2020 Update

on

Bone and Joint Infection in Adults

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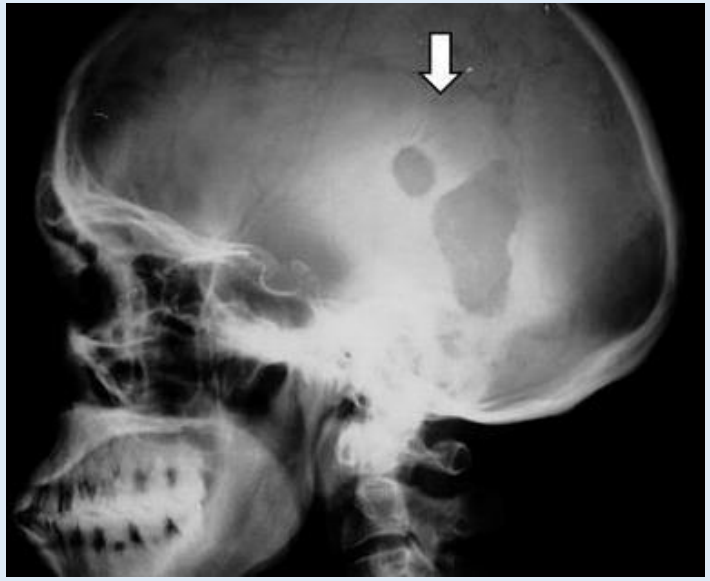
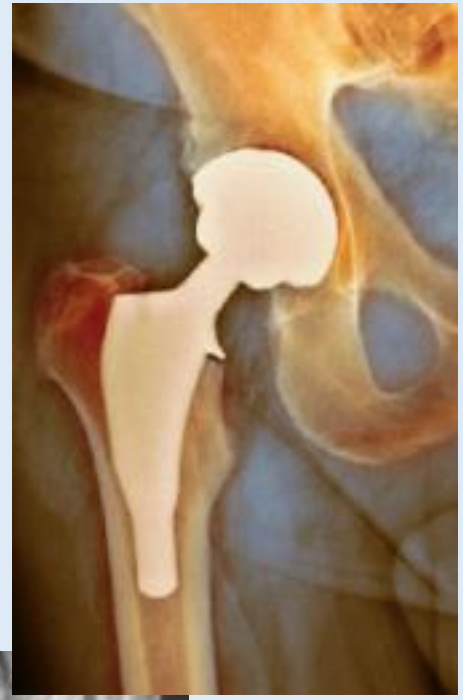
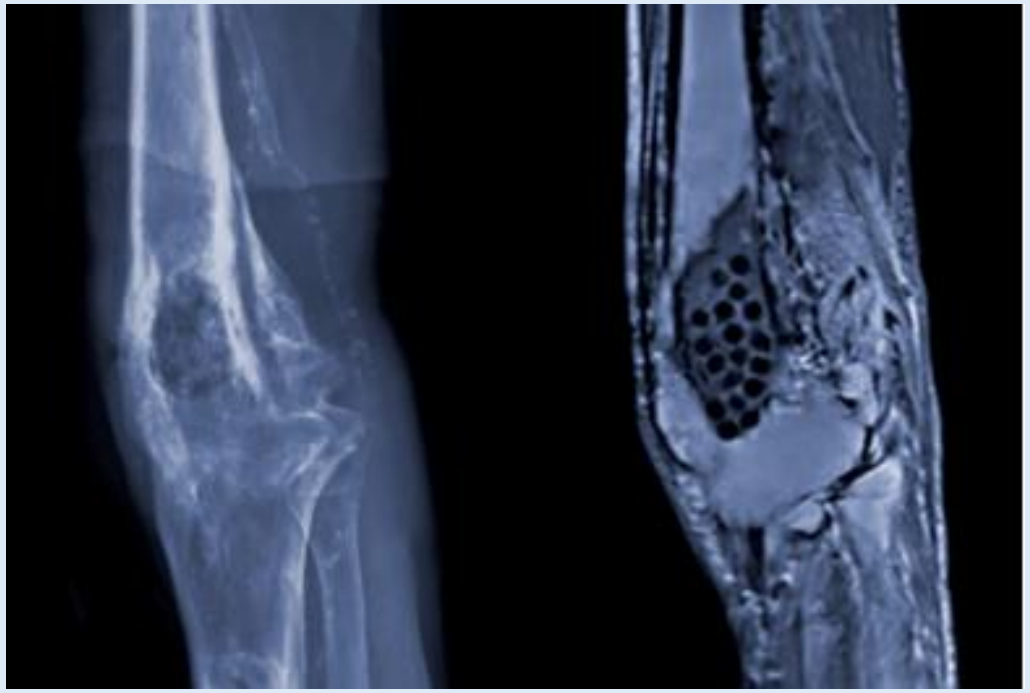
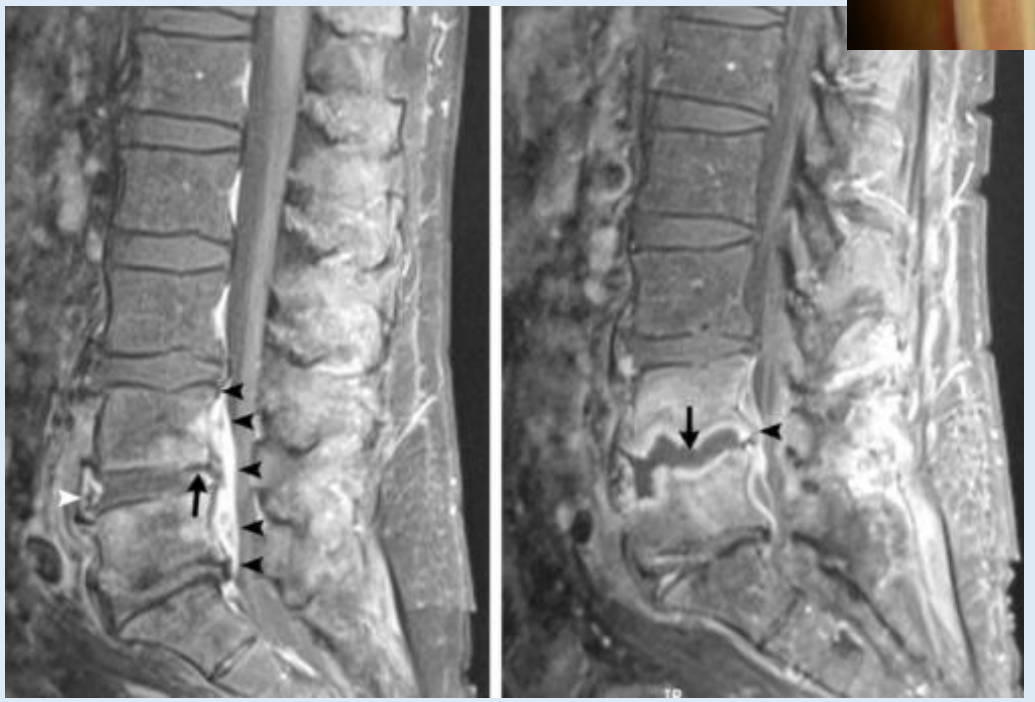
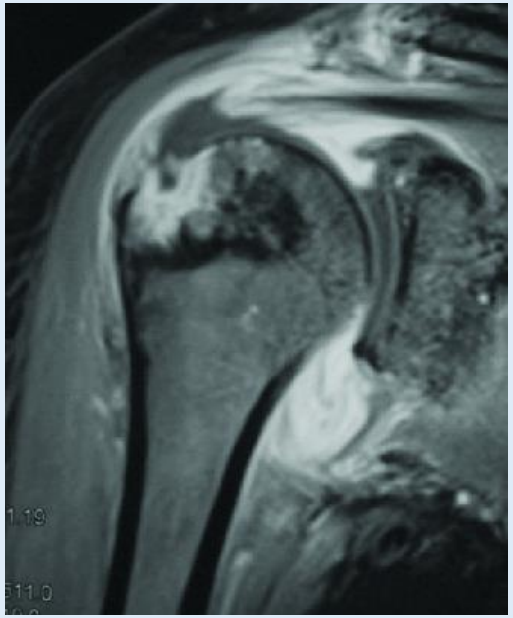
- Disclosers: none

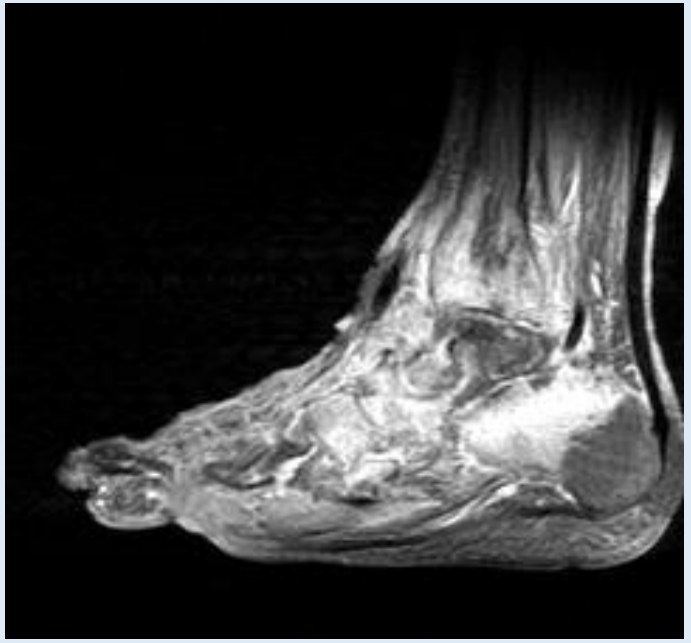




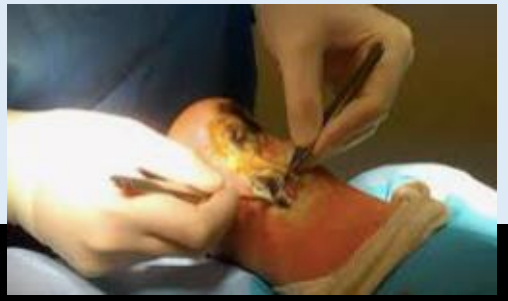


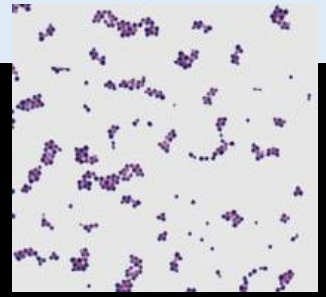






Osteomyelitis timeline





3000 BCE
Egyptian text describes a case of chornic wound following penetrating cervical spine injury

400 BCE
Infection after fracture recognized

1773
Hematogenous osteomyelitis recognized

1882
Staphylococci identified

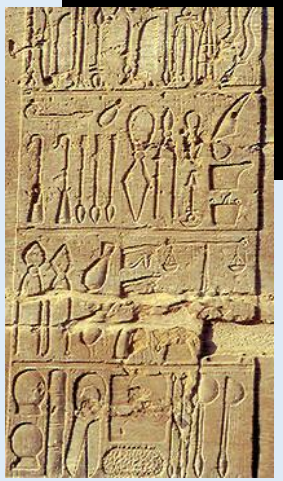
1940s
Advent of Penicillin

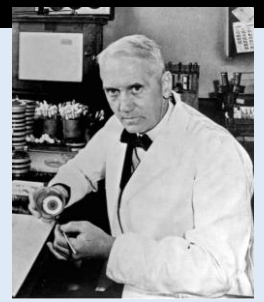
1960s-1990s
Extended antibiotic treatment, ?IV

