# General Principles in the Assessment and Treatment of Nonunions

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Previous Authors:

Peter Cole, MD; March 2004

Matthew J. Weresh, MD; Revised August 2006

Hobie Summers, MD & Daniel S. Chan MD; Revised April 2011

# Definitions

- Nonunion:  (reasonably arbitrary)
  - A fracture that is not currently healed and is not going to
- Delayed union:
  - A fracture that requires more time than usual to heal
  - Shows healing progress over time

# Definitions

- Nonunion: A fracture that is a minimum of 9 months post occurrence and is not healed and has not shown radiographic progression for 3 months (FDA 1986)

- Not pragmatic
  - Prolonged morbidity
  - Narcotic abuse
  - Professional and/or emotional impairment

# Definitions (pragmatic)

- Nonunion: A fracture that has no potential to heal without further intervention

All images unless indicated: Rockwood and Green's Fractures in Adults, 8th Edition 2015

# Classification

1. Hypertrophic
2. Oligotrophic
3. Atrophic = Avascular
4. Pseudarthrosis

Weber and Cech, 1976

# Hypertrophic

- Vascularized
- Callus formation present on x-ray
- “Elephant’s foot” - abundant callus
- “Horse’s hoof” - less abundant callus

Biology is more than sufficient but can’t consolidate
→ likely need mechanically favorable solution

# Oligotrophic

- Some/minimal callus on x-ray
  - Not an aggressive healing response, but not completely void of biologic activity
- Vascularity is present on bone scan

Is there sufficient biology / mechanics for healing?

# Atrophic

- No evidence of callous formation on x-ray
- Ischemic or cold on bone scan

Not enough biology → likely need biologically favorable solution

# Pseudarthrosis

- Typically has adequate vascularity
- Excessive motion/instability
- False joint forms over significant time

Sufficient biology but so much mechanical instability that the body is “tricked” into thinking there should be a joint there → likely need to reset the whole system

Hypertrophic

Oligotrophic

Atrophic

# Biomechanics of Nonunions

- Important factors for consideration
- Biologic and Mechanical environment
  - Presence or absence of infection
    - Septic vs Aseptic
  - Vascularity of fracture site
  - Stability – mechanical environment
  - Deformity
  - Bone involved and surrounding soft tissues

# Etiology of Nonunion

- Host factors
- Fracture/Injury factors
- Initial treatment of injury factors

- Complicating factor = Infection

# Etiology of Nonunion – Host

- Smoking
- Hormones and related
  - Diabetes melitus, Thyroid/ parathyroid disorders, testosterone/estrogen deficiency, Vit D deficiency, Ca and/or Phos abnormality
- Malnutrition
- Medications
  - Steroids, Chemotherapy (& XRT), Antivirals, Anticonvulsants, Immunosuppressives
- Bone quality, vascular status
- Balance, compliance with weight bearing restrictions
  - Psychiatric conditions, dementia

# Smoking

- Decreases peripheral oxygen tension
- Dampens peripheral blood flow
- Well documented difficulties in wound healing in patients who smoke

Schmitz, M.A. e.t. al. Corr 1999

Jensen J.A. e.t. al. Arch Surg 1991

# Systematic Literature Review

- Medline, Pubmed, Cochrane databases for Level I-III studies

- Search headings:
  - smoking, tobacco, nicotine WITH fracture, nonunion, delayed union, and healing

**J Bone Joint Surg Am. 2014 Apr 16;96(8):674-81. doi: 10.2106/JBJS.M.00081.**
**Cigarette smoking increases complications following fracture: a systematic review.**
Scolaro JA, Schenker ML, Yannascoli S, Baldwin K, Mehta S, Ahn J.

