ARTRITI SETTICHE

DIAGNOSI, MANAGEMENT, CLUE TERAPEUTICI

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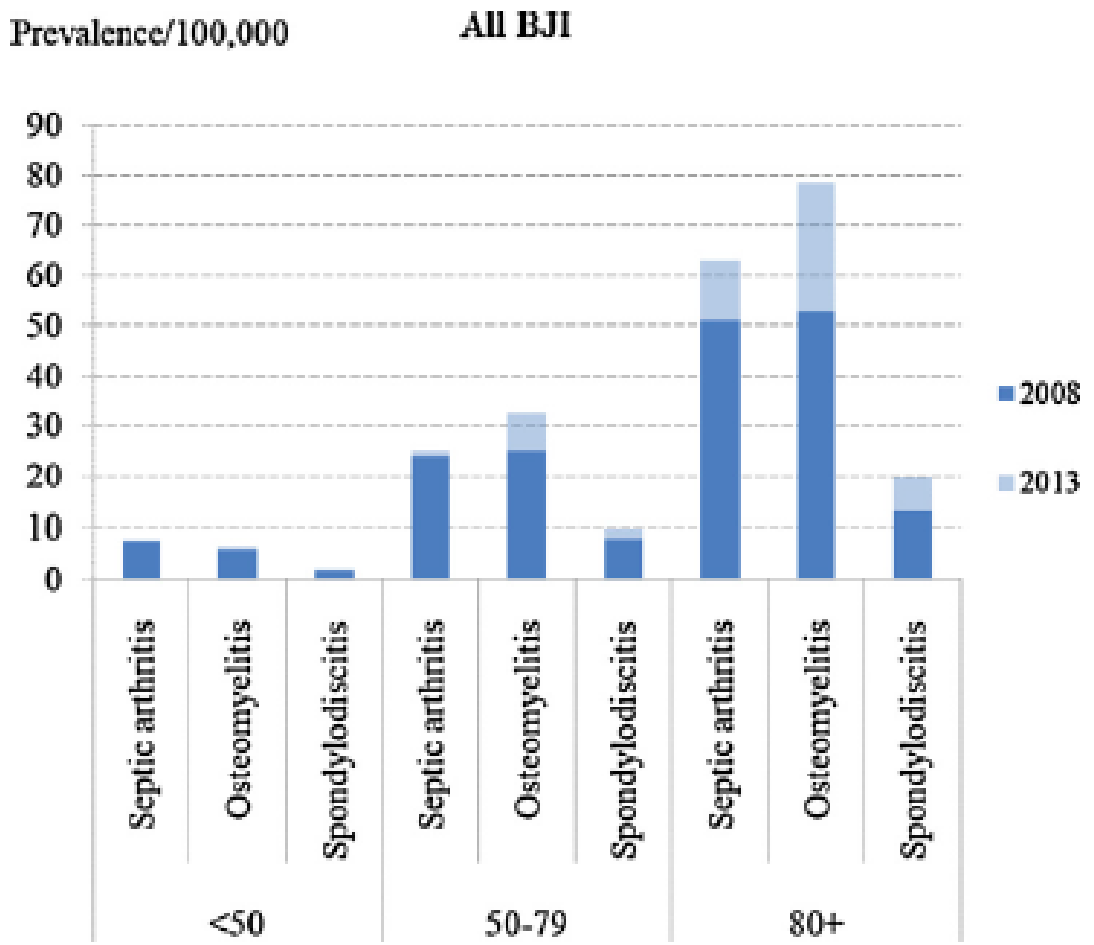
Changing epidemiology: the national before-after french study



Key features of bone and joint infection, Laurent E. et al. 2017.

SEPTIC ARTHRITIS: epidemiology, risk factors, mechanism of infection

2 cases per 100.000 / year

PJI is increasing: It is projected that by the year 2030, approximately 4 million THAs and TKAs will be performed per year in the United States

Mainly
- hematogenous: passing sinovyal membrane that has no limiting basal membrane, specially for micro organisms capable of adhere to synovial membrane (specially S. Aureus that still accounts for 55%)

and
- direct inoculation: mechanisms include bite wounds, trauma, arthroscopy, surgery and intra articular injection.

Table 1. Risk Factors for Septic Arthritis

Contiguous spread	**Hematogenous spread** *(continued)*
Skin infection, cutaneous ulcers[8,9]	Immunosuppressive medication[9,11]
Direct inoculation	Intravenous drug abuse[11]
Previous intraarticular injection[8,10]	Osteoarthritis[9]
Prosthetic joint: early and delayed[8] (Table 6)	Other cause of sepsis[9]
Recent joint surgery[8,10]	Prosthetic joint: late[8] (Table 6)
Hematogenous spread	Rheumatoid arthritis[8,9]
Diabetes mellitus[8,10]	Sexual activity (specifically for gonococcal arthritis)[12]
Human immunodeficiency virus infection[11]	**Other factors**
	Age older than 80 years[8]

Kurtz S et alJ Bone Joint Surg Am 2007
Geirsson AJ et al. Ann Rheum Dis. 2008

RISK FACTORS

Risk factors for septic arthritis of native joints

Preexisting joint diseases
- Rheumatoid arthritis
- Gout and pseudogout
- Osteoarthritis
- Lupus
- Trauma
- Recent surgery

Diabetes mellitus

Intravenous drug use

Cirrhosis

End-stage renal disease

Prednisone and other immunosuppressive medications

Skin diseases
- Psoriasis
- Eczema
- Skin ulcers

Human bite (fight bite)

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MAIN FEATURES

Joint distribution : 45% knee, 10% hip, 9 % ankle; polyarticular 10-20% (often asymmetrical, isolation of gram -, gonococci, pneumococci, group B streptococci)

Drug users: more often cartilaginous joints

Always consider atypical presentation and localization for atipical micro organisms

D.A. Wang et al. 2015

Microbiology

Mainly monomicrobial

Microbiology of 505 cases of septic arthritis in large series reporting data from 1999–2013

Bacteria	Number (%)
Staphylococci	282 (56)
Methicillin-sensitive *Staphylococcus aureus* (MSSA)	214 (42)
Methicillin-resistant *S aureus* (MRSA)	51 (10)
Coagulase-negative staphylococci	17 (3)
Streptococci	83 (16)
Unspecified streptococcal species	56 (11)
Viridans streptococci	7 (1)
Streptococcus pneumoniae	5 (1)
Other streptococcal species	15 (3)
Gram-negative rods	78 (15)
Pseudomonas aeruginosa	30 (6)
Escherichia coli	14 (3)
Proteus species	5 (1)
Klebsiella species	5 (1)
Others	21 (4)
Others	62 (12)
Polymicrobial	25 (5)
Anaerobes	3 (0.6)
Mycobacterium tuberculosis	9 (1.8)
Neisseria gonorrhoeae (gonococcus)	6 (1.2)
Miscellaneous	19 (4)

But also alphaviruses, Chikunguya, Parvovirus….