1980s-2000s
Improved surgical technique

Present day
Changing epidemiology, antibiotic resistance, rising costs

3000 BCE

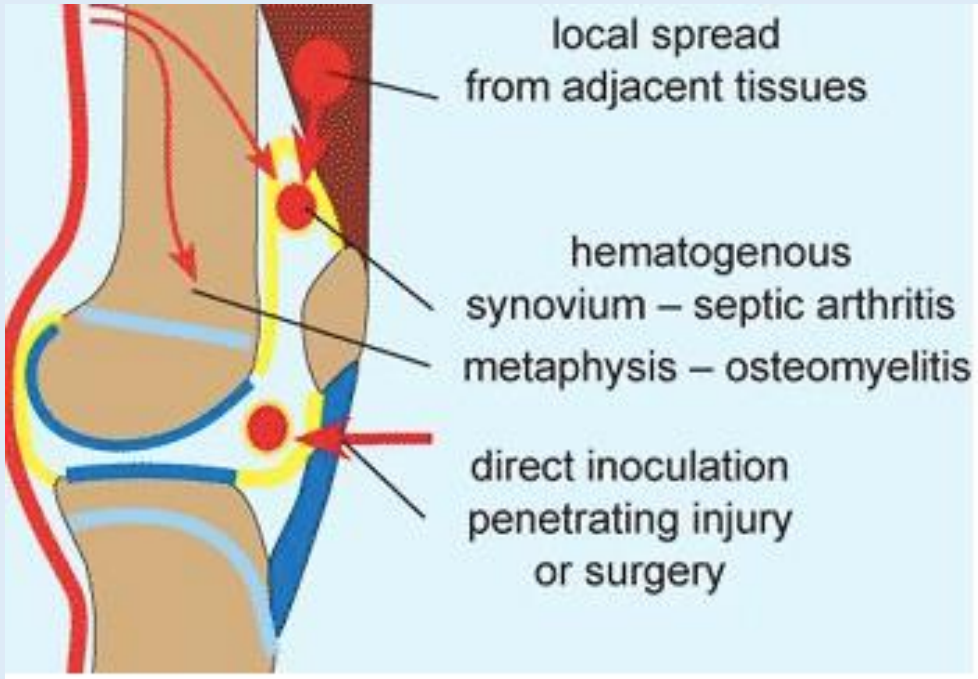




Osteomyelitis: a review of clinical features,
F A Waldvogel
New England Journal of Medicine, The.1969, Vol. 282(5), p. 260-6

Osteomyelitis: Pathogenesis

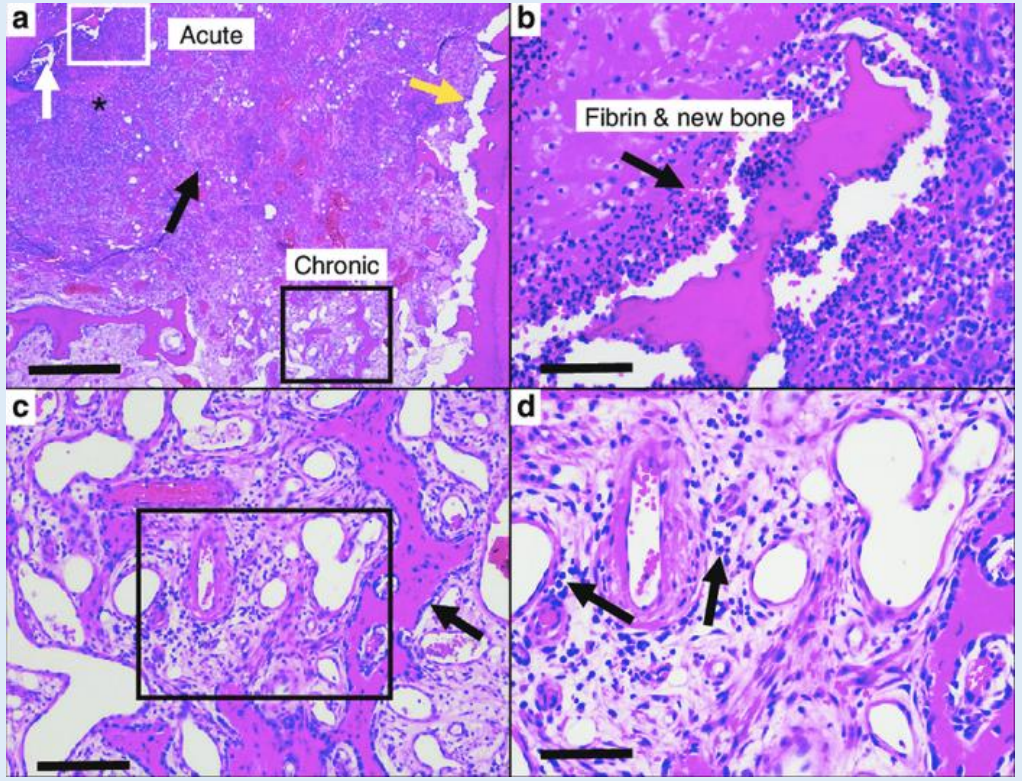
- Contiguous spread
- Direct inoculation
  - Trauma
    - Open fracture 3-25%
  - Surgery
- Hematogenous spread from a distant source



Acute vs chronic osteomyelitis

2018 International Consensus Meeting on Musculoskeletal Infection, Philadelphia, PA

“The greatest research priority identified is to update the clinical definitions of acute and chronic bone infection.”



Source: EA Masters et al,www.nature.com

Learning objectives-Bone and Joint Infection

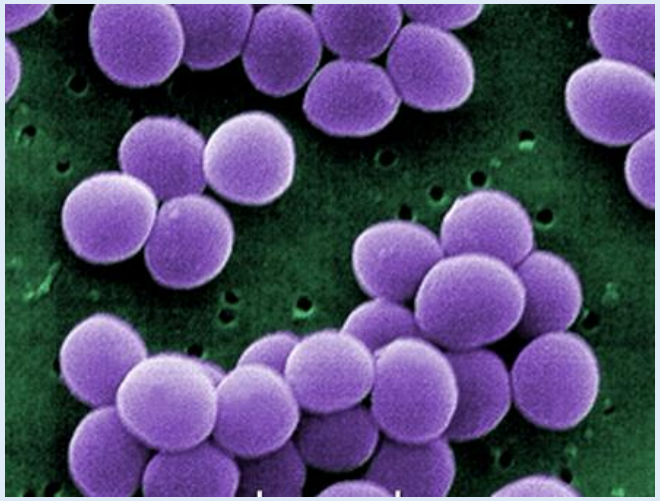
- Understand *Staphylococcus aureus* as the most common pathogen
- Become familiar with the diagnosis and management of
  - Diabetic foot osteomyelitis
  - Prosthetic joint infection
- Recognize the skeletal complications of injection drug use
- Review debates in antibiotic therapy
  - Role of Rifampin
  - IV vs PO
  - Duration of therapy

Learning objective

- Understand *Staphylococcus aureus* as the most common pathogen causing bone and joint infection

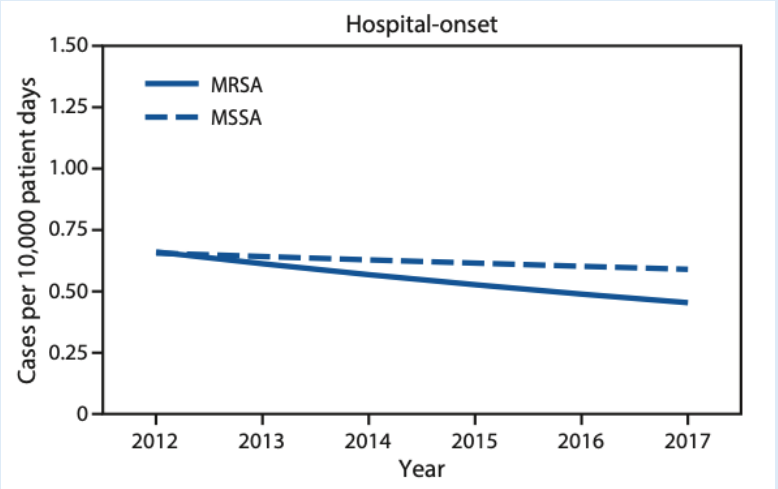
Staphylococci

- 75% of osteomyelitis is caused by staphylococci
- *S. aureus* - #1 pathogen
  - Hematogenous osteomyelitis
  - Device related infection
  - Opportunistic pathogen
- Antibiotic resistance
  - Methicillin resistant *S. aureus* (MRSA)
    - 50% in some regions
  - Vancomycin intermediate *S. aureus* (VISA)
  - Vancomycin resistant *S. aureus* (VRSA)



Staphylococcus aureus

- MRSA strain epidemiology
  - USA 100
    - Hospital-onset
  - USA 300
    - Community-onset
    - **Increased virulence and risk of metastatic infection**
- Reductions in invasive MRSA infection 2005-2012
  - Decline in Hospital-onset USA 100
- Progress has slowed



