TERAPIA DELLE INFEZIONI OSTEOARTICOLARI

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“ La grande percentuale di successi ottenuti con la terapia antibiotica nella maggior parte delle malattie ad eziologia batterica contrasta decisamente con la elevata percentuale di fallimenti nel trattamento delle infezioni osteoarticolari “

Waldvogel F.A. et al.: **Osteomyelitis** **Lancet** Vol. 364, Issue 9431, 369 - 379, 24 July 2004

Osteomieliti post-traumatiche

Osteomieliti ematogene

Spondilodisciti

Infezione mezzi osteosintesi

Piede diabetico

Artriti infettive

Pseudoartrosi infette

Infezione di protesi articolare

INFEZIONI OSTEOARTICOLARI
necessità di un team multidisciplinare

ORTOPEDICO

INFETTIVOLOGO

RADIOLOGO

MICROBIOLOGO

MEDICO NUCLEARE

CHIRURGO PLASTICO

FISIOTERAPISTA

……

CLASSIFICAZIONE

Table 1 – Waldvogel classification of osteomyelitis.

	Characteristics
Mechanism of bone infection	
Hematogenous	Secondary to bacterial transport through the blood. Majority of infections in children
Contiguous	Bacterial inoculation from an adjacent focus. E.g. : Post-traumatic Osteomyelitis, infections related to prosthetic devices
Associated with vascular insufficiency	Infections affecting the feet in patients with diabetes, hanseniasis or peripheral vascular insufficiency
Duration of infection	
Acute	Initial episodes of osteomyelitis. Edema, formation of pus, vascular congestion, thrombosis of the small vessels
Chronic	Recurrence of acute cases. Large areas of ischemia, necrosis and bone sequestra

Acute osteomyelitis evolves over several days or weeks, as opposed to chronic osteomyelitis, which is somewhat arbitrarily defined as long-standing infection that evolves over months or even years, characterised by the persistence of microorganisms, low-grade inflammation, and the presence of dead bone (sequestrum) and fistulous tracts.

Relapses in the same area and with accompanying fever are a clear sign of chronic osteomyelitis.

Clinical signs persisting for longer than 10 days are associated with the development of necrotic bone and chronic osteomyelitis.

Lew DP, Waldvogel FA Osteomyelitis.Lancet. 2004 Jul 24-30;364(9431):369-79.

CIERNY and MADER Staging System

Anatomic Type

Stage 1	Medullary osteomyelitis
Stage 2	Superficial osteomyelitis
Stage 3	Localized osteomyelitis
Stage 4	Diffuse osteomyelitis

Physiologic Class

A Host	Normal host
B Host	Systemic compromise (Bs)
	Local compromise (BL)
	Systemic & local compromise (B1s)
C Host	Treatment worse than the disease

EZIOLOGIA

MICROBIOLOGY OF OSTEOMYELITIS

COMMON (>50 %)

S. aureus
S. coagulase negative

Occasionally encountered (>25 %)

Streptococci
Enterococci
Pseudomonas spp.
Enterobacteriaceae
Anaerobes

Rarely encountered(< 5%)

M tuberculosis
MAC
Candida spp.
Aspergillus spp.
Brucella
Salmonella
Actinomyces

Chronic Osteomyelitis

Prevalent Etiology:

- *Staphylococcus aureus*
- Coagulase-negative *staphylococci*
- *Streptococcus* spp.
- *Enterococcus* spp.
- *Pseudomonas aeruginosa*
- Gram-negative enteric bacilli
- Anaerobic bacteria
- *Mycobacterium tuberculosis*
- Fungi

can be polymicrobial !

Nuermberger E, Osteomyelitis, Acute. John Hopkins ABX Guide. 2009

Osteomielite vertebrale

Table II. Microbiological results.

Organism	Blood only	Tissue only	Blood and tissue	Unknown site	Total cases[a]
Staphylococcus aureus					
MSSA	5	15	9	1	30
MRSA	7	10	12	0	29
Streptococci					
Streptococcus pneumoniae	4	0	0	0	4
Viridans Streptococcus NOS	2	1	0	0	3
Group B Streptococcus	1	2	1	0	4
Streptococcus bovis	1	0	0	0	1
Streptococcus equisimilis	1	0	0	0	1
Streptococcus infantarius	0	1	0	0	1
Streptococcus intermedius	0	0	1	0	1
Streptococcus mitis	1	1	1	0	3
Streptococcus anginosis	0	0	1	0	1
Streptococcus NOS	2	1	1	0	4
Gram-negative					
Escherichia coli	3	0	2	0	5
Klebsiella pneumoniae	2	2	1	0	5
Pseudomonas aeruginosa	0	1	0	0	1
Proteus mirabilis	0	2	0	0	2
Bacteroides fragilis	1	0	0	0	1
Coagulase-negative Staphylococcus	3	2	7	0	12
Enterococcus					
Enterococcus faecium	1	0	0	0	1
Enterococcus faecalis	0	1	0	0	1
Other					
Candida albicans	0	0	1	0	1
Veillonella parvula	0	1	0	0	1
Peptostreptococcus	1	0	0	0	1
Mycobacterium tuberculosis	0	2	0	0	2
Mycobacterium chelonae	0	1	0	0	1
Culture-negative	–	–	–	–	13
Missing culture	–	–	–	–	1
Total	35	43	37	1	130

MSSA, methicillin-sensitive Staphylococcus aureus; MRSA, methicillin-resistant Staphylococcus aureus; NOS, not otherwise specified.

[a]Total of 117 cases. Ten cases had 2 or more organisms isolated.

S. Weissman 2014

Spondilite tubercolare

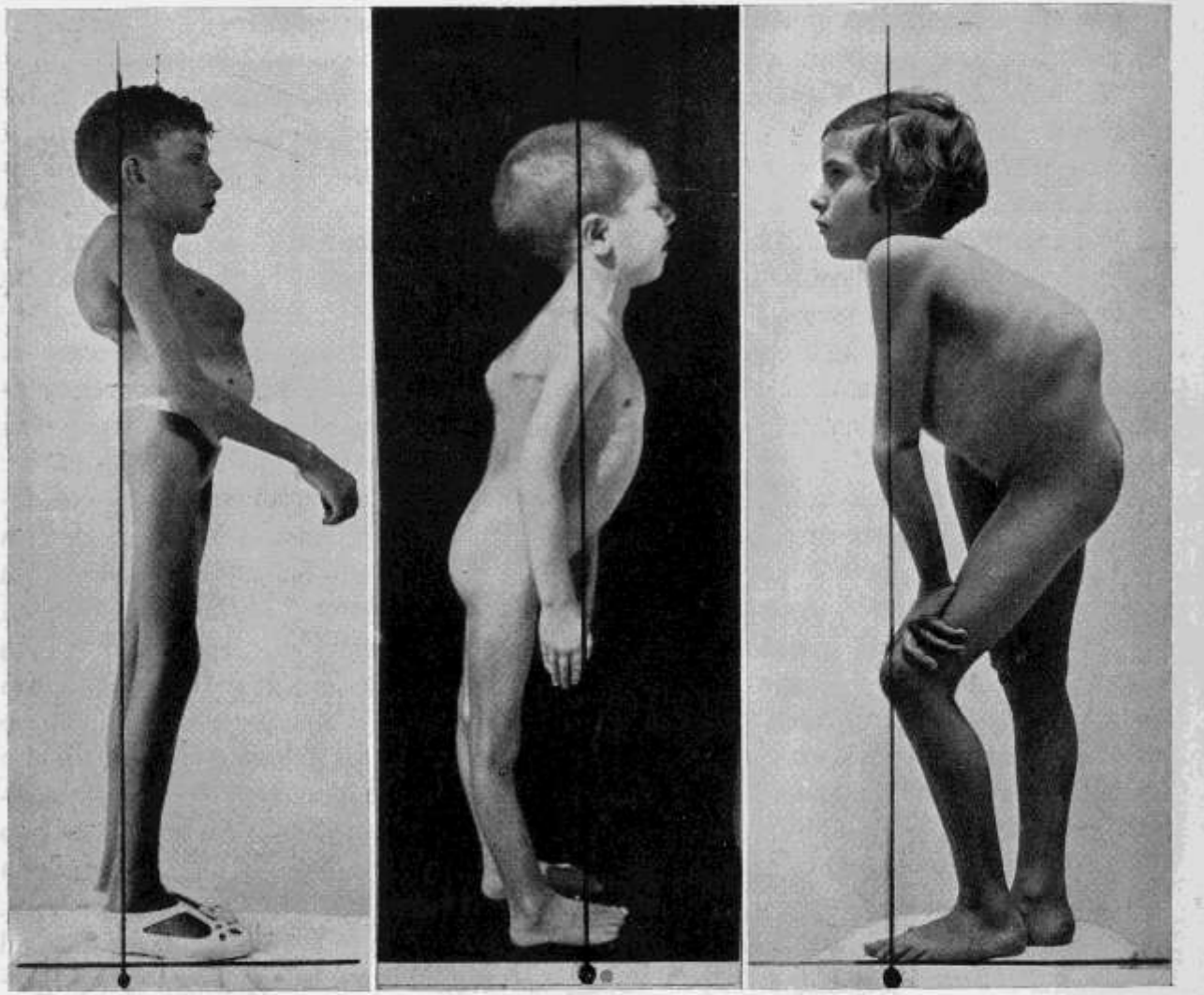


Fig. 34 Fig. 35 Fig. 36

Fig. 34 - *Spondilite dorsale a gibbo rotondo. Spostamento dell'appiombo indietro. Sproporzione fra il corpo e gli arti inferiori.* — Fig. 35 - *Gibbo aguzzo nella spondilite dorsale media. Recurvamento delle ginocchia per ristabilire l'equilibrio del corpo.* — Fig. 36 - *Gibbo dorso-lombare e contrattura psoica. Squilibrio del corpo che per sostenersi ha bisogno dell'appoggio delle mani sulle ginocchia*

DIAGNOSI

- CLINICA-ANAMNESTICA
- ESAMI BIOUMORALI (leucociti,formula, VES, PCR, fibrinogeno, interleuchina-6,alfa defensina …..)
- ESAMI MICROBIOLOGICI
- ESAME ISTOLOGICO
- RADIOLOGIA (Rx,ecografia,TAC, RM)
- MEDICINA NUCLEARE (scintigrafia, TAC PET)

Table 2. Diagnostic Imaging Studies for Osteomyelitis

Imaging modality	*Sensitivity (%)*	*Specificity (%)*	*Comments*
Computed tomography	67	50	Generally should not be used in osteomyelitis evaluation
Leukocyte scintigraphy	61 to 84	60 to 68	Combining with technetium-99 bone scintigraphy can increase specificity
Magnetic resonance imaging	78 to 90	60 to 90	Useful to distinguish between soft tissue and bone infection, and to determine extent of infection; less useful in locations of surgical hardware because of image distortion
Plain radiography (anteroposterior, lateral, and oblique views)	14 to 54	68 to 70	Preferred imaging modality; useful to rule out other pathology
Positron emission tomography	96	91	Expensive; limited availability
Technetium-99 bone scintigraphy	82	25	Low specificity, especially if patient has had recent trauma or surgery; useful to differentiate osteomyelitis from cellulitis, and in patients in whom magnetic resonance imaging is contraindicated

Information from references 24 through 30.

J Hatzenbuehler at al:

DIAGNOSTICA EZIOLOGICA

NELLA SPONDILODISCITE LA PRIMA URGENZA E'

LA <u>DIAGNOSTICA MICROBIOLOGICA</u>

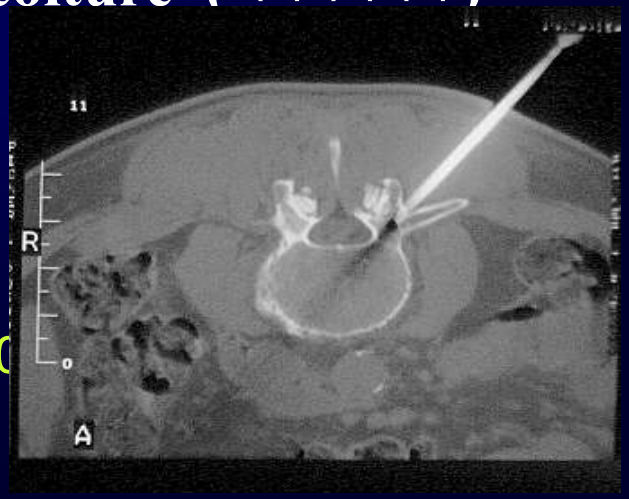
NON LA TERAPIA

una sepsi o una endocardite concomitante prevede l'inizio di una terapia ragionata subito dopo l'esecuzione di emocolture (++++++)

GOLD STANDARD

Nonostante puntuale prelievo e coltura 40

50% di mancata identificazione

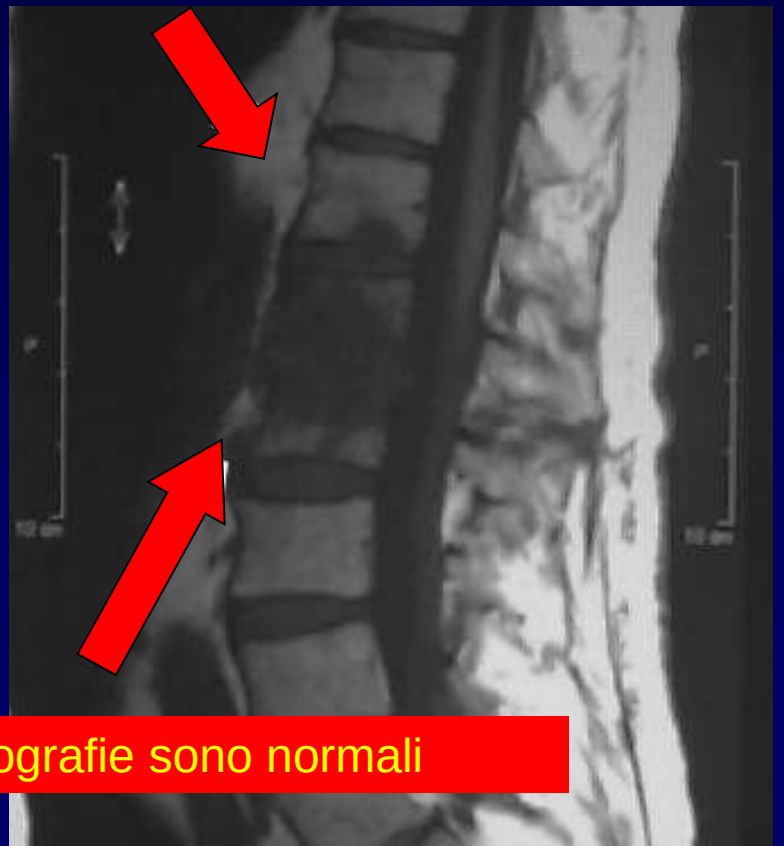


IMAGING

Non permette la diagnosi eziologica

RNM

ESAME DI RIFERIMENTO PER LA DIAGNOSI DI SPONDILODISCITE



Tanto più importante quanto le radiografie sono normali

IMAGING

Non permette la diagnosi eziologica

Positron Emission Tomography as Diagnostic Tool in Infection: Present Role and Future Possibilities

Sandip Basu, MBBS et.alSemin Nucl Med 39:36-51 © 2009 Published by Elsevier Inc.