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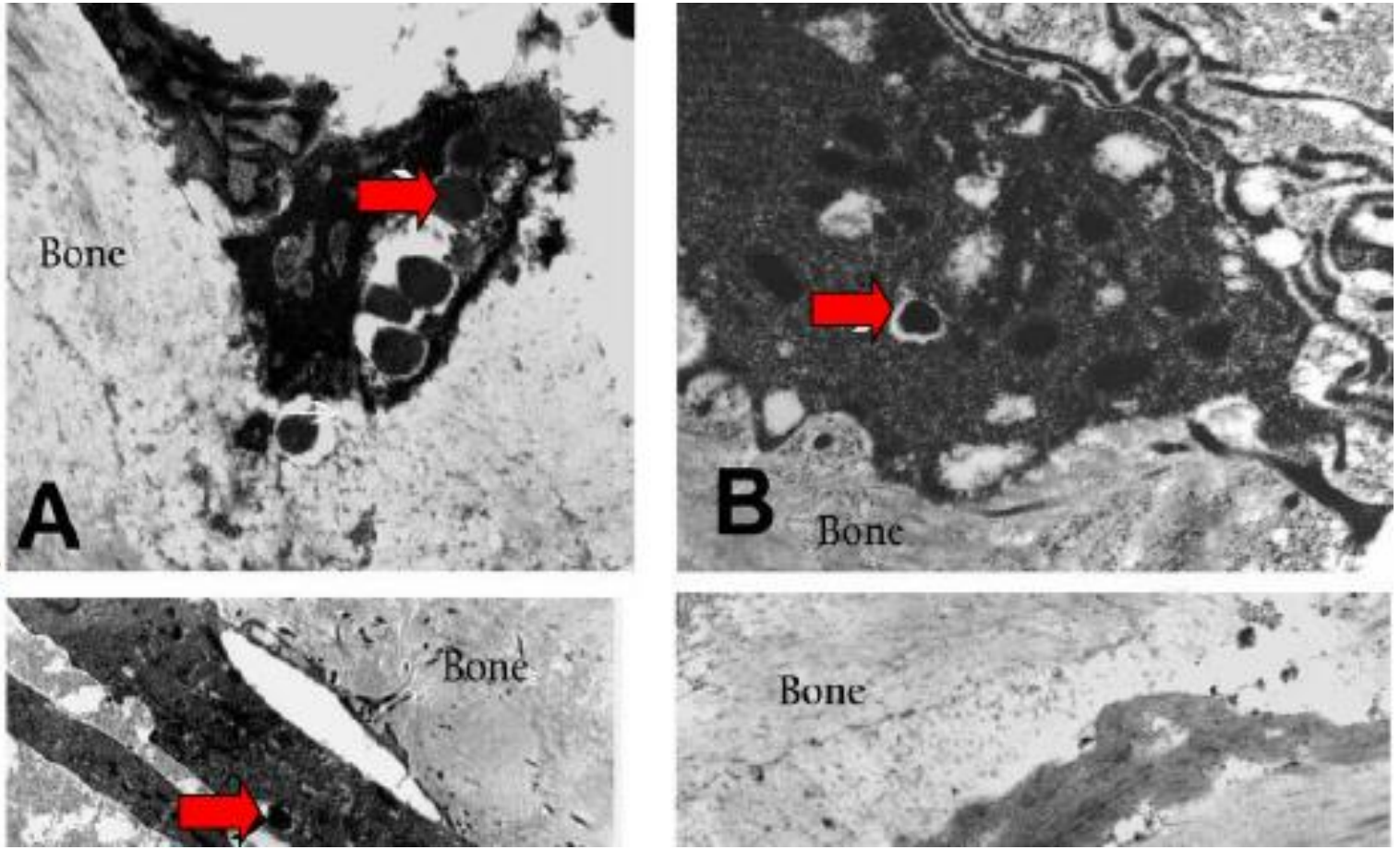
Staphylococcus aureus produces several surface adhesins that bind to extracellular matrix proteins and enable to enter the joint space and evade normal host defenses to cause symptomatic infection.

Evidence of an intracellular reservoir in osteocytes (A,B), osteoblasts (C) bone matrix (D) of a patient with recurren osteomyelitis

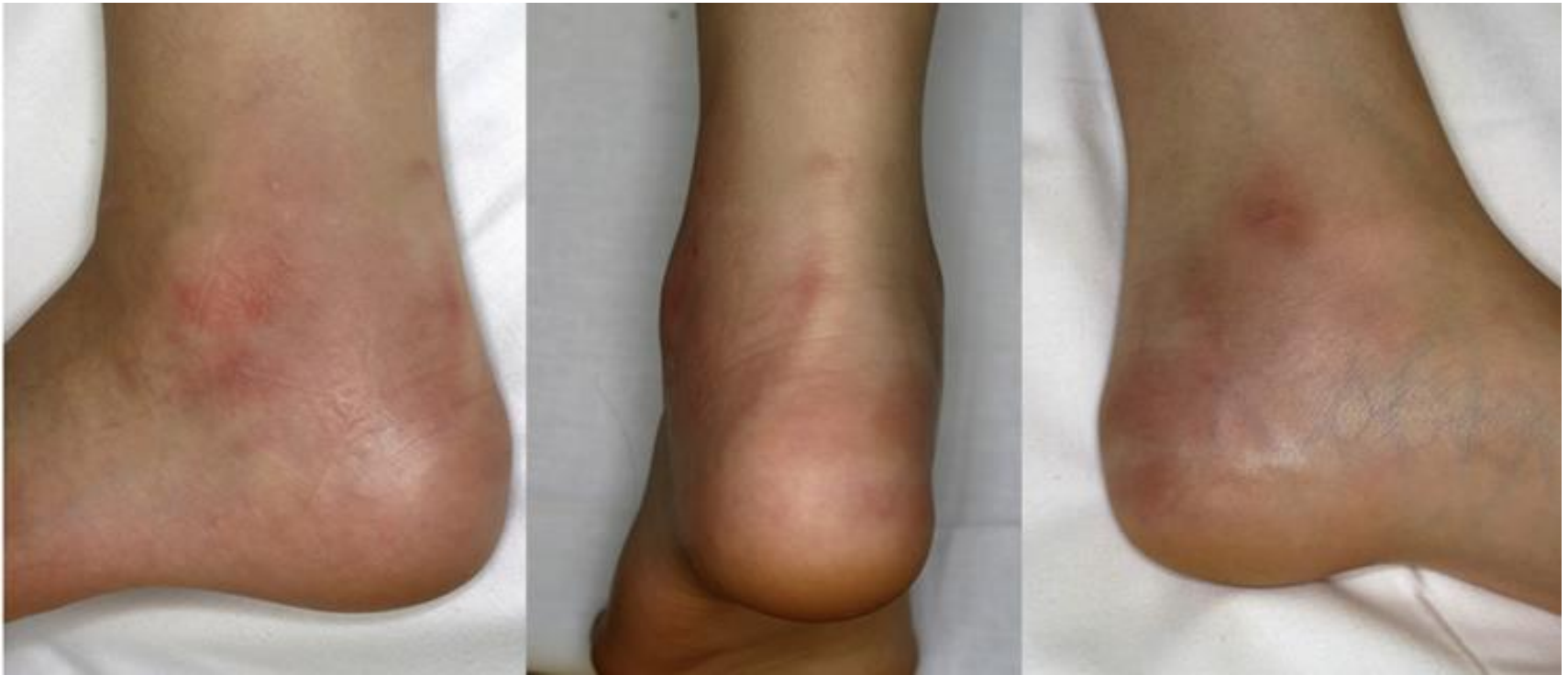


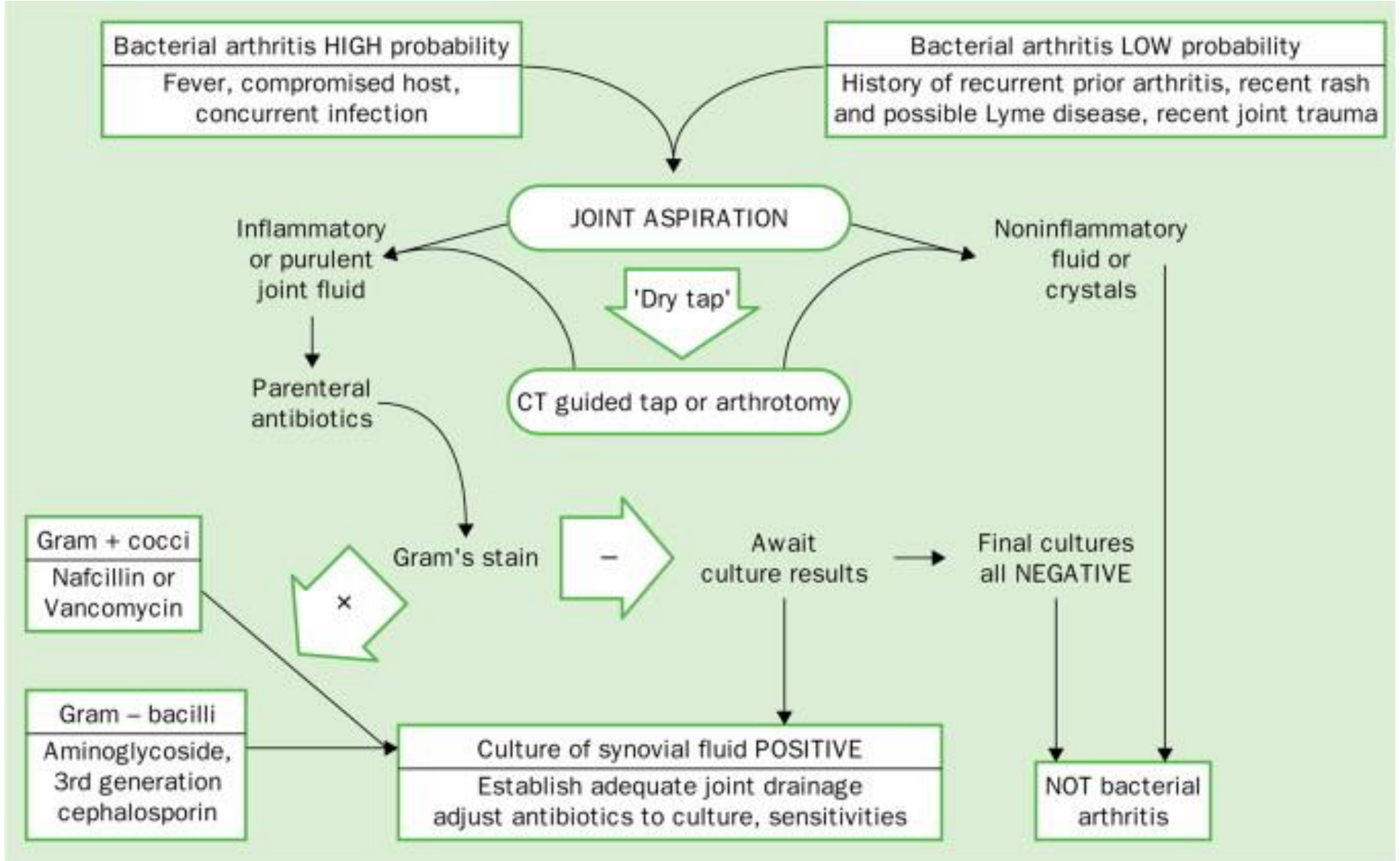
Ferry T et al. Curr Infect Dis Rep 2005.

