Regulatory considerations/FDA approval process/Use considerations

A. Devices
B. Biologic agents
C. Autologous tissues (i.e. Platelet rich plasma)
D. Cost
E. Side effects

A Traumatologist’s Perspective:
Fractures – Any Stage from Acute Fractures to Non-Unions
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There are clearly no well defined indications for use of a specific type of bone graft substitute or use of inductive factor when dealing with complex fractures or nonunions. This is especially true when treating acute bone loss in the setting of associated severe soft tissue damage or infected nonunions. The use of all of these new resources should be based on contemporary fracture or nonunion management principles and guided by current levels of evidence for use of these materials.

1) Common biological requirements for bone regeneration
   a) Cells: Adult progenitor cells from the marrow, periosteum, and other sources
   b) Blood supply: For the delivery of nutrients, oxygen, and systemic factors required for cell survival
   c) Molecules and their receptors: Provides for the induction of cells to proliferate and differentiate into osseous tissue (osteoinduction)
   d) Extracellular matrix: To provide a scaffold for cells (osteoconduction), and storage site for growth factors

2) Extracellular matrix:
   a) Properties for function
      i) Space filler (biocompatibility)
      ii) Structural properties (mechanical)
      iii) Microstructural (biological for cell surface adhesion/healing)
   b) ECM scaffolding characteristics
      i) Substrates for bone replacement
      ii) Resorption over time
      iii) Requires cells for cytokines or potency
      iv) Dependent upon defect types or loads
      v) Clinical studies frequently compare efficacy of osteobiologics to cancellous autograft as gold standard

3) Consideration for specific anatomic locations: Metaphyseal defects
   a) For most metaphyseal defects, it has been shown experimentally that a simple cancellous void will reconstitute on its own and heal completely given a sound biologic environment without the addition of any further grafting material. The danger here is that the subchondral surface will
collapse if this defect does not reconstitute fast enough to provide subchondral support with the initiation of weight bearing.

i) Conductive substrates: Issues

(1) Ca ceramics. CaSO₄ / CaPO₄
   (a) Incorporation characteristics, specifically rates of osteointegration
   (b) Ultimate compressive strength (mPa)
   (c) Delivery mechanism. Particulate vs. self-setting “cements”
   (d) Incorporation time vs. bone regenerated into defect
      (i) Cellular mediated vs. chemical degradation of materials
      (ii) Use of marrow concentrates to accelerate incorporation characteristics. “seeding the graft”
   (e) Multiple studies with good Level I and II evidence support use of both sulfate and phosphate materials for contained metaphyseal defects.
      (i) Demonstrated superiority over autogeous graft materials.

(2) Mechanical Factors
Use of conductive substrate materials in metaphyseal defects augmented with use of locking plates for plateau, distal femoral, and pilon fractures. One should be aware of the relative compressive strengths of these materials. The strength should match that of native cancellous bone. Also, one should be aware of the rate of degradation. This is important when considering timing of weight bearing. When the material begins to osteointegrate, the compressive strength will also begin to decrease. Thus weight bearing at this time can result in late articular collapse.
   (a) Minimal evidence currently available for use of locking plates in these locations.
   (b) No evidence currently available for use of these Ca ceramics for the solitary treatment of diaphyseal defects, either for acute bone loss or in nonunion situations.

4) Consideration for specific anatomic locations: Diaphyseal fractures and nonunions
   a) Use of adjuvant materials in this location depends on numerous factors
      i) Evaluation: Fracture site (the mid-shaft tibia fracture is usually a biologically “challenged” region)
         (1) The appropriate migration of cellular components to the site of bone graft or fracture is crucial in continuing the progression of the fracture healing cascade. Possible delivery of these cells to the region in question may be necessary.
         (2) Acute bone loss vs. non-union defect
         (3) Condition of soft tissues and “zone of injury” local environment
            (a) May require angiography / MRI to determine vascularity/viability of host defect.
               Most graft failures are as a result of inadequate or poor host nutrition to the local graft region as most fracture sites and nonunions are often at the site of thick scar and/or relative avascularity. There is no substitute for preparing the host recipient bed appropriately by resecting the avascular tissue and providing healthy tissue for revascularization phenomenon and thus success of the graft.
            (b) Flap/soft tissue coverage, including timing (i.e. reconstitution of inflammatory phase of fracture healing-neovascularization)
      (4) Size of defect
         (a) Minor defect (.< 1 cm bone loss/nonunion gap)
         (b) Critical size defects (circumferential bone loss / nonunion gap >1cm to 4 cm)
         (c) Massive defects (> 6 cm).
      (5) Infection status
      (6) Mechanical stability
   ii) Treatment: Acute defect/delayed union/subcritical defect (without total segmental loss) with internal fixation (i.e. plate/IM nail)
      (1) Graft options
         (a) Composite grafts
            (i) DBM + Autogenous cellular concentrates, +, - platelet gels (as carrier)
               1. Limited success with centrifuged aspirate alone (Connelly, Watson)
2. Concentration of CFU's in conjunction with carrier materials (Hernigou) (Jimenez, concentration expansion technique)

iii) Treatment: Acute critical sized defect/nonunion (segmental loss <4cm)