# Summary

- Increased risk of NONUNION
  - Overall — *15% higher, OR 2.31*
  - Tibia fractures ONLY — *15% higher, OR 2.42*
  - Open fractures ONLY — *12% higher, OR 2.06*
- Prolonged fracture healing times?
  - Overall — *24wks vs. 30wks*
  - Tibia fractures ONLY — *25wks vs. 32wks*
- Increased wound healing complications?
  - Deep — *OR 1.42*
  - Superficial — *OR 1.38*

# Diabetes (Neuropathic Fractures)

- Best studied in ankle and pilon fractures:
- Complicated diabetics – those with end organ disease – neuropathy, PVD, renal dysfunction
  - Increased rates of infection and soft tissue complications
  - Increased rates of nonunion, time to union significantly longer
  - Prolonged NWB required
- Inability to control response to trauma can result in hyperemia, osteopenia, and osteoclastic bone resorption
  - Charcot arthropathy

Kline et al, *Foot Ankle Int. 2009*
Wukick et al, *JBJS, 2008*

# Malnutrition

- Adequate protein and energy is required for wound healing
- Majority of organic phase of bone is protein
- Screening test:
  - serum albumin
  - total lymphocyte count
- Albumin less than 3.5 and lymphocytes less than 1,500 cells/ml is significant

Seltzer et.al. JPEN 1981

# Etiology of Nonunion – Fracture/Injury Factors

- High energy injury
  - Fracture mechanism
  - – MVC vs fall from standing
- Open or closed fracture
- Bone loss
- Soft tissue injury
- Bone involved and anatomic location

Sullivan M, unpublished

Think about the personality of the fracture!!

Open tibial shaft fx with bone loss vs closed nondisplaced proximal humerus fx

# Fracture Pattern

- Fracture patterns in higher energy injuries (i.e.: comminution, bone loss, or segmental patterns) have a higher degree of soft tissue and bone ischemia
- Acute compartment syndrome associated with tibial plateau and tibial shaft nonunion – surrogate for soft tissue injury

Blair, et al. JOT 2016

# Traumatic Soft Tissue Disruption

- Risk of nonunion is increased with open fractures
- More severe open fracture (e.g. Gustilo III B vs Type I) have higher risk

Gustilo et al. JOT 1984
Widenfalk et al. Injury 1979
Edwards et al. Ortho Trans 1979
Velazco et al. JBJS 1983
Westgeest et al. JOT 2016

# Tscherne Soft Tissue Classification

- Not all high energy fractures are open fractures. This classification emphasizes the importance of viability of the soft tissue envelope at the zone of injury.

Tscherne & Oestern, Unfallheilkunde 1982

# Tscherne Classification: closed fractures

Grade 0: Soft tissue damage is absent or negligible

Grade I: Superficial abrasion or contusion caused by fragment pressure from within

Grade II: Deep, contaminated abrasion associated with localized skin or muscle contusion from direct trauma

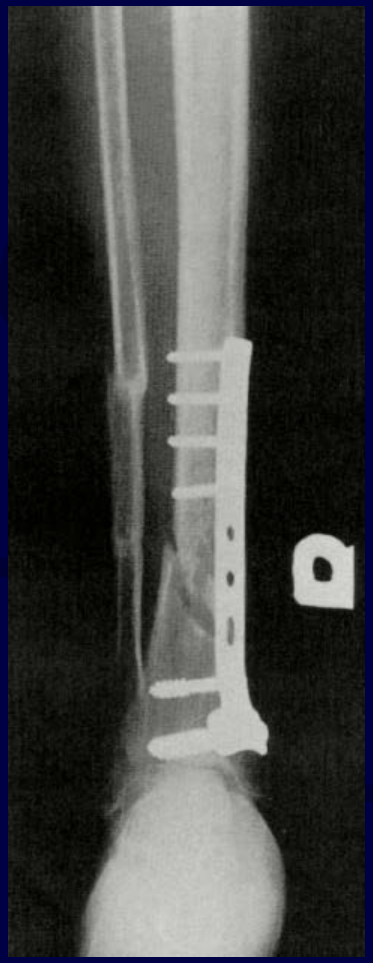
Grade III: Skin extensively contused or crushed, muscle damage may be severe. Subcutaneous avulsion, possible artery injury, compartment syndrome

Revascularization of ischemic bone fragments in fractures is derived from the soft tissue. If the soft tissue (skin, muscle, adipose) is ischemic, it must first recover prior to revascularizing the bone.

