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Osteomyelitis: Diagnosis and Treatment in 2022

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My Disclosures

- ***Peptilogics****-Medical Advisor on bone and joint research; 2020-present*

- *No other disclosures!*

Lecture Outline

- **Osteomyelitis: The Basics**
  - Pathogenesis and Classification
  - Microbiology
- **Diagnosis**
  - Bx path/Cx
  - Adjunctive testing-inflammatory markers
  - Imaging Modalities (alternatives to MRI)
- **Treatment**
  - Antibiotics
    - PO vs IV
    - Anti-biofilm Abx
    - Newer Abx/Agents
  - HBOT
  - Abx Beads
  - Phage
- ***FOR EACH TOPIC, I WILL PROVIDE MY OWN CONCLUSIONS BASED ON DATA REVIEWED**

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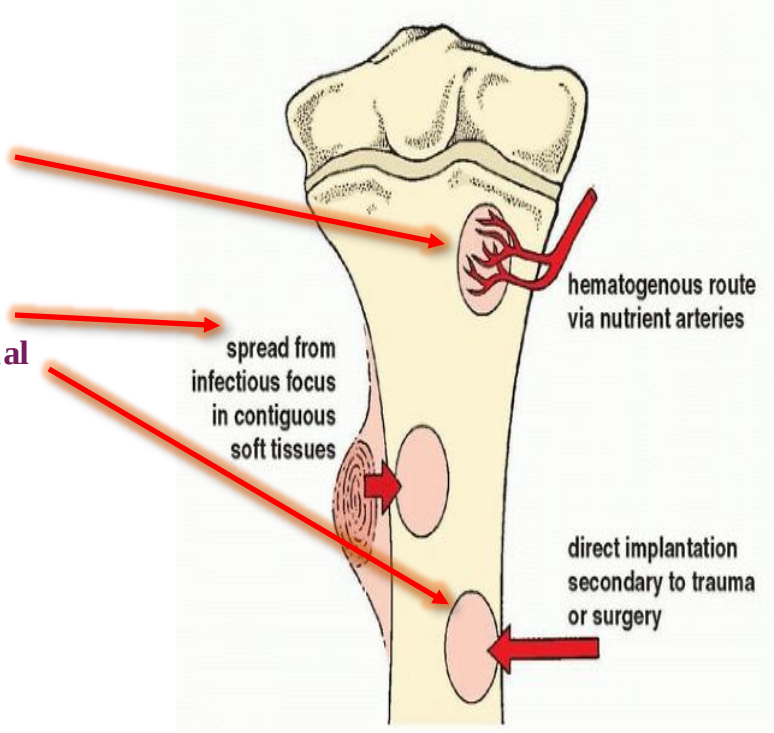
Osteomyelitis: The Basics

- **Two Mechanisms of Infection (Pathogenesis)**
  - **Hematogenous**-Common especially with vertebral osteomyelitis, and long bone infections in children→ Often **mono-microbial**
  - **Contiguous spread**- ulcers (diabetic/decubitus), vascular disease, trauma (fx), surgery→ Often **polymicrobial**
- **Two Types of Infection (Classification)**
  - Based on **path and clinical picture:**
  - **Acute**-Usually hematogenous and mono-microbial, sx more severe
  - **Chronic**-Usually contiguous and poly-microbial, sx less severe



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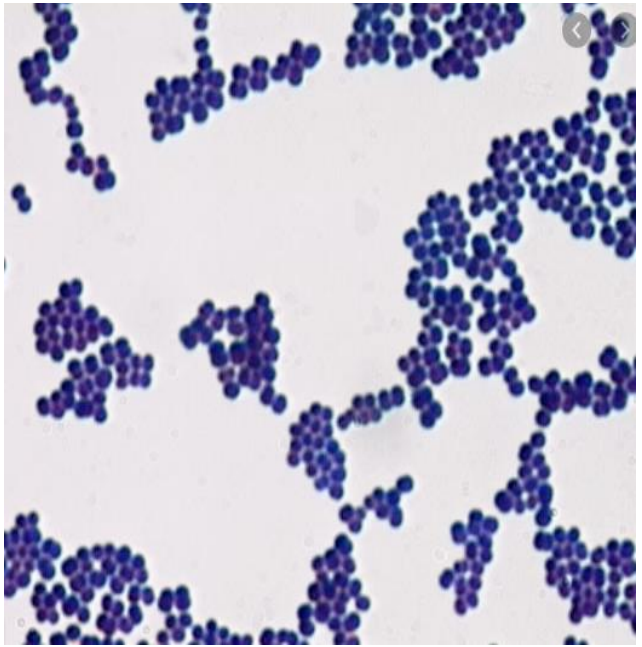
Microbiology