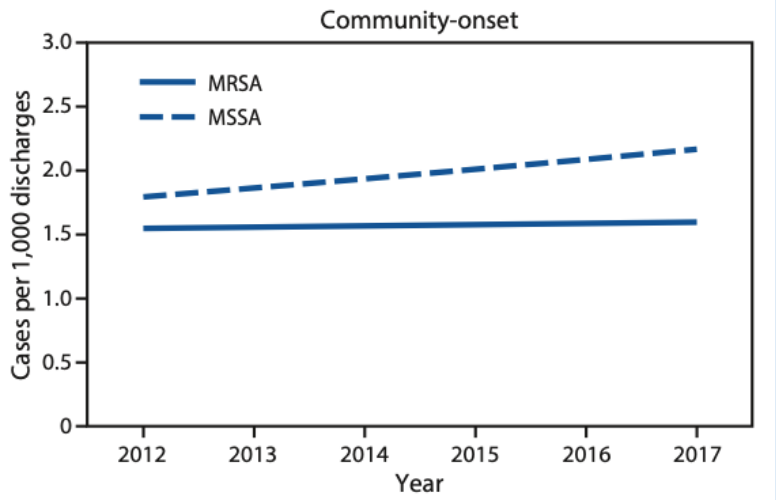


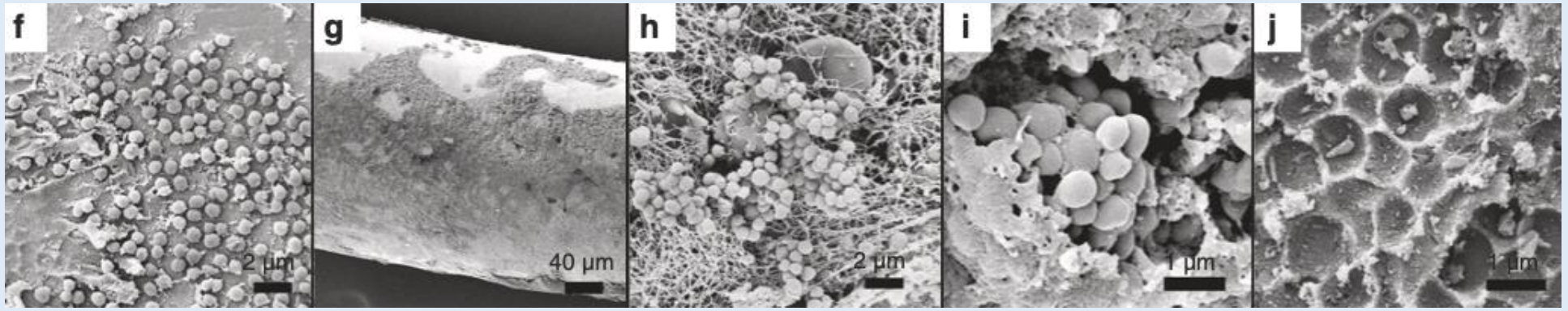
FIGURE 2. Adjusted* hospital-onset and community-onset rates of *Staphylococcus aureus* bloodstream infections — Premier and Cerner Hospitals, United States, 2012–2017

https://www.cdc.gov/mmwr

Staphylococcus aureus - biofilm

- Slow growing subpopulations of bacteria
  - Sessile bacteria in stationary growth phase
  - Distinct from planktonic bacteria
- Phenotypic diversity

- *S. aureus* is protected in biofilm
  - Resistant to environmental stress
  - Resistant to antibiotics
  - Resistant to host defenses
- **Formation within 14 days**



Source: EA Masters et al, www.nature.com

Learning objective

- Review the diagnosis and management of:
  - Diabetic foot osteomyelitis

Trends in the Epidemiology of Osteomyelitis

A Population-Based Study, 1969 to 2009

Investigation performed at the Departments of Health Sciences Research and Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota

TABLE IV Trends in Incidence of Osteomyelitis by Underlying Etiology or Location in Olmsted County (1969-2009)

	Time Period							
	1969-1979		1980-1989		1990-1999		2000-2009	
Etiology or Location	No.	Incidence Rate*	No.	Incidence Rate*	No.	Incidence Rate*	No.	Incidence Rate*
Diabetes mellitus-related	12	2.3 (1.0, 3.6)	31	4.4 (2.8, 6.0)	83	10.5 (8.2, 12.9)	80	7.6 (5.9, 9.2)
Hematogenous	16	1.4 (0.7, 2.2)	39	4.4 (2.9, 5.9)	38	3.6 (2.4, 4.8)	50	4.2 (3.0, 5.4)
Contiguous	50	6.0 (4.2, 7.8)	55	6.6 (4.7, 8.4)	86	9.7 (7.5, 11.8)	107	9.1 (7.4, 10.9)
Vertebral	3	0.5 (0, 1.0)	10	1.5 (0.5, 2.6)	21	2.5 (1.4, 3.6)	51	4.7 (3.4, 6.0)

*Age and sex-adjusted incidence rates per 100,000 person-years; values in parentheses are the 95% CI.

- 760 patients over 41 years
- Mean age increased from 38→57
- Overall incidence of osteomyelitis increased over time
- **Diabetes as a contributing factor doubled (13%→29%)**

Source: J Bone and Joint Surg Am. 2015

Cost of diabetic foot ulcers in the US

- 20% of patients with diabetes will develop foot ulcers
  - 25% may develop contiguous osteomyelitis
  - Risk of amputation is high
  - Ulcer + amputation is associated with 40-50% mortality at 5 yrs
- 2014: Annual cost in the US: $9-13 billion

Source: Rice JB, et al, Diabetes Care, 2014 and Butalia S et al. JAMA, 2008

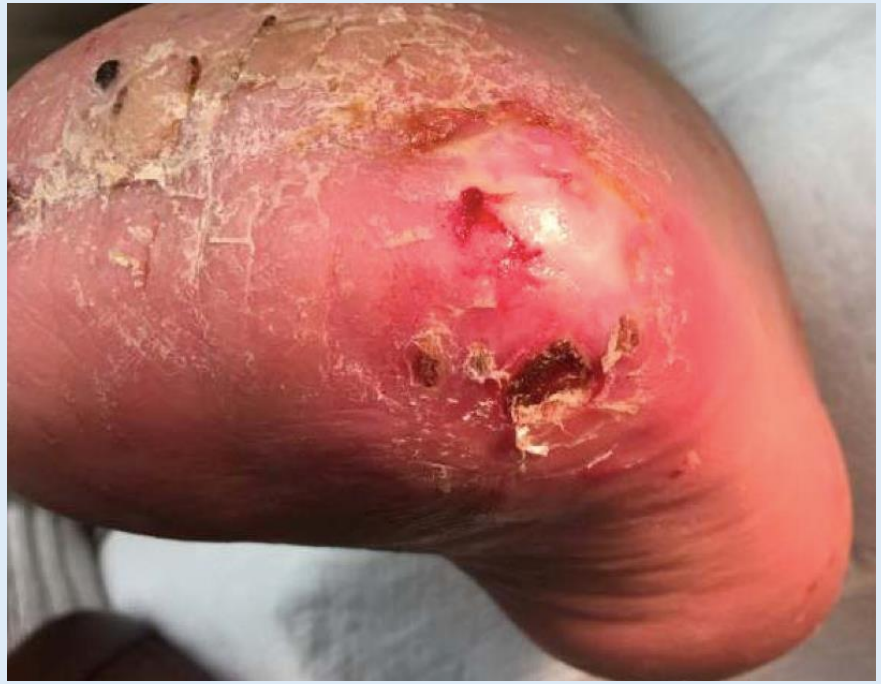
Patient 1

- A 63-year-old male presents to the ED with left foot swelling and an ulcer that has increased in size over the past 3 weeks
- He has a PMH of diabetes mellitus and peripheral arterial disease
- 2 months prior he was admitted with gangrene of the L 2nd and 3rd toes
- He underwent a lower extremity angioplasty + stent placement followed by transmetatarsal amputation at that time
- He is non-toxic appearing, 99.7
- L foot pulses are palpable
- ESR is 81 and CRP is 5

What does he have?

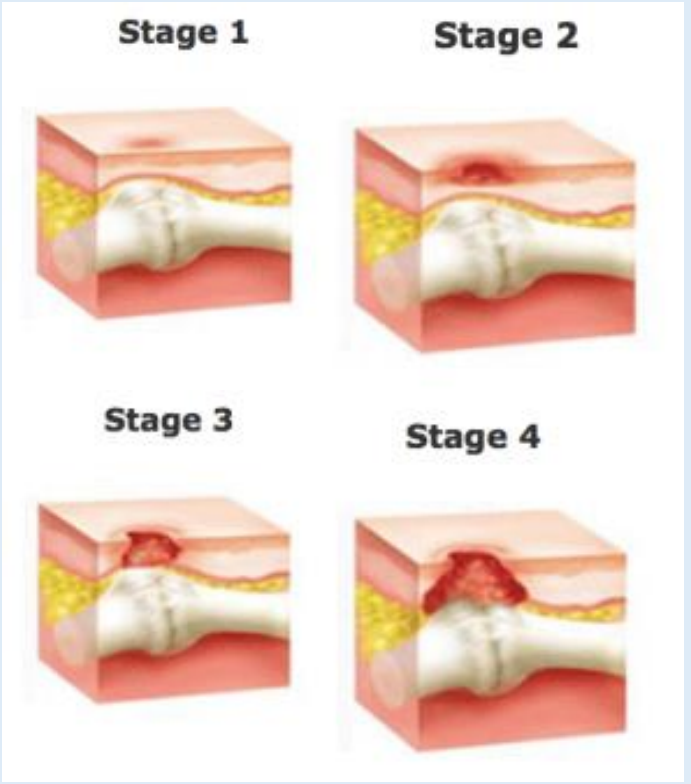
How do we prove it?

How should he be treated?



