Pocket Guide to Diagnosis & Treatment for the Periprosthetic Joint Infection (PJI)

PRO-IMPLANT FOUNDATION

PRO-IMPLANT Workshops: www.pro-implant.org
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DEFINITION (modified EBJIS criteria 2021)

Test	Infection Unlikely (all criteria fulfilled)	Infection Likely (two positive criteria)	Infection Confirmed (any positive criteria)
A. Clinical presentation			
Clinical features C-reactive protein (CRP)	Clear alternative reason for implant dysfunction	• Early loosening • Wound healing problems • Recent fever/bacteremia • Pus around prosthesis[a] • CRP >10mg/l	• Sinus tract • Exposed prosthesis
B. Laboratory			
Cell count in synovial fluid[b]	<1500/µl leukocytes and <65% PMN	>1500/µl leukocytes or >65% PMN	>3000/µl leukocytes or >80% PMN
Microbiology[c]	All cultures (incl. sonication) negative	Single positive culture or 1-50 CFU/ml (sonication)	>2 positive samples or >50 CFU/ml (sonication)
Histology[d]	Negative	Presence of ≥5 neutrophils in a single high power field (HPF)	Presence of ≥5 neutrophils in ≥5 HPF, visible microorganisms

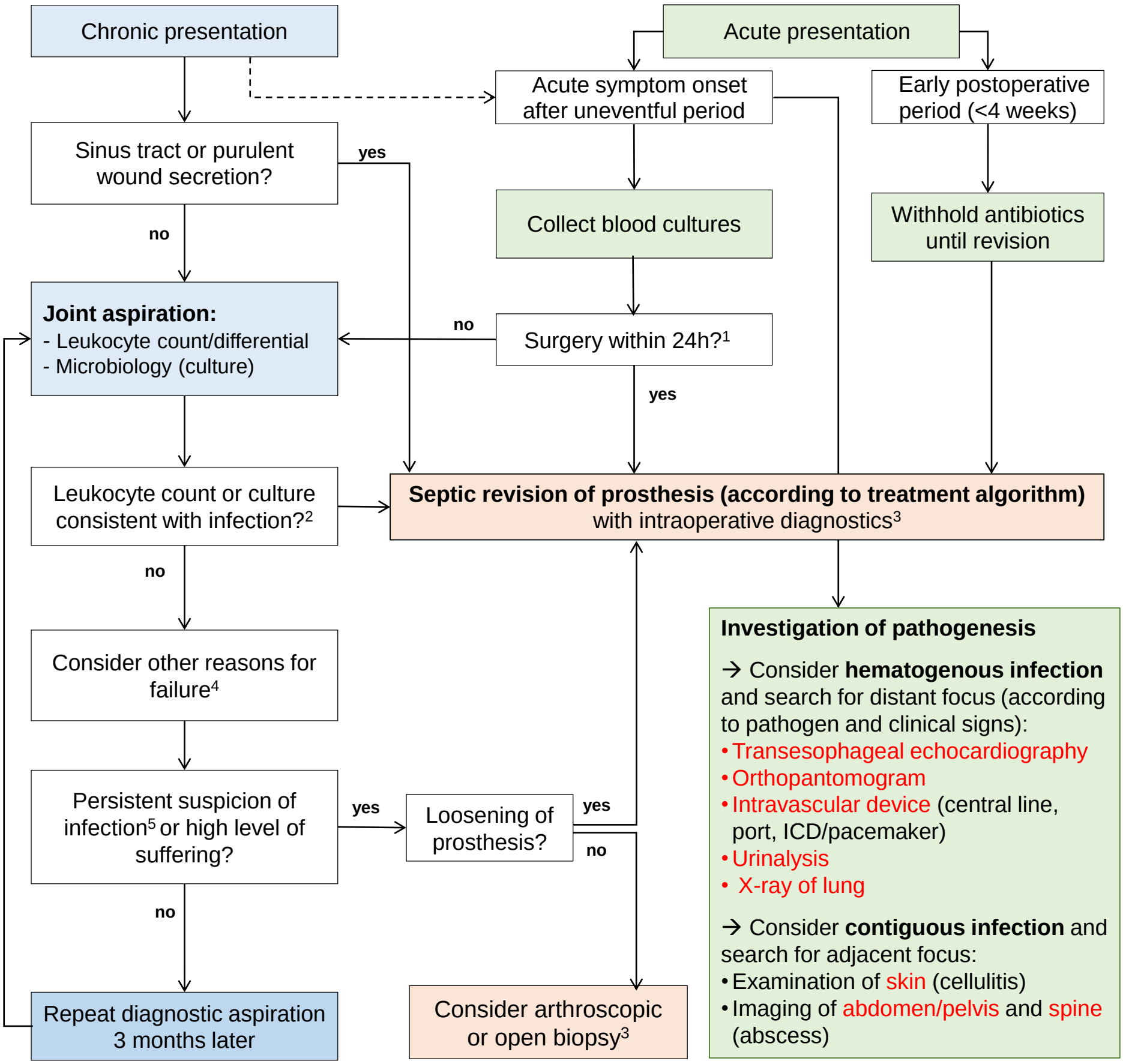
Modified from McNally M. et al. Bone Joint J. 2021. doi: 10.1302/0301-620X.103B1.BJJ-2020-1381.

