# Orthobiologics In Orthopaedic Trauma

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Previous Versions J. Tracy Watson (2007, 2010)

# Orthobiologics

- Orthobiologics combines advances in biotechnology, materials sciences and tissue biology to promote and enhance the body's natural ability to regenerate and repair musculoskeletal tissue.
- Represents the fastest growing segment of the US$ 33 billion global orthopedics market
- Global orthobiologics market ~ US$3.1 billion

# Orthobiologics in Orthopaedic Trauma

- Nonunion rate for fracture has been estimated at 5-10%
- Recent literature suggests a 5% rate overall (14% in tibia, 13.9% in femur) *Zura et al, Epidemiology of Fracture Nonunion in 18 Human Bones, JAMA Surgery 2016*
- An estimated 1.5 million bone grafting procedures are performed annually in the US *(Einhorn T., JBJSAm, 2003)*

# Orthobiologics in Orthopaedic Trauma

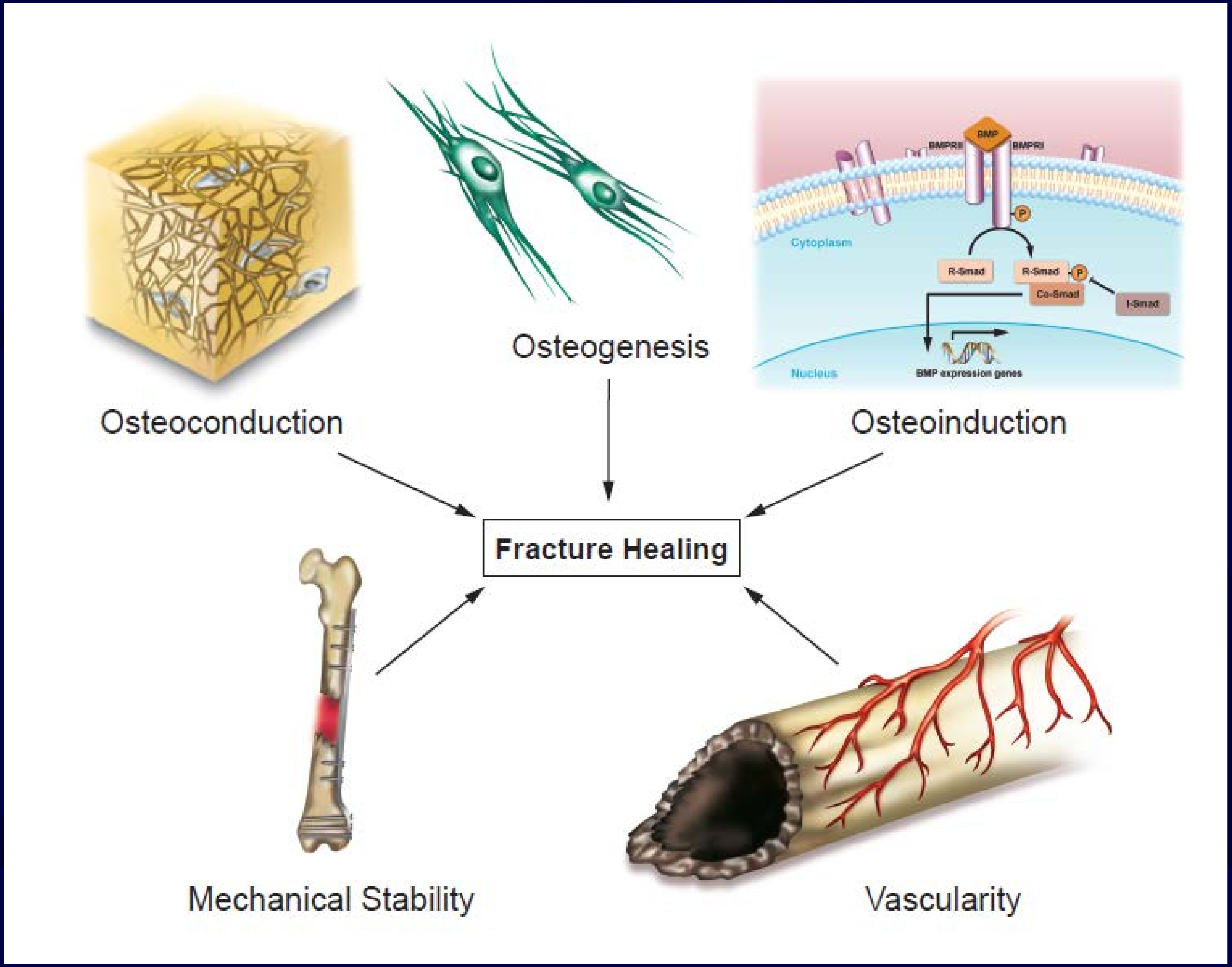
- Orthobiologics are typically used for the treatment of nonunions, delayed unions or bone defects in orthopaedic trauma
- Can be used in conjunction with autograft bone (‘bone graft extenders’) or instead of autograft (‘bone graft substitutes’)

