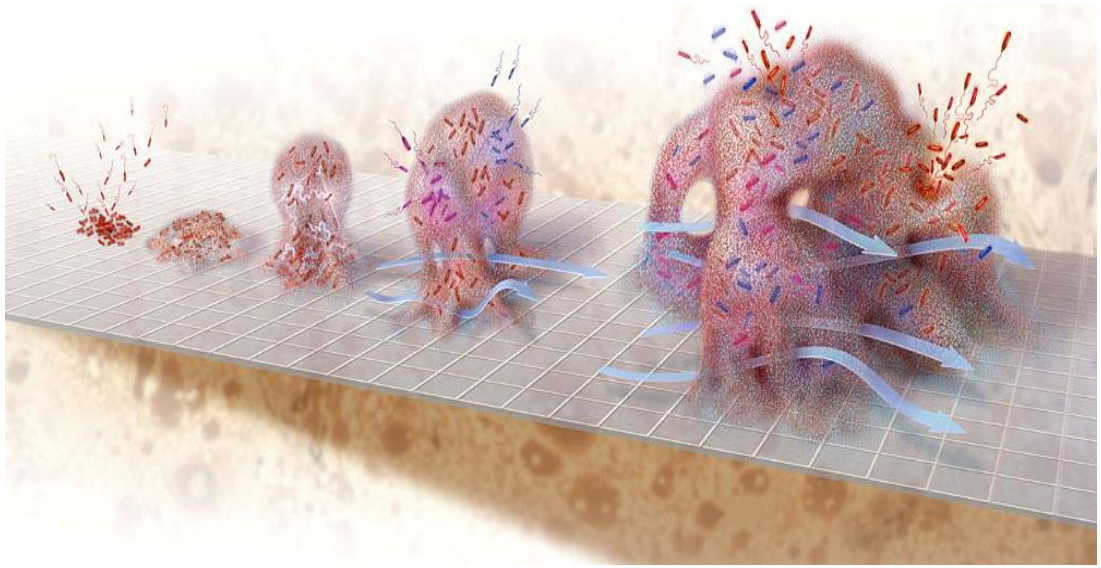
Infections of the locomotor system - modern concepts in diagnosis and treatment



Andrej Trampuz
Charité – University Hospital Berlin
Germany

CENTRUM MUSKULO SKELETALE CHIRURGIE

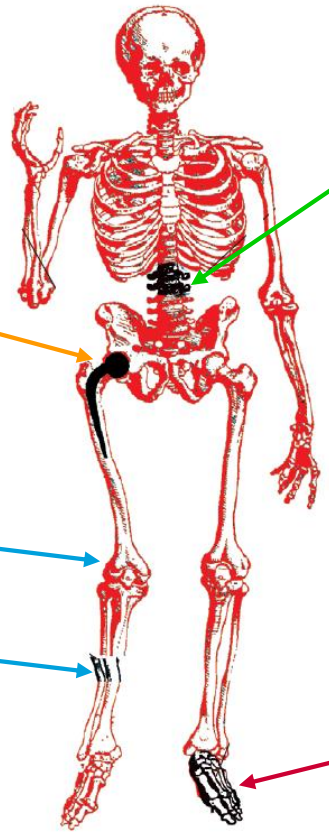
CHARITÉ

Infektions of the locomotor system

Periprosthetic joint infections
- CNS, *S. aureus*
- *Streptococcus* spp.
- *Enterococcus* spp.
- *Propionibacterium acnes*

Septic arthritis
- *S. aureus*
- Streptococci
- Enterococci

Posttraumatic osteomyelitis
- *S. aureus*
- Polymicrobial
- Gramnegative bacilli



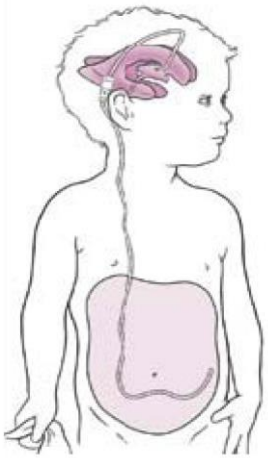
Spondylodiscitis
- *S. aureus*
- Gramnegative bacilli
- *Streptococcus* spp,
- *Mycobacterium tuberculosis*

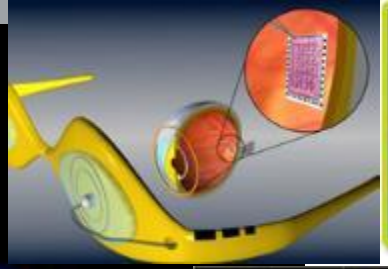
Diabetic foot infection
- *S. aureus*
- *Streptococcus* spp.
- *Enterococcus* spp.
- Gramnegative bacilli
- Anaerobes

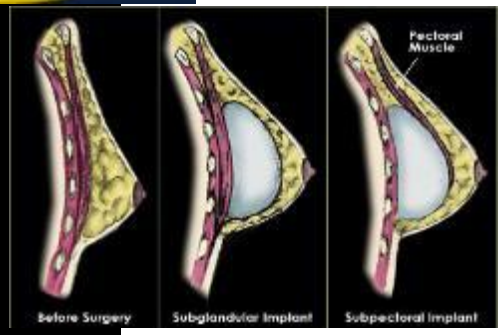
Staphylococcus aureus is the most common pathogen

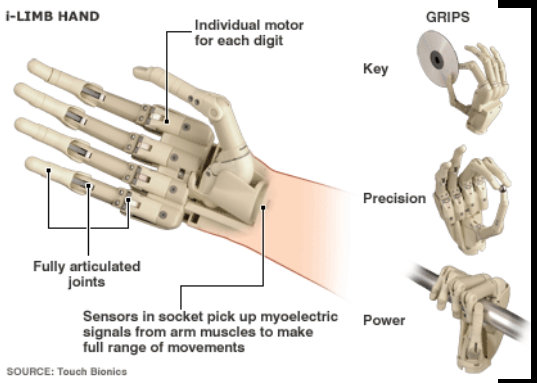
Science fiction: implant function better than native

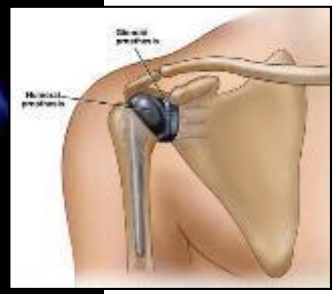
Implants improved life quality

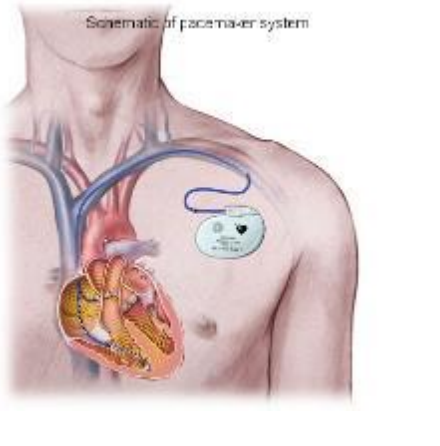


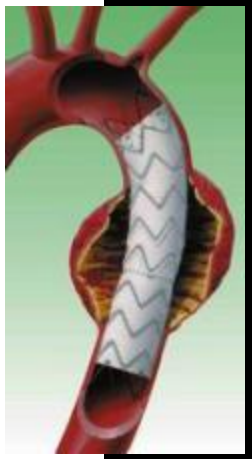


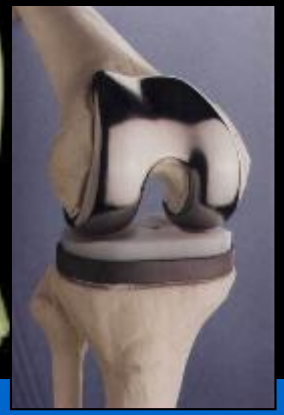

Pectoral Muscle
Before Surgery
Subglandular Implant
Subpectoral Implant

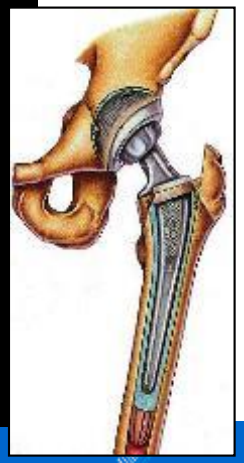

i-LIMB HAND
Individual motor for each digit
Fully articulated joints
Sensors in socket pick up myoelectric signals from arm muscles to make full range of movements
GRIPS
Key
Precision
Power
SOURCE: Touch Bionics




Schematic of pacemaker system

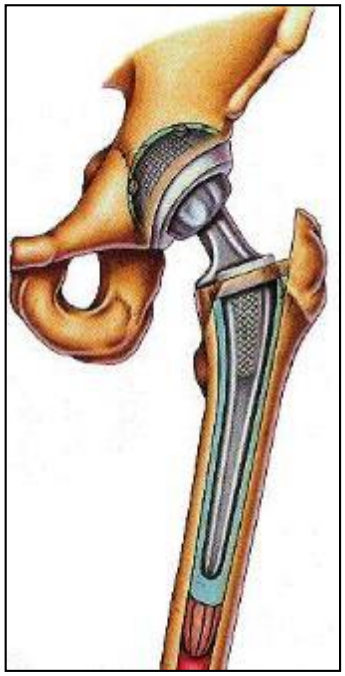


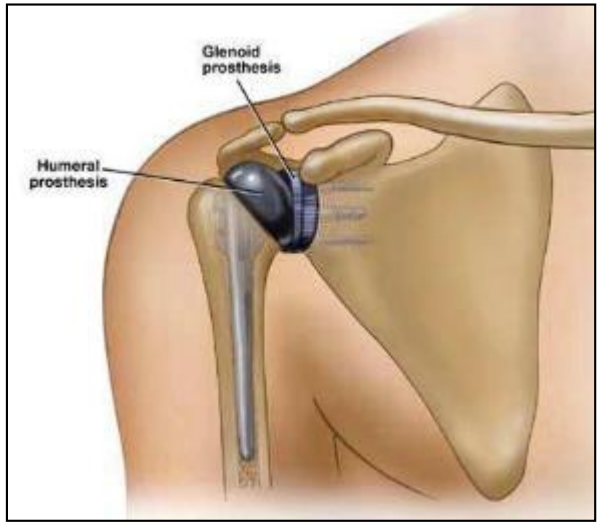




Joint replacement

- One of the most successful intervention in medicine
- Improved quality of life in the increasingly elderly population





Epidemiology of implanted devices

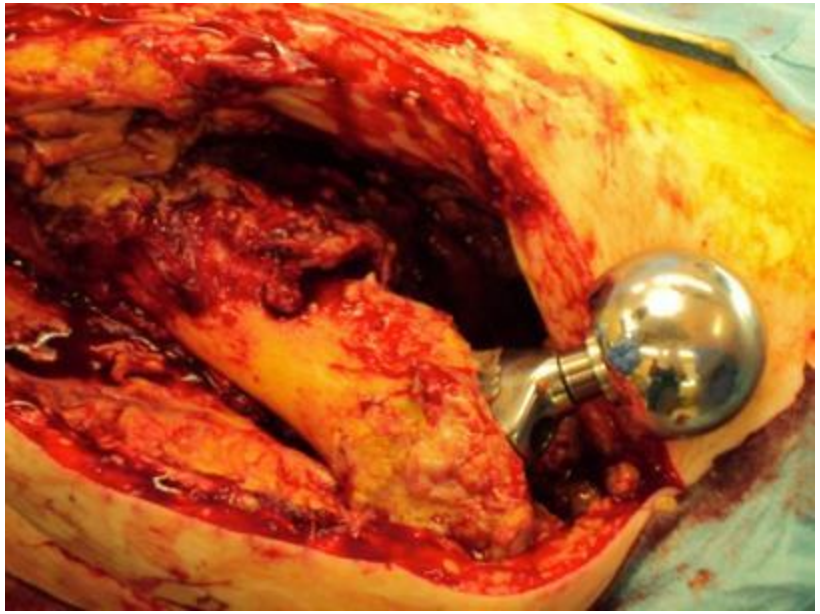
Device type	No. of devices implanted per year (2017) in Millions			Rate of revision	Rate of infection
	Germany	**Europe**	**World**	Mean	Range
Fracture fixation devices	0.71	3.5	7.9	10%	5-10%
Joint prostheses	**0.47**	**2.5**	**5.7**	**20%**	**5-10%**
Spinal implants	0.24	1.8	3.0	38%	5-10%
Vascular grafts	0.50	3.5	15.9	25%	5–10%
Heart pacemakers	0.80	8.0	28.7	15%	5–15%
Mechanical heart valves	0.35	2.8	8.7	10%	1–8%
Heart assist devices	0.12	0.9	4.1	65%	30-40%
Dental implants	1.0	5.5	25.2	10%	5-10%
Breast implants	0.3	2.9	18.2	20%	5-10%
TOTAL	**4.49**	**31.4**	**117.4**	**Ca. 25%**	**Ca. 5-10%**

Darouiche RO. *Clin Infect Dis* 2018

www.transparencymarketresearch.com

What should we do?

- Always aggressive tumor-like surgery?
- Mutilating surgery for the patient?
- Amputation?

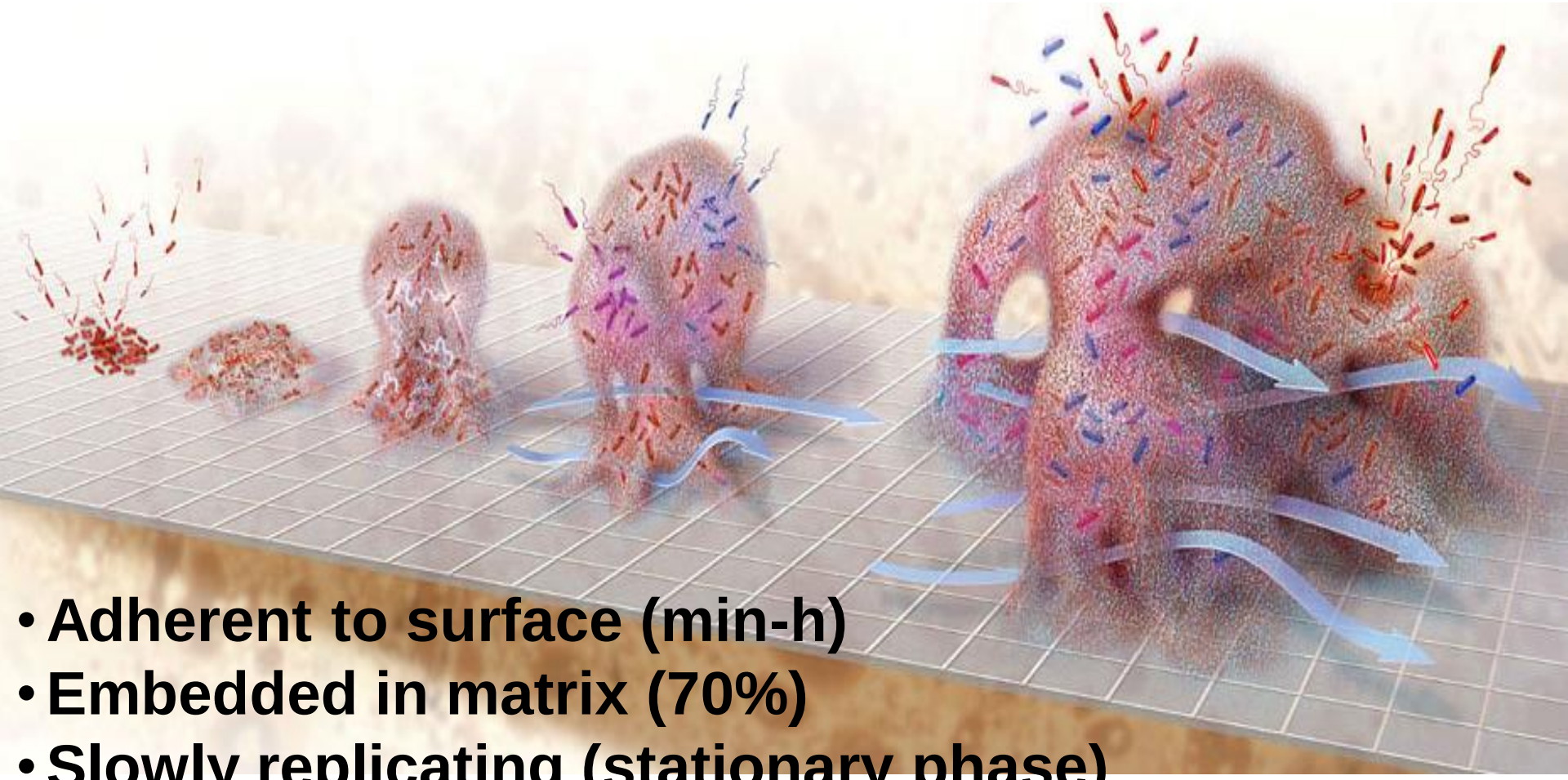


Biofilm and implants: difficult to treat?

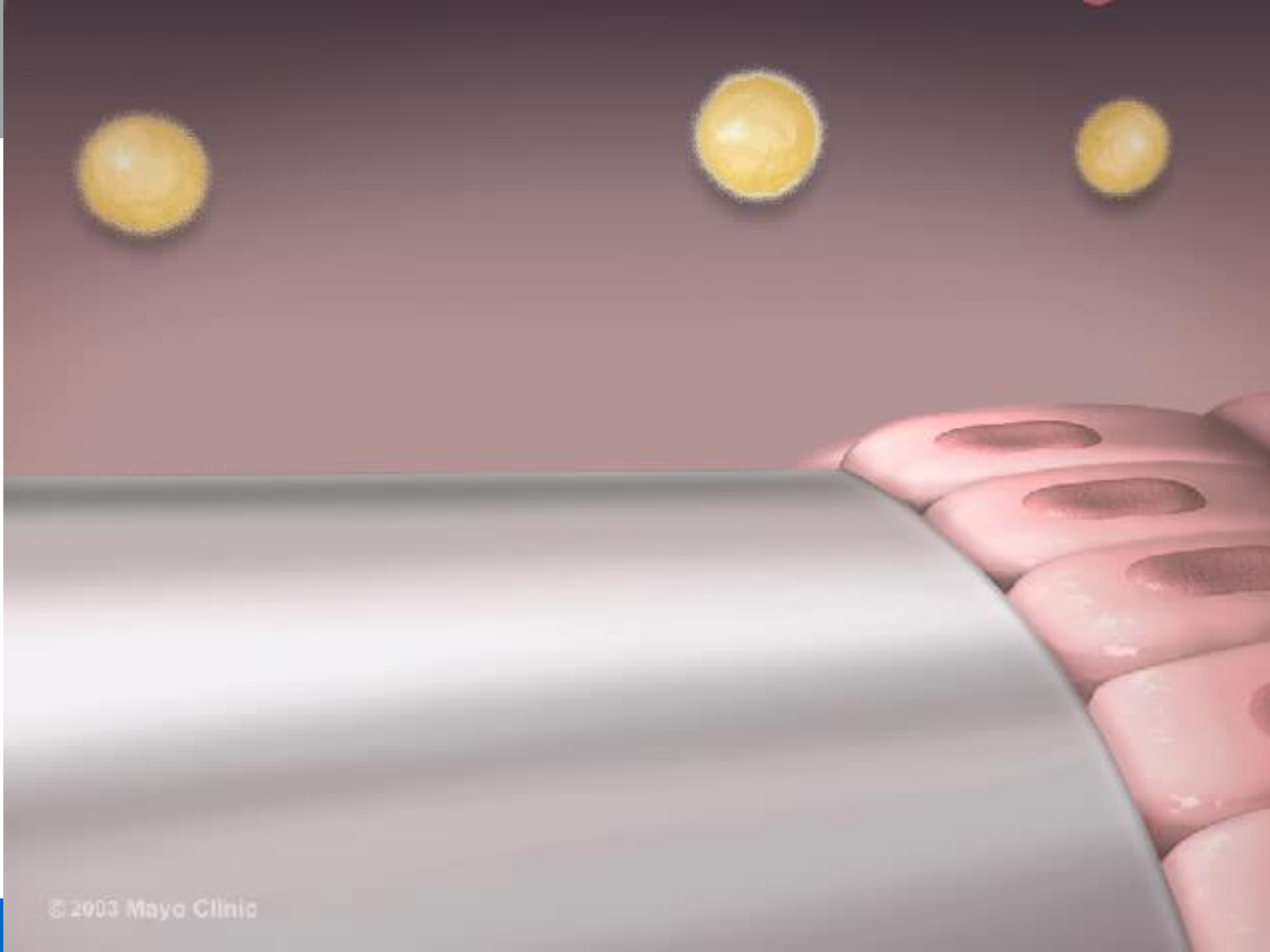
Planktonic bacteria & granulocytes

Biofilm

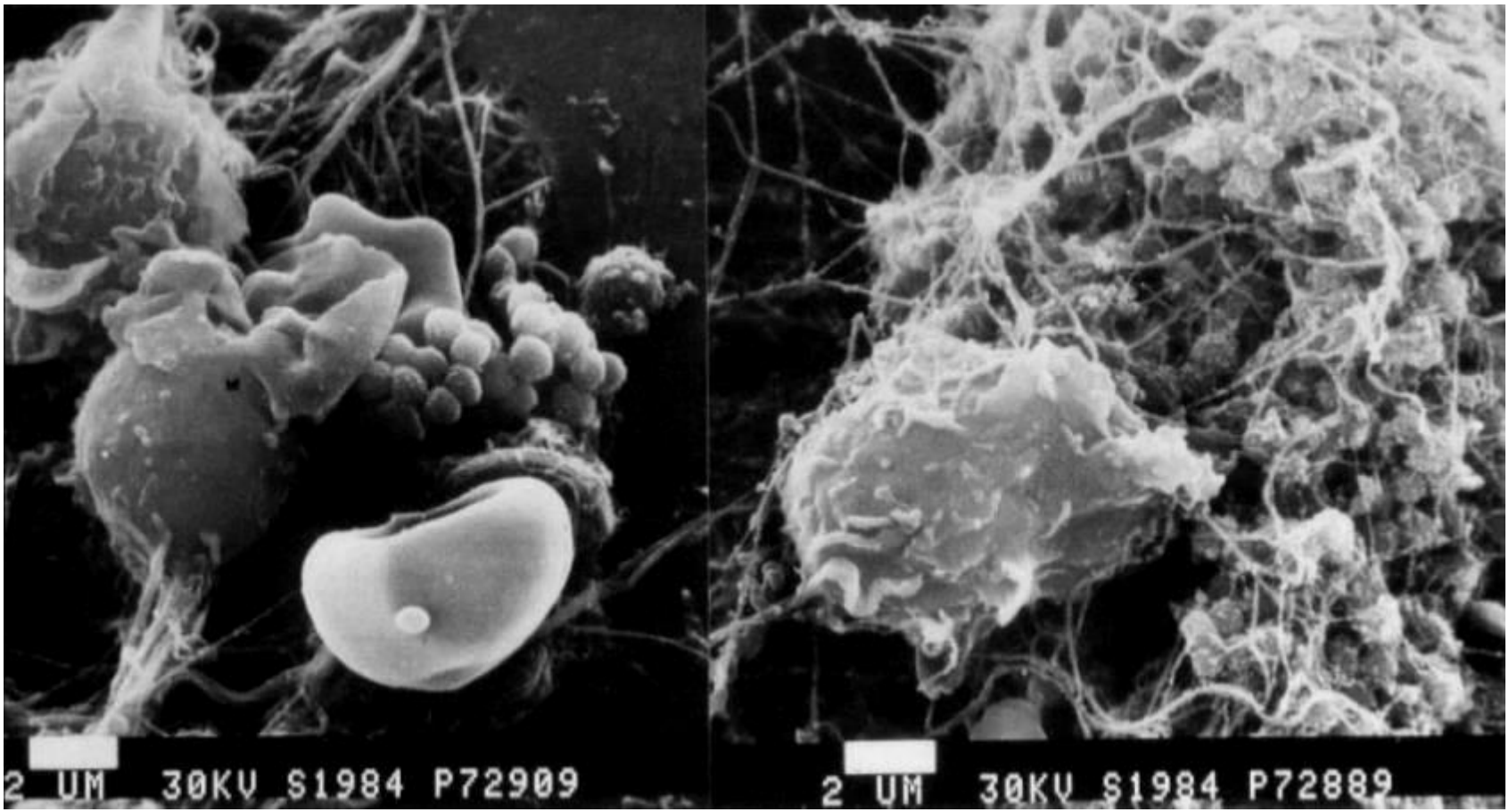
1 min 3 h 12 h 1 day → 3 days



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


© 2003 Mayo Clinic

Experimental foreign-body infection (*S. aureus*)



3 h after inoculation **24 h after inoculation**

⇒ Rapid adherence, no elimination by granulocytes.

