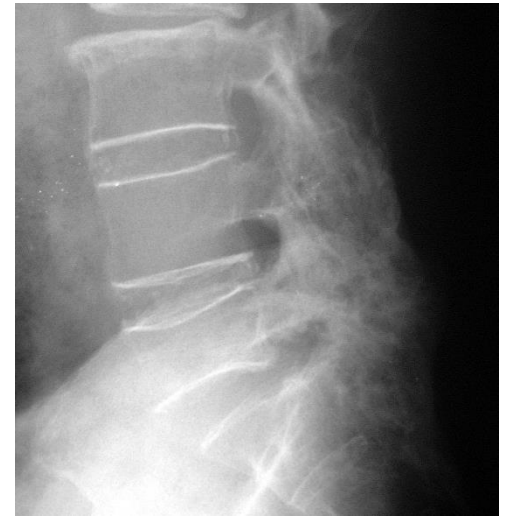
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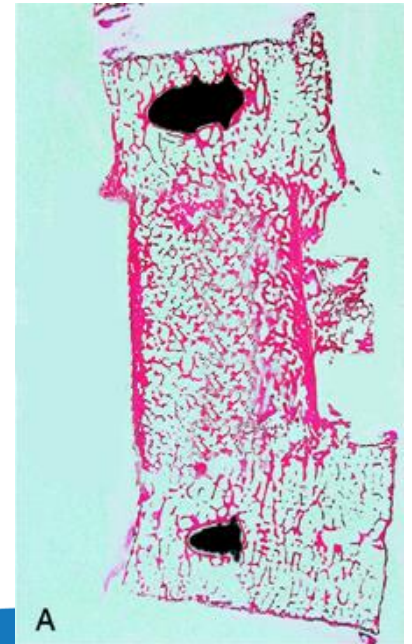
Introduction.

- Spinal fusion: treatment modality for the management of spinal conditions that require stabilization: symptomatic degenerative disk disease, infection, scoliosis, traumatic injuries, and spinal tumours.
- Several techniques are available to achieve stabilization of the lumbar spine: anterior lumbar interbody fusion (ALIF), posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF), direct lateral interbody fusion (XLIF), posterolateral only (intertransverse) fusion, and facet screw or pedicle screw/rod placement.
- Minimally invasive variations of these techniques have also been developed to minimize soft tissue dissection with the intention of minimizing intraoperative blood loss and complications as well as reducing postoperative pain and subsequent hospital stay.



Introduction.

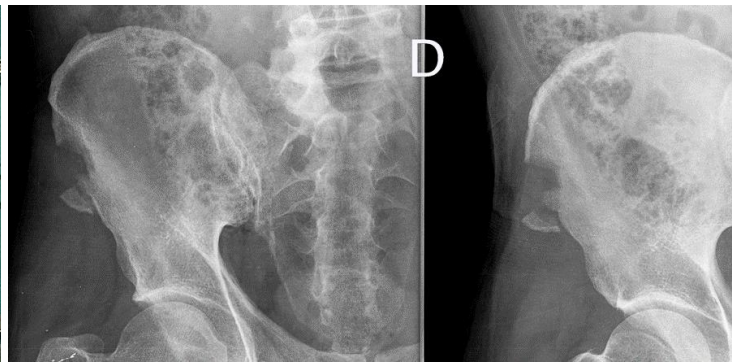
- Although difficult to diagnose, pseudarthrosis following lumbar fusion surgery is one of the most common complications, and together with the chronic pain and disability that ensues, is a common indication for revision surgery.
- Despite the recent advances in cage design and bone fusion extender materials, pseudoarthrosis remains a pressing issue occurring in 13%-41.4% of patients.
- Spinal coalition using patient's autologous graft is the gold standard surgical technique.



Introduction.