PET

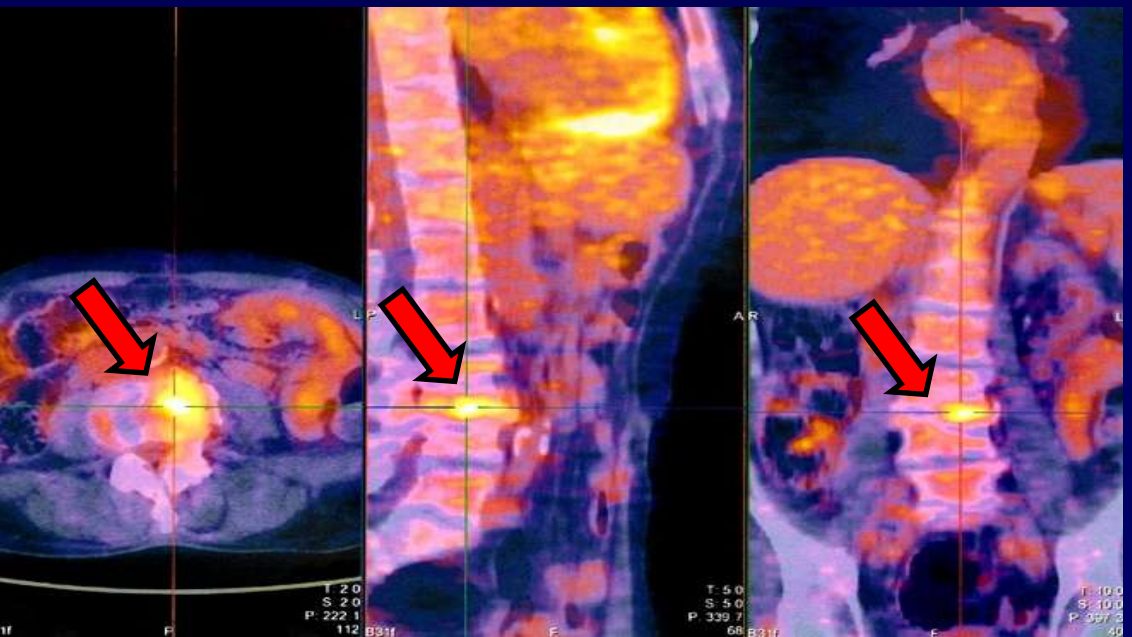
alta specificità e sensibilità

evidenzia l'attività del focolaio flogistico

RAZIONALE IMPIEGO:

- nelle forme rimaste dubbie alla risonanza

monitoraggio della risposta alla terapia antibiotica



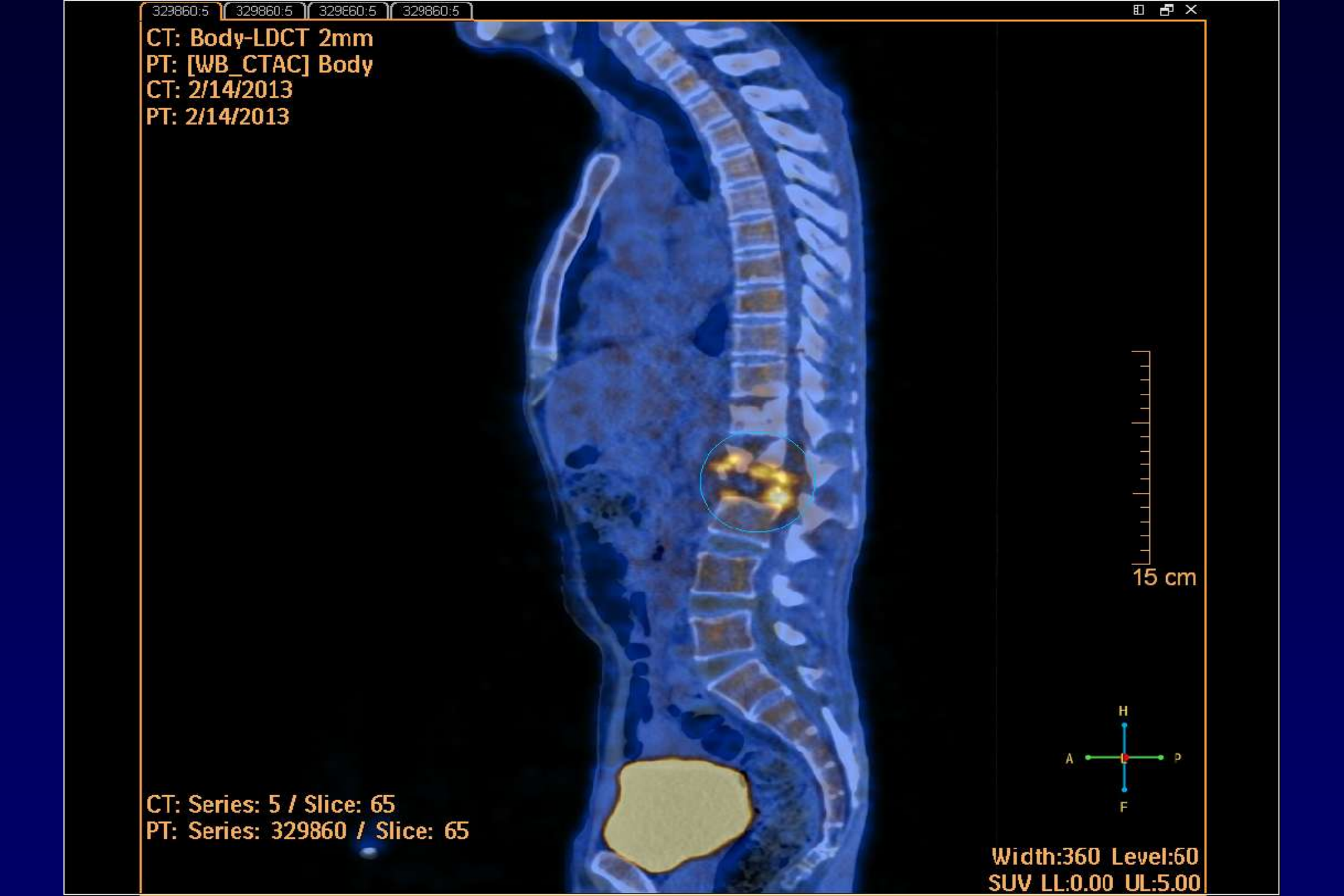
PET + inizio della terapia ragionata

dopo >3 settimane: nuova PET

se migliorata = terapia adeguata

se non migliorata

modificare la terapia


329860:5
329860:5
329860:5
329860:5
CT: Body-LDCT 2mm
PT: [WB_CTAC] Body
CT: 2/14/2013
PT: 2/14/2013
15 cm
H
A
P
F
CT: Series: 5 / Slice: 65
PT: Series: 329860 / Slice: 65
Width:360 Level:60
SUV LL:0.00 UL:5.00

DIAGNOSTICA EZIOLOGICA

NELLA SPONDILODISCITE LA PRIMA URGENZA E'

LA DIAGNOSTICA MICROBIOLOGICA

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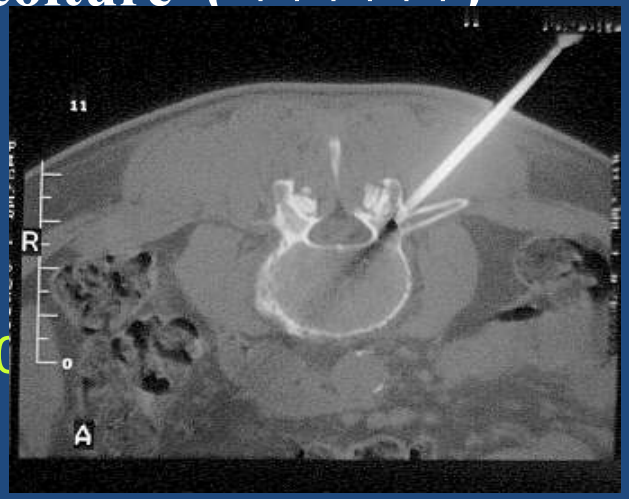
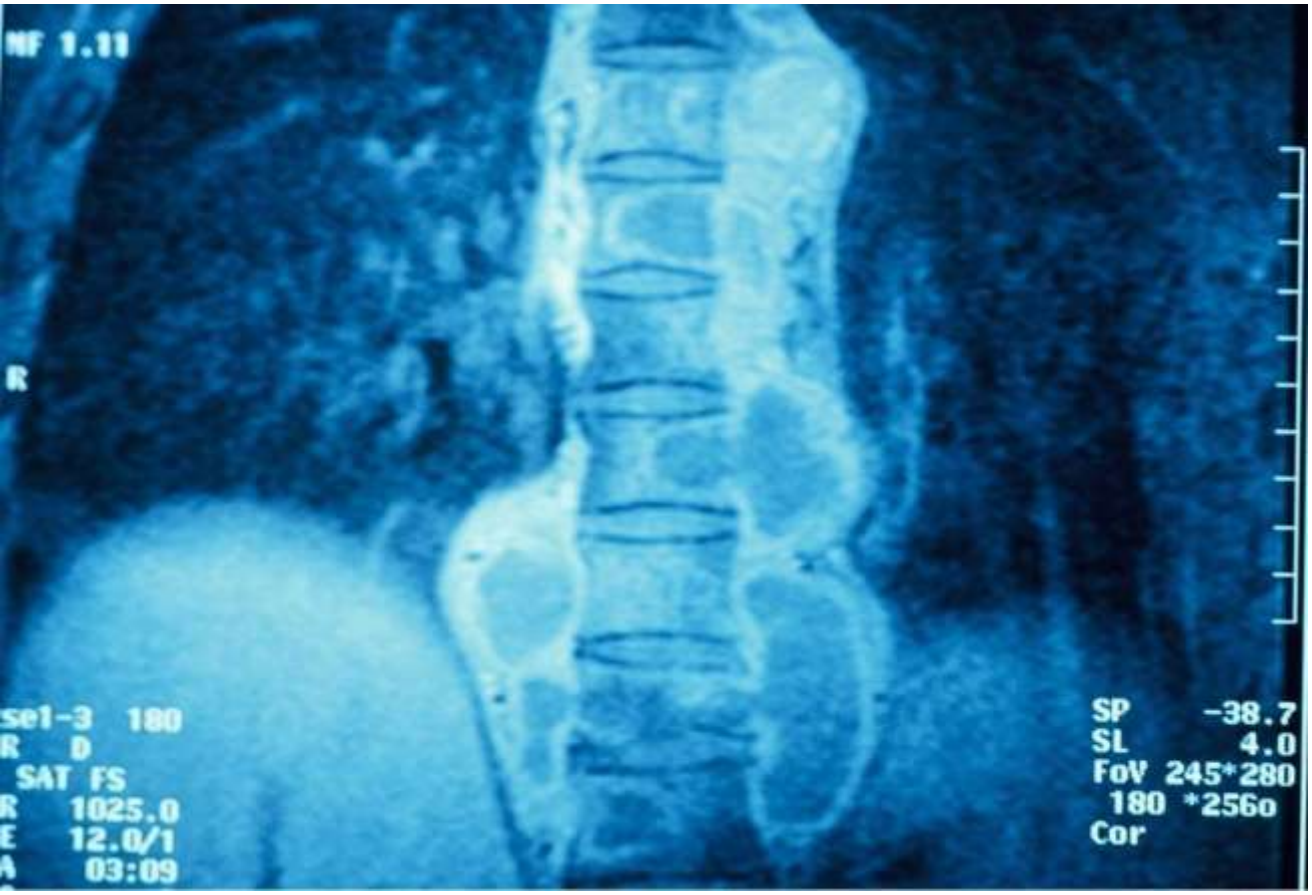
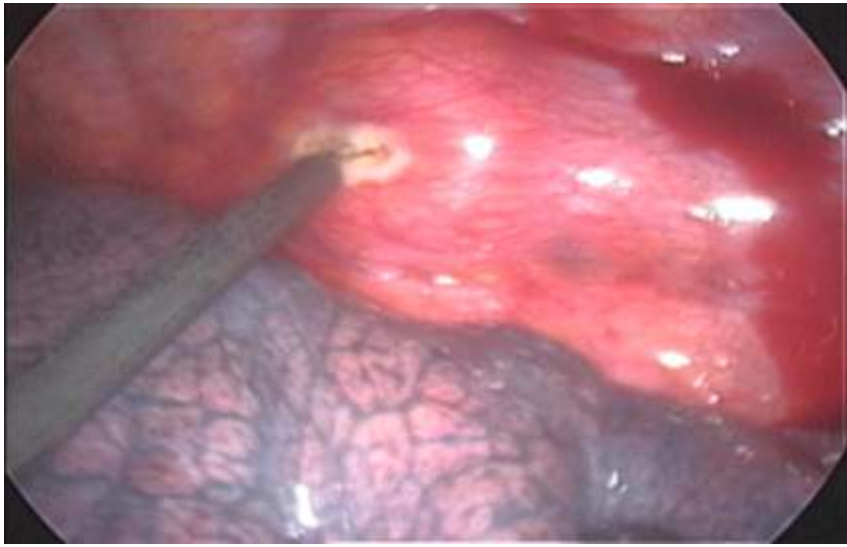
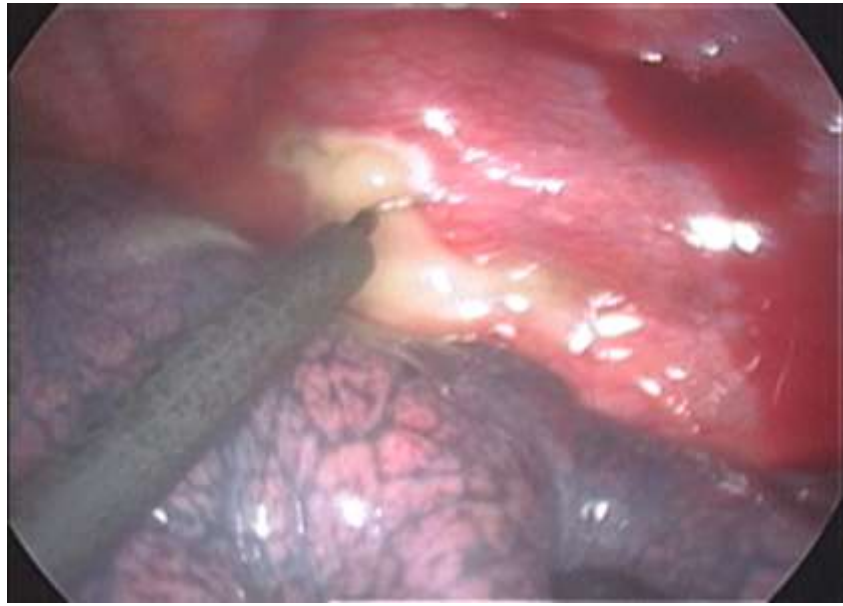



NF 1.11
R
se1-3 180
R D
SAT FS
R 1025.0
E 12.0/1
A 03:09
SP -38.7
SL 4.0
FoV 245*280
180 *256o
Cor





Terapia Antibiotica : Considerazioni

- **La terapia antibiotica deve essere possibilmente mirata**
- **Oltre che sulle caratteristiche dello spettro di azione, la scelta dell'antibiotico deve tenere conto della cinetica tissutale ed ossea**
- **L'antibiotico, preferibilmente battericida, deve essere efficace anche nei confronti dei batteri in fase di crescita stazionaria**

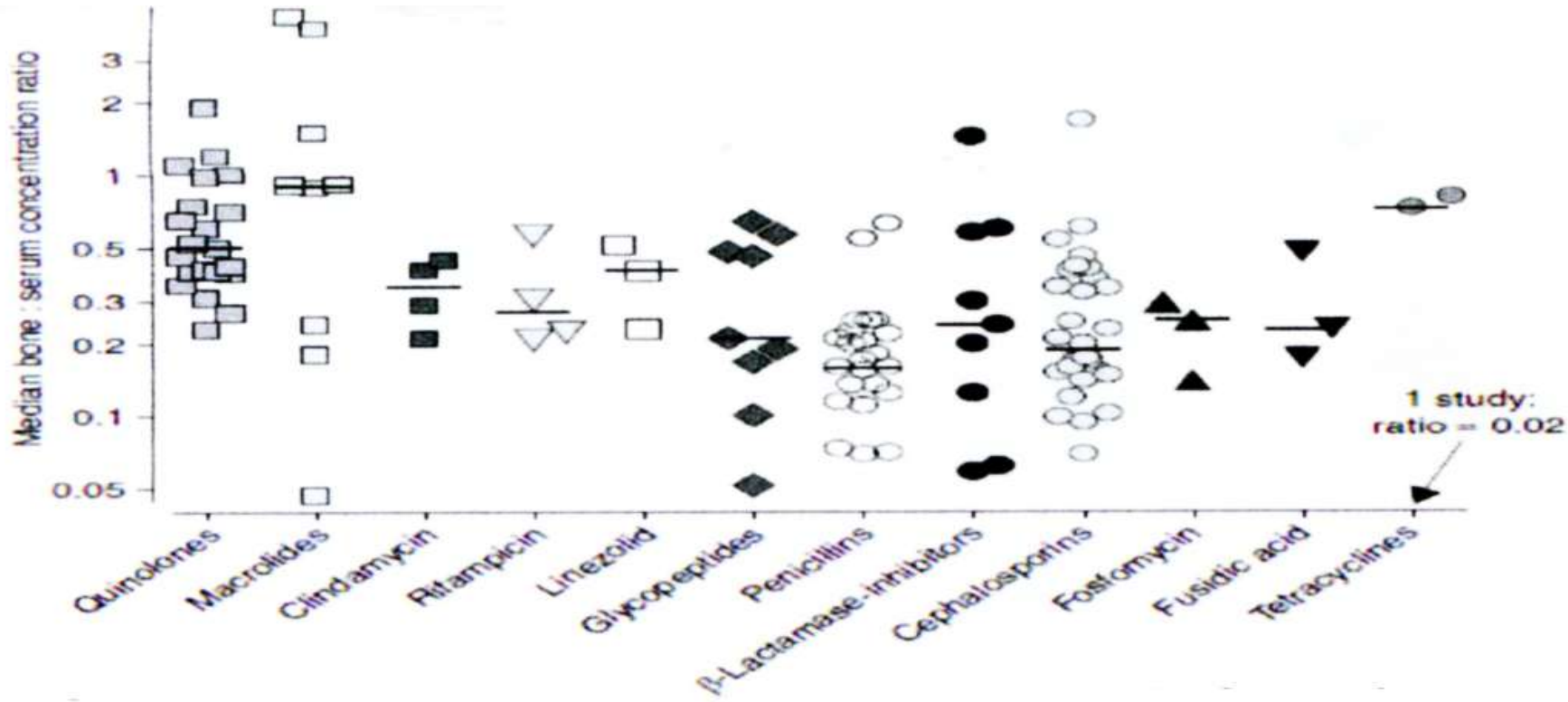
Diffusione degli antibiotici nel tessuto osseo

BUONA	SODDISFACENTE	MEDIOCRE
Rifampicina	Cefalosporine	Penicilline
Macrolidi	Fosfomicina	Aminoglicosidi
Lincosamidi	Carbapenemici	
Fluorochinoloni	Quinopristin/ dalfopristin	
Glicopeptidi		

BONE PENETRATION OF ANTIBIOTICS

ANTIBIOTIC	Time interval since last dose (h)	Bone/serum %
Amoxycillin Amoxycillin clavulanate Ampicillin sulbactam Piperacillin tazobactam	2 0,5-6 0,25-4 1	20-30 10 10-70 20-30
Ertapenem	1,6-23,8	15-20
Oxacillin	1	10
Ceftriaxone	0,2-8	20-50
Cefazolin	0,9	20
Cefepime	1-2	50-80
Ceftazidime	2	30-50
Clindamycin	1-2	20-45
Rifampin	3,5-4,5	50-60
Aminosidi	1-2	15-30
Trimetoprim		20-50
Tigecyclin	4-24	35-200
Levofloxacin	0,7-2	35-100
Ciprofloxacin	2-4,5	40
Vancomycin	1-7	30
Linezolid	0,9	40-60
Teicoplanin	4-16	50-65
Daptomycin	2	100

Figure 1. Human bone:serum ratios for various groups of antibacterials.