[a] Adverse local tissue reaction (ALTR) and crystal arthropathy can simulate pus ("pseudopus")
[b] Interpretation with caution in the first 6 weeks after surgery, in rheumatic joint disease (including crystalopathy), periprosthetic fracture or luxation, metallosis. Alpha defensin has high specificity and can be used as confirmation test. Leukocyte count should be determined within 24 h after aspiration by microscopy or automated counter; clotted specimens are treated with 10 µl hyaluronidase. PMN = granulocytes
[c] For highly virulent organisms (e.g. *S. aureus,* streptococci, *E. coli*) or patients under antibiotics, already one positive sample or <50 CFU/ml in sonication may confirm infection
[d] Other classifications such as SLIM-classification by Krenn and Morawietz may be considered equally.

CLASSIFICATION

	Acute PJI (immature biofilm)	Chronic PJI (mature biofilm)
Pathogenesis ▪ **Perioperative**	Early <4 weeks after surgery	Delayed (low-grade) ≥4 weeks after surgery (usually 3 months to 3 years)
▪ **Hematogenous or contiguous**	<3 weeks of symptom duration	≥3 weeks of symptom duration
Clinical features	Acute pain, fever, red/swollen joint, prolonged postoperative discharge (>7-10 days)	Chronic pain, loosening of the prosthesis, sinus tract (fistula)
Causative microorganism	High-virulent: *Staphylococcus aureus*, gram-negative bacteria (e.g. *Escherichia coli*, *Klebsiella, Enterobacter, Pseudomonas aeruginosa*)	Low-virulent: Coagulase-negative staphylococci (e.g. *Staphylococcus epidermidis*), *Cutibacterium spp.)*
Surgical treatment	Débridement & retention of prosthesis (change of mobile parts)	Complete removal of prosthesis (exchange in one, two or more stages)

DIAGNOSTIC ALGORITHM for suspected PJI



[1] The operation should be carried out by an experienced surgeon. In septic patients and/or suspected hematogenous PJI start antimicrobial treatment immediately after blood cultures and joint aspiration

