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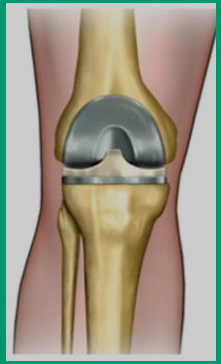
Joint infections: native and prosthetic

PD Dr. med. Nora Renz, Inselspital Bern

Journée de médicine interne, Delémont, 24.11.22



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Male, 48yo

- Atraumatic knee joint pain (left) for 2 days
- Otherwise healthy, no prior interventions at the knee
- Deep cut after gardening at dig III left hand 1 week ago
- Clinical examination: Swollen knee, painful motion, excess heat, no fever
- Lab: CRP 145mg/l, WBC 13.3G/l

- Joint aspiration:
  - Leukocyte count 34‘900/ul
  - 90% granulocytes
  - Microbiology pending

→ Septic arthritis suspected → arthroscopic irrigation, amoxicillin/clavulanic acid i.v.

Septic arthritis = emergency

Preservation of joint integrity dependent on time between symptom onset and introduction of adequate therapy

→ Delay results in irreversible damage of cartilage and joint

→ Time is cartilage

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Pathogenesis

hematogenous
Spreading phenomenon of bacteremia

80%

postinterventional
Direct inoculation (colonisation)

- Surgery
- Arthroscopy
- Infiltration/aspiration
- Bite injury
- Trauma

15%

contiguous
Direct spread form adjacent tissue

- Osteomyelitis
- Cellulitis
- Bursitis

5%

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Causative pathogens

- *S. aureus* (60%)
- Streptococci (20%)
- *Neisseria spp*. (*N. meningitidis, N. gonorrhoeae*)
- Other gram negative organisms (10%; neonates, IVDU, children < 4y, after trauma)

Exposure	Organism
IV drug abuse	*Pseudomonas* sp., fungi, *S. aureus*
After bite injury	*Pasteurella multocida*, *Capnocytophaga canimorsus*, oral flora of animals (and humans), *Eikenella*, *Fusobacterium*
After aspiration/injection	Coagulase negative staphylococci, skin flora
Sexual activity	*Neisseria gonorrhoeae*
Children <4y	*Kingella kingae, H. influenzae*

Margaryan D Orthopäde 2020

Clinical presentation

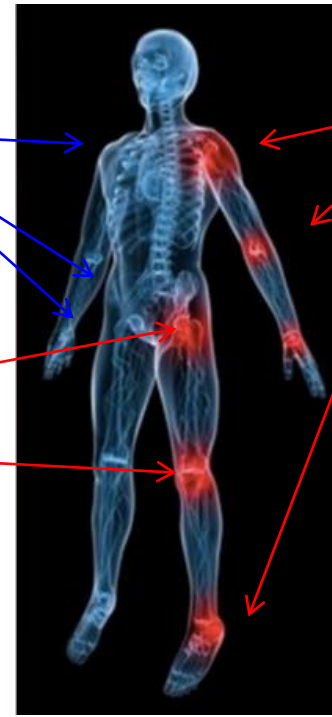
85% monoarticular

15% oligoarthritis (gonorrhoeal, persistent primary focus, preexisting arthropathy (RA))

Dubost JJ, Medicine 1992

Rare:
sternoclavicluar joint, ileosacral joint, symphysis pubica

5 -10% shoulder, wrist, ankle, elbow



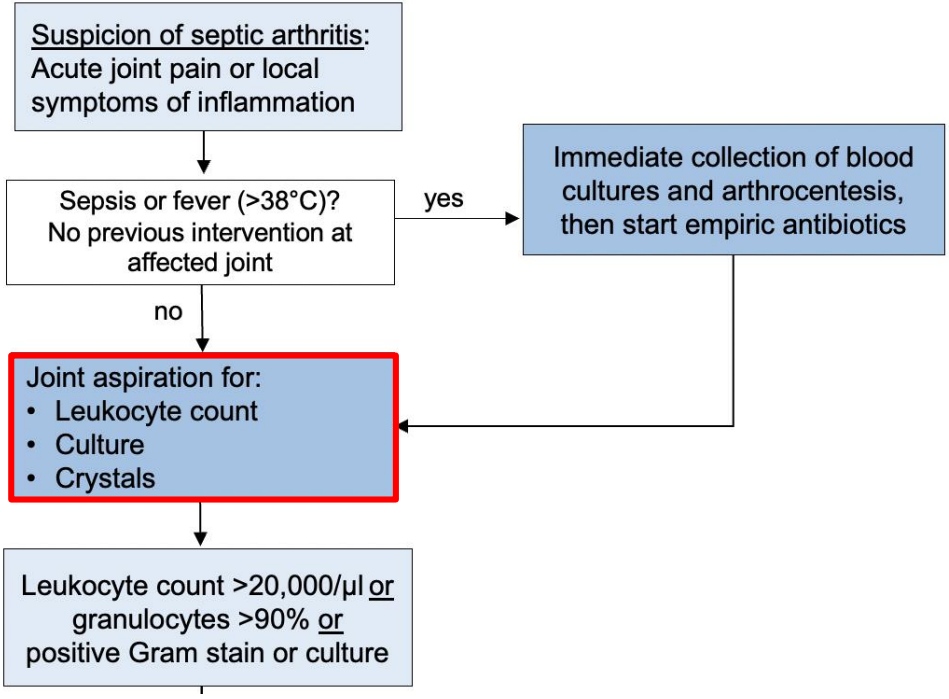
25% hip (esp. children)

55% knee

Pain (85%)
Local inflammation (78%)
Fever (57%)

Margaretten ME, JAMA 2007

Diagnostic algorithm



PIF Pocket Guide Septic Arthritis, V1, 2020 (modif.)

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Goals of joint aspiration

low sensitivity (<50%)
high specificity (>90%)

1. **Diagnostics:**
   - Cell count and differen
   - Culture, Gram stain
   - Crystals

   Presence of crystals doesn't exclude infection!

2. **First treatment:**
   - Relief of joint distension
   - Reduction of cartilage destroying leukocytes, toxins, enzymes and bacteria

- Sterile conditions!
- Avoid areas of cellulitis!
- No antibiotics before aspiration!

Perry CR Am J Orthop 1999, Mathews C Lancet 2010, Coakley G Rheumatology 2006, Soderquist B Scand J Infect Dis 1998

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Leukocyte count in synovial fluid

Value	Normal	Degenerative	Inflammatory (RA, reactive, psoriatic, PJI)	Infectious or crystals
Leukocytes, /µL	<200	200 - 2,000	2,000 – 20,000	>20,000
Neutrophils, %	<25	25 – 70	70 - 90	>90

Cut-off	Sensitivity	Specificity
>100‘000/µL	29%	99%
> 50‘000/µL	62%	92%
> 25‘000/µL	77%	73%
PMN >90%	73%	79%

Margaretten ME JAMA 2007

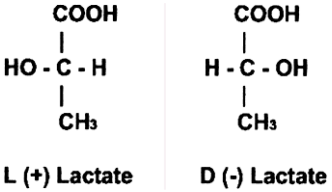
On the horizon: D-lactate

L-lactate (human cells)

(L-lactate-dehydrogenase)

D-lactate (bacteria)

(D-lactate-dehydrogenase)

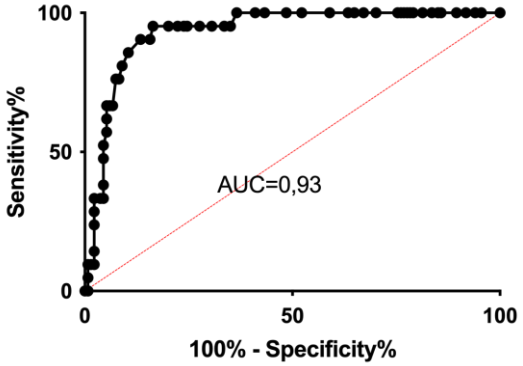


Still being validated prospectively...

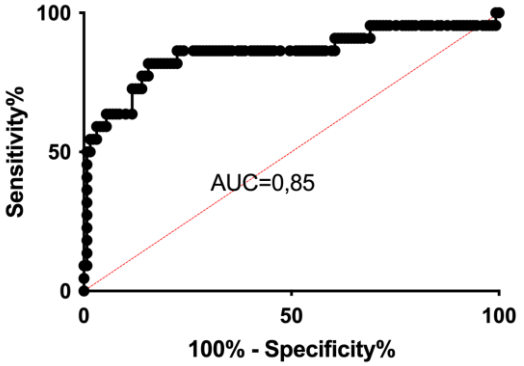
- **155 patients** included at Kantonsspital Aarau and Charité Berlin
- **21 (14%) with septic arthritis**: **positive culture in 17 pat. (80%)**

Performance of D-lactate

D-lactate (cut-off 0.035mmol/l)



Leukocyte count (>20.000/ul)



Tests	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC
D-lactate*, mmol/L	**90**	**87**	51	98	0,93
Leukocytes**, cell/µl	**81**	**83**	46	96	0,85

Karbysheva & Conen et al., manuscript in preparation

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  - 90% granulocytes
  - Microbiology: *S. aureus*
- Arthroscopy: Tissue biopsies: *S. aureus* in 3/3 samples
- Blood cultures: no growth

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Definition of septic arthritis

High suspicion of septic arthritis, if:
≥1 clinical feature and ≥1 laboratory finding present

Clinical features	
Signs and symptoms	New onset of: • Joint pain (non-traumatic origin) or • Local signs (redness, warmth, swelling, effusion) or • Limited range of motion
Laboratory findings	
Synovial fluid leukocyte count[1]	• >20,000/µl leukocytes[2] or • >90% granulocytes[2]
Synovial membrane histopathology	Inflammation compatible with infection
Microbiology[3]	Microbial growth[4] in: • Synovial fluid or • Synovial membrane tissue or • Blood culture (≥1 positive bottle)

PRO-IMPLANT Foundation Pocket Guide Septic Arthritis, V1, 2020 (modif.)

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Treatment

Time = cartilage

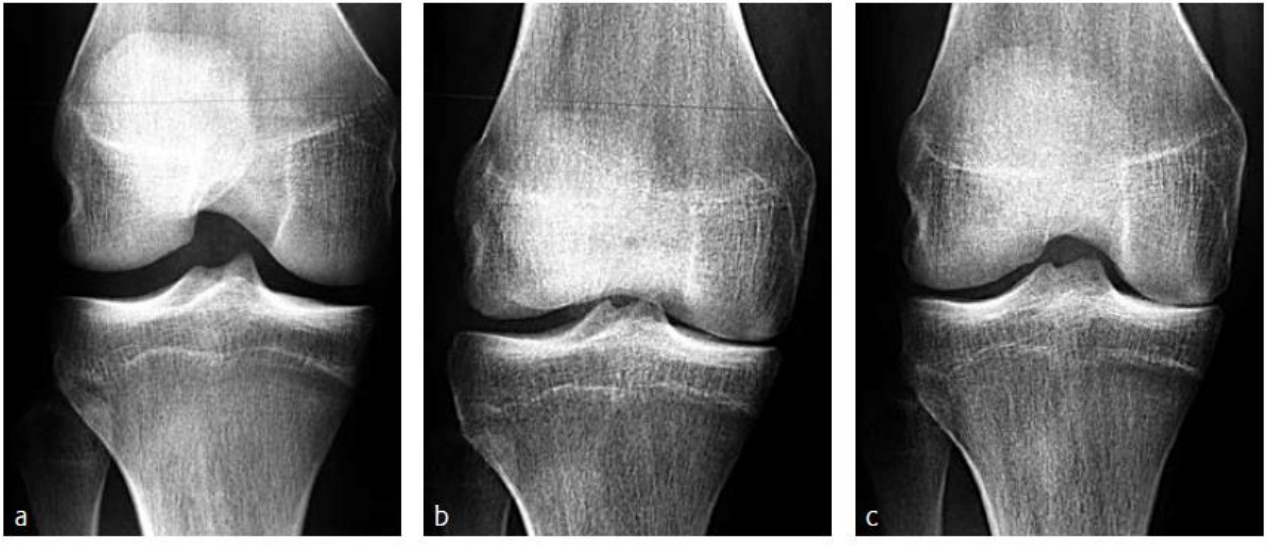

Fig 11.1-1a–c Rapid joint destruction in a 21-year-old athlete after mistreated septic arthritis with methicillin-susceptible *Staphylococcus aureus* (3 months between first and last x-rays).