# Orthobiologics in Orthopaedic Trauma

- Appropriate and effective clinical use of orthobiologics requires:
  1. understanding of the critical components of fracture healing
  2. Knowledge of which components the orthobiologic possesses
  3. Awareness of the evidence supporting its use and approved indications
  4. Recognition of the cost-effectiveness of the product

# Critical Components of Fracture Healing

*(Nauth et al., Advances in the Enhancement of Bone Healing and Bone Graft Substitutes, OKU Trauma 4, 2010)*




Reprinted with permission from Nauth A, Kuzyk PR, Einhorn TA, Schemitsch EH: Advances in the Enhancement of Bone Healing and Bone Graft Substitutes, in Schmidt AH, Teague DC (eds): *Orthopaedic Knowledge Update: Trauma 4.* Rosemont, IL: American Academy of Orthopaedic Surgeons, 2010, pp 133-143.

# Osteoconduction

- Provision of an appropriate scaffold to support the growth of bone and vasculature required for fracture healing
- Examples of osteoconductive grafts include: autograft, allograft, demineralized bone matrix, calcium phosphate
- A large portion of the orthobiologics market has focused on osteoconductive scaffolds

# Osteoconductive Agents

- Cancellous Allograft Bone
- Calcium Phosphate Cements/Putties
  - Hydroset *(Stryker)*
  - Norian SRS *(Synthes)*
  - Alpha-BSM *(Etex)*
  - Prodense *(Wright Medical)*
- Antibiotic Calcium Sulfate *(Osteoset T, Wright Medical)*
- Demineralized Bone Matrix (DBM) *(DBM-Stryker, DBX-Synthes, Puros-Zimmer, Tensix-Wright Medical)*

# Osteogenesis

- Presence of an appropriate population of cells capable of forming bone (osteoprogenitors)
- Examples of grafts possessing osteogenesis include: autograft and autogenous bone marrow aspirate

# Osteoinduction

- Appropriate signaling from growth factors or cytokines to initiate the fracture healing process
- Numerous growth factors have been identified as being osteoinductive or osteopromotive such as the bone morphogenetic proteins (BMPs), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF)
- Examples of available osteoinductive grafts include: autograft, autologous bone marrow, BMP *(Infuse, Medtronic)* and PDGF *(Augment Bone Graft, Wright Medical)*

# Osteinductive Agents

- Bone Morphogenetic Proteins (BMPs)
  - Rh BMP-2 *(Infuse, Medtronic)*
- Platelet Derived Growth Factor (PDGF)
  - PDGF/β-TCP *(Augment Bone Graft, Wright Medical)*

# Vascularity

- An adequate blood supply for the delivery of oxygen, nutrients, and progenitor cells is critical for fracture healing to occur
- Vascularity is critically dependent on viability of the vessels, soft tissues and muscles at the fracture site
- Examples of grafts that may enhance vascularity include: autograft (presence of vascular progenitors, angiogenic proteins), autologous bone marrow aspirate, BMP, PDGF

# Mechanical Stability

- Appropriate stability at the fracture site is necessary for healing to occur
- Stability is generally achieved by fracture immobilization (cast) or fracture fixation (plate, intramedullary nail etc…) but can be augmented by some grafts including : cortical autograft/allograft or calcium phosphate cements

# Mechanical Stability

- Tricortical Autograft *(Iliac Crest)*
- Cortical Allograft Struts
- Calcium Phosphate Cement *(compressive only)*

# The “Gold Standard”

- **Autogenous Iliac Crest Bone Graft (AICBG)**

- “Autograft bone is the only graft material with osteogenic, osteoinductive, and osteoconductive properties making it the ideal graft material and the gold standard to which all graft substitutes should be compared” *(Sen MK, Miclau T., Injury. Mar 2007)*

# The “Gold Standard”

- **Limitations:**
  - Morbidity/pain of graft harvest
  - Risks of NV injury, post-op pain, infection, fracture, hernia
  - Limited amount graft material (<5cm)
  - Up to 30% rate of unsatisfactory results in the treatment of traumatic segmental defects *(Suedkamp et al., JOT 1993)*

# Case 1: Atrophic Tibial Nonunion

- Young male patient previous tibia fracture secondary to motorcycle accident
- 1 year post tibial nailing
- No infection

# Case 1: Atrophic Tibial Nonunion


# Case 1: Atrophic Tibial Nonunion

# Case 1: Atrophic Tibial Nonunion

- Dx: Atrophic tibial nonunion
- Components Needed: osteoconduction, osteoinduction, osteogenesis, ?vascularity
- Selected Graft: *AICBG* combined with compression plating around the nail