Holden CE, JBJS 1972

# Etiology: Surgeon

- Excessive soft tissue stripping
- Improper or unstable fixation
  - Absolute stability
    - Gap due to distraction or poor reduction
  - Relative stability
    - Excessive motion



Wu CC, JOT 1996

# Etiology of Nonunion – Initial Treatment Factors

- Nonunion may occur after completely appropriate treatment of a fracture, or after less than appropriate treatment
- Was appropriate management performed initially?
  - Operative vs non-operative?
- Was the stability achieved initially appropriate?
- Consider:
  - Bone and anatomic location (shaft vs metaphysis)
  - Patient – host status, compliance with care

# Etiology of Nonunion – Initial Treatment Factors

- After operative treatment…..
- Was the appropriate implant and technique employed? (Fixation strategy)
  - Relative vs absolute stability?
  - Direct vs indirect reduction?
  - Implant size/length, number of screws, locking vs conventional
  - Location of incisions. Signs of poor dissection?
    - Iatrogenic soft tissue disruption, devascularization of bone

# Etiology of Nonunion – Initial Treatment Factors

- Is the current construct too flexible or too stiff?
- Implant too short?
- Bridge plating of a simple pattern with lack of compression?
- Why did the current treatment fail?
- Understanding the mode of failure for the initial procedure helps with planning the nonunion surgery

# Anatomic Location of Fractures

- Some areas of skeleton are at risk for nonunion due to anatomic vascular considerations i.e.:
  - Proximal 5th metatarsal, femoral neck, carpal scaphoid
- Open diaphyseal tibia fractures are the classic example with high rates of nonunion throughout the literature

# Infection

"Of all prognostic factors in tibia fracture care, that implying the worst prognosis was infection"

Nicoll EA, CORR 1974

# Infection

- May be obvious
  - Open draining wounds, erythema, inadequate soft tissue coverage
- Subclinical is more difficult
  - High index of suspicion
  - ESR, CRP may indicate infection and provide baseline values to follow after debridement and antibiotic therapy

# Infection

- *Nonunion should be considered infected until proven otherwise*
- Dramatic association between deep infection and nonunion
- Debridement, debridement, debridement
- Multiple cultures. Identify the bacteria
- Infectious disease consult is helpful
- Infected bone requires stability to resolve infection
- May achieve union in the presence of infection with appropriate treatment

Westgeest et al. JOT 2016

# Patient Evaluation

- History of injury and prior treatment
- Medical history and co-morbidities
- Physical examination
  - Including deformity!
- Imaging modalities
- Patient needs, goals, expectations

# Patient Evaluation – History of Injury

- Date and nature of original injury (high or low energy)
- Open or closed injury?
- Number of prior surgical procedures
- History of drainage or wound healing difficulties?
- Prior infection? Identify antibiotics used and bacteria cultured (if possible)
- Written timeline in complex cases
- Current symptoms – pain, deformity, motion problems, chronic drainage
- Ability to work and perform ADL's

# Patient Evaluation – Medical History

- Diabetes, endocrinopathies, vit D, etc
- Physiologic age – co-morbidities
  - Heart disease, COPD, kidney/liver disease
- Nutrition
- Smoking
- Medications
- Ambulatory/functional status now and prior to original injury

