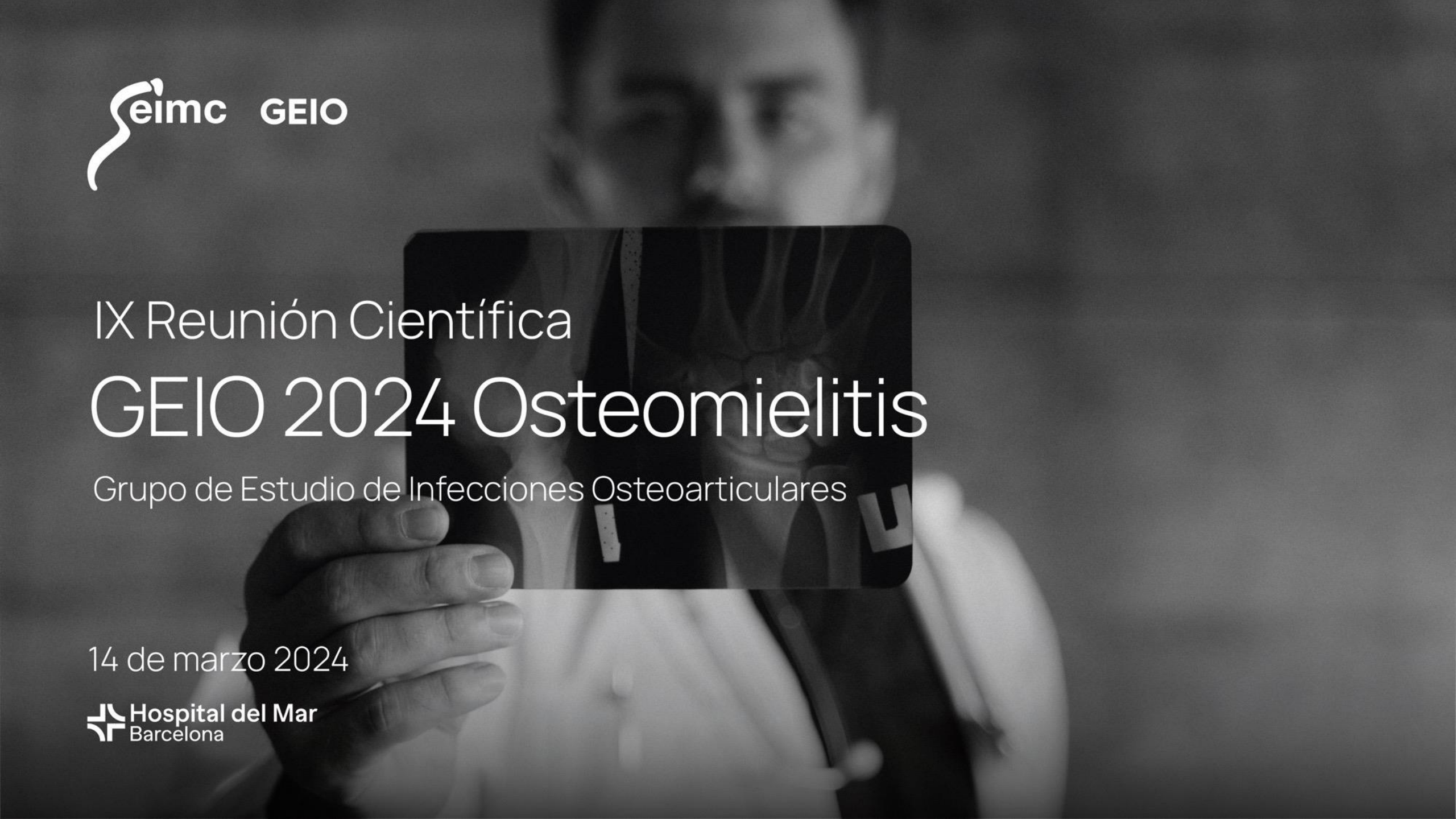


seimc GEIO

IX Reunión Científica

GEIO 2024 Osteomielitis

Grupo de Estudio de Infecciones Osteoarticulares

14 de marzo 2024

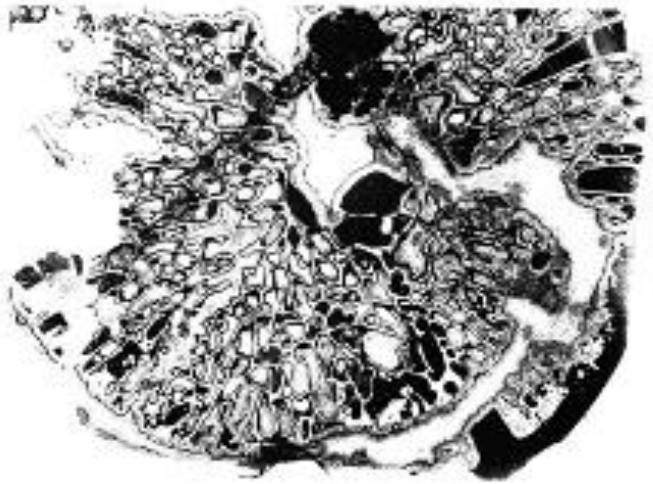
Hospital del Mar
Barcelona

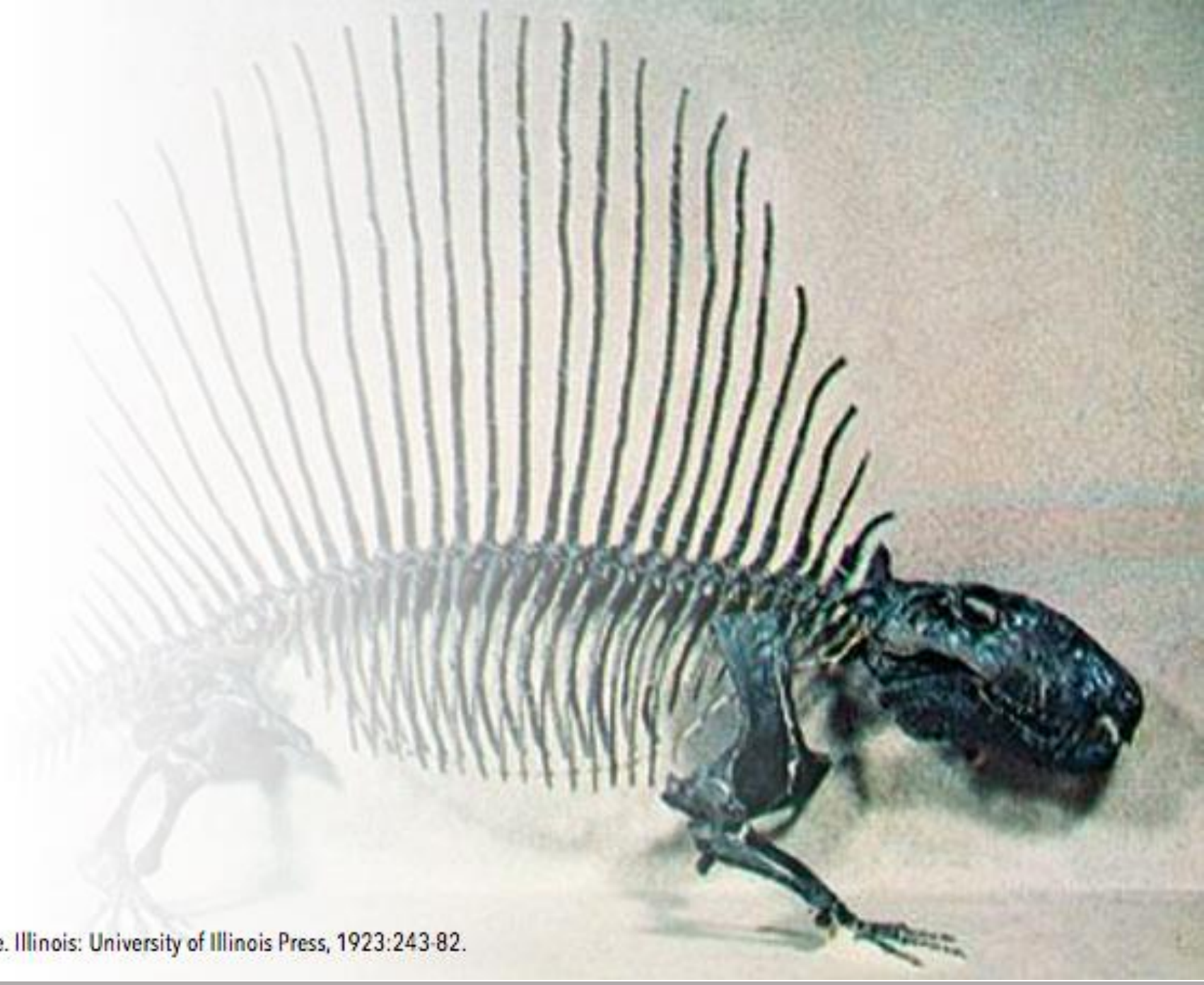
MESA 1: OSTEOMIELITIS DE HUESO LARGO

ESTADO ACTUAL EN EL MANEJO DE LA

OSTEOMIELITIS CRÓNICA DE HUESO LARGO EN ADULTOS

Dr. José Manuel Lomas Cabezas
Unidad Clínica de Enfermedades Infecciosas, Microbiología y Parasitología
Hospital Universitario Virgen del Rocío. Sevilla





Moodie RL. An introduction to the ancient evidences of disease. Illinois: University of Illinois Press, 1923:243-82.

Agenda

Revisión histórica

Patogénesis

Clasificación

Herramientas diagnósticas

Antibioterapia

sistémica/**local**

ASPECTOS HISTÓRICOS

Enfriamiento de los huesos (Albukasis; 936-1013)

Corrupción de los huesos (Avicena; 980-1037)

Abscessus in medulla (Bromfield; 1773)

Necrosis ósea (Gross; 1830)

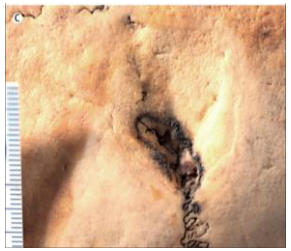
Carbunco del hueso (Pasteur; 1860)

Osteomielitis (Nélaton; 1844)

Breasted JH. *The Edwin Smith Surgical papyrus.* Chicago: The University of Chicago Press; 1930.
Nelaton A. Recherches Sur L'affection tuberculeuse des os. Thesis, Paris Faculty, 1836.

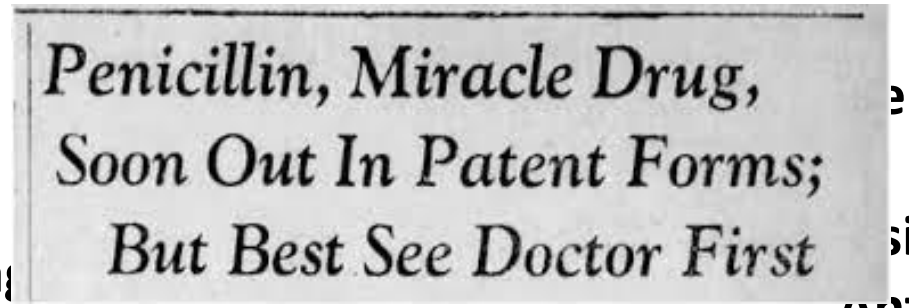
Manejo **médico** histórico de la osteomielitis

Antisépticos (ácido carbólico)
Lister, 1867



Bacteriófa
D'Herrelle, Albee, Paterson 1930

Sulfonamidas
1935, Domagk



1940

Streptomicina, 1944
Bacitracina, 1945
Tetraciclinas, 1948
Eritromicina, 1953
Penicilinas sintéticas, 1957
Cefalosporinas, 1957
Quinolonas, 1962

erapia antibiótica combinada
sis elevadas en CEC
Antibioterapia local
Uso de anticoagulantes
Gammaglobulina

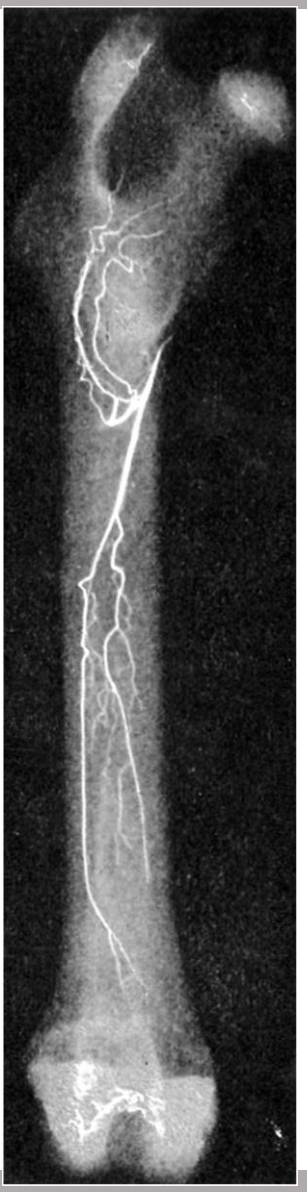
Chain E. Penicillin as a chemotherapeutic agent. Lancet 1940; 24:226–231