Ochsner et al, swiss orthopaedics and swiss society of infectious diseases, 2016

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Therapy

Joint decompression: ubi pus ibi evacua

Joint sterilization: Antimicrobial therapy

Functional healing: Early mobilisation, physiotherapy

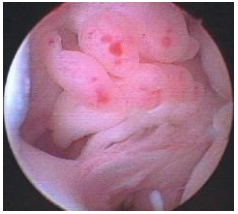
Treatment of primary focus

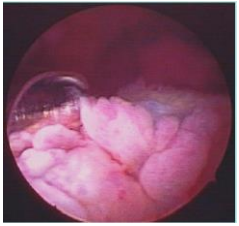
(if applicable)

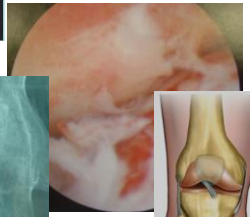
Gächter stages

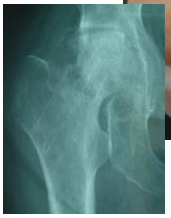
Arthroscopic and radiological classification, but can be used in open surgery

Stage	Criteria
1	Synovitis, cloudy fluid, possible petechiae, no radiological changes
2	Highly inflammatory synovitis, clumps of fibrin, pus, no radiological changes
3	Thickening of the synovial membrane (possibly several centimeters), adhesion with pouch formation, no radiological changes visible
4	Pannus formation, proliferation of aggressive synovitis on and later beneath the cartilage (subchondral erosions), radiological changes visible









Gächter A Inform Arzt 1985

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Joint decompression

Arthroscopy

- Large weight bearing joints
- Gächter stages 1-3

Arthrotomy

- Gächter stage 4
- After unsuccessful, repetitive arthroscopies
- Underlying osteomyelitis/bone sequester
- Extensive soft tissue involvement, including abscess

→ No scheduled re-arthroscopies are indicated, reinterventions depend on clinical and laboratory response

→ Repetitive joint aspirations only in small joints

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Antimicrobial treatment

- Start immediately after microbiological diagnostics
- Systemic, high dose and bactericidal antibiotic therapy
  - →Empirically: IV amoxicillin-clavulanate
- Treatment duration: 2-6 weeks
  - Depending on microorganism, clinical response, concomitant osteomyelitis, primary focus (endocarditis!)
    - → With osteomyelitis: 6 weeks
    - → *S. aureus*, gram-negative bacilli: 4 weeks
    - → Streptococci, *Haemophilus* spp.: 2-3 weeks

Stengel et al. Lancet Infect Dis 2001. Clerc et al. J Antimicrob Chemother 2011. Trampuz et al. Current Treatment Options in Infectious Diseases 2003. Coakley et al. Rheumatology 2006. Zimmerli et al. Arthroskopie 1994. Smith et al. CID 1995. Mathews et al. Lancet 2010. Kowalski et al. Infection 2014. Gjika et al. Ann Rheum Dis 2019. Uckay et al. Int J Infect Dis. 2013. Li et al. NEJM 2019 (OVIVA). Pérez-Prieto D et al. J Knee Surg 2017

Periprosthetic joint infection

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High susceptibility if implant in situ

Reference (Model)	Foreign body (FB)	Min. infectious dose no FB	with FB	Pathogen
Elek 1957 (Human)	Sutures	5×10^6	3×10^2	*S. aureus*
James 1961 (Mouse)	Sutures	10^6	$<10^3$	*S. aureus*
Zimmerli 1982 (Guinea pig)	Cages	$>10^7$	10^2	*S. aureus*
Widmer 1988 (Guinea pig)	Cages	$>10^7$	10^3	*S. epidermidis*

→ Implant multiplies infection risk more than 10’000fold

Elek SD Br J Exp Pathol 1957

Biofilm

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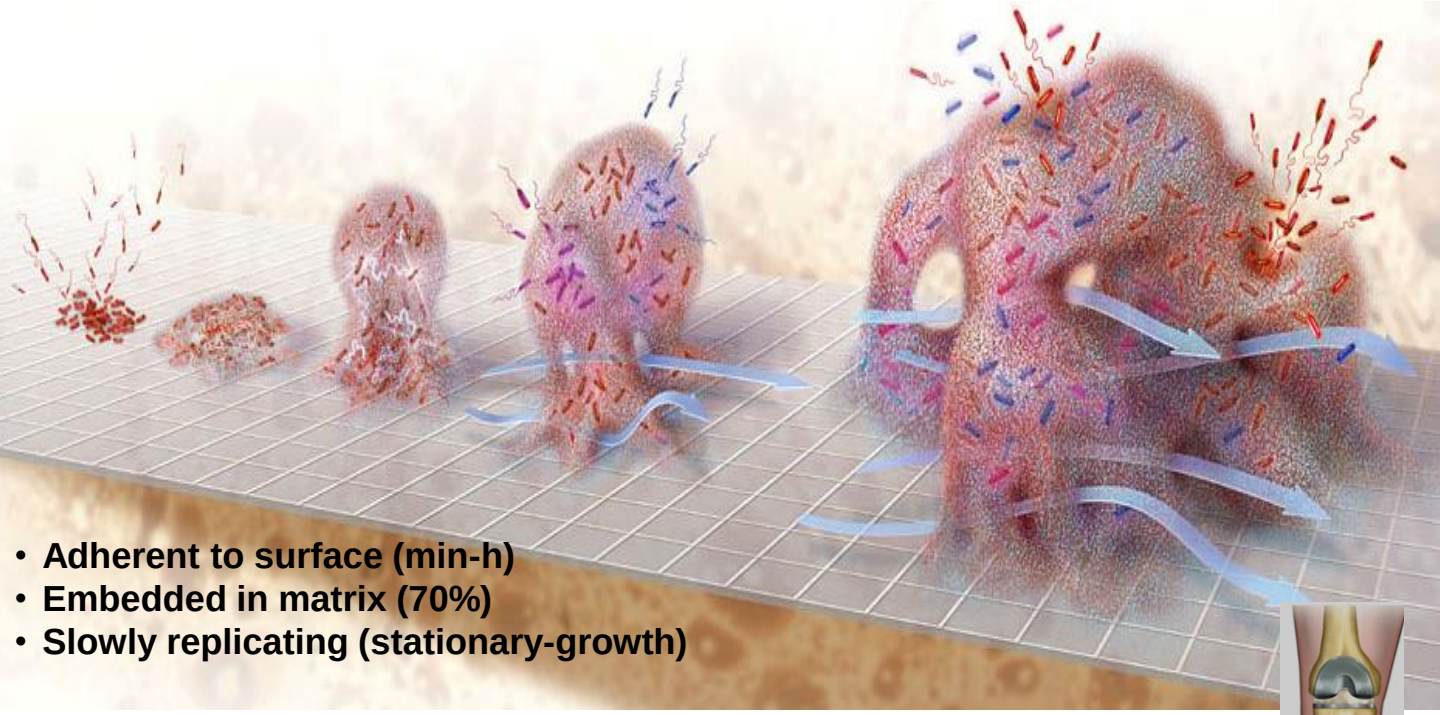
1 min 3 h 12 h 1 day → 3 days



- Adherent to surface (min-h)
- Embedded in matrix (70%)
- Slowly replicating (stationary-growth)

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Pathogenesis

peri-/postoperative
Direct inoculation (colonisation)

50-70%

hematogenous
Spreading phenomenon of bacteremia

20-35%

contiguous
Direct spread form adjacent tissue

~5%

Chronic (>4 weeks)
Old biofilm

Acute (<3-4 weeks)
Young biofilm

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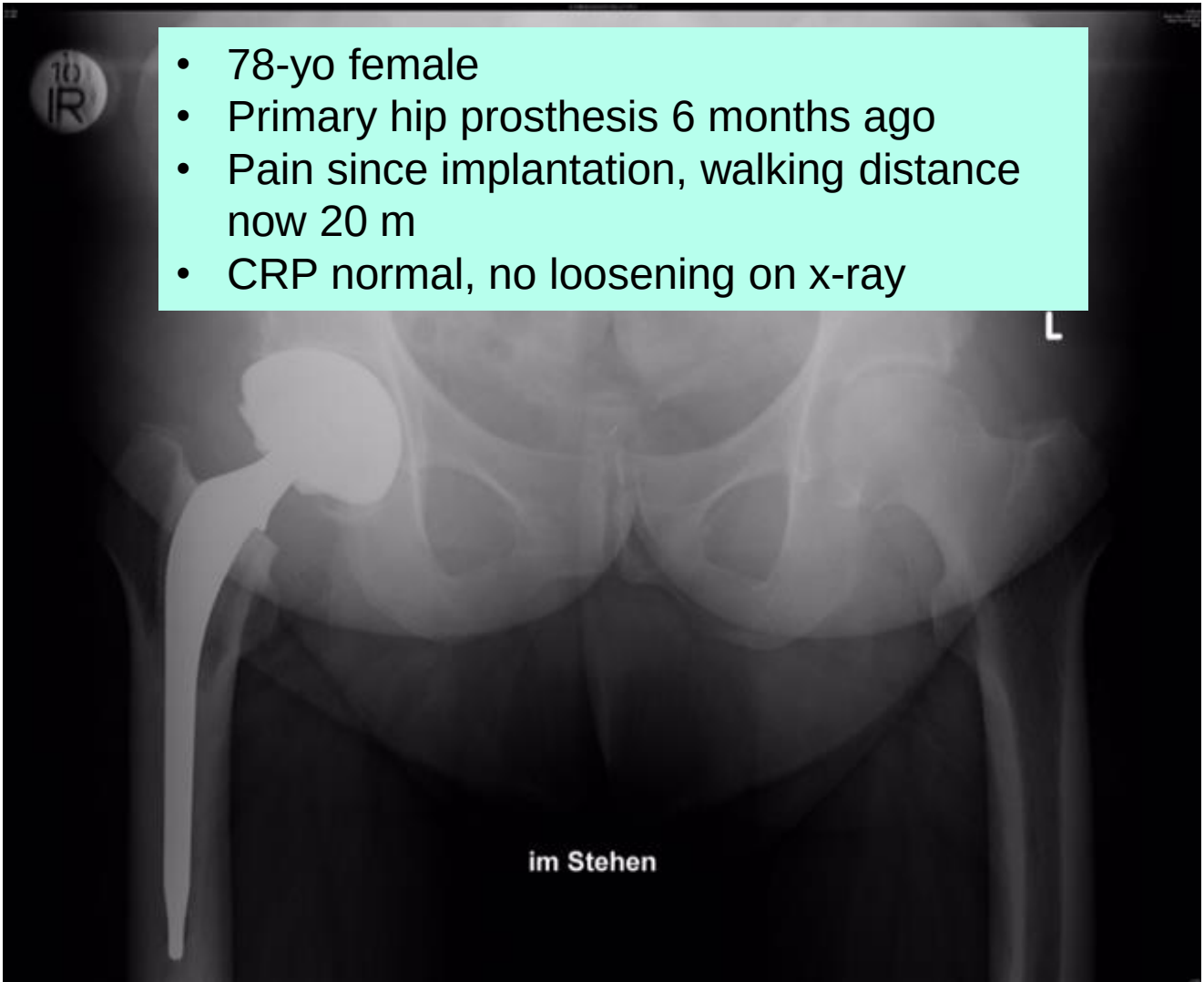
Pathogens

Pathogens	Frequency (%)
Coagulase-negative staphylococci (e.g., *S. epidermidis*) ✸	30-43
Staphylococcus aureus	12-23
Streptococcus and *Enterococcus* species ✸	12-19
Gram-negative rods (e.g., *Escherichia coli*)	10-17
Anaerobes (e.g., *Cutibacterium acnes*) ✸	4-10
Polymicrobial	10-20
Fungi (e.g., *Candida albicans*)	1-3
No pathogen	10-30