# Case 1: Atrophic Tibial Nonunion

## Healed radiographs 9 mos post-op


# Case 2: Distal Humeral Bone Defect/Nonunion

- 52 year old male polytrauma patient secondary to significant fall from height at work
- Multiple fractures including open distal humerus fracture with substantial metaphyseal bone loss
- Persistent metaphyseal bone defect in distal humerus 9 months post plate fixation
- No Infection

# Case 2: Distal Humeral Bone Defect/Nonunion


## Case 2: Distal Humeral Bone Defect/Nonunion

- Dx: Nonunion/bone defect distal humerus
- Components Needed: osteoconduction, osteoinduction, osteogenesis, ?vascularity
- Selected Graft: *AICBG*

# Case 2: Distal Humeral Bone Defect/Nonunion
# Immediate Post-op

# Case 2: Distal Humeral Bone Defect/Nonunion Healed at 9 months


# Reamer-Irrigator-Aspirator (RIA) Bone Graft
## (? "The New Standard")

- Reamer-Irrigator-Aspirator (RIA) can be used to harvest intramedullary reamings from the canal of the femur or tibia
- Good success rates in several case series in the literature, including treatment of large bone defects *(McCall et al, Orthop Clinics of N Am. 2010, Stafford & Norris, Injury. 2010)*
- Higher volumes of graft than AICBG

# Reamer-Irrigator-Aspirator (RIA) Bone Graft
## (? "The New Standard")

- Prospective comparison (RCT) has shown less harvest site morbidity and higher graft volumes, with similar efficacy to AICBG *(Dawson et al, JOT. Oct 2014)*
- Potential for major complications (femur fracture, cortical perforation, excessive blood loss) *(Lowe et al, JOT. Jan 2010)*

# RIA Bone Graft

*Synthes (Paoli, PA) product brochure*

# Case 3: Atrophic Tibial Nonunion (non-operative)

- 63 year old male heavy smoker with comorbidities
- Atrophic nonunion of distal tibia 9 months after conservative treatment with cast immobilization

# Case 3: Atrophic Tibial Nonunion (non-operative)


## Case 3: Atrophic Tibial Nonunion (non-operative)

- Dx: Atrophic nonunion distal tibia with risk factors for ongoing nonunion (smoking, comorbidities)
- Components Needed: osteoconduction, osteoinduction, osteogenesis, ?vascularity
- Selected Graft: *RIA bone graft* combined with tibial nailing

# Case 3: Atrophic Tibial Nonunion (non-operative)
Immediate Post-op


# Case 3: Atrophic Tibial Nonunion (non-operative) Healed 4 months postop


# Calcium Phosphate Cements

- “Ceramics”
- Biodegradable, highly porous, injectable cement that acts as an osteoconductive scaffold
- Provides osteoconduction and compressive strength
- Primarily indicated for subarticular, contained metaphyseal defects
- Good level I evidence to support its use in this setting, particularly in tibial plateau fractures *(Russell & Leighton, JBJS 2008, Bajammal et al, JBJS 2008)*
- Prolonged time to resorb has been a concern, hybrid calcium phosphate/sulfate products *(Prodense, Wright Medical)* may address this