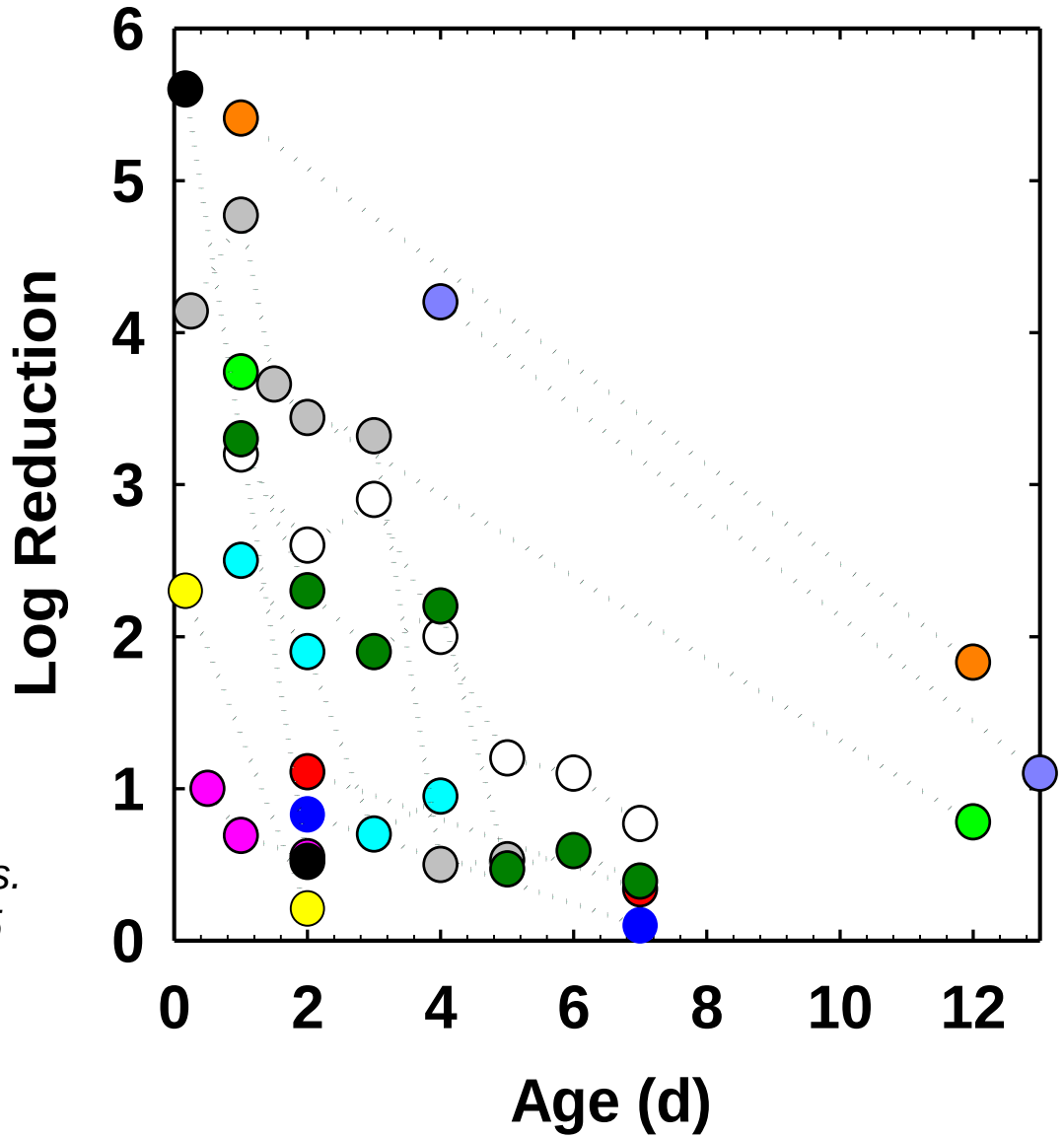
Zimmerli et al. J Infect Dis 1982

The „fatal“ attraction

- Foreign body = avascular tissue (local immune defect): frustrated phagocytosis
- Low number of bacteria (≈ 200) sufficient to cause biofilm on implant
- Mature biofilm (>3 weeks) impossible to eradicate without implantremoval

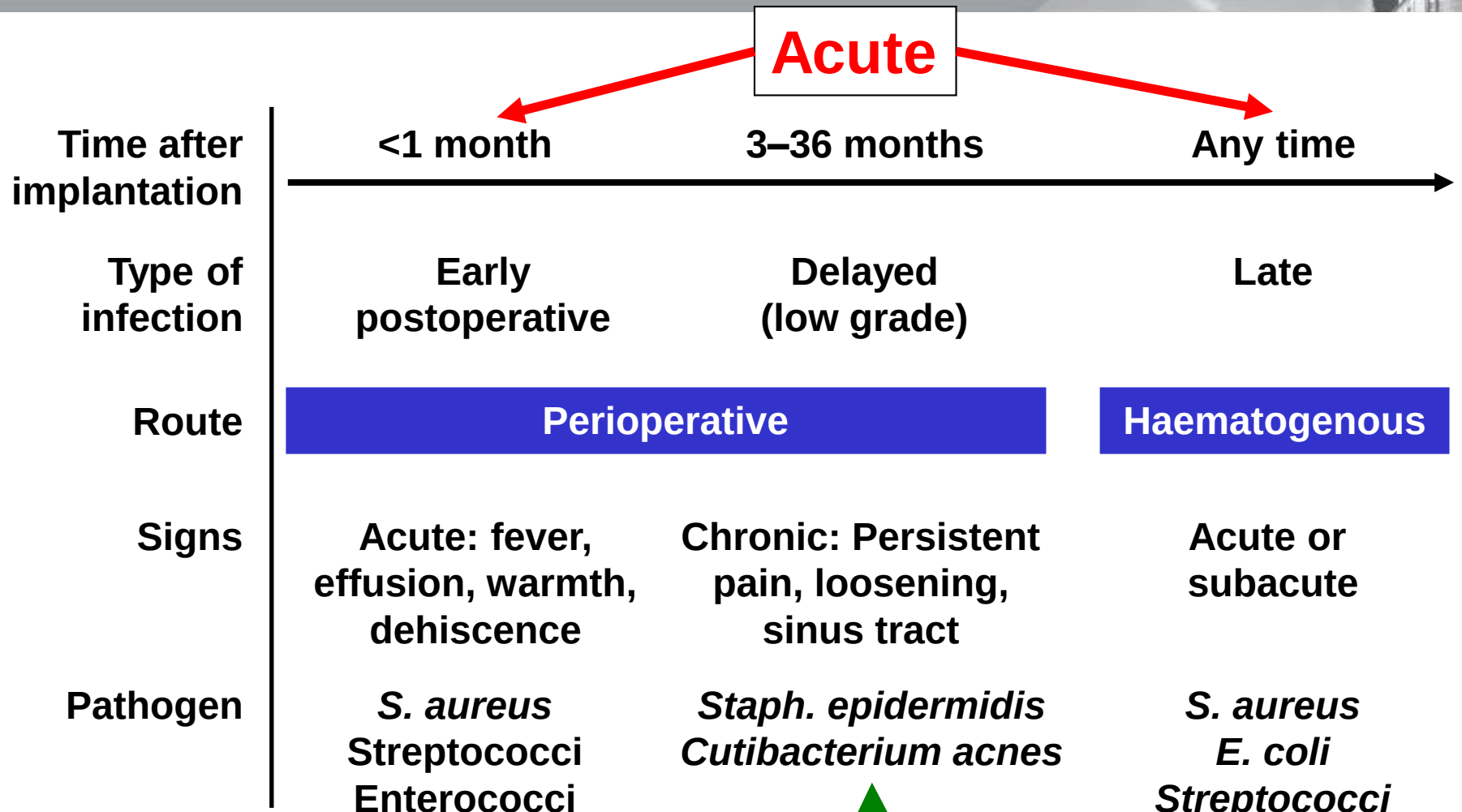
Killing depends on age of the biofilm (in vitro)

The older the biofilm, the lower the bacterial killing



Antimicrobial tolerance in biofilms.
In: Microbiol Spectr 3: June 2015

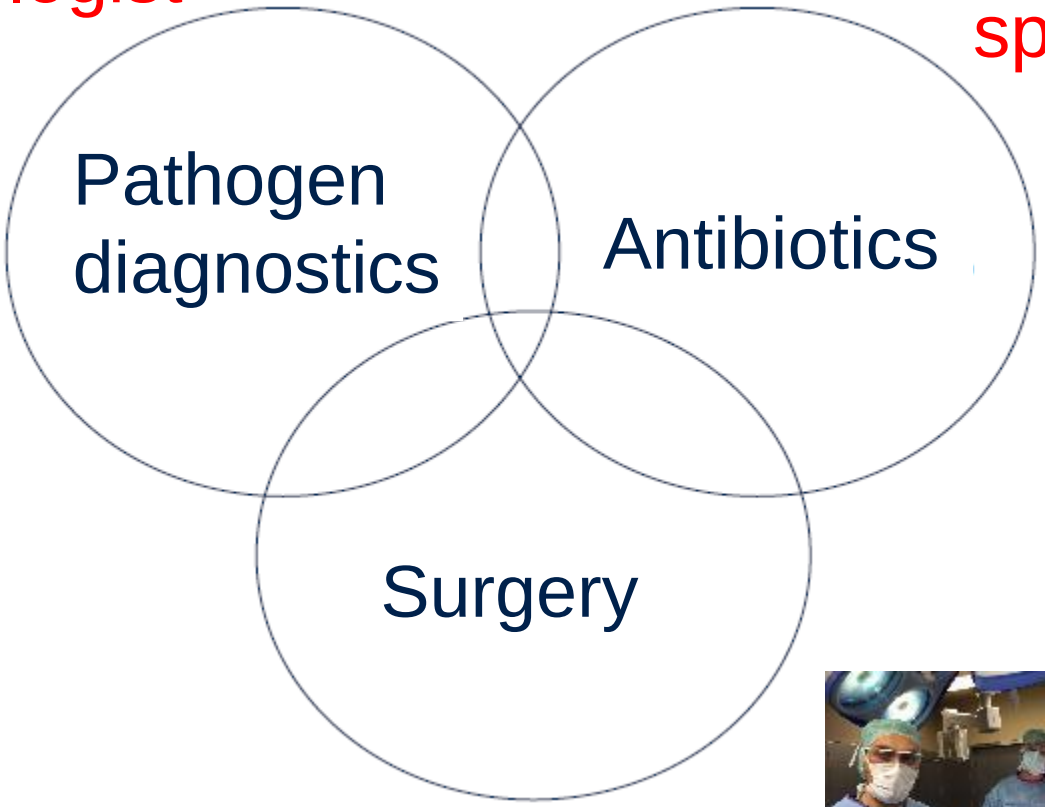
Classification: early – delayed – late



Key to success: Interdisciplinary concept

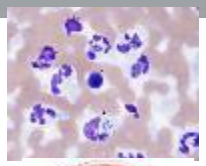
Microbiologist

Infectious diseases specialist



Ortho/trauma & Plastic surgeons

Key to success No. 2: Target the biofilm



Diagnosis

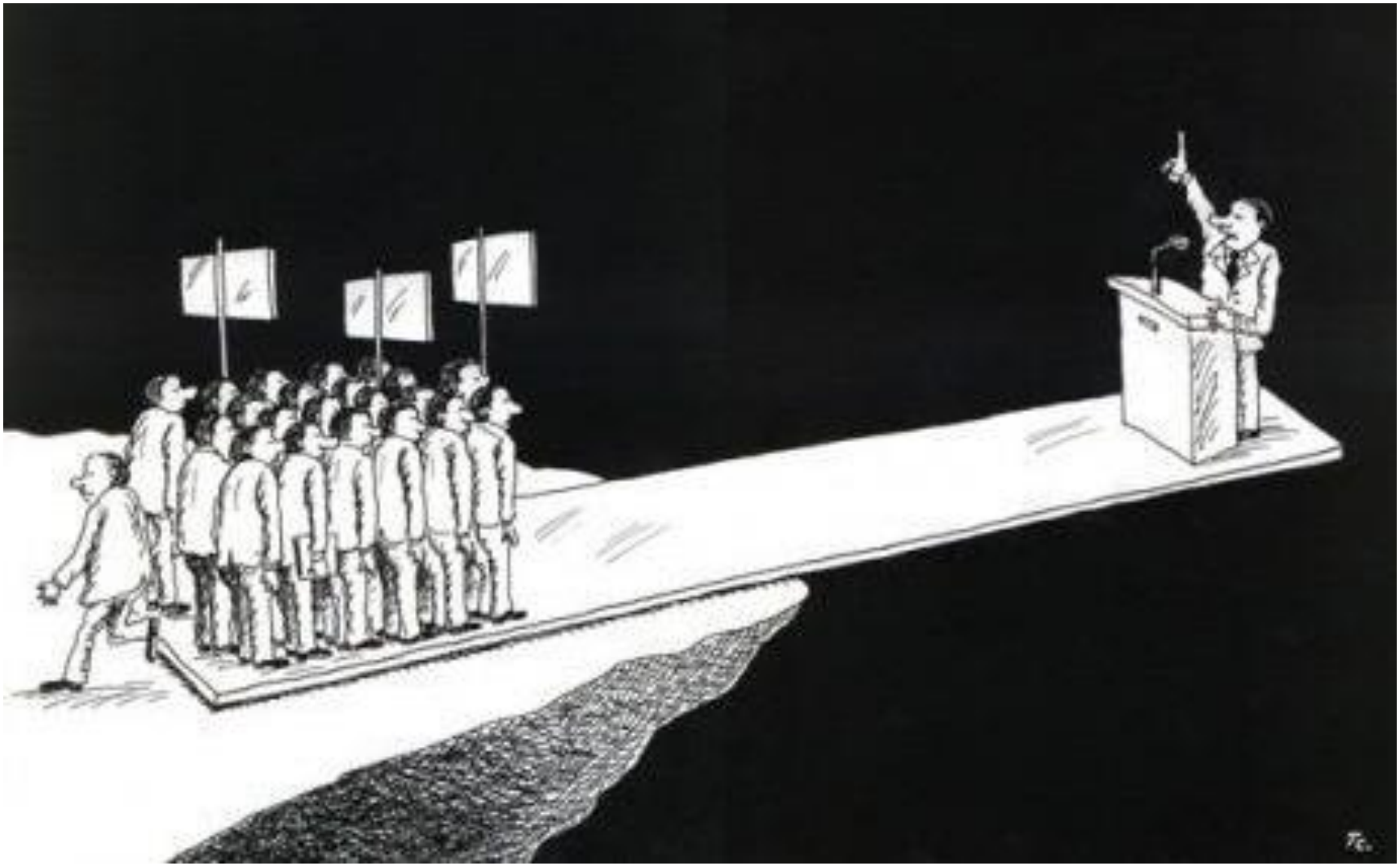
Antibiotics

Surgery

Directed against **biofilms**

Cure rate > 90%

Modern concepts




Ortho/trauma surgeons
Researchers
ID/microbiology
Septic surgery unit
Observers

THE BONE & JOINT JOURNAL EST. 1948

■ INSTRUCTIONAL REVIEW

A standardized interdisciplinary algorithm for the treatment of prosthetic joint infections

OUTCOME IN A CENTRALIZED AND SPECIALIZED DEPARTMENT

D. Karczewski,
T. Winkler,
N. Renz,
A. Trampuz,
E. Lieb,
C. Perka,
M. Müller

From Charité – Universitätsmedizin Berlin, Berlin, Germany

Aims

In 2013, we introduced a specialized, centralized, and interdisciplinary team in our institution that applied a standardized diagnostic and treatment algorithm for the management of prosthetic joint infections (PJIs). The hypothesis for this study was that the outcome of treatment would be improved using this approach.

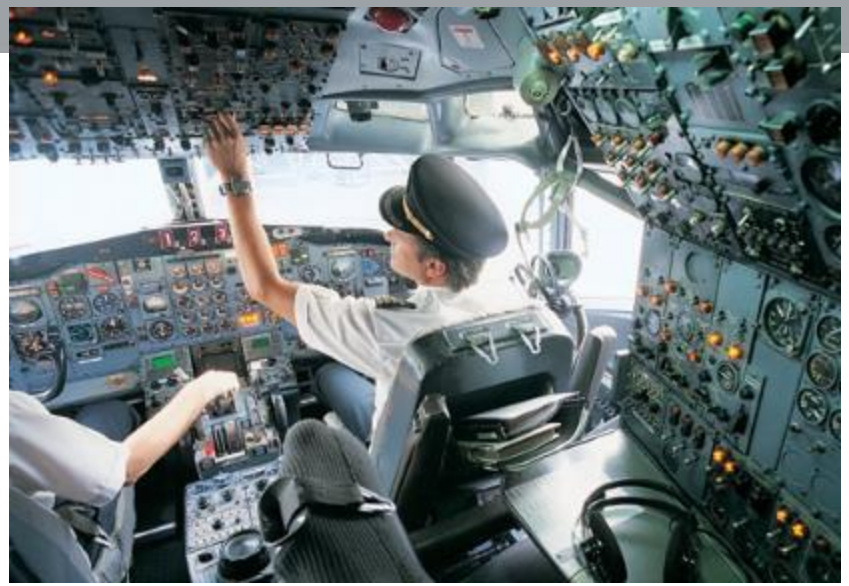
Patients and Methods

In a retrospective analysis with a standard postoperative follow-up, 95 patients with a PJI of the hip and knee who were treated with a two-stage exchange between 2013 and 2017 formed the study group. A historical cohort of 86 patients treated between 2009 and 2011 not according to the standardized protocol served as a control group. The success of treatment was defined according to the Delphi criteria in a two-year follow-up.

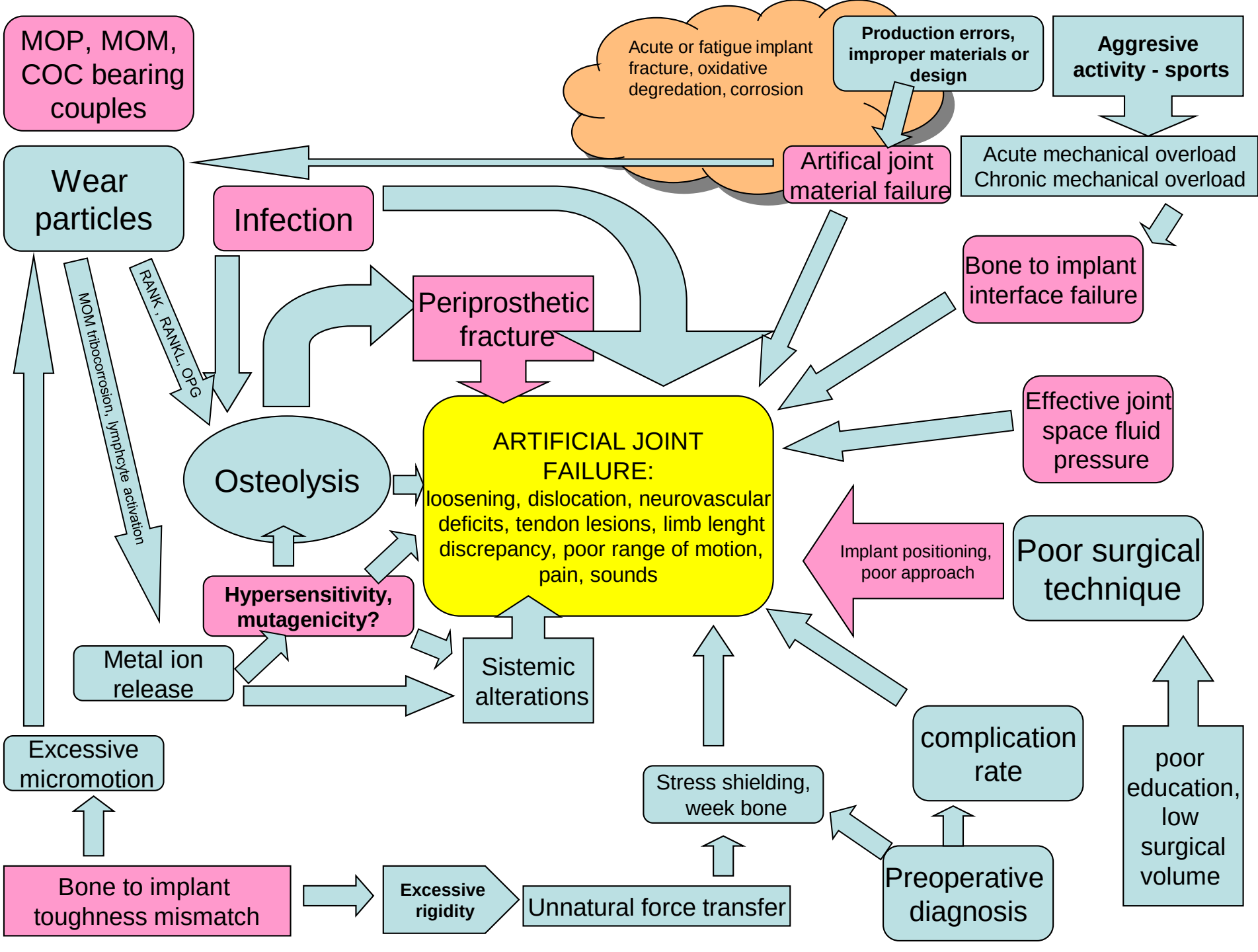
Results

Patients in the study group had a significantly higher Charlson Comorbidity Index (3.9 *vs* 3.1; p = 0.009) and rate of previous revisions for infection (52.6% *vs* 36%; p = 0.025), and tended to be older (69.0 *vs* 66.2 years; p = 0.075) with a broader polymicrobial spectrum (47.3% *vs* 33.7%; p = 0.062). The rate of recurrent infection (3.1% *vs* 10.4%; p = 0.048) and the mean time interval between the two stages of the procedure (66.6 *vs* 80.7 days; p < 0.001) were reduced significantly in the study group compared with the control group

Teamwork of experts



Is it an infection?