**Lines indicate the group medians, and each symbol indicates the median concentration ratio of one study.*

Terapia Antibiotica : Considerazioni

- **La via di somministrazione dell'antibiotico deve essere, almeno inizialmente, sempre quella endovenosa (fase di induzione) per almeno 4 settimane, seguita da una fase di estensione o consolidamento con antibiotici orali (switch-therapy) per poter sterilizzare i foci residui di infezione riducendo in tal modo le ricadute**
- **I farmaci devono essere usati a dosaggi elevati per poter raggiungere elevate concentrazioni in un tessuto con importanti modificazioni patologiche. Una terapia antibiotica a dosaggi non corretti porta molto spesso a ricadute di malattia**
- **La durata ottimale della terapia non è stabilita**

TERAPIA SOPPRESSIVA

La rimozione della protesi articolare infetta può non essere indicata se :

- **controindicazione all'intervento per le condizioni del paziente**
- **il risultato è una funzionalità non accettabile**
- **difficoltà nel rimuovere una protesi ben fissata**
- **rifiuto del paziente di sottoporsi a nuovi interventi**

Osteomielite ematogena - ossa lunghe

Sospetto clinico

Emocolture

RX , se dubbia RMN , se dubbia
Acuta : scintigafia con ^{99}Tc
Subacuta-cronica :scintigafia con leucociti marcati

Biopsia ossea

Terapia antibiotica empirica

- Ampicillina/sulbactam-Amoxiclavulanato
- Oxacillina + Ceftriaxone/Cefotaxime
- Teicoplanina + Ceftriaxone/Cefotaxime

Nel bambino

- Oxacillina o Teicoplanina + Cefalosporina 3a o Fluorochinolonico

Nell'adulto

In presenza di emoglobinopatia: Ciprofloxacina o Levofloxacina

Coltura positiva

Terapia mirata

- durata terapia : 4-6 settimane
- se necessaria toilette chirurgica.
- la durata della terapia e' di 6 settimane dopo l'intervento

Coltura negativa

Prosegue terapia empirica

Osteomielite da frattura esposta

Esami bioumorali

Toilette chirurgica

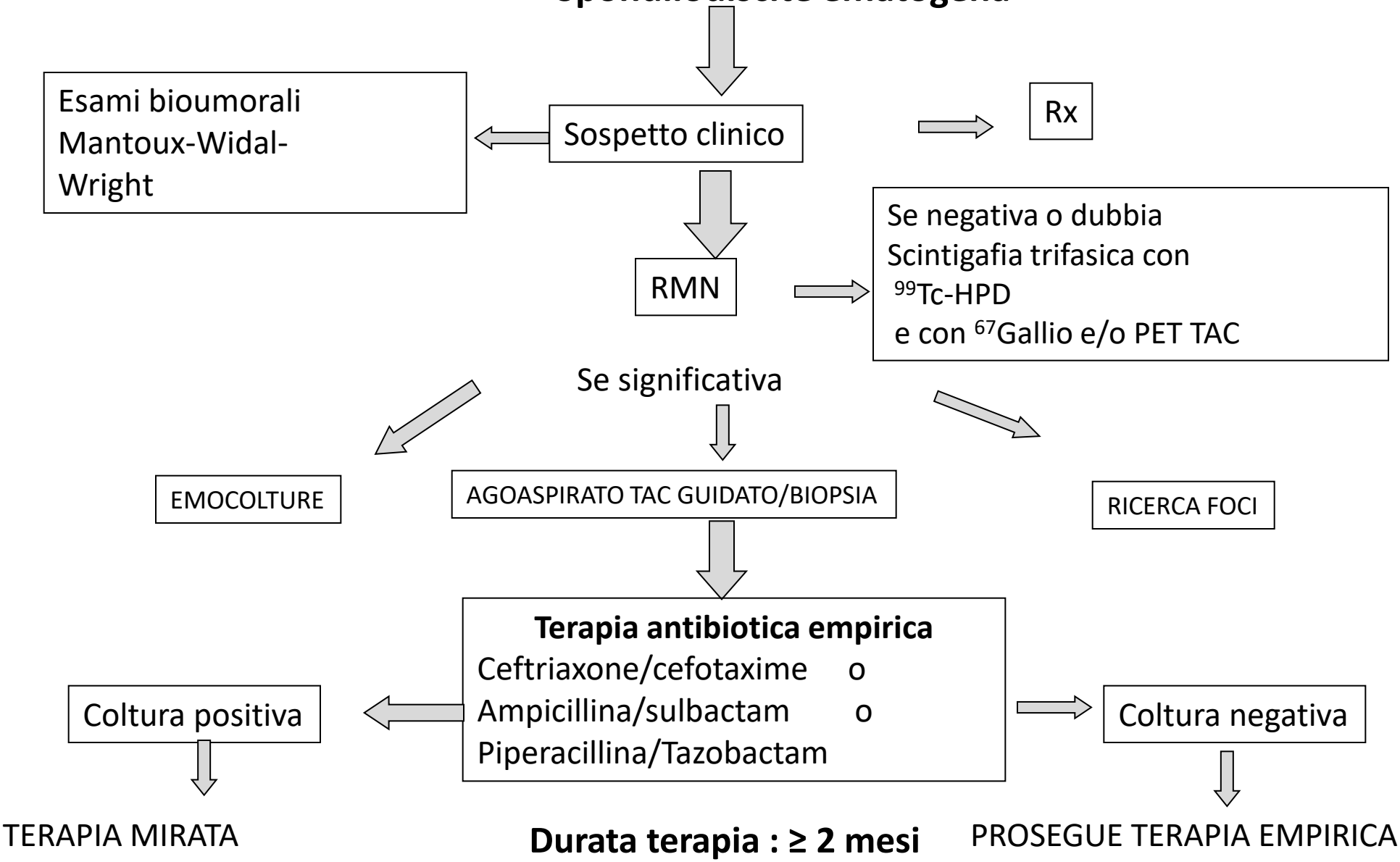
Rx standard

Terapia empirica

- Ampicillina/sulbactam
- Amoxiclavulanato
- Piperacillina/Tazobacatam

Durata terapia per 4-6 settimane

Spondilodiscite ematogena



Sulla base dei valori degli esami bioumorali (in particolare PCR) e soprattutto della RMN

Clinical Infectious Diseases

MAJOR ARTICLE

Optimal Duration of Antibiotic Therapy in Patients With Hematogenous Vertebral Osteomyelitis at Low Risk and High Risk of Recurrence

Ki-Ho Park,[1] Oh-Hyun Cho,[2] Jung Hee Lee,[3] Ji Seon Park,[4] Kyung Nam Ryu,[4] Seong Yeon Park,[5] Yu-Mi Lee,[6] Yong Pil Chong,[7] Sung-Han Kim,[7] Sang-Oh Lee,[7] Sang-Ho Choi,[7] In-Gyu Bae,[2] Yang Soo Kim,[7] Jun Hee Woo,[7] and Mi Suk Lee[1]

[1]Division of Infectious Diseases, Department of Internal Medicine, Kyung Hee University Hospital, Kyung Hee University School of Medicine, Seoul, [2]Department of Internal Medicine, Gyeongsang National University School of Medicine, Jinju, [3]Department of Orthopaedic Surgery, Kyung Hee University School of Medicine, and [4]Department of Radiology, Kyung Hee University Hospital, Kyung Hee University School of Medicine, Seoul, [5]Division of Infectious Diseases, Department of Internal Medicine, Dongguk University Ilsan Hospital, University of Dongguk College of Medicine, Goyang-si, [6]Department of Infectious Diseases, Busan Paik Hospital, Inje University College of Medicine, and [7]Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

(See the Editorial Commentary by Murillo and Lora-Tamayo on pages 1270–1.)

Background. The optimal duration of antibiotic treatment for hematogenous vertebral osteomyelitis (HVO) should be based on the patient's risk of recurrence, but it is not well established.

Methods. A retrospective review was conducted to evaluate the optimal duration of antibiotic treatment in patients with HVO at low and high risk of recurrence. Patients with at least 1 independent baseline risk factor for recurrence, determined by multivariable analysis, were considered as high risk and those with no risk factor as low risk.

Results. A total of 314 patients with microbiologically diagnosed HVO were evaluable for recurrence. In multivariable analysis, methicillin-resistant *Staphylococcus aureus* infection (adjusted odds ratio [aOR], 2.61; 95% confidence interval [CI], 1.16–5.87), undrained paravertebral/psoas abscesses (aOR, 4.09; 95% CI, 1.82–9.19), and end-stage renal disease (aOR, 6.58; 95% CI, 1.63–26.54) were independent baseline risk factors for recurrence. Therefore, 191 (60.8%) patients were classified as low risk and 123 (39.2%) as high risk. Among high-risk patients, there was a significant decreasing trend for recurrence according to total duration of antibiotic therapy: 34.8% (4–6 weeks [28–41 days]), 29.6% (6–8 weeks [42–55 days]), and 9.6% (≥8 weeks [≥56 days]) ($P = .002$). For low-risk patients, this association was still significant but the recurrence rates were much lower: 12.0% (4–6 weeks), 6.3% (6–8 weeks), and 2.2% (≥8 weeks) ($P = .02$).

Conclusions. Antibiotic therapy of prolonged duration (≥8 weeks) should be given to patients with HVO at high risk of recurrence. For low-risk patients, a shorter duration (6–8 weeks) of pathogen-directed antibiotic therapy may be sufficient.

Keywords. vertebral osteomyelitis; spondylitis; antibiotic; treatment; outcome.

Univariate analysis indicated that end-stage renal disease (ESRD), methicillin-resistant *S. aureus* (MRSA) infection, and undrained paravertebral/psoas abscesses were baseline risk factors for recurrence (Table 3). Multivariable analysis indicated that ESRD (adjusted odds ratio [aOR], 6.58; 95% confidence interval [CI], 1.63–26.54; $P = .008$), MRSA infection (aOR, 2.61; 95% CI, 1.16–5.87; $P = .02$), and undrained paravertebral/psoas abscesses (aOR, 4.09; 95% CI, 1.82–9.19; $P = .001$) were independent baseline risk factors for recurrence (Table 3). Overall, 191 (60.8%) patients with no baseline risk factors were classified as patients at low risk of recurrence, and 123

Table 2 Parenteral Antimicrobial Treatment of Common Microorganisms Causing Native Vertebral Osteomyelitis

Microorganism	First Choice[a]	Alternatives[a]	Comments[b]
Staphylococci, oxacillin susceptible	Nafcillin[c] sodium or oxacillin 1.5–2 g IV q4–6 h or continuous infusion or Cefazolin 1–2 g IV q8 h or Ceftriaxone 2 g IV q24 h	Vancomycin IV 15–20 mg/kg q12 h[d] or daptomycin 6–8 mg/kg IV q24 h or linezolid 600 mg PO/IV q12 h or levofloxacin 500–750 mg PO q24 h and rifampin PO 600 mg daily [122] or clindamycin IV 600–900 mg q8 h	6 wk duration
Staphylococci, oxacillin resistant [123]	Vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	Daptomycin 6–8 mg/kg IV q24 h or linezolid 600 mg PO/IV q12 h or levofloxacin PO 500–750 mg PO q24 h and rifampin PO 600 mg daily [122]	6 wk duration
Enterococcus species, penicillin susceptible	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses; or ampicillin sodium 12 g IV q24 h continuously or in 6 divided doses	Vancomycin 15–20 mg/kg IV q12 h (consider loading dose, monitor serum levels) or daptomycin 6 mg/kg IV q24 h or linezolid 600 mg PO or IV q12 h	Recommend the addition of 4–6 wk of aminoglycoside therapy in patients with infective endocarditis. In patients with BSI, physicians may opt for a shorter duration of therapy. Optional for other patients [124, 125]. Vancomycin should be used only in case of penicillin allergy.
Enterococcus species, penicillin resistant[e]	Vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	Daptomycin 6 mg/kg IV q24 h or linezolid 600 mg PO or IV q12 h	Recommend the addition of 4–6 wk of aminoglycoside therapy in patients with infective endocarditis. In patients with BSI, physicians may opt for a shorter duration of aminoglycoside. The additional of aminoglycoside is optional for other patients [124, 125].
Pseudomonas aeruginosa	Cefepime 2 g IV q8–12 h or meropenem 1 g IV q8 h or doripenem 500 mg IV q8 h	Ciprofloxacin 750 mg PO q12 h (or 400 mg IV q8 h) or aztreonam 2 g IV q8 h for severe penicillin allergy and quinolone-resistant strains or ceftazidime 2 g IV q8 h	6 wk duration Double coverage may be considered (ie, β-lactam and ciprofloxacin or β-lactam and an aminoglycoside).
Enterobacteriaceae	Cefepime 2 g IV q12 h or ertapenem 1 g IV q24 h	Ciprofloxacin 500–750 mg PO q12 h or 400 mg IV q12 hours	6 wk duration
β-hemolytic streptococci	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses or ceftriaxone 2 g IV q24 h	Vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	6 wk duration Vancomycin only in case of allergy.
Propionibacterium acnes	Penicillin G 20 million units IV q24 h continuously or in 6 divided doses or ceftriaxone 2 g IV q24 h	Clindamycin 600–900 mg IV q8 h or vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	6 wk duration Vancomycin only in case of allergy.
Salmonella species	Ciprofloxacin PO 500 mg q12 h or IV 400 mg q12 h	Ceftriaxone 2 g IV q24 h (if nalidixic acid resistant)	6–8 wk duration

CID 2015
IDSA
GUIDELINES

Table 3. Selected Oral Antibacterial Agents With Excellent Oral Bioavailability Commonly Used to Treat Patients With Native Vertebral Osteomyelitis

Oral Agents	Comments
Metronidazole 500 mg PO tid to qid	Can be used in the intital course of NVO due to Bacteroides species and other susceptible anaerobes.
Moxifloxacin 400 mg PO once daily	Is not recommended for use in patients with staphylococcal NVO, but may be used in patients with NVO due to Enterobacteriaceae and other susceptible aerobic gram-negative organisms.
Linezolid 600 mg PO bid	Can be used in the intital course of NVO due to oxacillin-resistant staphylocci when first-line agents cannot be used.
Levofloxacin 500–750 mg PO once daily	Is not recommended for use in patients with staphylococcal NVO as monotherapy but may be used in patients with NVO due to Enterobacteriaceae and other susceptible aerobic gram-negative organisms.
Ciprofloxacin 500–750 mg PO bid	Is not recommended for use in patients with staphylococcal NVO but may be used in patients with NVO due to Enterobacteriaceae and other susceptible aerobic gram-negative organisms including Pseudomonas aeruginosa and Salmonella species.
TMX-SMX 1–2 double strength tabs PO bid	Is not recommended for use in patients with staphylococcal NVO but may be recommended as a second-line agent in patients with NVO due to Enterobacteriaceae and other susceptible aerobic gram-negative organisms. May need to monitor sulfamethoxazole levels.
Clindamycin 300–450 mg PO qid	Recommended as second-line choice for sensitive staphylococcal NVO.
Doxycycline and rifampin	Mostly used in patients with brucellar NVO.