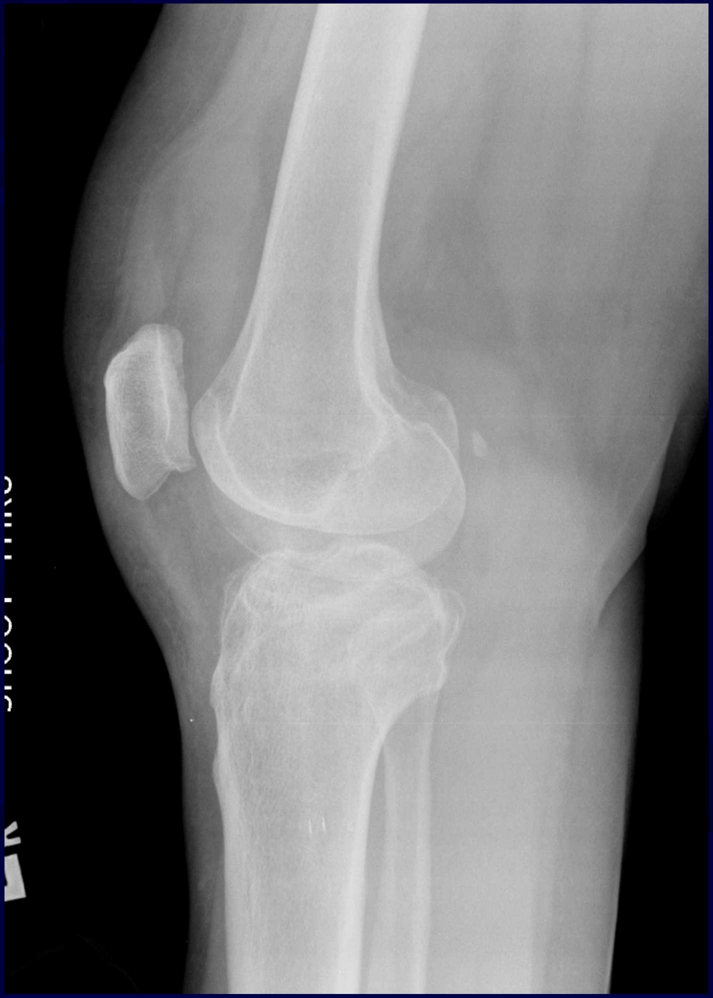
# Calcium Phosphate Cements

- Available Products:
  - Hydroset *(Stryker)*
  - Norian SRS *(Synthes)*
  - Alpha-BSM *(Etex)*
  - Prodense *(Wright Medical)*
- Antibiotic Calcium Sulfate *(Osteoset T, Wright Medical)*

# Case 4: Split-Depression Tibial Plateau Fracture

- 61 year old female low energy tibial plateau fracture

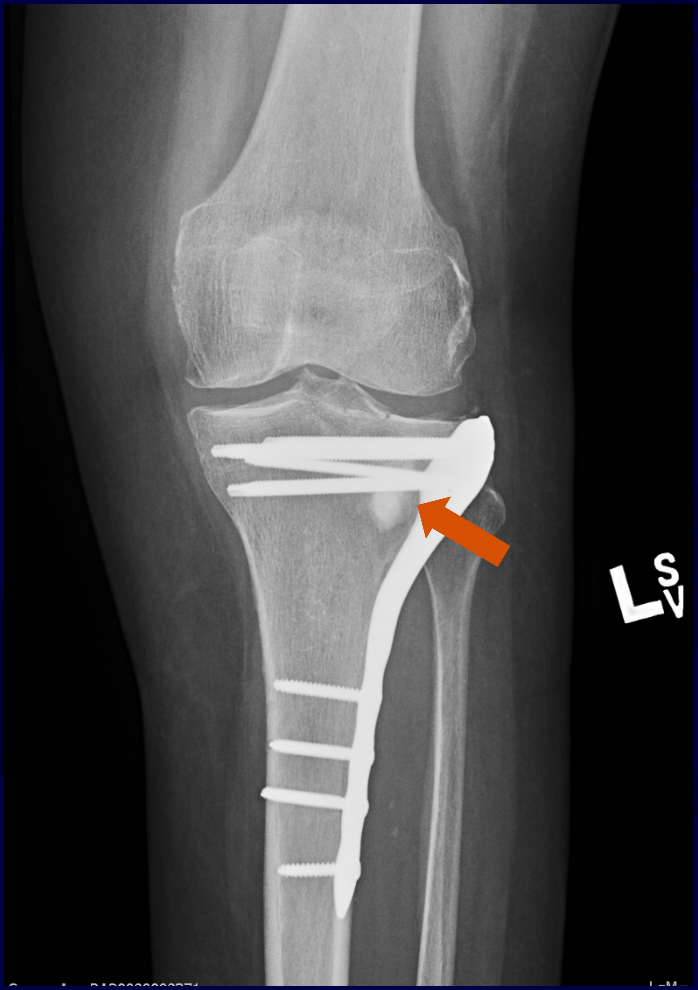
# Case 4: Split-Depression Tibial Plateau Fracture



## Case 4: Split-Depression Tibial Plateau Fracture

- Dx: After elevation of the articular surface a contained metaphyseal defect will be present
- Components Needed: osteoconduction and mechanical stability *(compressive strength to prevent articular subsidence)*
- Selected Graft: *Calcium Phosphate Cement*