✸ Low virulent pathogens (→ Low grade infections)

Corvec S. Int J Artif Organs. 2012, Tande AJ. Clin Microbiol Rev. 2014

- 78-yo female
- Primary hip prosthesis 6 months ago
- Pain since implantation, walking distance now 20 m
- CRP normal, no loosening on x-ray



Untersuchungsauftrag

Material:

Fragestellung:

Aspiration 6 months after implantation

Mikroskopische Untersuchungen

Grampräparat	Leukozyten	mässig
	Mikroorganismen	nicht nachweisbar

Kulturelle Ergebnisse

1. **Staphylococcus epidermidis** nach Anreicherung

S = sensibel I = intermediär R = resistent f = folgt N = negativ P = positiv

	1.
Ampicillin	R
Amoxicillin + Clavulansäure	R
Cefalotin	R
Ceftriaxon	R
Gentamycin	R
Norfloxacin	R
Ciprofloxacin	R
Levofloxacin	R
Cotrimoxazol	R
Tetrazyklin	S
Imipenem	R
Penicillin	R
Oxacillin	R
Clindamycin	R
Erythromycin	S
Rifampicin	S
Vancomycin	S
Fusidinsäure	R

High leukocyte count in joint aspirate (34,000/µl)

Low grade infection of the THA

validiert durch: Irene Grohsellus

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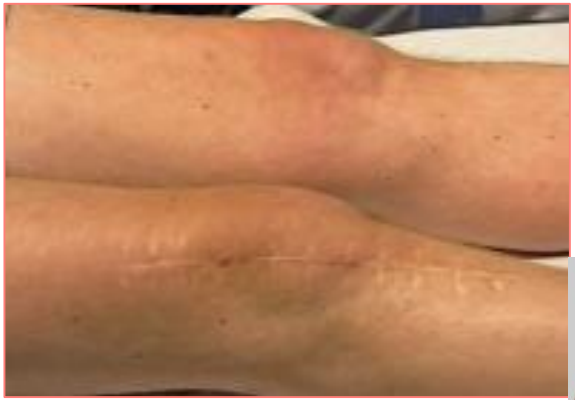
Clinical presentation



Specific situations

Chronic signs/symptoms

With **sinus tract**

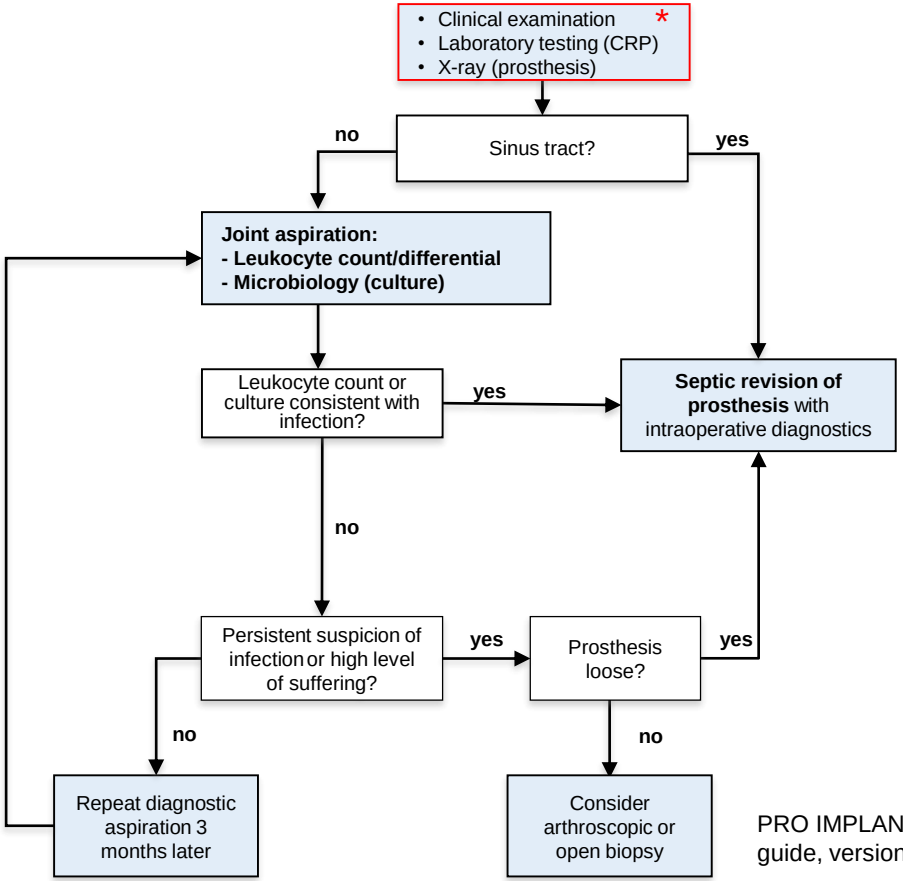
Without any clinical signs

Acute signs/symptoms

Early postoperative

Late acute onset

Diagnostic algorithm (chronic symptoms)



* **Consider other reasons:**
- Aseptic loosening
- Periprosthetic fracture
- Dislocation
- Muscular pathology
- Wear
- Metallosis

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Preoperative CRP

Population: Culture-positive PJI 2012-2014 (retrospective analysis)

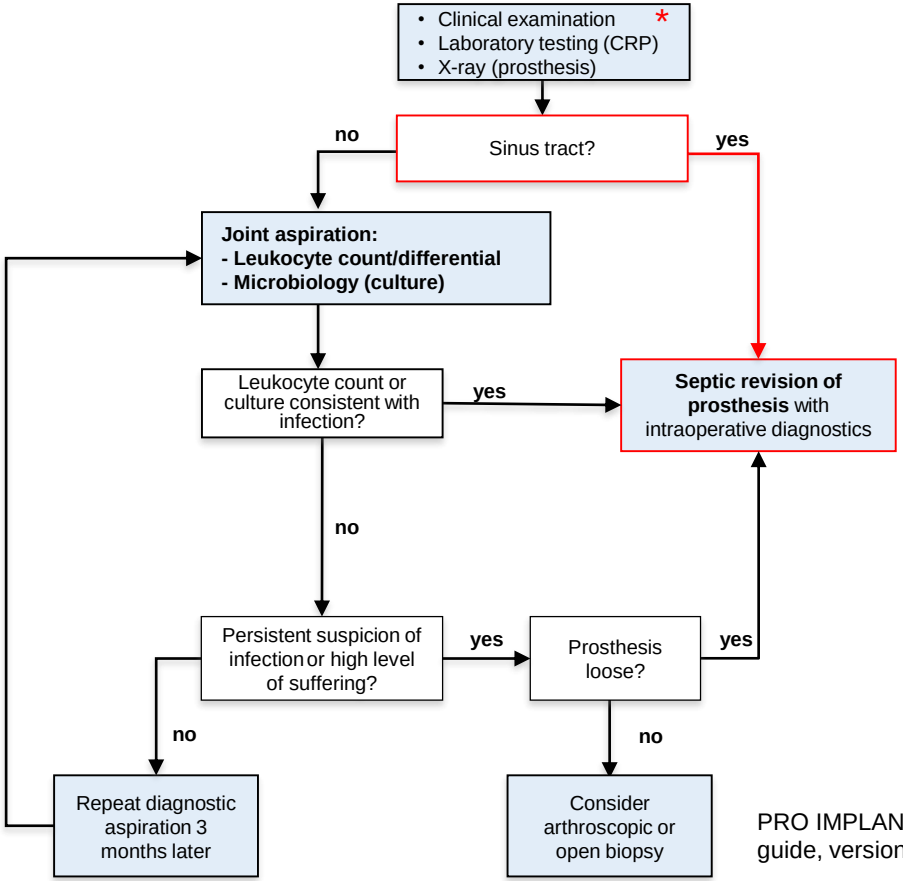
Results:

- 78 cases (32 knees, 31 hips, 14 shoulders, 1 elbow)
- Preoperative CRP levels **< 8 mg/l** in **26 patients (33.3%)**
  - Organisms:
    - **12 coagulase-negative staphylococci**
    - 5 *Staphylococcus aureus*
    - **4 *Cutibacterium acnes***
    - 3 Gram-negative bacteria
    - 1 each *Candida albicans* and *Streptococcus dysgalactiae*

Preoperative CRP is of little value in the diagnosis of (chronic)PJI

Pérez-Prieto D, Int. Orthop., 2017

Diagnostic algorithm (chronic symptoms)



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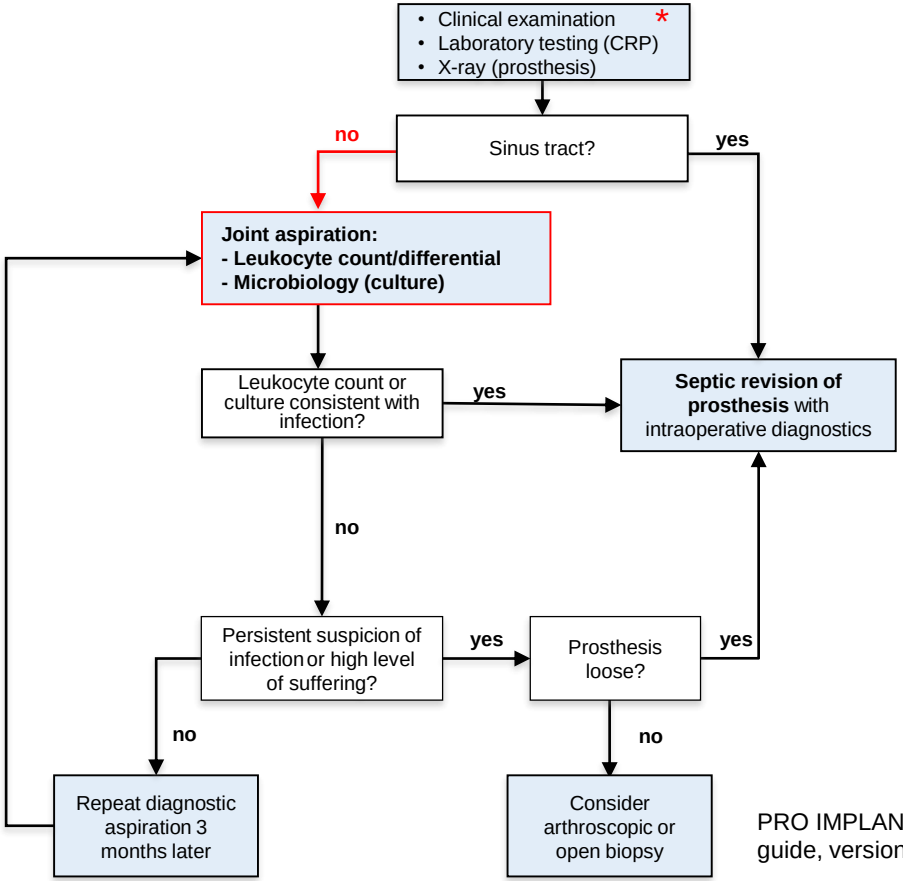

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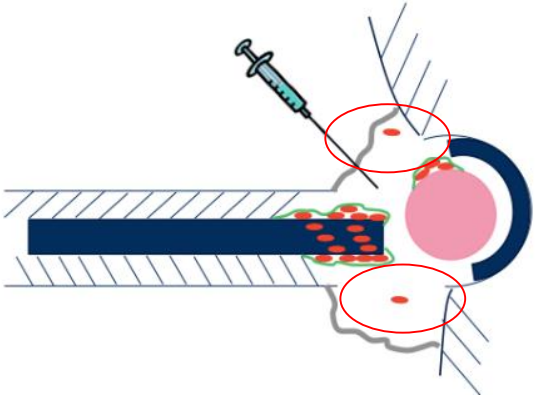
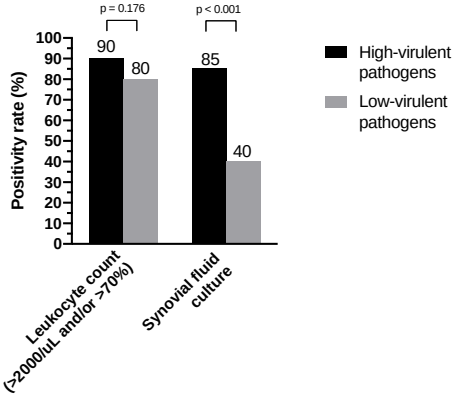
Routine synovial fluid tests

Analysis of synovial fluid of 142 patients with prosthetic failure

Diagnostic test	Aseptic failure (n = 65)	PJI (n = 77)	Sensitivity (%)	Specificity (%)
Culture (n = 142)	1	40	52	98





Morgenstern C, DMID 2017, Schulz P et al, Infection, 2020

Difficulties with leukocyte count

Confounders

- Postoperative period (6 weeks)
- Rheumatologic disease
- After trauma/periprosthetic fracture
- Relapsing dislocations
- Metallosis

- Sinus tract
- Low virulent pathogens?