Manejo **quirúrgico** histórico de la osteomielitis

Erradicación del hueso necrótico
Avicena, siglo IX

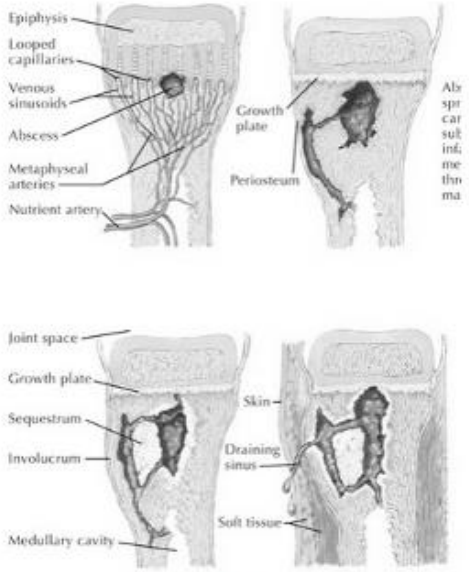
PATOGÉNESIS y CLASIFICACIÓN de la osteomielitis crónica

PATOGÉNESIS



Osteomielitis crónica de hueso largo

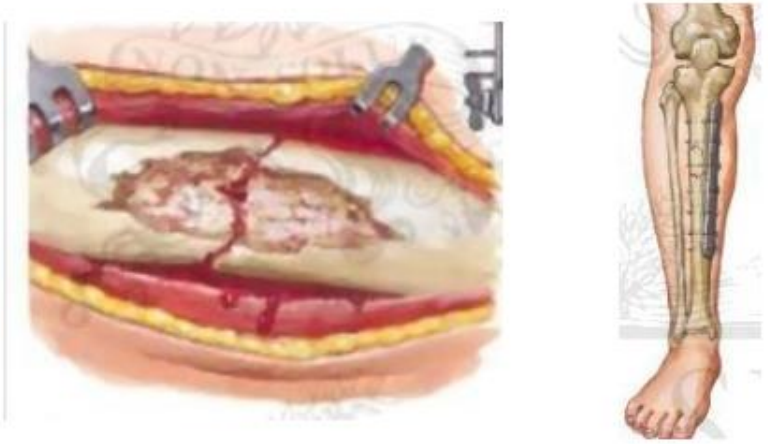
Hematógena



20%

Foco contiguo

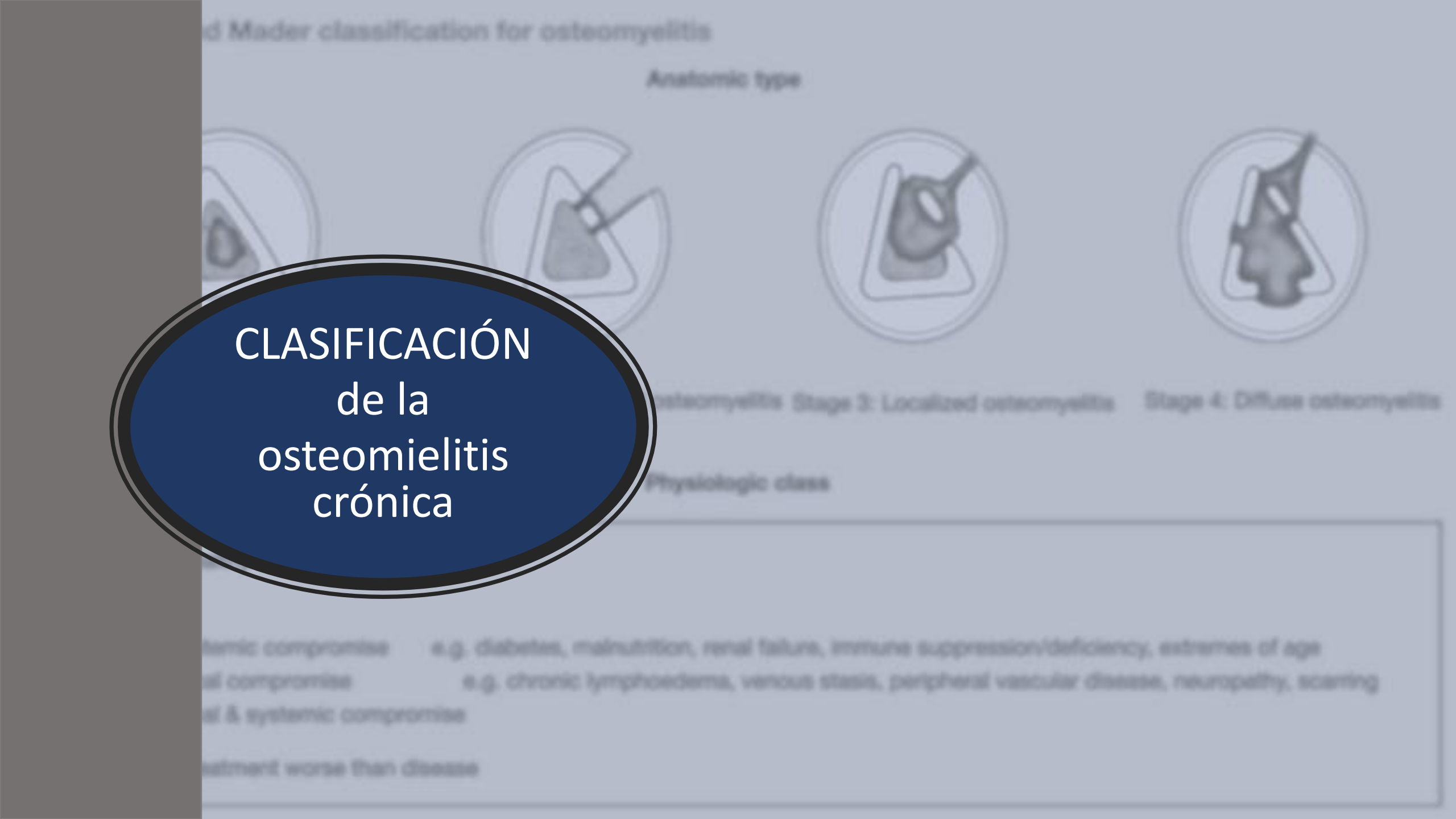
(fracturas abiertas, asociada a implantes)



80%

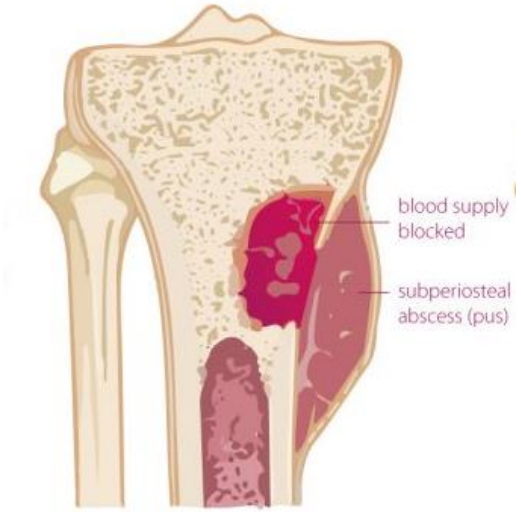
Hobo T. Für Pathogenese der a Kuten-hematogenenOsteomyelitis, mit Birwaksichtigung der vital Farbungslehre.Acta Scholae Med Univ Kioto 1921;4:1—4.

CLASIFICACIÓN de la osteomielitis crónica

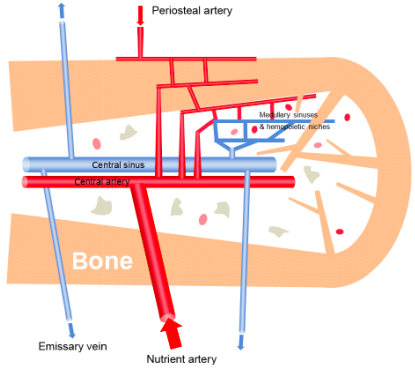


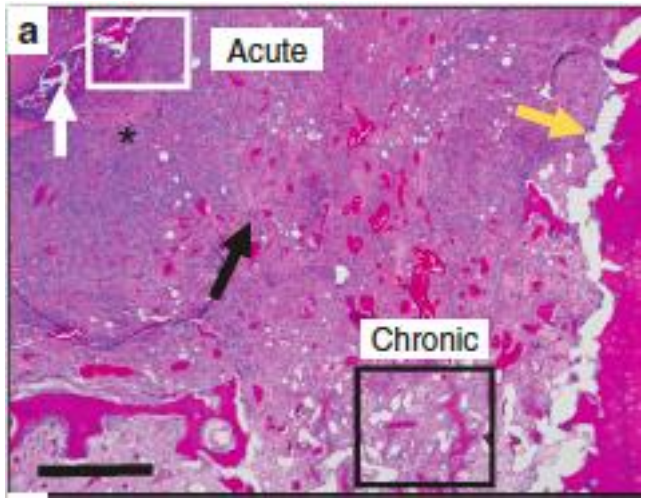
CLASIFICACIÓN “TEMPORAL”

Osteomielitis aguda

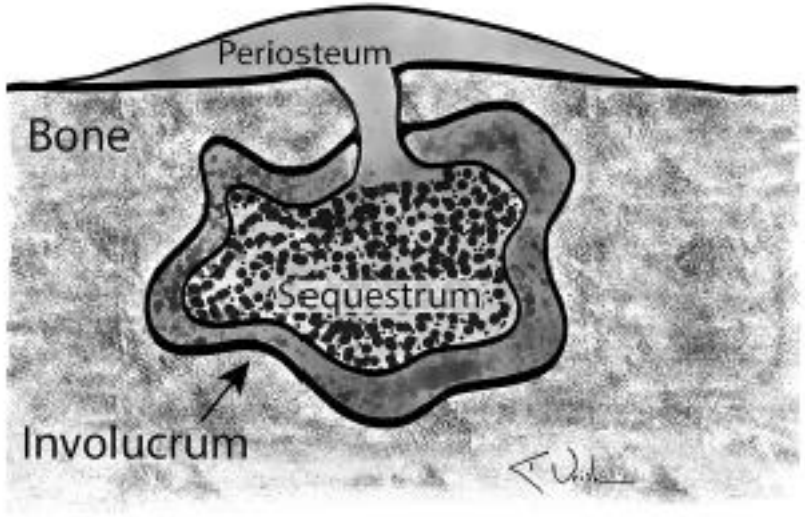


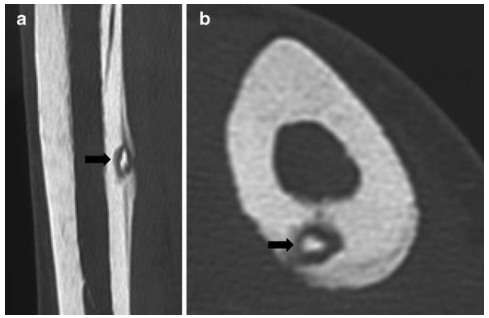
<4-6 semanas





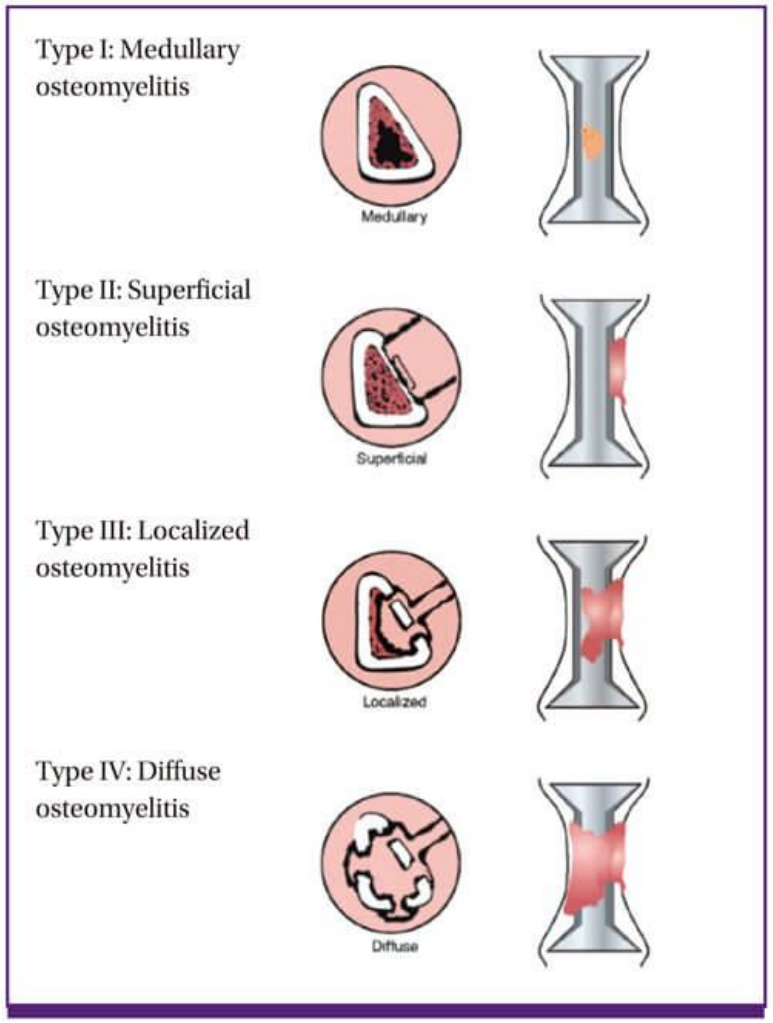
Osteomielitis crónica





Lazzarini L,. Osteomyelitis in long bones. J Bone Joint Surg Am. 2004 ;86(10):2305-18
Beck-Broichsitter BE,. Current concepts in pathogenesis of acute and chronic osteomyelitis. Curr Opin Infect Dis. 2015 ;28(3):240-5
Brodie, B. C. Pathological researches respecting the diseases of joints. Med Chir. Trans.1813; 4: 210–280.