# Case 4: Split-Depression Tibial Plateau Fracture 6 Months Post-Op (orange arrow indicates Calcium Phosphate cement)



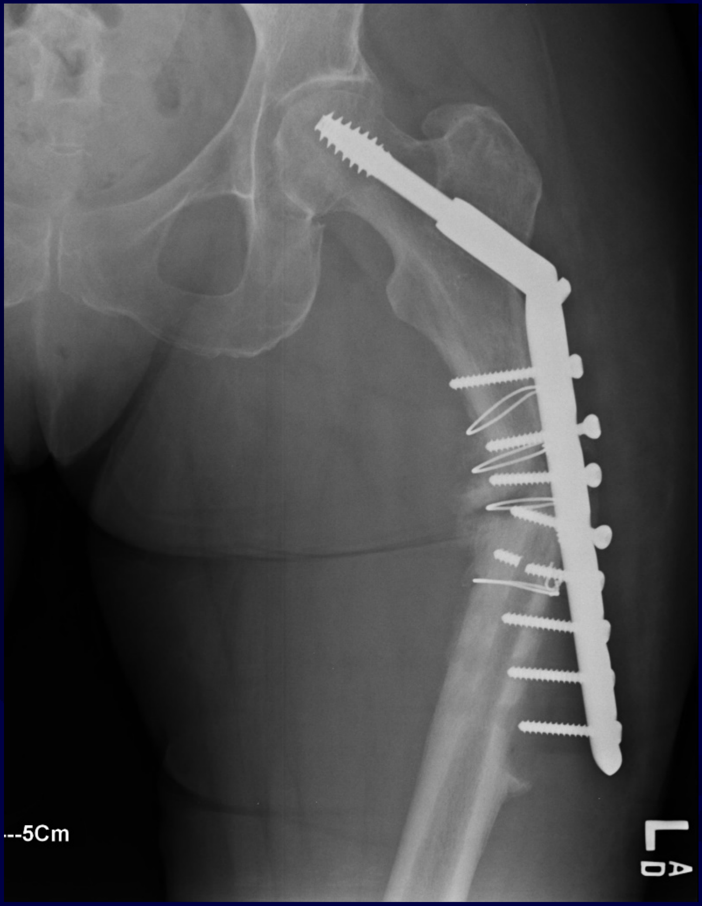

# Antibiotic Calcium Sulfate

- Osteoset T *(Wright Medical)*
- Rapidly resorbed osteoconductive material impregnated with antibiotics (Tobramycin)
- Primary indication is infected bone defects or nonunion
- There is level I evidence to support its use in this setting *(Mckee et al, JOT Aug 2010)*

# Case 5: Infected Subtrochanteric Femur Nonunion

- 58 year old female 9 months post ORIF of subtrochanteric Femur fracture
- Draining sinus and elevated ESR & CRP

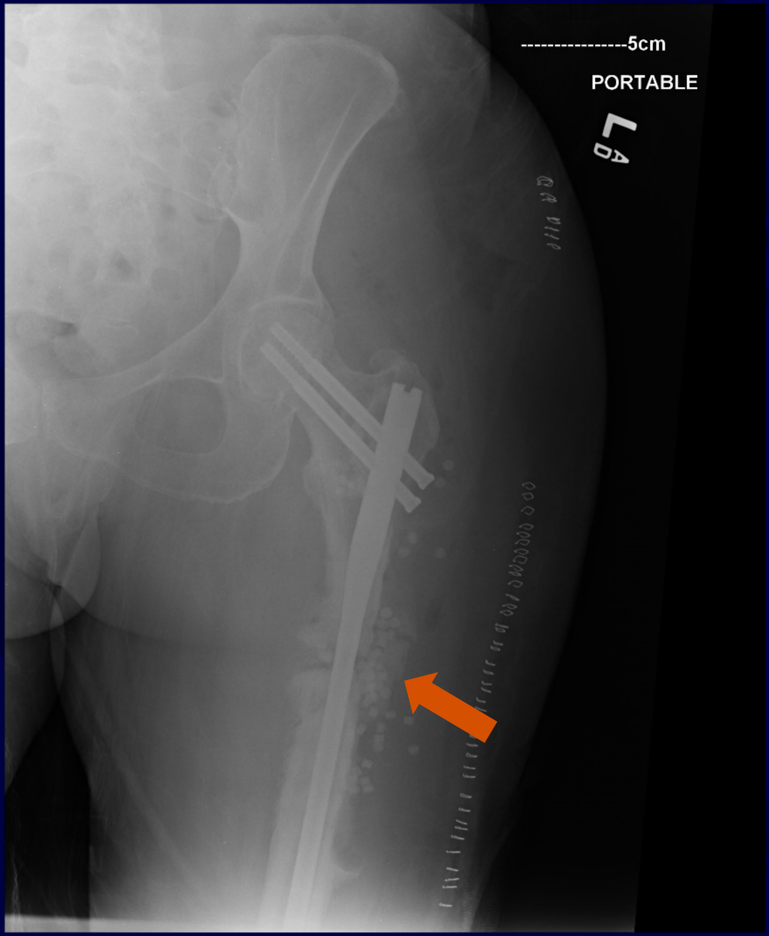
# Case 5: Infected Subtrochanteric Femur Nonunion




## Case 5: Infected Subtrochanteric Femur Nonunion

- Dx: Infected nonunion of subtrochanteric femur
- Components Needed: osteoconduction, local antibiotic delivery
- Selected Graft: *Osteoset T* and revision to IM nail (combined with culture-specific systemic antibiotic therapy)

# Case 5: Infected Subtrochanteric Femur Nonunion
## Immediate Post-op (orange arrow indicates Osteoset T pellets)




# Case 5: Infected Subtrochanteric Femur Nonunion
# 1 year f/u radiographs


# Demineralized Bone Matrix (DBM)

- DBM is demineralized allograft bone that functions as an osteoconductive scaffold and possesses some degree of osteoinductive proteins
- Investigation has demonstrated a high degree of variability in the amount of osteoinductive proteins between products and between lots of the same product
- From a practical point of view the amount of osteoinductive protein is likely insufficient to effectively impact bone healing
- DBM is most commonly used as a ‘bone graft extender’ with autograft bone or combined with autogenous bone marrow aspirate