- **>50% of cases: Staphylococci (MSSA, MRSA, CoNS)**
- **~25-50% of cases**: Streptococci, Enterococci, Pseudomonas, Enterobacter, Proteus, E. coli, Serratia, **anaerobes**
- **Rare (<5%) of cases:** NTMs, fungi (endemic dimorphs, Candida, Aspergillus), Actinomyces, Brucella, Salmonella



Berbari, et al. Mandell vol 1, 7th ed.

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Diagnostic Basics

- Bone biopsy and culture- **GOLD STANDARD**
  - Closed needle vs. open surgical biopsy
  - **HOLD on starting antibiotics until bone cultures obtained, unless:**
    - **Soft tissue infection present** in conjunction with bone infection
    - **Sepsis syndrome** (bacteremic, febrile, toxic)
- Probe to bone test
  - **Positive predictive value 89%**
  - **Negative predictive value 56%**
- ESR/CRP-**Usually elevated**, but may be normal (chronic)
- Imaging- **MRI is TEST of choice (95% Sn, 88% Sp, >90% PPV/NPV)**

Berendt, et al. Diabetes Res Met and Rev, 2008	Definite OM	Probable OM	Possible OM	Unlikely OM
Post Test Probability	>90%	51-90%	10-50%	<10%
Criteria	Bone cx+/path+ **OR** Pus in bone found **OR** Atraumatically detached bone frag. removed **OR** 2 probable, OR 1 probable + 2 possible, OR 4 possible criteria	Bone cx/path discordance **OR** MRI + clinical picture **OR** Visible cancellous bone in ulcer site **OR** 2 possible criteria	MRI+ alone **OR** Probe to bone + **OR** Visible cortical bone **OR** ESR>70 mm/hr with no other clear cause **OR** Non-healing wound despite offloading/perfusion >6 weeks	No signs/symptoms of inflammation **AND** Normal imaging **AND** No visible bone or persistent ulcer despite wound care
Management	Treat	Additional investigations +/- treatment	Additional investigations	No additional investigations or treatment

Bone bx

2012 IDSA Guidelines: "…although **there is debate about value of bone cx**…bone bx using an appropriate method remains the recommended method for definitive dx of DFO"

However.. is bone bx always needed?

Although considered the Gold Standard, bone bx has some possible disadvantages:

- **Often expensive to do**
- **Technical skill needed, as well as time (2-3 days+)**
- **Confusing to interpret (Sn 40-60%)**
  - Bone Bx Path vs. Culture?→**Berendt at al., Diabetes Metab Res Rev 2008** (systematic review, diabetic foot OM)

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In addition…

How often does a bone bx change management?

Hirschfeld, et al., Open Forum Infect Dis, Oct 2017-Retrospective review of 203 bone bx's from 185 patients→138 cases received empiric Abx post bx. Only 3 cases where Abx were drastically changed, Abx narrowed in 4 cases, and DC'd completely in only 8 cases

Mikus, et al., JVIR, 2013- Retrospective review of 42 bone biopsies for OM→ Only 12 were positive, and only 1 cx result equated to change in Abx treatment and duration (guided by imaging and clinical impression)

Conclusions:

-Further high quality studies needed to cement the utility of bone bx as definitive Gold Standard for OM

-**Consider obtaining** in sicker patients, those with risk factors for atypical infection or those who have not responded to Abx trial (prior Abx exposure) and those with no surgical plans

-When obtained, **obtain BOTH path and culture** to maximize diagnostic yield, **AND** incorporate imaging, adjunctive testing and clinical picture in securing a dx

Adjunctive Testing

ESR/CRP-what is their role?