Diabetic foot infection – osteomyelitis diagnosis

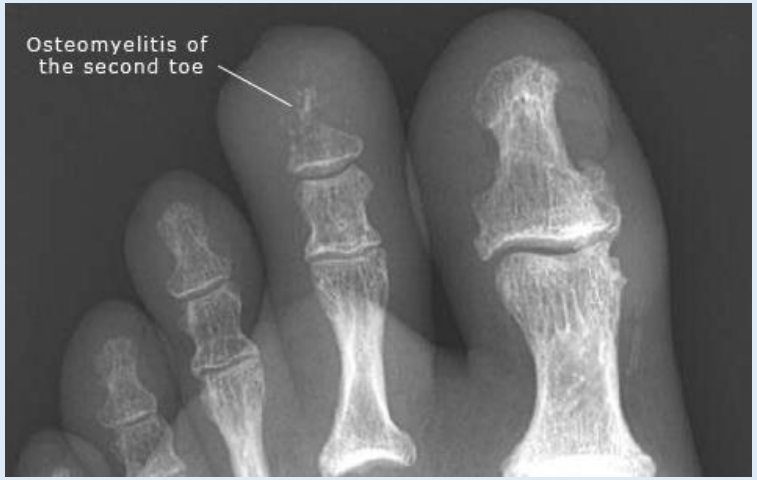
- Neuropathy + vascular insufficiency + hyperglycemia + minor trauma
  - → skin ulcer →contiguous osteomyelitis
- Suspect osteomyelitis in all foot ulcers
  - Especially if the ulcer is
    - Longstanding (>6 weeks)
    - Over a prominent bone
- Clinical examination
  - Ulcer surface area >2 cm^2 – high PPV
  - Positive probe to bone test – high PPV

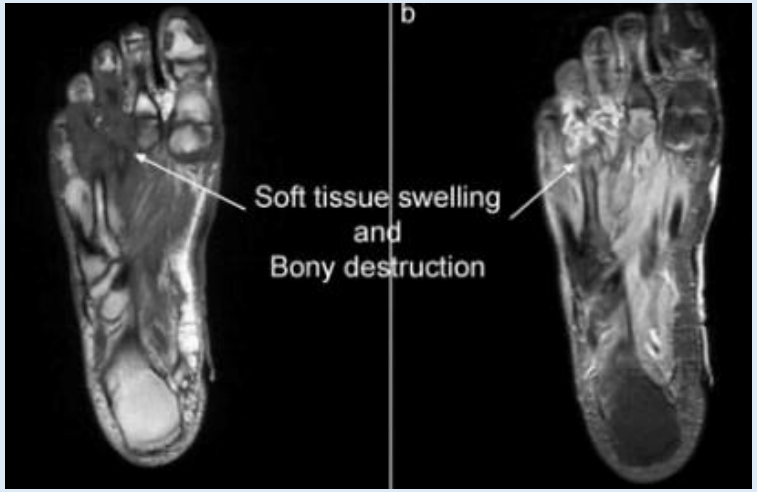


Lipsky B et al, CID, 2012

Diabetic foot infection – osteomyelitis diagnosis

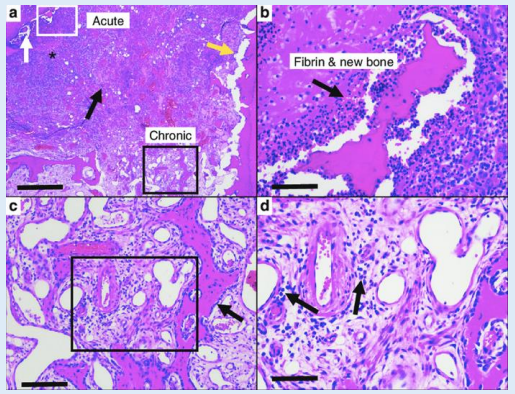
- ESR and CRP are often elevated
- WBC is often normal
- Imaging
  - Conventional radiograph
  - Cross sectional
    - Magnetic resonance imaging (MRI)
    - Computed tomography (CT)
  - Other
    - Nuclear medicine studies
    - FDG PET scan





Diabetic foot infection – osteomyelitis diagnosis

- Pathogen identification
  - **Withhold antibiotics unless signs of systemic illness**
  - *S. aureus* and streptococci are often identified
  - Contiguous infection may be polymicrobic
  - Bone biopsy via surgical sampling or needle aspiration
  - *S*uperficial culture (swab) unreliable
    - *S. aureus* correlates more frequently with deep cultures
- Histopathology
  - Sent from the proximal bone margin



Diabetic foot osteomyelitis management

- Indications for surgery
  - Poor arterial blood supply
  - Infected, devitalized bone, joint space, soft tissue
  - Compartment syndrome
  - Sepsis
  - Prosthetic heart valves
- Antibiotic therapy
  - Diabetic foot infection IDSA guideline (2012)
  - International working group on the diabetic foot (IWGDF) (2019)
  - Empiric coverage → tailor to culture results
    - Coverage for *Pseudomonas aeruginosa* is usually unnecessary
    - Consider coverage for MRSA
  - Route?
    - Initial parenteral therapy may be beneficial but oral therapy likely adequate
  - Duration?
    - Based on degree of surgical resection and severity of infection

Alllahhabdadi , Diiab Foot Ankle, 2016; IWGDFguidelines.org 2019; IDSA guideline for diabetic foot infection, 2012

Six-Week Versus Twelve-Week Antibiotic Therapy for Nonsurgically Treated Diabetic Foot Osteomyelitis: A Multicenter Open-Label Controlled Randomized Study

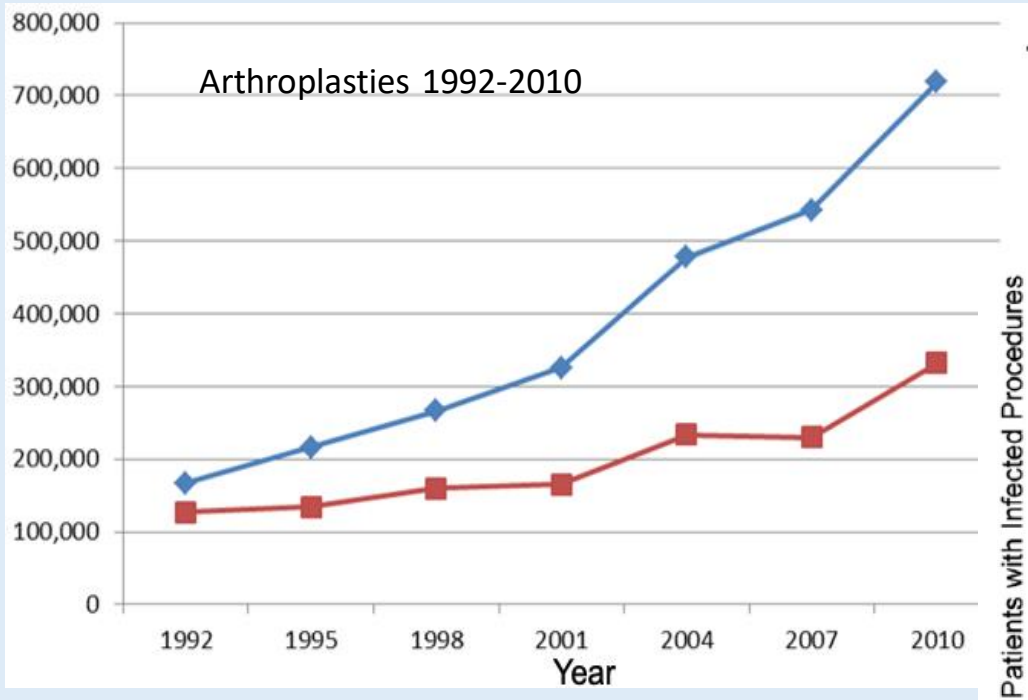
- Prospective, randomized trial of 40 patients
- All patients had positive bone biopsy cultures
- Patients with vascular compromise and/or gangrene were excluded
- Compared 6 vs 12 weeks of antibiotic therapy without surgical intervention
- 66% of patients were in remission at 12 months
  - 60% in 6 week arm
  - 70% in 12 week arm
  - p=0.50