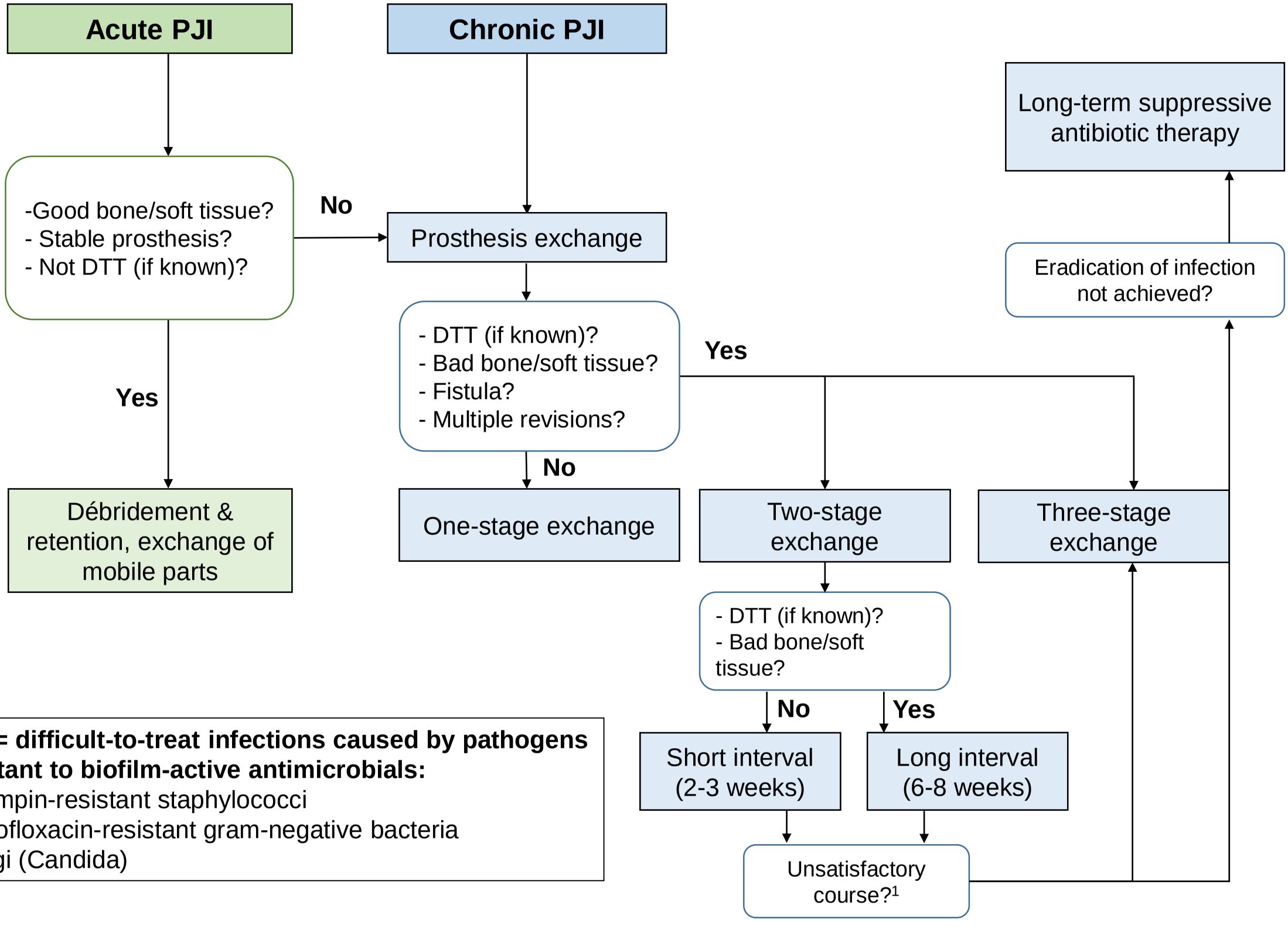
[2] For highly virulent organisms (e.g., *S. aureus, E. coli*) already one positive sample confirms infection, for low-virulent organisms (e.g., *S. epidermidis, C. acnes*) ≥2 positive samples are required to confirm infection

[3] Including biopsies for histopathology and microbiology +/- sonication of prosthesis/mobile parts

[4] Other reasons include aseptic loosening, periprosthetic fracture, dislocation, muscular pathology, wear of bearing components, metallosis

[5] Elevated CRP, risk history (prolonged secretion or revision surgery after primary implantation), early loosening of prosthesis