Diagnostic efficacy: a matter of sensitivity and specificity

CLINICAL PRESENTATION:

Acute joint pain, swelling, warmth, erythema, decreased range of motion, fever, and malaise as classical presentation are non constant and therefore not reliable





Goldenberg et al., Lancet, 1998

Table 3. Examination Of Synovial Fluid.

	Normal	Noninflammatory	Inflammatory	Septic
Clarity	Transparent	Transparent	Cloudy	Cloudy
Color	Clear	Yellow	Yellow	Yellow
WBC/mL	<200	<200-2000	200-50,000	>50,000
PMNs (%)	<25%	<25%	>50%	>50%
Culture	Negative	Negative	Negative	>50% positive
Crystals	None	None	Multiple or none	None
Associated conditions	—	Osteoarthritis, trauma	Gout, pseudogout, spondyloarthropathies, rheumatoid arthritis, Lyme disease, systemic lupus erythematosus	Nongonococcal or gonococcal septic arthritis

A systematic review demonstrated that the combination of synovial fluid leukocyte count and percentage neutrophils was the best tool to predict bacterial arthritis before culture results became available

Margaretten et al. Am Med Assoc 2007

INVESTIGATION

Synovial Fluid Analysis

	WBC/mm^3	Color	Viscosity
Normal	< 150	Colorless/Straw	High
Noninflammatory	< 3,000	Straw/Yellow	High
Inflammatory	> 3,000	Yellow	Low
Septic (purulent)	> 50,000	Pus/Mixed	Mixed
Hemorrhagic	Similar to blood	Red	Low

D.A. Wang Best Practice & Research Clinical Rheumatology (2015)

Diagnostic tools

Gram stain has a sensitivity and specificity of 37% and 99%

Gram stain and culture of synovial fluid should be sent in any case of undiagnosed arthritis. Antibiotic therapy should be deferred until after synovial fluid is sampled. The involvement of rheumatology, orthopedic surgery, or interventional radiology may be necessary to obtain synovial fluid

Blood cultures should be obtained in all patients with suspected septic arthritis. At least one-third of patients with septic arthritis have associated bacteremia.

Immunosuppressed patients may lack synovial leukocytosis

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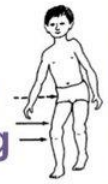
Transient Synovitis vs Septic Arthritis of Hip

Kocher's Clinical Criteria*

* Each Criteria = 1 point

Non-weight bearing 	 > 38.5°C	ESR >40mm/hr	WBC >12K

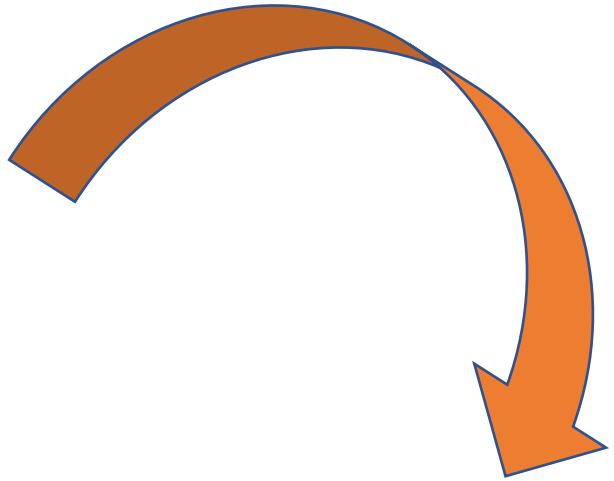
Calculate total points to predict the probability of septic arthritis[1]

0	1	2	3	4
Points 2%	Points 9.5%	Points 35%	Points 73%	Points 93%

[1] Kocher M, Mandiga R, Zurakowski D, Barnewolt C, Kasser J. Validation of a clinical prediction rule for the differentiation between septic arthritis and transient synovitis of the hip in children. *J Bone Joint Surg Am.* 2004;86-A(8):1629-1635.

There is still inadequate external validation of the criteria. In another study, 0 predictor = 16% probability of septic arthritis[2].

[2] Caird M, Flynn J, Leung Y, Millman J, D'Italia J, Dormans J. Factors distinguishing septic arthritis from transient synovitis of the hip in children. A prospective study. *J Bone Joint Surg Am.* 2006;88(6):1251-1257



- CRP > 2.0 Caird et al *JBJS* 2006
  - 5 predictors 98%
  - 4 predictors 93%
  - 3 predictors 83%

Markers for early diagnosis

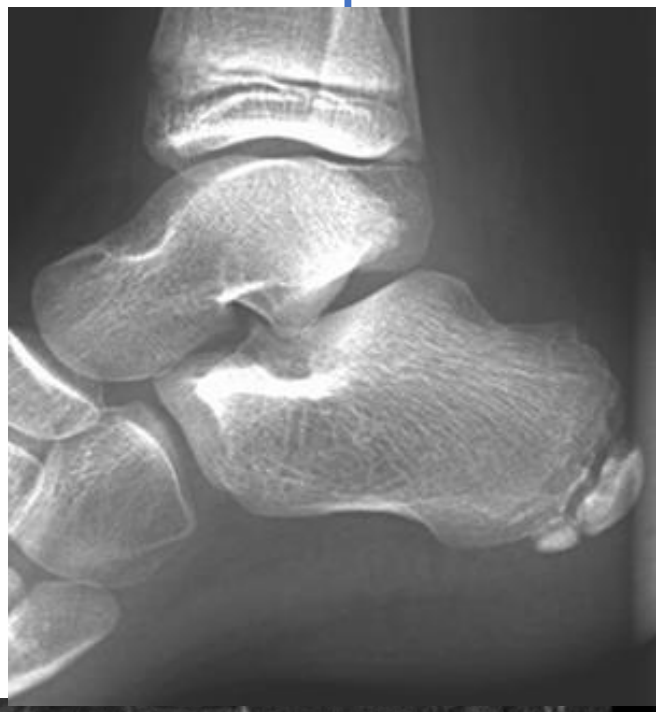
- PCT Metanalysis : 10 study, 838 patients: better than pcr, non conclusive
- Presepsin in synovial fluid, preliminary study with 100% sensivity ad specificity (18 patients)
- Synovial lactate is comparable to other diagnostic tools, useful in emergency setting
- Preliminary data to show that a combination of leukocyte esterase and glucose strips can be used to diagnose septic arthritis rapidly at the point of with a positive predictive value of 94% and a negative predictive value of 98%.