# Patient Evaluation – Physical Exam

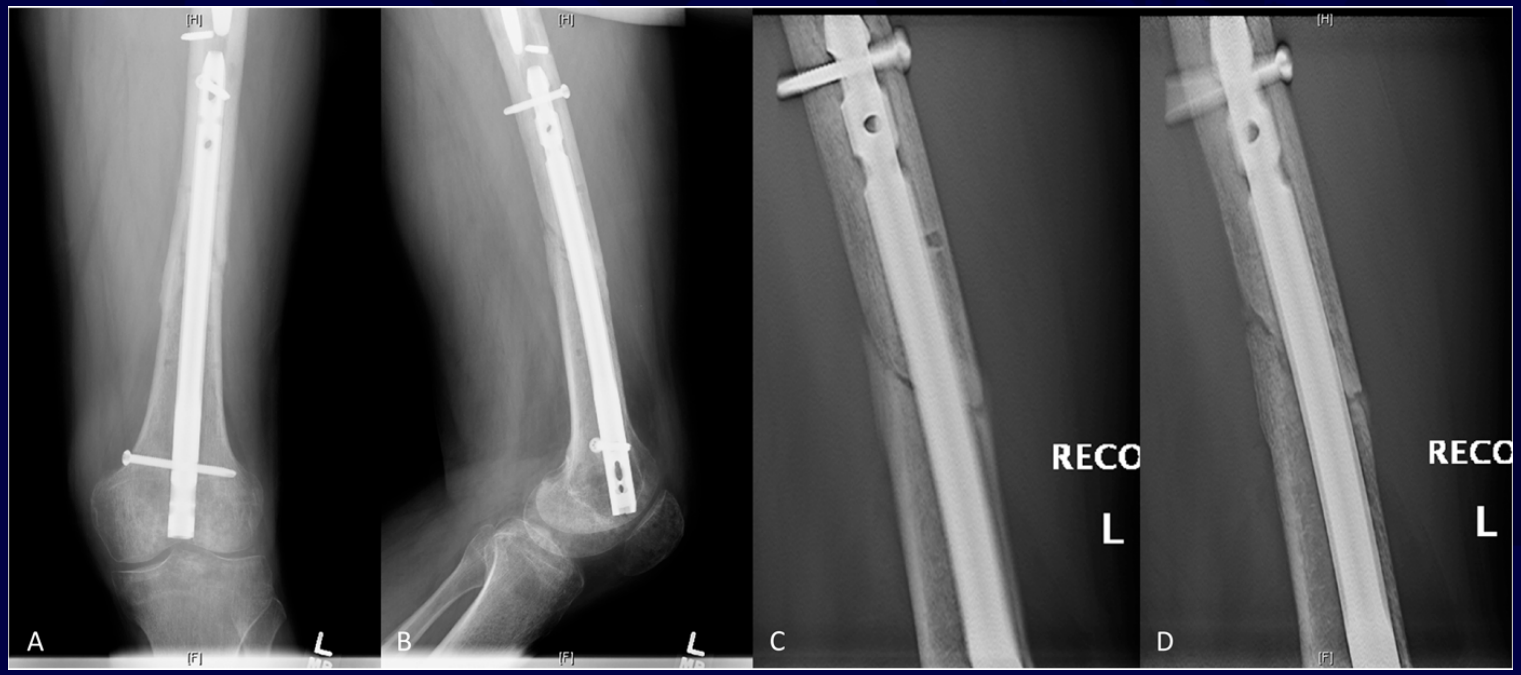
- Appearance of limb
  - Color, skin quality, prior incisions, skin grafts
  - Erythema or drainage
- Range of motion of all joints
- Pain – location and contributing factors
- Strength, ability to bear weight
- Vascular status and sensation
- Deformity
  - Clinically = Length, alignment, AND rotation

# Patient Evaluation - Imaging

- Any injury-related imaging available – plain film and CT
- Serial plain radiographs from injury to present are extremely helpful (hard to get)
- Most current imaging – orthogonal x-rays, typically diagnostic for nonunion
  - Healing of 3 out of 4 cortices without pain is typically considered union.
- Obliques may be helpful for radiographic diagnosis of nonunion
- CT can be helpful but metal artifact can make it difficult
- Radiographic Union Scale for Tibia (RUST) seems reliable
  - Litrenta J et al, JOT 2015

# Patient Evaluation – Imaging Tomography

- CT and MRI have replace linear tomography
- Consider Digital Tomography if available




Anari et al. JOT 2016

# University of Texas Medical Branch Classification of Adult Osteomyelitis

Cierny-Mader Classification

## Anatomic Type

- Medullary
- Superficial
- Localized
- Diffuse

## Physiologic Class

- A-Host

Healthy Immune System

- B-Host

Local compromise (BL)