# Bone Morphogenetic Protein (BMP)

- BMPs are commercially available osteoinductive proteins that are available off-the-shelf and can be used on their own, in combination with an osteoconductive scaffold (eg cancellous allograft), or in combination with autograft bone
  - rhBMP-7 *(OP-1, Olympus Biotech) - NO LONGER AVAILABLE*
  - rhBMP-2 *(Infuse, Medtronic)*
- There is level I evidence to support the use of BMP as an alternative to autograft for nonunion or bone defect management *(Jones et al, JBJS 2006 & Friedlaender et al, JBJS 2001)*

# Bone Morphogenetic Protein (BMP)

- The use of BMPs in nonunion or bone defect surgery is currently an off-label indication
- BMP-2 (Infuse, Medtronic) is currently indicated for the treatment of acute, open tibia fractures treated with an intramedullary (IM) nail within 14 days of injury

# Case 6: Subtrochanteric Femur Nonunion (multiple previous failed surgeries)

- Young male trauma patient with ongoing nonunion of the proximal femur
- Original injury was caused by a high velocity gunshot wound (assault rifle)
- He has undergone multiple previous surgeries for nonunion and infection
- Currently his femur is not infected, but he has a persistent nonunion, a bone defect and a bent IM nail

# Case 6: Subtrochanteric Femur Nonunion (multiple previous failed surgeries)

# Case 6: Subtrochanteric Femur Nonunion (multiple previous failed surgeries)

- Dx: Atrophic subtrochanteric femoral nonunion with bone defect
- Components Needed: osteoconduction, osteoinduction, osteogenesis, ?vascularity
- Selected Graft: *AICBG + BMP* combined with revision IM nailing (the use of BMP in this setting is an off-label indication)

# Case 6: Subtrochanteric Femur Nonunion Immediate Post-op

# Case 6: Subtrochanteric Femur Nonunion
# Healed 1 year post-operatively

# Case 7: Periprosthetic Femur Nonunion

- 38 year old female with a history of JRA and previous bilateral THAs and TKAs
- Presents with an atrophic nonunion of her femur below a well-fixed THA 9 months following fixation