CLASIFICACIÓN ANATOMO-FISIOLÓGICA (CIERNY-MADER)



Physiological class	
A host	Normal host
B host	Systemic compromise (Bs), local compromise (Bl), or systemic and local compromise (Bls)
C host	Treatment worse than the disease

Type of compromise	Factors
Systemic (Bs)	Malnutrition
	Renal, hepatic failure
	Diabetes mellitus
	Chronic hypoxia
	Immune disease
	Malignancy
	Extremes of age
	Immunosuppression or immune deficiency
Local (B1)	Chronic lymphedema
	Venous stasis
	Major-vessel compromise
	Arteritis
	Extensive scarring
	Radiation fibrosis
	Small-vessel disease
	Neuropathy
	Tobacco abuse (≥2 packs/d)

Mader JT,. Staging and staging application in osteomyelitis. Clin Infect Dis. 1997 ;25(6):1303-9.

CLASIFICACIÓN BACH

	Bone involvement	Antimicrobial options	Coverage by soft tissue	Host status
Uncomplicated	B_1 Cavitary infection without joint involvement (including cortical, medullary and non-segmental cortico-medullary)	A_x Unknown / culture negative osteomyelitis A_1 All isolates: • Sensitive to ≥ 80% of susceptibility tests and resistant to ≤ 3 susceptibility tests	C_1 Direct closure possible: Plastic surgery expertise not required	H_1 Well-controlled disease or Patient is fit and well
Complex	B_2 Segmental infection without joint involvement B_3 Any bone infection with associated joint involvement	A_2 Any isolate: • Sensitive to < 80% of all susceptibility tests performed or • Resistant to ≥ 4 susceptibility tests or • Resistant to antibiofilm antibiotics in the presence of an implant	C_2 Direct closure not possible: Plastic surgery expertise required	H_2 Patient with poorly controlled comorbidity or Severe comorbidity (with evidence of end-organ damage) or Recurrent osteomyelitis after previous debridement
Limited options		A_3 Any isolate: • Sensitive to 0 or 1 susceptibility test performed		H_3 Unfit for definitive surgery despite specialist intervention or Patient declines surgery

Hotchen AJ,. The BACH classification of long bone osteomyelitis. Bone Joint Res. 2019; 8(10):459-468

MICROBIOLOGÍA de la osteomielitis crónica

MICROORGANISMOS

2001-2004
166 pacientes

Cultivo negativo 34%
Polimicrobiano 29%

SAMS 22%
SAMR 10%
ECN16%
Enterobacterales 16%
Anaerobios 9%
Streptococcus spp. 7%
Enterococcus spp 5%
P aeruginosa 5%

Hospital primario
72 (51.1%)[1]

2019-2020
141 pacientes

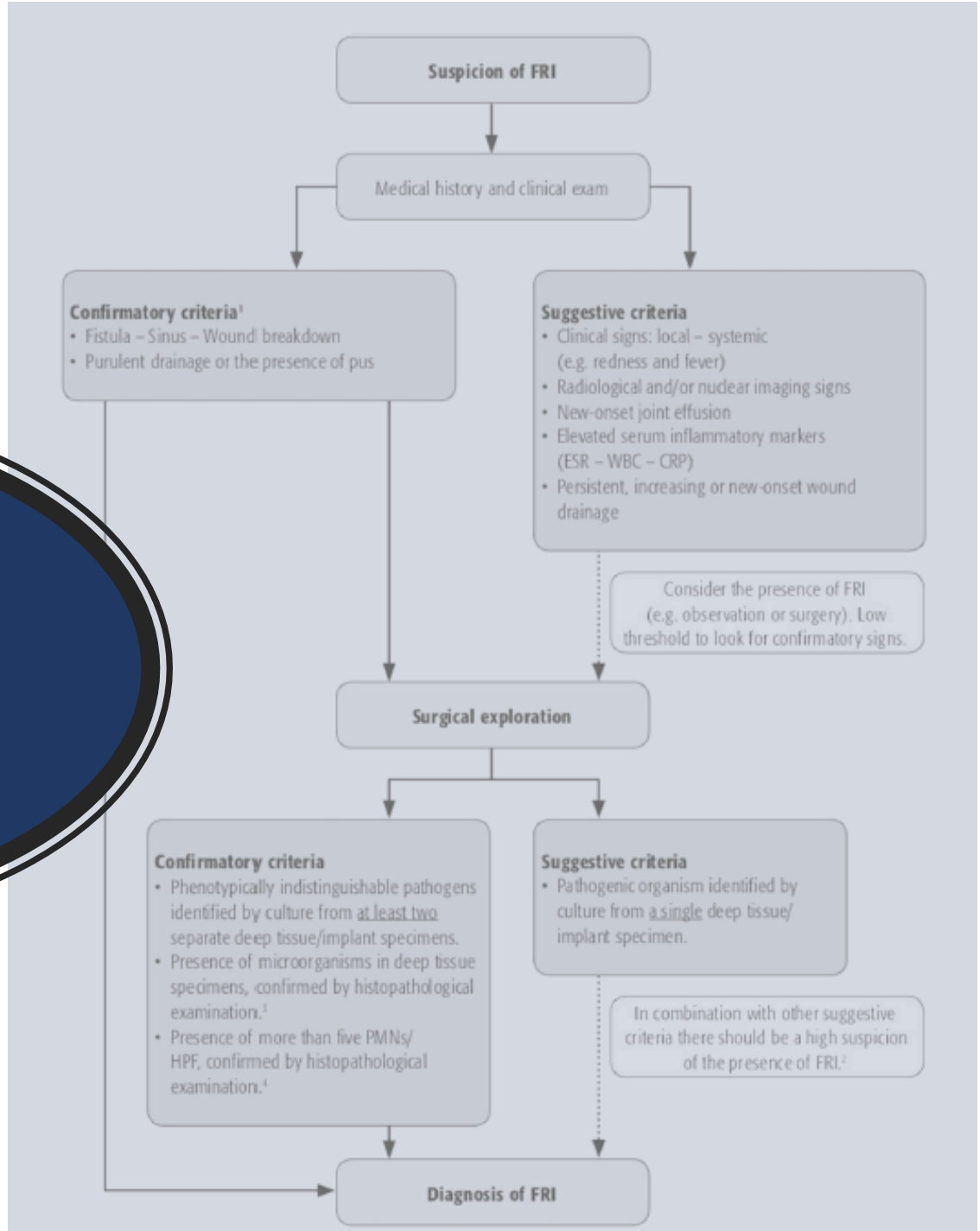
Cultivo negativo 25%

Growth from Referral Microbiology Samples	Growth Reported from Intra-Operative Sampling	Number
'Complete match'		
Yes	Same as referral microbiology	16 (18.2%)
No	No growth	6 (6.8%)
'Partial match'		
Yes	Same as referral microbiology with additional isolates	8 (9.1%)
'Non-match'		
No	Significant growth	6 (6.8%)
Yes	Isolates not present on referral microbiology samples	52 (59.1%)

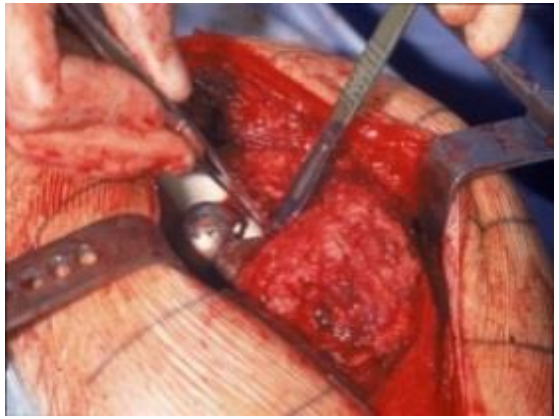
1. Torundas (45%), cirugia previa (28%), biopsia (27%), HC (4%)

Sheehy SH. The microbiology of chronic osteomyelitis: prevalence of resistance to common empirical anti-microbial regimens. J Infect. 2010;60(5):338-43.
Hotchen AJ. . Pre-Referral Microbiology in Long Bone Infection: What Can It Tell Us? Antibiotics (Basel). 2022 Dec 22;12(1):13.

DIAGNÓSTICO de la osteomielitis crónica



DIAGNÓSTICO DEFINITIVO



Fístula
Drenaje purulento

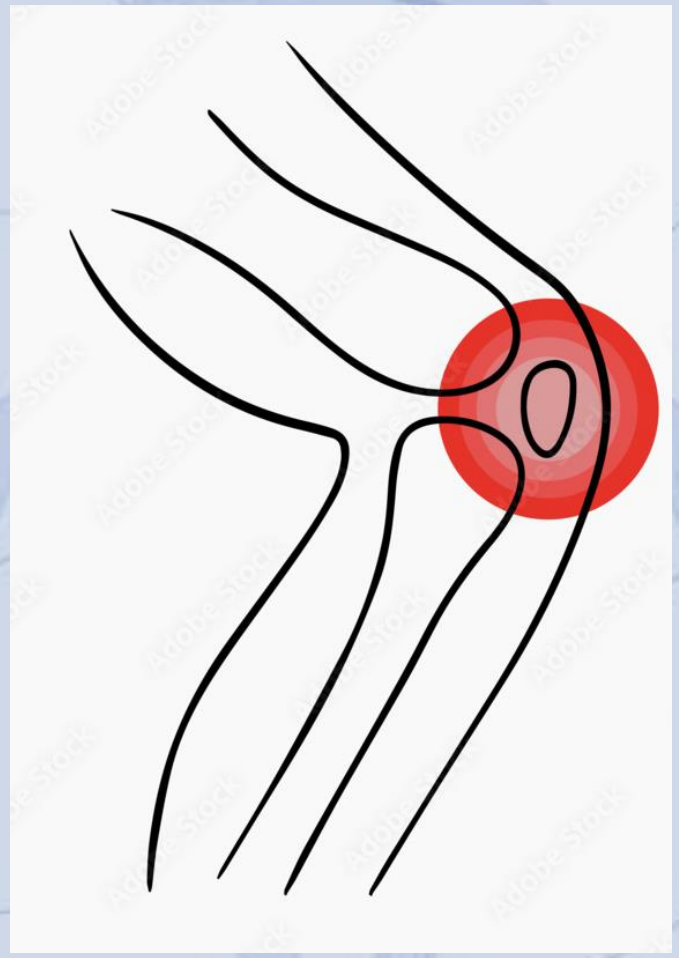
Exploración quirúrgica
Microorganismo
≥2 muestras separadas

Pruebas de imagen

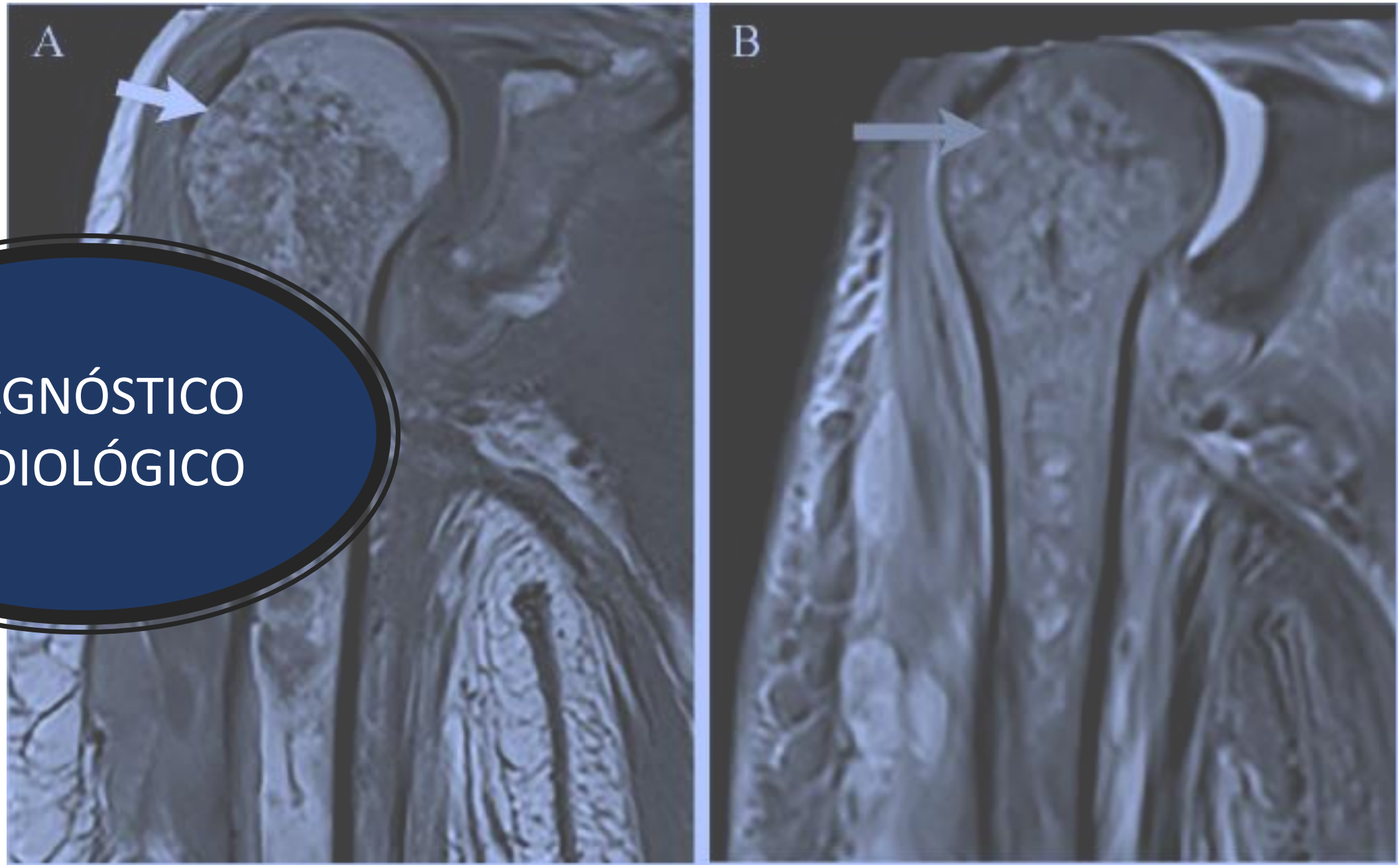
Histopatología

Metsemakers WJ. Fracture-related infection: A consensus on definition from an international expert group. Injury. 2018
Govaert GAM. Diagnosing Fracture-Related Infection: Current Concepts and Recommendations. J Orthop Trauma 2020;34:8–17