Systemic compromise (BS)

- C-Host

Treatment is worse than disease

Anatomic Type + Physiologic Class = Clinical Stage

# Radionuclide Scanning – Infected Nonunion?

- Technetium - 99 diphosphonate
  - Detects repairable process in bone ( not specific)
- Gallium - 67 citrate
  - Accumulates at site of inflammation (not specific)
- Sequential technetium or gallium scintigraphy
  - Only 50-60% accuracy in subclinical ostoemyelitis

Esterhai et al. J Ortho Res. 1985

Smith MA et al. JBJS Br 1987

# Labeled Leukocyte Scan – Infected Nonunion?

- Good with acute osteomyelitis, but less effective in diagnosing chronic or subacute bone infections
- Sensitivity 83-86%, specificity 84-86%
- Technique is superior to technetium and gallium to identify infection

Nepola JV e.t. al. JBJS 1993

Merkel KD e.t. al. JBJS 1985

# MRI – Infected Nonunion?

- Abnormal marrow with increased signal on T2 and low signal on T1
- Can identify and follow sinus tacts and sequestrum
- Mason study- diagnostic sensitivity of 100%, specificity 63%, accuracy 93%

Modic MT et al. Rad Clin Nur Am 1986

Mason MD et al. Rad 1989

# Patient Evaluation – Goals & Expectations

- What are the patient's goals and needs?
  - Household ambulation vs marathon runner
- Pain relief expectations
- Range of motion expectations
  - Long standing nonunions may have stiff adjacent joints
- Risks to neurovascular structures (radial nerve in humerus nonunion)

# Treatment

- Nonoperative
- Operative

# Nonoperative

- Electrical stimulation
- Ultrasound
- Extracorporeal shock wave therapy

# Electrical Stimulation

- Applied mechanical stress on bone generates electrical potentials
  - Compression = electronegative potentials = bone formation
  - Tension = electropositive potentials = bone resorption
- Basic science suggests e-stim upregulates TGF-β and BMP's suggesting osteoinduction

# Three Modalities of Electric bone Growth Stimulators

- 1. Direct current - implantation of cathode in bone and anode on skin
- 2. Inductive coupling – pulsed electromagnetic field with device on skin
- 3. Capacitive coupling - electrodes placed on skin, alternating current
- SR/MA suggests improvement in pain and healing but not function

Mollon et al, JBJS 2008
Aleem IS et al, Sci Rep 2016 (SR)

# Contraindication to Electric Stimulation

- Synovial pseudoarthrosis
- Electric stimulation does not address associated problems of angulation, malrotation and shortening – deformity!!

# Evidence for use of Electrical Stimulation

- Pain
  - Statistically significant improvement in pain scores with e.stim
- Function
  - no improvement with e.stim.
- Preventing and treating non union –
  - Significantly greater union with e.stim. Number needed to treat = 7.
- Irrespective of e.stim modality

Pooled meta-analysis data from Aleem, et al, 2016

# Ultrasound

- Piezoelectric transducer generates an acoustic pressure wave
- Some evidence to show faster healing in fresh fractures
- Evidence is moderate to poor in quality with conflicting results
- SR/MA suggests there may be improvement in healing but not function

Busse et al, BMJ 2009
Rutten S et al, JBJS Rev 2016 (SR)

# LIPUS (**L**ow **I**ntensity **P**ulsed **U**ltra**S**ound)

- TRUST Data
  - Multicenter, double blinded, randomized controlled clinical trial → LIPUS vs Sham unit
  - Open and closed tibial shaft fractures treated with IM nail
  - No difference between groups in:
    - Union rate
    - SF-36 score
    - Time to full weight bearing
    - Return to pre-injury status
  - Study stopped early due to lack of efficacy of LIPUS

TRUST (Trial to re-evaluate ultrasound in the treatment of tibial fractures) Busse et al, 2016