- **2012 IDSA Guidelines**: **ESR>60 mm/hr, CRP >3.2 mg/dL** can HELP to distinguish diabetic foot OM from soft tissue infection (Fleischer et al, *J. Foot and Ankle Surg* 2009-case controlled study of 54 DFU patients)

- **But, there is disagreement on what cutoffs are best…**
  - **ESR>67 mm/hr**, Sn 84%, Sp of 75%; **CRP >1.4 mg/dL** Sn 85%, Sp 83% (Mikhail et al. *J Low Extrem Wounds* 2013-prospective study of 61 DFI patients)
  - **ESR>70 mm/hr** higher risk of OM (Markanday et al, OFID, 2014)-**variable studies!**
  - **ESR>70 and ulcer size >2cm²** increased Sp to 84% (*J Fam Pract*., 2015)
  - ESR remained elevated up to **3 months**, and CRP improved **within a week** s/p Tx—**use ESR to monitor OM more reliably?** (Mikhail et al)
  - **ESR>60, CRP >7.9 mg/dL** optimal in distinguishing OM from SSTI, ESR better to rule out OM initially, CRP can help distinguish OM/SSTI if ESR high (Lavery et al. CORR 2019)

Little data I could find on combining ESR/CRP, and with chronic OM, these tests do not seem to be helpful in guiding management on their own

Adjunctive Testing

Another possible marker for OM:

Procalcitonin:

Meta-analysis #1 (110 studies): Value of **0.5 ng/mL Sn 88%, Sp 81%** in **bacterial infections in general**(Simon et al, CID 2004)

Meta-analysis #2 (7 studies, 583 patients): Values **of ≥0.2 ng/mL Sn/Sp of 90%** for **acute bone/joint infections** (Shen et al. , *Eur Journ of Clin Micro and Infect Dis*, 2013)

Conclusions:

ESR/CRP need to be **incorporated with other diagnostic modalities** to help secure dx of OM and **can NOT be used on their own** to reliably make this dx (Berendt, et al.)

ESR seems to be **better marker to follow longitudinally** once treatment started

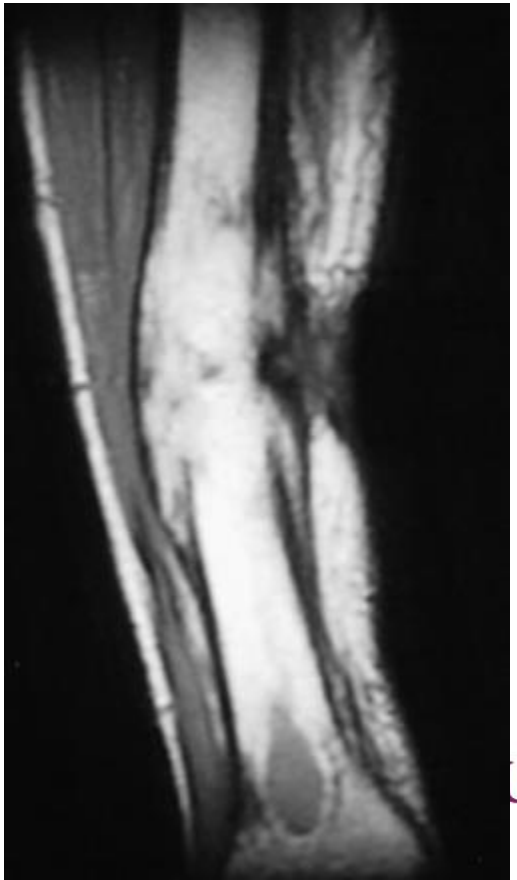
There **is possible role for PCT up front** in dx of **acute OM**

For chronic OM, inflammatory markers are **generally NOT helpful** unless elevated at baseline