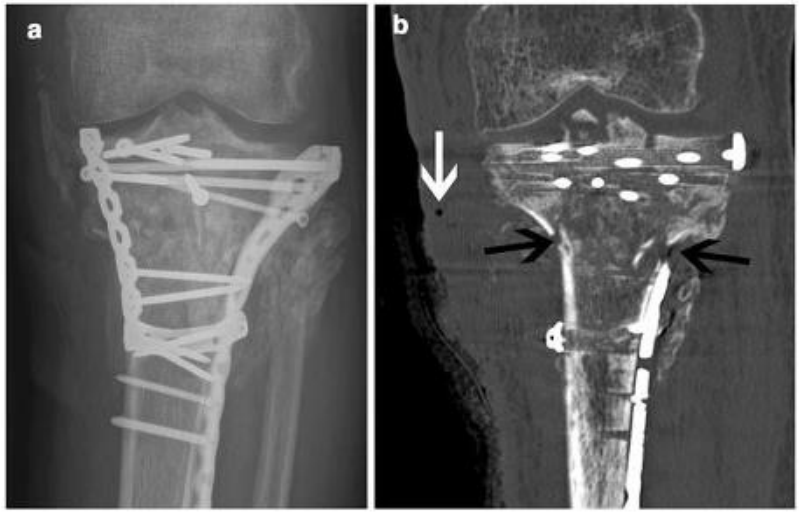
SOSPECHA CLINICA

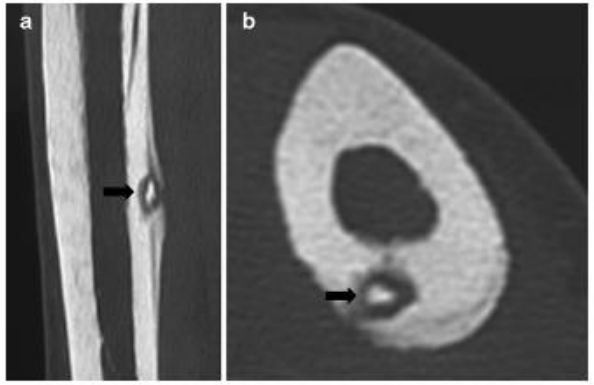


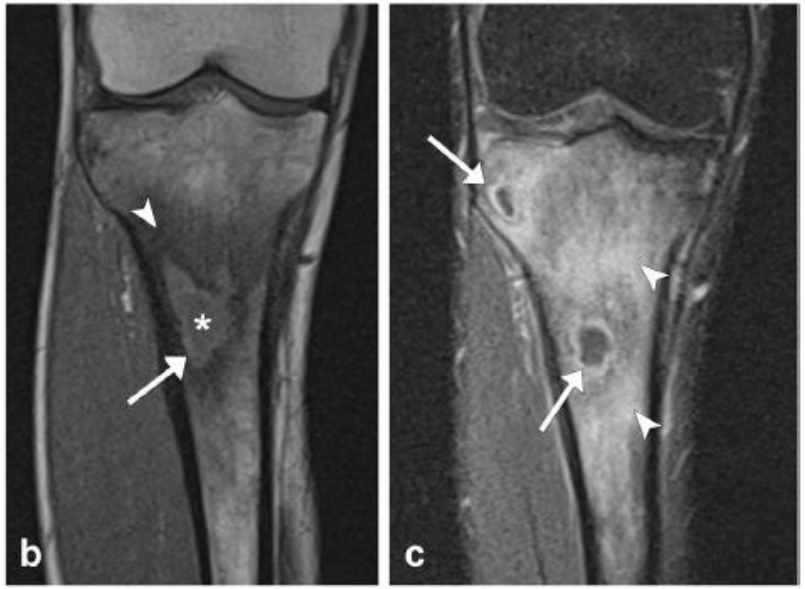
DIAGNÓSTICO RADIOLÓGICO



RADIOLOGIA



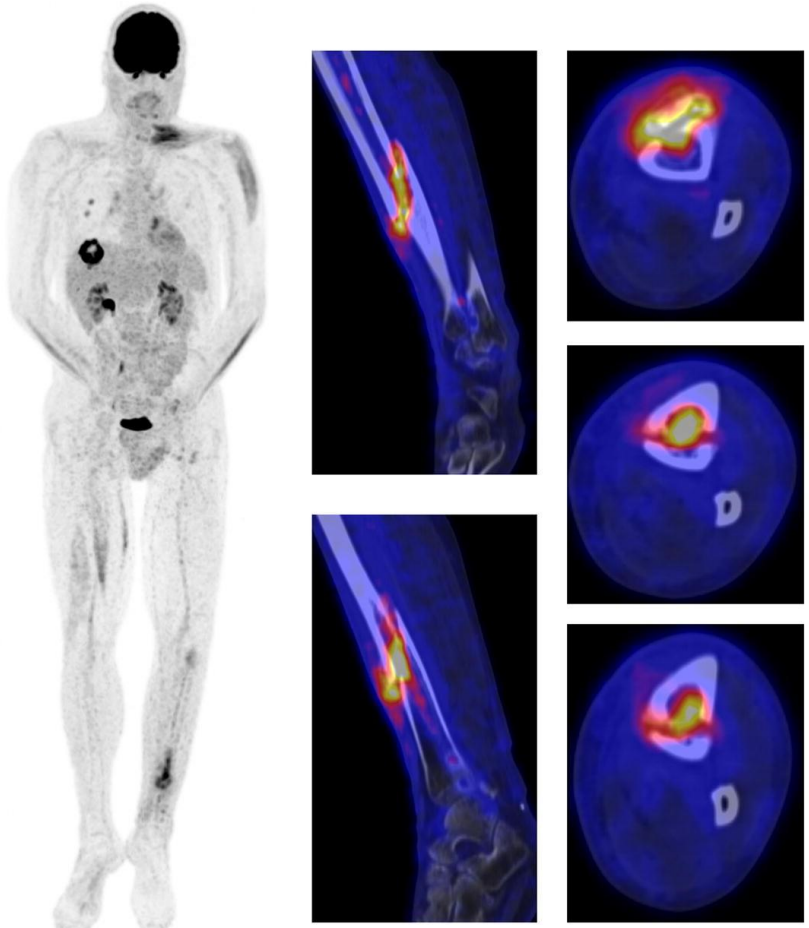


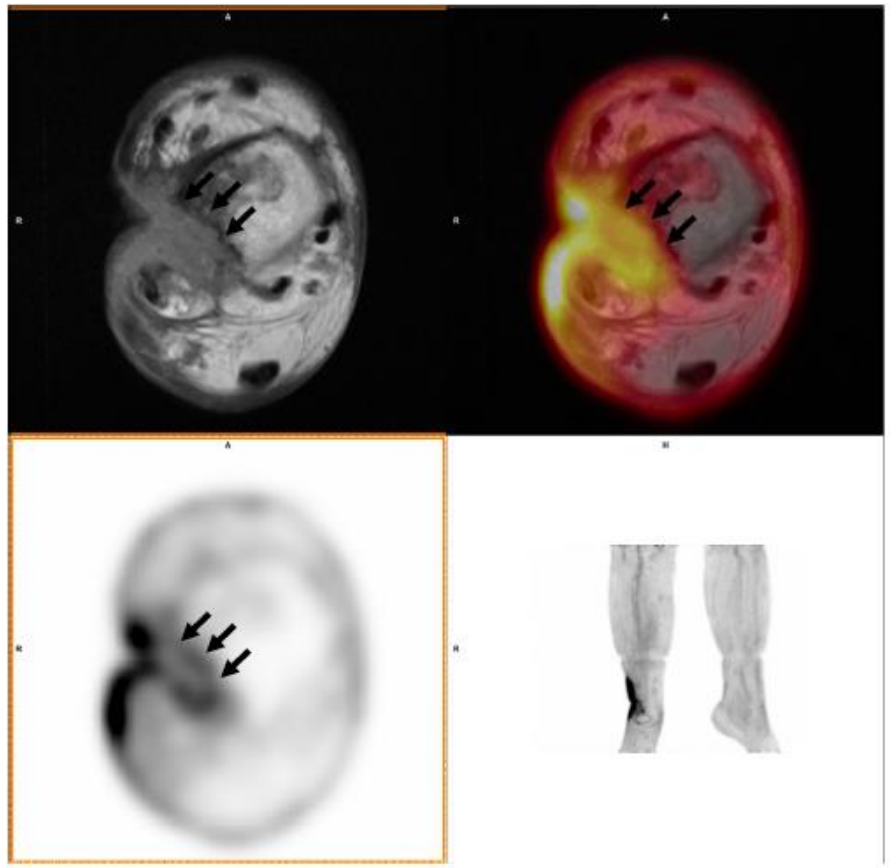


Butt WP. The radiology of infection. Clin Orthop Relat Res. 1973 Oct;(96):20-30
Peel TN. Imaging in osteoarticular infection in adults. Clin Microbiol Infect. 2023: S1198
Crim J. Update on MRI findings of osteomyelitis of long bones in the adult population. Skeletal Radiol. 2022; 51(9):1787-1796

PRUEBAS DE IMAGEN HÍBRIDAS

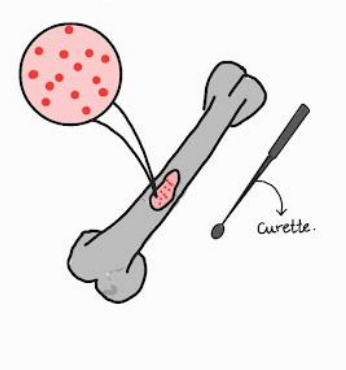
PET-TAC & PET-RMN

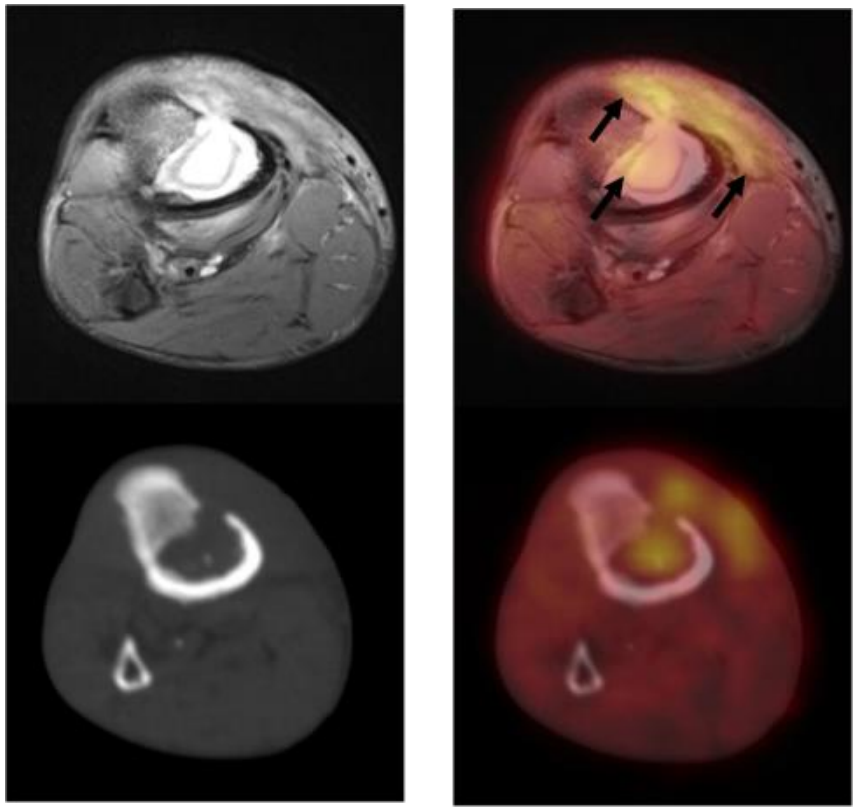




Wenter V,. The diagnostic value of [(18)F]FDG PET for the detection of chronic osteomyelitis and implant-associated infection. Eur J Nucl Med Mol Imaging. 2016;43(4):749-61