# Extracorporeal Shock Wave Therapy

- Single impulse acoustic wave with a high amplitude and short wavelength.
- Microtrauma induced in bone thought to stimulate neovascularization and cell differentiation
- Clinical studies are of a poor level and no strong evidence for use in nonunions is available

Biedermann et al, J Trauma 2003
Petrisor B et al, Indian J Orthop 2009 (SR)

# Operative Treatment

- Debridement and hardware removal
- Plate osteosynthesis
- Intramedullary nailing
- External fixation

- Autogenous bone graft
  - ICBG, RIA
- Bone marrow aspirate
- Allograft bone
- Demineralized bone matrix
- BMP's
- Platelet concentrates

# Autogenous Bone Marrow Aspirate

- Transplant osteoprogenitor and mesenchymal stem cells to nonunion site
- Osteoinductive, not osteoconductive
- Level III and IV studies available
- Positive correlation between number of progenitor cells in aspirate and amount of callous
- Animal data positive but no high level clinical

Hernigou et al, JBJS 2005
Gianakos A et al, JOT 2016 (SR)

# BMP's

- rhBMP-2 and rhBMP-7 have been shown to be equivalent to autologous iliac crest for delayed reconstruction of tibial bone defects
- May be a reasonable alternative to ICBG for the management of nonunion
- Very expensive!!

Jones et al, JBJS 2006
Friedlaender et al, JBJS 2001
Dai J et al, PLoS One 2015 (SR)

# Autogenous Bone Grafting

- Considered the “gold standard”
- Osteoinductive - contain proteins and other factors promoting vascular ingrowth and healing
- Osteogenic – contains viable osteoblasts, progenitor cells, mesenchymal stem cells
- Osteoconductive - contains a scaffolding for which new bone growth can occur
- ICBG versus more recent RIA from femur?

# Reamer-Irrigator-Aspirator Bone Graft Harvest

(Synthes, West Chester, PA, USA)

- Compared to posterior or anterior ICBG
  - Greater Volume
  - Less operative time
  - No difference in union rates
  - Less expensive for larger defects
  - ??Less donor site morbidity
  - ??More significant complications

Dawson J, et al, JOT 2014

# Complications associated with Reamer-Irrigator-Aspirator

(Synthes, West Chester, PA, USA)

- Femur fracture – eccentric reaming or over-reaming
- Hemodynamic instability due to massive and rapid blood loss

Giori N, et al, JOT 2010. Donders J, et al, JOT 2016

# Surgical/Fixation Strategy

- Define nonunion type
  - Hyper-, oligo-, atrophic, or pseudarthrosis
- Fracture location – diaphysis vs metaphysis
- Infected vs Aseptic
- Deformity?
- Patient/host factors
- Goals and expectations

# Plate Osteosynthesis

- Correction of malalignment
  - Osteotomy may be required, planning always required
- Compression in hypertrophic cases
- Immediate mobilization, likely NWB
- Requires adequate soft tissue coverage
  - More dissection required for plating and osteotomy in deformity correction
- Bone graft as needed

# Plate Osteosynthesis

- Soft tissue and bony dissection are extremely important!
- Preserve periosteum and muscular attachment to bone
  - Concept of “working window”
  - Only expose the necessary amount of bone to do the case, maintain vascularity

# Plate Osteosynthesis:
## Osteoperiosteal Decortication

- Management of the bone…
  - Do not simply elevate the periosteum off the bone!!
  - Use a sharp chisel or osteotome to elevate an osteoperiosteal flap
  - Sharp chisel and a mallet to take some good, vascularized bone with the periosteum
  - Provides excellent environment for bone graft to produce callous as the elevated bone remains vascularized by the periosteum

Binod B et al, Arch Orthop Trauma Surg 2016

# Intramedullary Nailing

- Mechanically stabilizes long bone nonunions as a load sharing implant
  - May allow for early weight bearing
- Must manage malalignment
  - Starting and ending points, entrance and exit angle of each fragment
- Initially destroys endosteal blood supply (will recover) but increase periosteal blood supply