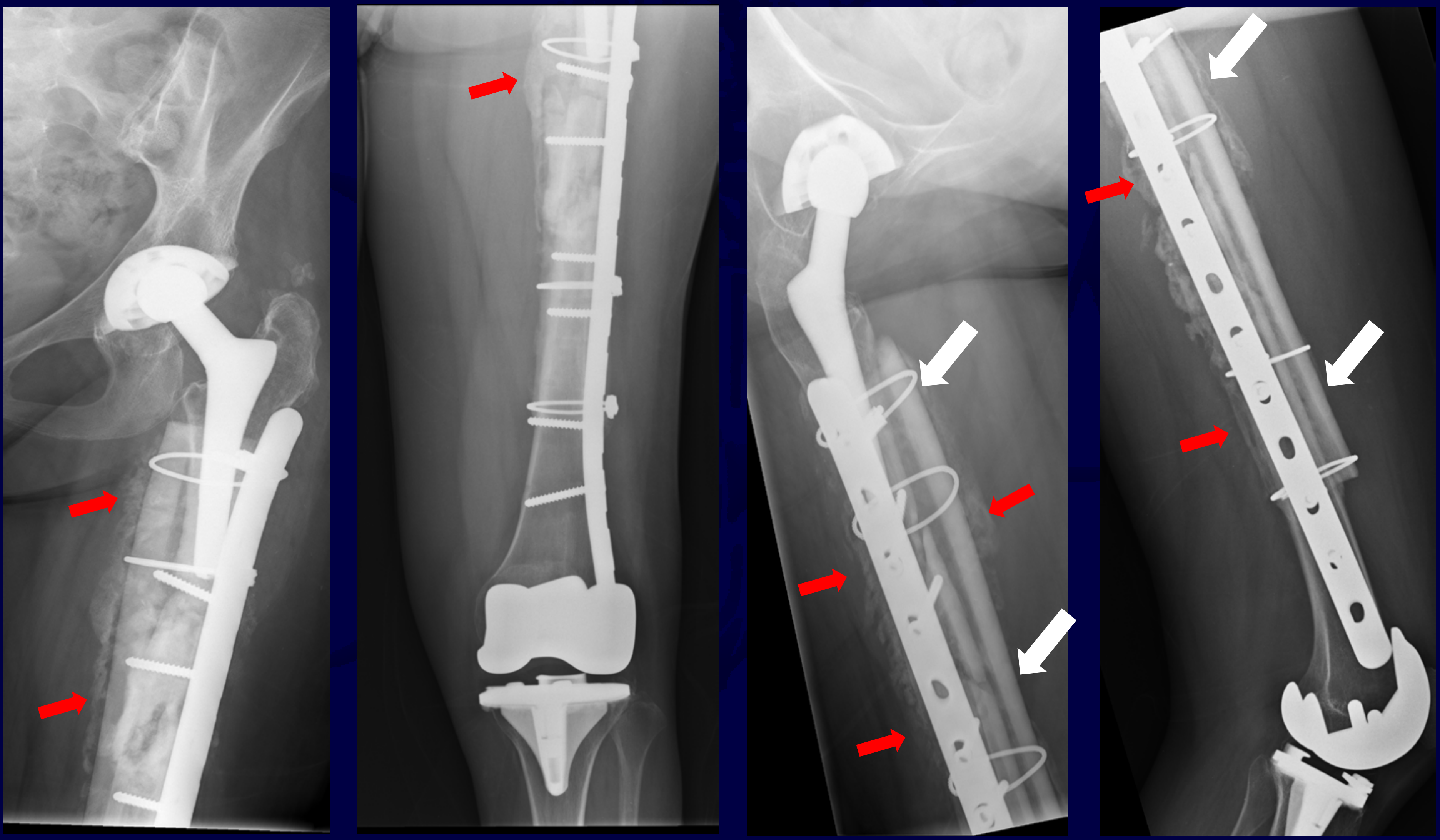
# Case 7: Periprosthetic Femur Nonunion


# Case 7: Periprosthetic Femur Nonunion

- Dx: Atrophic nonunion of the proximal femur (presence of the THA presents challenges for fixation/stability, in addition a significant portion of the femur appears sclerotic and may have impaired vascularity/healing potential)
- Components Needed: osteoconduction, osteoinduction, osteogenesis, vascularity, mechanical stability
- Selected Graft: *BMP, cancellous allograft and anterior cortical strut allograft* combined with revision plate fixation (the use of BMP in this setting is an off-label indication)

# Case 7: Periprosthetic Femur Nonunion
# Healed at 9 months

(white arrows indicate anterior strut graft, red arrows indicate healing where cancellous allograft and BMP was placed)



# Platelet Derived Growth Factor (PDGF)

- PDGF is an osteopromotive and pro-angiogenic protein that is available in the recombinant form as an off-the-shelf product combined with beta-tricalcium phosphate (β-TCP) as Augment Bone Graft *(Wright Medical)*
- This product has osteoinductive, osteoconductive and pro-angiogenic capacities
- There is level I evidence to support the use of PDGF as an alternative to autograft for foot & ankle fusion surgery *(DiGiovanni et al, JBJS 2013)*
- The use of PDGF for nonunions or bone defects currently represents an off-label indication

# Case 8: Proximal Humerus Pseudarthrosis

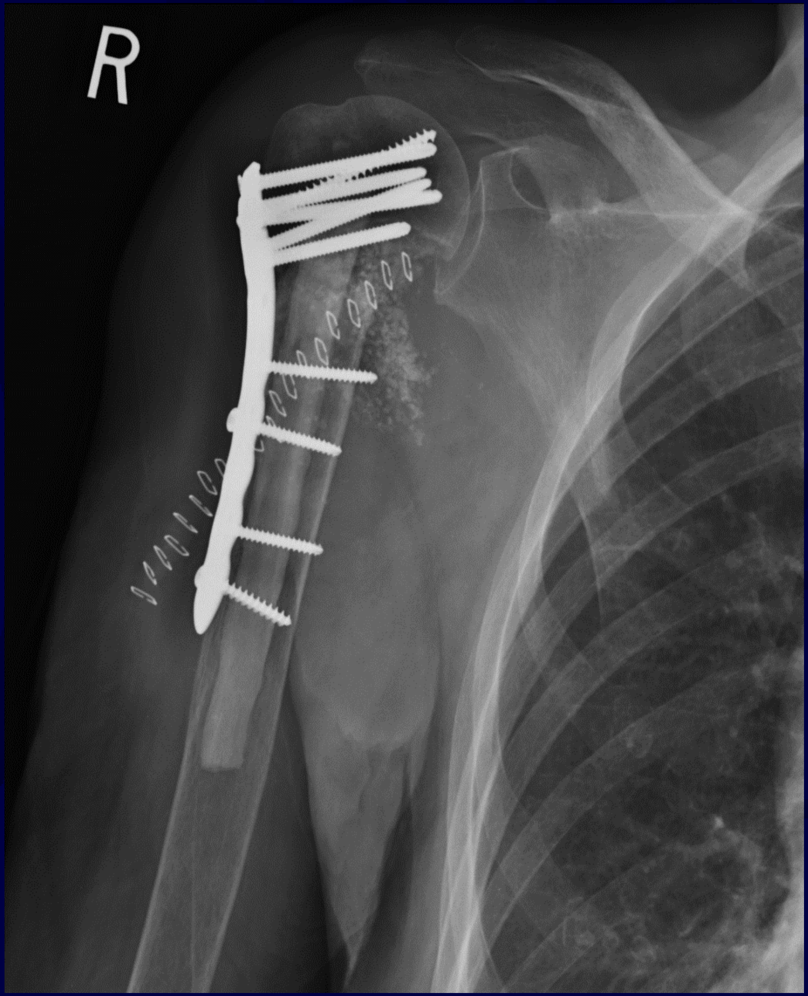
- Elderly female patient with a pseudarthrosis of the proximal humerus 9 months following non-operative treatment