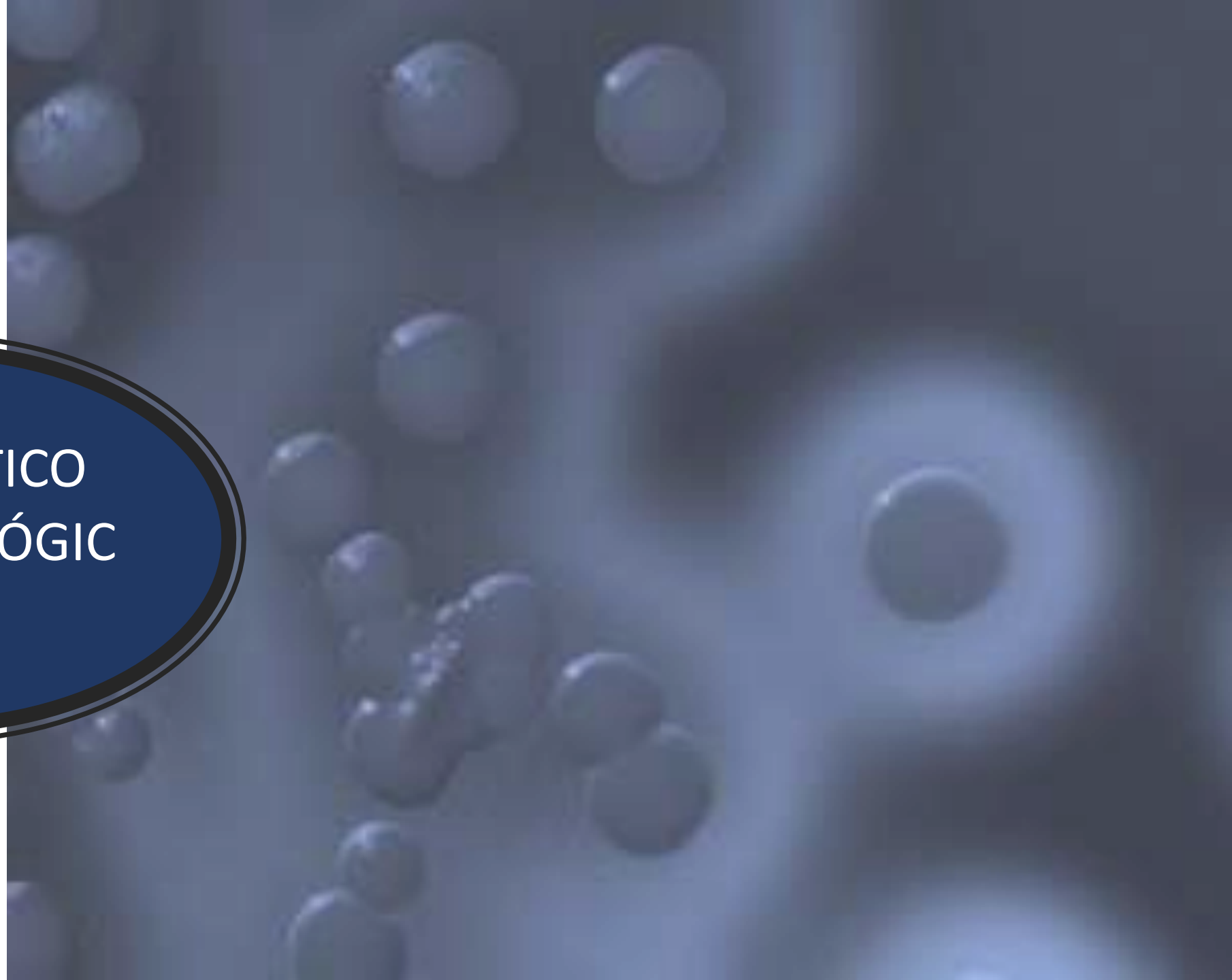
PRUEBAS DE IMAGEN HÍBRIDAS
PLANIFICACIÓN QUIRÚRGICA





Elsheikh A. Role of 18F-FDG PET-CT in Pre-Operative Planning of Surgical Debridement in Chronic Osteomyelitis. Indian J Orthop. 2022; 56(12):2237-2244.

DIAGNÓSTICO MICROBIOLÓGICO



DIAGNÓSTICO MICROBIOLÓGICO

MUESTRAS INTRAOPERATORIAS

Suspender antibioterapia al menos 14 días antes

≥5 muestras

Fragmentos óseos necróticos

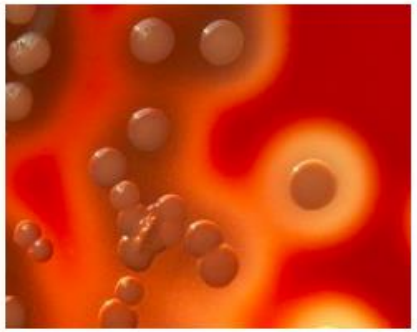
Tejidos blandos adyacentes

Sitio de fractura

Interfase implante-hueso

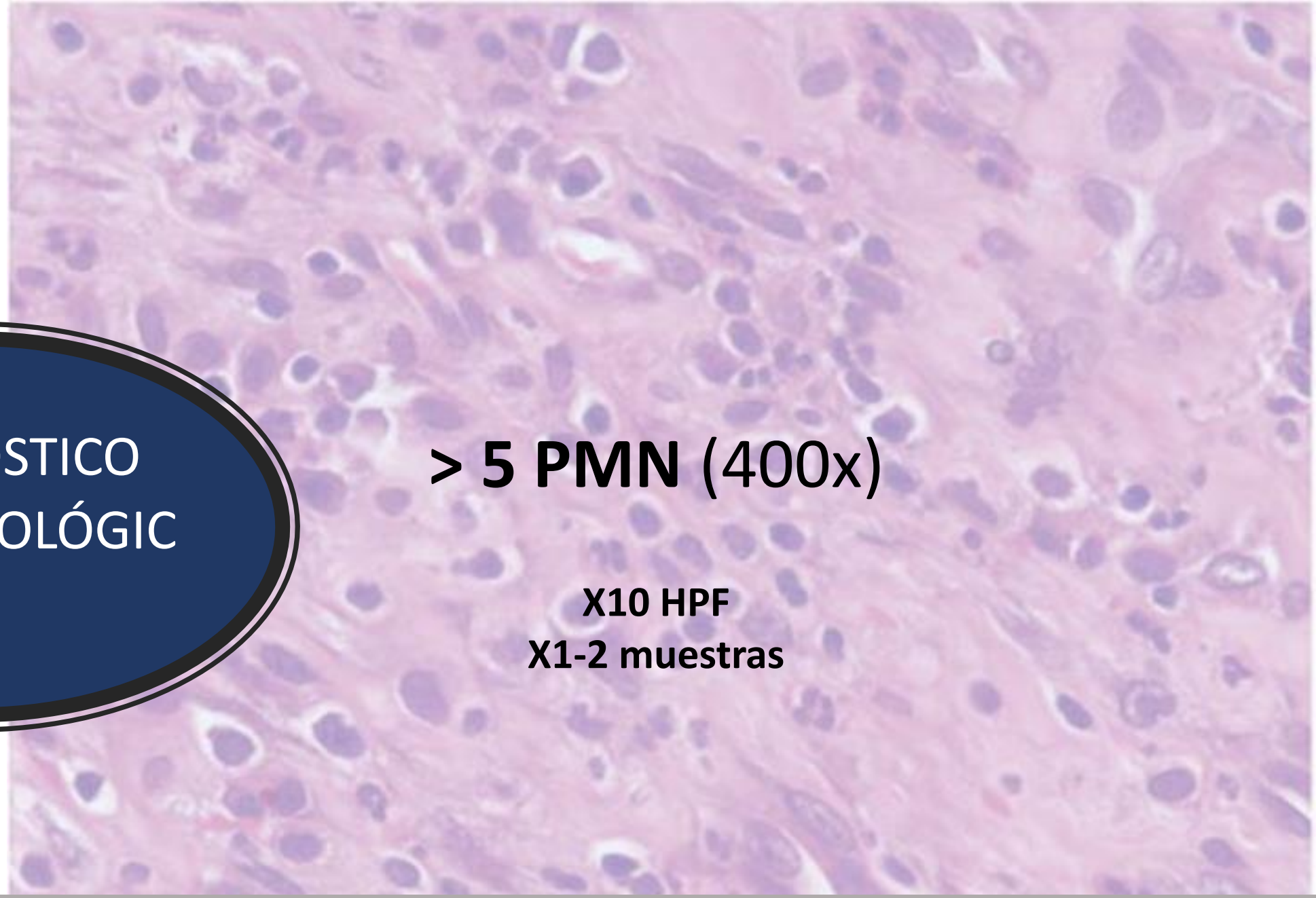
Implante (sonicación)

≥2
mismo microorganismo



Govaert GAM. Fracture-Related Infection (FRI) Consensus Group. Diagnosing Fracture-Related Infection: Current Concepts and Recommendations. J Orthop Trauma. 2020;34(1):8-17

DIAGNÓSTICO HISTOPATOLÓGICO



> 5 PMN (400x)

X10 HPF
X1-2 muestras

Morgenstern M,. The value of quantitative histology in the diagnosis of fracture-related infection. Bone Joint J. 2018 ;100-B(7):966-972.

TRATAMIENTO MÉDICO

ANTIBIOTERAPIA SISTÉMICA

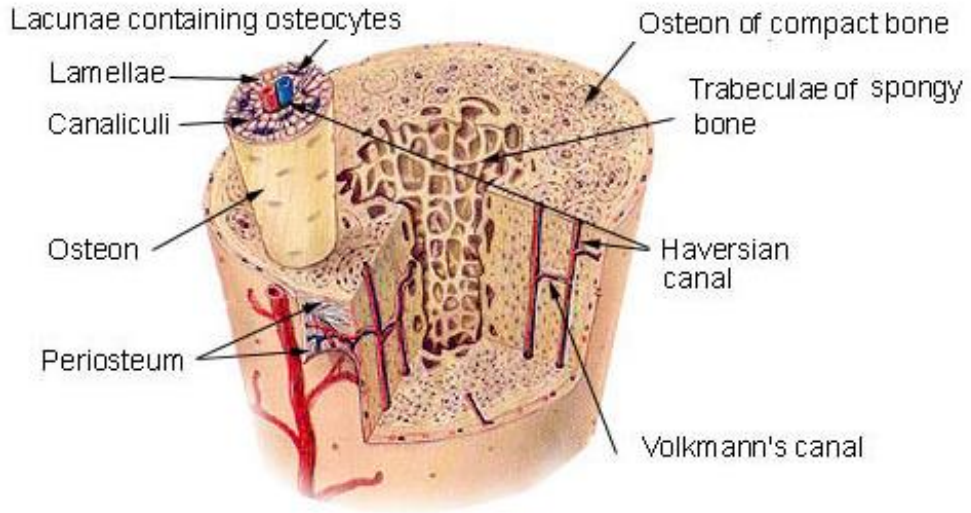
REVIEW ARTICLE
Clin Pharmacokinet 2009; 48 (2): 89-124
0312-5963/09/0002-0089/$49.95/0

Penetration of Antibacterials into Bone

Pharmacokinetic, Pharmacodynamic and Bioanalytical Considerations

Medular>cortical

Difusión ósea[1]		
Buena (>30%) (<15%)	**Moderada (15-30%)**	**Pobre**
Fluoroquinolonas	Clindamicina	Penicilina
Linezolid	Glicopeptidos	Clavulánico
Doxiciclina	Cefalosporinas	Metronidazol
Cotrimoxazol	Fosfomicina	
Rifampicina	Tazobactam	
	Dalbavancina	
	Oritavancina	



Landersdorfer CB.. Penetration of antibacterials into bone: pharmacokinetic, pharmacodynamic and bioanalytical considerations. Clin Pharmacokinet. 2009

ANTIBIOTERAPIA SISTÉMIC

Original Contribution

May 20, 1998

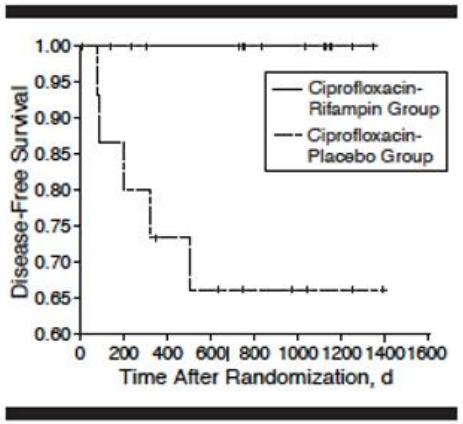
Role of Rifampin for Treatment of Orthopedic Implant-Related Staphylococcal Infections