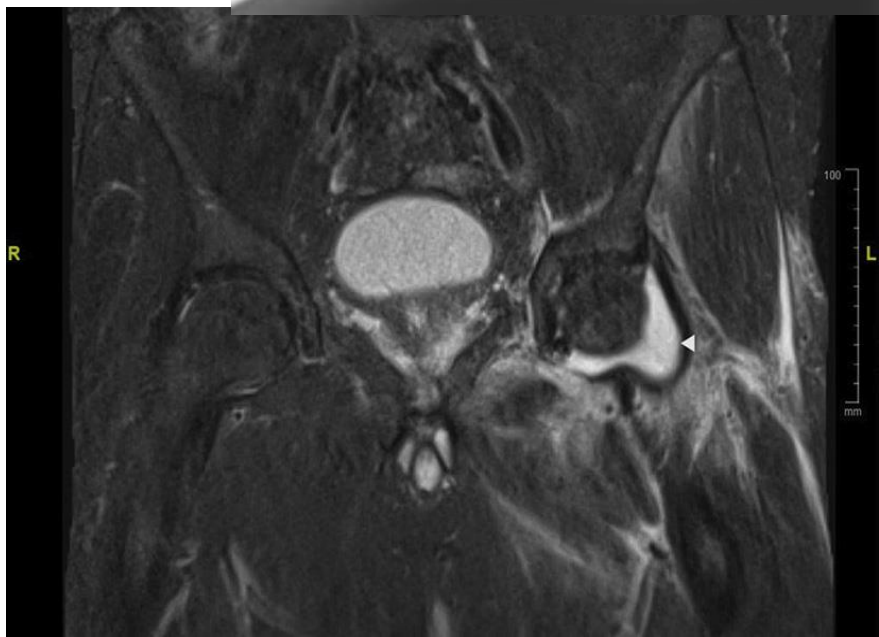
Radiology is rarely helpful in the diagnosis of septic arthritis

X-rays do not reliably distinguish between arthritis and other conditions (but a plain radiograph always should be obtained)

US can prove utility in the diagnosis and management

CT not useful in early diagnosis but may allow visualization of joint effusion, soft tissue swelling, and para-articular abscesses





Nair R et al.Infect Dis Clin N Am 31 (2017)

Synovial biopsy

- Synovial biopsy is rarely necessary but may be indicated if there is evidence of concurrent contiguous osteomyielitis in rare cases in which joint aspiration fails to provide a satisfactory sample for diagnostic testing or when infection or coinfection with M. tuberculosis or other slow growing pathogens is a possibility

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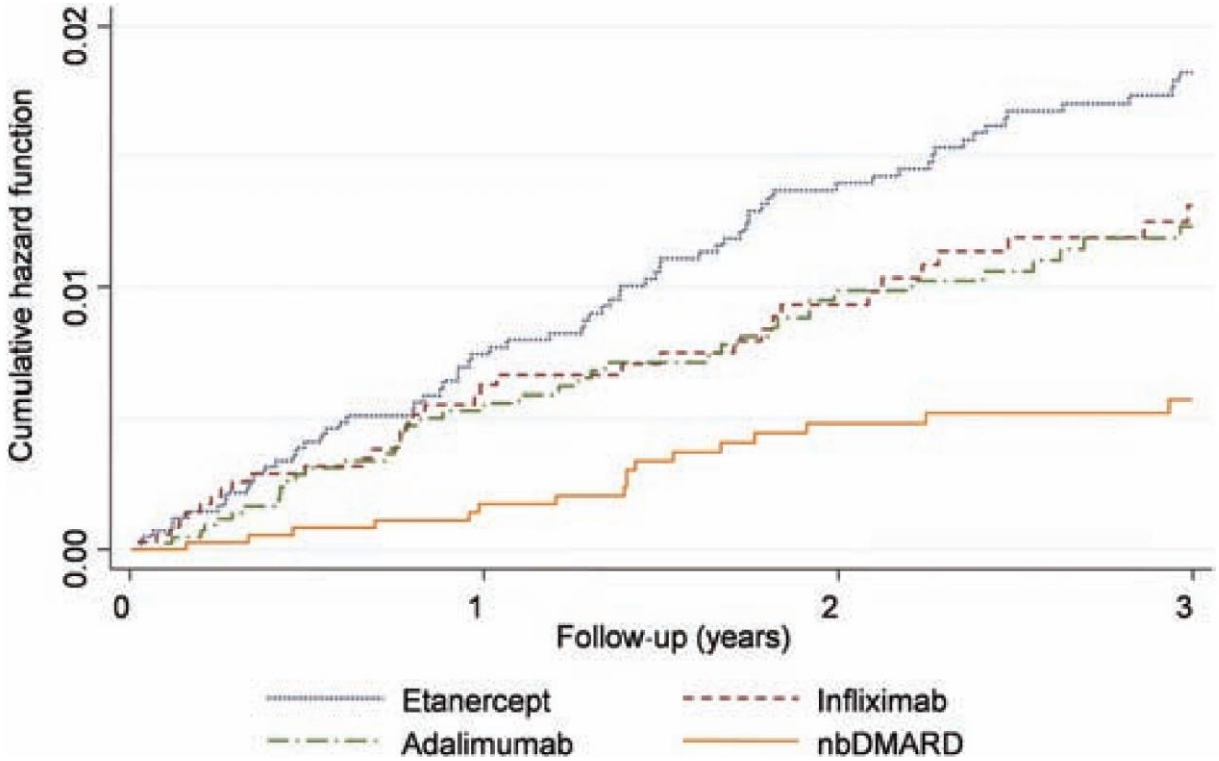
Risk of septic arthritis in patients with rheumatoid arthritis and the effect of anti-TNF therapy: results from the British Society for Rheumatology

Galloway JB et al., Ann Rheum Dis 2011



They found that the use of **anti-TNF therapy** was associated with **2x** the risk of septic arthritis

The risk of developing septic arthritis among patients with rheumatoid arthritis:

- **11881** anti-TNF agent-treated
- **3673** non-biological disease-modifying antirheumatic drug-treated

Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials

Salliot et al., Ann Rheum Dis 2009;68(1):25e32

- **Anti-interleukin-1**
  - **Anakinra**
    - The risk of serious infectious increased when a high dose of anakinra was used
    - Among the serious infections occurring in anakinra-treated patients were osteomyelitis, cellulitis, bursitis, infected bunion, and gangrene
  - **Rilonacept**
    - Limited
    - Case of MOTT or NTM (nontuberculous mycobacterial) olecranon bursitis in a patient receiving rilonacept for an unapproved indication in combination with intra-articular glucocorticoid injections **(Koo S et al., Infect Dis Clin N Am; 2010)**

Treatment Duration

1. It is challenging to determine the duration of therapy for septic arthritis
2. Although most guidelines recommend 2-6 weeks for native joints (2week os + 4week ev or 4week ev)
3. In some studies, inflammatory markers have been used to determine when to stop antibiotics

Smith JW et al. CMI; 2006
Darley ESR et al., JAC, 2004
Mathews CJ et al. Lancet 2010

Wherever possible, joint drainage is paramount in the diagnosis and treatment of septic arthritis.

Hassan A et al. J Clin Rheumatol 2017

Clin Rheumatol (2011) 30:707–710
DOI 10.1007/s10067-010-1672-3

BRIEF REPORT

What are we doing about septic arthritis? A survey of UK-based rheumatologists and orthopedic surgeons

- Terapia antibiotica + drenaggio/lavaggio artroscopico (70%)
- Terapia antibiotica + artrotomia (2,5%)
- Terapia antibiotica + artrocentesi ripetute (25%)
- Terapia antibiotica (2,5%)
- Terapia antibiotica + cortisonici (dati solo nei bambini)

Butt U et al. Clin Rheumatol. 2011

New anti gram-positives antibiotics

		cSSSi	CAP	HAP	VAP	note
Ceftarolina *Zinforo*	Pfizer	X	X			No VAP 600 mg bid
Ceftobiprolo *Mabelio*	Correvio		X	X		No VAP 500 mg bid
Telavancina * *Vibativ*	Astellas	X		X	X	Once-daily 10 mg/Kg; No IR
Dalbavancin *Xydalba*	Angelini	X				IV single dose 1500 mg dose
Oritavancin	Menarini	X				IV Single dose 1200 mg
Tedizolid *Sivextro*	MSD	X				200 mg IV/OS X 6 days
Delafloxacin	Menarini	X				450 mg bid/OS 300 mg bid/IV

** When alternative treatment is not suitable*

Dosing and PK of of New Gram-Positive Antibiotics

Table 2. Dosing and Pharmacokinetics of New Gram-Positive Agents [5,17,18,27,40-42]						
Drug	Tedizolid phosphate	Linezolid	Dalbavancin	Oritavancin	Telavancin	Vancomycin
Drug Class	Oxazolidinone	Oxazolidinone	Lipoglycopeptide	Lipoglycopeptide	Lipoglycopeptide	Glycopeptide
Dosing	200 mg oral or intravenous daily	600 mg oral or intravenous every 12 hours	1000 mg intravenous followed one week later by 500 mg intravenous	1200 mg single intravenous infusion (over 3 hours)	10 mg/kg intravenous every 24 hours	1000 mg (or 15-20 mg/kg) intravenous every 12 hours
C_{max} (mcg/mL)	Oral: 2.0 Intravenous : 2.3	Oral: 12.7- 21.2 Intravenous : 12.9-15.1	287	138	93.6-108	63
T_{max} (hours)	Oral: 2.5 Intravenous : 1.1	Oral: 1.03- 1.28 Intravenous : 0.5	NR	Immediately following 3-hour infusion	NR	Immediately following 60-minute infusion
Half-life (hours)	12	4.6	346	245	8.0-8.1	4-6 hours
$AUC_{0-infinity}$ (mcg•h/m L)	Oral: 23.8 Intravenous : 26.6	Oral: 91.4- 138 Intravenous : 80.2-89.7	23,44	2,800	747	NR