MOP, MOM, COC bearing couples
Acute or fatigue implant fracture, oxidative degredation, corrosion
Production errors, improper materials or design
Aggresive activity - sports
Wear particles
Artifical joint material failure
Acute mechanical overload
Chronic mechanical overload
Infection
Bone to implant interface failure
MOM tribocorrosion, lymphcyte activation
RANK , RANKL, OPG
Periprosthetic fracture
Effective joint space fluid pressure
Osteolysis
ARTIFICIAL JOINT FAILURE:
loosening, dislocation, neurovascular deficits, tendon lesions, limb lenght discrepancy, poor range of motion, pain, sounds
Implant positioning, poor approach
Poor surgical technique
Hypersensitivity, mutagenicity?
Metal ion release
Sistemic alterations
Excessive micromotion
complication rate
Stress shielding, week bone
poor education, low surgical volume
Bone to implant toughness mismatch
Excessive rigidity
Unnatural force transfer
Preoperative diagnosis

About 20% of prosthesis fail: Infection or aspetic reason?

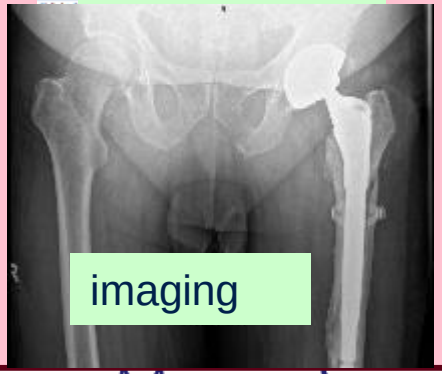
preoperative

Diagnosis

intraoperative

History & clinical presentation

laboratory



imaging

joint puncture

cytology microbiology histopathology

intraoperative sampling

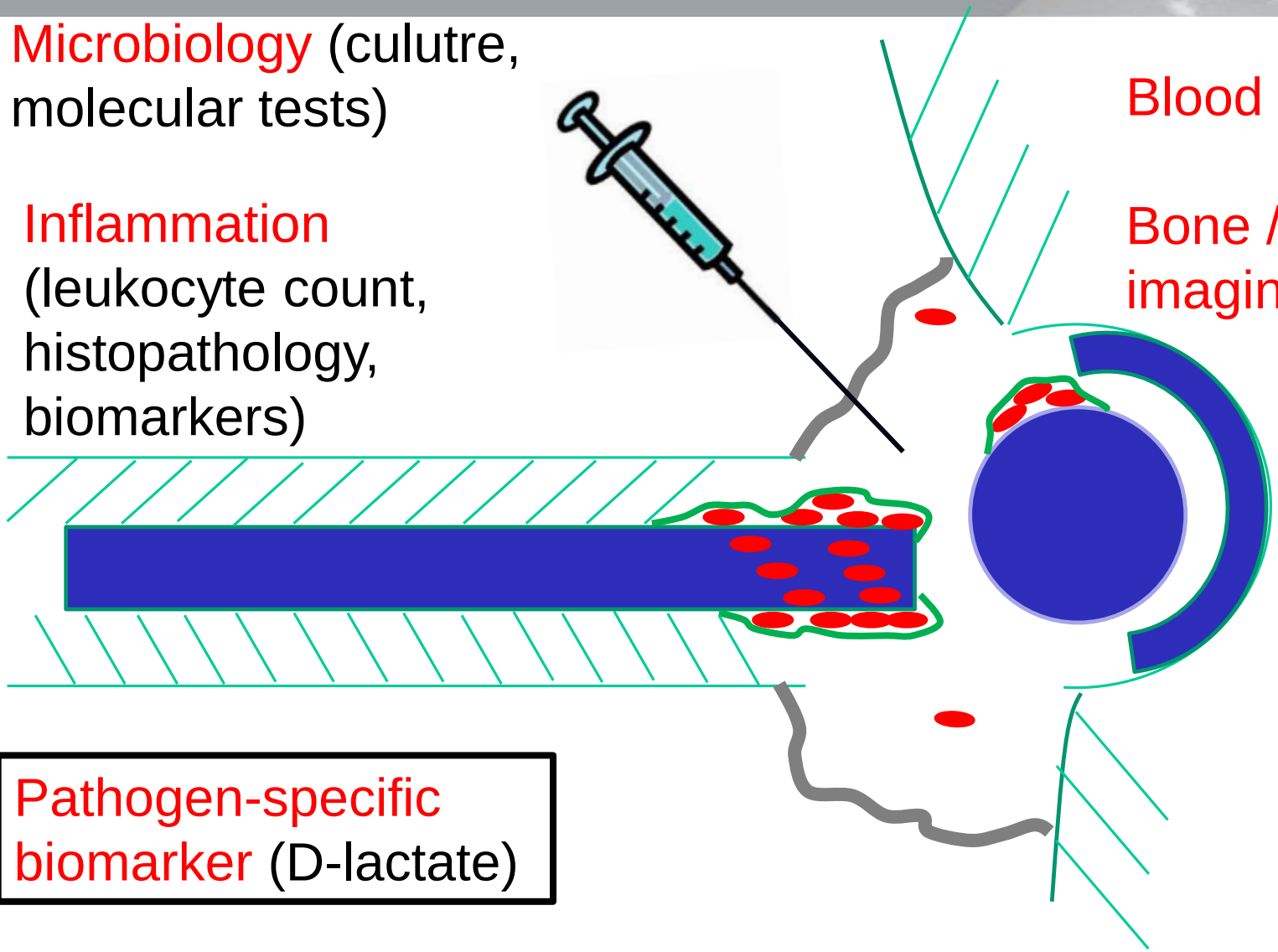
microbiology histopathology

sonication

Joint aspiration

Microbiology (culutre, molecular tests)

Inflammation (leukocyte count, histopathology, biomarkers)

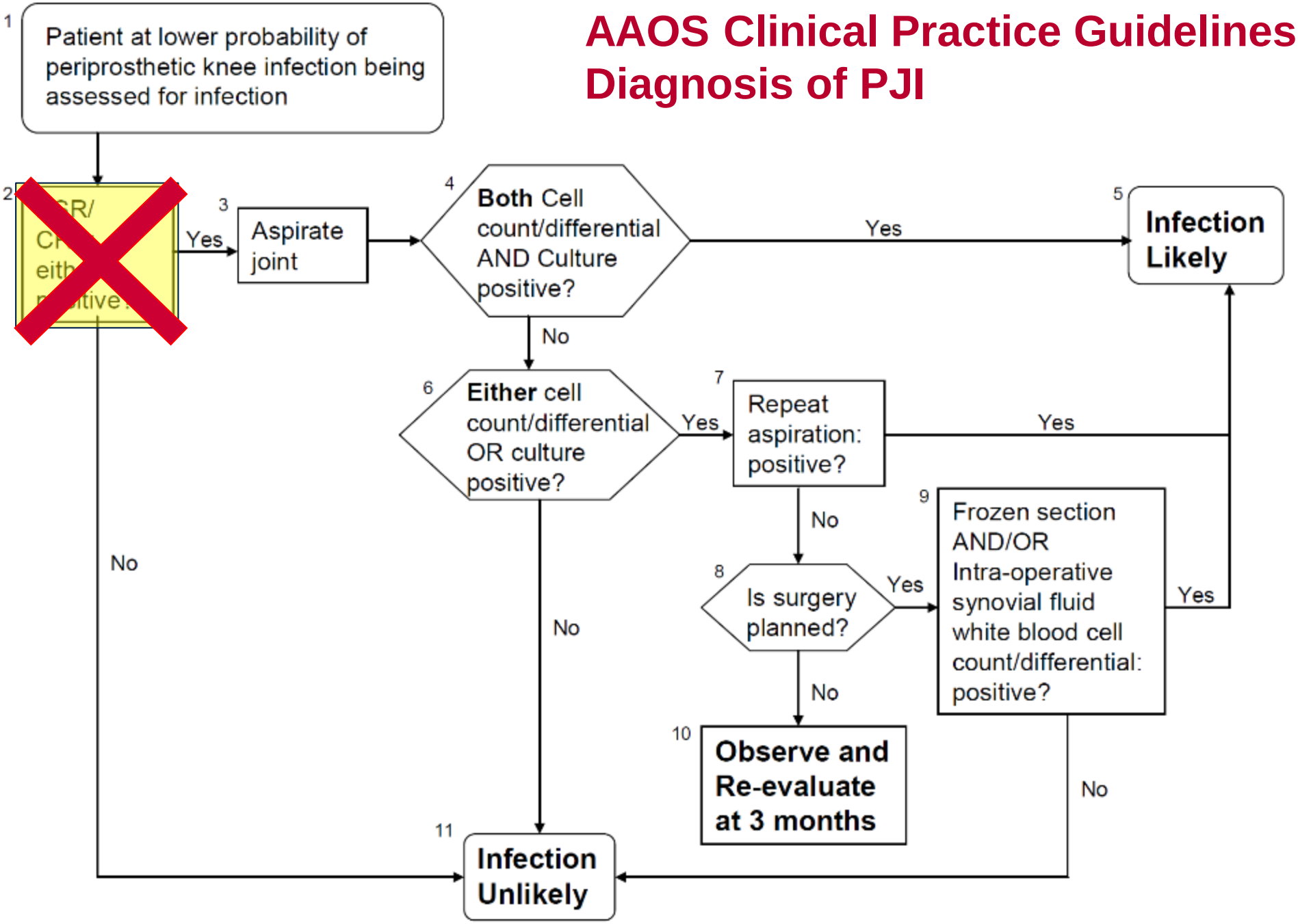


Blood tests

Bone / implant imaging

Pathogen-specific biomarker (D-lactate)

AAOS Clinical Practice Guidelines
Diagnosis of PJI



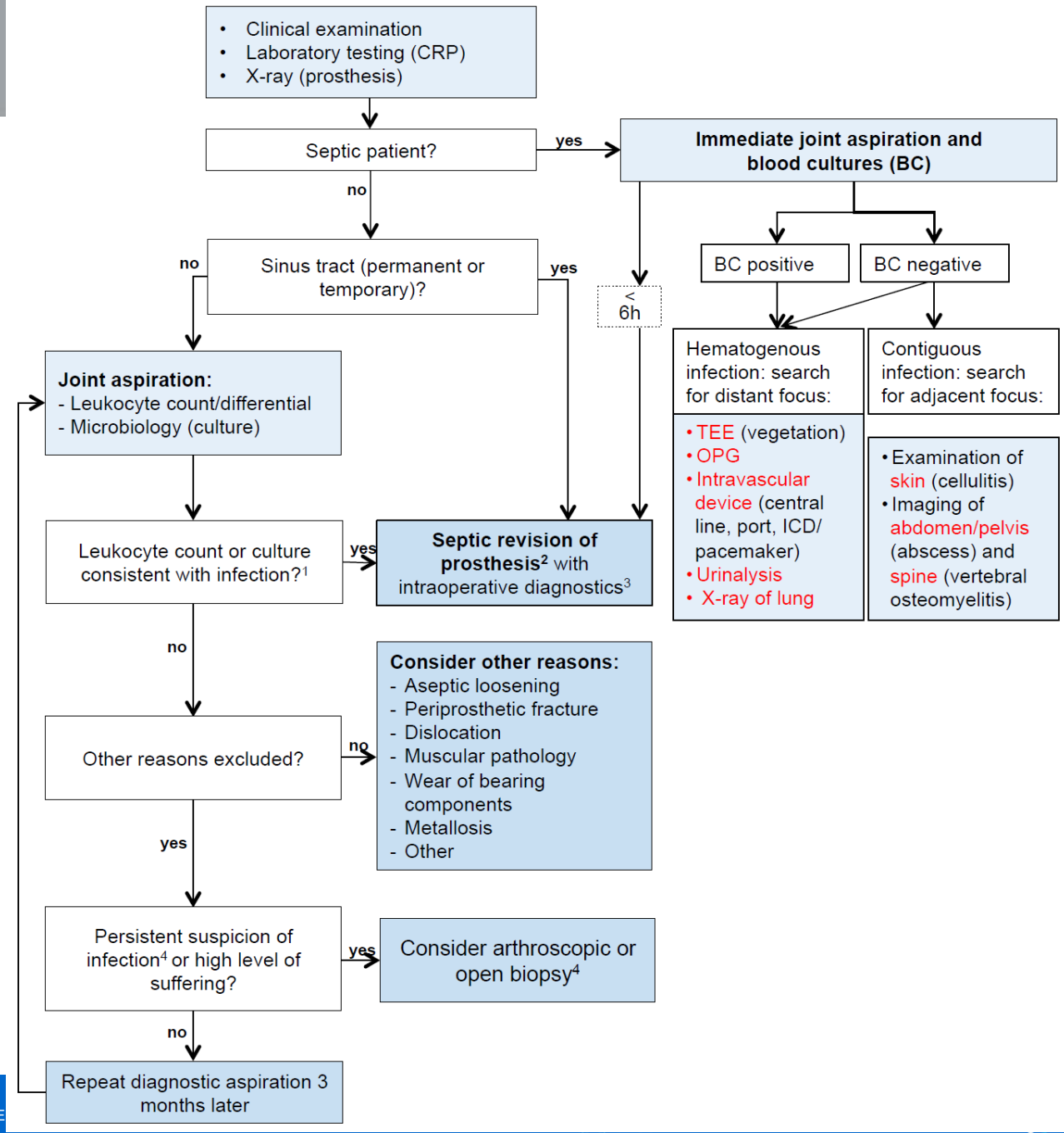
Is it an infection?

The ostrich effect

Ostri[illegible]ary their heads [illegible] the sand to avoid danger (legend).

In humans: Avoid an apparent risk by pretending it doesn't exist.

DIAGNOSTIC ALGORITHM



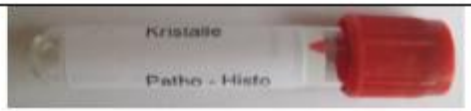
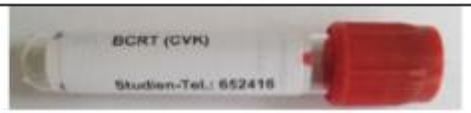
Approach

Early prosthesis loosening (within 3 years of implantation) and **persistent pain** are:

Highly suggestive for low-grade PJI

Arthrocentesis kit

Arthrocentesis-kit

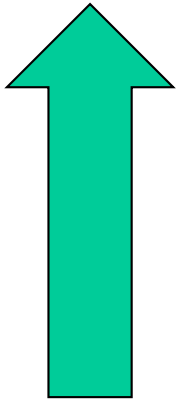
Priorität	Röhrchen	(mindest-) Volumen	Sonstiges	Zweck	Ziel	
1	EDTA (Lila)	1 ml	Zellzahlanmeldung per S… sorgfältig schütteln!!	Zellzahl	Verteilerlabor …rpost: 1213	
2	BK-Flasche	mind. 1ml	MiBi-Schein	MiBi	MiBi	
3	Rot	0,5 ml	Patho-/Histo-Schein	Kristalle	**Patho-/Histologie Verteilerlabor** Rohrpost: 1213	
4	NATIV (in der Spritze)	1 ml	MiBI-Schein „NATIV“	MiBi	**MiBi Verteilerlabor** Rohrpost: 1213	
5	Rot	1,5 - 2 ml	Bitte unterschriebenes Einwilligungsformular mitschicken	Kalorimetrie + PCR	**Ortho-Op Dispatcher** Rohrpost: 1605 **mit unterschriebenem Einwilligungsformular!!**	

Leukocyte count

Microbiology (cultures)

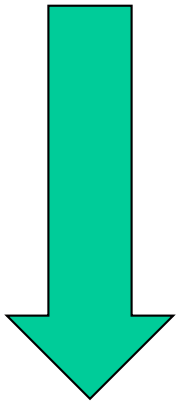
If **aspirated synovial fluid volume <5 ml** distribute the obtained synovial fluid **according to the priority column** (otherwise vials can be completely filled up)

Leukocyte count: not always reliable



Potentially false high

- 6 weeks postoperative
- rheumatologic disease
- after trauma/periprosthetic fracture/ dislocation



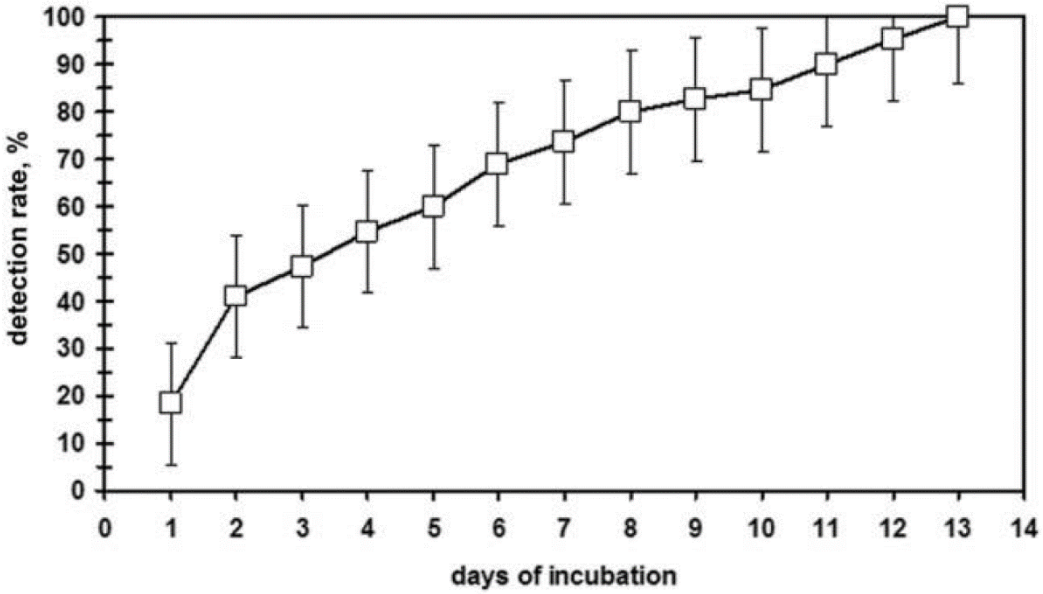
Potentially false low

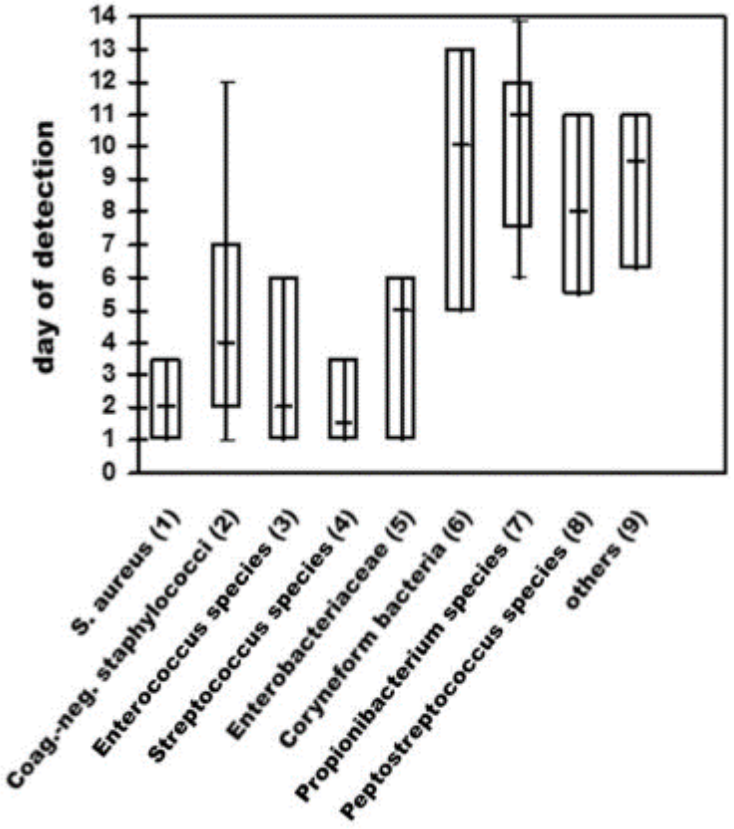
- sinus tract
- leukopenia
- Low-grade infection *(Cutibacterium acnes)*

Intraoperative tissue culture

Obtain ≥3 tissue specimens

- Interface tissue-prosthesis, no swabs
- For culture and histology
- Prolonged culture incubation: 10-14 d (anaerobes)
- Culture sensitivity: 60-80%





Schäfer P. Clin Infect Dis 2008

Sonication of implants

Removed implants

May 2005–Feb 2007

Vortex, 30 s

Sonication, 1 min, 40 kHz

Standard method
(≥3 tissue biopsies)