Disadvantages of Autologous Bone Graft

- Limited supply
 - Large quantities required.
 - Revision / previous harvested
 - Minimally invasive spinal fusion
- Quality of bone compromised
 - Elderly.
 - Osteoporotic.
- Bone graft is still a relatively invasive procedure.
 - Possibility of significant donor site morbidity and significant postoperative complications (eg. Infection, hematoma, intractable pain, fracture, Neurovascular injury).



Overview of biologics in spine arthrodesis.

Properties of the grafts.

- **Osteoconduction:** Is a physical effect by which the matrix of the graft forms a scaffold that favors outside cells to penetrate the graft and form new bone. It's based in provide passive porous scaffold upon which new bone can form.
- **Osteoinduction:** Is a Chemical process by which molecules contained in the graft convert the neighboring cells into osteoblasts which it turn form new bone. It's based in induce differentiation of stem cell into osteogenic cells.
- **Osteogenesis:** Refers to the formation or developement of new bone by cells contained in the graft. It's based in provide stem cells with osteogenic potential, which directly lays down new bone.

Overview of biologics in spine arthrodesis

GRAFT OPTIONS	OSTEO-CONDUCTIVE	OSTEO-INDUCTIVE	OSTEOGENIC
AUTOGRAFT	+	+	+
ALLOGRAFT	+	+/-	-
DEMINERALISED BONE MATRIX	+	+	-
CERAMICS	+	-	-
MESENCHIMAL STEM CELLS	-	-	+
rhBMP	-	+	-

Kannan A et al J Spinal Disord Tech 2015; 28: 163-70

Overview of biologics in spine arthrodesis

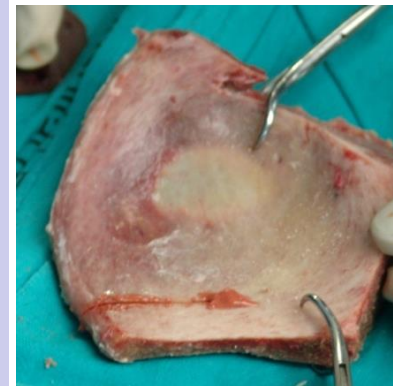
GRAFT OPTIONS	ADVANTAGES	DISADVANTAGES
AUTOGRAFT-ILIAC CREST	<ul style="list-style-type: none"> • Viable osteoprogenitor cells and growth factors. • Biologically compatible. • No risk of disease transmission. • Can have structural cortical graft. 	<ul style="list-style-type: none"> • Finite volume. • Quality can be compromised. • Donor-site morbidity 10 to 39%
AUTOGRAFT-LOCAL BONE	<ul style="list-style-type: none"> • Viable osteoprogenitor cells and growth factors. • Biologically compatible. • No risk of disease transmission. • Minimal morbidity. 	<ul style="list-style-type: none"> • Finite volume. • Unclear efficacy when used alone and with insufficient volume.



Kannan A et al J Spinal Disord Tech 2015; 28: 163-70

Overview of biologics in spine arthrodesis

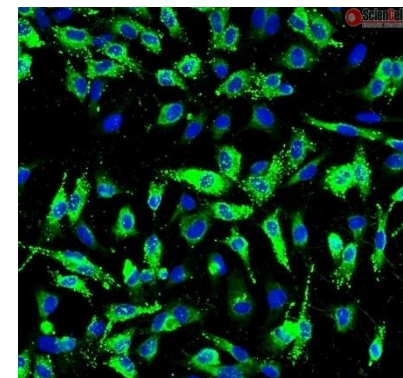
GRAFT OPTIONS	ADVANTAGES	DISADVANTAGES
ALLOGRAFT BONE BANK	<ul style="list-style-type: none"> • Abundant availability. • Low cost. 	<ul style="list-style-type: none"> • Potential risk of bio-incompatibility and disease transmission. • No active osteoprogenitor cells.
DEMINERALISED BONE MATRIX (DBM).	<ul style="list-style-type: none"> • Synergistic proteins and growth factors. • Multiple forms e.g. chips, paste, strips.. • Abundant availability. 	<ul style="list-style-type: none"> • Variability in composition and efficacy (even batch-to-batch).