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Terapia della tubercolosi vertebrale

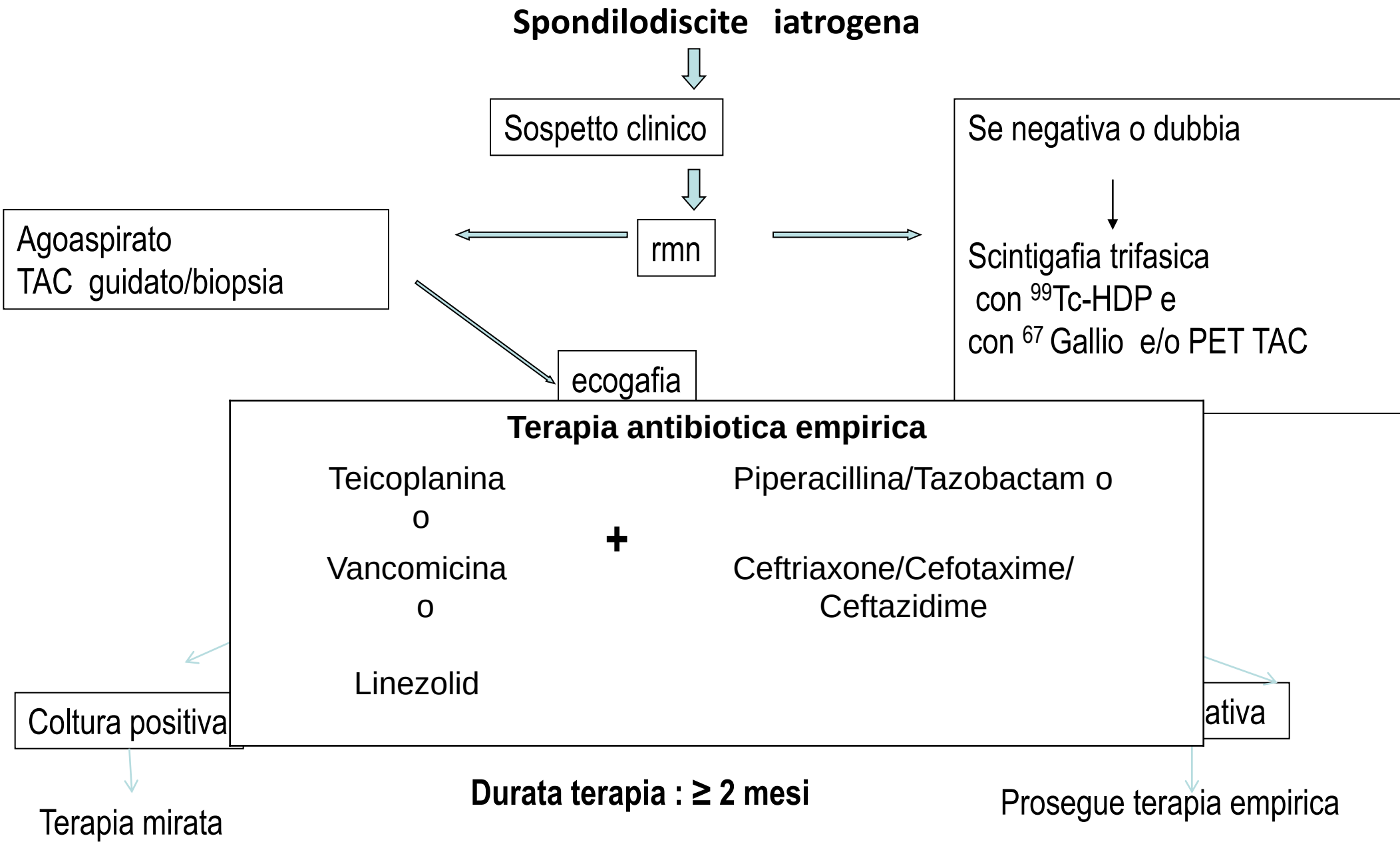
Nella tubercolosi vertebrale vengono utilizzati i medesimi protocolli terapeutici della tubercolosi polmonare, tuttavia la rarità della malattia fa si che non è ancora stata stabilita una durata ottimale della terapia.
La durata della terapia varia dai 9 ai 18 mesi a seconda dei vari autori e in base alla gavità della malattia. Un trattamento di 9 – 12 mesi è comunque la prassi più diffusa.

Protocollo standard per la cura della tubercolosi vertebrale

Fase Iniziale	Fase di Mantenimento
ISONAZIDE, RIFAMPICINA, PIRAZINAMIDE, ETAMBUTOLO giornalmente o 3 volte la settimana (a giorni alterni)* per 2 - 3 mesi	**ISONAZIDE, RIFAMPICINA giornalmente o 3 volte la settimana (a giorni alterni)* per 7- 9 mesi**

***Il regime 3 volte la settimana è consigliato solo sotto osservazione DOT**

Associata alla terapia medica è importante il riposo assoluto a letto inizialmente, il drenaggio chirurgico di raccolte ascessuali paravertebrali, l'uso di busti ortopedici e la fisioterapia, mentre gli interventi chirurgici di decompressione e stabilizzazione in uno o due tempi sono indicati solo in caso di tubercolosi vertebrale complicata (plegia o instabilità).



Sulla base dei valori degli esami bioumorali (in particolare PCR) e soprattutto della RMN

Dosaggi consigliati nelle osteomieliti

•Teicoplanina	12 mg/Kg
•Vancomicina	30 mg/Kg
•Ceftriaxone	2 g/die
•Cefotaxime	2 g x 3 die
•Ampicillina/sulbactam	3 g x 3-4/die
•Amoxiclavulanato	2,2 g x 3 die
•Oxacillina	2 g x 4-6/die
•Rifampicina	600/900 mg/die
•Levofloxacina	500 mg x 2 die
•Ciprofloxacina	400 mg x 3 e.v. /die 500-750 mg X 2/die
•Bactrim	2 cp x 2/die
•Minociclina	100 mg x 2 /die

Schemi di terapia orale nelle infezioni ossee (terapia sequenziale)

Coltura negativa
• Rifampicina + Levofloxacina
•Rifampicina + Cotrimoxazolo
Coltura positiva per S. aureo MS
• Amoxicillina/clavulanato
•Levofloxacina
•Cotrimossazolo
Coltura per S. aureo MS
•Rifampicina + Acido fusidico
• Rifampicina + Cotrimoxazolo
•Rifampicina + Levofloxacina
•Linezolid
• Minociclina
Coltura positiva per batteri Gram negativi
• Amoxicillina/ acido clavulanico
•Ciprofloxacina
•Levofloxacina

Terapia antibiotica long-term o terapia soppressiva

- La scelta della terapia antibiotica soppressiva viene considerata quando il trattamento chirurgico è controindicato, quando la rimozione dell'impianto è tecnicamente difficoltosa, quando non è necessario ottenere la funzionalità della protesi, quando il paziente rifiuta l'intervento chirurgico.

I migliori risultati sono stati ottenuti con i seguenti antibiotici o associazoni:

- **RIFAMPICINA + FLUOROCHINOLONI**
- **RIFAMPICINA + ACIDO FUSIDICO**
- **RIFAMPICINA + COTRIMOXAZOLO**
- **FUOROCHINOLONI**
- **COTRIMOXAZOLO**
- **MINOCICLINA**

- La durata ottimale della terapia soppressiva non è codificata

ALTRI APPROCCI TERAPEUTICI

- BIOFILM/ QUORUM SENSING
- GROWTH FACTOR/GENE THERAPY
- PULSED ELECTROMAGNETIC FIELS/ULTRASOUND
- PLATELET RICH PLASMA
- HYPERBARIC OXYGEN THERAPY

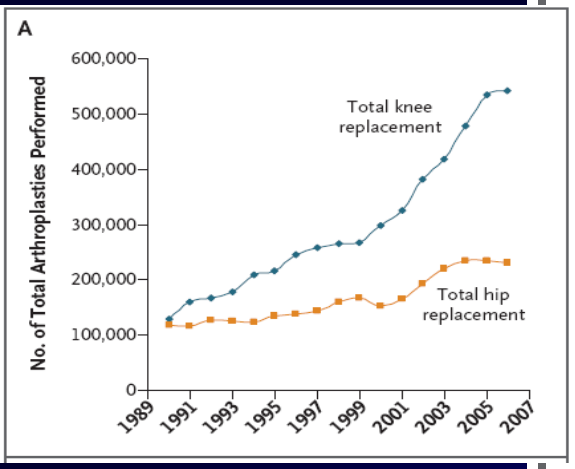
INFEZIONI PROTESICHE

PROTESI ARTICOLARI ITALIA 2013

~ 200.000 protesi impiantate S.I.O.T.

- **1 MILIONI DI ITALIANI SONO PORTATORI DI PROTESI ARTICOLARI**
- **In aumento le revisioni**
- **Aumentate le protesi di spalla (~ 9.000) 70% inverse**
- **Flessione del 4 % nel corso del 2014**

ASSOBIOMEDICA



B

No. of Prosthetic-Joint Infections

7000
6000
5000
4000
3000
2000
1000
0

1989
1991
1993
1995
1997
1999
2001
2003
2005

Infected total knee arthroplasty

0.8 - 1.9% → 2.2 %*

Infected total hip arthroplasty

0.3 - 1.7% → 2.2 %*

N ENGL J MED 361;8 NEJM.ORG AUGUST 20, 2009

* Tande, A.J. Et al:Prosthetic Joint Infection *Clin. Microbiol. Rev.* 2014, 27(2):302.DOI:10.1128/CMR.00111-13.

Clinical Infectious Diseases Advance Access published December 6, 2012

IDSA GUIDELINES

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

Douglas R. Osmon,[1] Elie F. Berbari,[1] Anthony R. Berendt,[2] Daniel Lew,[3] Werner Zimmerli,[4] James M. Steckelberg,[1] Nalini Rao,[5,6] Arlen Hanssen,[7] and Walter R. Wilson[1]

[1]Division of Infectious Diseases, Mayo Clinic College of Medicine, Rochester, Minnesota; [2]Bone Infection Unit, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Trust, United Kingdom; [3]Division of Infectious Diseases, Department of Internal Medicine, University of Geneva Hospitals, [4]Basel University Medical Clinic, Liestal, Switzerland; [5]Division of Infectious Diseases, Department of Medicine, and [6]Department of Orthopaedic Surgery, University of Pittsburgh School of Medicine, Pennsylvania, and [7]Department of Orthopedics, Mayo Clinic College of Medicine, Rochester, Minnesota

Table 1. Classification of prosthetic joint infections

Category	Early	Delayed	Late
Presenting after surgery	1st month	2nd–6th month	> 6th month
Acquisition	During implantation	During implantation	Haematogenous
Aetiology	*Staphylococcus aureus*, *Streptococcus* spp., GNB	*Staphylococcus epidermidis*	*Staphylococcus aureus*, *Streptococcus* spp., *Staphylococcus epidermidis*, bacilli
Treatment	Retention[a]	Remove	Retention[a]

[a]If duration of symptoms is < 1 month, prosthesis is stable, and pathogen is susceptible to oral antibiotics with activity against surface-adhering microorganisms.

J. Barbera´n

TABLE 2 Test characteristics and relative costs of several preoperative tests for diagnosis of prosthetic joint infection[b]

Test	Joint(s)	Threshold value or finding	Sensitivity (%)	Specificity (%)
Peripheral blood				
WBC	Hip and knee	11,000 □10^9 cells/liter[a]	45	87
CRP	Hip and knee	10 mg/liter[a]	88	74
ESR	Hip and knee	30 mm/h[a]	75	70
IL-6	Hip and knee	10 pg/ml[a]	97	91
Procalcitonin	Hip and knee	0.3 ng/ml	33	98
Imaging				
Plain radiograph	Hip	Lucency or periosteal new bone formation	75	28
Triple-phase bone scan	Late hip	Increased uptake in all 3 phases	88	90
Bone scan/labeled leukocyte scan	Late hip and knee	Incongruent images	64	70
FDG-PET scan	Hip and knee	Various	82.1	86.6
Synovial fluid analysis				
Cell count	Knee	1,100 cells/□	90.7	88.1
Neutrophil percentage	Knee	64%	95.0	94.7
Cell count	Hip	4,200 cells/□	84.0	93.0
Neutrophil percentage	Hip	80%	84.0	82.0
Cell count	Knee (□6 wk after implantation)	27,800 cells/□	84.0	99.0
Neutrophil percentage	Knee (□6 wk after implantation)	89%	84.0	69.0
Culture	Hip and knee		72.0	95.0

[a] Median threshold for studies included in the meta-analysis.

[b] WBC, white blood cell count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; □LR, positive likelihood rati

AJ TANDE 2014

DIAGNOSTICA

"LA CLINICA CON LA STORIA DEL PZ"

PREOPERATORIA

SANGUE
- GB VES PCR -
PCT IL-6 -

IMAGING
- Rx
- Scintigrafia Tc. Leu. N.C.
- ECO TC RM (PET)

LIQUIDO SINOVIALE
- Cellularità
- Gram
- Colturale

INTRAOPERATORIA

+++ colturali
Es.istologico

MATERIALE ESPIANTATO
. coltura

NUOVE METODICHE
Sonicazione
PCR
Calorimetria

EZIOLOGIA

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE
CURRENT CONCEPTS
◄ Previous Volume 351:1645-1654 October 14, 2004 Number 16 Next ►

Prosthetic-Joint Infections

Werner Zimmerli, M.D., Andrej Trampuz, M.D., and Peter E. Ochsner, M.D.

Table 1

Commonly identified microorganisms causing prosthetic joint infection.

Microorganism	frequency (%)
Coagulase-negative staphylococci	30–43
Staphylococcus aureus	12–23
Streptococci	9–10
Enterococci	3–7
Gram-negative bacilli	3–6
Anaerobes	2–4
Polymicrobial	10–12
Unknown	10–11

Common causes of prosthetic-knee and prosthetic-hip infection

- Gram-positive cocci (approximately 65%)
  - Coagulase-negative staphylococci
  - *Staphylococcus aureus*
  - Streptococcus species
  - Enterococcus species
- Aerobic gram-negative bacilli (approximately 6%)
  - Enterobacteriaceae
  - *Pseudomonas aeruginosa*
- Anaerobes (approximately 4%)
  - Propionibacterium species
  - Peptostreptococcus species
  - *Finegoldia magna*
- Polymicrobial (approximately 20%)
- Culture-negative (approximately 7%)
- Fungi (approximately 1%)

N ENGL J MED 361;8 NEJM.ORG AUGUST 20, 2009

COMMON CAUSE OF PROSTHETIC JOINT INFECTION

Infection	% of patients with prosthetic joint infection					
	Hip and knee					
	All time periods[a]	Early infection[b]	Hip[c]	Knee[c]	Shoulder[d]	Elbow[e]
Staphylococcus aureus	27	38	13	23	18	42
Coagulase-negative *Staphylococcus*	27	22	30	23	41	41
Streptococcus species	8	4	6	6	4	4
Enterococcus species	3	10	2	2	3	0
Aerobic Gram-negative bacilli	9	24	7	5	10	7
Anaerobic bacteria	4	3	9	5		
Propionibacterium acnes					24	1
Other anaerobes					3	0
Culture negative	14	10	7	11	15	5
Polymicrobial	15	31	14	12	16	3
Other	3					

[a] Data aggregated from 2,435 joints
[b] Data aggregated from 637 joints
[c] Data from 1,979 hip and 1,427 knee PJIs from the Mayo Clinic Prosthetic Joint Infection Database
[d] Data aggregated from 199 shoulders
[e] Data aggregated from 110 elbows

Prosthetic Joint Infection *Clin. Microbiol. Rev.* 2014, 27(2):302.