Trampuz A *et al*. *N Engl J Med* 2007;357:654–663

The NEW ENGLAND JOURNAL of MEDICINE

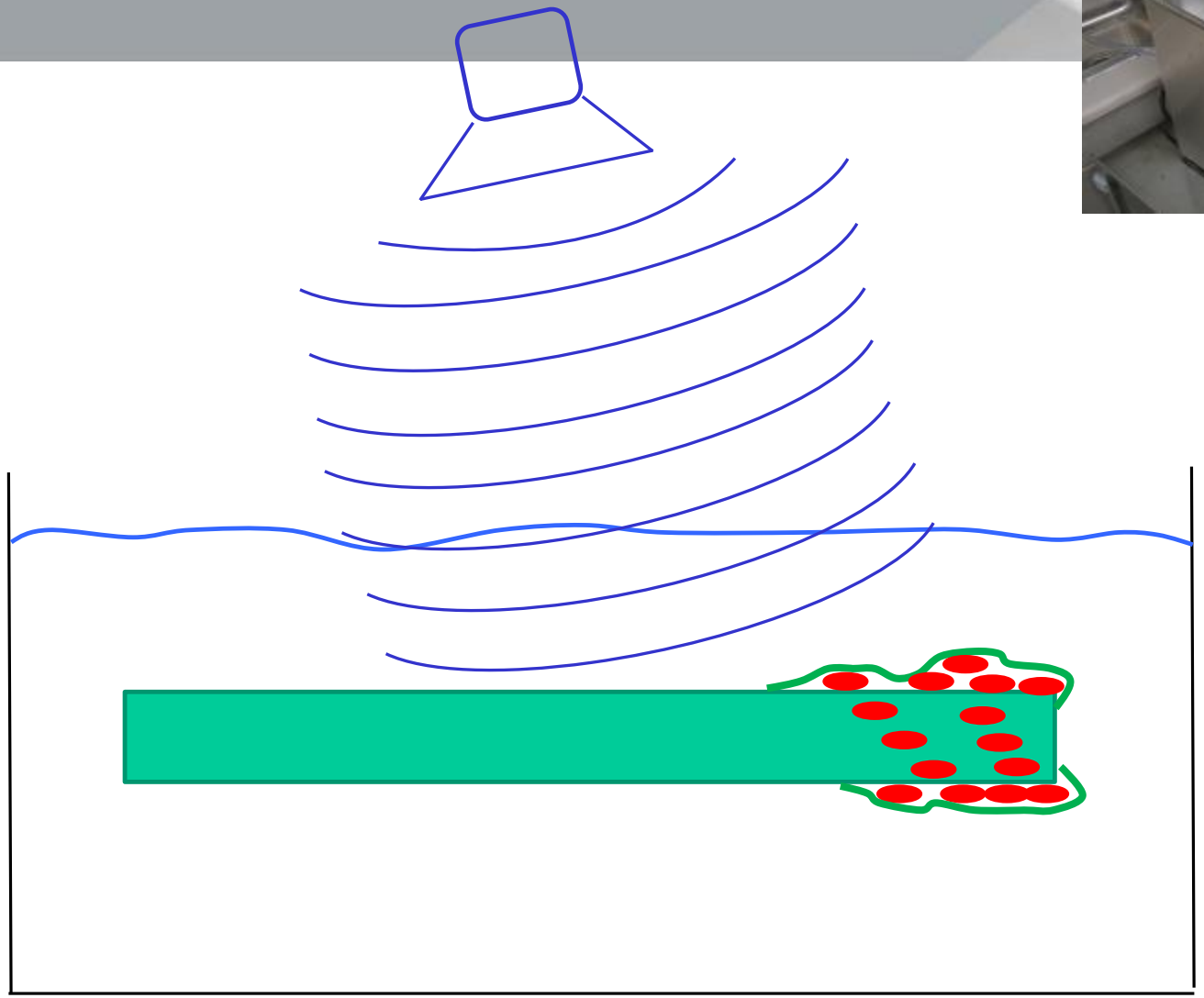
ORIGINAL ARTICLE

Sonication of Removed Hip and Knee Prostheses for Diagnosis of Infection

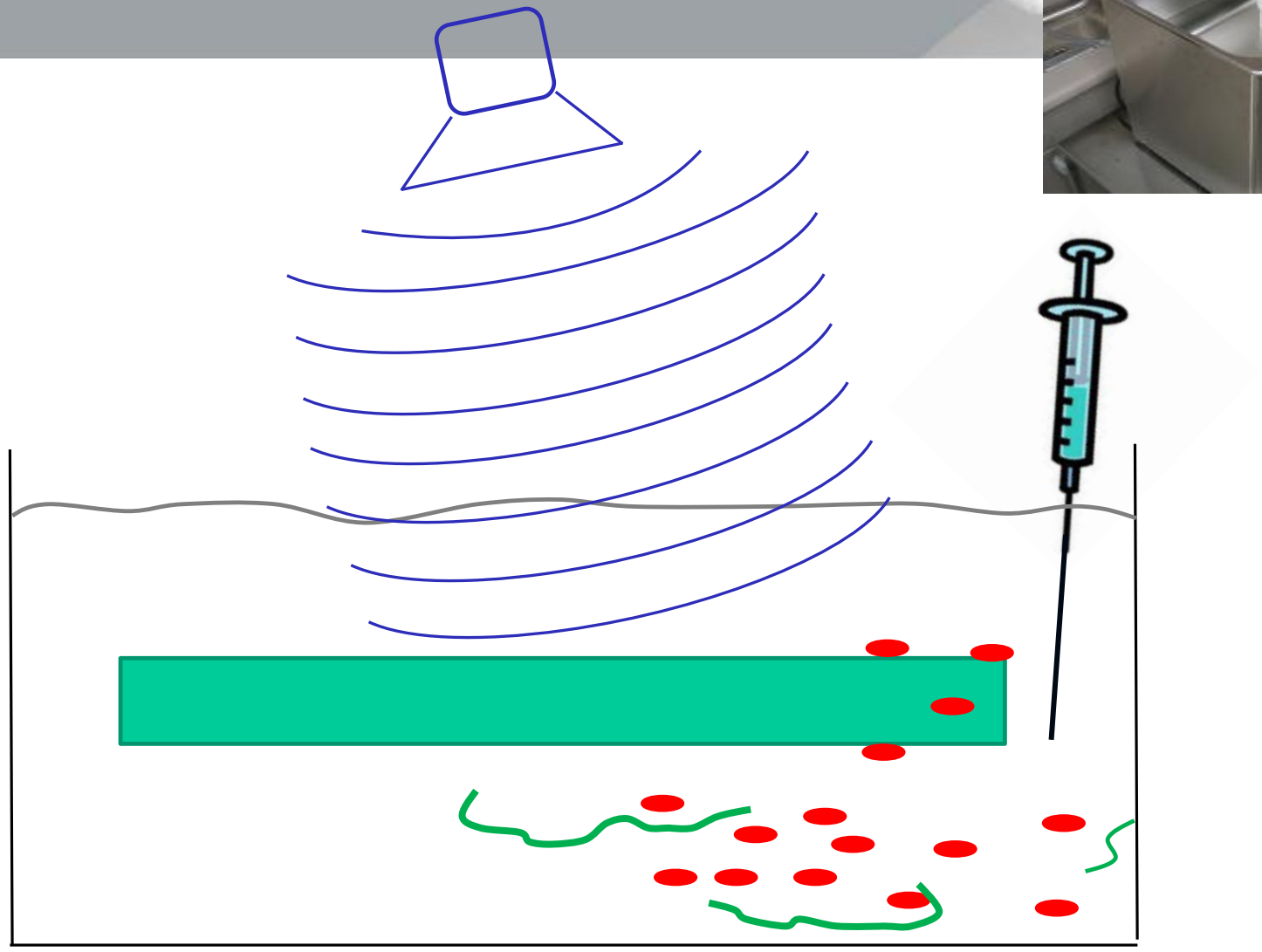
Andrej Trampuz, M.D., Kerryl E. Piper, M.S., Melissa J. Jacobson, A.S., Arlen D. Hanssen, M.D., Krishnan K. Unni, M.D., Douglas R. Osmon, M.D., Jayawant N. Mandrekar, Ph.D., Franklin R. Cockerill, M.D., James M. Steckelberg, M.D., James F. Greenleaf, Ph.D., and Robin Patel, M.D.

N ENGL J MED 357;7 WWW.NEJM.ORG AUGUST 16, 2007

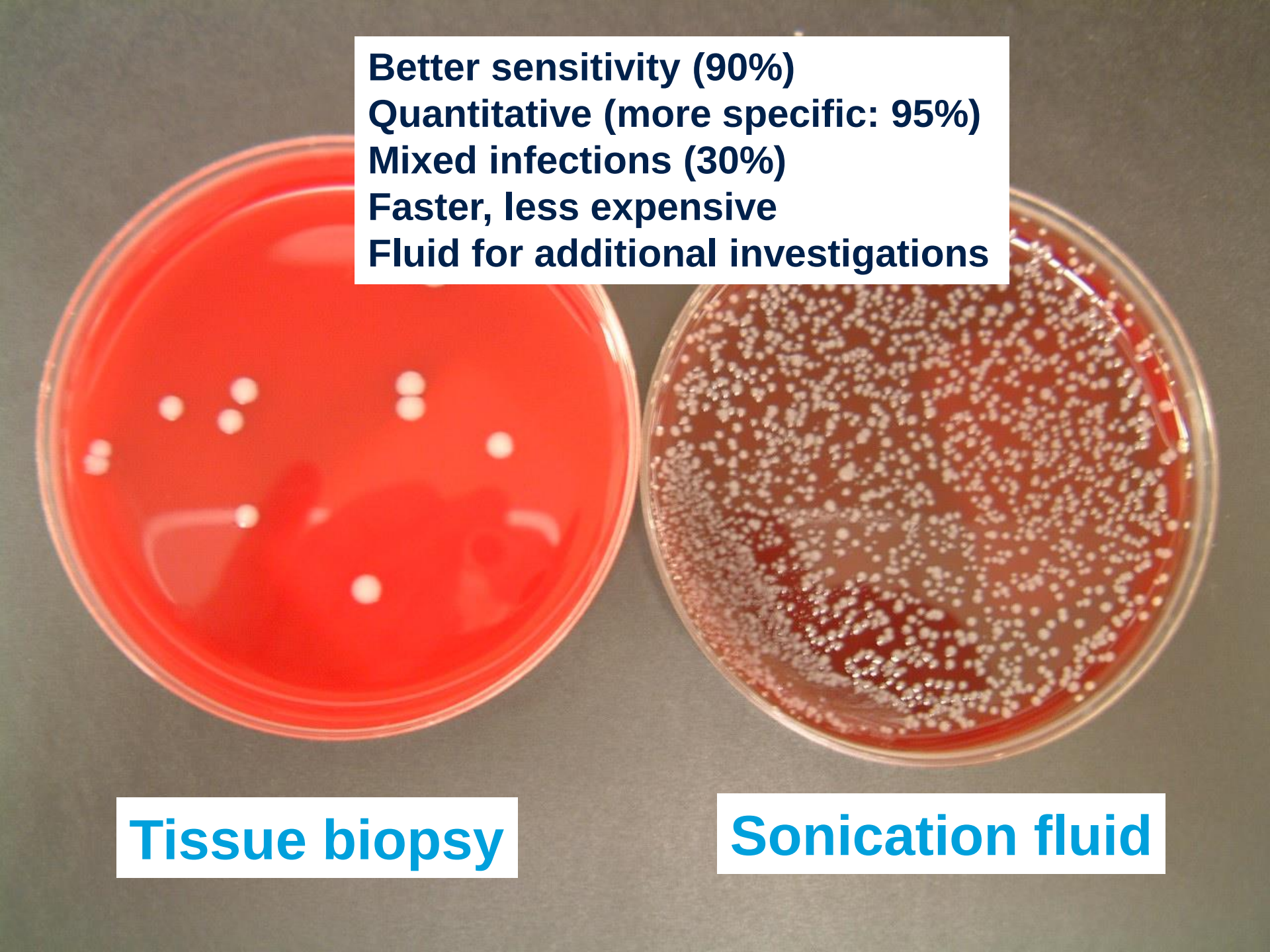
Sonication – biofilm bacteria



Sonication – biofilm bacteria



Trampuz A et al. N Engl J Med 2007


Better sensitivity (90%)
Quantitative (more specific: 95%)
Mixed infections (30%)
Faster, less expensive
Fluid for additional investigations
Tissue biopsy
Sonication fluid

Definition criteria

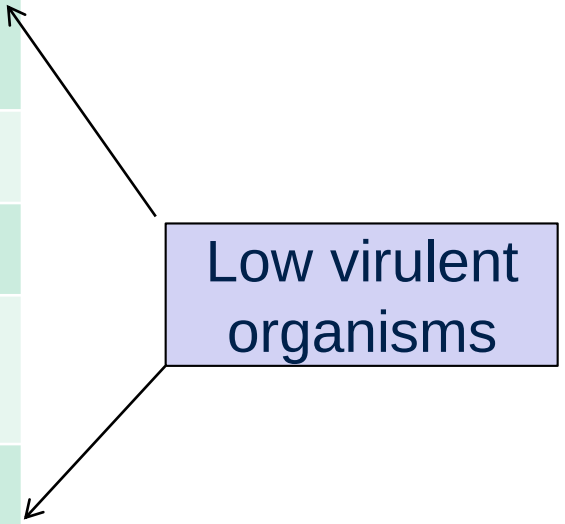
Diagnosis of periprosthetic joint infection is confirmed if at least 1 criteria is fulfilled:

Criterion	Explanation	Sensitivity	Specificity
Clinical features	Sinus tract (fistula) or visible purulence around the prosthesis	20-30%	100%
Leukocyte count in synovial fluid	>2000/µl leukocytes or ≥70% granulocytes	90%	95%
Histology	Inflammation in periprosthetic tissue (type 2 or type 3 after Morawietz & Krenn)	70-90%	95%
Microbiology	Growth in: - Synovial fluid - ≥2 periprosthetic tissue samples* - Sonication fluid (≥ 50 CFU/ml)	 45-75% 60-80% 80-90%	 95% 92% 95%

*For highly virulent organisms (e.g. *S. aureus*, *E. coli*) 1 positive tissue sample is sufficient.

Microbiology of PJI

Microorganism	Frequency
Coagulase-negative staphylococci (e.g. *Staphylococcus epidermidis)*	30-43%
Staphylococcus aureus	12-23%%
Streptococci & enterococci	12-19%
Gram-negative bacilli (e.g. *Escherichia coli*)	10-17%
Anaerobes (e.g. *Cutibacterium acnes*)	4-10%
Mixed infections[1]	10-20%
Fungi (e.g. *Candida albicans*)[1]	1-3%
Culture negative	10-30%

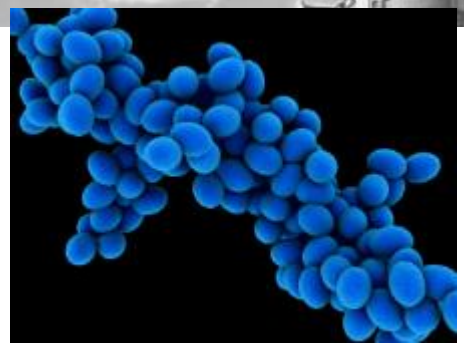


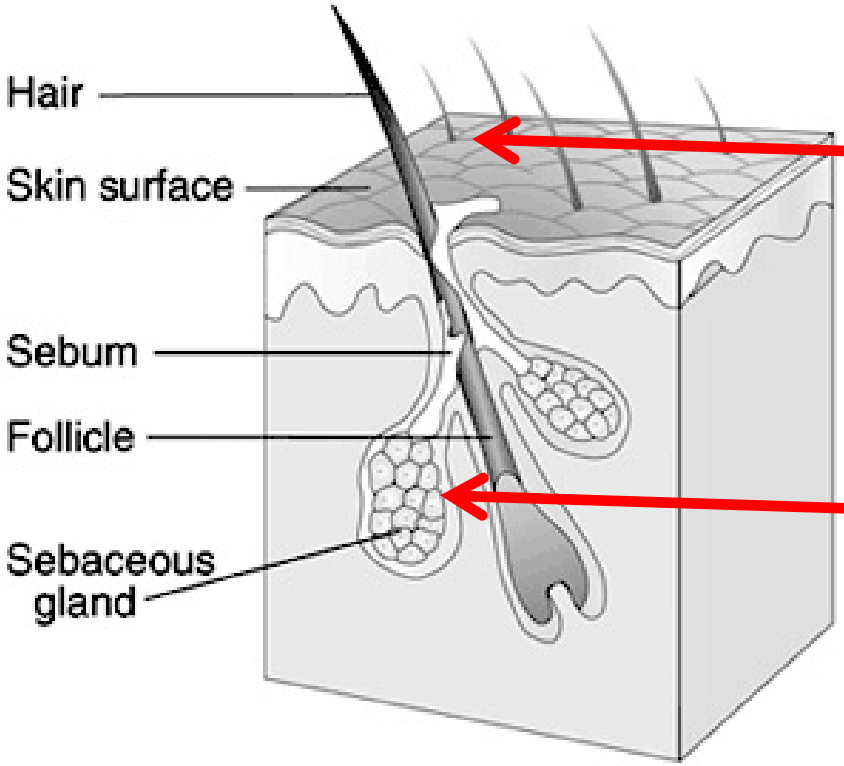
[1] Often after VAC-therapy or fistula (with antibiotic therapy)

Corvec IJAO 2012; Tande CMR 2014

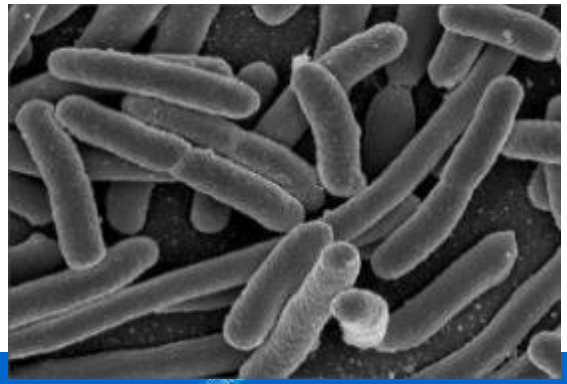
Normal skin flora

100.000 bacteria/cm^2





- **Staphylococci**
  - Staphylococcus epidermidis
  - *Staphylococcus aureus*
- **Anaerobes**
  - *Cutibacterium acnes*



Modern treatment algorithm of PJI

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

Prosthetic-Joint Infections

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

Zimmerli W *et al. N Engl J Med* 2004:351:1645–1654

Treatment concept

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

Cure rate >90%

What is the contribution of the surgeon on treatment sccuess in PJI?

Infectious Diseases

- 0%
- 20%
- 40%
- 60%
- 80%
- 100%

Orthopedic surgeons

- 0%
- 20%
- 40%
- 60%
- 80%
- 100%

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- 80%
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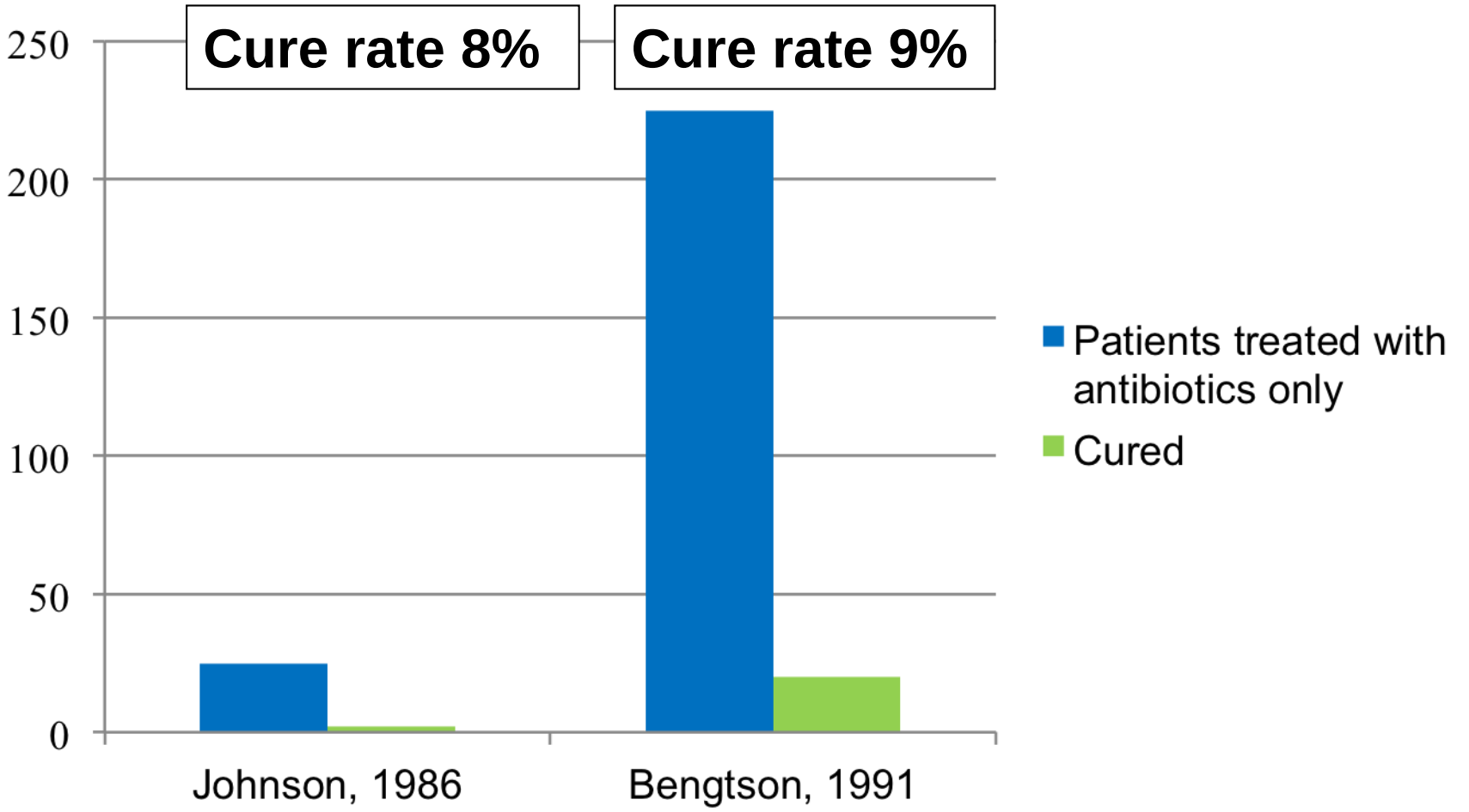
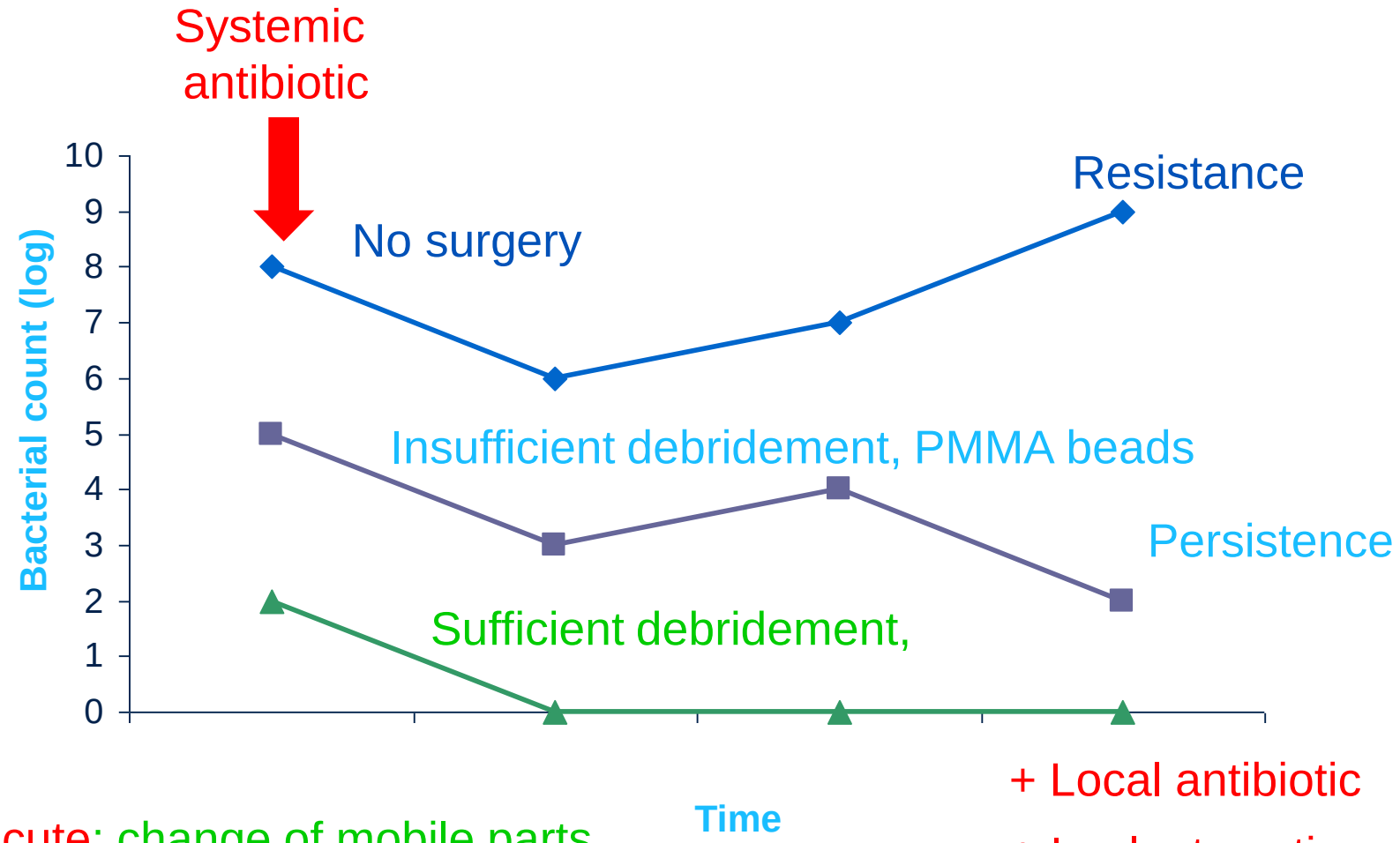
Antibiotics without surgery