Imaging: MRI

- **TEST OF CHOICE REGARDLESS OF TYPE OF OM (acute vs chronic)**
- **CANNOT PERFORM IF CERTAIN H/W IN PLACE**

- **82-100% sensitive**
- **75-96% specific**



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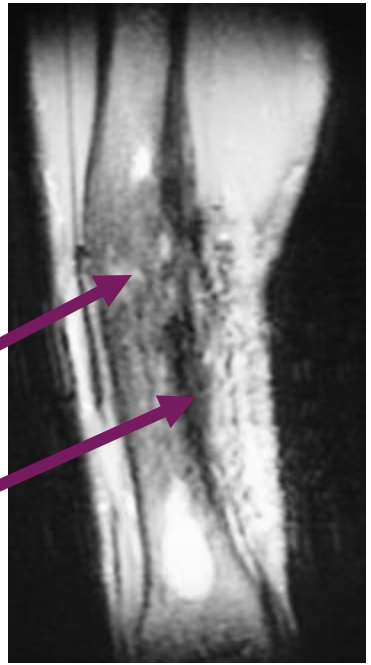
MRI



- Acute Osteomyelitis:
  - Marrow fat replaced by edema
    - T1 dark, T2 bright
- Chronic: thickened/damaged cortex
  - Low signal on all scans (T1/T2)
- Cellulitis: **no marrow changes**

Diagnostics: When MRI Can't Be Used

- **Consider the following imaging modalities:**
  - **Tc Bone Scan:** Sn of ~95%, Sp only 25-33%, many false +'s. **NPV is good (90%)**
  - **Indium(WBC) Scan**: Sn/Sp in high 80s%, can be **combined with Tc scan to improve overall Sp of Tc scan (23%→~80%), low Sn spinal OM**
  - **Gallium Scan:** Sn 81%, Sp 69%, **Alternative test of choice for vertebral OM** when combined with Tc Scan **(Sn 91%, Sp 90%)**

Conclusion: Be aware of these alternative imaging modalities for the diagnosis of OM, if MRI cannot be done for some reason

DIAGNOSTIC TESTS FOR OSTEOMYELITIS

Test	Sen	Spec	PPV	NPV
3-phase bone scan	95%	33%	53%	90%
Gallium scan	81%	69%	71%	80%
Indium WBC scan	88%	85%	86%	87%
MRI	95%	88%	93%	92%

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Treatment: Antibiotic Selection

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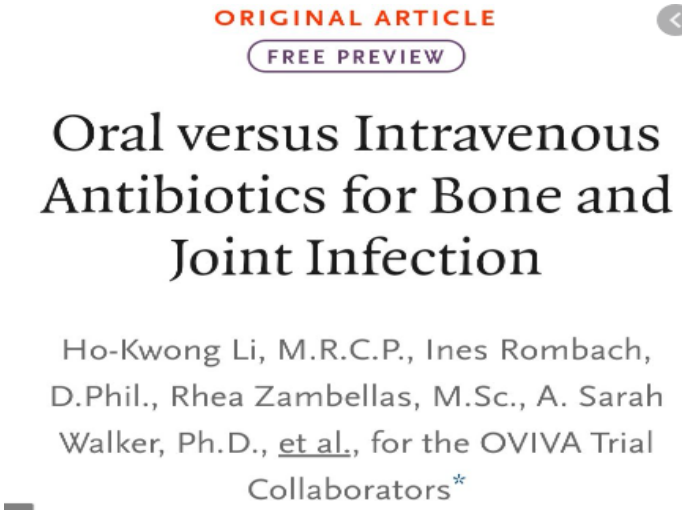
PO vs. IV: THE OVIVA TRIAL

- Li, HK et al. " Oral vs Intravenous Antibiotics for Bone and Joint Infection" NEJM, 2019

- **The Study:**
  - **Multi-Centered, Randomized, Open Label Non-Inferiority Study**
  - 1054 patients, 26 hospitals in the U.K., enrolled between 2010-2015
  - **Primary Outcome**: Tx failure within 1 year after randomization
  - **Conclusions**: PO Abx were non-inferior

- **The Issues:**
  - High rate of adverse events
  - **Abx were not pre-specified in protocol of study**
  - Open Label Study (bias)
  - **No comparison between efficacy of PO and IV Abx regimens**
  - **Rifampin more commonly used in PO group**