A Randomized Controlled Trial

Werner Zimmerli, MD; Andreas F. Widmer, MD, MSc; Marianne Blatter, MD; et al

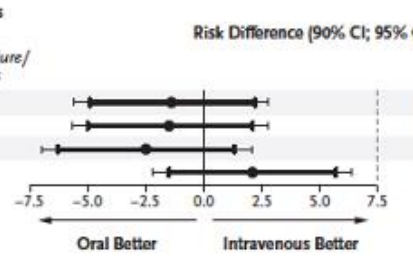
Author Affiliations

JAMA. 1998;279(19):1537-1541. doi:10.1001/jama.279.19.1537



OVIVA

Subgroup	Oral Group (patients with treatment failure/total no. of participants)	Intravenous Group (patients with treatment failure/total no. of participants)	Risk Difference (90% CI; 95% CI)
Intention-to-treat population	70.0/527	77.3/527	−1.4 (−4.9 to 2.2; −5.6 to 2.9)
Modified intention-to-treat population	67/509	74/506	−1.5 (−5.0 to 2.1; −5.7 to 2.8)
Per-protocol population	61/466	69/443	−2.5 (−6.3 to 1.3; −7.0 to 2.1)
Worst-case sensitivity analysis	85/527	74/527	2.1 (−1.5 to 5.7; −2.2 to 6.4)



Zimmerli W. Role of Rifampin for Treatment of Orthopedic Implant–Related Staphylococcal Infections : A Randomized Controlled Trial. *JAMA.* 1998
Li HK. Oral versus Intravenous Antibiotics for Bone and Joint Infection. N Engl J Med. 2019

ANTIBIOTERAPIA SISTÉMICA

Secuenciación oral precoz (≤7 días)

Uso de fármacos con elevada biodisponibilidad y difusion ósea

(rifampicina, fluoroquinolonas, linezolid, cotrimoxazol, clindamicina, doxiciclina)

Añadir rifampicina en infecciones estafilocócicas

Priorizar fluoroquinolonas en infecciones por BGN

LGP de acción prolongada (TAS, interacciones…)

Rappo U. Dalbavancin for the Treatment of Osteomyelitis in Adult Patients: A Randomized Clinical Trial of Efficacy and Safety. Open Forum Infect Dis. 2018;6(1):ofy331

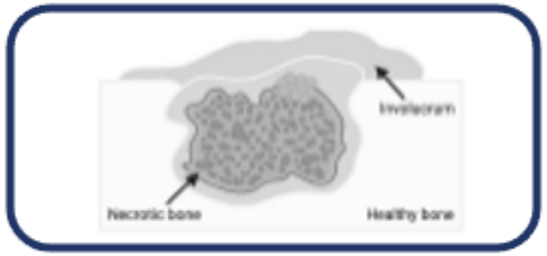
DURACIÓN de la ANTIBIOTERAPIA SISTÉMICA EN LA OSTEOMIELITIS CRÓNICA

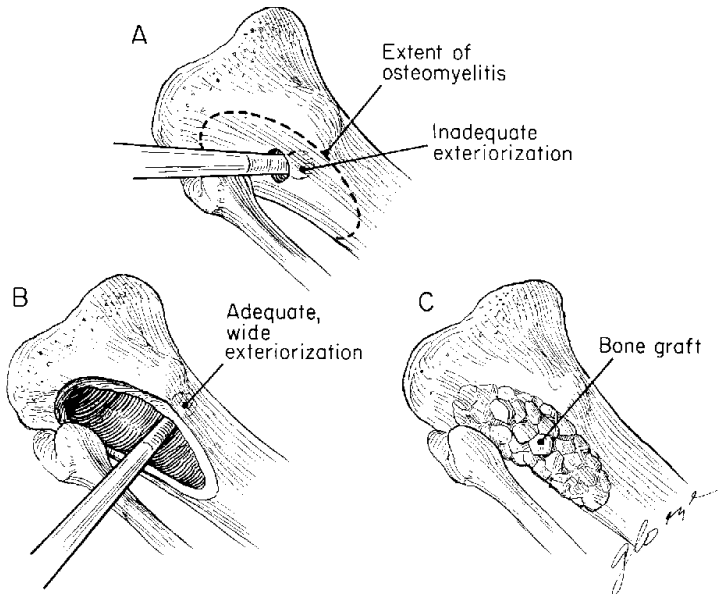
5 dias

1-6

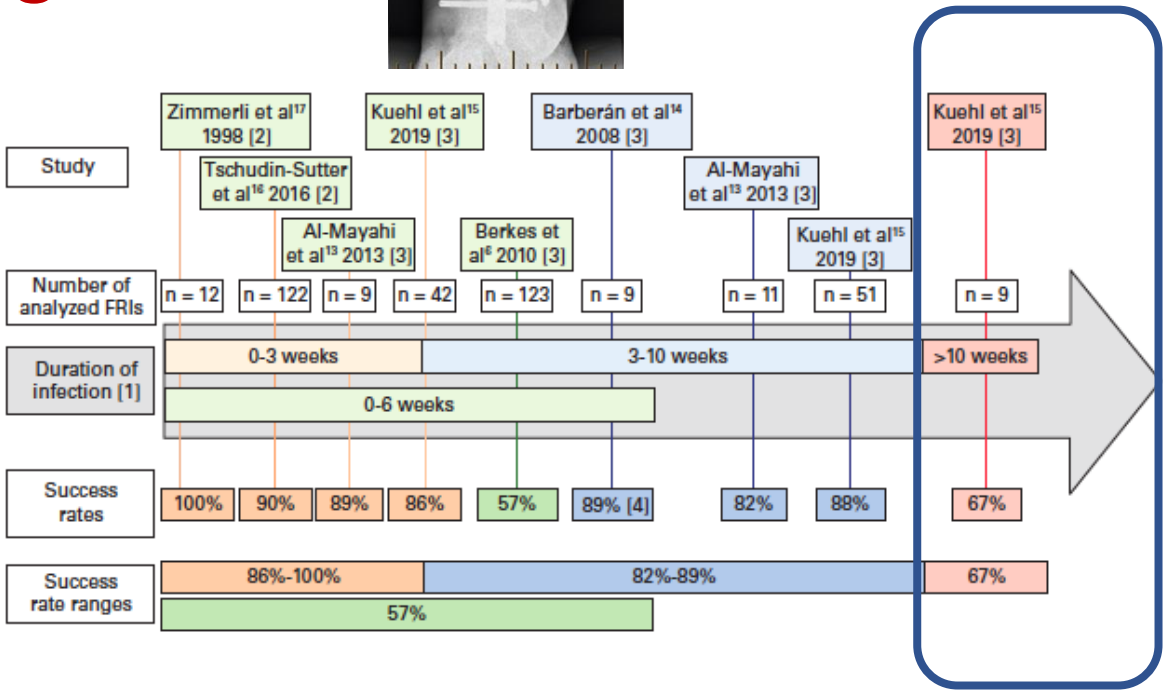
8-12 semanas

RECURRENCIAS





30%

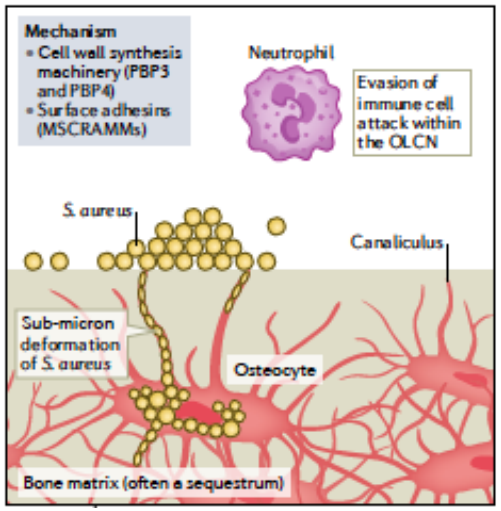


Morgernsten M. The influence of duration of infection on outcome of debridement and implant retention in fracture-related infection. Bone Joint J 2021;103-B(2):213–221.

Tice AD. Outcomes of osteomyelitis among patients treated with outpatient parenteral antimicrobial therapy. Am J Med. 2003;114:723–8.

Simpson A. Chronic Osteomyelitis. The effect of the extent of surgical resection on infection. J Bone Joint Surg Br. 2001;83-B(3):403–407.

RECURRENCIAS



pH bajo

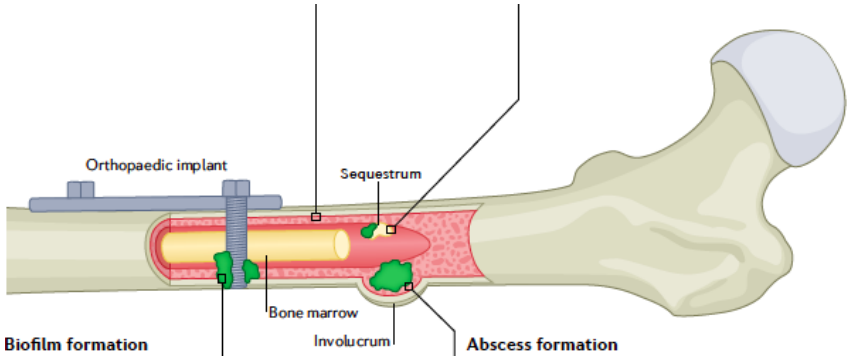
escasa disponibilidad de oxígeno y nutrientes

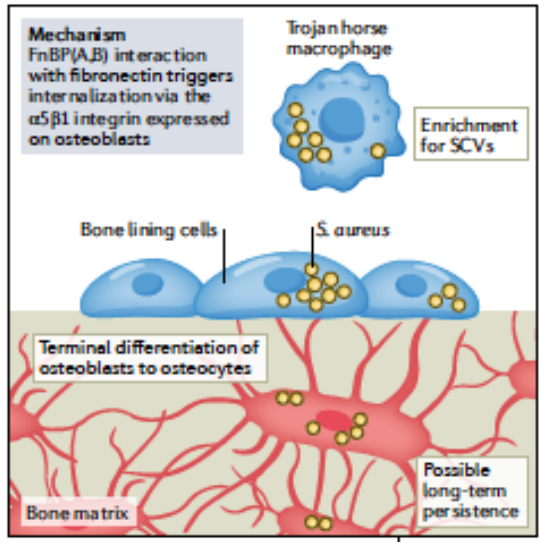
infección intracellular

invasion del OLCS

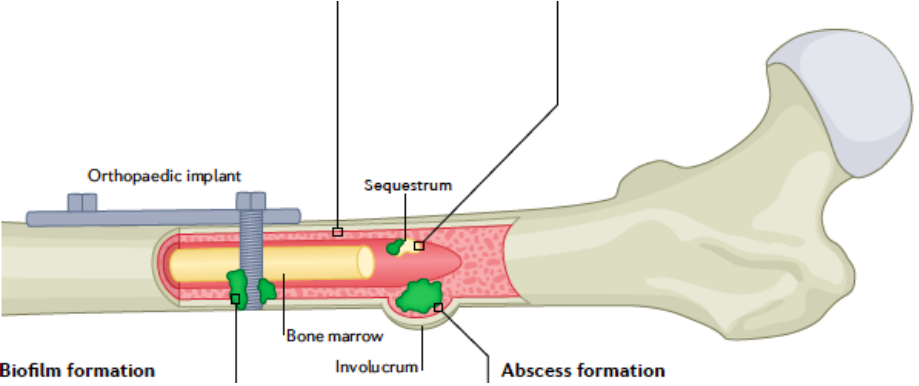
microabscesos

agregados sinoviales





Masters EA. Skeletal infections: microbial pathogenesis, immunity and clinical management. Nat Rev Microbiol. 2022 .



En estas condiciones…

las concentraciones de antibióticos necesarias para erradicar la infección **(100-1000 x CMI)**