STRATEGIE TERAPEUTICHE

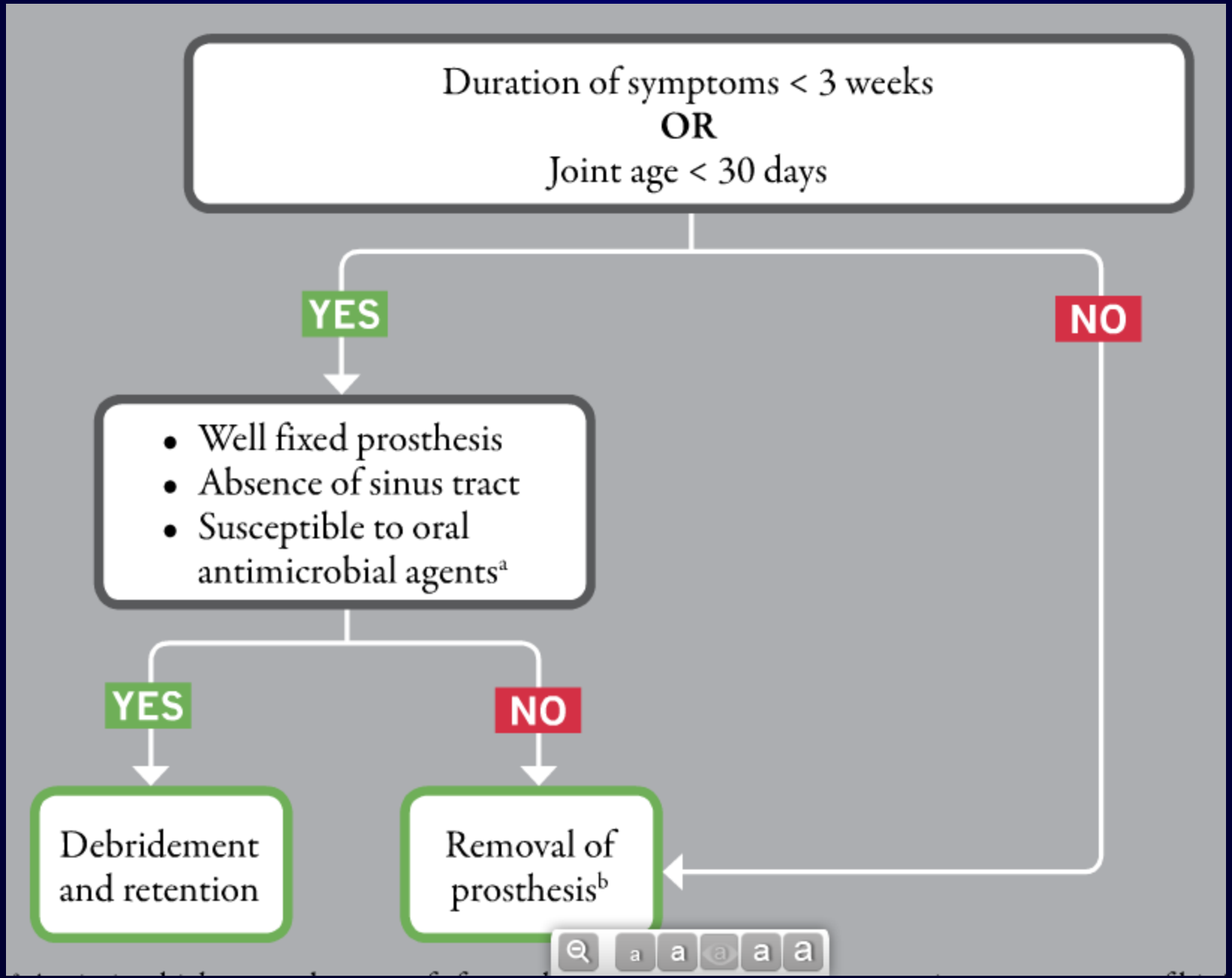
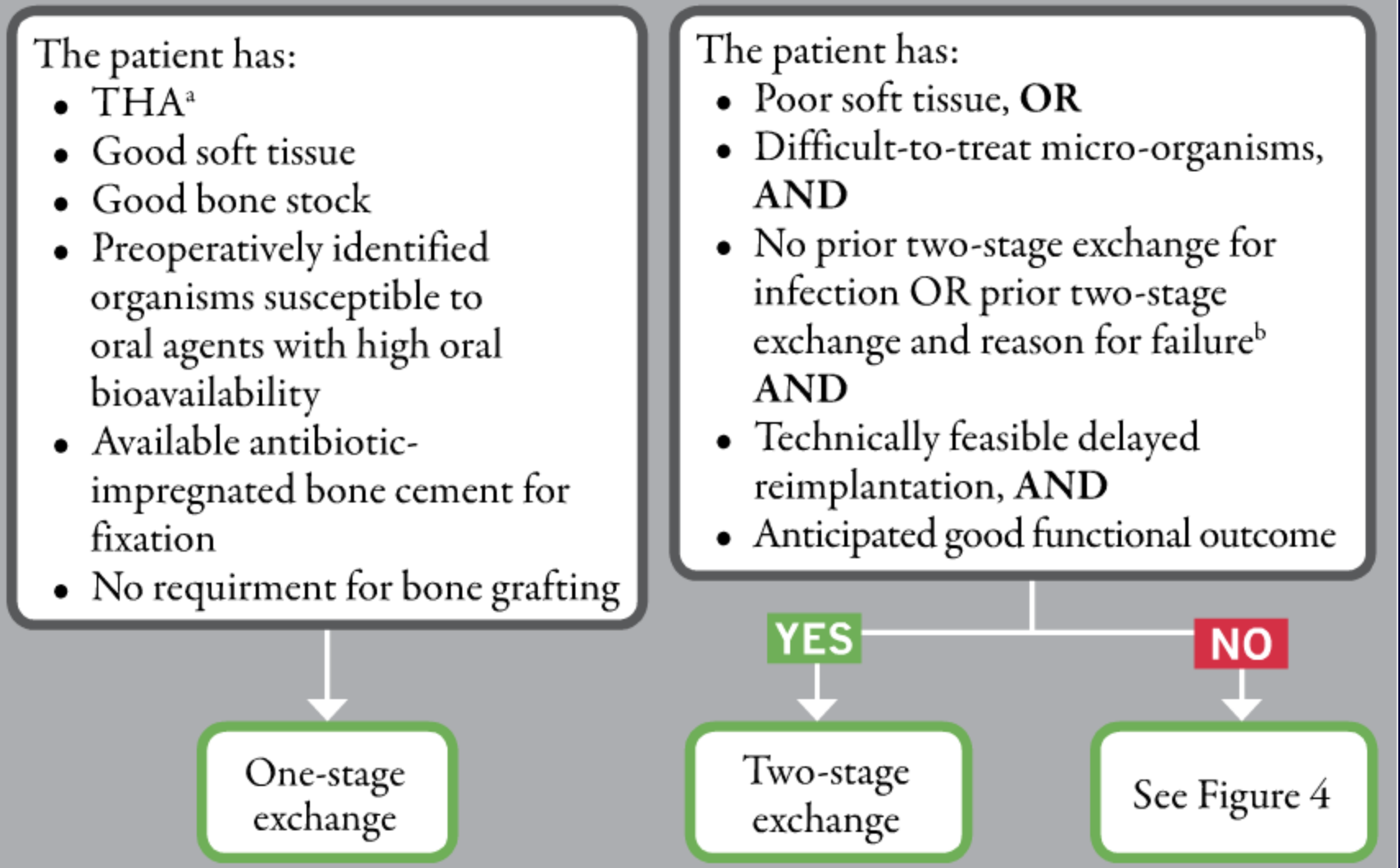

Duration of symptoms < 3 weeks
OR
Joint age < 30 days
YES
NO
Well fixed prosthesis
Absence of sinus tract
Susceptible to oral antimicrobial agents[a]
YES
NO
Debridement and retention
Removal of prosthesis[b]

Figure 3. Management of PJI-III - Removal of Prosthesis



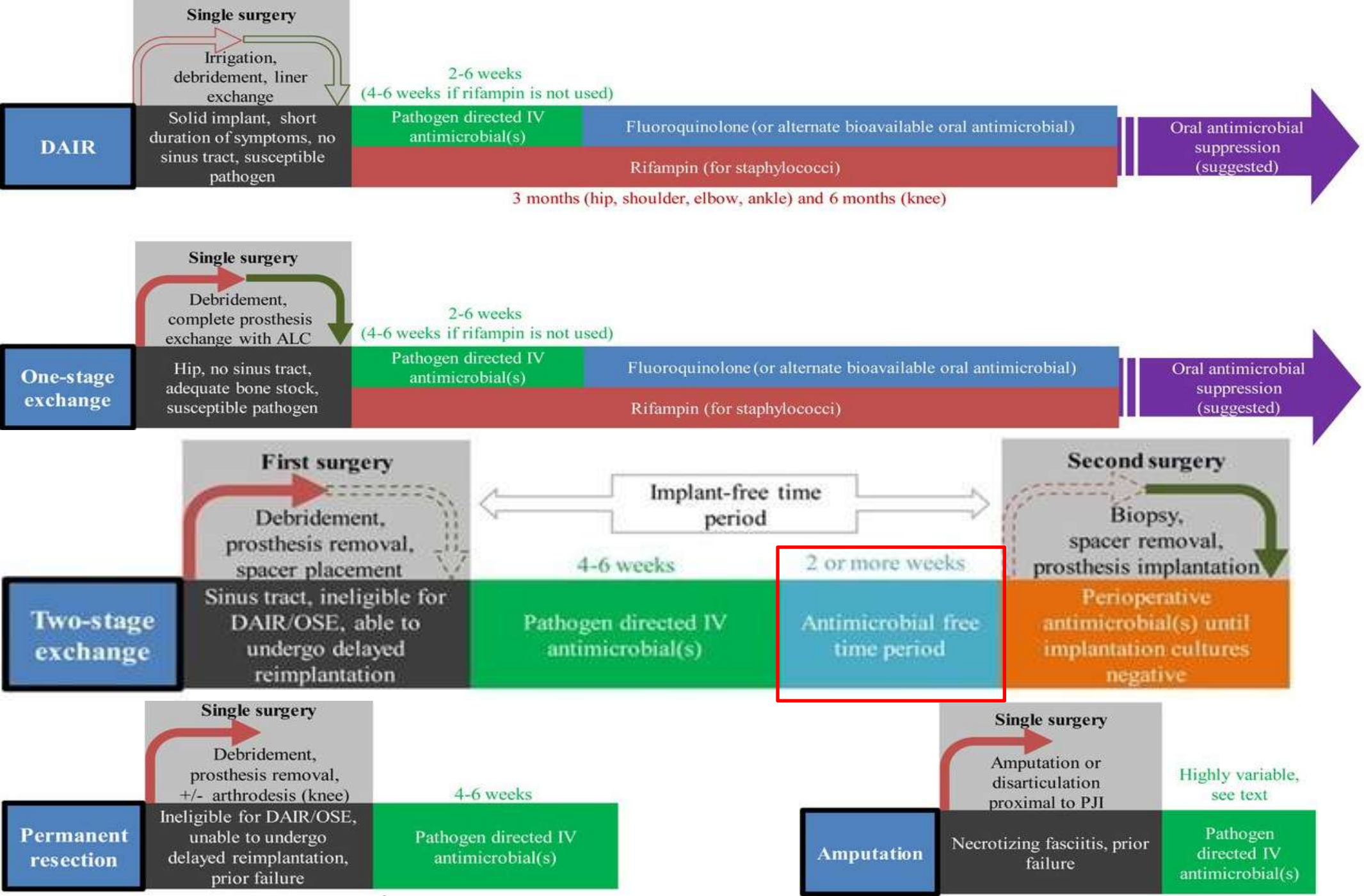
[a] Uncommonly performed in the US

[b] Relative indications -- See full text guide

PJI :DIFFERENTI STRATEGIE MEDICHE E CHIRURGICHE

- **debridement “aperto” o artroscopico senza rimozione della protesi**
- **sostituzione in 1 o 2 tempi chirurgici**
- **rimozione senza reimpianto /artrodesi ,**
- **amputazione/disarticolazione**
- **terapia antimicrobica soppressiva cronica senza intervento chirurgico**

L'obiettivo di ogni strategia chirurgica è rimuovere tutto il tessuto infetto e parte o tutto l’impianto per diminuire carica batterica e biofilm permettendo alla terapia antibiotica post-operatoria di eradicare la restante infezione .



Tande A. J. Et al:Prosthetic Joint InfectionClin. Microbiol. Rev. April 2014vol. 27 no. 2 302-345

Table 2. Intravenous or Highly Bioavailable Oral Antimicrobial Treatment of Common Microorganisms Causing Prosthetic Joint Infection (B-III Unless Otherwise Stated in Text)

Microorganism	Preferred Treatment[a]	Alternative Treatment[a]	Comments
Staphylococci, oxacillin-susceptible	Nafcillin[b] sodium 1.5–2 g IV q4-6 h or Cefazolin 1–2 g IV q8 h or Ceftriaxone[c] 1–2 g IV q24 h	Vancomycin IV 15 mg/kg q12 h or Daptomycin 6 mg/kg IV q 24 h or Linezolid 600 mg PO/IV every 12 h	See recommended use of rifampin as a companion drug for rifampin-susceptible PJI treated with debridement and retention or 1-stage exchange in text
Staphylococci, oxacillin-resistant	Vancomycin[d] IV 15 mg/kg q12 h	Daptomycin 6 mg/kg IV q24 h or Linezolid 600 mg PO/IV q12 h	See recommended use of rifampin as a companion drug for rifampin-susceptible PJI treated with debridement and retention or 1-stage exchange in text
Enterococcus spp, penicillin-susceptible	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses or Ampicillin sodium 12 g IV q24 h continuously or in 6 divided doses	Vancomycin 15 mg/kg IV q12 h or Daptomycin 6 mg/kg IV q24 h or Linezolid 600 mg PO or IV q12 h	4–6 wk. Aminoglycoside optional Vancomycin should be used only in case of penicillin allergy
Enterococcus spp, penicillin-resistant	Vancomycin 15 mg/kg IV q12 h	Linezolid 600 mg PO or IV q12 h or Daptomycin 6 mg IV q24 h	4–6 wk. Addition of aminoglycoside optional
Pseudomonas aeruginosa	Cefepime 2 g IV q12 h or Meropenem[d] 1 g IV q8 h	Ciprofloxacin 750 mg PO bid or 400 mg IV q12 h or Ceftazidime 2 g IV q8 h	4–6 wk Addition of aminoglycoside optional Use of 2 active drugs could be considered based on clinical circumstance of patient. If aminoglycoside in spacer, and organism aminoglycoside susceptible than double coverage being provided with recommended IV or oral monotherapy
Enterobacter spp	Cefepime 2 g IV q12 h or Ertapenem 1 g IV q24 h	Ciprofloxacin 750 mg PO or 400 mg IV q12 h	4–6 wk.
Enterobacteriaceae	IV β-lactam based on in vitro susceptibilities or Ciprofloxacin 750 mg PO bid		4–6 wk
β-hemolytic streptococci	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses or Ceftriaxone 2 g IV q24 h	Vancomycin 15 mg/kg IV q12 h	4–6 wk Vancomycin only in case of allergy

IDSA 2013

Table 3. Common Antimicrobials Used for Chronic Oral Antimicrobial Suppression (B-III Unless Otherwise Stated in Text)[a,b]

Microorganism	Preferred Treatment	Alternative Treatment
Staphylococci, oxacillin susceptible	Cephalexin 500 mg PO tid or qid or Cefadroxil 500 mg PO bid	Dicloxacillin 500 mg PO tid or qid Clindamycin 300 mg PO qid Amoxicillin-clavulanate 500 mg PO tid
Staphylococci, oxacillin-resistant	Cotrimoxazole 1 DS tab PO bid Minocycline or doxycycline100 mg PO bid	
β-hemolytic streptococci	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	Cephalexin 500 mg PO tid or qid
Enterococcus spp, penicillin susceptible	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	
Pseudomonas aeruginosa	Ciprofloxacin 250–500 mg PO bid	
Enterobacteriaceae	Cotrimoxazole 1 DS tab PO bid	β-lactam oral therapy based on in vitro susceptibilities
Propionibacterium spp	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	Cephalexin 500 mg PO tid or qid Minocycline or doxycycline 100 mg PO bid

Abbreviations: bid, twice daily; DS, double strength; PO, per oral; qid, 4 times daily; tid, 3 times daily.

[a] Antimicrobial dosage needs to be adjusted based on patients' renal and hepatic function. Antimicrobials should be chosen based on in vitro susceptibility as well as patient drug allergies, intolerances, and potential drug interactions or contraindications to a specific antimicrobial.

[b] Clinical and laboratory monitoring for efficacy and safety should occur based on the clinical judgment of the clinician caring for the patient. The possibility of prolonged QTc interval and tendinopathy should be discussed and monitored when using fluoroquinolones. The possibility of *Clostridium difficile* colitis should also be discussed when using any antimicrobial.