	Vancomycin	Teicoplanin	Telavancin	Dalbavancin	Oritavancin
T1/2	8 hrs	70 hrs	8 hrs	204 hrs	245 hrs
Vd	0.7 L/kg	1.0 L/kg	0.13 L/kg	0.22 L/kg	1.25 L/kg
Binding	55%	90%	90%	93%	85%
Dose	15-20 mg/kg every 12 hrs	variable	10 mg/kg every 24 hrs	1000 +500 mg 1 week (or 1 shot)	1200 mg x 1

Twice daily

Every 1 or 2 days

Once daily

Once a week

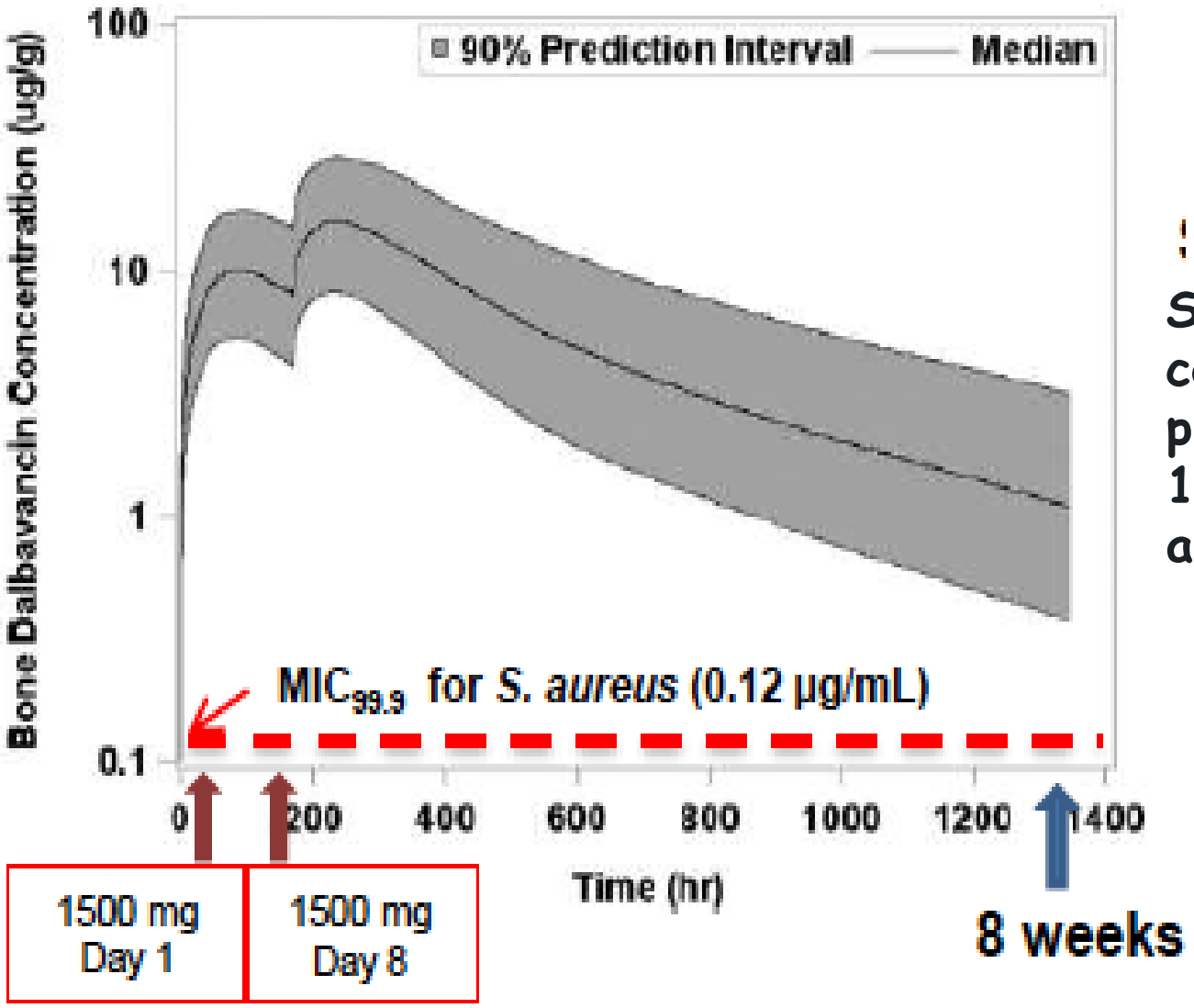
Once!

Comparative *in vitro* Activity of New Gram-Positive Antibiotics

Table 1. *In vitro* Activity (MIC_{90} in µg/ml) of New Gram-Positive Agents[4,6-9, 29,30,36,37-39]

	Tedizolid[a]	Linezolid[b]	Dalbavancin[c]	Oritavancin[d]	Telavancin[e]	Vancomycin[f]
Methicillin-susceptible *S. aureus*	0.5	2-4	0.06	0.06	0.06	1
Methicillin-resistant *S. aureus*	0.5	2-4	0.06	0.06	0.06	1
Vancomycin-intermediate *S. aureus* (VISA)	0.5	4	0.5-2*	1	0.12	8
Heterogenous VISA	0.5	1	0.5	2	0.12	2
Linezolid-resistant *S. aureus* (*cfr*-gene mediated resistance)	0.5-1*	8-32*	---	---	0.06¥	1
Linezolid-resistant *S. aureus* (23S rRNA mutations)	8	>32	---	---	0.06¥	2

Extended-duration dosing and distribution of dalbavancin into bone and articular tissue.



Simulated mean concentration time profile in bone with 1,5 g IV on days 1 and 8

Dunne MW et al, Antimicrob Agents Chemother ***2015 59:1849-55.***

Dalbavancin for the Treatment of Osteomyelitis in Adult Patients: A Randomized Clinical Trial of Efficacy and Safety

Open Forum Infectious Diseases®

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[1]Clinical Development, Allergan plc, Madison, New Jersey; [2]Orthopedic and Trauma Department, Cherkasy Regional Hospital, Cherkasy, Ukraine; [3]Medical Affairs, Allergan plc, Jersey City, New Jersey

Background. Osteomyelitis is a challenging infection that can involve 4–6 weeks of intravenous (IV) antibiotics. Dalbavancin, approved for acute bacterial skin and skin structure infections, has potent activity against gram-positive pathogens. This study assessed the efficacy and safety of dalbavancin as a 2-dose regimen for osteomyelitis.

Methods. This study was a randomized, open-label, comparator-controlled trial in adults with a first episode of osteomyelitis defined by clinical symptoms, radiologic findings, and elevated C-reactive protein. Patients were randomized 7:1 to dalbavancin (1500 mg IV on days 1 and 8) or standard of care (SOC) for osteomyelitis (oral or IV) per investigator judgment for 4–6 weeks. The primary endpoint was clinical response at day 42, defined as recovery without need for additional antibiotics in the clinically evaluable (CE) population. Clinical response was also assessed at day 21, 6 months, and 1 year.

Results. Eighty patients were randomized to dalbavancin (n = 70) or SOC (n = 10). All had baseline debridement; *Staphylococcus aureus* was the most common pathogen (60% of patients). Clinical cure at day 42 was seen in 65/67 (97%) and 7/8 (88%) patients in the dalbavancin group and SOC group in the CE population, respectively. Clinical response was similar in the dalbavancin group at day 21 (94%), 6 months, and 1 year (96%). Treatment-emergent adverse events occurred in 10 patients in the dalbavancin group; no patient discontinued treatment due to an adverse event.

Conclusions. A 2-dose regimen of weekly dalbavancin is effective and well tolerated for the treatment of osteomyelitis in adults.

Clinical Trials Registration. NCT02685033.

Keywords. osteomyelitis; dalbavancin; gram-positive.