# Case 8: Proximal Humerus Pseudarthrosis

# Case 8: Proximal Humerus Pseudarthrosis

- Dx: Pseudarthrosis of the Proximal Humerus (the limited bone and osteopenia of the humeral head presents a challenge for fixation/stability)
- Components Needed: osteoconduction, osteoinduction, osteogenesis, ?vascularity, mechanical stability
- Selected Graft: *PDGF/β-TCP+ IM Fibular strut allograft* combined with locking plate fixation (the use of *PDGF/β-TCP* in this setting is an off-label indication)

# Case 8: Proximal Humerus Pseudarthrosis
Immediate Post-op



# Case 8: Proximal Humerus Pseudarthrosis
# Healed radiographs 1 year post-op

# Case 9: Radial Shaft Bone Defect

- Young male trauma patient with a low velocity gunshot wound to his forearm resulting in a radial shaft fracture with substantial (3.5 cm) bone defect

# Case 9: Radial Shaft Bone Defect

## Pre-op and Intra-op radiographs demonstrating bone defect


## Case 9: Radial Shaft Bone Defect

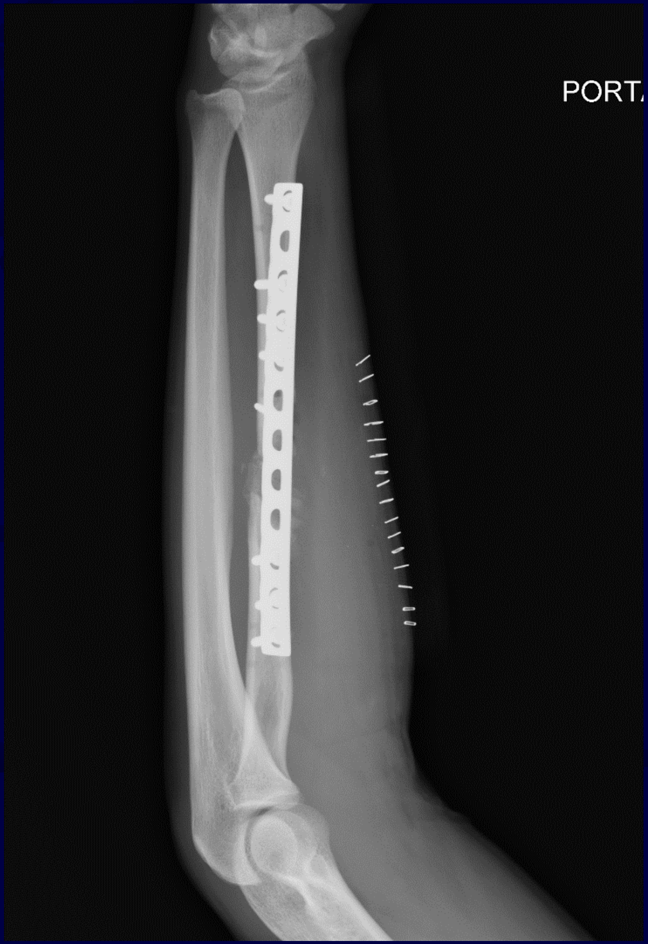
- Dx: 3.5 cm bone defect in radial shaft
- Components Needed: osteoconduction, osteoinduction, osteogenesis, vascularity
- Selected Graft: *Induced Membrane (Masquelet) technique* followed by grafting at 6 weeks with *AICBG & PDGF/β-TCP* (the use of *PDGF/β-TCP* in this setting is an off-label indication)

# Case 9: Radial Shaft Bone Defect

Post-op radiograph following fixation and insertion of antibiotic cement spacer into defect (red arrows)

# Case 9: Radial Shaft Bone Defect

Immediate post-op radiographs following removal of cement spacer and insertion of autograft/PDGF into the bone defect 6 weeks following index surgery

# Case 9: Radial Shaft Bone Defect

Healed radiographs at 4 months post grafting

# Conclusions

- An understanding of the ‘Critical Components’ of Fracture Healing is important
- Allows the surgeon to assess the need for, and the proper selection of the vast Orthobiologic products and strategies available in orthopaedic trauma

# Recommended Reading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# Recommended Reading


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# Recommended Reading


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11. DiGiovanni CW, Lin SS, Baumhauer JF, et al. Recombinant human platelet-derived growth factor-BB and beta-tricalcium phosphate (rhPDGF-BB/beta-TCP): an alternative to autogenous bone graft. *J Bone Joint Surg Am.* 2013;95(13):1184-1192.

# Thank You