ORIGINAL ARTICLE

FREE PREVIEW

Oral versus Intravenous Antibiotics for Bone and Joint Infection

Ho-Kwong Li, M.R.C.P., Ines Rombach, D.Phil., Rhea Zambellas, M.Sc., A. Sarah Walker, Ph.D., et al., for the OVIVA Trial Collaborators*

Conclusions: Use of PO Abx (good bone penetration) can be **considered** in **uncomplicated cases** where **good source control has been achieved,** otherwise more studies needed and would stick with SOC

Treatment: Addressing Biofilm

Are certain Abx better at doing this?

- Overwhelming majority of studies focused on **Staphylococci**
- Overwhelming majority are ***in vitro*** studies

In vitro studies support potential biofilm activity in following Abx against Staphylococci (MSSA, MRSA and CoNS):

- **Rifampin** (never as monotherapy, development of resistance high)**—most available data**
- **Daptomycin-** in vitro data for Staph
- **Tetracyclines-** in vitro data for Staph and some GN's
- **Quinolones-** In vitro data for Staph and some GN's

All of the above have good bony penetration when administered!

Conclusions: Clinical studies needed, but in the setting of **Staphylococcal bony infections** with associated h/w (potential for biofilm formation high), would consider using the above Abx as part of an Abx treatment regimen whenever possible

Newer Drugs to Consider

- **Dalbavancin:** Long acting, approved for SSTI, IV
  - **Retrospective studies**--Almangour et al. (*Diag Microbiol Infect Dis* 2019), Morata et al (AAC, 2019)—Dalbavancin good for OM/septic arthritis, low side effects
  - Rappo et al., OFID 2019-RCT comparing dalba vs. SOC in OM after I+D, clinical cure achieved at D42 97% dalba, 88% SOC. No significant differences up to 1 year between groups → reinforces above findings, but **MORE STUDIES NEEDED!**
- **Delafloxacin**: Covers MRSA, approved for SSTI/PNA, PO
  - No studies regarding treatment of OM yet, **STAY TUNED!**
- **Ceftaroline:** Covers MRSA, approved for SSTI/PNA, IV
  - **CAPTURE Study** (2019)- Phase 4 clinical trial, 150 pts with Gram positive OM given ceftaroline, 92.7% clinical success (clinical cure with no further need for Abx or improvement with switch to another Abx), included patients with DM, PVD, h/w, MSSA/MRSA.
- **Tedizolid:** Better side effect profile vs linezolid, PO
  - Limited data, ? Efficacy with MRSE/MRSA FB-OM in rat model (Park et al.)-tedizolid/rifampin was effective
  - Benavent, et al. (*Antibiotics*, 2021)—retrospective study of 51 patients, overall cure rate was 83%
  - **Pending clinical trial-STAY TUNED**!

CONCLUSIONS: Be aware of these Abx options and talk with your ID physician to see if they could be employed in certain situations

Treatment: Abx Beads

What is it:

- **Combining Abx with PMMA cement into 'beads' near site of infection**
- Widely accepted, but…
  - What Abx to place into PMMA (vanco/gent?), and at what doses/concentrations?
  - Best delivery vehicle-PMMA vs biodegradables?
  - How long should they be kept in place?

The Data:

- Majority of studies analyzing beads are derived from **animal models**
  - Mendel, et al. *Arch Orthop Trauma Surg*, 2005-Gent beads in Staph aureus OM infections in rats
  - Evans et al. CORR, 1993-Gent PMMA beads + IV CTX and I+D for chronic OM in rabbits (100% success), better than beads (79%) or IV Abx (92%) alone
  - Nelson, et al, *J Orthop Res*, 1997-Use of calcium pellet aminoglycoside beads with I+D in animals-93% clearance of infection

Treatment: Abx Beads

Clinical data is Less Robust However:

- Patzakis et al. CORR, 1993-Retrospective study, 100% cure of chronic OM with PMMA beads, **but only 12 patients**
- Calhoun et al, CORR, 1993-RCT (52 patients), PMMA gent beads x 4 weeks vs systemic Abx in infected non-unions-- **cure rates were 89% vs 83%!**
- Blaha, et al. CORR, 1993-Multicenter RCT **showed no difference in cure between beads and systemic Abx**
- Bor et al, BMC 2021—Retrospective study of only 16 patients**, all did well**

Conclusions:

Possible benefits may exist in incorporating the use of Abx Beads, **especially in chronic OM**, however **larger RCTs are needed to better establish role of Abx beads, as well as clarify what concentrations and durations are optimal**

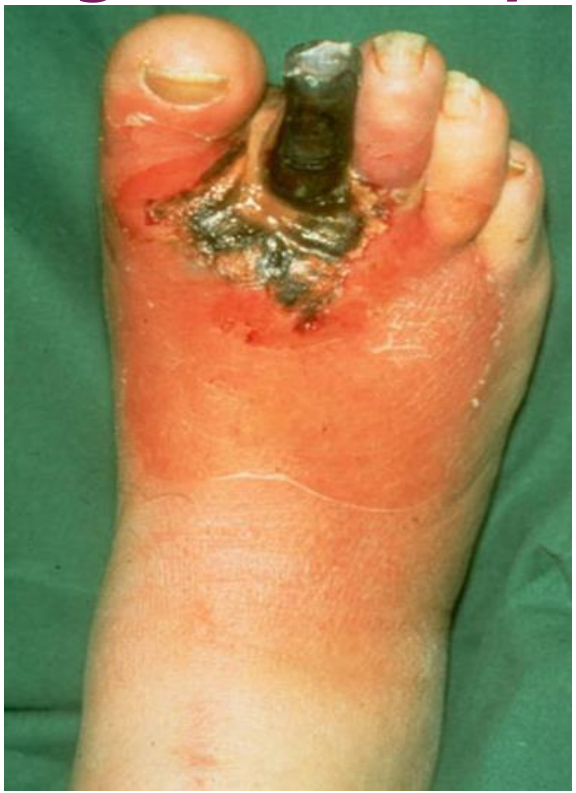
Treatment: Improving Vascularity

Hyperbaric Oxygen Therapy (HBOT):
Use of 100% O2, at >1 atm (usually 2-2.5 atm) from 90-120 mins, x ~40 sessions

Theoretical Benefits:

- Increased angiogenesis
- Increased immune system activation (phagocytosis, lysis)
- Increased collagen formation and osteogenesis

…But has HBOT been reliable in the treatment of OM?



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HBOT Therapy: The Data

Case reports and nonrandomized studies abound---there are few RCTs

- **2004**- Kranke et al. *Cochrane Database Systematic Review*→5 trials, 4 associated with DFU.
  - HBOT reduced major surgeries, may have improved ulcer healing at 1 year.
  - However, based on **multiple shortcomings** (low patient #'s, methodological issues, poor reporting, etc), these recommendations were to be interpreted with caution.
  - **For OM, no clear recommendations could be made, given lack of any good quality studies (RCTs)**

- …They tried again in 2012-12 RCT trials analyzing effects of chronic wound healing with HBOT vs none (10 trials involving DFU)→**recommendations were basically the SAME**

- **2012**-Peters et al, *Diabetes Metab Res Rev*→ Systematic Review of 22 studies again involving DFU (29 RCTs, 4 cohort).
  - **Only 2 studies** regarding HCT, **no clear improvement in infection outcomes noted with HBOT**