Table 1. Demographics and Baseline Patient and Disease Characteristics in the Safety Population

Characteristic[a]	Dalbavancin (n = 70)	Standard of Care (n = 10)
Age, mean (SD; range), y	49.2 (13.3; 26–79)	54.4 (15.3; 29–79)
Male sex[b]	59 (84.3)	5 (50.0)
Race		
White	70 (100)	10 (100)
Ethnicity		
Not Hispanic/Latino	70 (100)	10 (100)
Body mass index, kg/m^2		
Mean (SD)	26.1 (5.1)	30.7 (7.4)
Median (min, max)	24.7 (18.6, 40.1)	33.8 (21.6, 40.3)
Diabetes[c]	10 (14.3)	5 (50.0)
Predisposing factors at site of osteomyelitis		
Prior fracture and surgical repair	33 (47.1)	4 (40.0)
Prior fracture	2 (2.9)	0
Surgical intervention		
Debridement and open biopsy	70 (100)	10 (100)
Vacuum-assisted closure of wound	8 (11.4)	3 (30)
Skin graft	1 (1.4)	1 (10)
Aztreonam use	8 (11.4)	1 (10)

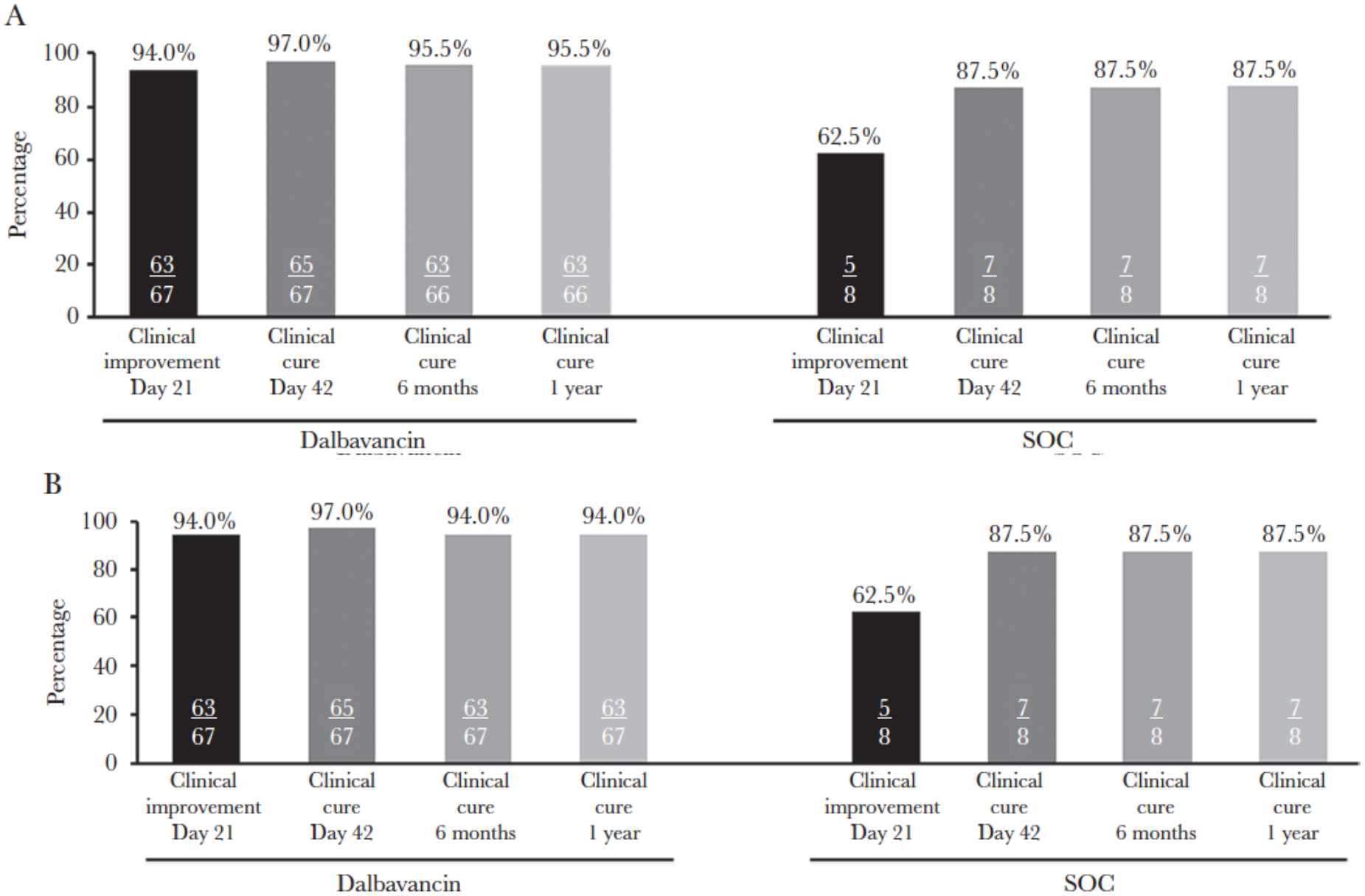

Figure 2. Clinical outcomes in the (A) CE and (B) mITT populations. Abbreviations: CE, clinically evaluable; CRP, C-reactive protein; IV, intravenous; mITT, modified intent-to-treat; SOC, standard of care.

PROSTHESIS JOINT INFECTIONS: DIFFERENCES WITH NATIVE SA

Table 1
Threshold value for cell counts of laboratory tests used in diagnosis of prosthetic joint infections

Peripheral Blood (Hip and Knee)	Synovial Fluid Analysis (Neutrophil Percentage)
• WBC: 11,000 × 10^9 cells/liter	• Knee: 1100 cells/μL (64%)
• CRP: 10 mg/L	27,800 cells/μL (89%) if <6 wk after implantation
• ESR: 30 mm/h	• Hip: 4200 cells/μL (80%)
• IL-6: 10 pg/mL	
• Procalcitonin: 0.3 ng/mL	

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; WBC, white blood cell count.

Data from Tande AJ, Patel R. Prosthetic joint infection. Clin Microbiol Rev 2014;27(2):302–45.

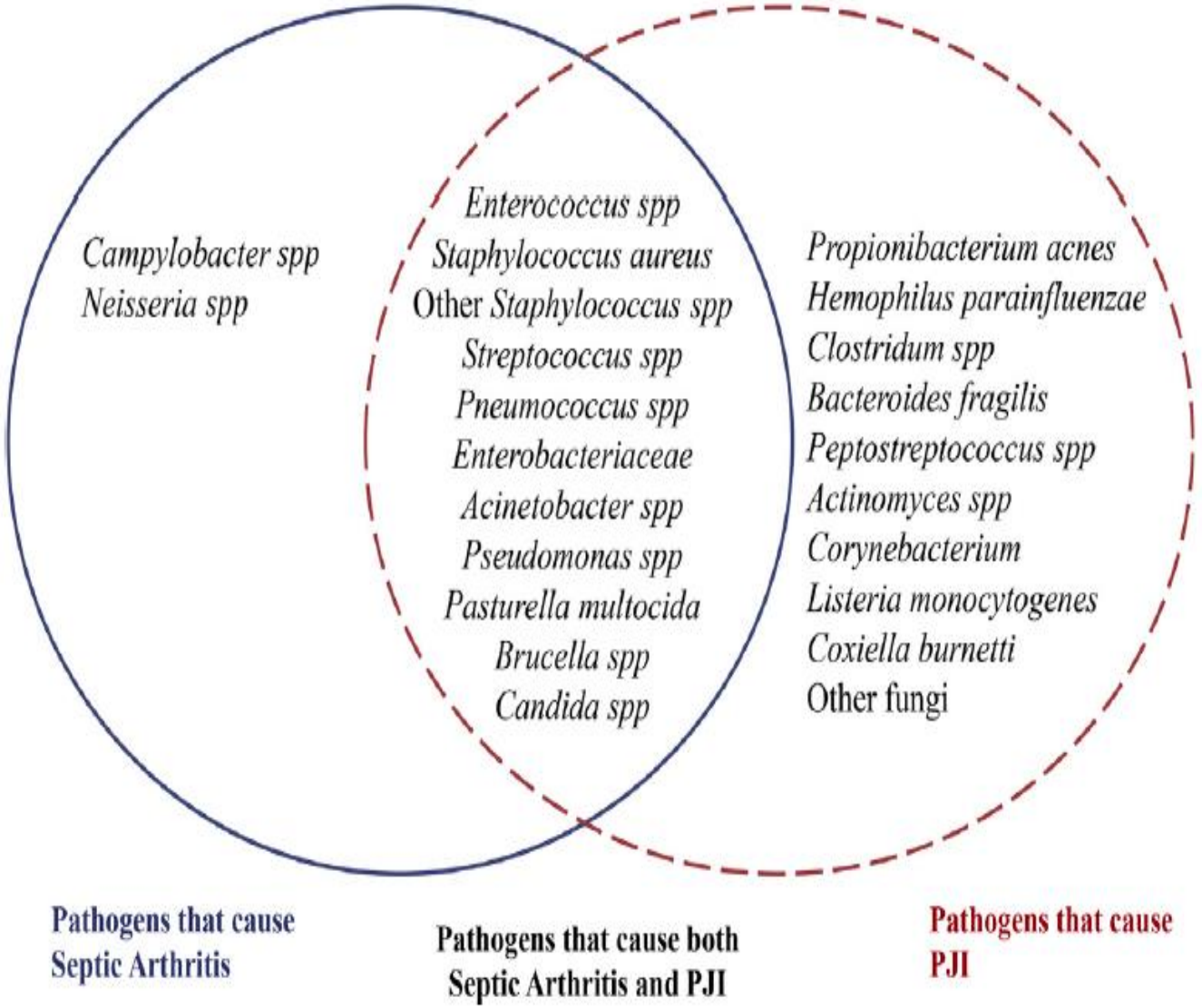

Fig. 1. Venn diagram for pathogens that cause septic arthritis and prosthetic joint infections (PJIs).