Table 1
Success rate of PJI treatment using I&D, as determined by the percentage of eradicated infections

Authors, Year	Site	Number of Eradicated Infections	Number of Total Implants	Success Rate (%)
Aboltins et al,[14] 2007	Hip, knee	18	20	90.0
Azzam et al,[15] 2010	Hip, knee	40	104	38.4
Bradbury et al,[16] 2009	Knee	3	19	15.8
Brandt et al,[17] 1997	Hip, knee	12	33	36.3
Chiu Chen,[18] 2007	Knee	12	20	60.0
Choi et al,[19] 2011	Knee	10	32	31.3
Crockarell et al,[20] 1998	Hip	4	19	21.1
Deirmengian et al,[21] 2003	Knee	11	31	35.4
Estes et al,[22] 2010	Hip, knee	18	20	90.0
Fehring et al,[23] 2013	Hip, knee	32	86	37.2
Gardner et al,[24] 2011	Knee	5	10	50.0
Hartman et al,[25] 1991	Knee	8	11	72.7
Ivey et al,[26] 1990	Knee	3	10	30.0
Klouche et al,[27] 2011	Hip	9	12	75.0
Koyonos et al,[28] 2011	Hip, knee	64	102	62.7
Krasin et al,[29] 2001	Hip	5	7	71.4
Marculescu et al,[30] 2006	Hip, knee	56	91	56.5
Mont et al,[31] 1997	Knee	10	24	41.7
Odum et al,[32] 2011	Hip, knee	46	150	30.7
Peel et al,[33] 2013	Hip, knee	94	112	83.9
Rasul et al,[34] 1991	Knee	2	6	33.3
Schoifet Morrey,[35] 1990	Knee	7	31	22.6
Segawa et al,[36] 1999	Knee	5	10	50.0
Tsukayama et al,[37] 1996	Hip	25	35	71.4
Tsumura et al,[38] 2005	Knee	6	10	60.0
Van Kleunen et al,[39] 2010	Hip, knee	10	18	55.6
Vilchez et al,[40] 2011	Hip, knee	40	65	69.2
Wasielewski et al,[41] 1996	Knee	8	10	80.0

AF Chen 2014

I&D=
Irrigation and
Debridement

Table 2
Success rate of PJI treatment using 1-stage exchange arthroplasty, as determined by the percentage of eradicated infections

Authors, Year	Site	Number of Eradicated Infections	Number of Total Implants	Success Rate (%)
Buechel et al,[49] 2004	Knee	20	22	90.9
Callaghan et al,[51] 1999	Hip	22	24	91.7
Göksan Freeman,[54] 1992	Knee	16	18	88.9
Hansen et al,[48] 2013	Hip	15	27	55.6
Jenny et al,[52] 2013	Knee	41	47	87.2
Klouche et al,[55] 2012	Hip	38	38	100.0
Lu et al,[56] 1997	Knee	8	8	100.0
Raut et al,[46] 1996	Hip	14	15	93.3
Romanò et al,[57] 2012	Knee	167	204	81.9
Scott et al,[58] 1993	Knee	7	10	70.0
Von Foerster et al,[59] 1991	Knee	76	104	73.1
Zeller et al,[60] 2014	Hip	149	157	94.9

AF Chen 2014

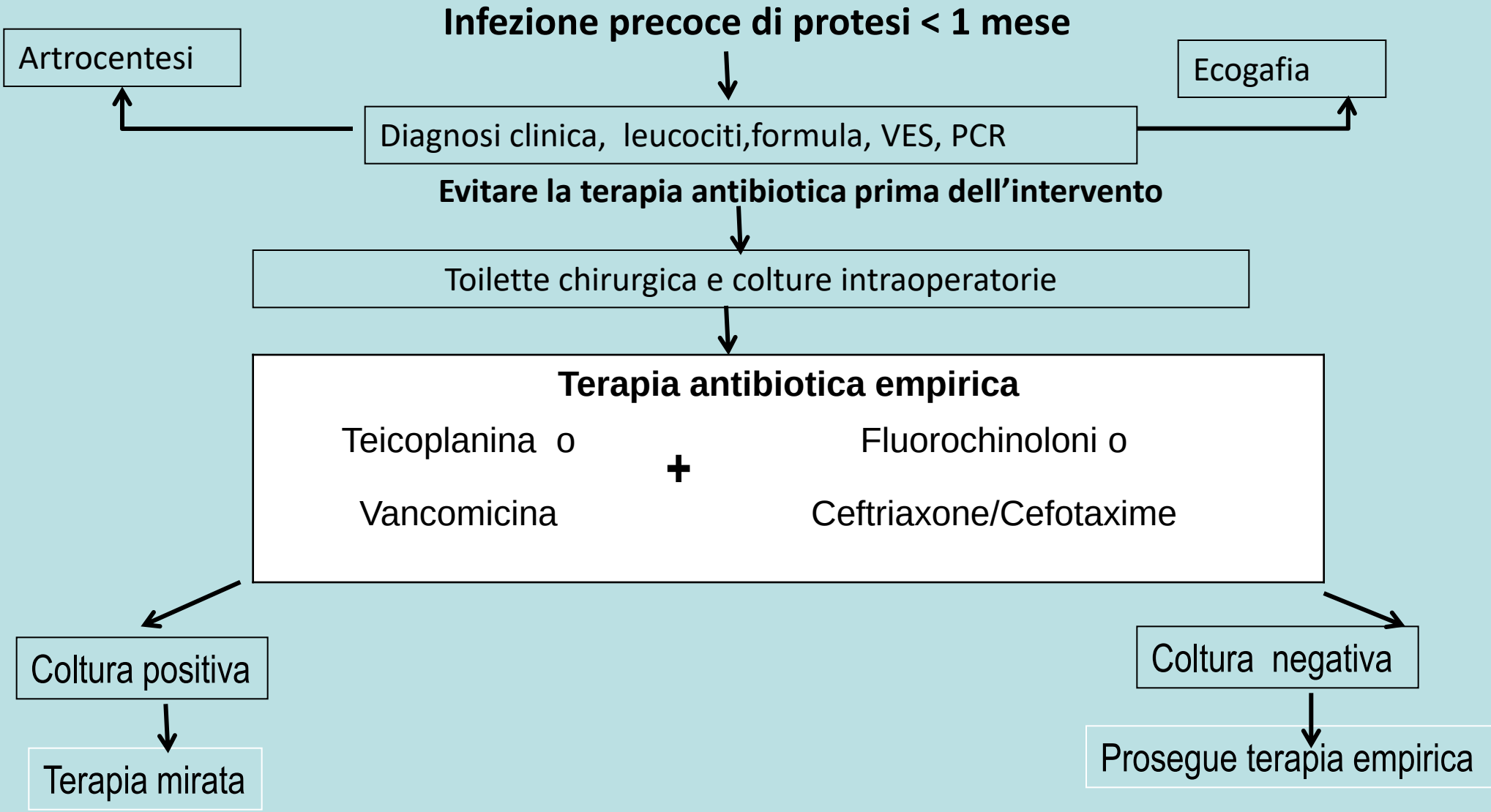
1 STAGE

AF Chen 2014

2 STAGE

Table 3
Success rate of PJI treatment using 2-stage exchange arthroplasty, as determined by the percentage of eradicated infections

Authors, Year	Site	Number of Eradicated Infections	Number of Total Implants	Success Rate (%)
Anderson et al,[89] 2009	Knee	24	25	96.0
Borden Gearen,[87] 1987	Knee	10	11	90.9
Emerson et al,[88] 2002	Knee	44	48	91.7
Fehring et al,[64] 2000	Knee	51	55	92.7
Freeman et al,[85] 2007	Knee	69	76	90.8
Gacon et al,[90] 1997	Knee	24	29	82.8
Goldman et al,[61] 1996	Knee	58	64	90.6
Gooding et al,[77] 2011	Knee	101	115	87.8
Haddad et al,[76] 2000	Knee	41	45	91.1
Haleem et al,[78] 2004	Knee	81	96	84.4
Hanssen et al,[91] 1994	Knee	79	89	88.8
Hirakawa et al,[92] 1998	Knee	41	55	74.5
Hoad-Reddick et al,[75] 2005	Knee	34	38	89.5
Hofmann et al,[67] 2005	Knee	44	50	88.0
Hofmann et al,[70] 2005	Hip	26	27	96.3
Hsieh et al,[86] 2004	Hip	122	128	95.3
Hsu et al,[79] 2007	Knee	25	28	89.3
Huang et al,[93] 2006	Knee	20	21	95.2
Insall et al,[83] 1983	Knee	10	11	90.9
Karpas Sponer,[82] 2003	Hip	18	18	100.0
Klouche et al,[55] 2012	Hip	45	46	97.8
Lonner et al,[94] 2001	Knee	44	53	83.0
Masri et al,[84] 1994	Knee	22	24	91.7
McPherson et al,[95] 1997	Knee	20	21	95.2
Meek et al,[96] 2004	Knee	52	54	96.3
Ocguder et al,[97] 2010	Knee	15	17	88.2
Pietsch et al,[98] 2003	Knee	22	24	91.7
Pitto et al,[99] 2005	Knee	19	19	100.0
Rosenberg et al,[100] 1988	Knee	12	15	80.0
Scott et al,[58] 1993	Knee	7	7	100
Van Thiel et al,[101] 2011	Knee	53	60	88.3
Whiteside,[102] 1994	Knee	28	33	84.8
Windsor et al,[103] 1990	Knee	34	38	89.5
Younger et al,[85] 1997	Hip	45	48	93.8



Durata terapia : 2 – 3 mesi (2 settimane dopo normalizzazione PCR)
Nei mesi successivi monitorare esami bioumorali (leucociti, formula, VES, PCR)

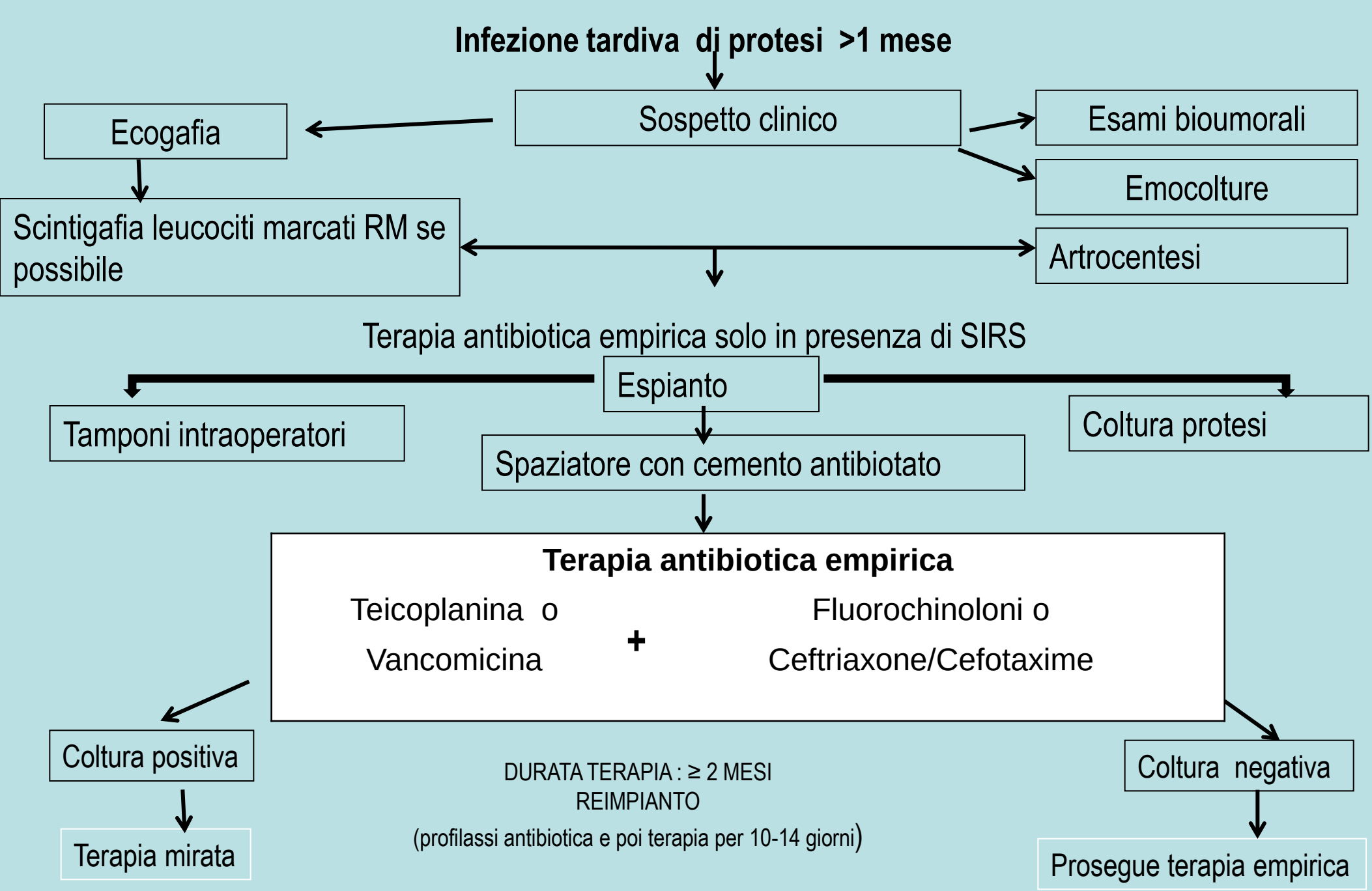

Infezione tardiva di protesi >1 mese
Sospetto clinico
Ecogafia
Esami bioumorali
Emocolture
Scintigafia leucociti marcati RM se possibile
Artrocentesi
Terapia antibiotica empirica solo in presenza di SIRS
Espianto
Tamponi intraoperatori
Coltura protesi
Spaziatore con cemento antibiotato
Terapia antibiotica empirica
Teicoplanina o
Vancomicina
+
Fluorochinoloni o
Ceftriaxone/Cefotaxime
Coltura positiva
Terapia mirata
DURATA TERAPIA : ≥ 2 MESI
REIMPIANTO
(profilassi antibiotica e poi terapia per 10-14 giorni)
Coltura negativa
Prosegue terapia empirica

Table 2. Intravenous or Highly Bioavailable Oral Antimicrobial Treatment of Common Microorganisms Causing Prosthetic Joint Infection (B-III Unless Otherwise Stated in Text)

Microorganism	Preferred Treatment[a]	Alternative Treatment[a]	Comments
Staphylococci, oxacillin-susceptible	Nafcillin[b] sodium 1.5–2 g IV q4-6 h or Cefazolin 1–2 g IV q8 h or Ceftriaxone[c] 1–2 g IV q24 h	Vancomycin IV 15 mg/kg q12 h or Daptomycin 6 mg/kg IV q 24 h or Linezolid 600 mg PO/IV every 12 h	See recommended use of rifampin as a companion drug for rifampin-susceptible PJI treated with debridement and retention or 1-stage exchange in text
Staphylococci, oxacillin-resistant	Vancomycin[d] IV 15 mg/kg q12 h	Daptomycin 6 mg/kg IV q24 h or Linezolid 600 mg PO/IV q12 h	See recommended use of rifampin as a companion drug for rifampin-susceptible PJI treated with debridement and retention or 1-stage exchange in text
Enterococcus spp, penicillin-susceptible	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses or Ampicillin sodium 12 g IV q24 h continuously or in 6 divided doses	Vancomycin 15 mg/kg IV q12 h or Daptomycin 6 mg/kg IV q24 h or Linezolid 600 mg PO or IV q12 h	4–6 wk. Aminoglycoside optional Vancomycin should be used only in case of penicillin allergy
Enterococcus spp, penicillin-resistant	Vancomycin 15 mg/kg IV q12 h	Linezolid 600 mg PO or IV q12 h or Daptomycin 6 mg IV q24 h	4–6 wk. Addition of aminoglycoside optional
Pseudomonas aeruginosa	Cefepime 2 g IV q12 h or Meropenem* 1 g IV q8 h	Ciprofloxacin 750 mg PO bid or 400 mg IV q12 h or Ceftazidime 2 g IV q8 h	4–6 wk Addition of aminoglycoside optional Use of 2 active drugs could be considered based on clinical circumstance of patient. If aminoglycoside in spacer, and organism aminoglycoside susceptible than double coverage being provided with recommended IV or oral monotherapy
Enterobacter spp	Cefepime 2 g IV q12 h or Ertapenem 1 g IV q24 h	Ciprofloxacin 750 mg PO or 400 mg IV q12 h	4–6 wk.
Enterobacteriaceae	IV β-lactam based on in vitro susceptibilities or Ciprofloxacin 750 mg PO bid		4–6 wk
β-hemolytic streptococci	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses or Ceftriaxone 2 g IV q24 h	Vancomycin 15 mg/kg IV q12 h	4–6 wk Vancomycin only in case of allergy

Table 3. Common Antimicrobials Used for Chronic Oral Antimicrobial Suppression (B-III Unless Otherwise Stated in Text)[a,b]

Microorganism	Preferred Treatment	Alternative Treatment
Staphylococci, oxacillin-susceptible	Cephalexin 500 mg PO tid or qid or Cefadroxil 500 mg PO bid	Dicloxacillin 500 mg PO tid or qid Clindamycin 300 mg PO qid Amoxicillin-clavulanate 500 mg PO tid
Staphylococci, oxacillin-resistant	Cotrimoxazole 1 DS tab PO bid Minocycline or doxycycline100 mg PO bid	
β-hemolytic streptococci	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	Cephalexin 500 mg PO tid or qid
Enterococcus spp, penicillin susceptible	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	
Pseudomonas aeruginosa	Ciprofloxacin 250–500 mg PO bid	
Enterobacteriaceae	Cotrimoxazole 1 DS tab PO bid	β-lactam oral therapy based on in vitro susceptibilities
Propionibacterium spp	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	Cephalexin 500 mg PO tid or qid Minocycline or doxycycline 100 mg PO bid

Abbreviations: bid, twice daily; DS, double strength; PO, per oral; qid, 4 times daily; tid, 3 times daily.

[a] Antimicrobial dosage needs to be adjusted based on patients' renal and hepatic function. Antimicrobials should be chosen based on in vitro susceptibility as well as patient drug allergies, intolerances, and potential drug interactions or contraindications to a specific antimicrobial.

[b] Clinical and laboratory monitoring for efficacy and safety should occur based on the clinical judgment of the clinician caring for the patient. The possibility of prolonged QTc interval and tendinopathy should be discussed and monitored when using fluoroquinolones. The possibility of *Clostridium difficile* colitis should also be discussed when using any antimicrobial.