Optimal cut-off?

- Lower?
- 2000/ul or 70% PMN?
- 3000/ul or 80% PMN?
- Higher?

→ the higher the more specific
→ the lower the more sensitive

Renz N J Bone Joint Surg Am 2018

PMN = polymorphonuclear cells = granulocytes

Alternative tests in synovial fluid?

Synovial calprotectin may be a valuable biom osis of a PJI, especially in the exclusion of an infection. With a later elatively rapid quantitative diagnosis can be made. The m is easy to use.

Wouthuyzen-Bakker M, Bone Joint J 2017

No novel test outperformed leukocyte count to date

The high specificity and negative predictive value. A negative result may ex negate the need for further diagnostic tests.

Shafafy R, Bone Joint J 2015

D-Lactate?

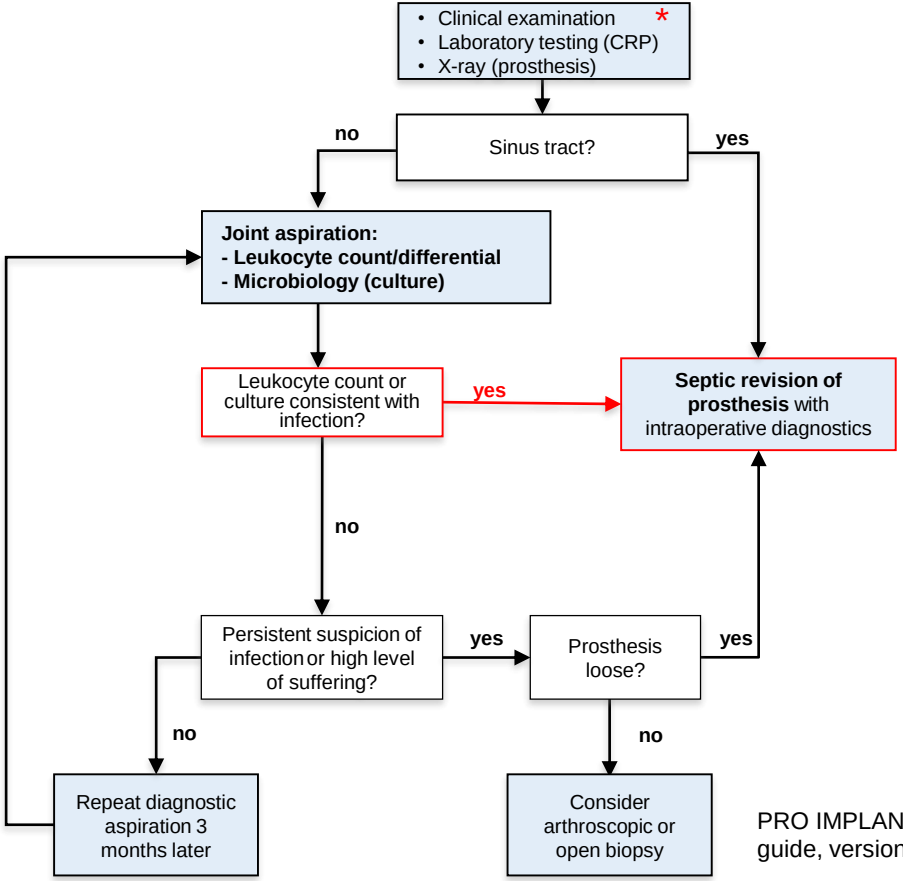
Conclusion: A positive α-defensin test result was significantly more sensitive and specific for pr gnostic testing and should be considered when managing periprosthetic joint infection.

Frangiamore SJ, J A

It appears that serum D-dimer is a promising marker for the diagnosis of PJI. This test may also have a great utility for determining the optimal timing of reimplantation.

Shahi A, J Bone Joint Surg (Am) 2017

Diagnostic algorithm (chronic symptoms)



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Intraoperative diagnostics

Superior to preoperative diagnostics

Microbiology

- ≥ 3-5 samples
- Representative area
- 10-14d incubation
- Molecular diagnostics

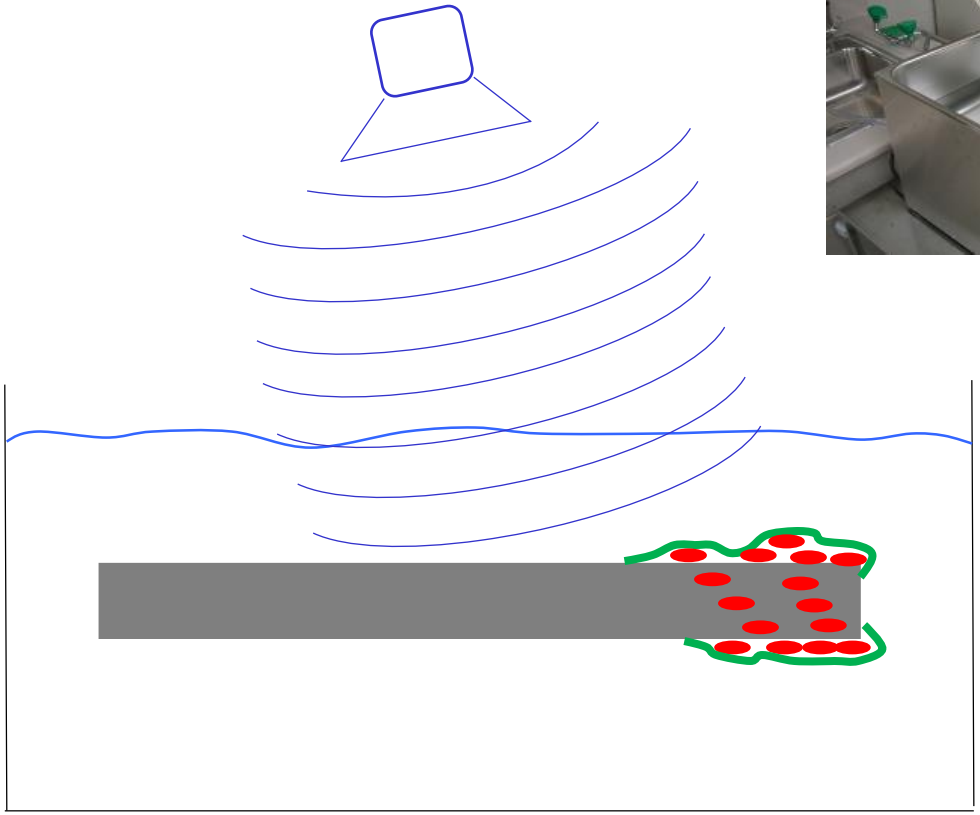
Histopathology

- Various classifications proposed

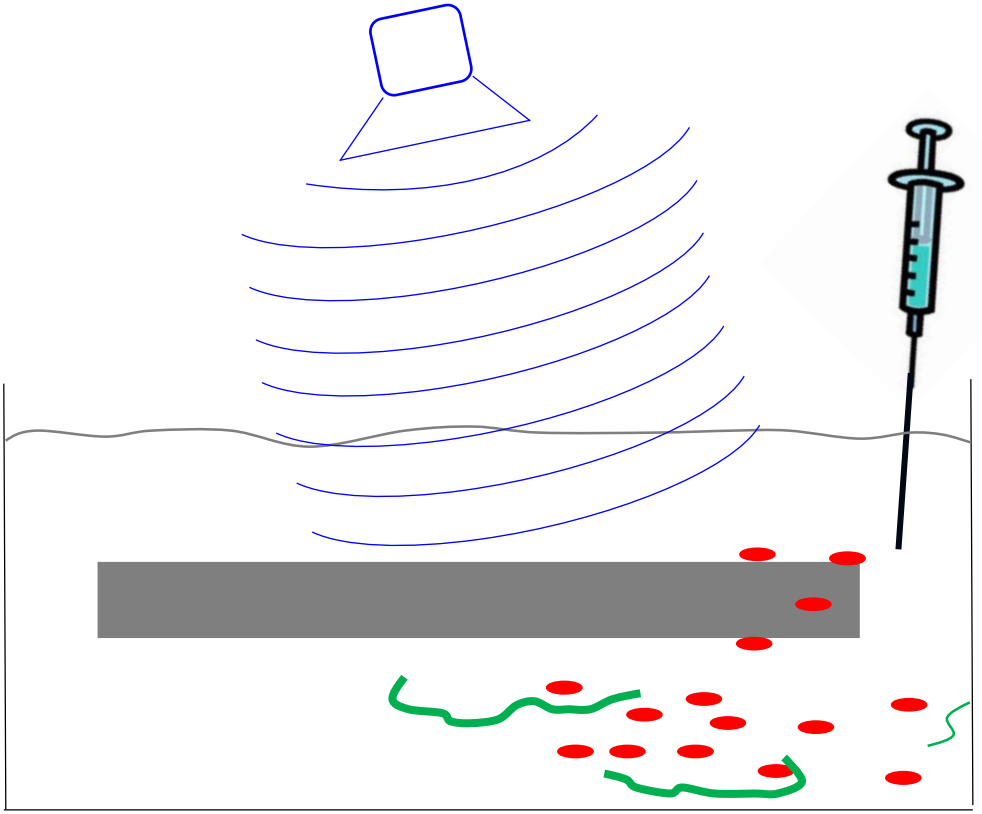
Sonication

- Culture
- Molecular diagnostics

Sonication



Sonication



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Sonication

Tissue biopsy

Sonication fluid

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

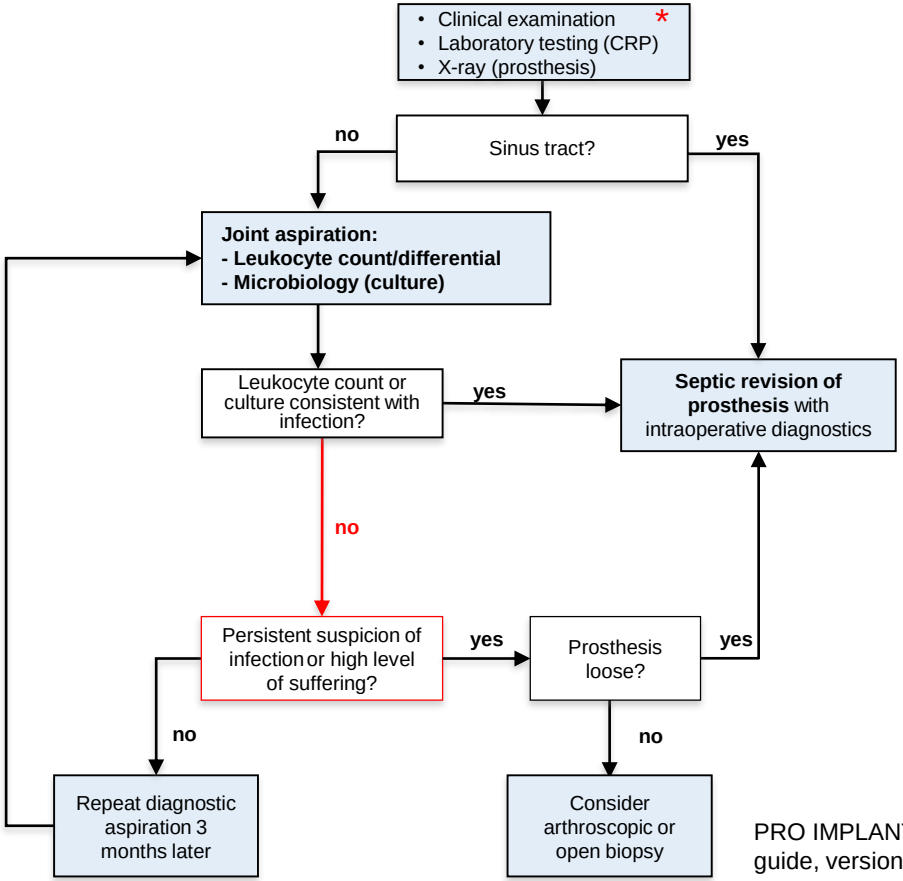
Sonication of Removed Hip and Knee Prostheses for Diagnosis of Infection

Andrej Trampuz, M.D., Kerryl E. Piper, M.S., Melissa J. Jacobson, A.S., Arlen D. Hanssen, M.D., Krishnan K. Unni, M.D., Douglas R. Osmon, M.D., Jayawant N. Mandrekar, Ph.D., Franklin R. Cockerill, M.D., James M. Steckelberg, M.D., James F. Greenleaf, Ph.D., and Robin Patel, M.D.