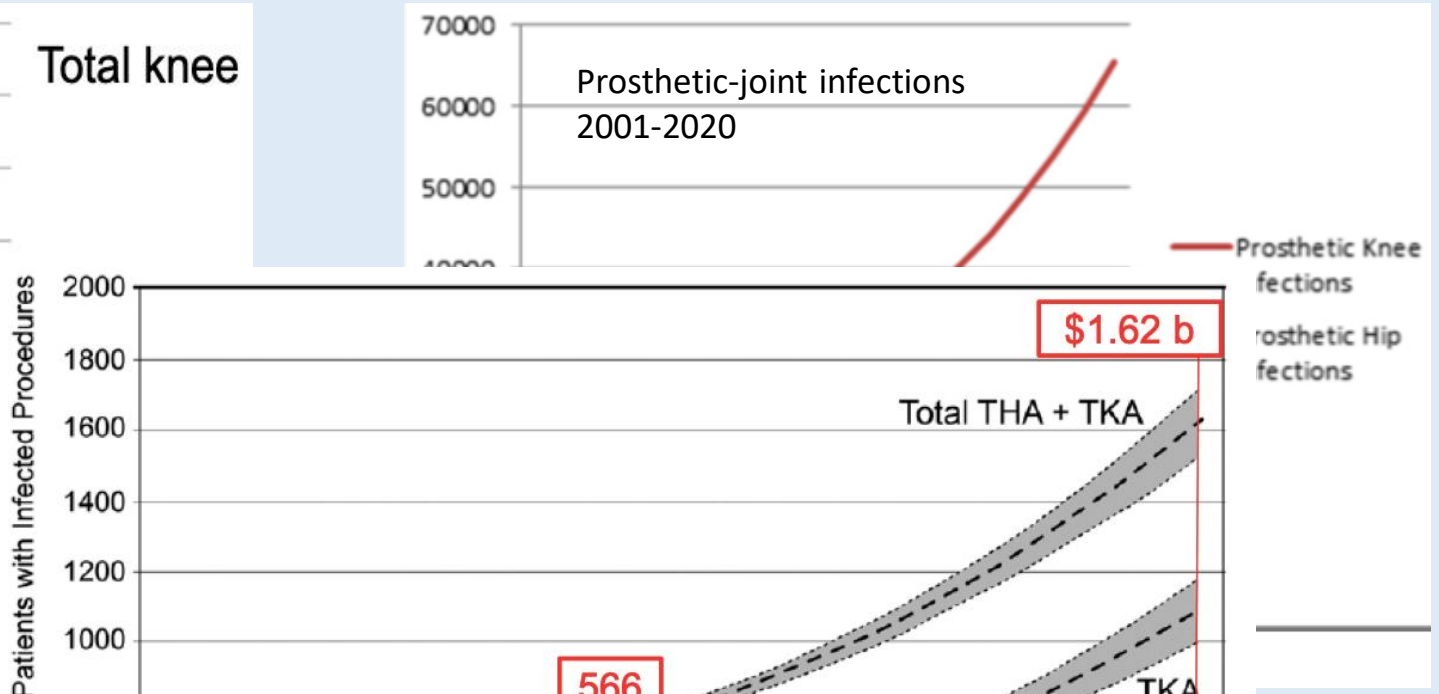
Tone A, et al. Diabetes Care, 2015

Learning objective

- Review the diagnosis and management of:
  - Prosthetic joint infection

Epidemiology of Prosthetic joint infection





THR
2030: 635,000→ 2060: 1.2 million
TKR
2030 1.3 million→ 2060: 2.6 million

Source: CDC.org and Kutz et al, J of Arthroplasty, 2012

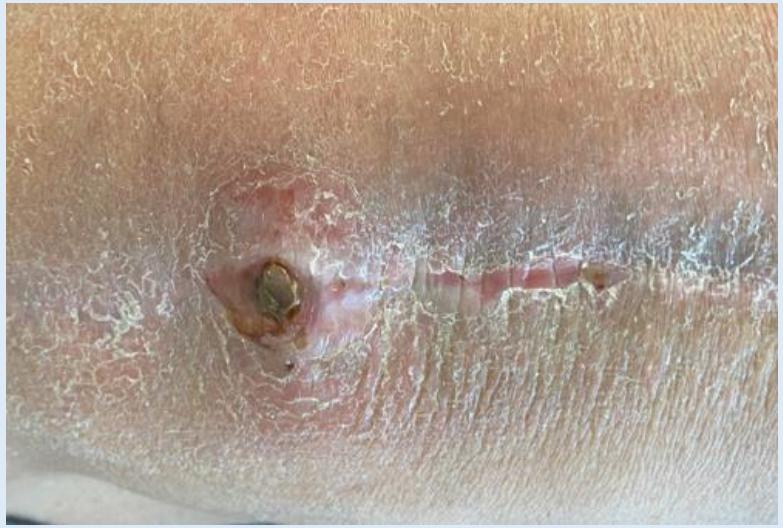
Patient 2

- A 72-year-old female with PMH of DJD, Chron's disease (prior adalimumab)
- She is s/p left THA 4 years ago and left hip revision for mechanical loosening 8 weeks ago (OR cultures negative)
- She presents with hip pain, new swelling over the hip incision and formation of a blister x 4 days
- She is non-toxic appearing, T 100.5

What does she have?

How do we prove it?

How should she be treated?

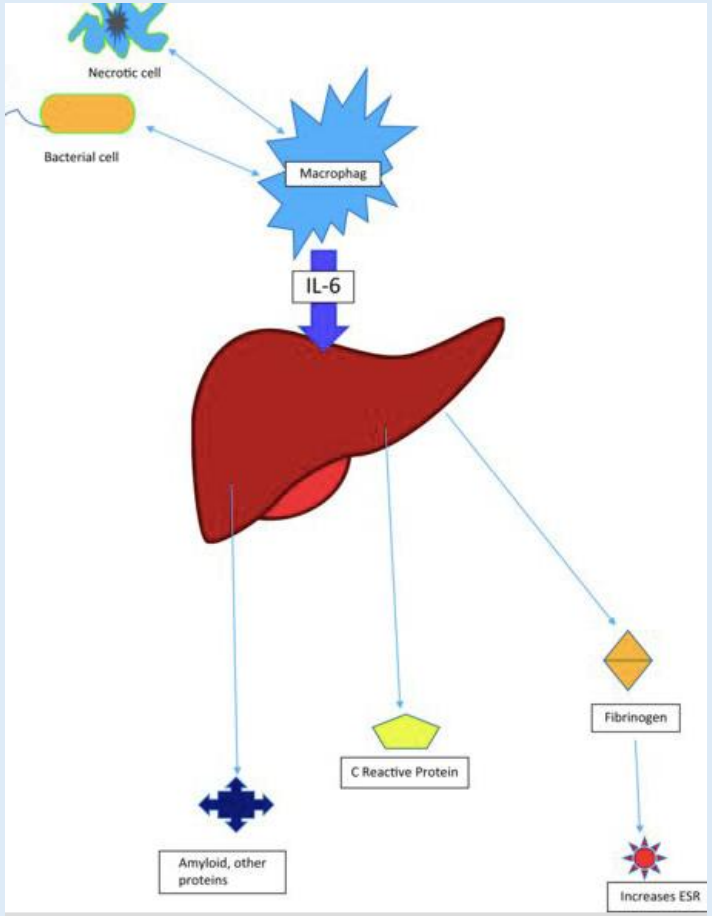


Criteria for diagnosis of prosthetic joint infection

	2011		2013		2018	
	Musculoskeletal Infection Society[6]		Infectious Diseases Society of America[7]		International Consensus[8]	
	Definitive evidence	Supportive evidence	Definitive evidence	Supportive evidence	Definitive evidence	Supportive evidence
Sinus tract communicating with the prosthesis	x		x		x	
Identical microorganism isolated from ≥2 cultures	x		x		x	
Purulence surrounding the prosthesis		x	x			
Acute inflammation of periprosthetic tissue		x		x		x
A single culture with any microorganism		x				x
A single culture with a virulent microorganism				x		
Elevated synovial fluid leukocyte count		x				x
Elevated synovial fluid neutrophil percentage		x				x
Elevated serum ESR and CRP		x				x

Biomarkers for PJI

- Serum biomarkers
  - ESR and CRP
  - Interleukin-6
    - Precursor to CRP
- Synovial fluid biomarkers
  - CRP, Interleukin-6, Alpha-defensin
- Emerging biomarkers
  - Early immune response
- The ideal biomarker
  - Reliable and reproducible
  - Sensitive and specific
  - Provide risk stratification
  - Cost effective



Pathways for the production of acute phase reactants.

NEJM 2005

Pathogen identification – prosthetic joint infection

- Gold standard = culture for aerobic and anaerobic organisms
  - Synovial fluid aspiration
  - 3-6 periprosthetic tissue samples
  - Sonication of the prosthesis
- Culture-negative infection
  - 7-19%
  - Antibiotic exposure
  - Fastidious organisms
  - Atypical pathogen

- **Withhold antibiotics for at least 2 weeks unless systemically ill**

Molecular diagnostics for PJI

- Goal: increase diagnostic yield in comparison to traditional culture
- Polymerase chain reaction (PCR)
  - 16s rRNA gene primers
  - Specific multiplex primers
- Next-generation sequencing (direct from specimen)
  - Can potentially identify any pathogen and resistance genes
  - Shotgun metagenomic sequencing
  - 16S amplicon targeted NGS
  - Challenges: contamination/specificity, reference data base, cost

Surgical management - PJI

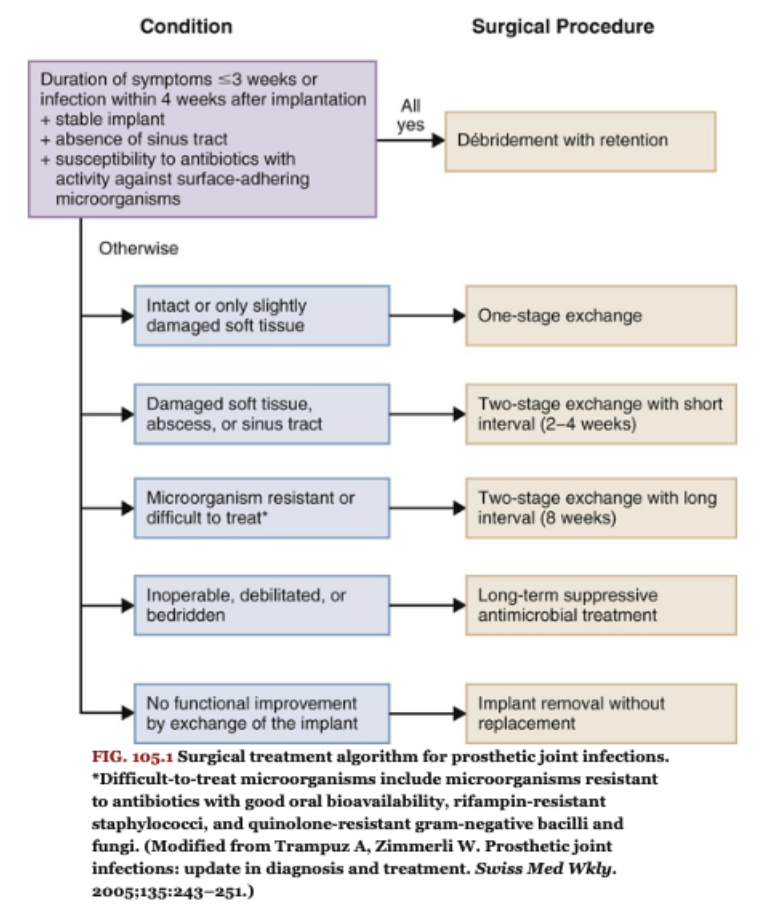


FIG. 105.1 Surgical treatment algorithm for prosthetic joint infections. *Difficult-to-treat microorganisms include microorganisms resistant to antibiotics with good oral bioavailability, rifampin-resistant staphylococci, and quinolone-resistant gram-negative bacilli and fungi. (Modified from Trampuz A, Zimmerli W. Prosthetic joint infections: update in diagnosis and treatment. *Swiss Med Wkly.* 2005;135:243–251.)

Source: Swiss Med Weekly, 2005

Questions

- Time interval from index surgery to DAIR (Debridement, Antibiotics, Implant Retention)?
- Single stage vs two-stage revision?
- Role of antibiotic laden cement?

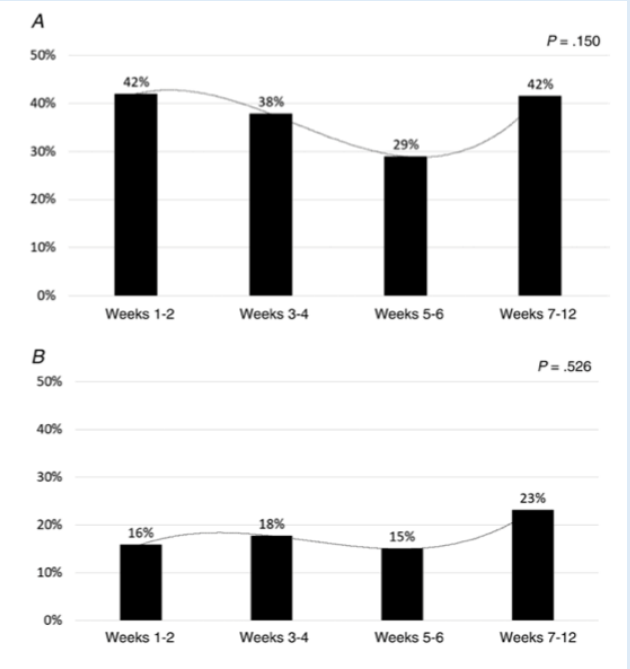
Debridement, Antibiotics, and Implant Retention Is a Viable Treatment Option for Early Periprosthetic Joint Infection Presenting More Than 4 Weeks After Index Arthroplasty

Claudia A M Löwik, Javad Parvizi, Paul C Jutte, Wierd P Zijlstra, Bas A S Knobben, Chi Xu, Karan Goswami, Katherine A Belden, Ricardo Sousa, André Carvalho, Juan Carlos Martínez-Pastor, Alex Soriano, Marjan Wouthuyzen-Bakker ✉

- 769 patients from 4 countries with early PJI (<90 days)
- Treated with DAIR and followed for at least 1 year
- Time interval from index arthroplasty to DAIR did not predict treatment failure or implant retention

Conclusion:

- The development of biofilm is a variable process
- DAIR can be considered more than 4 weeks after index surgery



Clinical Infectious Diseases, 2019

Figure 1. Failure rates according to time interval from index arthroplasty to DAIR (n = 769). The definitions of treatment failure and implant failure are described in the Material and Methods section of the paper. *A*, Treatment failure. *B*, Implant failure. Abbreviation: DAIR, debridement, antibiotics, and implant retention.