NO son alcanzables con una antibioterapia sistém

Retirada de implantes

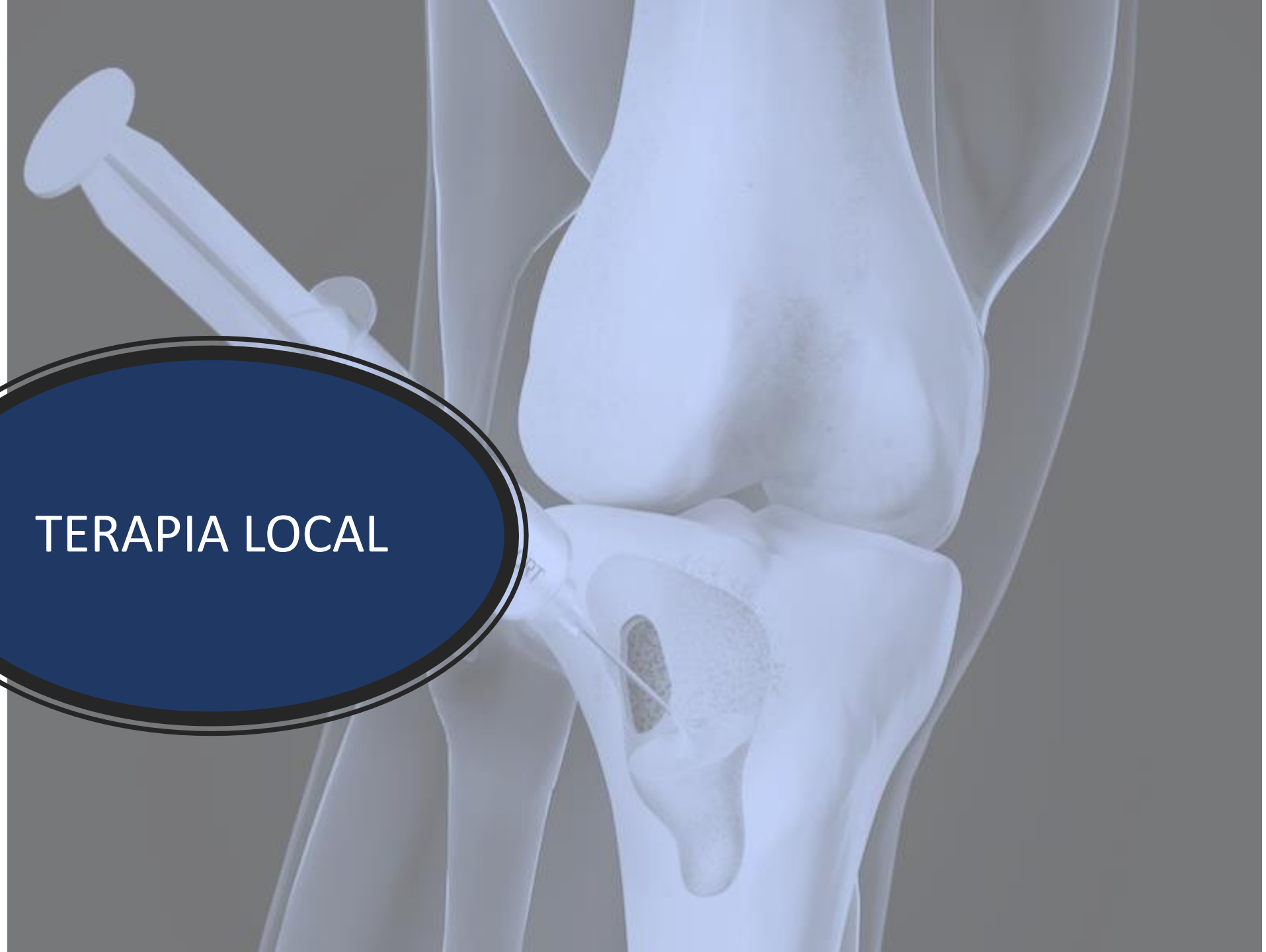
Resecciones radicales

y/o

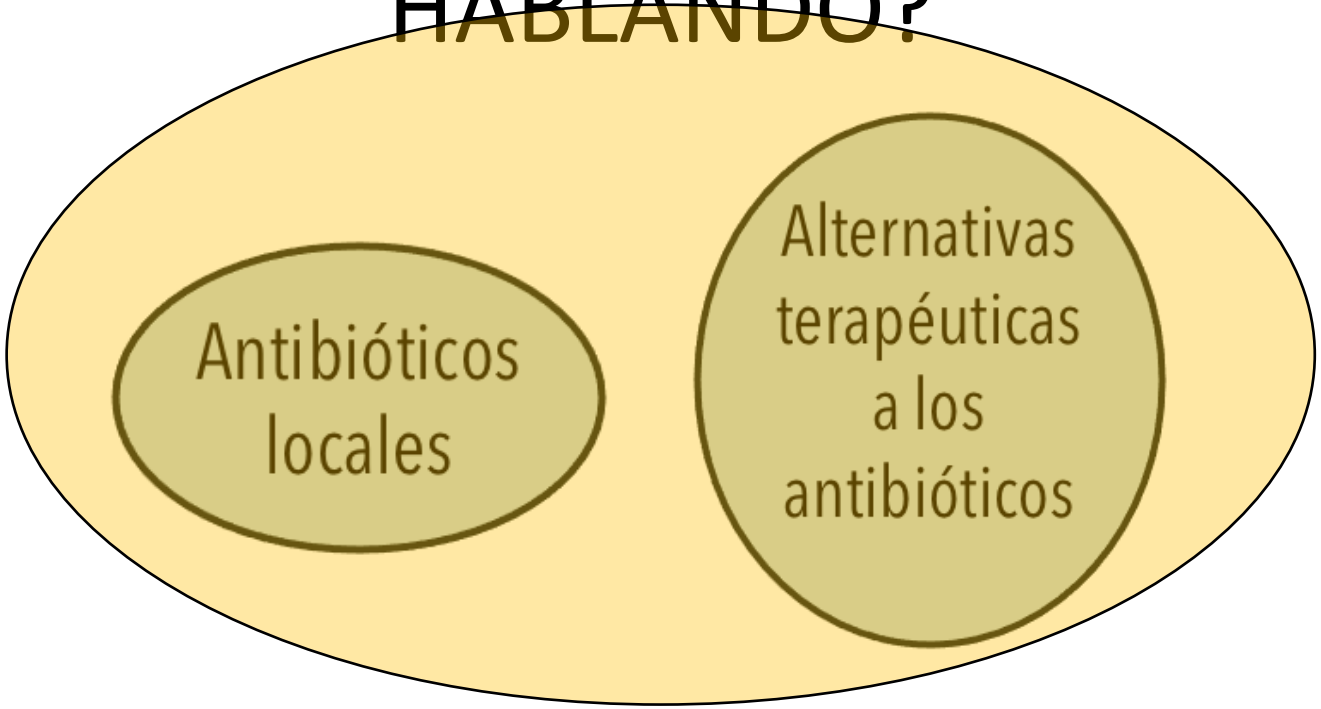
ALTERNATIVAS
a la antibioterapia sistémica

Mah T-FC, O'Toole GA. Mechanisms of biofilm resistance to antimicrobial agents. Trends Microbiol. 2001;9:34–9.

TERAPIA LOCAL



¿DE QUE ESTAMOS HABLANDO?



liberación sostenida
concentración adecuada
biodegradable

Limitar duración antibioterapia sistémica

Acto quirúrgico único

Sustitutos óseos
Nanomateriales

TERAPIA LOCAL

SUSTITUTOS ÓSEOS

cementos óseos (PMMA)
cerámicas biodegradables
cristales bioactivos

biocompatibles

estables mecánicamente

porosos

permeables

biodegradables

Sustitutos óseos[Atb]

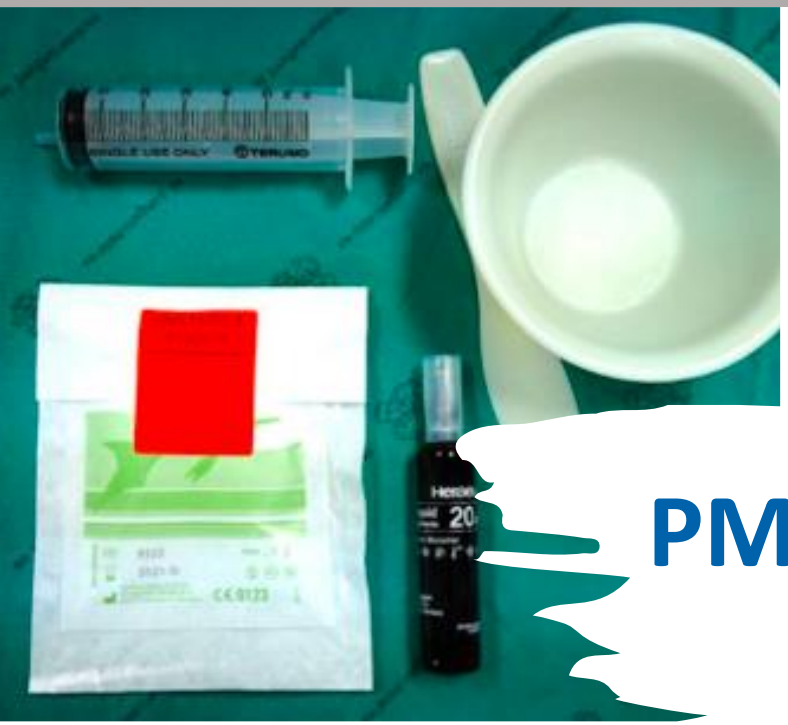
ausencia de toxicidad sistémica

ausencia de toxicidad local

estabilidad térmica

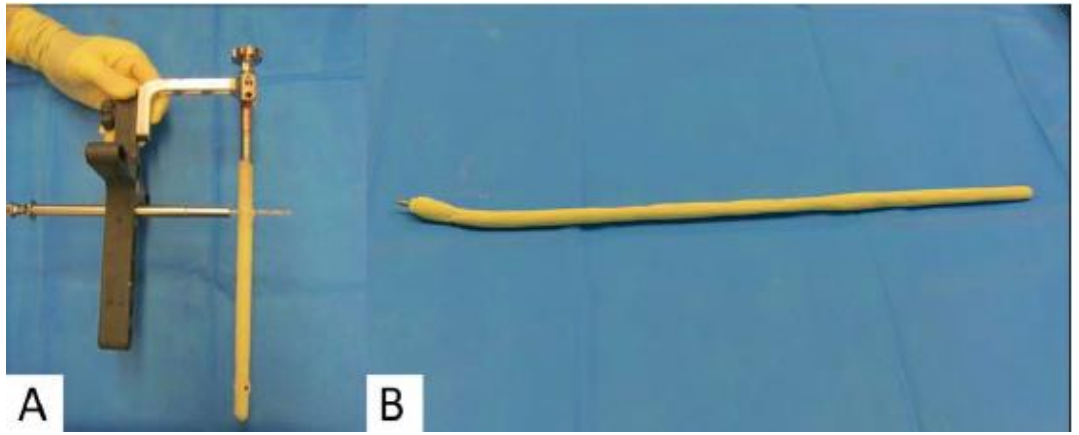
Rathbone CR, Cross JD, Brown KV, et al. Effect of various concentrations of antibiotics on osteogenic cell viability and activity. J Orthop Res. 2011;29:1070–1074.
Antoci V Jr, Adams CS, Hickok NJ, et al. Antibiotics for local delivery systems cause skeletal cell toxicity in vitro. Clin Orthop Relat Res. 2007;462:200–206.

CEMENTOS ÓSEOS-PMMA



Atb

PMMA



CHARNLEY J. Anchorage of the femoral head prosthesis to the shaft of the femur. J Bone Joint Surg Br. 1960
Buchholz HW. Infection prevention and surgical management of deep insidious infection in total endoprosthesis]. Chirurg. 1972.

PMMA Atb

NORMAS BÁSICAS

PMMA ⇄ **Atb**

PMMA	Atb
Cambios en la viscosidad	Forma de polvo
Alteración de la rigidez	Hidrosolubles
Modificación de la resistencia mecánica	Termoestables

PMMA Atb

RECOMENDACIONES PRÁCTICAS

Normas generales para garantizar la estabilidad mecánica

≤ 4g Atb y <10% mezcla por 40g PMMA

Evitar >2 Atb

Atb estériles en polvo

Priorizar preparados comerciales

vancomicina
gentamicina
tobramicina
clindamicina

V + G
V + T
C + G

PMMA Atb

Preparados caseros “off label”

Linezolid
Daptomicina
Fosfomicina

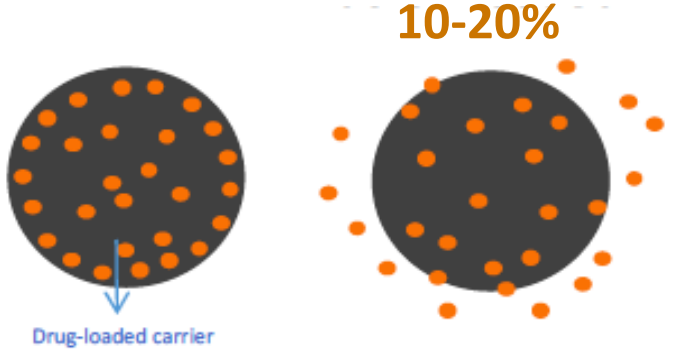
Carbapenemes
Ciprofloxacino

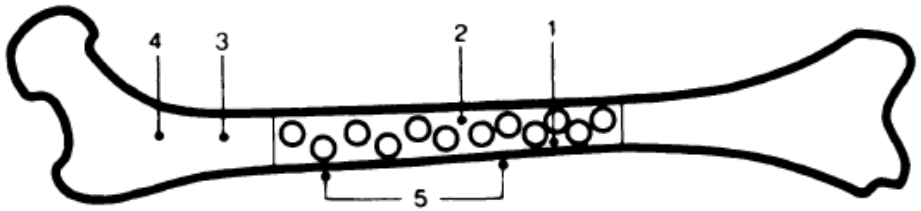
Voriconazol

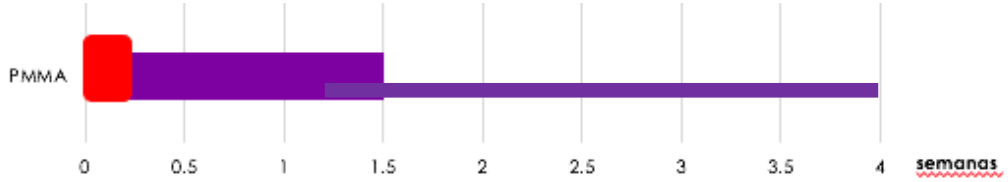
Cefalosporinas
Tetraciclinas

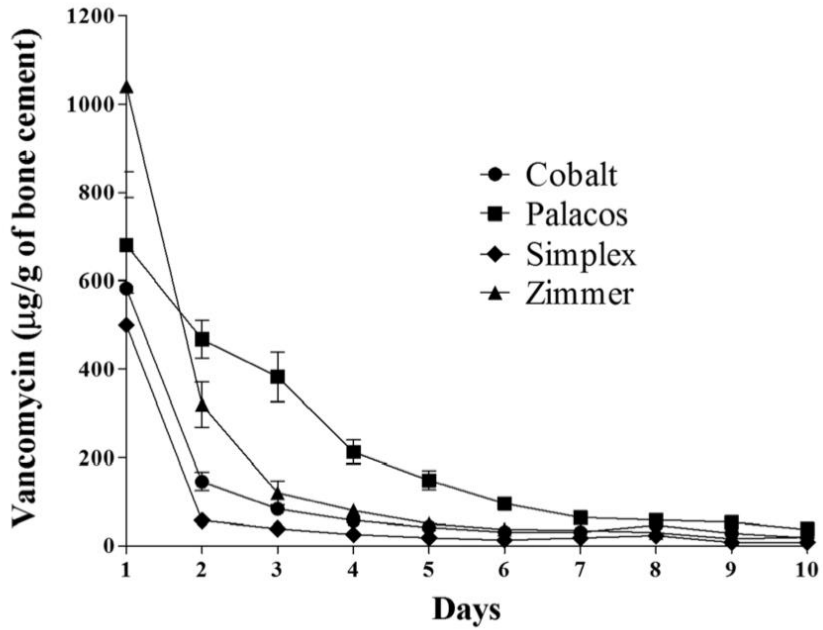
Rifampicina
Metronidazol
Anfotericina B

LIBERACIÓN de antibióticos desde PMMA









concentraciones subterapéuticas

?promoción de resistencias

Meeker DG. Comparative Study of Antibiotic Elution Profiles From Alternative Formulations of Polymethylmethacrylate Bone Cement. J Arthroplasty. 2019;