- Better sensitivity than tissue cultures
- Quantitative method
- Better detection of mixed infections
- Faster

Trampuz A. NEJM 2007

Diagnostic algorithm (chronic symptoms)



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PRO IMPLANT Foundation pocket guide, version 9 (modified)

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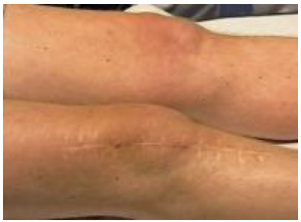

Acute signs/symptoms

Early postoperative

Late acute onset

Acute infections

Early postoperative (< 4-6 weeks)

Leukocyte count not discriminative, threshold unknown (10.000-28.700/µl)

Parvizi J et al J Arthroplasty 2014, Bedair H et al CO

No antibiotics prior to revision

Late acute onset

Mostly hematogenous

Zimmerli W et al NEJM 2004

→blood cultures

(Joint aspiration)

Septic revision with intraoperative cultures

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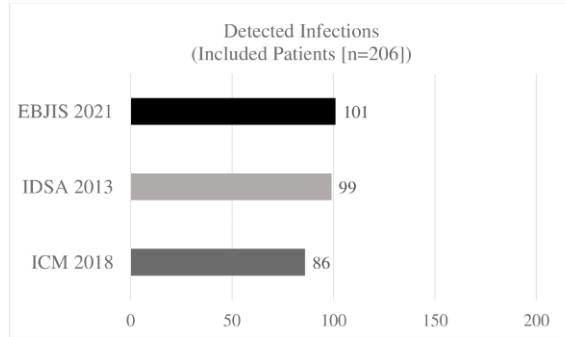
EBJIS definition

	Infection Unlikely	Infection Likely	Infection Confirmed
	All findings negative (A ✗ B ✗ C ✗)	*Two positive findings* (A B or A C)	*Any positive finding* (A or B)
A CLINICAL			
Clinical features	Clear alternative reason for implant dysfunction	• Early radiographic loosening • Wound healing problems • Recent fever/bacteraemia • Purulence around prosthesis • CRP > 10mg/l	Sinus tract communication with the joint +/- visualization of prosthesis
C-reactive protein			
B LABORATORY			
Synovial fluid	• Leukocyte count ≤ 1500 • PMN ≤ 65%	• Leukocyte count > 1500 • PMN > 65%	• Leukocyte count > 3000 • PMN > 80% • Positive Alpha-defensin
Microbiology	• All cultures negative • No growth on sonication	• Single positive culture (aspiration or intra-operative) • > 1 CFU/ml any organism on sonication	• ≥ 2 positive samples with the same microorganism • > 50 CFU/ml any organism on sonication
Histology	Negative	Presence of ≥ 5 neutrophils in a single HPF	• Presence of ≥ 5 neutrophils in ≥ 5 HPF • Visible microorganisms
C RADIOLOGY			
Nuclear imaging	Negative 3-phase isotope bone scan	Positive white blood cell labelled scintigraphy	

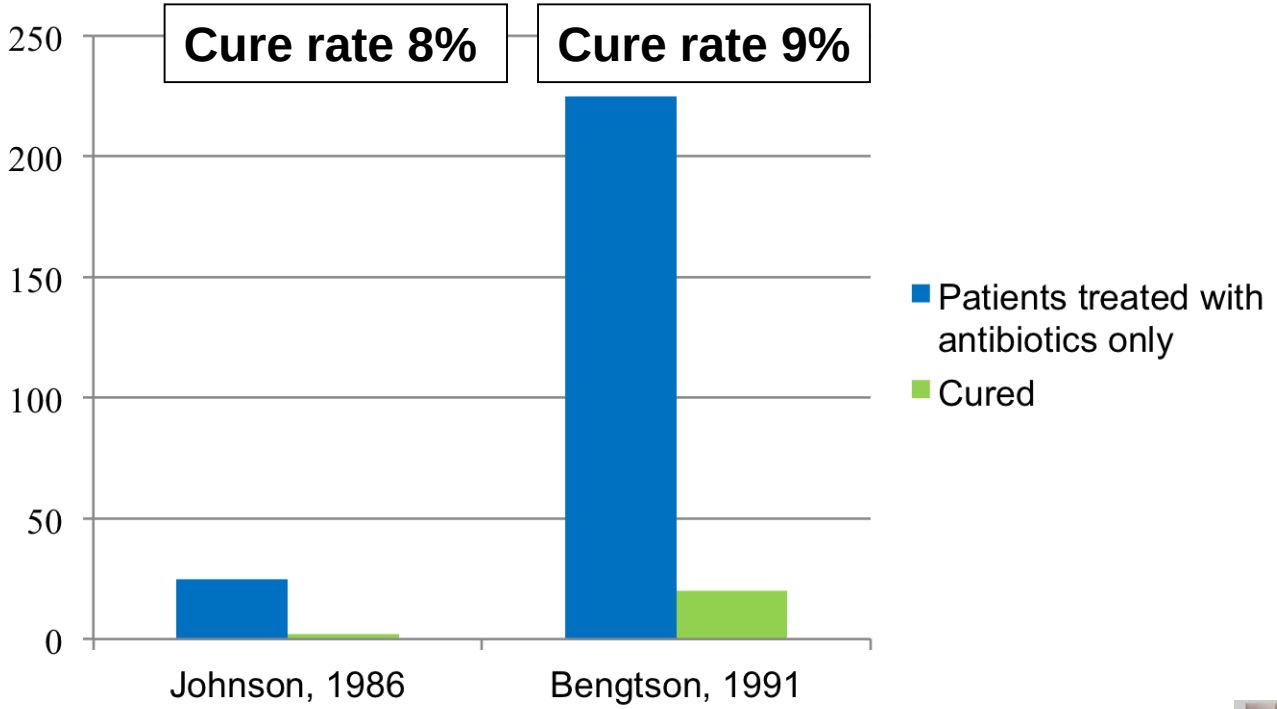


McNally M BJJ 2021, Sigmund IK BJR 2022

Treatment concept

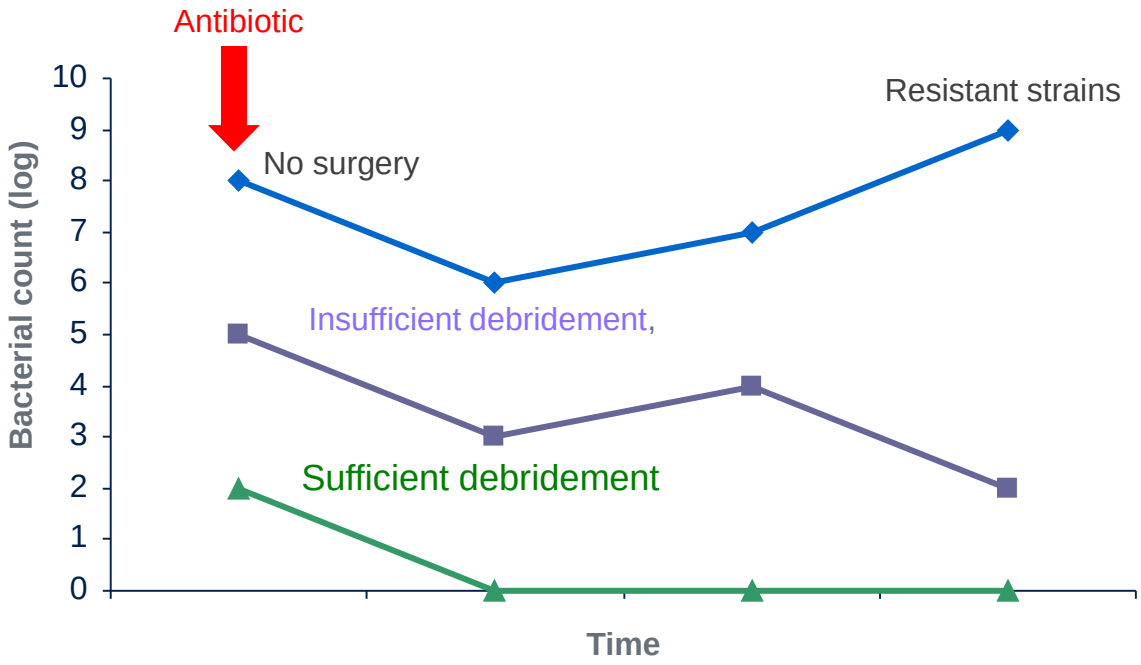
To achieve high treatment success, a concerted surgical and antimicrobial concept is needed