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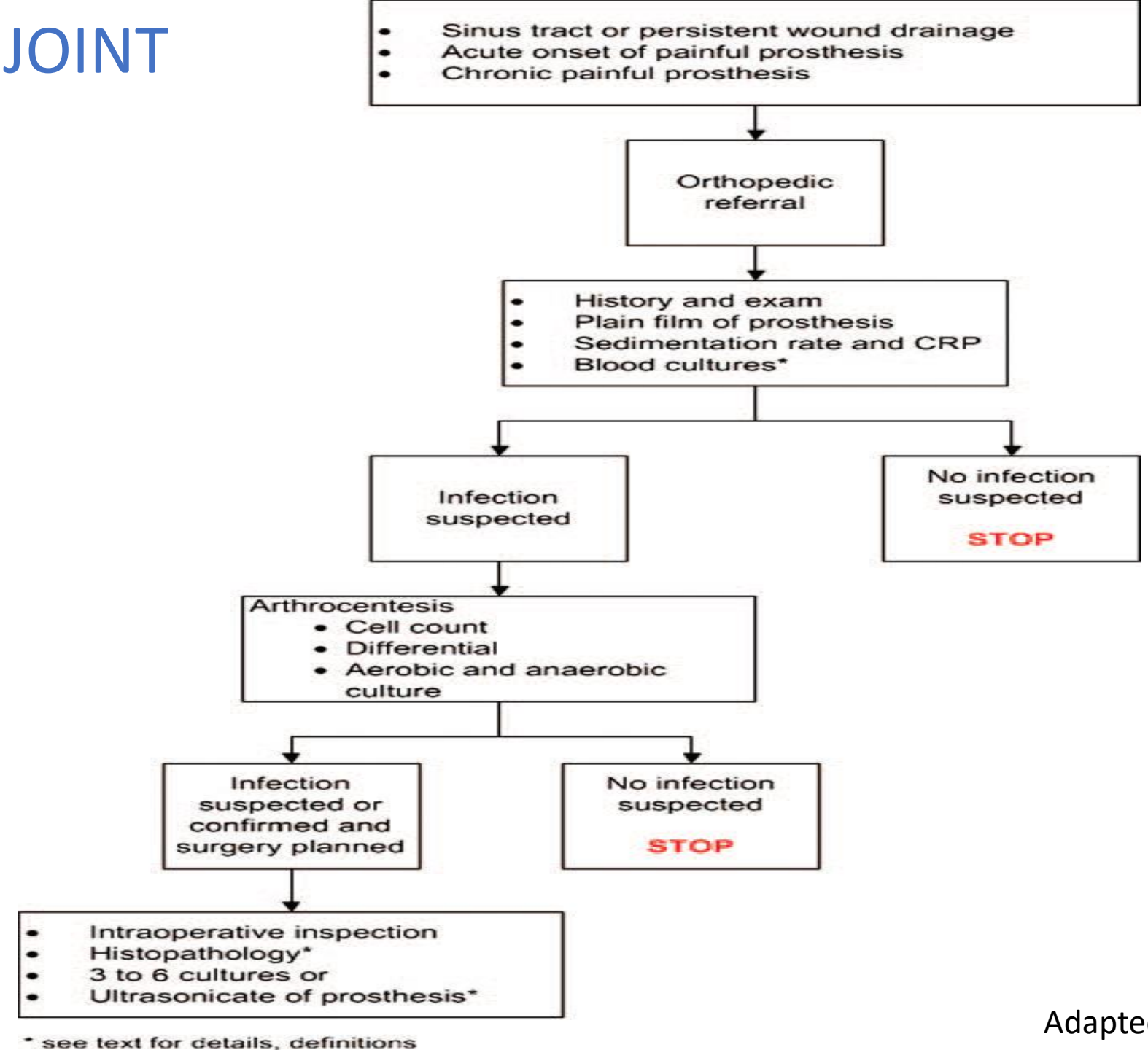
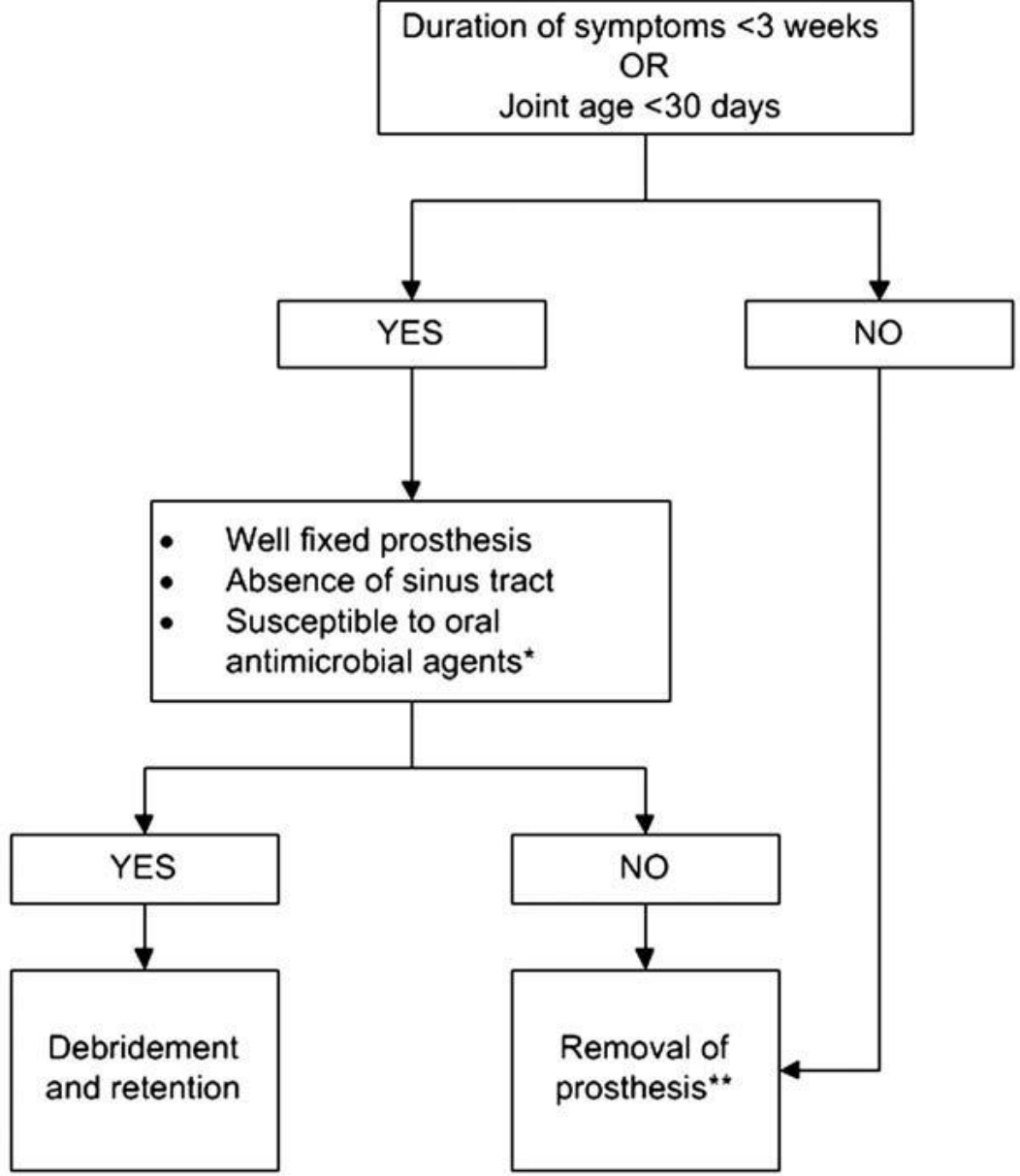
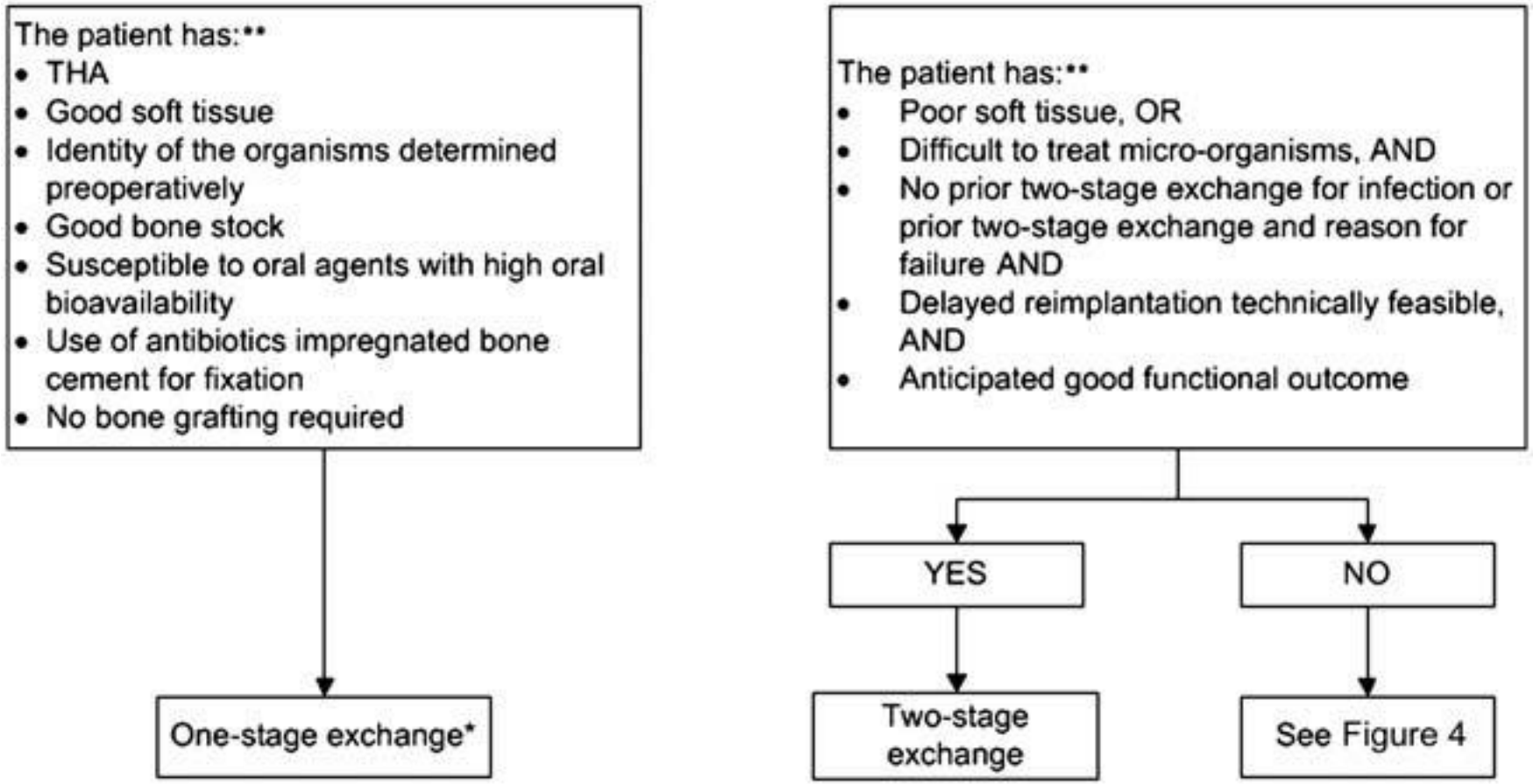
PROSTHETIC JOINT INFECTIONS