Antibiotic therapy for PJI

Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America[a]

- Choice, route, duration?
- Retention of hardware
  - 2-6 weeks of IV antibiotic therapy in combination with Rifampin for *Staphylococcal* infection followed by 3-6 months of PO antibiotic suppression
- Removal of hardware
  - 4-6 weeks of pathogen specific IV or highly bioavailable PO antibiotic therapy
  - RCT 2019 - 123 patients 4 vs 6 weeks of therapy after implant removal with no difference in remission rate at 2 yrs

- Recognize the skeletal complications of injection drug use

Infectious skeletal complications in injection drug use

- Pathogens from the skin or injected substance gain entrance into the body if nonsterile technique is used
- Hematogenous seeding (heart valves, joints, bones, central nervous system)
  - Vertebrae is the #1 site of hematogenous seeding
  - Unusual sites of infection – sternoclavicular, sternochondral, sacroiliac, pubic symphysis
- Endocarditis – 33% in vertebral infection
- *S. aureus* is the primary pathogen including high rates of MRSA
- Other pathogens include
  - Streptococci
  - Oral flora
  - Candida species
  - Pseudomonas aeruginosa
  - Enterobacteriaceae
  - Molds
  - Mycobacterial infection
  - Polymicrobic infection

Source: Yuschk E, et al. Cureus 2019 and Bauer D, et al. International Orthop, 2017

Opioid use and increased rates of invasive infection

143. Opioid Use and Hospitalizations for Endocarditis, Osteomyelitis, and Central Nervous System Abscess among Adults — New York City, 2001–2014

Chaorui Huang, MD, PhD, MS; David Lucero, PhD; Denise Paone, EdD; Ellenie Tuazon, MPH and Demetre Daskalakis, MD; New York City Department of Health and Mental Hygiene, New York, New York

Table 1. Log-binomial Regression Analysis Stratified by Age Groups to Evaluate the Association between Opioid Use and Hospitalizations for Endocarditis, Osteomyelitis, and Central Nervous System Abscesses among Adults — New York City, 2001–2014

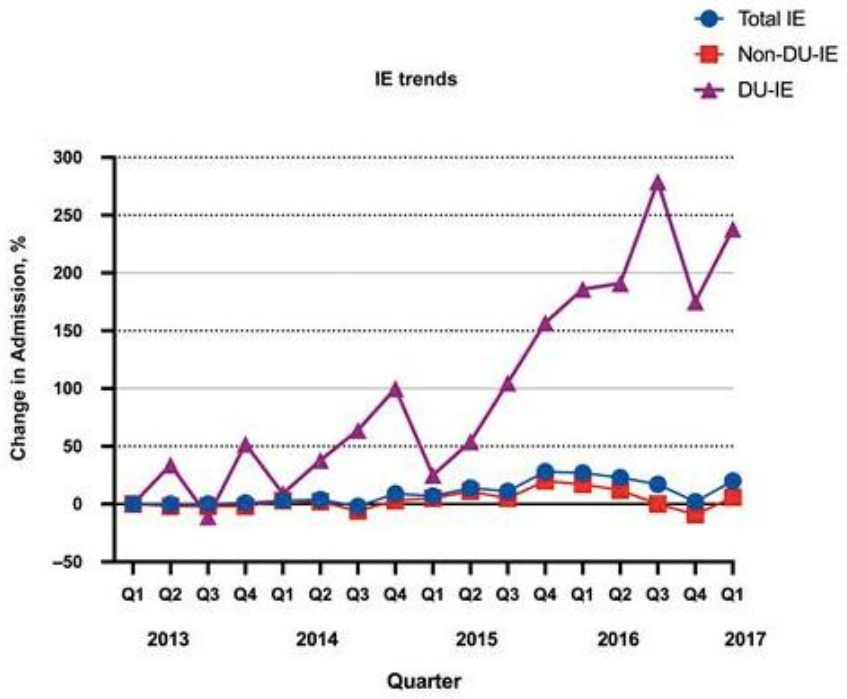
Age Group (yr)*	Risk Ratio (95% CI)		
	Endocarditis	Osteomyelitis	CNS Abscess
Overall (≥18)	2.6 (2.5–2.7)	1.1 (1.1–1.1)	1.9 (1.8–2.1)
18–44	4.2 (3.9–4.5)	0.8 (0.7–0.8)	1.5 (1.3–1.8)
45–64	1.9 (1.8–2.0)	1.2 (1.1–1.2)	2.0 (1.8–2.3)
65–84	0.8 (0.6–1.1)	1.2 (1.1–1.3)	2.0 (1.3–3.2)
≥85	1.7 (0.4–6.8)	0.8 (0.2–2.4)	results not reliable

CNS: Central Nervous System; CI: Confidence Interval

*Overall rates are corrected by age, sex, race, and borough, whereas age group-specific rates are corrected by sex, race, and borough

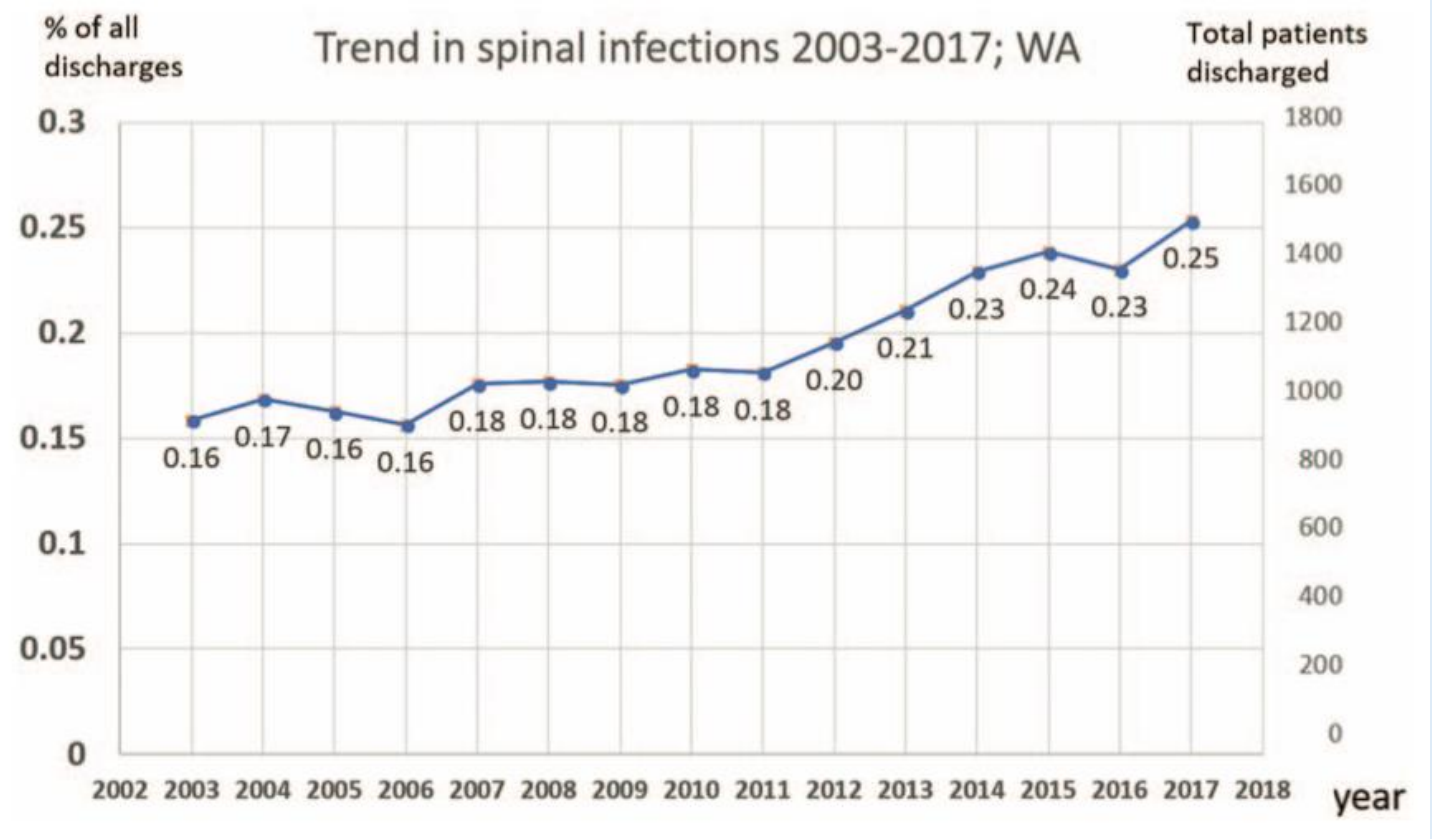
Percentage change in PA infectious endocarditis admissions over time (2013-2017)

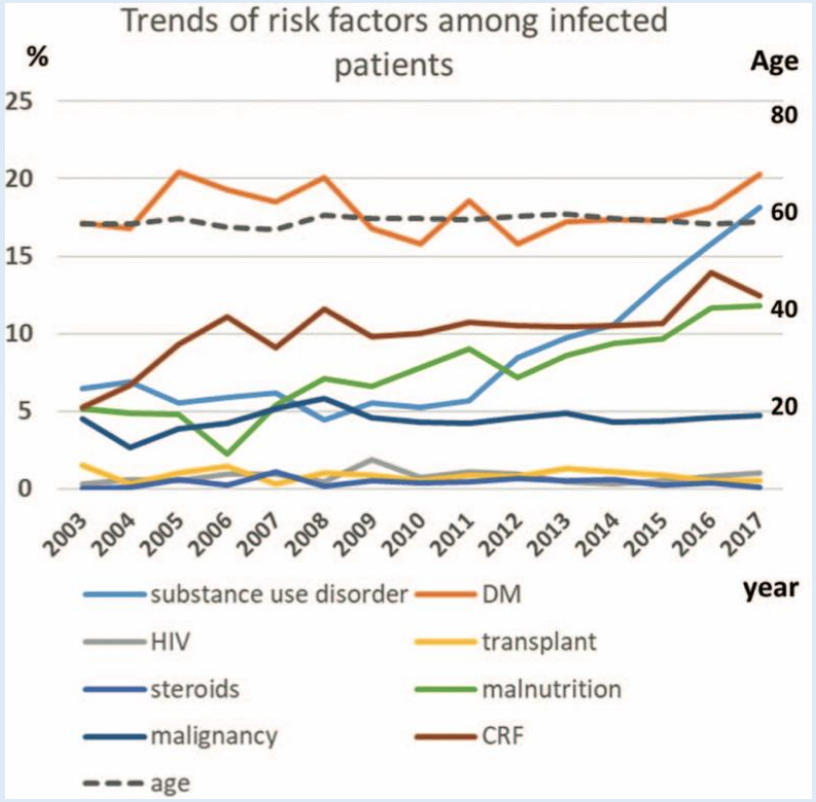
Figure 1.