Antibiotics without surgery

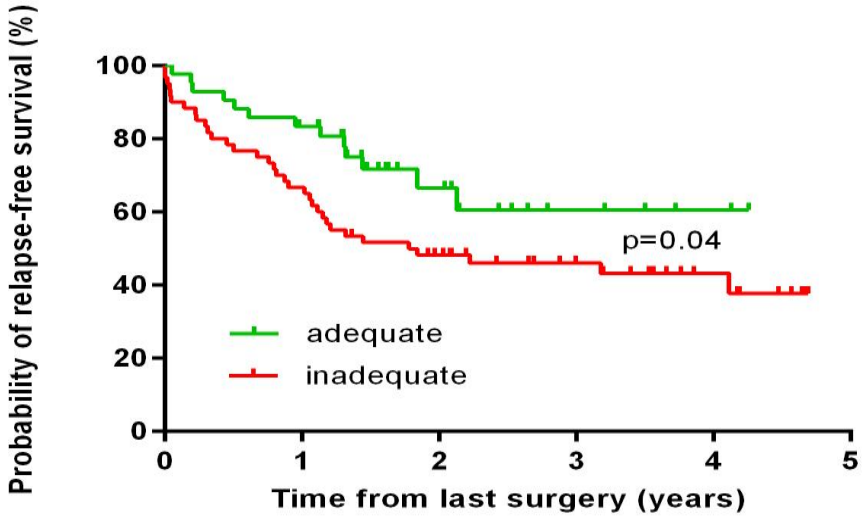


Johnson J Bone Joint Surg Br 1986; Bengtson. Acta Orhop Scand 1991

Sufficient debridement



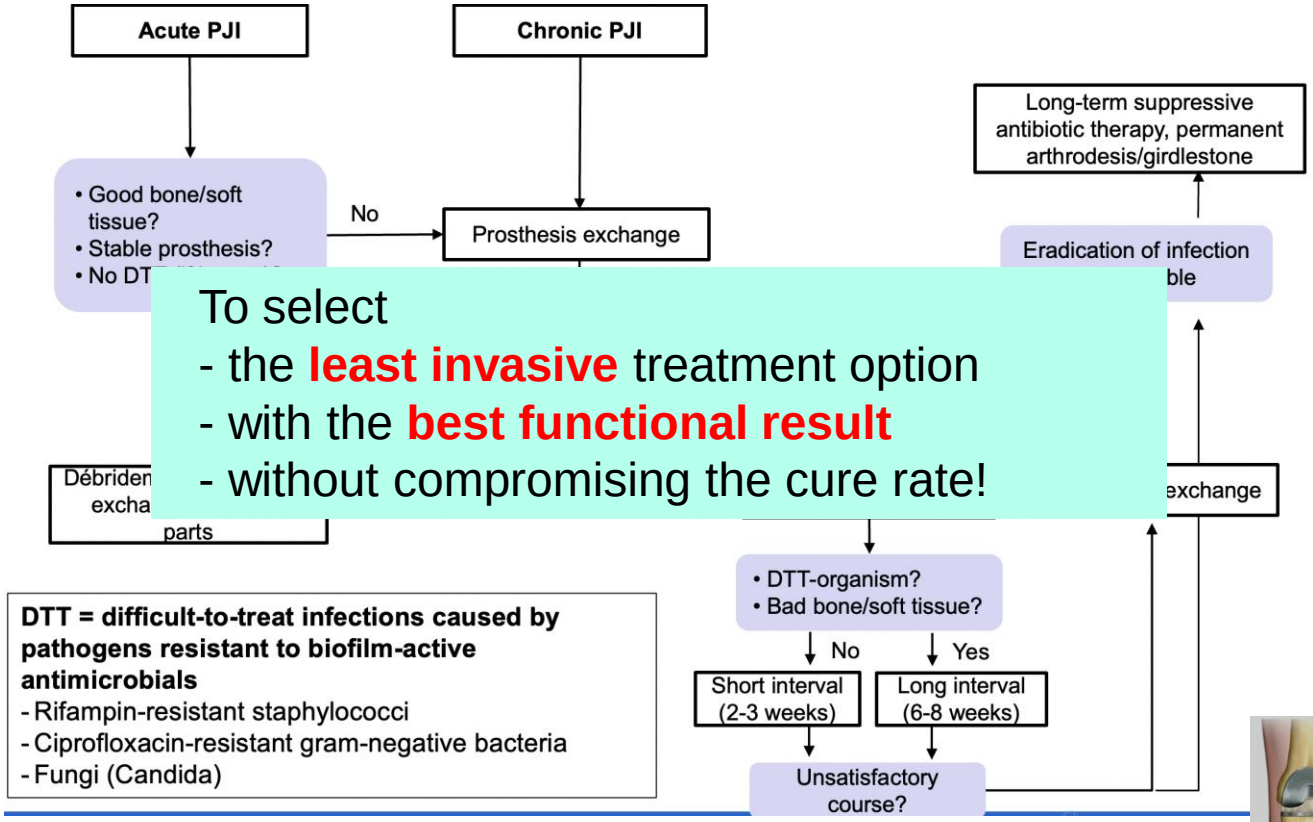
Relevance of adequate antimicrobial therapy



Number at risk						
adequate	43	33	13	5	2	0
inadequate	60	40	26	16	8	0

Gellert M. Int J Antimicrob Agents 2020

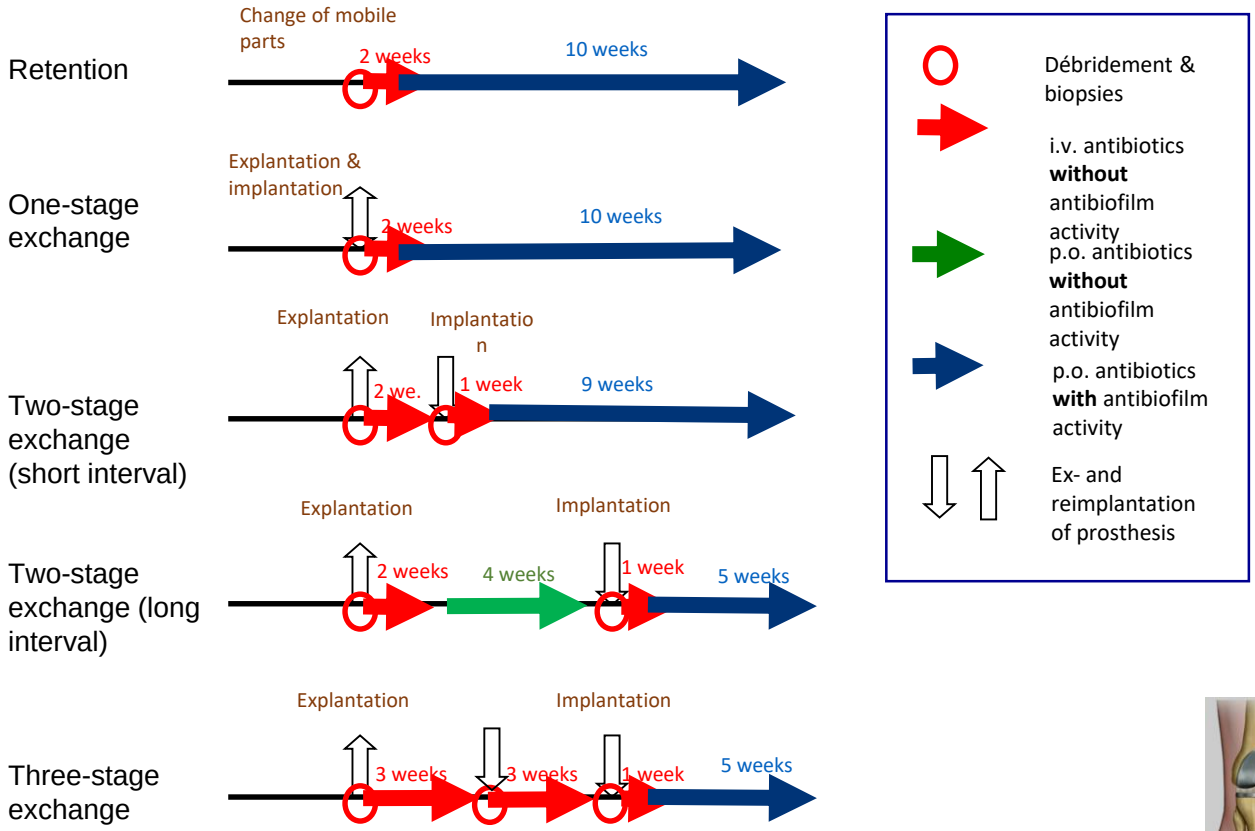
Treatment algorithm



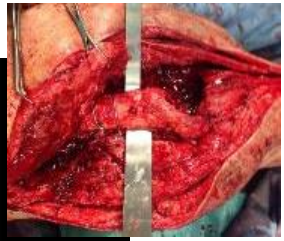
To select
- the **least invasive** treatment option
- with the **best functional result**
- without compromising the cure rate!

DTT = difficult-to-treat infections caused by pathogens resistant to biofilm-active antimicrobials
- Rifampin-resistant staphylococci
- Ciprofloxacin-resistant gram-negative bacteria
- Fungi (Candida)

Surgical procedures



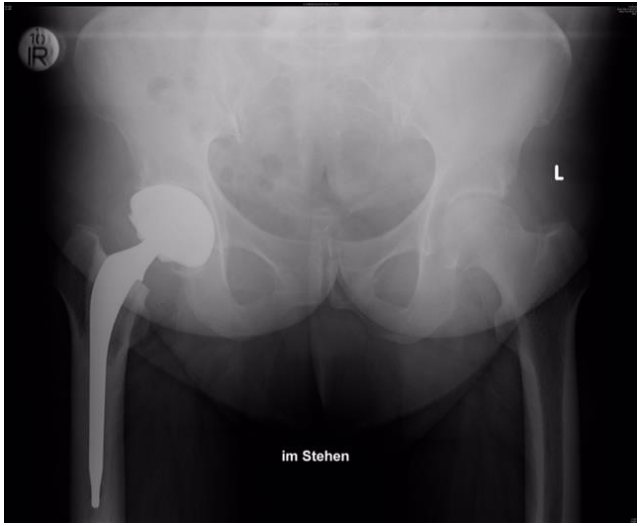
Removal of all foreign material



INSELGRUPPE

78yo female

- Primary hip prosthesis 6 months ago
- Pain since implantation
- Joint aspiration: Leuk 34‘000/ul, *S. epidermidis*

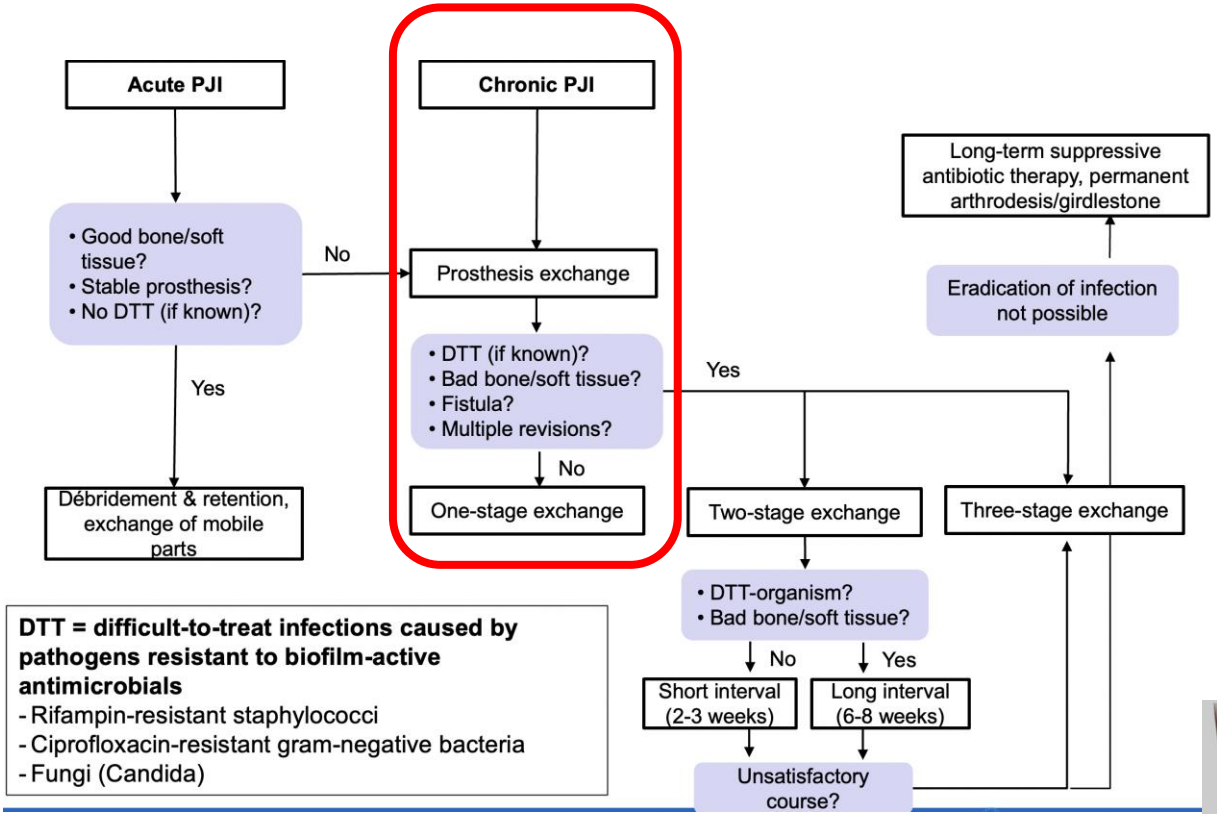


1. **Staphylococcus epidermidis**

S = sen

	1.
Ampicillin	R
Amoxicillin + Clavulansäure	R
Cefalotin	R
Ceftriaxon	R
Gentamycin	R
Norfloxacin	R
Ciprofloxacin	R
Levofloxacin	R
Cotrimoxazol	R
Tetrazyklin	S
Imipenem	R
Penicillin	R
Oxacillin	R
Clindamycin	R
Erythromycin	S
Rifampicin	S
Vancomycin	S
Fusidinsäure	R

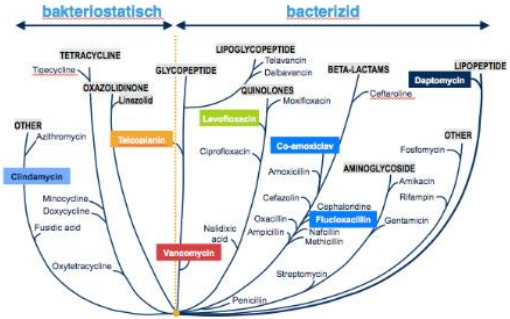
Treatment algorithm



PRO-IMPLANT Foundation pocket guide PJI, version 9

Choice of antibiotics

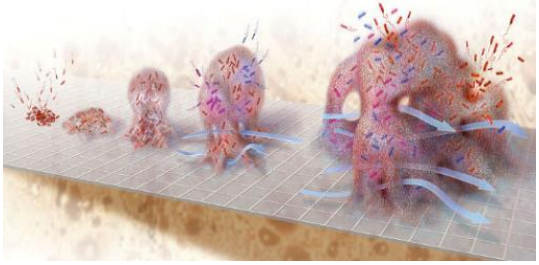
Bactericidal activity



Good oral bioavailabilty

Good bone penetration

Biofilm activity



INSELGRUPPE

How much ends up in the bone?