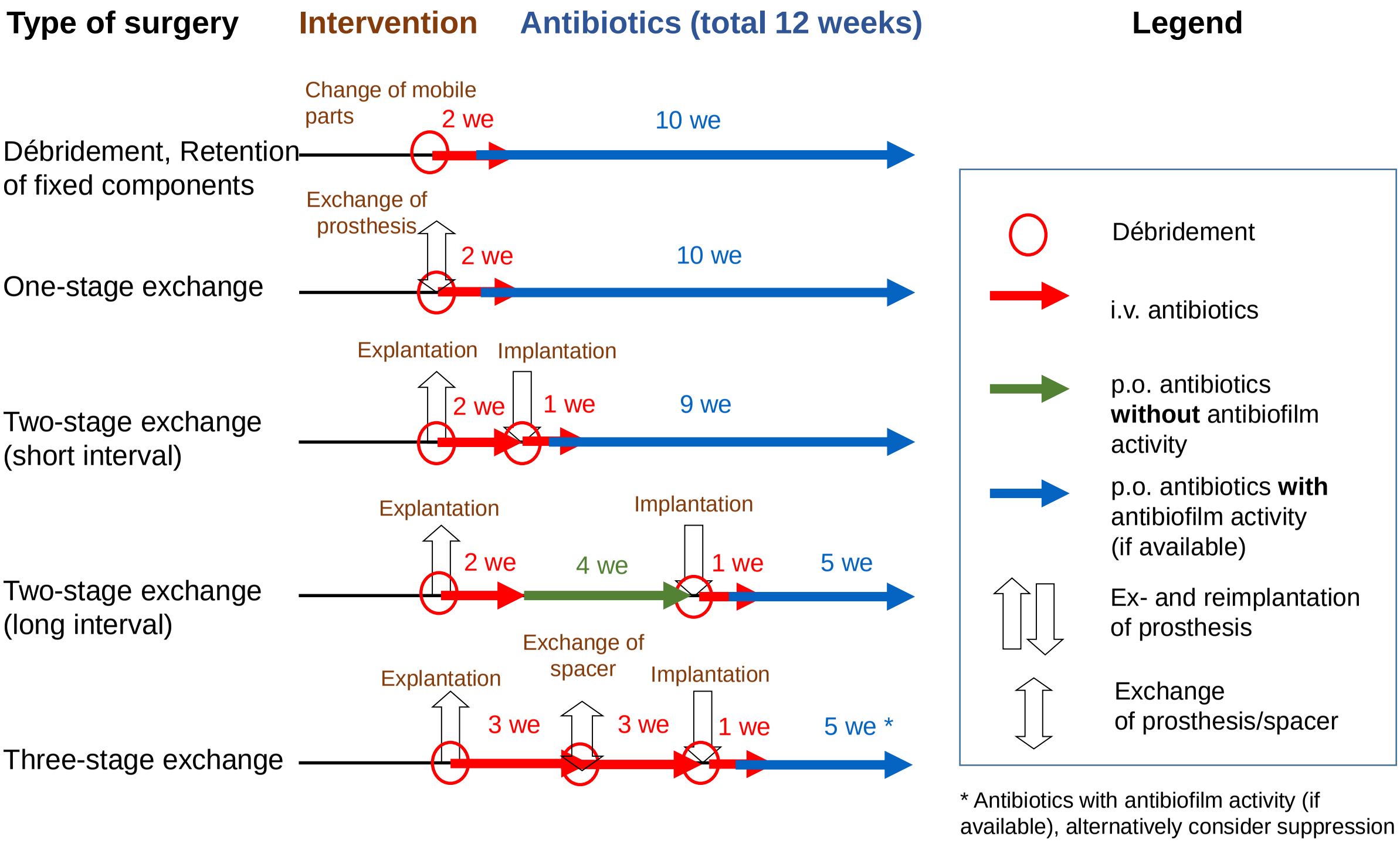
TREATMENT ALGORITHM



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

[1] clinical signs of infection, elevated CRP, intraoperative pus, compromised tissue

SURGICAL PROCEDURES



* Antibiotics with antibiofilm activity (if available), alternatively consider suppression

RECOMMENDED ANTIMICROBIAL TREATMENT

Empiric antibiotic therapy:

- Ampicillin/sulbactam[c] 3 x 3 g i.v. or amoxicillin/clavulanic acid 3 x 2.2 g i.v.
- (+/- vancomycin[f] 2 x 1 g i.v. in septic patients, known MRSA-carriers, multiple previous surgeries, suspected low-grade infection)

Interval / suppressive therapy (check antimicrobial susceptibility and patient tolerability)

Microorganism	**Antibiotic** (according to susceptibility, dose see table below)
Staphylococcus spp.	Cotrimoxazole, doxycycline, clindamycin
Streptococcus/Enterococcus	Amoxicillin, doxycycline (linezolid for ampicillin-resistant enterococci)
Anaerobes (gram-positive)	Amoxicillin, doxycycline, clindamycin
Anaerobes (gram-negative)	Metronidazole, clindamycin
Gram-negative bacteria	Ciprofloxacin, cotrimoxazole
Fungi (*Candida spp.)*	Fluconazole (voriconazole, if fluconazole resistant)