# Intramedullary Nailing

- Can be performed without direct exposure or dissection of the fracture soft tissue envelope
- Or can be performed in conjunction with an open exposure of the nonunion site and bone grafting
- Not applicable in articular nonunions and malunions

# IM Nail Dynamization

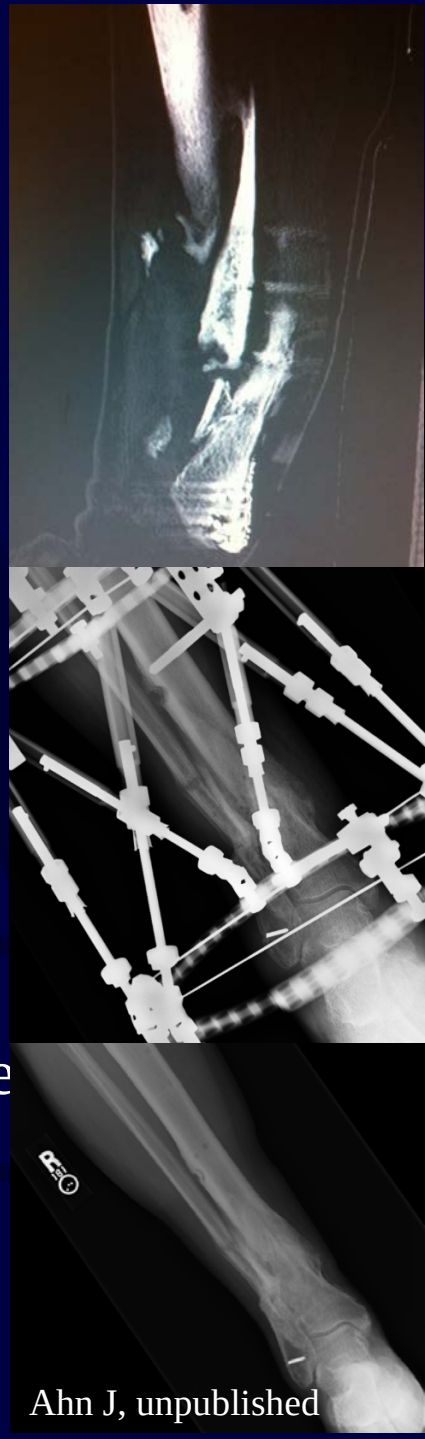
- Removal of interlocking bolt(s) to allow for axial compression at nonunion with weight bearing
- Commonly performed technique for nonunion management when IM nail is in place
- Extremely limited data to support this technique
- 83% success rate in tibial nonunion management
- Litrenta, et al. 2015

# IM Exchange Nailing

- Replacing IM nail with larger IM nail → increased stability ($r^4$)
- Medullary reaming → reactive vascularity
- limited data to support this technique (stronger than dynamization data)
- 90% success rate in tibial nonunion management
- Litrenta, et al. 2015

# External Fixation

- Excellent for gradual malalignment correction
- Useful in the management of infected nonunions
  - Allows for repeat debridements with stability
  - Soft tissue coverage without contaminated hardware in wound
- Allows for bone transport for large intercalary defects
- Can generate large compressive forces at nonunion
- Allows mobilization of joints
  - May be bulky and difficult for patients to manage
  - Pin infections common
- In complex cases, may be good for limb salvage but may require a long period of time



Ahn J, unpublished

# Nonunions
## Summary

- Definition- a fracture that has not and is not going to heal
- Types- hypertrophic, oligotrophic, atrophic, pseudarthrosis
  - If bone forming but not consolidated → improve biomechanics
  - If not enough bone → increase biology
- Assessment- host, injury/fracture, prior treatment; infected?
- Assessment- exam, radiography, CT/MR, serologic markers
- Treatment- address what is lacking in biology and/or mechanics
- Treatment- systemic/pharmacologic, electric/ultrasound/BMP/MSCs/graft, plate/nail/fixator

# References

## (in order of appearance)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# Thank You