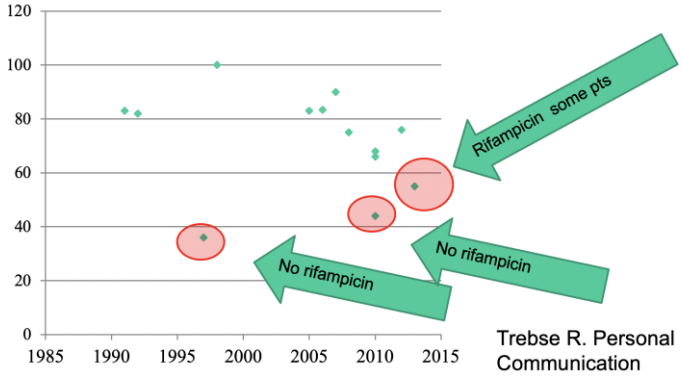
Substance	Oral bioavailability	Bone penetration
Amoxicillin/clavulanic acid	50%	10-15%
Cefuroxim, cefadroxil	50%	12%
Levofloxacin	100%	77%
Rifampicin	80%	51%
Cotrimoxazol	85%	55%
Clindamycin	90%	45%
Linezolid	100%	85%

Sanford Guide to Antimicrobial Therapy 2015. 45nd ed.
Lorian. Antibiotics in Laboratory Medicine. 5th ed.

Biofilm activity I

Rifampin for staphylococcal PJI

Early postop. and late acute PJI: Rifampicin-susceptible staphylococci



Trebse R. Personal Communication

Clin Infect Dis. 2021 May 10;ciab426. doi: 10.1093/cid/ciab426. Online ahead of print.

If, when, and how to use rifampin in acute staphylococcal periprosthetic joint infections, a multicentre observational study

Mark Beldman [1], Claudia Löwik [1], Alex Soriano [2], Laila Albiach [2], Wierd P Zijlstra [3], Bas A S Knobben [4], Paul Jutte [1], Ricardo Sousa [5], André Carvalho [5], Karan Goswami [6], Javad Parvizi [6], Katherine A Belden [7], Marjan Wouthuyzen-Bakker [8]

INSELGRUPPE

Rifampin

Do not use

- During interval
- Before surgery (high bacterial amount)
- In open wounds
- As single antibiotic (monotherapy)

Approach to intolerance

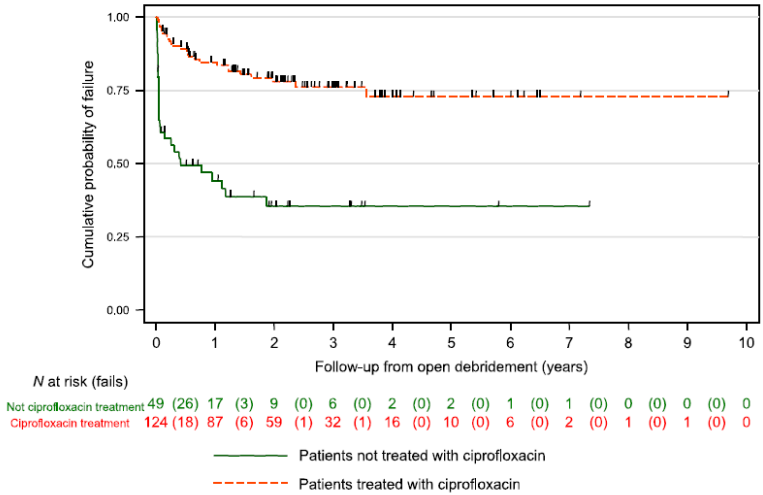
1. Drug holidays for 2-3 days
2. Decrease dose (minimal 2x300mg/d)
3. Give an antiemetic before intake (eg Zofran 4mg 30min ahead)
4. Give it once daily (600mg) before bedtime
5. Switch to oral suspension
6. Switch to rifabutin (Mycobutin®)

- Check for interactions
- Monitor liver enzymes

Achermann Y Infection 2013

Biofilm activity II

Ciprofloxacin in gram-negative PJI



Success rates:

- Overall: 68% (118/173)
- With cipro: 79%
- Without cipro: 40%

Rodriguez-Pardo; CMI, 2014

.... Aboltins CA, CMI,2011; Jaen, Rev Esp Quimioter, 2012; Martinez-Pastor; AAC, 2009

Empiric treatment

- No specific exposure:

→ Amoxicillin/Clavulanic acid (Augmentin)

- Sinus tract, VAC, multiple revisions etc:

→ Piperacillin/Tazobactam (Tazobac)

- Several previous revisions, MRSA-carrier, (one-stage exchange):

→ Vancomycin (Vancocin) or Daptomycin (Cubicin)

INSELGRUPPE

Targeted therapy

EMPFOHLENE ANTIBIOTIKATHERAPIE

Empirische Antibiotikatherapie:
Ampicillin/Sulbactam[c] 3 x 3 g i.v. (+/- Vancomycin[e] 2 x 1 g bei septischen Patienten, bekannten MRSA-Trägern, multiplen Voroperationen und Vd. a. Low-Grade Infekt)

Gezielte Antibiotikatherapie (Deeskalation, sobald Pathogen(e) bekannt):

Mikroorganismus (rot: Problemerreger)	Antibiotikum[a] (Empfindlichkeit überprüfen)	Dosis[b] (blau: Nierenadaption notwendig)	Gabe
***Staphylococcus* spp.**			
- Oxacillin-/Methicillin-empfindlich	Flucloxacillin[c]	4 x 2 g	i.v.
	(oder Fosfomycin)	(3 x 5 g)	i.v.
	+		
	Rifampicin[d]	2 x 450 mg	p.o.
	für 2 Wochen, dann (je nach Antibiogramm):		
	- Levofloxacin oder	2 x 500 mg	p.o.
	- Cotrimoxazol oder	3 x 960 mg	p.o.
	- Doxycyclin oder	2 x 100 mg	p.o.
	- Fusidinsäure	3 x 500 mg	p.o.
	+		
	Rifampicin[d]	2 x 450 mg	p.o.
- Oxacillin-/Methicillin-resistent	Daptomycin oder	1 x 8 mg/kg	i.v.
	Vancomycin[e]	2 x 1 g	i.v.
	(oder Fosfomycin)	(3 x 5 g)	i.v.
	+		
	Rifampicin[d]	2 x 450 mg	p.o.
	für 2 Wochen, dann in Kombination wie oben für Oxacillin-/Methicillin-empfindliche Staphylokokken		
- Rifampicin-resistent	Vancomycin oder Daptomycin für 2 Wochen (wie oben), dann: Langzeitsuppression für ≥1 Jahr, abhängig von Empfindlichkeit (z.B. mit Cotrimoxazol, Doxycyclin oder Clindamycin).		
***Streptococcus* spp.**	Penicillin G[c] oder	4 x 5 Millionen U	i.v.
	Ceftriaxon	1 x 2 g	i.v.
	für 2-4 Wochen, dann:		
	Amoxicillin oder	3 x 1000 mg	p.o.
	Levofloxacin	2 x 500 mg	p.o.
	(ggf. Suppression für 1 Jahr)		
***Enterococcus* spp.**			
- Penicillin-empfindlich	Ampicillin[c] +	4 x 2 g	i.v.
	Gentamicin[f]	2 x 60-80 mg	i.v.
	(+/- Fosfomycin)	(3 x 5 g)	(i.v.)
	für 2-3 Wochen, dann:		
	Amoxicillin	3 x 1000 mg	p.o.
- Penicillin-resistent	Vancomycin[e] oder	2 x 1 g	i.v.
	Daptomycin	1 x 10 mg/kg	i.v.
	+		
	Gentamicin[f]	2 x 60-80 mg	i.v.
	(+/- Fosfomycin)	3 x 5 g	i.v.
	für 2-4 Wochen, dann:		
	Linezolid (max. 4 Wochen)	2 x 600 mg	p.o.
- Vancomycin-resistent (VRE)	Individuell; Entfernung des Implantates oder lebenslängliche Suppression notwendig, z.B. mit Doxycyclin (falls empfindlich).		

Mikroorganismus (rot: Problemerreger)	Antibiotika[a] (Empfindlichkeit überprüfen)	Dosis[b] (blau: Nierenadaption notwendig)	Gabe
Gramnegative Erreger			
- Enterobacteriaceae (*E. coli, Klebsiella, Enterobacter* etc.)	Ciprofloxacin	2 x 750 mg	p.o.
- Nonfermenter (*Pseudomonas aeruginosa, Acinetobacter* spp.)	Piperacillin/Tazobactam oder	3 x 4, g	i.v.
	Meropenem oder	3 x 1 g	i.v.
	Ceftazidim	3 x 2 g	i.v.
	+		
	Tobramycin	1 x 300 mg	i.v.
	(oder Gentamicin)	1 x 240 mg	i.v.
	für 2-3 Wochen, dann:		
	Ciprofloxacin	2 x 750 mg	p.o.
- Ciprofloxacin-resistent	Abhängig vom Antibiogramm: Meropenem i.v. 3 x 1 g, Colistin 3 x 3 Mio E i.v. und/oder Fosfomycin 3 x 5 g i.v., dann orale Suppression.		
Anaerobier			
- Gram-positiv (*Propionibacterium, Peptostreptococcus, Finegoldia magna*)	Penicillin G[c] oder	4 x 5 Millionen E	i.v.
	Ceftriaxon	1 x 2 g	i.v.
	+		
	Rifampicin[d]	2 x 450 mg	p.o.
	für 2 Wochen, dann:		
	Levofloxacin oder	2 x 500 mg	p.o.
	Amoxicillin	3 x 1000 mg	p.o.
	+		p.o.
	Rifampicin[d]	2 x 450 mg	
- Gram-negativ (*Bacteroides* spp., *Fusobacterium* spp.)	Ampicillin/Sulbactam[c]	3 x 3 g	i.v.
	für 2 Wochen, dann:		
	Metronidazol	3 x 400 mg	p.o.
Candida spp.	Caspofungin oder	1 x 50 mg (1.Tag 70 mg)	
- Fluconazol-empfindlich	Anidulafungin	1 x 100 mg (1.Tag 200 mg)	i.v.
	für 1-2 Wochen, dann:		
	Fluconazol (Suppression für ≥1 Jahr)	1 x 400 mg	p.o.
- Fluconazol-resistent	Individuell (z.B. mit Voriconazol 2 x 200 mg p.o.); Entfernung des Implantates oder ggf. lebenslange Suppression.		
Kultur-negativ	Ampicillin/Sulbactam[c]	3 x 3 g	i.v.
	für 2 Wochen, dann:		
	Levofloxacin +	2 x 500 mg	p.o.
	Rifampicin[d]	2 x 450 mg	p.o.