TERAPIA DELLE INFEZIONI DA MICRORGANISMI MULTIRESISTENTI

I BATTERI MULTIRESISTENTI

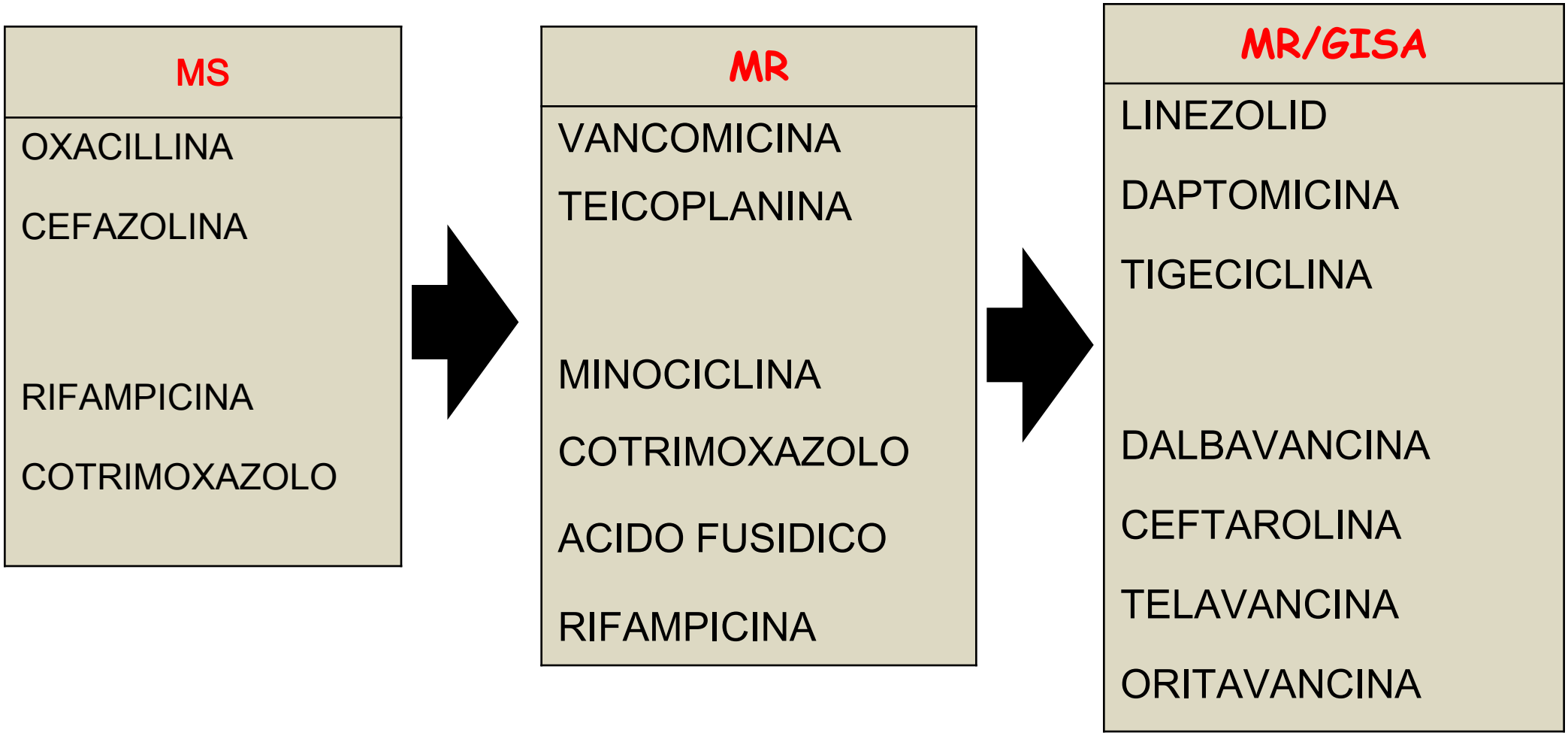
- **Pneumococco resistente alla penicillina**
- **Stafilococchi MRSA , VISA e VRSA**
- **Enterococchi VR**

- ***Pseudomonas* resistenti ai carbapenemici**
- ***Acinetobacter* e S. *maltophilia* multiresistenti**
- **Enterobatteri produttori di ESBL E KPC**

- **M. *Tuberculosis* MDR/XDR/TDR**

STAFILOCOCCHI

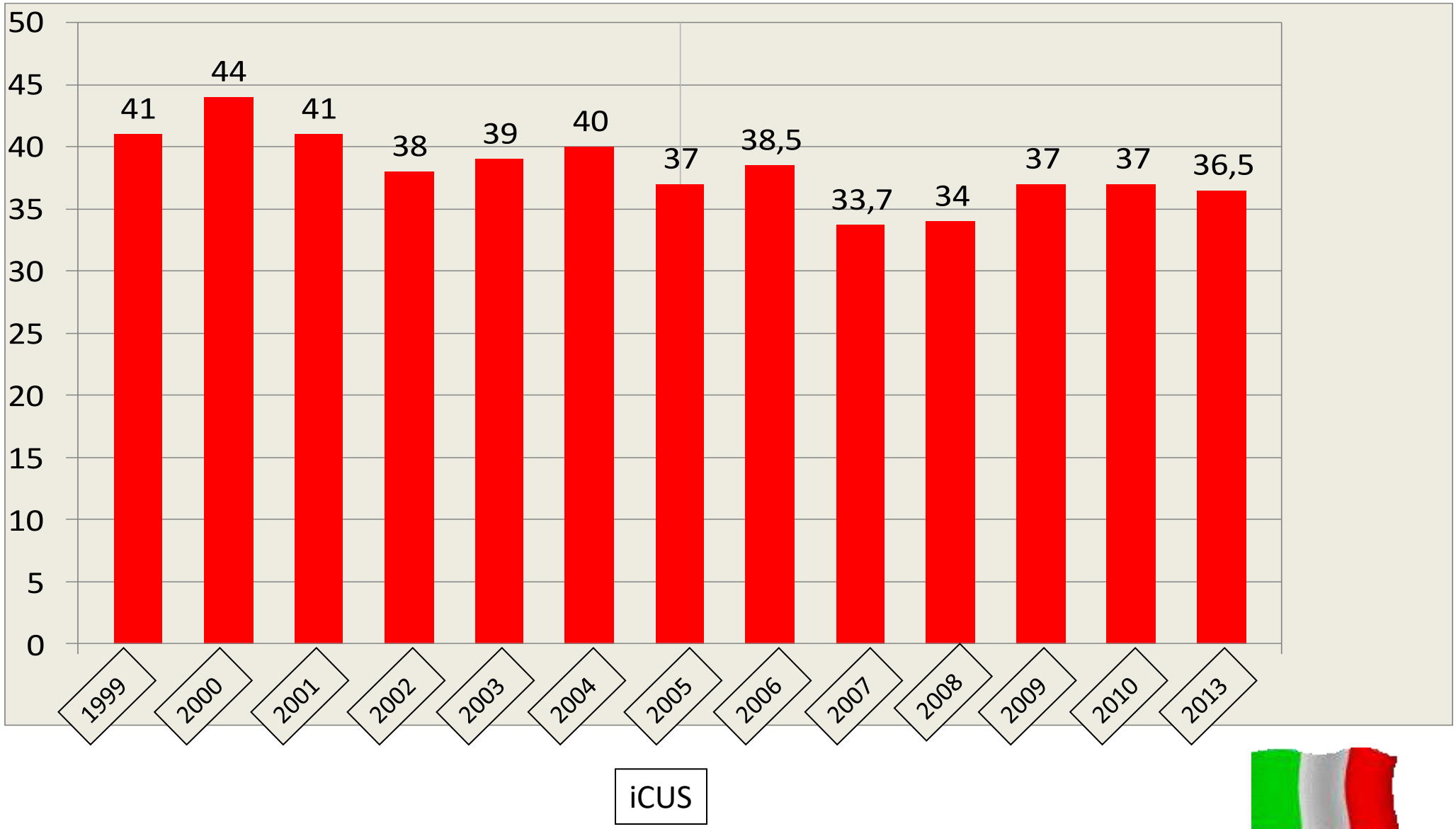
ANTIBIOTICI AD ATTIVITA' ANTISTAFILOCOCCICA



Stafilococco Aureo Meticillino Resistente

MRSA

Rate of invasive MRSA in Italy: 1999-2010



iCUS

Vancomycin MIC "creep" (Aumento delle MIC tra i ceppi di MRSA sensibili alla vancomicina)

	MIC_{50}	MIC_{90}
1985 MSSA	0.06	0.12
2004 MSSA	2.0	2.0
1985 MRSA →	0.12	0.25
2004 MRSA →	2.0	2.0

* P< 0.0001 - Kapadia M. et al 45° ICAAC abs E-807

TERAPIA DELLE INFEZIONI DA MRSA
(nelle infezioni da MSSA la terapia d'elezione è l'oxacillina)

CMI VANCOMICINA
≤ 1

VANCOMICINA
TEICOPLANINA

CMI VANCOMICINA
≥1

BATTERIEMIE
SEPSI
ENDOCARDITI

DAPTOMICINA

POLMONITI
INFEZIONI SNC

LINEZOLID*

SSSI

TIGECICLINA
DAPTOMICINA
LINEZOLID

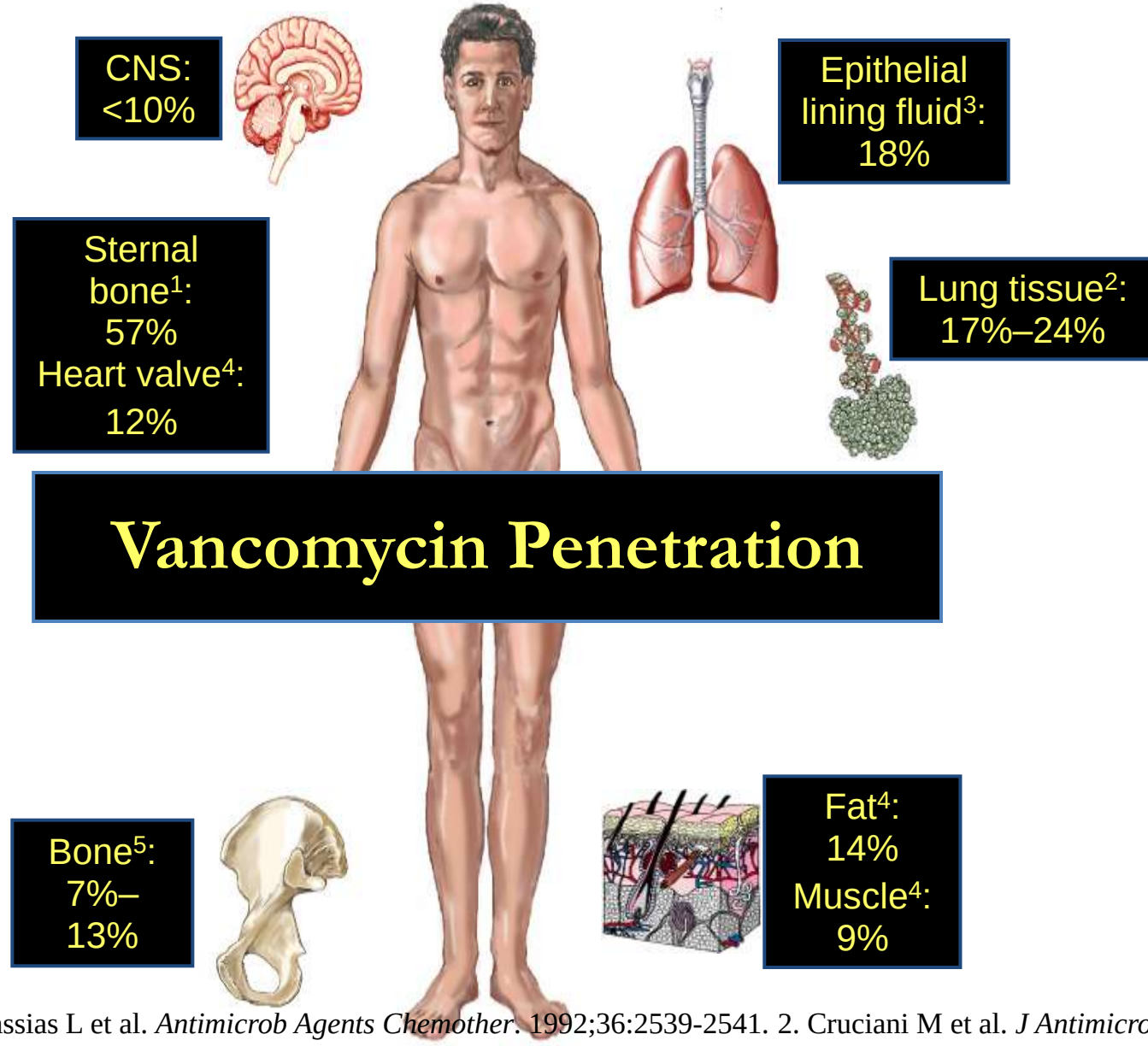
OSTEOMIELITI

DAPTOMICINA*
LINEZOLID*

* Indicazioni off label per le osteomieliti e per le infezioni del SNC

GLICOPEPTIDI

VANTAGGI	LIMITI
➢Uso consolidato	➢Posologia (vanco 25-30 mg/Kg dose carico poi 15-20 mg/Kg in 2-3 somministrazioni; teico 6-12 mg/kg)
➢Tollerabilità (teico)	➢Aumento MIC (vanco e teico??)
➢Resistenza limitata	➢Diffusibilità tissutale
➢Costi (vanco)	➢Attività batteriostatica/battericida
	➢Necessità dose da carico (teico)
	➢Costo teicoplanina



1. Massias L et al. *Antimicrob Agents Chemother*. 1992;36:2539-2541. 2. Cruciani M et al. *J Antimicrob Chemother.* 1996;38:865-869. 3. Lamer C et al. *Antimicrob Agents Chemother.* 1993;37:281-286. 4. Daschner FD et al. *J Antimicrob Chemother*. 1987;19:359-362. 5. Graziani AL et al. *Antimicrob Agents Chemother*. 1988;32:1320-1322.

DAPTOMICINA

VANTAGGI	LIMITI
➢Effetto battericida	➢Inattività nelle RTI
➢Tollerabilità	➢Posologia (4-6-8-10-12) ?
	➢Limitate indicazioni
	➢Daptomycin non susceptible DNS
	➢Costo

LINEZOLID

VANTAGGI	LIMITI
➢Diffusibilità tissutale	➢Effetto batteriostatico
➢Attività su Gram positivi multiresistenti	➢Tollerabilità (28 giorni)
➢Spettro ristretto	➢Limitate indicazioni (uso off label?)
➢ Costo	

TIGECICLINA

VANTAGGI	LIMITI
➢Ampio spettro	➢Ampio spettro
➢Attività su germi multiresistenti	➢Effetto batteriostatico
➢Diffusibilità tissutale	➢Tollerabilità G.I.
➢Limitate indicazioni	➢Limitate indicazioni (uso off label?)
	➢Costo

BATTERI GRAM -

TERAPIA DELLE INFEZIONI DA ENTEROBATTERI PRODUTTORI DI ESBL

1. **IMIPENEM**
   MEROPENEM
   ERTAPENEM

2. **Tigeciclina (non attiva su Proteus mirabilis e Proteus indolo+)**

3. **Colimicina (non attiva su Proteus spp., Providencia spp., Morganella morganii, Serratia marcescens)**

4. **Fosfomicina**

LE NUOVE RESISTENZE

Protocolli di terapia delle infezioni da batteri multiresistenti (CARBAPENEMASI PRODUTTORI)

K. pneumoniae KPC: typical XDR phenotype

Antibiotic	MIC mg/L(S/I/R)
Amp/Sulb	>32 R
Pip/Tazo	>128 R
Ceftriaxone	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>32 R
Imipenem	>32 R
Meropenem	>32 R
Aztreonam	>64 R
Amikacin	>64 R
Gentamicin	2 S
Tobramycin	>16 R
Ciprofloxacin	>4 R
Fosfomycin	32 S
Tigecycline	1.5 I
Colistin	0.4 S

Treatment options:

- Colistin
- Carbapenem (especially if MIC relatively low)
- Tigecycline (HD)
- Gentamicin
- Fosfomycin HD
- Rifampin (test synergy)

Combination regimens (open issues)

Hirsch & Tam – JAC 2010
Qureshi *et al* – AAC 2012
Tumbarello *et al* - CID 2012

Terapia delle KPC (Kebsiella pneumoniae produttrice di carbapenemasi o altri enterobatteri produttori di carbapenemasi= CRE)

•COLIMICINA dose da carico 9 milioni poi
4,5 milioni x 2 /die
+
MEROPENEM* 2 gr x 3 /die
Oppure
IMIPENEM* 1 gr x 3-4 /die

•COLIMICINA dose come sopra
+
MEROPENEM* dose come sopra
IMIPENEM* dose come sopra
+
FOSFOMICINA 4 -6 gr x 4/die
Oppure
TIGECICLINA 100 o 150 mg x 2 / die

* Scelta basata sul valore della CMI ; il carbapenemico deve essere utilizzato anche nei casi in cui le CMI superino, non di molto, il breakpoint di resistenza (MIC sino a 16-32)