Wahlig H, et al. The release of gentamicin from polymethylmethacrylate beads. An experimental and pharmacokinetic study. J Bone Joint

SUSTITUTOS ÓSEOS-PMMA

No es biodegradable

Cuerpo extraño

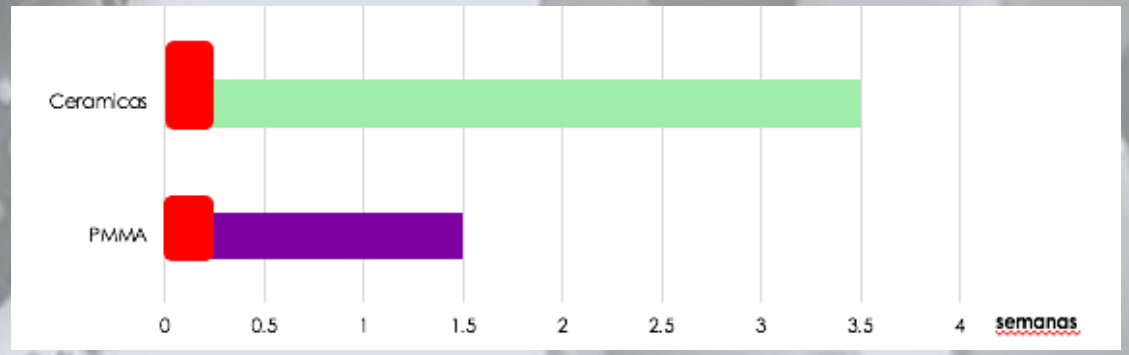
Sustrato para la biopelícula
Requiere una segunda cirugía

van de Belt H, et al. Surface roughness, porosity and wettability of gentamicin-loaded bone cements and their antibiotic release. Biomaterials. 2000
Neut D, et al. Biomaterial-associated infection of gentamicin-loaded PMMA beads in orthopaedic revision surgery. J Antimicrob Chemother. 2001

CERÁMICAS BIODEGRADABLES

sulfato cálcico

sulfato cálcico + hidroxiapatita



tobramicina®
gentamicina®
vancomicina®

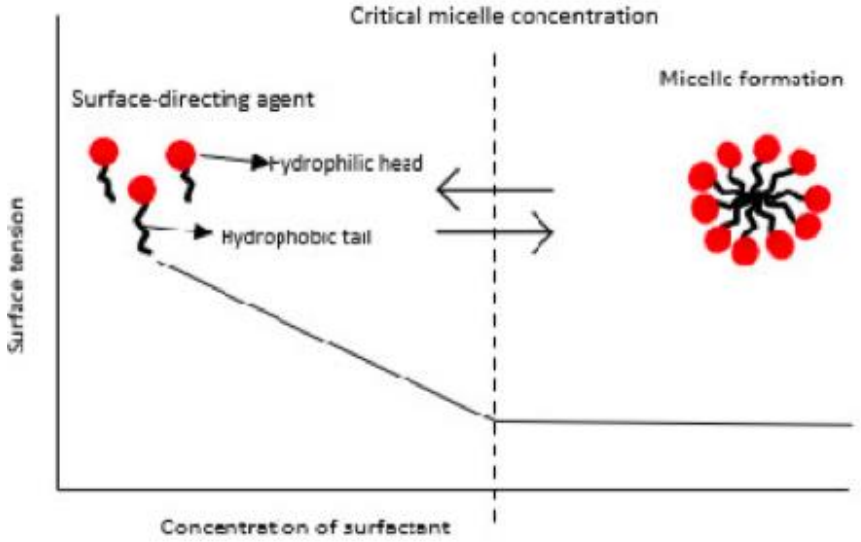
Ferguson JY. . The use of a biodegradable antibiotic-loaded calcium sulphate carrier containing tobramycin for the treatment of chronic osteomyelitis: a series of 195 cases. Bone Joint J. 2014.

Levack AE.. Identifying alternative antibiotics that elute from calcium sulfate beads for treatment of orthopedic infections. J Orthop Res. 2022.

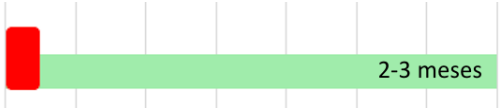
CERÁMICAS BIODEGRADABLES

Cristales bioactivos

BAG-S53P4[Atb]



tobramicina
vancomicina
doxiciclina



Szewczyk A. Mesoporous Silica-Bioglass Composite Pellets as Bone Drug Delivery System with Mineralization Potential. Int J Mol Sci. 2021

Mistry S. Biological analysis of an innovative biodegradable antibiotic eluting bioactive glass/gypsum composite bone cement for treating experimental chronic MRSA osteomyelitis. J Pharm Anal. 2022

Almasri D. Prosthetic Joint Infections: Biofilm Formation, Management, and the Potential of Mesoporous Bioactive Glass as a New Treatment Option. Pharmaceutics. 2023

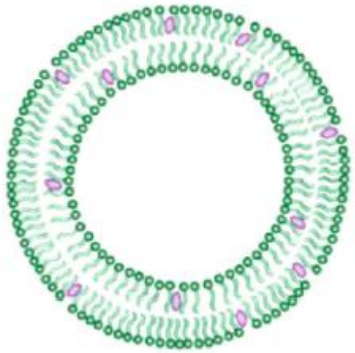
Nanomateriales[Atb]

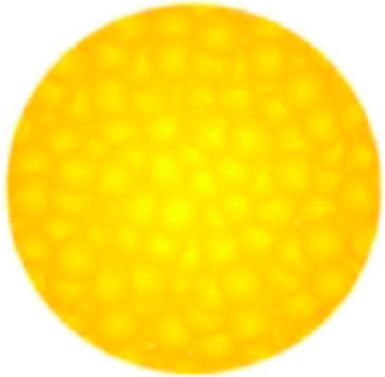
- Gran superficie de contacto
- Optimización liberación Atb (hidrofílicos o lipofílicos)
- Actividad antimicrobiana intrínseca (metales, chitosán)
- Dianas específicas
- Potencial actividad intracelular
- Muchos son biodegradables

Guo P, et al. Therapeutic Nanotechnology for Bone Infection Treatment - State of the Art. Curr Drug Deliv. 2018

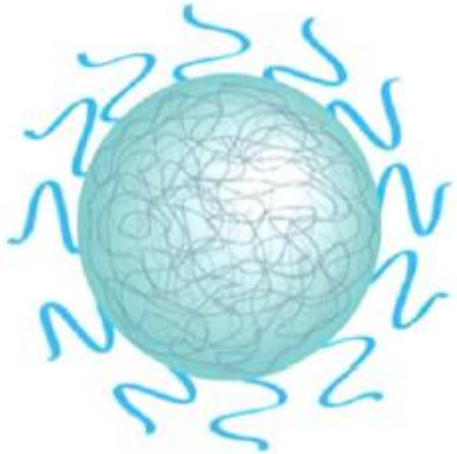
Nanomateriales[Atb]

Liposomas

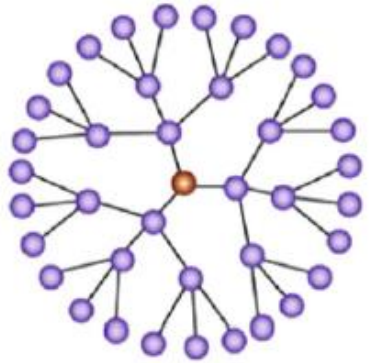




Metales
(plata, titanio)



Nanopartículas
Poliméricas
(**PLGA**, PEG,
chitosan)



Hidroxiapatita
Alginato cálcico
Silicio
mesoporoso

Fibroína (seda)

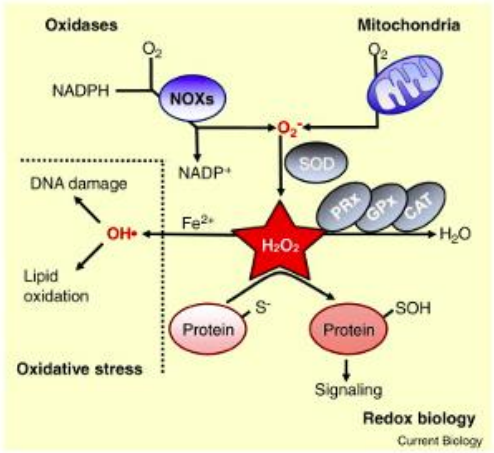
Shuaishuai W. Implantable biomedical materials for treatment of bone infection. Front Bioeng Biotechnol. 2023 ;11:1081446

Nanomateriales

Limitaciones

Toxicidad

nanopartículas metálicas

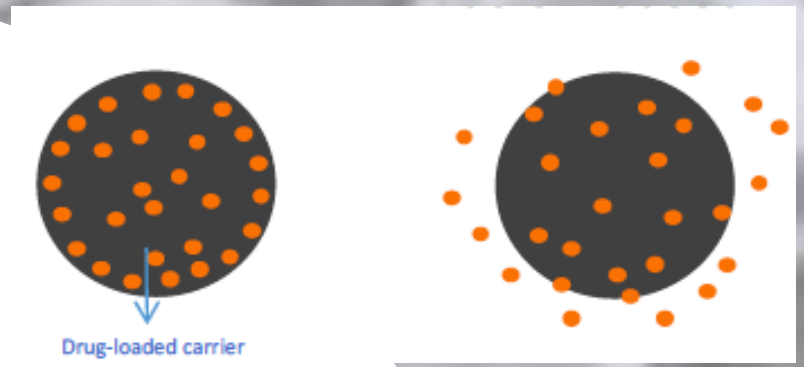


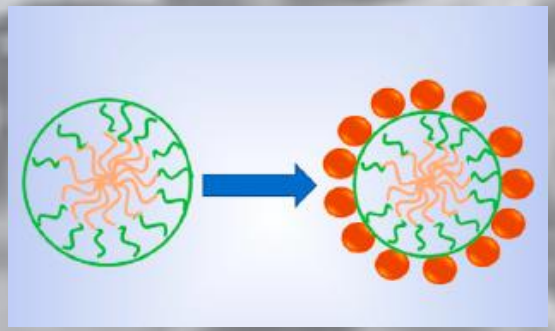
Transporte

Hidrogeles

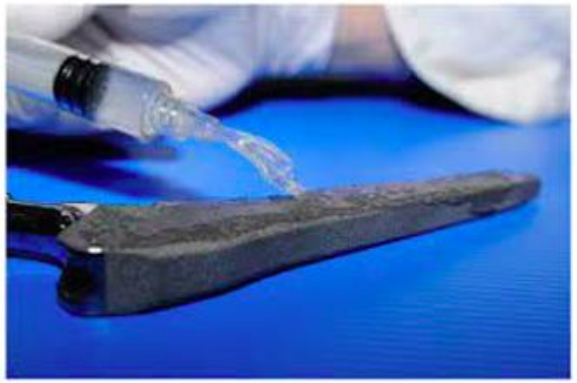
Zhang H, et al. Bone/cartilage targeted hydrogel: Strategies and applications. Bioact Mater. 2022;23:156-169.

Hidrogeles





Profilaxis



Tratamiento

D'Este M. An Antibiotic-Loaded Hydrogel Demonstrates Efficacy as Prophylaxis and Treatment in a Large Animal Model of Orthopaedic Device-Related Infection. Front Cell Infect Microbiol. 2022;12:826392.

Zhang P,. Vancomycin-loaded silk fibroin microspheres in an injectable hydrogel for chronic osteomyelitis therapy. Front Bioeng Biotechnol. 2023 ;11:1163933

"Penicillin can never do what surgery can do”

WINGFIELD-MORRIS HOSPITAL. FIELDEN WARD.

V 437