Source: OFID, 2019 and CID, 2019

Opioid use and increased rates of invasive infection

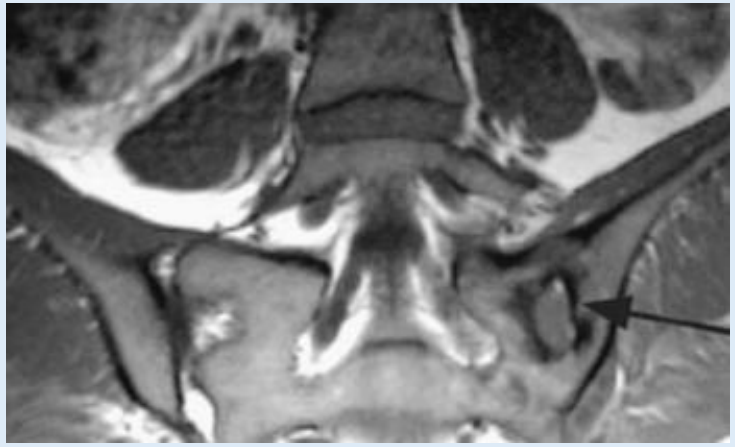




Source: SPINE 2018 Volume 44, pp 291–297

Patient 3

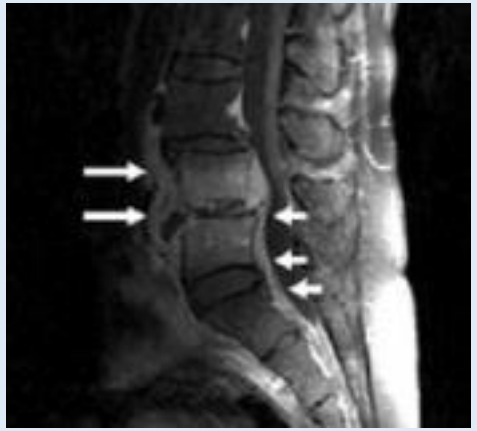
- A 30-year-old female with active IVDU presents with a 1 week history of low back, L buttock, leg and thigh pain, fevers and malaise
- On exam she is toxic and lethargic
- T 101.7, 120, 106/57, 22
- Systolic murmur
- Scars over both forearms
- Point tenderness over the L spine and L buttock
- L leg weakness

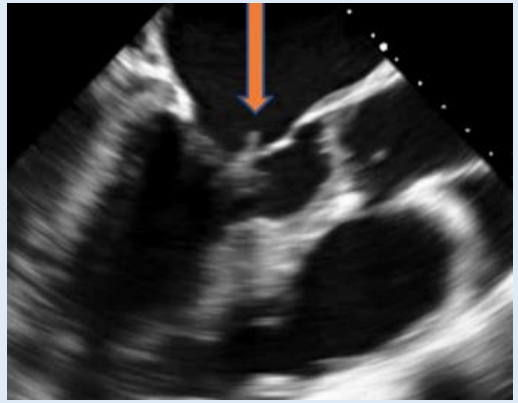


What does she have?

How do we prove it?

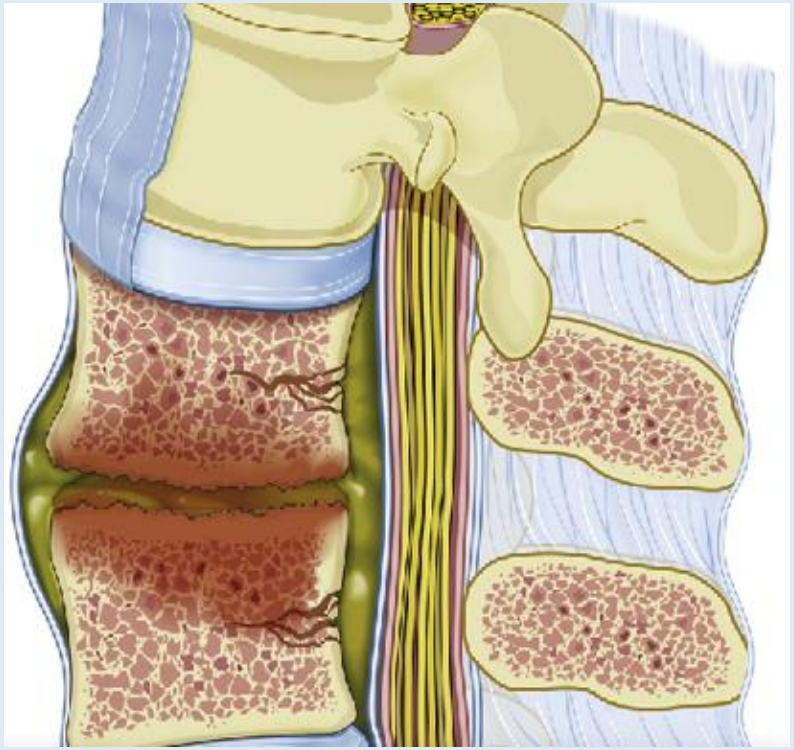
How should she be treated?





Vertebral osteomyelitis

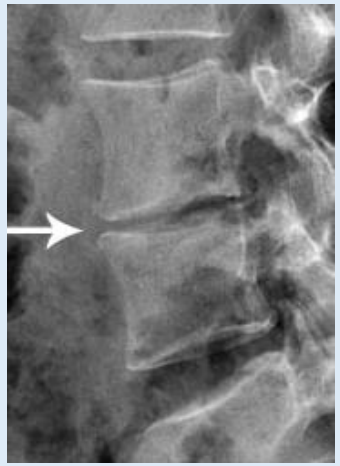
- Discitis
  - Primary infected disc space
- Spondylodiscitis
  - involvement of adjacent vertebral bodies
- Abscess
  - Retropharyngeal
  - Mediastinal
  - Iliopsoas
  - **Epidural**
    - **Meningitis**
    - **Spinal cord compression**
- Symptoms
  - Back pain 85%
  - Fever 30-60%
  - Neurologic impairment 33%

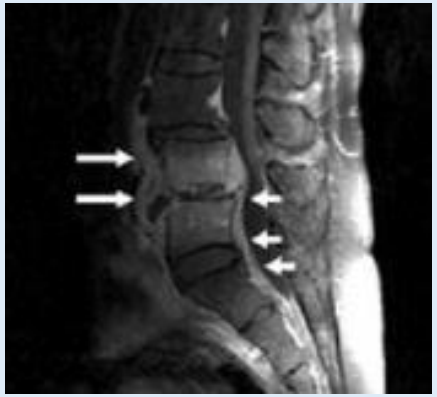


Source: Inf Dis Clin N Am 2017

Vertebral osteomyelitis

- Diagnosis
  - **Hold antibiotics unless systemically ill or neurologically compromised**
  - Blood cultures – positive in 60%
    - *S. aureus* bacteremia precludes the need for biopsy
  - ESR/CRP
  - Imaging
    - Conventional radiograph
    - MRI is the test of choice
    - **Echocardiography TTE vs TEE**
  - Biopsy or abscess drainage culture
    - Aerobic, anaerobic and fungal cultures
    - Consider cultures for mycobacteria and Brucella species
    - Histopathology
  - Negative cultures
    - Prior antibiotic exposure
    - Atypical infection
    - Sampling error → pursue a second sample if the first is negative





Vertebral osteomyelitis

- Management
  - Surgical indications
    - Abscess drainage
    - Spinal instability, neurologic compromise
    - Failure on antibiotics alone
    - Spinal implant infection – remove if possible
  - Antibiotic treatment - Native vertebral osteomyelitis IDSA guideline (2015)
    - 6 weeks of targeted parenteral or highly bioavailable oral therapy
    - Unknown optimal duration
  - Follow up
    - Clinical improvement at 4 weeks
    - 25% improvement in ESR and CRP at 4-8 weeks
    - MRI is less helpful
    - Fusion between infected vertebrae can take 1-2 years
  - **Risk factors for recurrence**
    - **Undrained abscess, endocarditis, end-stage renal disease, MRSA, immunosuppression**

Challenges in antibiotic treatment in patients who use drugs

- Patients may leave the hospital against medical advice (AMA) or are discharged for unsafe behavior
  - Higher readmission rates
  - Increased 30-day mortality for patients leaving AMA
- Enrollment in OPAT programs is impractical
- Medication adherence remains a challenge
  - ?Shortened duration
  - ?Oral therapy
  - ?Long half-life parenteral antibiotics (Dalbavancin, Oritavancin)

Sources: PLOS 1, 2015 and J Gen Int Med 2010

Dalbavancin: lipoglycopeptide antibiotic with a long half-life allowing for weekly dosing

Dalbavancin as Secondary Therapy for Serious *Staphylococcus aureus* Infections in a Vulnerable Patient Population

Bryson-Cahn C, et al., OFID, 2019

- 32 IVDU patients
  - Treated for *S. aureus* infection, 88% MRSA
  - 14 osteomyelitis, 9 endocarditis
  - Most patient received a single injection
  - 56% - clinical cure, 13% clinical failure, 31% lost to follow up

Real-world experience with dalbavancin therapy in gram-positive skin and soft tissue infection, bone and joint infection