Kannan A et al J Spinal Disord Tech 2015; 28: 163-70

Overview of biologics in spine arthrodesis

GRAFT OPTIONS	ADVANTAGES	DISADVANTAGES
CERAMICS	<ul style="list-style-type: none"> • Immediate strength. • Abundant availability. • Lack of immunogenicity • No risk of disease transmission. 	<ul style="list-style-type: none"> • Mechanical properties dependant on composition • Can have brittle structure with low tensile strength.
MESENCHIMAL STEM CELLS (MSCs)	<ul style="list-style-type: none"> • Self renewal • Plasticity • Multi-lineage potential. • Live growth factors. 	<ul style="list-style-type: none"> • Lacks innate structural support. • Variability in processing • Varying concentrations of osteoprogenitor cells.



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Overview of biologics in spine arthrodesis

GRAFT OPTIONS	ADVANTAGES	DISADVANTAGES
RECOMBINANT HUMAN BONE MORPHOGENETIC PROTEIN. (rhBMP)	<ul style="list-style-type: none">• Increased fusion rates.• Abundant availability.• Lack of immunogenicity.• No risk of disease transmission.• Involved in differentiation maturation, and proliferation of mesenchymal precursor cells into osteogenic cells.	<ul style="list-style-type: none">• Potential adverse effects: prevertebral swelling, seroma formation, retrograde ejaculation, osteolysis, heterotopic ossification, possible involvement in oncologic disease processes.• High cost.

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Fusion rates in posterolateral fusion.

GRAFT OPTIONS	Nº of Studies	Nº of patients fused	Fusion Rate	Range
ICBG	23	1103	79	40-100
Local Bone alone	8	637	89	65-95
Allograft alone	4	141	52	0-92
BMA concentrated	2	34	85	78-91
BMP-2	3	201	94	90-100
ceramics	16	603	87	5-100
DBMs	3	171	89	63-97
Autologous growth factors	4	154	74	54-100

Hsu WK et al. Global Spine J 2012; 2: 239-48

Recombinant Human Bone Morphogenetic Protein (rhBMP)

Safety and Effectiveness of rhBMP-2 for spinal fusion. (Simmonds MC et al. Ann Intern Med 2013: 158(12); 877-89.

Meta-analysis of Individual-Participant data from 11 of 17 trials sponsored by Medtronic (n1302). Additional aggregate adverse event extracted from 35 published observational studies.

- BMP improves **rates of fusion** compared with ICBG
- BMP improves **back pain and quality of life** compared with ICBG at between 6 and 12 months after surgery (not significant).
- Increased risk for **pain** in the immediate postsurgical period.
- May be associated with an increased **risk of cancer**.
- May increase the risk for **heterotopic bone formation, osteolysis, radiculitis and retrograde ejaculation**.

Effectiveness and harms of rhBMP-2 in spine fusion.

(Fu R et al. Ann Intern Med 2013: 158(12); 890-902.

- Systemic Review and Meta-analysis of 13 RCTs and 31 cohort studies.
- Lumbar spine fusion: rhBMP-2 and iliac crest bone graft were **similar** in overall success, fusion and other effectiveness measures.
- ALIF: rhBMP-2 was associated with significantly increased **risk for retrograde ejaculation and urogenital problems**.

Recombinant Human Bone Morphogenetic Protein (rhBMP)

Considerations about Fusion Rates in Spine.