[a] **Gesamtdauer** der Therapie: **12 Wochen**, ca. 2 Wochen intravenös (i.v.), dann oral (p.o.).
[b] **Laborkontrolle** 2x/Woche: Leukozyten, C-reaktives Protein, Kreatinin/eGFR, Leberenzyme (AST/GOT und ALT/GPT). Dosisanpassung nach Nierenfunktion und Körpergewicht (<40 kg oder >100 kg)
[c] **Penicillin-Allergie** vom NICHT-Typ 1 (z.B. Exanthem): Cefazolin (3 x 2 g i.v.). Bei Anaphylaxie (= Typ 1-Allergie mit Quincke-Ödem, Bronchospasmus, anaphylaktischem Schock) oder Cephalosporin-Allergie: Vancomycin (2 x 1 g i.v.) oder Daptomycin (1 x 8 mg/kg i.v.). Ampicillin/Sulbactam ist äquivalent zu Amoxicillin/Clavulansäure (3 x 2.2 g i.v.).
[d] **Rifampicin** erst nach Prothesen-Wiederaufbau und bei trockenen Wundverhältnissen bzw. gezogenen Drainagen einsetzen; Dosisreduktion auf 2 x 300 mg bei Alter >75 Jahre
[e] Bestimmung des **Vancomycin**-Talspiegels mindestens 1x/Woche, Blutabnahme unmittelbar vor nächster Gabe. Zielwert: 15-20 µg/ml.
[f] **Gentamicin** nur anwenden, wenn Gentamicin **high-level (HL)** empfindlich getestet wird (im Mikrobiologie-Labor nachfragen). Bei Gentamicin HL-resistenten Enterokokken: Gentamicin durch Ceftriaxon (1 x 2 g i.v.) ersetzen

The NEW ENGLAND JOURNAL of MEDICINE

IV or oral?

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA)

- 639 implant-associated infections (prosthesis or osteosynthesis)
- 376 chronic osteomyelitis (w/o implant)
- 39 spinal infections

→ Treatment failure
- IV group 74/506 (14.6%)
- Oral group 67/509 (13.2%)

Oral treatment

✓ = non-inferior

✓ Less complications

✓ shorter hospital stay

Li HK New Engl Journal Medicine 2019

Switch from IV to oral when...
... CRP is nearly normalized
... wound is closed and dry
... organism and its susceptibility is known
→ usually after 1-2 weeks

The NEW ENGLAND JOURNAL of MEDICINE

Duration

ORIGINAL ARTICLE

Antibiotic Therapy for 6 or 12 Weeks for Prosthetic Joint Infection

410 patients from 28 French centers, randomly assigned to receive antibiotic therapy for 6 or 12 weeks

Subgroup	6-Wk Therapy	12-Wk Therapy	Risk Difference (95% CI)
	no. of patients with event/total no. (%)		*percentage points*
All patients	32/190 (16.8)	15/188 (8.0)	8.9 (2.2 to 15.6)
Surgical procedure			
Débridement	23/75 (30.7)	11/76 (14.5)	16.2 (2.9 to 29.5)
Two-stage revision	6/40 (15.0)	2/41 (4.9)	10.1 (−3.1 to 23.3)
One-stage revision	3/75 (4.0)	2/71 (2.8)	1.2 (−4.8 to 7.1)
Affected joint			
Hip	19/122 (15.6)	9/117 (7.7)	7.9 (−0.2 to 16.0)
Knee	13/68 (19.1)	6/71 (8.5)	10.7 (−0.9 to 22.2)
Episode of prosthetic joint infection			
First	27/162 (16.7)	13/160 (8.1)	8.5 (1.4 to 15.7)
At least the second	5/28 (17.9)	2/28 (7.1)	10.7 (−7.0 to 28.4)

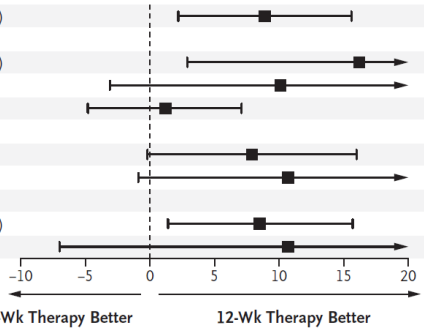
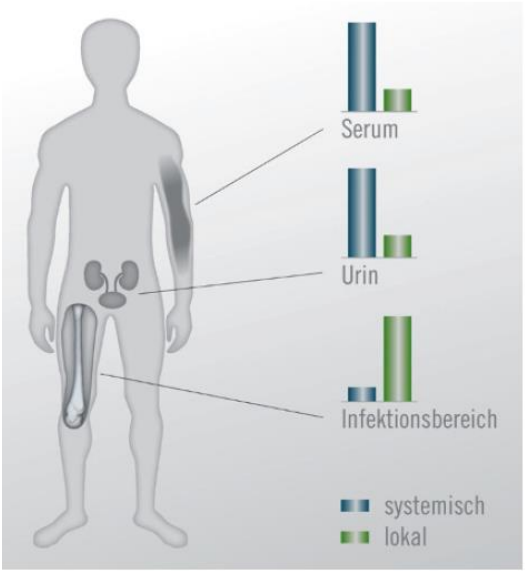
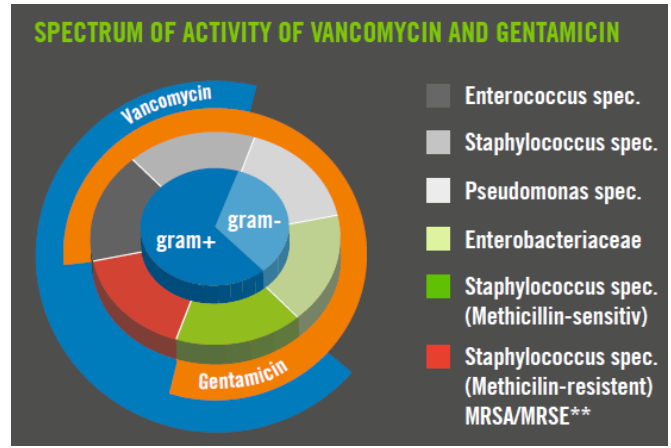


Figure 2. Exploratory Subgroup Analyses of Persistent Infection within 2 Years after the Completion of Antibiotic Therapy (Primary Outcome).

Bernard L New Engl Journal Medicine 2021

Local antibiotics in cement



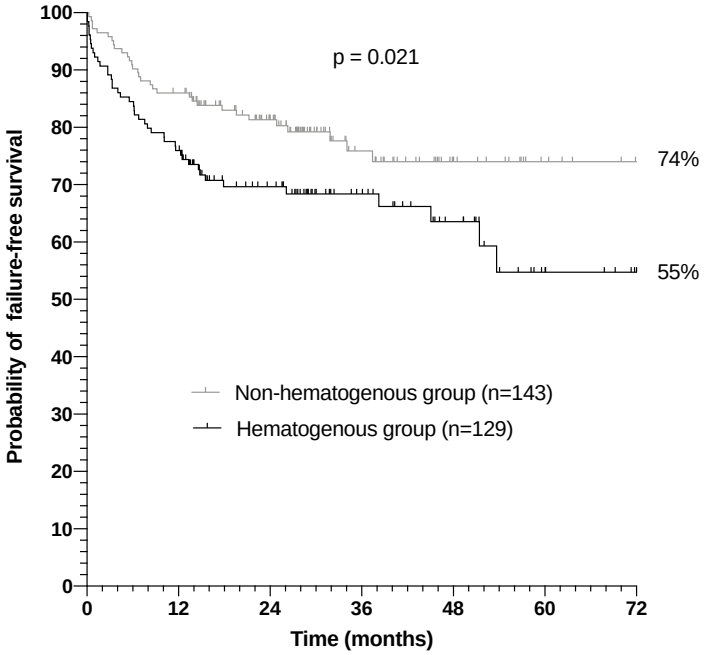


Concentrations of antibiotics:
Systemic: 1x80mg i.m. gentamicin)
Local: 1.25% gentamicin in cement

→10-100-fold local concentration!
→Minimal systemic effects

Wahlig 1987, Kühn D., Unfallchirurg, 2017

Outcome Inselspital PJI cohort



No. at risk							
Non-hematogenous	143	123	84	42	22	1 1	6
Hematogenous	129	99	60	35	21	8	1

Retrospective analysis of 272 PJIs

Renz N, in preparation

Take home - Epidemiology

	Septic arthritis 	PJI 
Pathogenesis	**Hematogenous** >> postinterventional	**Postoperative** > hematogenous
Acuity	Mostly **acute**	Acute and chronic **(Low Grade Infections**) balanced
Pathogen	Mostly of **high** virulence	Of **high and low** virulence

Take home - Diagnostics

	Septic arthritis 	PJI 
Joint aspiration	**1. Leukocyte count** (>20'000/ul or PMN >90%) 2. Microbiology (sensitivity ⬆) 3. Crystals	**Leukocyte count** (>2'000/ul or PMN >70%) 2. Microbiology (sensitivity ⬇) (Crystals)
Blood cultures	Always if no prior intervention	Only if hematogenous route suspected
Biopsies	Microbio and pathology	Microbio and pathology
Sonication	✕	✓

If you think of infection, aspirate the joint!

Take home - Treatment

	Septic arthritis 	PJI 
Surgery	• Mandatory (most cases) • Open or arthroscopic • Irrigation +/- synovectomy • according to Gächter	• Mandatory • Open • Retention or exchange of implant • according to acuity, local conditions, pathogen
Antibiotics	• Bactericidal activity • i.v. → oral • 2-4 weeks	• Bactericidal activity • Biofilm-active • +/- local treatment • i.v. → oral • 12 weeks

INSELGRUPPE

Merci de votre attention!

nora.renz@insel.ch

Intraoperative tissue culture

INSELGRUPPE

Obtain ≥3-5 tissue specimens

- Interface tissue-prosthesis, no swabs

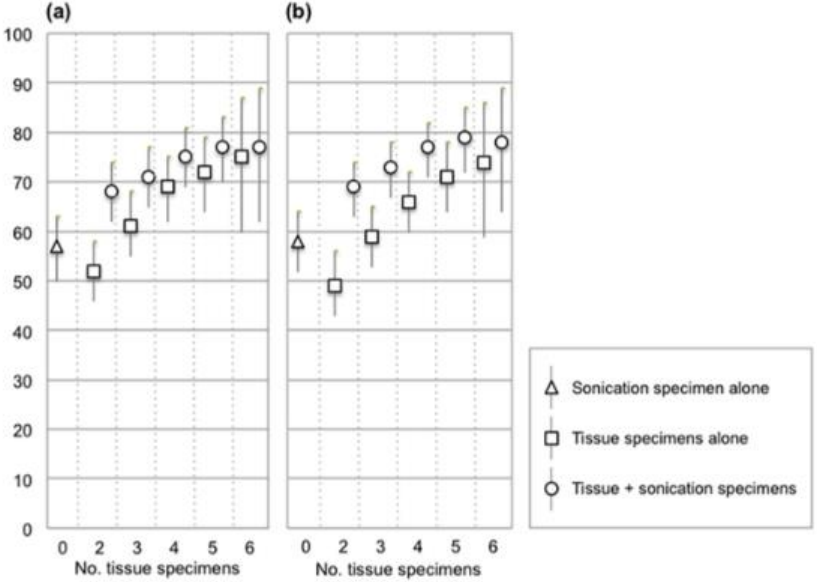


FIG 1 Sensitivity and 95% confidence intervals for sonication, increasing numbers of tissue samples, and sonication and tissue culture combined for clinical (a) and composite (b) definitions of infection. The effect of tissue sample number was modeled using a computer algorithm to randomly sample required number of specimens from the full set of specimens obtained in each case (see Materials and Methods).

Dudareva M, JCM 2018