Adapted from IDSA guidelines



*Antimicrobial agents that are recommended for prolonged use for chronic suppression or treatment of biofilm bacteria (see text for details)
**See Figure 3 and recommendation 18 and accompanying Evidence Summary for possible exceptions



*Uncommonly performed in the U.S.
**Relative indications see text

PJI MANAGEMENT

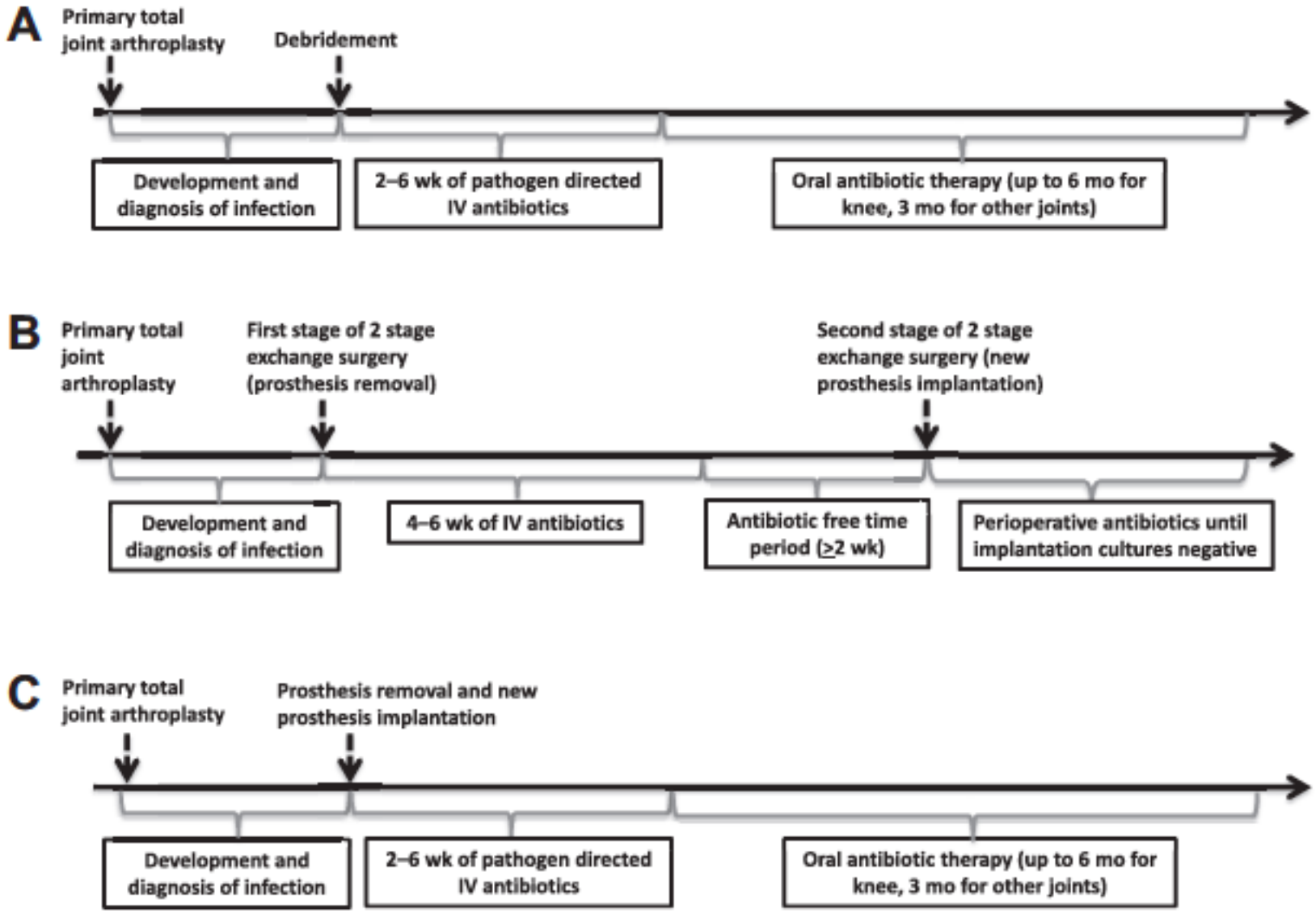


Fig. 2. Guideline recommended surgical and medical management for prosthetic joint infections. (*A*) Debridement. (*B*) Two-stage exchange. (*C*) One-stage exchange. IV, intravenous.