- **Higher fusion** rates with improvement outcomes in prospective analysis of interbody fusion rates with no untoward effects attributable to rhBMP-2 (Slosar PJ et al, Spine j 2007;7(3):301-7).
- **Effective arthrodesis and significant clinical improvement in short and long fusions**, both primary and revision, in Lumbar TLIF with rhBMP-2 for spinal Deformity, Spondylolisthesis and degenerative disease at 5-year follow-up (Crandall et al, Spine 2013 38(13);1128-36).
- Use of rhBMP-2 **decreased the risk of fusion failure** at all time intervals and decreased the rate of reoperation compared to AICBG in lumbar fusion – Meta-analysis of 10 RCTs (Chen Z et al. Arch Orthop trauma Surg 2012; 132 (12): 1725-40)
- Use of rhBMMP-2 **reduced operative time**, additional surgical treatments and **non-union rate** compared to autograft in lumbar fusion. Meta-analysis of 8 RCTs (Noshchenko A et al. J Spinal Disord tech 2014: 27(3); 117-35.)

Recombinant Human Bone Morphogenetic Protein (rhBMP)

Considerations about Fusion Rates in Spine.

- BMP is superior to ICBG in achieving fusion in long constructs to the sacrum in adult spinal deformity and effect is dose/concentration dependent – 4 to 14 year Follow-up (Kim HJ et al Spine 2013;38(14), 1209-15)
- rhBMP significantly improves the chances of radiographical fusion compared to autografts in instrumented posterolateral lumbar fusion – multicentre prospective RCT (Hurlbert RJ et al. Spine 2013;38(25):2139-48).
- Use rhBMP-2 resulted in significantly improved fusion rate in ALIF and PLF but not PLIF/TLIF compared to without- Systematic review (Galimberti F et al Spine 2015;40(14):1132-9)
- Clinical efficiency of rhBMP-2 is equal or superior to that of allogenic or autologous bone graft in respect to fusion rate, low back pain disability, patient satisfaction and rate of reoperations. Systematic review of all published RCTs and controlled series (Faudez A et al. Int Orthop 2016; mar 10 epub).

Recombinant Human Bone Morphogenetic Protein (rhBMP)

Considerations about Complications.

A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned ([Carragee E et al Spine J 2011, 11\(6\); 471-91](#)).

- ALIF: increase rates of **implant displacement, subsidence, infection, urogenital events and retrograde ejaculation**.
- PLIF: associated with **radiculitis, ectopic bone formation, osteolysis and poorer global outcomes**.
- PLF: risk of adverse effects equivalent to or greater than of iliac crest bone graft harvesting.

Complications with the use of BMP-2 in spine surgery ([Tannoury et al Spine J 2014: 14:552-9](#))

- Lumbar spine
 - **Antibodies formation** (no pernicious effect with re-exposure).
 - Postoperative **radiculitis / ectopic** bone formation esp. in TLIF.
 - Postoperative **nerve injury** (seroma and haematoma in TLIF).
 - Vertebral **osteolysis and/or edema**.
 - **Retrograde ejaculation** with ALIF.
- Cervical spine.
 - **Dysphagia, neck swelling, haematoma**.
 - **Seroma** in posterior approach.

Recombinant Human Bone Morphogenetic Protein (rhBMP)

Considerations about Complications.

- BMP use with anterior cervical fusion was associated with an increased incidence of complications but **not in thoracolumbar and posterior cervical fusions**. Retrospective review of 55.862 cases in SRS M&M database (Williams BJ et al, Spine 2011; 36(20); 1685-91)
- **Very few complications directly related to rhBMP** (0.1 to 0.6% with its use in posterolateral Spine Fusion (Glassman SD et al Spine 2011; 36 (22); 1849-54).
- rhBMP use and location of use in adult deformity surgery, at reported doses, **do not increase acute major complications, neurological or wound complications**. Prospective multicenter study (Bess S et al. Spine 2014; 39(3); 233-42).
- Rate of acute complications **not different in paediatric patients** treated with versus those treated without rhBMP. Analysis of 4658 patients (Rocque BG et al J neurosurg Paediatr 2014;14(6):635-43).

Recombinant Human Bone Morphogenetic Protein (rhBMP)

Considerations about the Risk of Cancer.