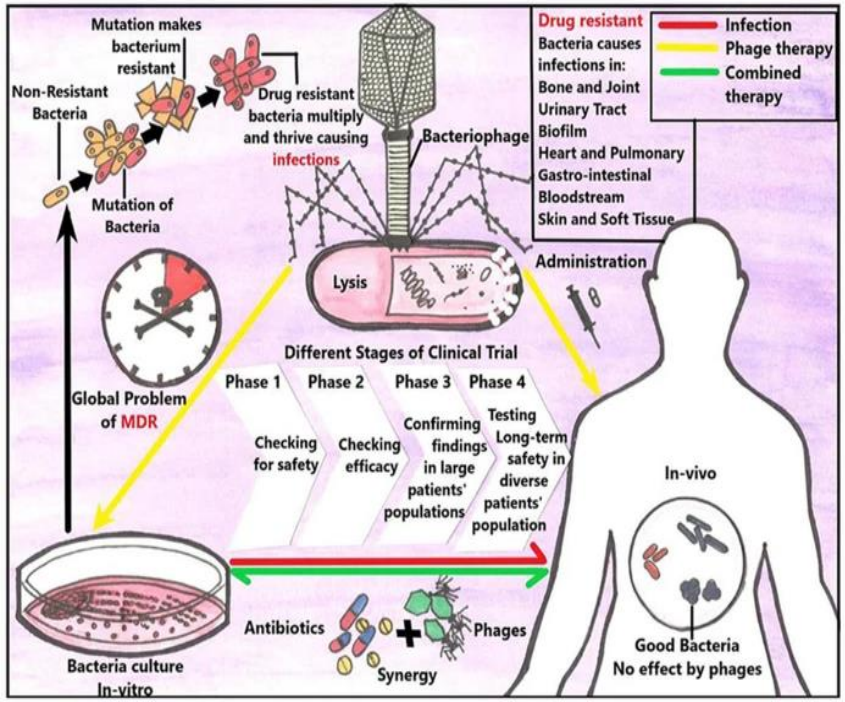
- **2018**-Savvidu, et al. *Orthopedics:* Systematic Review→460 patients analyzed
  - All had received Abx and surgical I+D
  - All were chronic OM, **73.5% overall success rate** with no relapses

HBOT

Conclusions: HBOT **should NOT** be first line treatment for acute or chronic OM, considerations for providing this therapy should be made on **case by case basis**, weighing in economic factors (cost), patient factors (comorbidities), severity of wound and implications regarding treatment failure (salvage)

Phage Therapy

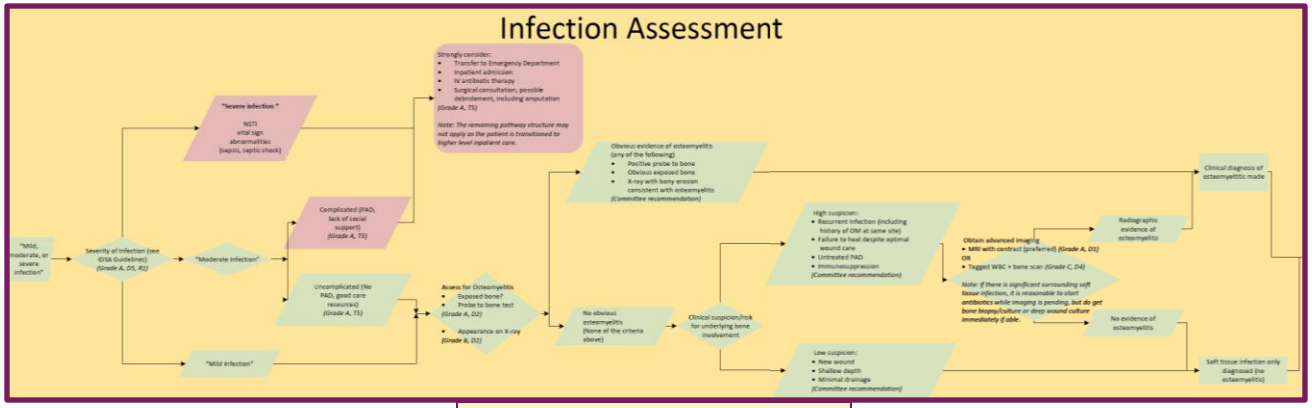
- Introduction of bacteria-specific virus into area of bony infection
- Evolving data-OM, PJI, DFIs all being analyzed
- Particularly useful for MDRO organisms or when source control cannot be achieved (implant(s) in place)
  - Genvirere, et al, 2021: Systematic review of 20 cases focusing on phage results for all bone/joint infections (no RCTs identified however)—overall success rate 71%