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

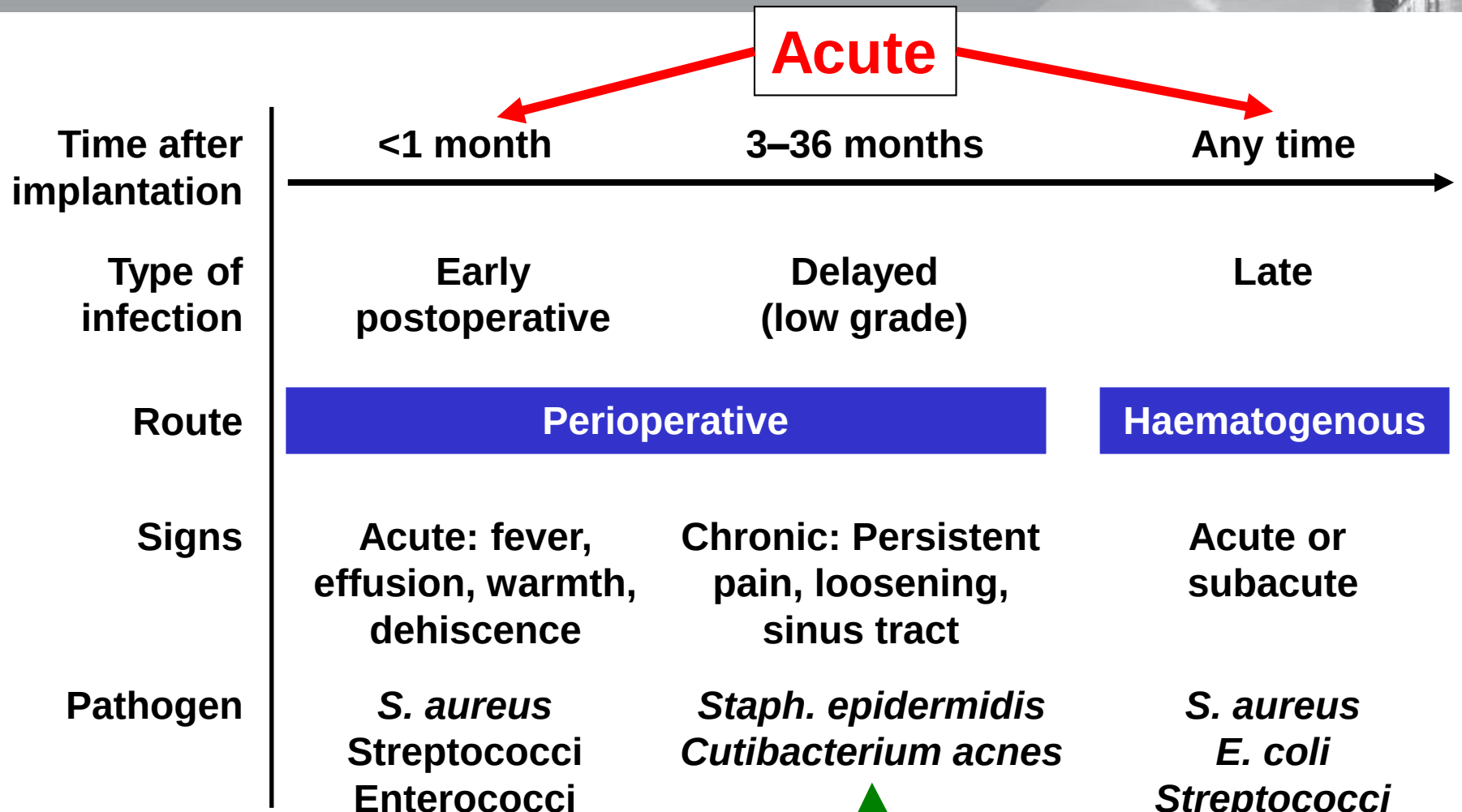
The solution to pollution is dilution (of microbes)



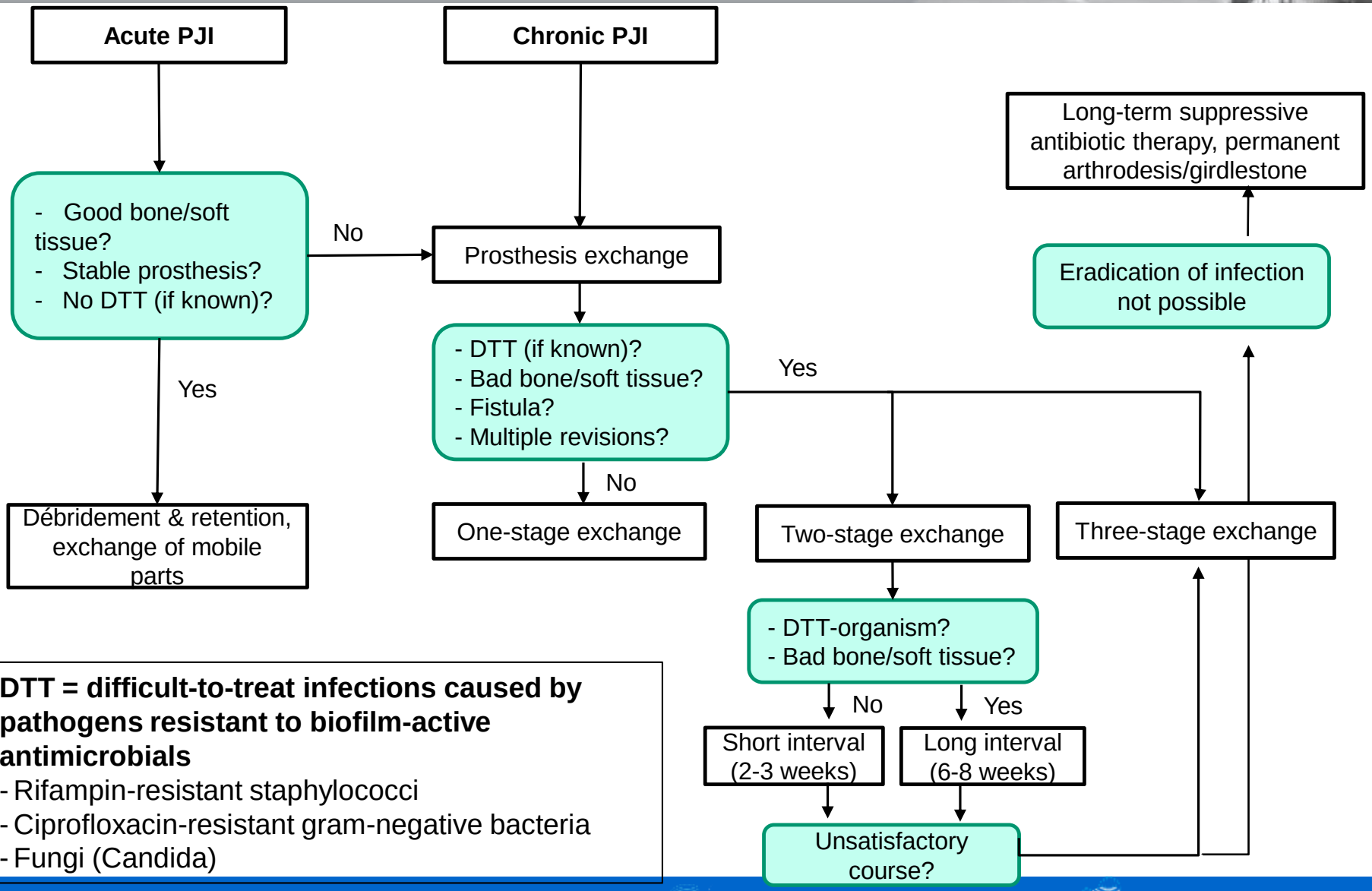
Acute: change of mobile parts
Chronic: Change of prosthesis

+ Local antibiotic
+ Implant coating
+ Bacteriophage therapy

Classification: early – delayed – late



Treatment algorithm



DTT = difficult-to-treat infections caused by pathogens resistant to biofilm-active antimicrobials

- Rifampin-resistant staphylococci
- Ciprofloxacin-resistant gram-negative bacteria
- Fungi (Candida)

Acute infection

Prolonged discharge: early postoperative PJI?

- C-reactive protein (CRP) should decrease after surgery!
- Exclude other reasons of prolonged discharge (coagulopathy, hematoma, albumin deficiency)

→ revision surgery if prolonged secretion (>7 days)

Acute pain & fever, 10 y after implantation

Chronic infection

- 78-y-o female
- Primary hip prosthesis 4 months ago
- Since implantation pain, walking distance now 20 m
- CRP normal, no loosening on x-ray

Aspiration 4 months after implantation

Untersuchungsauftrag
Material:
Fragestellung: Allgemeine Bakteriologie

Mikroskopische Untersuchungen

Grampräparat	Leukozyten	mässig
	Mikroorganismen	nicht nachweisbar

Kulturelle Ergebnisse

1. **Staphylococcus epidermidis** nach Anreicherung

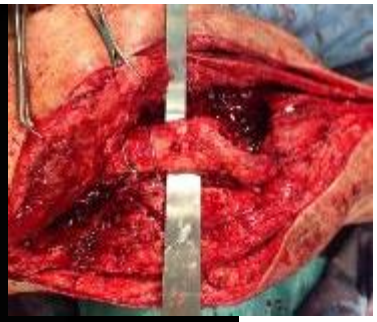
S = sensibel I = intermediär R = resistent f = folgt N = negativ P = positiv

	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

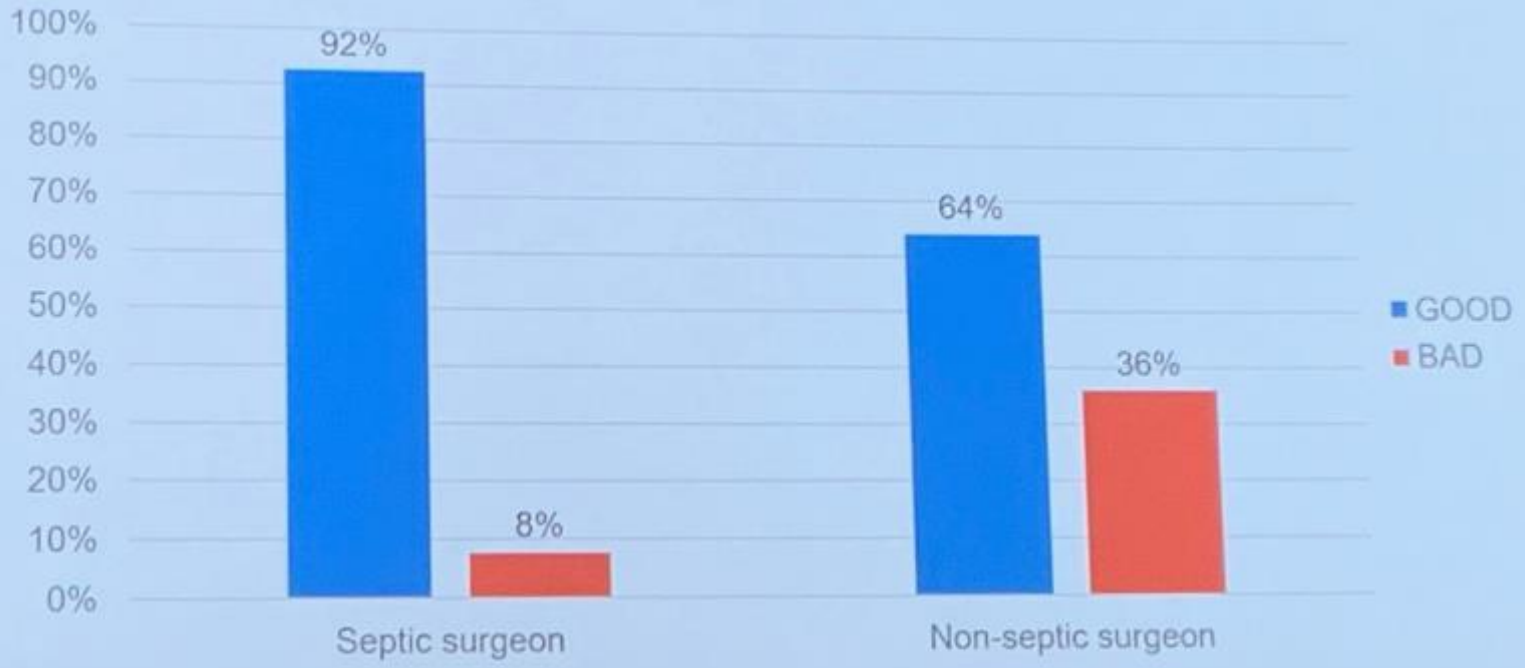
High leukocyte count in joint aspirate (59,000/µl)

validiert durch: Irene Grohsellus

Chronic: Removal of all foreign material



Results : Overall success rate

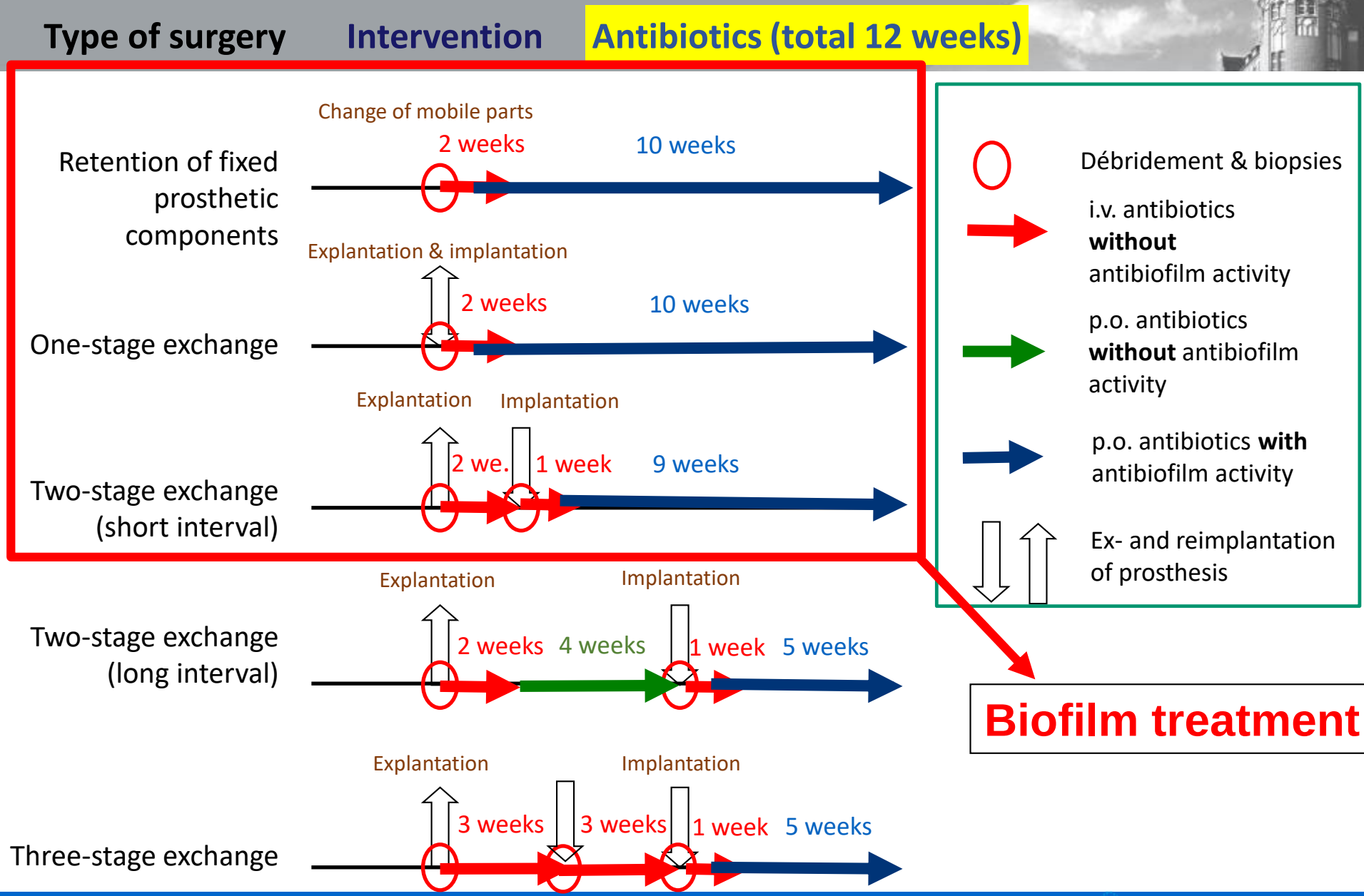


Non-septic surgeons have a higher failure rate ($p < 0.05$)

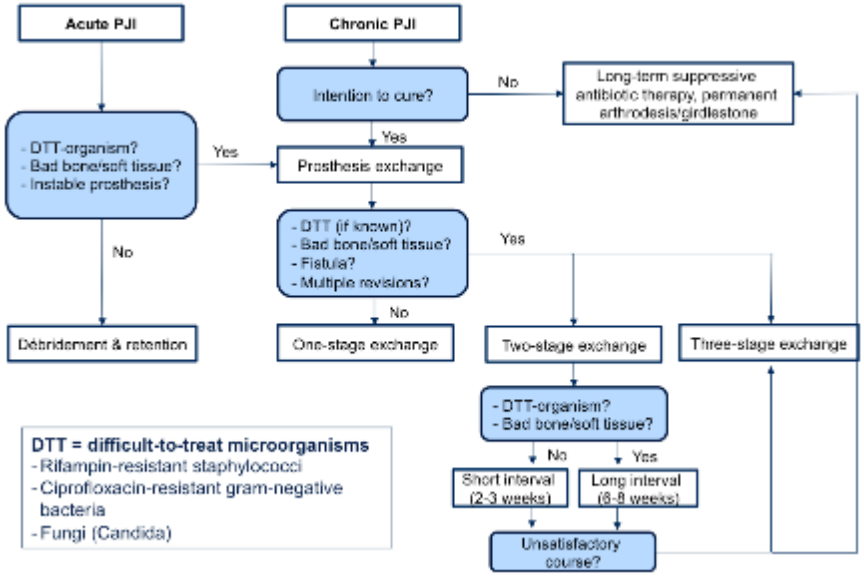
The European Bone & Joint Infection Society

Borens O. Presented at EBJIS in Antwerpt, September 2019

Surgical procedures



Aim of PJI-algorithm



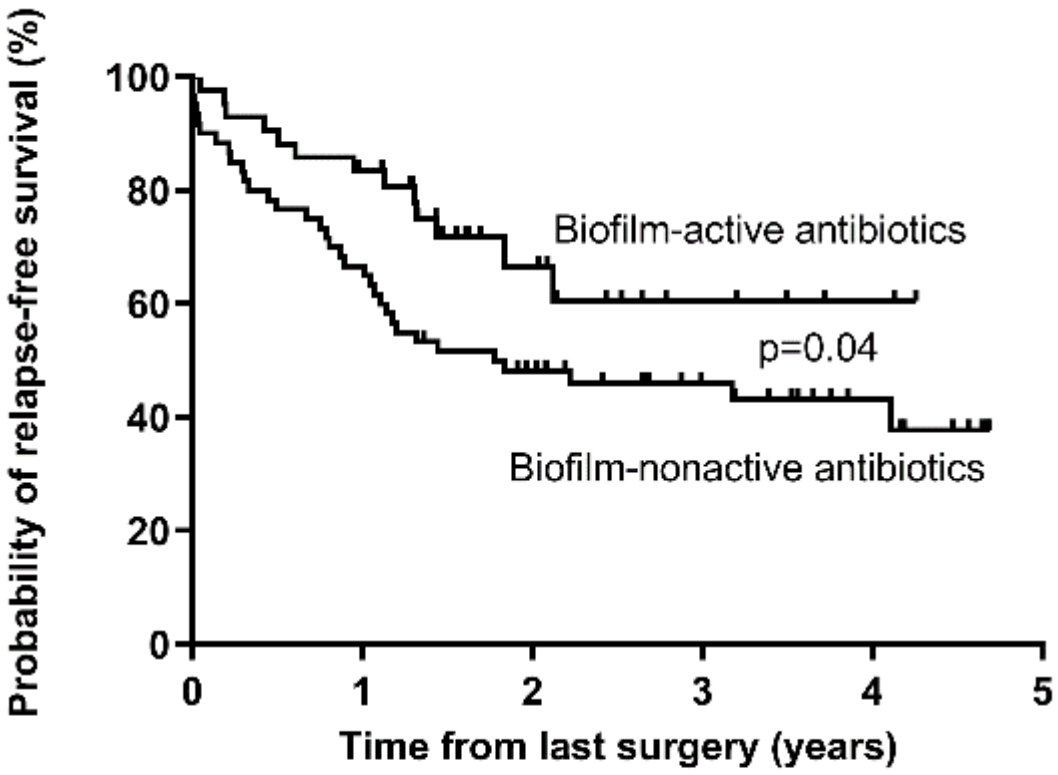
To select the

- **least invasive** treatment option depending on the present features
- with the **best functional result**
- without compromising the cure rate!