- **Cancer risk increased** with rhBMP-2 but event rates were low and cancer was heterogeneous (Fu R et al. Ann Intern Med 2013 (12) 890-902)
- Use of rhBMP-2 in spinal fusion may **be associated with increased risk for cancer** (Simmonds MC et al Ann Intern med 2013: 158(12);877-89.
- BMP-2 **stimulates angiogenesis in developing tumours** in tumours formed from A549 cells injected S.C. into thymic node mice (Langenfeld EM et al Molecular Cancer Research 2004; 2(3): 141-9).
- **Slightly increased** risk of new onset of tumours without statistical significance- review of 26 studies (184,324 subjects) (Vavken J et al Eur Spine j 2015; mar 14 epub)
- **No association with cancer risk** or any individual cancer types following lumbar fusion surgery with rhBMP-2 A retrospective cohort study of 146,278 subjects (Cooper GS et al Spine 2013: 38(21); 1862-8).
- **No conclusive evidence** that application of the common formulations of BMP during spinal surgery results in the formation of cancer locally or at a distant site (Cahill KS et al J neurosurg Spine 2015;23 (1):86-93).
- Off-label use of rhBMP provided high fusion rates with **no evidence of significantly increased cancer risk** (malham GM et al Spine 2015;40(22)1737-42).
- There was **no increased in overall cancer** incidence among those receiving rhBMP. Study of 16,914 patients. (Dettori JR et al, Spine 2016 June 3(Epub ahead of print)

Future lines of research

BMP-2 Binding Peptide Amphiphile (PA) Nanofibers

(Lee SS et al. Adv Health mater. 2015;4; 131-41)

- Superior fusion rates while effectively reducing therapeutic dose of BMP-2 by fold in posterolateral fusion rate in rat model.

B2A Peptide Enhanced Ceramic Granules (Prefix)

(Sadar Z et al. J Neurosurg Spine 2015;22(4): 358-66)

- Signaling peptide that enhances BMP-2 function.
- Small RCT for TLIF followed to 12 months.
- Safe alternative to Iliac Crest Bone Graft.
- Prefix 750 possibly shows superior radiographic fusion compared to ICBG at 12 months.

Stem cells

- In recent years, stem cells have become a focus of regenerative medicine.
- Adult stem cells, harvested directly from bone marrow, adipose tissue or blood have the ability to undergo mitosis as well as multipotent differentiation into a variety of cell lineages.
- The goal of stem cell therapy is to replace or replenish diseased tissue through the localized differentiation of transplanted stem cells into cells which advance the healing process or directly restore the tissue physically.



Stem cells

Research in animals.

- Adult allogeneic MPCs delivered using an osteoconductive scaffold were both safe and efficacious in animals spine interbody and posterolateral fusion models.
- These results support the use of allogeneic MPCs can be an alternative to AG for lumbar interbody spinal fusion procedures.
- A comparison of commercially available demineralized bone matrices with and without human mesenchymal stem cells in a rodent spinal fusion model. Hayashi T et al J Neurosurg Spine. 2016 Mar 11;1-5.
- Bone marrow-derived mesenchymal stem cells assembled with low-dose BMP-2 in a three-dimensional hybrid construct enhances posterolateral spinal fusion in syngeneic rats. Hu T et al Spine J. 2015 Dec 1;15(12):2552-63
- Allogeneic mesenchymal precursor cells (MPCs) combined with an osteoconductive scaffold to promote lumbar interbody spine fusion in an ovine model. Wheeler DL et al Spine J. 2016 Mar;16(3):389-99.
- Allogeneic mesenchymal progenitor cells for posterolateral lumbar spine fusion in sheep. Wheeler DL et al Spine J. 2014 Mar 1;14(3):435-44.