Tobudic S et al., Infection, 2019

- 72 patients
  - 20 - osteomyelitis (65% clinical response, 46% with surgical intervention)
  - 14 - vertebral osteomyelitis (50% clinical response)
  - 8 – PJI (75% clinical response, all with surgical intervention)
  - Average duration of therapy 8-12 weeks, majority sequential therapy

Learning objectives

- Review debates in antibiotic therapy for bone and joint infection:
  - Role of Rifampin
  - IV vs PO
  - Duration of therapy

Antibiotic bone penetration

Table 4. Pharmacokinetics of Oral Antibiotics[1,16,20,21]

Antibiotic	Serum level µg/mL[b] (Free drug)	% Bone Concentration	MIC90[c] MSSA	CLSI[d] Breakpoints *E. coli*
Amoxicillin (500mg[a])	5.5-7.5	3-31%	--	≤8
Amox/clav (875mg)	2.2-11.6	3-30%/1-14%	1	≤8/4
Cephalexin (500mg)	12-30	18%	4	≤2 (cefazolin)
Cefpodoxime (400mg)	4.5-7	15-30%	4	≤2

[a]milligram; [b]micrograms per milliliter; [c]minimum inhibitory concentration that inhibits 90% of isolates; [d]CLSI: Clinical Laboratory Standard Institute

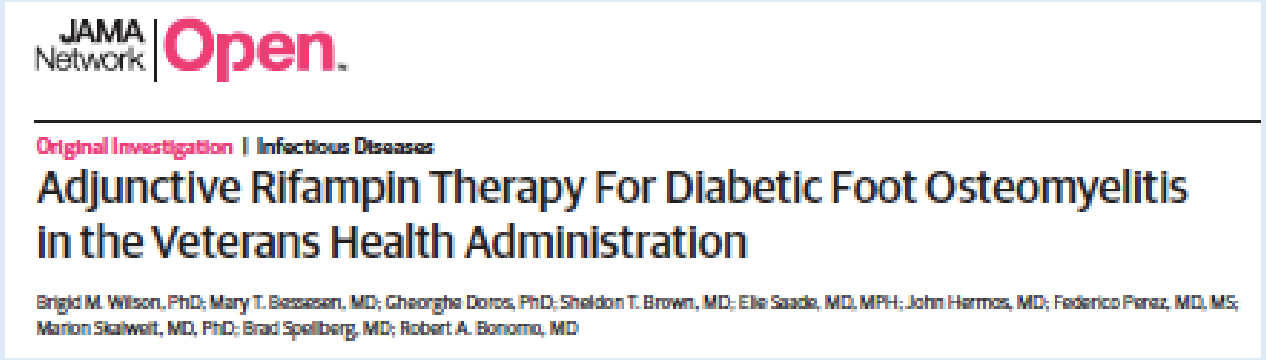
Table 5. Pharmacokinetics of Oral Antibiotics[1,16,20,21]

Antibiotic	Serum level µg/mL (Free drug)	% Bone Concentration	MIC90 MSSA	CLSI Breakpoints *E. coli*
Ciprofloxacin (750mg)	4.3	27-48%	1	≤1
TMP-SMX (160mg)	1.72	50%/15%	2/38	≤2/38
Linezolid (600mg)	11-21.1	40-50%	4	--
Clindamycin (600mg)	7.5	40-67%	0.5	--
Doxycycline (100mg)	2.6	2-86%	4	≤4

Source: Landersdorfer C and Bullita J, Clin Pharmacokinet 2009
CLSI, 2018

Rifampin – implant related infection

- Clinical evidence to support its use in implant related infection?
  - Zimmerli. JAMA. 1998 - staphylococcal infection
    - Ciprofloxacin + Rifampin vs Ciprofloxacin + placebo
    - 100% cure in the Rifampin group vs 58% cure in placebo group (p=0.02)
  - Lora-Tamayo, CID. 2013 - multicenter study of *S. aureus* PJI
    - Rifampin was an independent predictor of treatment success in a multivariate analysis
- How to use it? - Combination drug
  - Rifampin (inducer of cytochrome P450) lowers serum levels of
    - Clindamycin, Fusidic acid, Moxifloxacin, Doxycycline, Linezolid, Trimethoprim-sulfamethoxazole
  - Successful outcomes in staphylococcal PJI reported with:
    - 78% cure - Clindamycin (600 mg TID) + Rifampin (450mg BID)
      - Leijtens et al. *BMC Inf Dis* 2017
    - 89% cure - Moxifloxacin (400mg QD) + Rifampin (450mg BID)
      - Wouthuyzen-Bakker et al. *Int J Antim Ag* 2018
  - BID dosing may diminish drug interactions
- Rifabutin/Rifapentine?



- What are the amputation and mortality outcomes of patients treated with and without adjunctive Rifampin for diabetic foot osteomyelitis?
- 6174 veterans with diabetic foot osteomyelitis
- Combined endpoint of mortality or amputation
  - Significant difference found in those treated with the early initiation of Rifampin (26.9%) vs those without (37%), p=0.02
- **Investigation of Rifampin to Reduce Pedal Amputations for Osteomyelitis in Diabetics (VA INTREPID)-enrolling now**

Route of antibiotic therapy for osteomyelitis

- Goals of IV therapy:
  - Quickly obtain ideal plasma concentrations of drug
  - Beneficial early in infection
- Extended IV therapy:
  - It may take 3-6 weeks for infected bone to revascularize
  - Cure rates of 67-90% reported in randomized controlled trials
- Intravascular catheter - can be associated with infection and thromboembolic disease
- Oral antibiotic therapy
  - Less invasive for patients, lowers cost, decreases hospital length of stay
- Prolonged antibiotic therapy (IV/PO)
  - Antimicrobial resistance
  - Toxicity

ORIGINAL ARTICLE

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., Martin A. McNally, F.R.C.S.(Orth.), Bridget L. Atkins, F.R.C.P., Benjamin A. Lipsky, M.D., Harriet C. Hughes, M.A.(Cantab.), Deepa Bose, F.R.C.S., Michelle Kümin, Ph.D., Claire Scarborough, M.R.C.P., Philippa C. Matthews, D.Phil., et al., for the OVIVA Trial Collaborators*

- Comparison of standard parenteral therapy with an early switch to oral therapy
- 1,054 patients from 26 UK centers
  - Majority had *Staphylococcal* infection (bacteremia excluded)
    - 10% MRSA
  - 60% involved hardware
- Primary endpoint was treatment failure at one year
- Extended therapy was allowed after initial six week course
- Adjunctive rifampin was used in 41% of IV regimens and 55% of PO regimens
- Treatment failure occurred in 14.6% of parenteral regimens and 13.2 % of PO regimens
- **Oral therapy was found to be non-inferior to parenteral therapy**
  - Associated with decreased length of stay
  - No significant difference in serious adverse events

NEJM Jan 2019

Intermediate switch from IV to PO therapy

- Can we consider intermediate course (2-3 weeks) of IV therapy followed by transition to highly bioavailable PO therapy?
- IV to PO conversion is a goal for antimicrobial stewardship programs in less severe infections

Role of early intravenous to oral antibiotic switch therapy in the management of prosthetic hip infection treated with one- or two-stage replacement

J Antimicrob Chemother 2011

Is switching to an oral antibiotic regimen safe after 2 weeks of intravenous treatment for primary bacterial vertebral osteomyelitis?

Flury et al, BM Inf Dis 2014

Duration of antibiotics for osteomyelitis

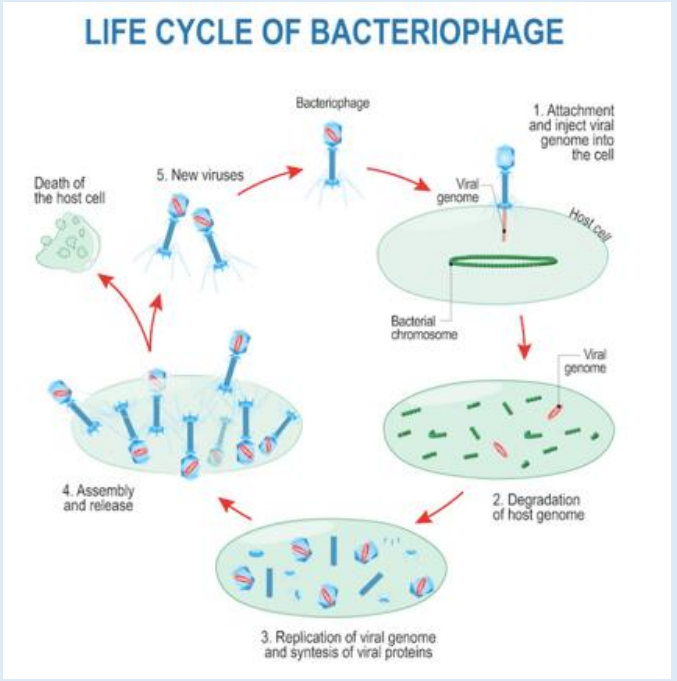
- Support for shorter duration therapy
  - Adequate surgical debridement
  - Diabetic foot osteomyelitis with good vascular supply, ?6 weeks
  - Prosthetic joint infection after implant removal, ?4 weeks
  - Acute hematogenous osteomyelitis (non-vertebral), ?2-3 weeks
- Groups at risk for failure
  - Recurrent infection – PJI requiring multiple surgeries
  - Vertebral osteomyelitis
    - Undrained abscess, endovascular infection, MRSA, immunosuppression
    - Lower recurrence rates in high risk patients treated with 6-8 weeks+
- Individualized duration
  - Acute vs chronic infection
  - Response to therapy

Phage therapy for bone and joint infection

Successful Treatment of Antibiotic-resistant, Poly-microbial Bone Infection With Bacteriophages and Antibiotics Combination

Clinical Infectious Diseases, Volume 69, Issue 11, 1 December 2019,

- Bacteriophages are natural viruses that infect and lyse their bacterial targets
- Highly specific, abundant in nature, well tolerated
- ?Potential
  - Treatment for MDR bacterial infection
  - Penetration of biofilm
- Questions
  - Dosing and administration schedule
  - Susceptibility with and without antibiotics
  - Patient selection
  - Workflow



Conclusions – bone and joint infection

- Early diagnosis is key
- Antibiotic selection, duration of therapy and surgical intervention should be individualized based on available guidelines
- The good news:
  - A majority of patients with osteomyelitis can be managed successfully and often cured
  - Collaborative, well designed studies are ongoing


Thank You