Prosthetic join infection: Outcome

Variable	Long interval w/o optimal AB (n =19)	Long interval with optimal AB (n =19)	Short interval with optimal AB (n = 19)
Patient age (years)	68,5 ± 7,7	68,6 ± 14,4	65,4 ± 9,6
Duration from implantation to infection (years)	**3,2 ± 3,0**	**5,7 ± 5,1**	**4,2 ± 3,9**
Interval from explantation to reimplantation	66,7 ± 12,8	66,7 ± 38	15,9 ± 5,8
Length of hospital stay (days)	25,7 ± 8,6	30 ± 10	30 ± 7
Follow-up (months)	25,2 (7-68)	18,3 (6–29)	17,8 (8-19)
Aufenthalt in Geriatrie im Intervall (d)	204	210	0
Relapse of the infection	**6 (32%)**	**1 (5%)**	**0 (0%)**
No. revisionens in interval (median)	2	2	0

Surgery without «proper» antibiotics



Number at risk						
Biofilm-active	43	33	13	5	2	0
Biofilm-nonactive	60	40	26	16	8	0

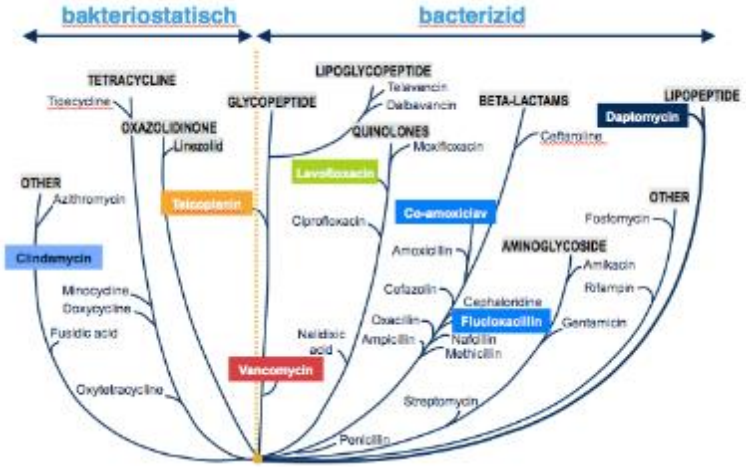
Biofilm-active antibiotics improved outcome of knee PJI:

6-year prospective cohort with 103 patients

Gellert M, Hardt S et al. IJAA 2019 (in press)

Properties of antibiotics

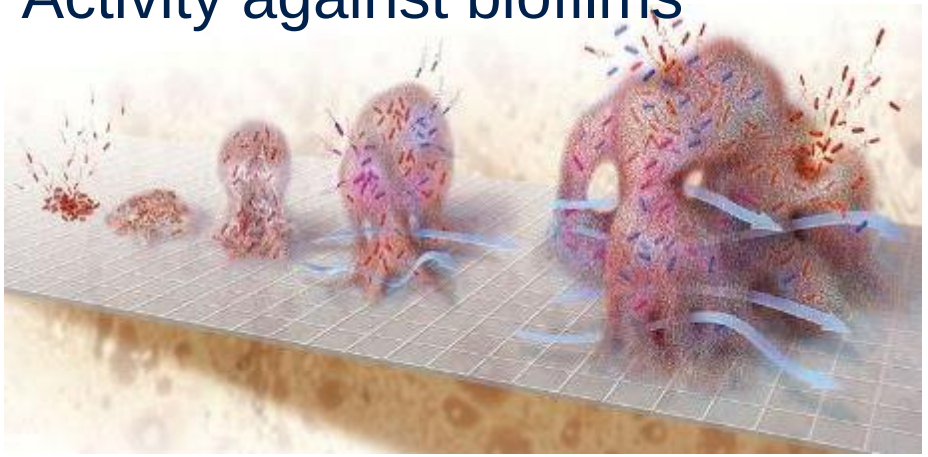
Bactericidal activity



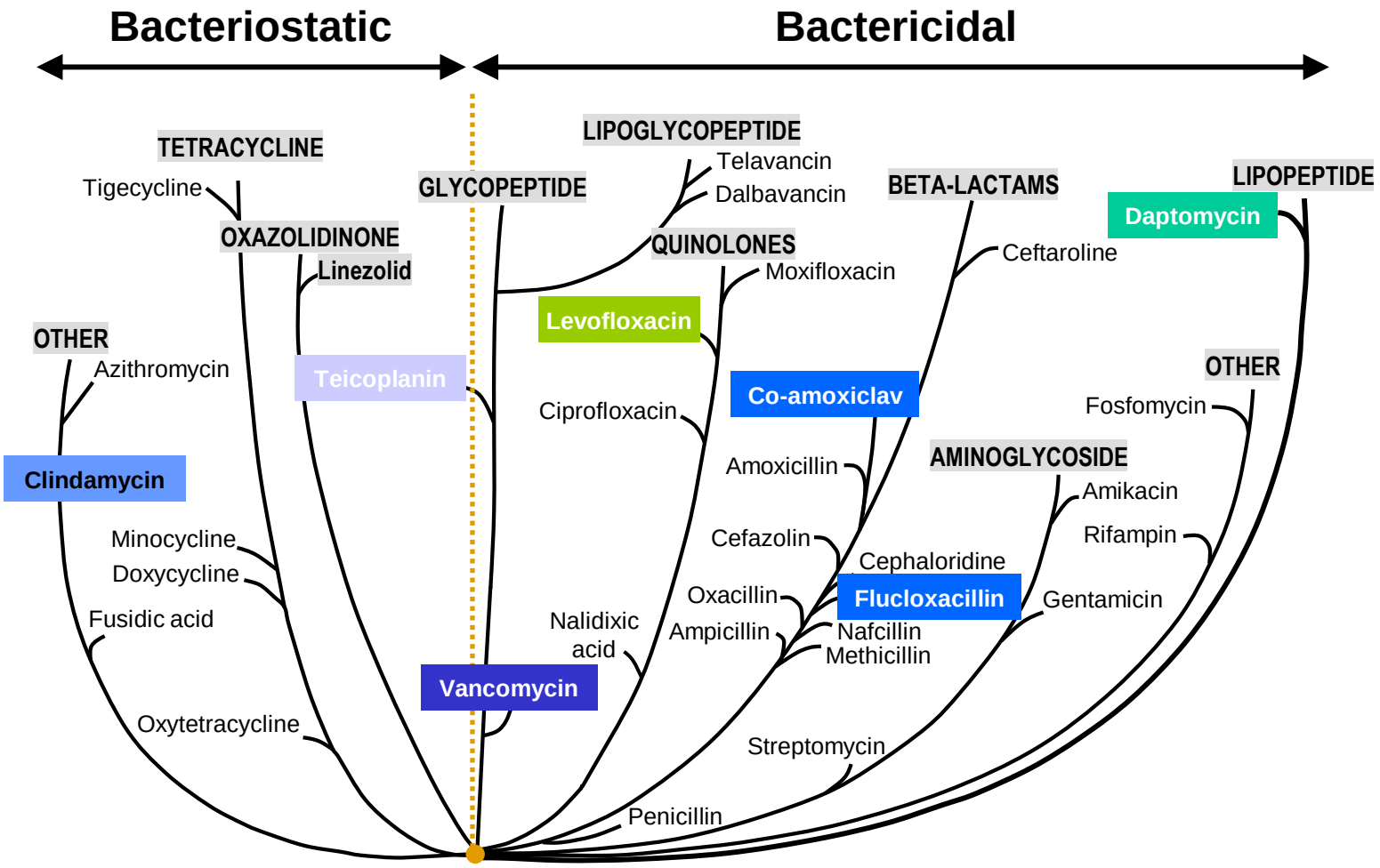
Good oral bioavailability

Good bone penetration

Activity against biofilms



Activity of antibiotics



Rolinson GN. *Int J Antimicrob Agents* 2007;29:3–8

Switch to oral treatment after surgery

When...

... CRP is nearly normalized

... wound is closed and dry

... organism and its susceptibility is known

→ usually after 1-2 weeks

How much ends up in the bone?

Drug	Oral bioavailability	Bone penetration
Ampicillin/Sulbactam	50%	7%
Cefuroxim, cefadroxil	50%	12%
Levofloxacin	100%	77%
Rifampin	80%	51%
Cotrimoxazole	85%	55%
Clindamycin	90%	45%
Linezolid	100%	85%

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

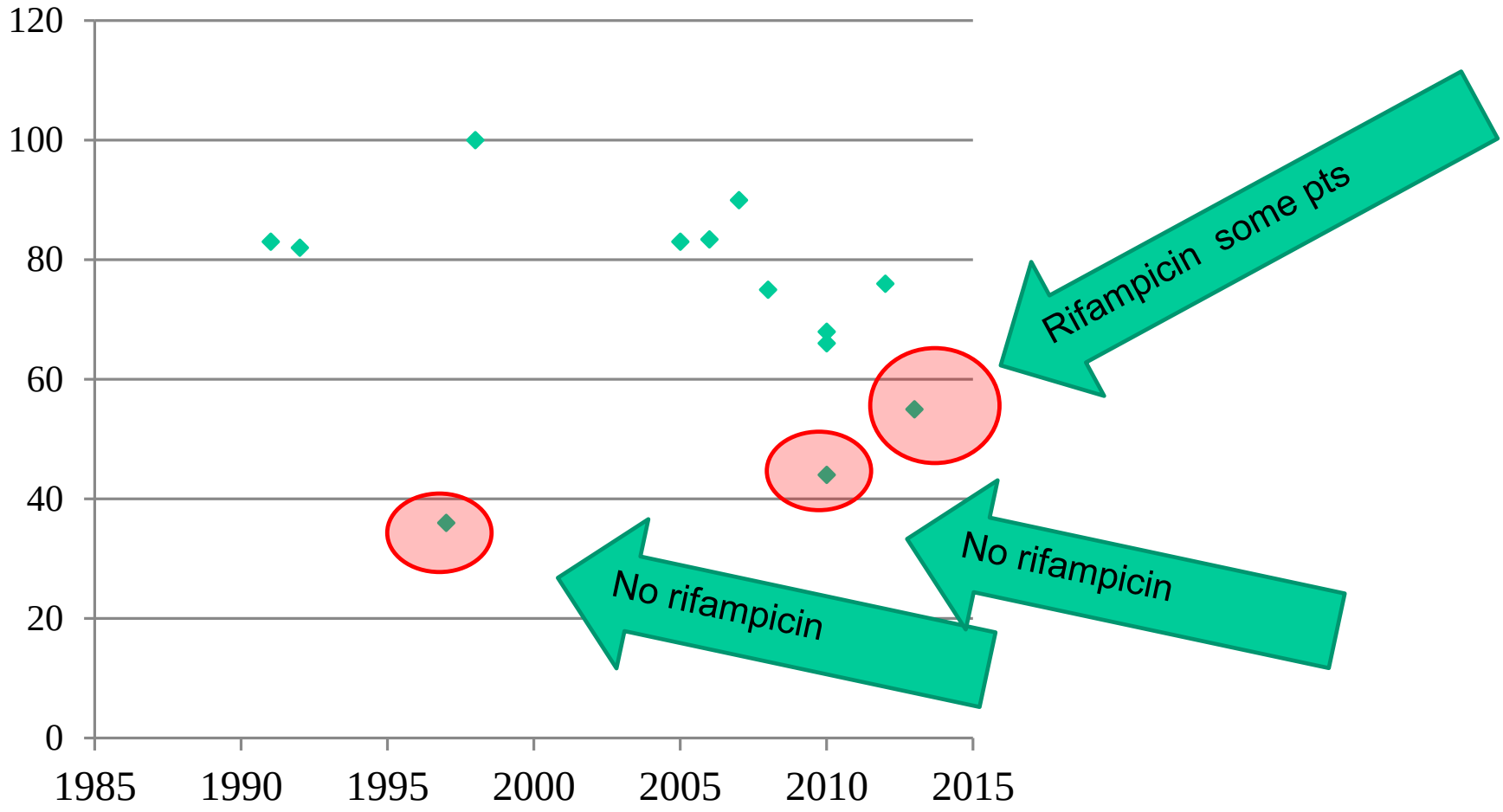
Antibiotics with biofilm-activity

- **Staphylococci**: rifampin (in combination)
- **Gram-negative rods:** ciprofloxacin
- **Streptococci:** penicillin G or ceftriaxon (then amoxicillin p.o.)
- **Enterococci**: ampicillin/amoxicillin + fosfomycin + gentamicin

Rifampin – precious but delicate

Role of rifampicin in staphylococcal PJI

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



Rifampin: Quick emergence of resistance

Do not use:

- Before surgery
- In the interval before re-implantation of prosthesis
- In open wounds
- As single antibiotic (monotherapy)

Strategy: long interval (6 weeks)

No prosthesis	Prosthesis
Osteomyelitis therapy = Suppression	Biofilm-active therapy = Eradication
No rifampin during interval!	rifampin

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

Therapy during interval: suppression

- Aim: suppression of the infection (no eradication)

- used substances:

Organism	substance
Staphylococci	Cotrimoxazol, Doxycyclin, Clindamycin
Streptococci	Amoxicillin, Clindamycin, Levofloxacin
Enterococci	Amoxicillin, (Linezolid)
Anaerobes	Clindamycin, Amoxicillin, Metronidazole
Gram negative organisms	Ciprofloxacin, Cotrimoxazol

- Seamless intake until implantation (no drug holidays)

Pocket Guide: www.pro-implant-foundation.org

Pocket Guide zur Diagnostik und Behandlung von periprothetischen Infektionen

PRO-IMPLANT FOUNDATION

Version 8
01. Oktober 2018

Individuelle Beratung über das Onlineportal: cs.pro-implant-foundation.org
PRO-IMPLANT Workshops: www.pro-implant-foundation.org

DEFINITION

Vorliegen einer periprothetischen Infektion, wenn ≥1 Kriterium erfüllt ist:

Untersuchung	Kriterium	Sensitivität	Spezifität
Klinik	Fistel oder Eiter um die Prothese[a]	20-30%	100%
Leukozytenzahl im Punktat[b]	>2000/µl Leukozyten oder >70% Granulozyten (PMN)	≈90%	≈95%
Histologie	Entzündung im periprothetischen Gewebe[c]	73%	95%
Mikrobiologie	Erregernachweis in • Synovialflüssigkeit oder • ≥2 Gewebeproben[d] oder • Sonikat ≥ 50 Kolonien/ml[e]	45-75% 60-80% 80-90%	95% 92% 95%

[a] Bei der Metall-Metall Gleitpaarung kann Eiter durch Abrieb simuliert werden („Pseudopus"), die Leukozytenzahl ist normal oder erhöht (Metalldebris sichtbar)
[b] Bei rheumatischer Arthropathie, Luxationen, periprothetischer Fraktur, Vorliegen einer Fistel und 6 Wochen postoperativ nicht verwertbar. Die Leukozytenzahl sollte innerhalb von 24 Stunden bestimmt werden (Mikroskopie oder automatisierte Auszählung); geronnene Proben werden mit 10 µl Hyaluronidase versetzt
[c] entspricht Typ 2 oder 3 nach Krenn und Morawietz (≥23 Granulozyten/10 HPF)
[d] Bei hoch-virulenten Erregern (z.B. *S. aureus*, *E. coli,* streptococci) oder Patienten unter Antibiotika ist der Nachweis in einer Gewebeprobe signifikant
[e] Unter Antibiotikatherapie, bei *S. aureus* und Anaerobiern können schon <50 Kolonien/ml relevant sein

Pocket Guide zur Diagnostik und Behandlung von Implantat-assoziierten Infektionen nach Frakturversorgung

PRO-IMPLANT FOUNDATION

Version 3
01. Oktober 2018

Nutzen Sie für individuelle Empfehlungen das Beratungsportal unter: cs.pro-implant-foundation.org.
Besuchen Sie unseren Workshop: www.pro-implant-foundation.org.

DEFINITION

	Untersuchung	Kriterium	
Infektion möglich	Anamnese	• Ruhe-/Nachtschmerz • prolongierte Wundsekretion • Revisionen und Antibiotikatherapien postoperativ	
	Bildgebung	• Infektionskallus • Sequester • Osteolysen	• Implantatlockerung • Pseudarthrose • Sklerosen
Infektion bestätigt[1]	Klinik	• Fistel • Pus/sichtbares Implantat • Positive „probe to implant"	
	Histologie	Entzündung im periimplantären Gewebe (>5 Neutrophile pro Gesichtsfeld bei 400x Vergrösserung)	
	Mikrobiologie	Erregernachweis in: • ≥2 periimplantären Gewebeproben[2] • Sonikationsflüssigkeit (≥ 50 KBE/ml)[3]	

[1] Bei mind. einem erfüllten Kriterium ist die Infektion bestätigt
[2] Bei hoch-virulenten Erregern (z.B. *S. aureus, E. coli*) und Patienten unter Antibiotika ist bereits der Nachweis in einer Gewebeprobe für die Diagnose der Infektion ausreichend
[3] Unter Antibiotikatherapie, bei *S. aureus* und Anaerobiern können schon <50 Kolonien/ml relevant sein

Vodič za dijagnostiku i liječenje periprostetičkih zglobnih infekcija (PZI)

PRO-IMPLANT FOUNDATION

Verzija 7: Studeni 2017

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Za više informacija prijavite se na našu radionicu: www.pro-implant-foundation.org/events/workshops

DEFINICIJA

Periprostetička zglobna infekcija, kada je ≥1 uvjeta ispunjeno:

Test	Kriterij	Osjetljivost	Specifičnost
Klinička slika	Sinus trakt (fistula) ili pojava gnojne sekrecije oko endoproteze[a]	20-30%	100%
Broj leukocita u sinovijalnoj tekućini[b]	> 2000/µl leukocita ili > 70% granulocita (PMN)	≈90%	≈95%
Histologija periprostetičkog tkiva[c]	Upala (≥23 granulocita na 10 puta uvećanom polju)	73%	95%
Mikrobiologija	Rast mikroorganizama: • U sinovijalnoj tekućini ili • ≥2 uzorka tkiva[d] ili • U sonifikacijskoj tekućini (>50 CFU/ml)[e]	45-75% 60-80% 80-90%	95% 92% 95%

[a] Endoproteze s nosećim dodirnim površinama metal-metal mogu oponašati stvaranje gnojnog sadržaja («pseudognoj»), broj leukocita je uglavnom normalan (metaloza)
[b] Broj leukocita može biti povišen do 6 tjedana nakon operacijskog zahvata bez infekcije, kod reumatoidnog artritisa (uključujući pseudogiht), periprostetičkog prijeloma ili iščašenja. Broj leukocita u uzorku potrebno je odrediti najkasnije 24h po aspiraciji korištenjem mikroskopa ili automatskog brojača; za razrjeđivanje uzorka moguće je dodati 10 µl hijaluronidaze)
[c] Klasifikacija po Krenn i Morawietz-u: PZI odgovara tipu 2 ili tipu 3
[d] Za izrazito virulentne organizme (npr. *S. aureus*, streptococci, *E. coli*) ili za bolesnike na antibiotskoj terapiji, dovoljan je jedan uzorak koji potvrđuje dijagnozu PZI
[e] Na antibiotskoj terapiji, za *S. Aureus i anaerobe*, <50 CFU/ml može biti značajno

Vodič za dijagnostiku i liječenje infekcija povezanih s implantatom nakon fiksacije prijeloma

PRO-IMPLANT FOUNDATION

Verzija 2: Listopad 2017

Za detaljne preporuke možete nas kontaktirati na adresi:: cs.pro-implant-foundation.org
Za više informacija prijavite se na našu radionicu: www.pro-implant-foundation.org/events/workshops

DEFINICIJA

	Test	Kriterij
Sumnja na infekciju	Anamneza	• Bol u mirovanju/po noći • Produžena sekrecija rane • Revizija ili antibiotska terapija postoperativno
	Radiološke pretrage	• Inficirani kalus • Sekvestar • Osteoliza • Razlabavljenje implantata • Pseudartroza • Kortikalna skleroza
Potvrđena infekcija	Klinička slika	• Sinus trakt (fistula) • Vidljiva gnojna sekrecija oko implantata • Pozitivan test sondom za ispitivanje implantata
	Histologija	Infekcija peri-implantatskog tkiva (>5 neutrofila na 400x uvećanom polju)
	Mikrobiologija	Rast mikroorganizama: • ≥2 uzorka peri-implantatskog tkiva[2] • U sonifikacijskoj tekućini (≥ 50 CFU/ml)[3]

[1] Ispunjenje već 1 kriterija potvrđuje infekciju
[2] Za izrazito virulentne organizme (npr. S. aureus, streptococci, E. coli) ili za bolesnike na antibiotskoj terapiji, dovoljan je jedan uzorak koji potvrđuje dijagnozu
[3] Na antibiotskoj terapiji, za S. Aureus i anaerobe, <50 CFU/ml može biti značajno

Pocket Guide: www.pro-implant-foundation.org

Pocket Guide zur Diagnose & Behandlung von Wirbelsäuleninfektionen

PRO-IMPLANT FOUNDATION

Version 1: 1. März 2018

Nutzen Sie für individuelle Beratungen das Onlineportal unter: cs.pro-implant-foundation.org.