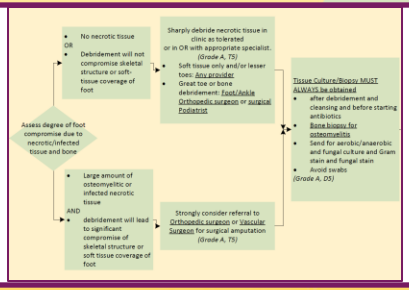


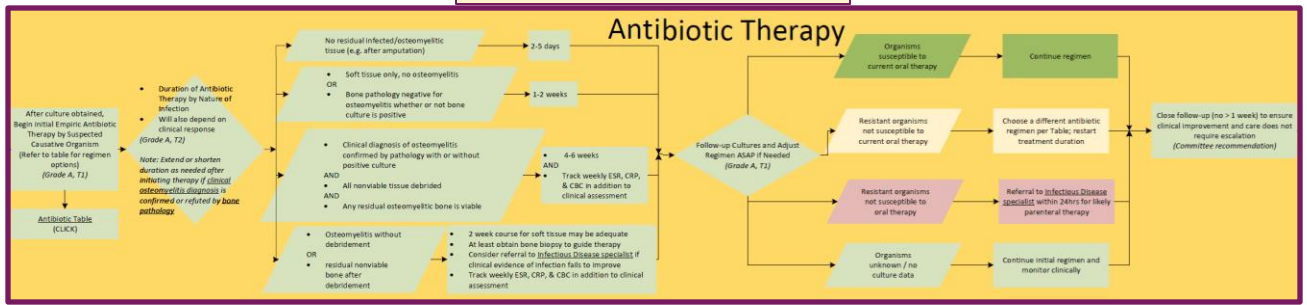
THE FUTURE

- Local therapies
  - Abx Infusions, Nanotechnology, Abx coated devices, UV, Flaps/grafts
- Immune therapy
  - Biologics, Antibodies, Phage therapy, Growth Factors
- Imaging
  - PET CT, newer techniques
- Nanotechnology
- Newer Antibiotics (local and systemic)

….Stay tuned!







Oral Antibiotic Dosing Table

Organism Targeted	Antibiotic Regimen
MSSA, Strep.	Cephalexin† Amoxicillin-Clavulanate† Clindamycin
+ MRSA coverage*	Clindamycin Linezolid Trimethoprim-sulfamethoxazole† + Cephalexin† or Doxycycline
+ Gram negative bacilli	Trimethoprim-sulfamethoxazole† + Amoxicillin-clavulanate†
+ Psuedomonas	Clindamycin + Ciprofloxacin† or Levofloxacin†

*MRSA coverage indicated if patient has a history of MRSA infection/colonization
†Ensure dosing is adjusted for patient's renal function

Ciprofloxacin	500 mg every 12 hours (or, if there is concern for Pseudomonas aeruginosa, 750 mg every 12 hours)	Yes
Clindamycin	300 to 450 mg every 6 to 8 hours	No
Doxycycline	100 mg orally every 12 hours	No
Levofloxacin	500 mg every 24 hours (or, if there is concern for P. aeruginosa, 750 mg every 24 hours)	No

Table 11. Suggested Route, Setting, and Duration of Antibiotic Therapy, by Clinical Syndrome

Site of Infection, by Severity or Extent	Route of Administration	Setting	Duration of Therapy
Soft-tissue only			
Mild	Topical or oral	Outpatient	1–2 wk; may extend up to 4 wk if slow to resolve
Moderate	Oral (or initial parenteral)	Outpatient/ inpatient	1–3 wk
Severe	Initial parenteral, switch to oral when possible	Inpatient, then outpatient	2–4 wk
Bone or joint			
No residual infected tissue (eg, postamputation)	Parenteral or oral	…	2–5 d
Residual infected soft tissue (but not bone)	Parenteral or oral	…	1–3 wk
Residual infected (but viable) bone	Initial parenteral, then consider oral switch	…	4–6 wk
No surgery, or residual dead bone postoperatively	Initial parenteral, then consider oral switch	…	≥3 mo

Questions?