Mesenchymal Stromal Cells for Spinal Fusion Data from ongoing clinical trial

(Code: XCEL-MT-10-01; EudraCT: 2010-023998-18)

Ruth Coll¹, Enric Cáceres^{2,6}, Ana García², María Teresa Ubierna³, Alex del Arco⁴, Guillem Saló⁵, Margarita Codinach¹, Margarita Blanco¹, Arnau Pla¹, Joan García¹ • ¹XCELIA-Advanced Therapies Division of the Blood and Tissue Bank of Catalonia (Banc de Sang i Teixits), Barcelona, Spain; ²Hospital Universitari Vall d'Hebron, Barcelona, Spain; ³Hospital Universitari Germans Trias i Pujol, Badalona, Spain; ⁴Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; ⁵Hospital del Mar, Barcelona, Spain; ⁶Hospital Universitari Quirón Dexeus, Barcelona, Spain.

- XCEL-MT-OSTEO-ALPHA is an advanced therapy medicinal product (ATMP) based on "ex-vivo" expanded autologous bone marrow mesenchymal stromal adult cells (MSC) fixed in allogeneic bone tissue (Patent P201030238).
- This is a multicenter (5 centers), prospective, randomized, two-arms, parallel-group, single-dose, open-label with centralized blinded assessor, phase I-IIa clinical trial.
- Patients are randomized (1:1) to the experimental treatment (spinal fusion + XCEL-MT-OSTEO-ALPHA) or the standard treatment with ICBG
- Patients randomized to the XCEL-MT-OSTEO-ALPHA are to be programmed for bone marrow extraction 3 weeks prior to surgery. Once released, XCEL-MT-OSTEO-ALPHA is directly applied to the concerned spine area.



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- Follow-up at month 12 reveals production of bone bridges at the posterolateral assessed area
- Present data suggest that the use of XCEL-MT-OSTEO-ALPHA for spinal fusion is feasible and safe.
- XCEL-MT-OSTEO-ALPHA possibly provides a new treatment option for this pathology .



Stem cells

- It is likely that stem cells and scaffolds will play a critical role in the future for replacing diseased tissue in disease processes and in enhancing host tissue to achieve more reliable spine fusion.
- MCSs look promising in lumbar spine surgery, both to block the aging of the disc both to accelerate the fusion processes in arthrodesis.
- The recent advancements in stem cell-based technologies for both spine fusion and the treatment of degenerative disc disease is promising and indicative that stem cells will undoubtedly play a major role clinically.
- Mesenchymal Stem cells (MSCs) in lumbar spine surgery: a single institution experience about red bone marrow and fat tissue derived MSCs. Clinico radiological remarks on a consecutive series of 22 patients. Piccirilli M et al J Neurosurg Sci. 2015 Jun 17.
- Mesenchymal stem cell allograft as a fusion adjunct in one- and two-level anterior cervical discectomy and fusion: a matched cohort analysis. McAnany SJ et al Spine J. 2016 Feb;16(2):163-7.
- Stem cells in preclinical spine studies. Werner BC et al Spine J. 2014 Mar 1;14(3):542-51.
- Mesenchymal stem cells derived from vertebrae (vMSCs) show best biological properties. Barbanti Brodano G et al Eur Spine J. 2013 Nov;22 Suppl 6:S979-84.
- Enhancement of posterolateral lumbar spine fusion using recombinant human bone morphogenetic protein-2 and mesenchymal stem cells delivered in fibrin glue. Liu Z et al J Biomater Appl. 2016 Apr 7.

Take at home message.

- Autologous bone graft is the gold standard in spine fusion.
- To avoid the disadvantages of ABG has been developed different graft substitutes.
- rhBMP is the graft substitute who achieve the highest rates of fusion in spine surgery, at least equal at autologous bone graft.
- Nevertheless, BMP has been associated with a high complications rate, specially when it's used in anterior surgery.
- The research with Stem cells is promising and indicative that stem cells will undoubtedly play a major role clinically in spine fusion.



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