Terapia delle KPC (Kebsiella pneumoniae produttrice di carbapenemasi o altri enterobatteri produttori di carbapenemasi= CRE)

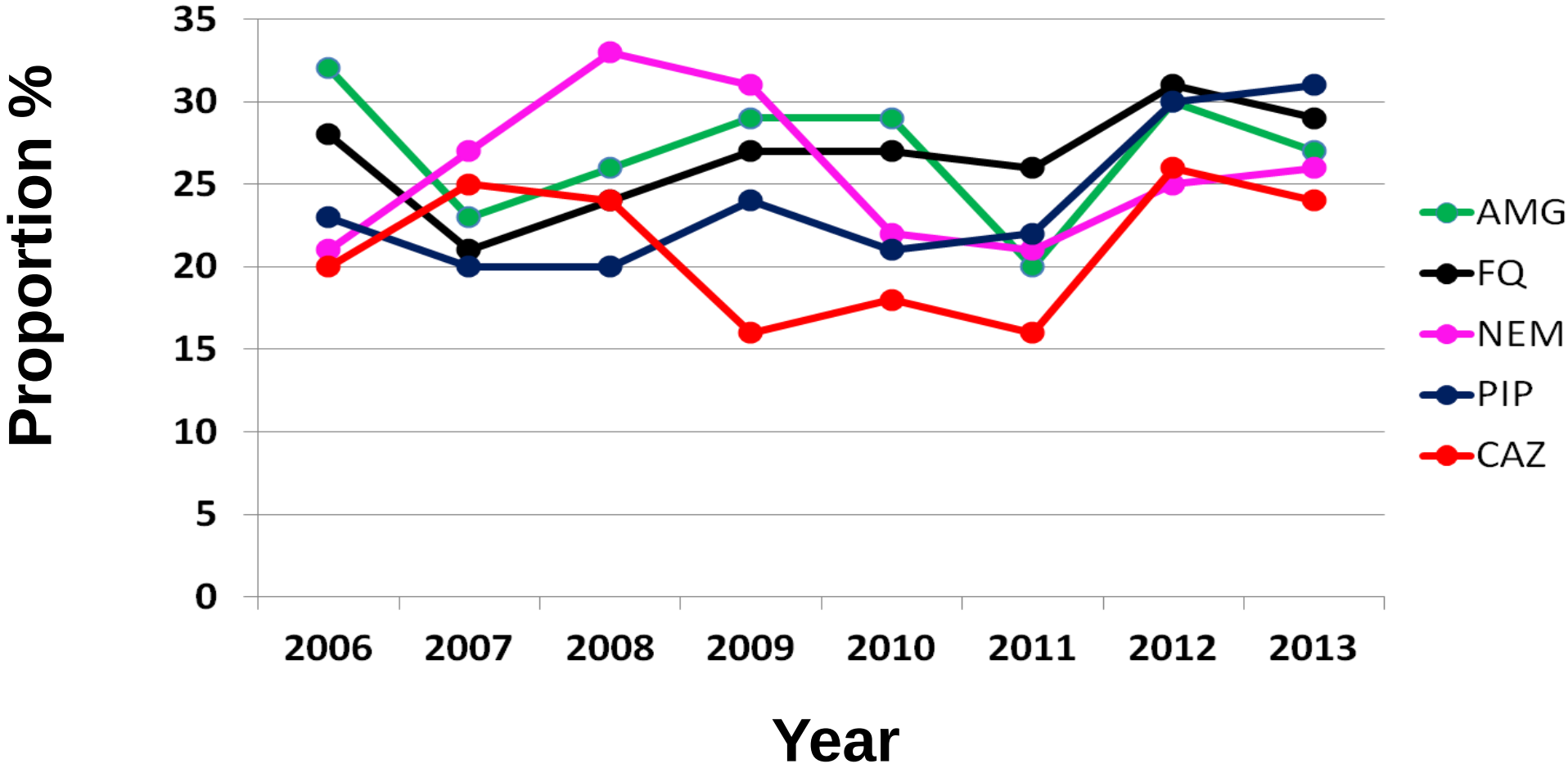
NEL CASO DI MIC > 32 PER I CARBAPENEMI

•COLIMICINA dose da carico 9 milioni poi
4,5 milioni x 2 /die
+
TIGECICLINA 100 o 150 mg x 2 / die
Oppure
FOSFOMICINA 4 -6gr x 4 / die

CEFTAZIDIME/AVIBACTAM

PSEUDOMONAS AERUGINOSA

Pseudomonas aeruginosa resistance trends, Italy



Terapia delle infezioni da Pseudomonas aeruginosa MDR

1. COLIMICINA (9 milioni dose da carico poi 4,5 milioni x 2 / die)
   +
   RIFAMPICINA 600 -900 mg /die (l'uso prescinde dalla sensibilità in vitro)

---

2. COLIMICJNA (dose come sopra)
   +
   FOSFOMICINA (4 gr x 4 / die) (solo se è dimostrata una sensibilità in vitro)

---

3. **CEFTOLOZANE/TAZOBACTAM**

4. CEFTAZIME (2 gr x 3 /die),
   CEFEPIME (2 gr x 3 /die),
   PIPERACILLINA/TAZOBACTAM (4 gr x 4 / die),
   IMIPENEM (1 gr x 3-4/die),
   MEROPENEM (1gr x 3-4, 2 gr x 3 /die)
   +
   CIPROFLOXACINA (400 mg x 3 / die)
   oppure
   LEVOFLOXACINA (500 mg x 2 / die)
   oppure
   AMIKACINA

Terapia derivante da test di sinergia in vitro

Le panresistenze

-- ESAMI BATTERIOLOGICI --

MARZO 2015

Emocolture in aerobiosi su braccio dx

Esame microscopico	*Batteri Gram-negativi*, Dato non definitivo soggetto a validazione di processo.
Esame colturale in aerobiosi	Esame in corso...
Esame colturale per lieviti	Esame in corso...

Emocolture in anaerobiosi su braccio dx

Esame microscopico	*Batteri Gram-negativi*
Esame colturale in anaerobiosi	*Klebsiella pneumoniae*, Ceppo con ridotta sensibilità ai carbapenemi, la terapia con carbapenemi potrebbe risultare scarsamente efficace o inefficace.; ceppo da considerarsi resistente a tutte le cefalosporine, aztreonam e penicilline

-- antibiogramma
Klebsiella pneumoniae

AMIKACINA	R	MIC >=64;
AMOX / AC-CLAV	R	MIC >=32;
CEFEPIME	R	MIC >=64;
CEFOTAXIME	R	MIC >=64;
CEFTAZIDIME	R	MIC >=64;
CIPROFLOXACINA	R	MIC >=4;
COLISTINA	R	MIC 8;
FOSFOMICINA	R	MIC 128;
GENTAMICINA	R	MIC >=16;
IMIPENEM	R	MIC >=16;
MEROPENEM	R	MIC >=16;
PIPER+TAZOBACTAM	R	MIC >=128;
TRIM.+SULFAMET	R	MIC >=320;

TIGECICLINA MIC = 8

Esame colturale per lieviti	Nessuno sviluppo

FARMACI ANTI-MRSA

- **GLICOPEPTIDI (vancomicina-teicoplanina)**
- **LINEZOLID**
- **DAPTOMICINA**
- **TIGECICLINA**
- **.....novità???**
- CEFTOBIPROLO
- CEFTAROLINA
- TEDIZOLID
- TELAVANCINA
- DALBAVANCINA
- ORITAVANCINA

Antimicrob Agents Chemother. 2016 Aug 22. pii: AAC.01248-16. [Epub ahead of print]

Activity of Tedizolid in Methicillin-Resistant Staphylococcus aureus Experimental Foreign Body-Associated Osteomyelitis.

Park KH[1], Greenwood-Quaintance KE[2], Mandrekar J[3], Patel R[4].

Author information

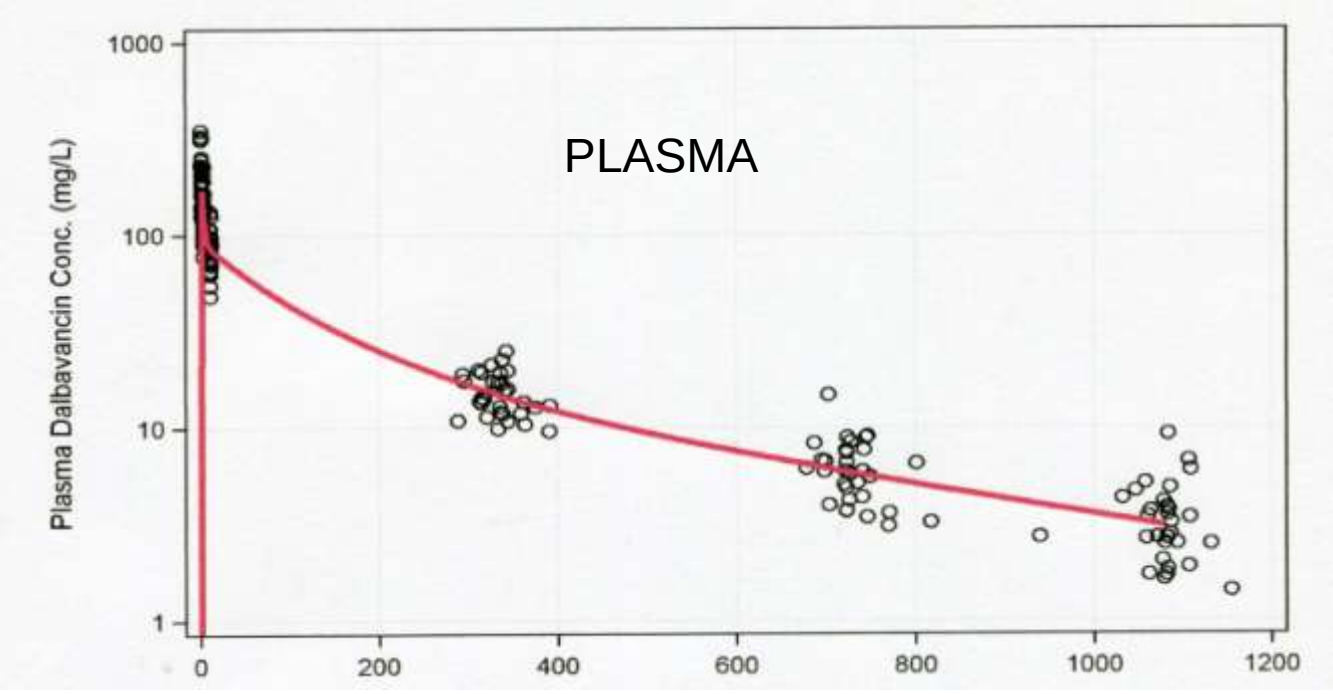
Abstract

BACKGROUND: We compared tedizolid alone and with rifampin against rifampin and vancomycin plus rifampin in rat model of methicillin-resistant Staphylococcus aureus (MRSA) foreign body-associated osteomyelitis.

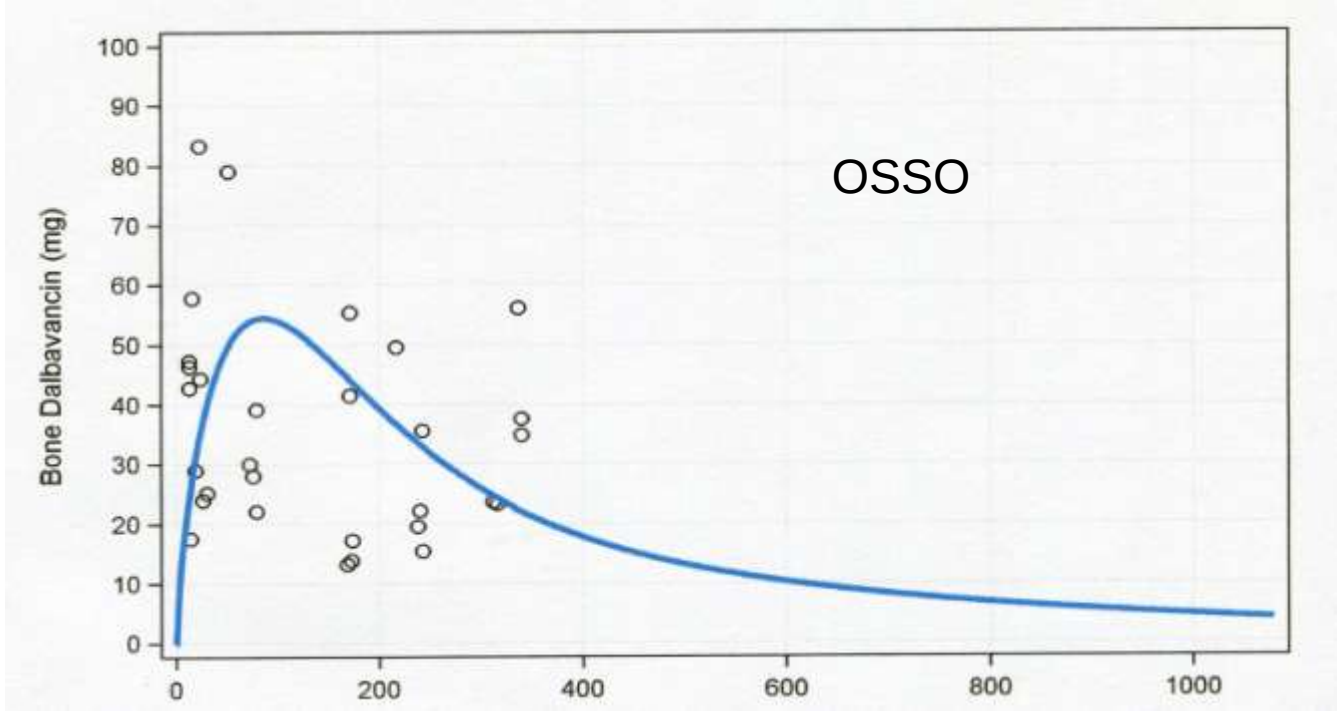
METHODS: The study strain was a prosthetic joint infection-associated isolate. Steady-state pharmacokinetics for intraperitoneal administration of tedizolid, vancomycin, and rifampin were determined in uninfected rats. MRSA was inoculated into the proximal tibia, and a wire was implanted. Four weeks later, rats were treated intraperitoneally for 21 days with tedizolid (n=14), tedizolid plus rifampin (n=11), rifampin (n=16), or vancomycin plus rifampin (n=13). Seventeen rats received no treatment. After treatment, quantitative bone cultures were performed. Blood was obtained for determination of drug trough concentrations in the tedizolid and tedizolid plus rifampin group.

RESULTS: The mean peak plasma concentration and mean AUC_{0-24} for tedizolid were 12 μg/ml and 60 μg·h/ml, respectively. The bacterial loads in all treatment groups were significantly lower than control; those in tedizolid plus rifampin-treated animals were not significantly different from those in vancomycin plus rifampin-treated animals. The range of mean plasma trough concentrations in the tedizolid group was 0.44-0.73 μg/ml. Although neither tedizolid nor vancomycin resistance was detected in isolates recovered from bones, rifampin resistance was detected in 10 animals (63%) in the rifampin group, 8 animals (73%) in the tedizolid plus rifampin group, and a single animal (8%) in the vancomycin plus rifampin group.

CONCLUSION: Tedizolid alone or combined with rifampin was active in a rat model of MRSA foreign body osteomyelitis. Emergence of rifampin resistance was noted in animals receiving tedizolid plus rifampin.



DALBAVANCINA



AAC 2016

Table 4. Dalbavancin Tissue Concentration (Safety Population)

Mean (SD) Tissue Concentration		Hours (Days) postdose that samples were collected					
		12 (0.5)	24 (1)	72 (3)	168 (7)	240 (10)	336 (14)
Plasma (µg/ml)[a]	N	31	ND	ND	ND	ND	31
		85.3 (18.9)					15.3 (4.1)
Synovium[b] (µg/g)	N	3	3	3	4	2	3
		25.0 (0)	17.9 (7.8)	19.5 (4.9)	19.2 (8.9)	25.0 (0)	15.9 (7.9)
Synovial fluid[b] (µg/ml)	N	1	4	3	2	3	2
		22.9	27.4 (10.8)	19.2 (4.9)	11.6 (3.3)	13.9 (1.0)	6.2 (1.7)
Bone (µg/g)	N	5	5	5	5	5	5
		6.3 (3.1)	5.0 (3.5)	4.6 (3.8)	3.8 (2.7)	3.7 (2.2)	4.1 (1.6)
Skin[b] (µg/g)	N	2	3	2	2	1	2
		19.4 (7.9)	12.5 (6.5)	13.8 (1.4)	15.7 (1.0)	21.6	13.8 (2.1)

[a]Mean plasma concentrations in 31 subjects at 772 and 1080 hours were 6.2 (2.4) and 3.4 (1.7), respectively. ND, Not detected; SD, standard deviation; [b]Concentrations above the upper limit of quantification are reported as 25 µg/unit

FARMACI GRAM -

- .....novità???
- CEFTOLOZANE/TAZOBACTAM
- CEFTAZIDIME/AVIBACTAM