DEFINITION

Spondylodiszitis ist bestätigt, wenn alle 3 Kriterien vorhanden sind:

Test	Kriterium
Klinik	Akute oder chronische Rückenschmerzen
Bildgebung	Computertomographie (CT) oder Magnetresonanztomographie (MRI) vereinbar mit Spondylodiszitis
Mikrobiologie oder Histologie	Erregernachweis in der Blutkultur oder Gewebe des Wirbelkörpers oder Diskus[1] Akute oder chronische Entzündung im Gewebe

Spondylodese-assoziierte Infektion ist bestätigt, wenn ≥1 Kriterium vorhanden ist:

Test	Kriterium
Klinik	• Fistel oder Wunddehiszenz • Sichtbarer Eiter • Positiver „probe-to-implant" Test
Histologie	Entzündung im peri-implantären Gewebe
Mikrobiologie	Signifikanter Erregernachweis[2] in: • ≥2 peri-implantären Gewebeproben • Sonikat (≥ 50 KBE/ml)

[1] Niedrig-virulente Hauterreger müssen im klinischen Kontext (vorherige Infiltrationen? Intravaskuläres Device in situ?) interpretiert werden

[2] Für hoch-virulente Erreger (z.B. *S. aureus, E. coli*, Streptokokken) oder Patienten unter Antibiotikatherapie reicht eine positive Probe aus bzw. kann ein Sonikationsresultat mit <50 KBE/ml signifikant sein.

Suggestive Kriterien für Infektion:	
• Prolongierte Wundsekretion	• Schrauben-/Implantatlockerung
• Sekundäre Wunddehiszenz	• Pseudarthrose

Pocket Guide für Diagnostik & Behandlung von Intra-kraniellen Neurochirurgischen Infektionen

PRO-IMPLANT FOUNDATION

Version 1: 1 Mai 2019

KLASSIFIKATION nach betroffenem Gewebe/Fremdkörper

Gruppe	Infektionstyp
Extradurale Infektionen	• Knochendeckelinfektion (mit Fixationsmaterial)
	• Kranioplastikinfektion (PMMA, PEEK, Titan, Keramik)
	• Postoperatives Epiduralempyem (mit / ohne Duraplastik)
Intradurale Infektionen	• Postoperative Meningitis
	• Postoperativer Hirnabszess
	• Postoperatives Subduralempyem (mit/ohne Duraplastik)
Andere Device-assoziierte Infektionen	• Ventrikuloperitoneal (VPS)- / Ventrikuloatrialshunt (VAS)-Infektion
	• Externe ventrikuläre oder lumbale Drainage (EVD/ELD)-Infektion
	• Neurostimulator-Infektion

[1] Nahtmaterial gilt nicht als Fremdmaterial

KLASSIFIKATION nach Zeitpunkt des Auftretens[2]

	Frühe Infektion (akut)	Verzögerte / späte infektion (chronisch)
Zeitpunkt	≤ 6 Wochen nach Implantation	> 6 Wochen nach Implantation
Biofilm	"Unreif"	"Reif"
Chirurgisches Prinzip	Débridement und Erhalt des Implantates möglich	Entfernung oder Wechsel des Implantates notwendig (1- od. 2-zeitig)

[2] Nur für implantat-assoziierte Infektionen (mit Biofilmen) relevant

Abkürzungen:	
EVD/ELD: Externe ventrikuläre/lumbale Drainage	PMMA: Poly-Methyl-Methacrylate
VPS/VAS: Ventrikuloperitoneal-/Ventrikuloatrialshunt	PEEK: Polyether Ether Ketone
	ZNS: Zentrales Nervensystem

Hinweis: Viele Empfehlungen basieren auf Expertenmeinung, da keine soliden klinischen Daten vorliegen und die Durchführung dafür designter Studien schwierig ist. Der Pocket Guide soll eine praktische Hilfe für die klinische Praxis sein.

Vodič za dijagnostiku i liječenje infekcija kralješnice

PRO-IMPLANT FOUNDATION

Verzija 1: Studeni 2019

Za detaljne preporuke možete nas kontaktirati na adresi: cs.pro-implant-foundation.org

DEFINICIJA

Osteomijelitis kralješnice, ukoliko su 3 uvjeta ispunjena:

Test	Kriterij
Klinička slika	Akutna ili kronična bol u leđima
Dijagnostika	Kompjuterizirana tomografija (CT) ili magnetska rezonancija sugestivna za osteomijelitis kralješnice
Mikrobiologija ili Histologija	Rast mikroorganizama na hemokulturi ili tkivu kralješnice[1] Akutna ili kronična upala tkiva kralješnice

Infekcija kralješnice povezana s implantatima, ukoliko je ≥1 kriterij ispunjen:

Test	Kriterij
Klinička slika	• Poremećaj cijeljenja rane ili fistula • Vidljiva gnojna sekrecija oko implantata • Pozitivan test sondom za ispitivanje implantata
Histologija	Upala u peri-implantatskom tkivu
Mikrobiologija	Signifikantan rast mikroorganizama[2] u: • ≥2 uzorka peri-implantatskog tkiva • Sonifikacijskoj tekućini (≥ 50 CFU/ml)

[1] Nisko virulentni kožni patogeni moraju se interpretirati u kliničkom kontekstu (prethodne infiltracije? Prisutan intravaskularni implantat?)

[2] Za visoko virulentne mirkoorganizme (npr. *S. aureus, E. coli*, streptococci) ili u pacijenata s antibiotskom terapijom se već jednom pozitivnom kulturom dokazuje infekcija te sonifikacija <50 CFU/ml može također biti signifikantna

Potporni kriteriji za infekciju:

- Produžena sekrecija rane
- Sekundarna dehiscencija rane
- Razlabavljenje implantata/vijaka
- Pseudartroza

EFORT open reviews

Periprosthetic joint infection: current concepts and outlook

Petra Izakovicova[1]
Olivier Borens[2]
Andrej Trampuz[3]

EFORT Open Rev 2019;4:468-475.

CONSULTATION SERVICE PORTAL

cs.pro-implant-foundation.org

PRO-IMPLANT
FOUNDATION

CENTRUM MUSKULO SKELETALE CHIRURGIE

CHARITÉ

Consultation Portal

One Case Consultation FREE OF CHARGE

Coupon valid during introductory period
(from 11 September through 30 November 2019)

How does the PRO-IMPLANT Consultation Portal work?

1. Register first at: www.pro-implant-foundation.org
2. Choose: "Consultation Portal"
3. Click on "Purchase" and choose "SC-1 (single case)"
4. Apply Coupon-Code: **CP-FREE**
   Free coupon is only applicable for SC-1 (single case)
5. Follow further steps
6. Click "Add New Case"

CENTRUM MUSKU

CHARITÉ

Consultation service: www.pro-implant-foundation.org

THE CONSULTATION SERVICE IS PROVIDED BY AN INTERDISCIPLINARY TEAM:

We provide practical advice on diagnosis, prevention and treatment of implant-associated infections, based on current knowledge and scientific evidence

- INFECTIOUS DISEASES SPECIALISTS
- ORTHOPEDIC AND TRAUMA SURGEONS
- MICROBIOLOGISTS AND PHARMACISTS

AVAILABILITY AND PRICE:

During the test period, the consultation service is free of charge. Further information is available at **cs.pro-implant-foundation.org.**

LEGAL DISCLAIMER:

PRO-IMPLANT Foundation accepts no liability for the content or the consequences of any actions taken on the basis of the advice provided. The received information is treated confidentially.

CONSULTATION REQUESTS ARE SUBMITTED THROUGH WEB-BASED PORTAL OR BY PHONE

Register first at the PRO-IMPLANT website free of charge: www.pro-implant-foundation.org

1. Log-in on the Consultation Service portal
2. Enter relevant patient information
3. Optional: upload images or files

WEB CONTACT

Reply is provided **within 24 hours** on weekdays.

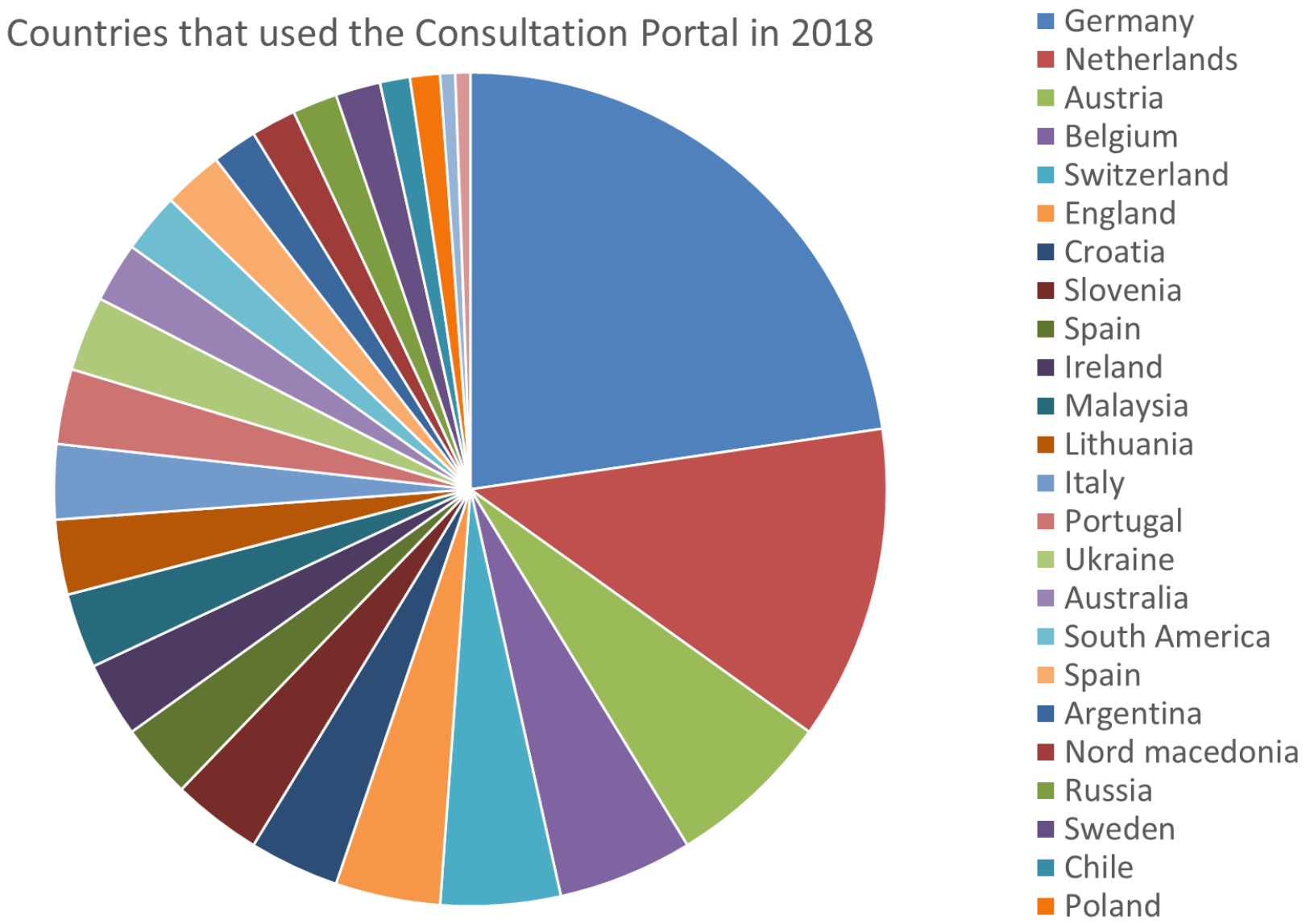
PHONE CONTACT

Available on weekdays, from 8 am to 6 pm.

CENTRUM MUSKULO SKELETALE CHIRURGIE

CHARITÉ

Year 2018: 3267 consultations



Goals of the presentation

Infection is the best possible complication, if…

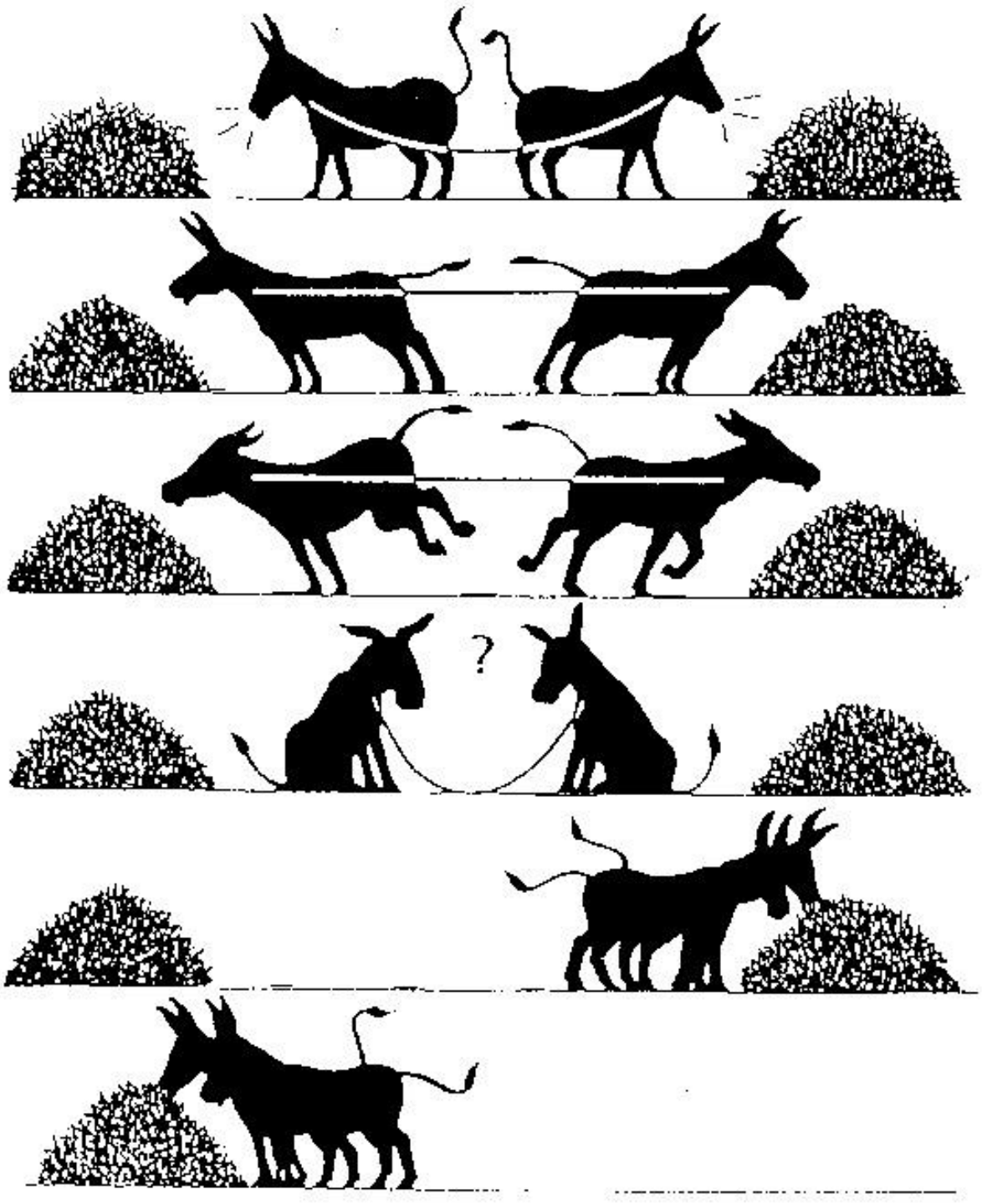
…appropriate diagnostic is combined with

…correct surgery and

…efficient anti-biofilm agents.

Cure rate >90%

Infection is the best possible complication



Thank you

andrej.trampuz@charite.de

Focus on implant, bone and joint-associated infections:

- Surgery: New concepts (retention, 1-stage, 2-stage short interval)
- Diagnosis: Fast innovative methods
- Antibiotics: Active against biofilms

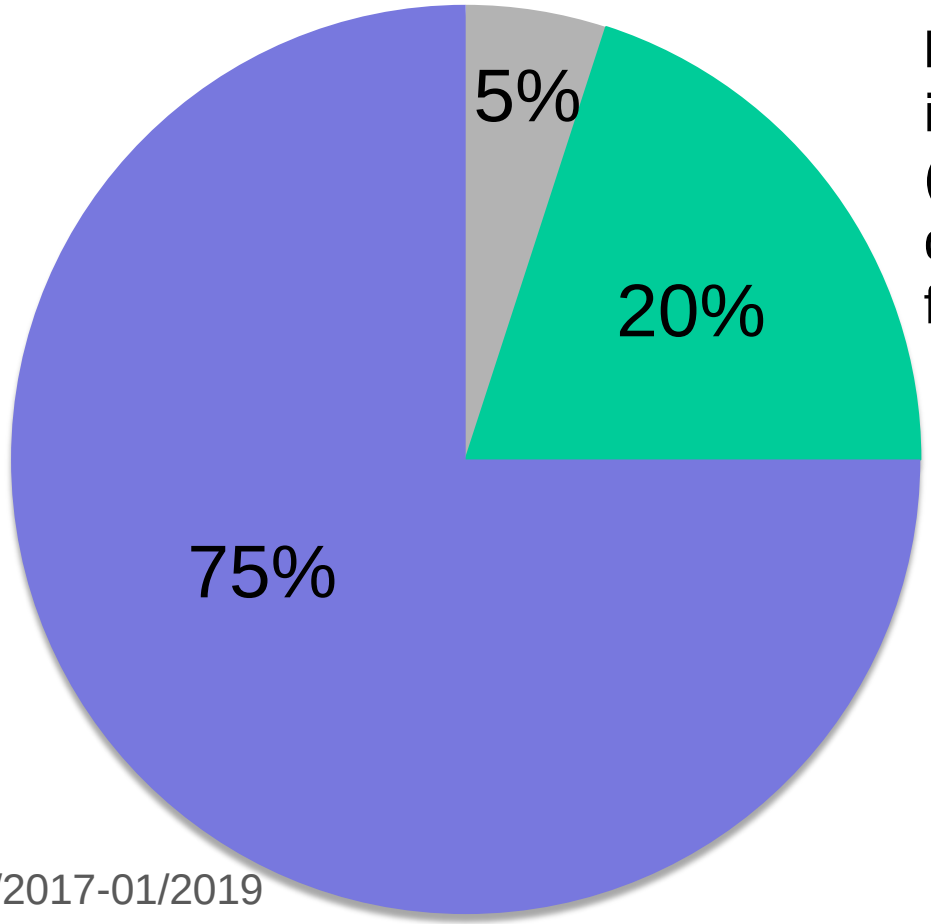
CENTRUM MUSKULO SKELETALE CHIRURGIE

CHARITÉ

Future developments and outlook

Pathogenesis of PJI

Contiguous spread from adjacent infected tissue



Hematogenous infection (spread from a distant infection focus)

Postoperative infection

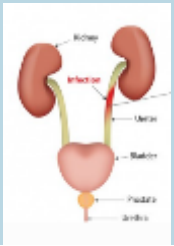
PJIs treated at Charité, 01/2017-01/2019

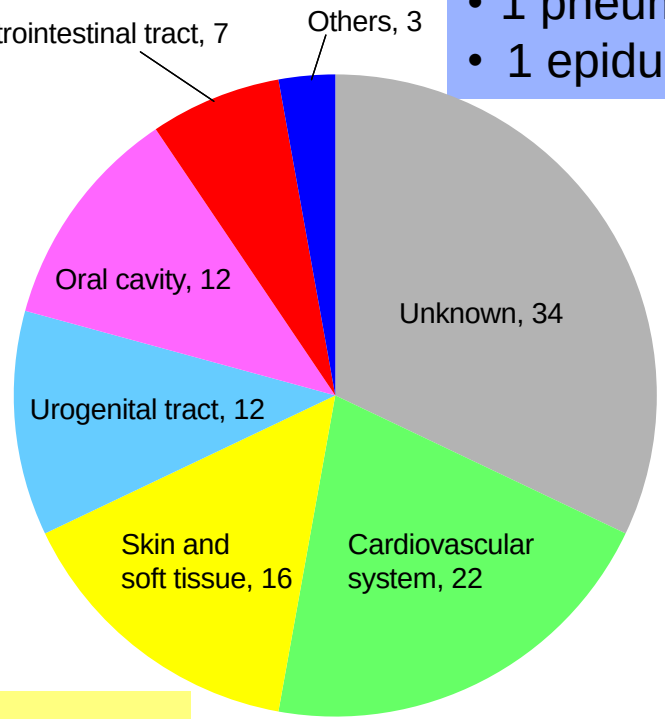
Primary foci: cohort of 106 episodes

- 1 (+3?) colon adenoma
- 1 GI bleeding
- 2 GI infections

- 7 dental treatments
- 5 dental infections

- 2 manipulations
- 10 infections





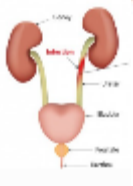
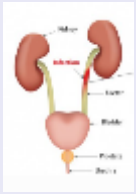
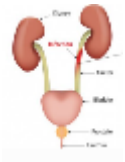
- 1 contralat. PJI
- 1 pneumonia
- 1 epidural abscess

- 9 skin erosion (pedicure, skin disease, chronic ulcers)
- 7 skin and soft tissue infections

- 14 endocarditis
- 5 infected CIED
- 3 catheter infections

Rakow A et al. CMI 2018

Investigation of cause

Pathogen	Source	Diagnostics
Staphylococci	  	Blood cultures Echocardiography (TEE) Skin examination
Streptococci • S. oralis/mitis	 	Orthopantomogram (OPTG), dentist, TEE
• S. agalactiae • S. dysgalactiae	   	Urinanalysis, imaging abdomen, skin examination, OPTG
• S. bovis/gallolyticus		Colonoscopy
Enterococci	  	Urinanalysis, TEE
Enterobacteriaceae	 	Urinanalysis, CT Abdomen

Renz N., Chirurg, 2017

Alternative tests in synovial fluid?