(1) Graft options
(a) BMP-2 implantation at time of wound closure (open tibia fracture) (BESTT study results)(Level I)
(b) Segmental defects up to 4 cm (Bucholz, Jones et.al)(Level I)
(c) BMP-7 (McKee et al., Canadian open tibial shaft study)
(d) BMP-7 for nonunions (equivalent efficacy between autograft and BMP-7)(Level I)
(e) Providing scaffolding for mesenchymal cell infiltration. Depending on the temporal relationship of the delivery of the inductive factor to the cell population in question, will determine the specific effect that each protein has on the fracture healing cascade. It is important that these stem cells have the appropriate available conductive surface to allow them to migrate to the surface and function as specifically induced.
(f) Providing colony forming units (CFU's) (Hernigou) (Level II and III)

iv) Treatment: Large segmental defects

(1) Staged reconstruction
(a) Antibiotic spacer / beads / rods
   (i) Carrier for inductive materials
   (ii) Carrier for antibiotics
      1. PMA
      2. CaSO₄
(b) Development of vascularized pseudo-membranes (Masquelet technique)( Level III and IV)
   (i) Grafting directly into vascularized pseudo-membrane
   (ii) Membrane directed bone regeneration

(2) Bone transport
(a) Segmental bone loss remains problematic and usually requires massive quantities of graft material to bridge large structural defects. These options include composite graft utilizing transplant of autogenous cellular material in combination with a competent osteoconductive substrate as well as inductive proteins. Problems here include the lack of rapid remodeling, and as such, these defects are prone to fatigue failure and stress fracture. Large segmental defects often require bone transport versus free tissue transfer such as vascularized iliac crest or free fibula transfer, or combinations of both. (Level II, III , IV)
(b) Ultrasound directed rapid transport of over nail with autodistractors
(c) Augmentation of rapid regenerate with BMP's

(3) Free tissue transfer
(a) Combination methodologies with bone transport and inductive factor augmentation
   (i) Free fibula transfer in combination with distraction Osteogenesis as well as augmentation of distraction and docking sites with inductive proteins.

(4) Titanium cage/graft /IM nail for defect replacement (Lindsey) (Level III, IV)
(5) Intramedullary grafting, including Reamer, Irrigator, Aspirator (RIA) techniques for graft harvest in combination with other techniques (i.e induced membrane via cement spacers) (Level VI)
(a) RIA grafts placed into induced membrane from a cement spacer (avg of 60cc graft harvested from RIA, McCall et..al, OTA 2007)
   (i) Avg. defect of 6.6 cm
   (ii) 58% healed 1st graft, 85% healed after 2nd grafting
References


42. Hernigou P et al; Percutaneous Autologous Bone-Marrow Grafting for Nonunions. *J. Bone and Joint Surg.,* 87-A No. 7 July 2005


7:54 – 7:59 am

**Orthobiologics: The Sports Medicine Perspective in 2010**
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I will address three major areas:
1. Tendonopathy
2. Tendon healing
3. Articular cartilage healing/regeneration

I will emphasize 2 major pathophysiologic principles related to tendonopathy and tendon healing:

1. Emerging data suggests that there is fundamental and important interaction between:
   i. mechanical load
   ii. inflammatory mediators
   iii. matrix metalloproteinases (MMP’s)

2. Fetal wounds heal by tissue regeneration in contrast to reactive scar formation in post-natal human. We can use lessons from embryologic development and studies of fetal wound healing (“scarless healing”) to discover novel methods for connective tissue healing.

Consideration of these mechanisms suggests novel treatments....

**Role of Mechanical Load:**
Stress deprivation leads to up-regulation of inflammatory mediators (IL-1) and MMP's (collagenase). These MMP’s affect matrix remodeling, usually leading to detrimental changes in material properties.

**Mechanism of Tendonopathy (Steve Arnoczky):**
Microscopic collagen fiber failure → cells in injured area are exposed to less load → resulting stress deprivation leads to upregulation of interleukin-1 and MMP-13 → decreased structural and mechanical properties

**Clinical implications:** We need to consider how modulation of mechanical load (magnitude, frequency, onset of loading, etc.) affects tendon healing.

**Inflammation in Healing:**
- Fetal wounds heal by tissue regeneration in contrast to reactive scar formation in post-natal human “Scarless healing” in fetal wounds
- Absence of inflammatory response in fetal tissue appears to be a primary mechanism for this phenomena
- Cell signals expressed during inflammation lead to healing by fibrosis
- Inflammation is very complex  
  Inflammatory cells have both catabolic and anabolic actions