Test		Sensitivity	Specificity
Alpha-defensin (lateral flow test)		67% Kasparek MF, JA 2016	93%
Leukocyte esterase		81% Wyatt MC, JBJS 2016	97%
D-Lactate		94% Karbysheva S, personal communication	98%
Multiplex-PCR		60% Morgenstern C, DMID, 2017	89%

Synovial fluid D-lactate

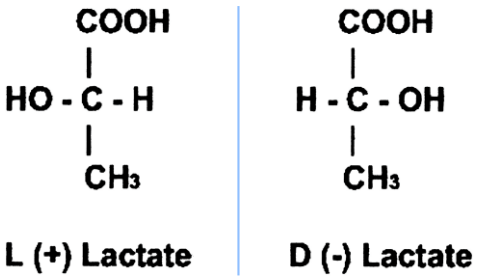
Lactic acid

L-lactate is constantly produced during metabolism and exercise

D-lactate is produced by bacteria as a product of bacterial fermentation

D-Lactate production in mammals is extremely low, with normal serum concentrations in the nano to micromolar range *(nMol - µMol)*.

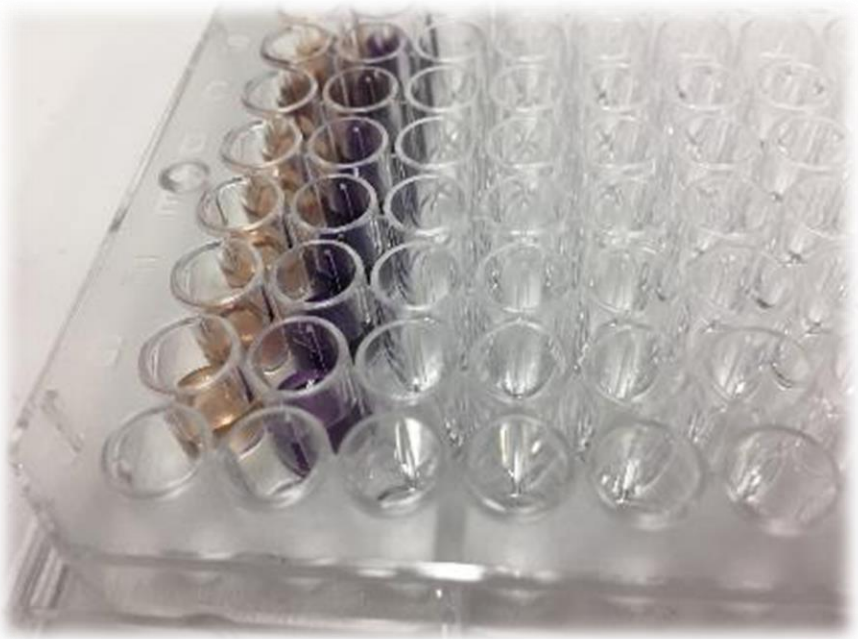
D-lactate concentration is increased to millimolar range *(mMol)* in bacterial infection.



L. Szalay 2003; Sh.M. Smith 994

Wellmer A. *2001; Gratacós J. 1995*

Synovial fluid D-lactate, a bacterial-specific marker



Measurement of *D-lactate*

- ✓ Volume of sample: 50 µl of synovial fluid
- ✓ Incubation: 30 min at +37^0 C
- ✓ Determination: standard microplate absorbance reader (λ = 570-600 nm)

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Performance of synovial fluid D-lactate for the diagnosis of periprosthetic joint infection: A prospective observational study

Katsiaryna Yermak[a,1], Svetlana Karbysheva[a,b,1], Carsten Perka[a], Andrej Trampuz[a,b,*], Nora Renz[a]

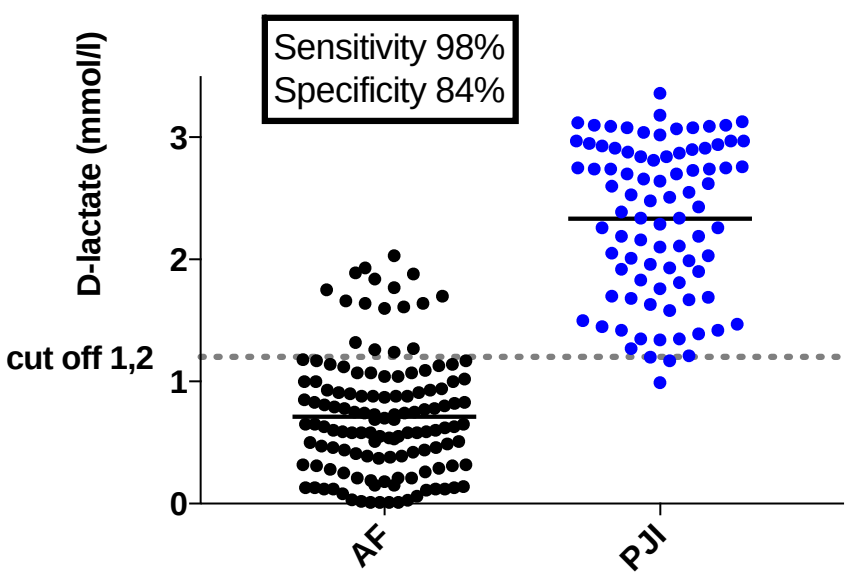
[a] *Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Center for Musculoskeletal Surgery (CMSC), Augustenburger Platz 1, D-13353 Berlin, Germany*

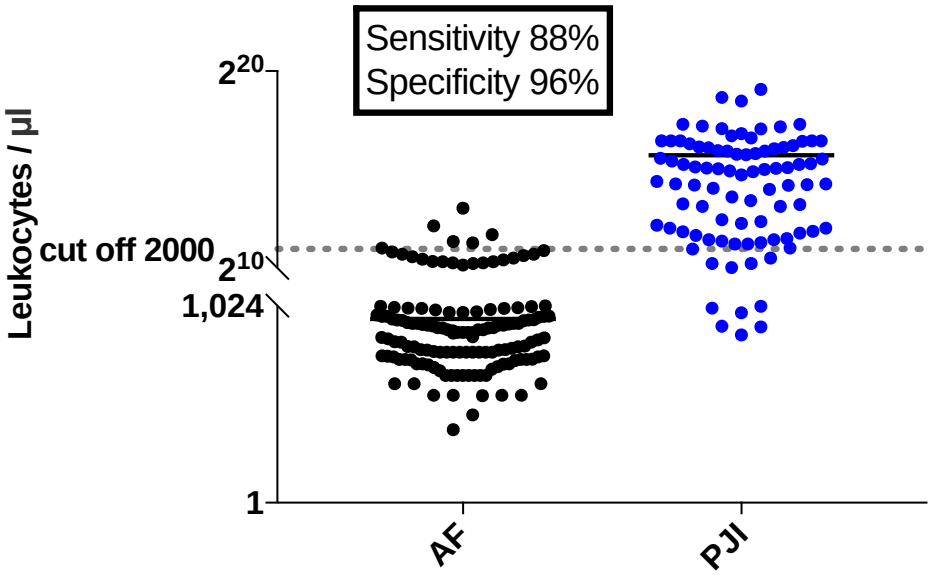
[b] *Berlin-Brandenburg Center for Regenerative Therapies, Charité – Universitätsmedizin Berlin, Germany*

Published August 2019

D-Lactate in synovial fluid of prosthetic joints

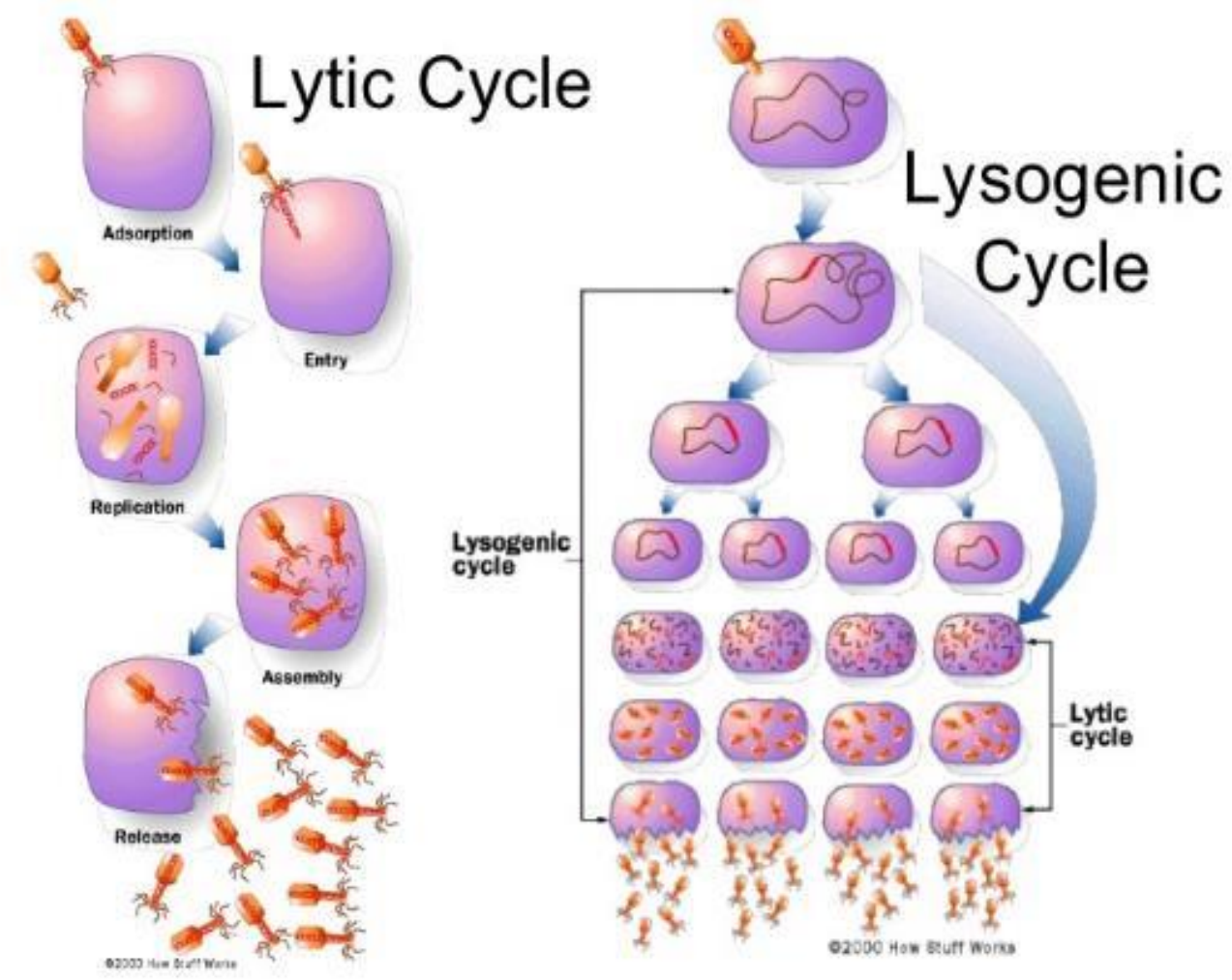
Concentration of SF D-lactate was significantly higher in patients with PJI compared to those with aseptic failure (p<0,0001)





SF D-lactate test had better sensitivity to confirm PJI (98%) compared to leucocytes (88%)

Virulent phages



DEFENSIE
LA DÉFENSE

VOORRANG AAN VREDE
PRIORITÉ À LA PAIX

Use of phages in military medicine

- **Red Army** (Finnish campaign and WWII)
- **German Army** (North Africa campaign)
- **British Army** in India
- **Japanese Army**
- **Chinese Army** (Korean War)

Anti-dysenterial phage preparations in first aid box

.be

ELIAVA institute, Tbilisi, Georgia

About 800 people used to work at the “Bacteriophage”, of whom 120 engaged in research.

During the Soviet period, the Eliava Institute elaborated novel biological preparations against: anthrax, rubies, tuberculosis, brucellosis, salmonellosis, dysentery.

After the collapse of the Soviet Union, the Institute was partly privatized.

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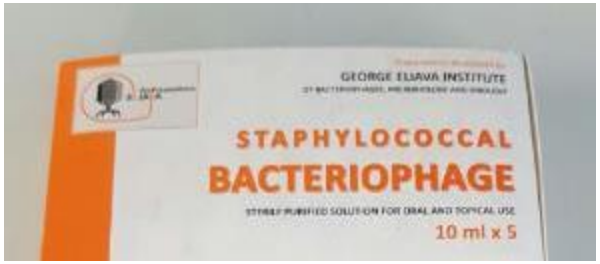
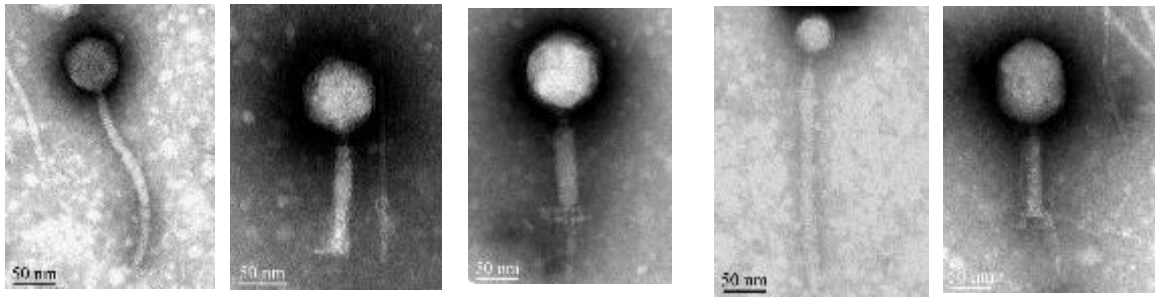
Sb-1 and Pyo-phage





CHARITÉ
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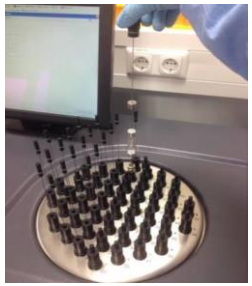
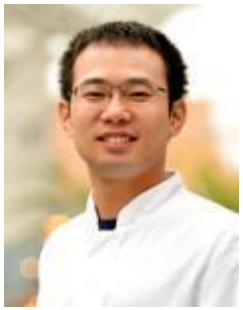
Projects with bacteriophages

1. Evaluating activity of **commercial phage preparations** vs. biofilm.
2. Evaluating best strategies for ***in vivo*** **administration** of phages.
3. Establishing ***ex vivo* & *in vivo*** **models** for evaluation of bacteriophages activity vs biofilm infections.
4. Creating a **phage libary**: Finding & isolating novel phages & select the best candidates for phage therapy.



Galleria mellonella ***in vivo*** **model**



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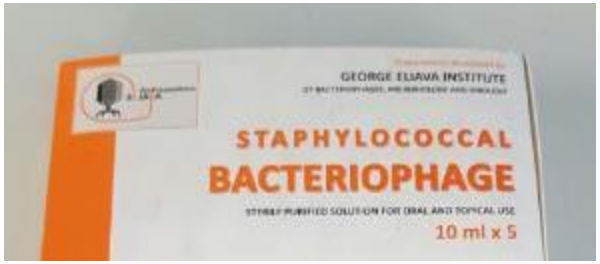
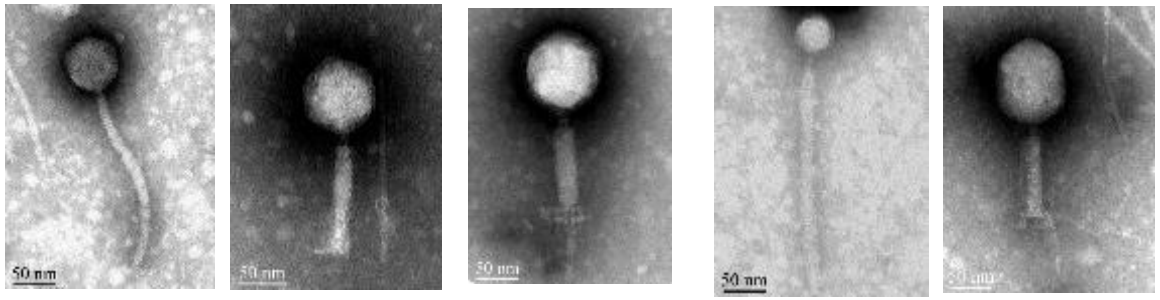
Sb-1 and Pyo-phage





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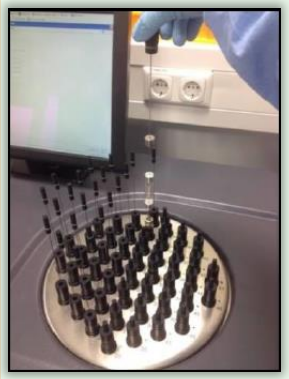
Anti-biofilm activity

10^6 CFUs/mL MRSA

Increasing PFUs/ml

Porous glass bead

24h
37° C

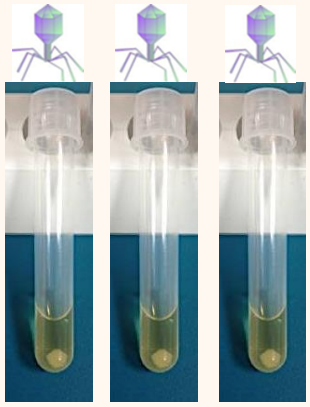


Biofilm **prevention**

10^6 CFUs/mL MRSA

Porous glass bead

24h
37° C



24h, 37° C

3x Wash

Biofilm **eradication**

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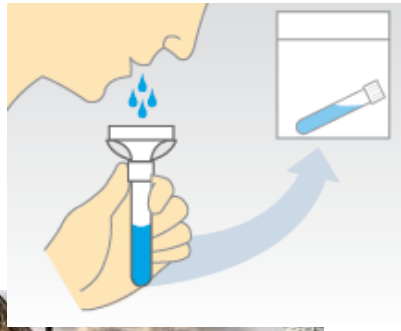
Phage isolation

- **Sources**: Human saliva, sewage, river water
- **Clinical strains used as hosts**: *S. aureus, S. epidermidis and E. coli strains* from PJI patients



Isolation of bacteriophages displaying lytic antibacterial activity from the plaque of lysis

Evaluation of the susceptibility of a panel of clinical isolates to newly isolated phages (spot-assay)

CHARITÉ

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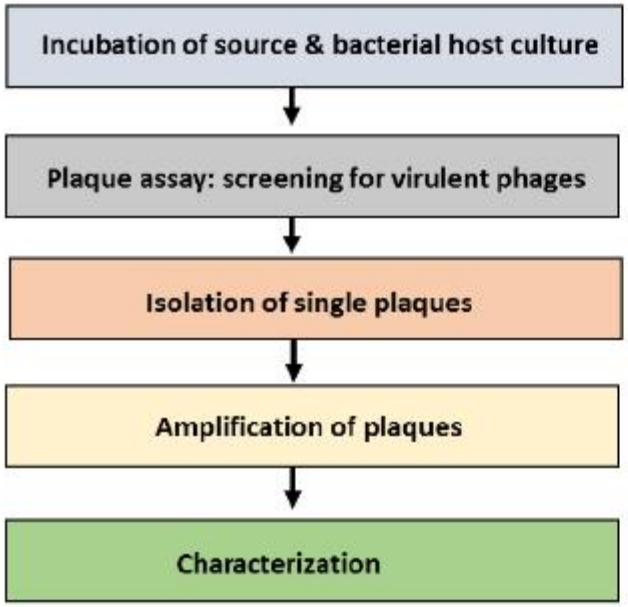
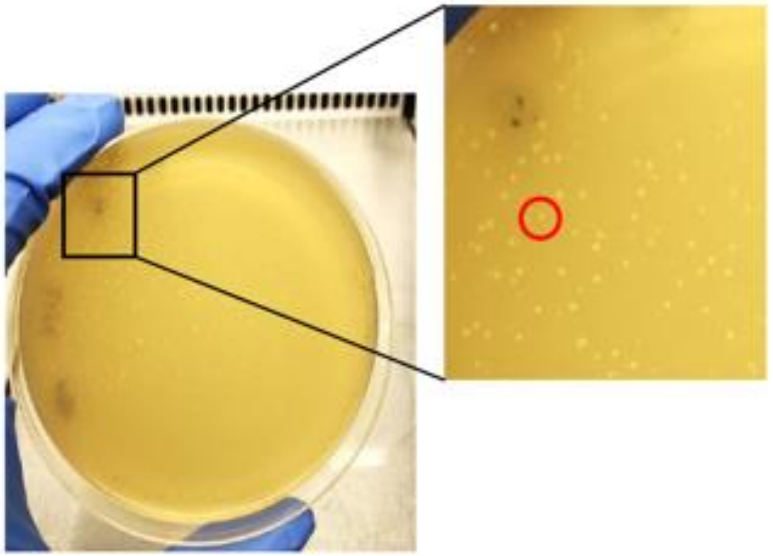
Plaque assay

- **Sources:** human saliva, sewage, river water
- **Bacterial host strains:** *S. aureus*, *S. epidermidis*, *E. coli* (laboratory strains & strains previously isolated from PJI)





In vitro activity of phages vs P.aeruginosa

Newly isolated phages

Staphylococcus aureus

Name	Source for isolation	Host strain
AbkG	Saliva (No.1)	MRSA ATCC 43300
AbkM	Saliva (No.2)	MRSA ATCC 43300
AbkA	Saliva (No.3)	MRSA ATCC 43300
AbkK	Saliva (No.4)	MRSA ATCC 43300
AbkE	Saliva (No.5)	MRSA ATCC 43300
AbkT	Saliva (No.6)	MRSA ATCC 43300

Escherichia coli

Name	Source for isolation	Host strain
Abk3	Sewage	*E. coli* 3
Abk4	Saliva (No. 2)	*E. coli* 4
Abk8	Sewage	*E. coli* 8
Abk9	Sewage	*E. coli* 9
Abk11	River water	*E.coli* ATCC 25922
AbK13	Sewage	*E.coli* ATCC 25922
Abk14	Saliva (No1)	*E.coli* ATCC 25922

Staphylococcus epidermidis: **no phages were detected in any of the tested sources**

80 years old woman

MDR *P. aeruginosa* PJI of a total knee arthroplasty and chronic osteomyelitis

Previous two-stage exchange and antibiotic treatment failed

Unconventional Approach

Surgical treatment

- Two-stage exchange
- PMMA (1g gentamycin, 1g clindamycin per 40g PMMA)

Local use of phages

- Custom prepared phage

Antibiotic treatment (i.v)

- Colistin
- Ceftazidime
- Meropenem

Institute ELIAVA

CENTRUM MUSKULO SKELETALE CHIRURGIE

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Local use of phages

- The surgical site was cleaned with 2-3% sodium bicarbonate solution

- No antiseptics

- 4 intraoperatively placed drains were used as local delivery system

- First, single intraoperative loading dose of phage were administrated

- Then, three times a day for 5 days through drains