Targeted eradication therapy (deescalate as soon as the pathogen is known)**:**

Microorganism (red: difficult-to-treat)	**Antibiotic**[a] (check pathogen susceptibility before)	**Dose**[b] (blue: renal adjustment needed)	**Route**
***Staphylococcus* spp.**			
- Oxacillin-/methicillin-susceptible	Cefazolin[c]	3 x 2 g	i.v.
	+/- Fosfomycin[d]	2 x 8 g (or 3 x 5 g)	i.v.
	for 2 weeks, followed by (according to susceptibility)		
	Rifampin[e] +	2 x 450 mg	p.o.
	- Levofloxacin or	2 x 500 mg	p.o.
	- Cotrimoxazole or	3 x 960 mg	p.o.
	- Doxycycline or	2 x 100 mg	p.o.
	- Fusidic acid	3 x 500 mg	p.o.
- Oxacillin-/methicillin-resistant	Daptomycin or	1 x 8 mg/kg	i.v.
	Vancomycin[f]	2 x 1 g	i.v.
	+/- Fosfomycin[d]	2 x 8 g (or 3 x 5 g)	i.v.
	for 2 weeks, followed by an oral **rifampin** combination as above		
- Rifampin-resistant	Intravenous treatment for 2 weeks (as above), followed by long-term suppression according to susceptibility for ≥1 year		
***Streptococcus* spp.**	Penicillin G[c] or	4 x 5 million U	i.v.
	Ceftriaxon	1 x 2 g	i.v.
	for 2-4 weeks, followed by:		
	Amoxicillin or	3 x 1g	p.o.
	Doxycycline	2 x 100 mg	p.o.
	(consider suppression for 1 year)		
***Enterococcus* spp.**			
- Ampicillin-susceptible	Ampicillin	4 x 2 g	i.v.
	+ Gentamicin[g]	1 x 120 mg	i.v.
	+/- Fosfomycin	2 x 8 g (or 3 x 5 g)	i.v.
	for 2-3 weeks, followed by:		
	Amoxicillin	3 x 1000 mg	p.o.
	Doxycycline	2 x 100 mg	
- Ampicillin-resistant	Vancomycin[f] or	2 x 1 g	i.v.
	Daptomycin	1 x 10 mg/kg	i.v.
	+/- Fosfomycin	2 x 8 g (or 3 x 5 g)	i.v.
	for 2-4 weeks, followed by		
	Linezolid (max. 4 weeks)	2 x 600 mg	p.o.
- Vancomycin-resistant (VRE)	Individual; removal of the implant or life-long suppression necessary (for instance with doxycycline, if susceptible)		

Microorganism (red: difficult-to-treat)	Antibiotic[a] (check susceptibility before)	Dose[b] (blue: renal adjustment needed)	Route
Gram-negative			
- Enterobacterales	Ciprofloxacin[h]	2 x 750 mg	p.o.
- Nonfermenters (*Pseudomonas aeruginosa, Acinetobacter* spp.)	Piperacillin/tazobactam or	4 x 4.5 g	i.v.
	Meropenem or	3 x 2 g	i.v.
	Ceftazidime (or cefepime)	3 x 2 g	i.v.
	+ Gentamicin or	1 x 240 mg	i.v.
	Tobramycin	1 x 300 mg	i.v.
	for 2-3 weeks, followed by:		
	Ciprofloxacin	2 x 750 mg	p.o.
- Ciprofloxacin-resistant	Depending on susceptibility: meropenem 3 x 2 g i.v., colistin 3 x 3 million U i.v., fosfomycin[d] 2 x 8 g (or 3 x 5 g) i.v., followed by oral suppression.		
Anaerobes			
- Gram-positive[i] (*Cutibacterium, Peptostreptococcus, Finegoldia magna*)	Penicillin G[c] or	4 x 5 million U	i.v.
	Ceftriaxon	1 x 2 g	i.v.
	for 2 weeks, followed by:		
	Rifampin[e] +	2 x 450 mg	p.o.
	- Levofloxacin or	2 x 500 mg	p.o.
	- Amoxicillin or	3 x 1g	p.o.
	- Doxycycline	2 x 100 mg	p.o.
- Gram-negative (*Bacteroides spp.*, *Fusobacterium* spp.)	Ampicillin/sulbactam[c]	3 x 3 g	i.v.
	for 2 weeks, followed by		
	Metronidazol	3 x 400 mg or 3 x 500 mg	p.o.
Candida spp.	Caspofungin[j]	1 x 70 mg	i.v.
- Fluconazole-susceptible	Anidulafungin	1 x 100 mg (1st day: 200 mg)	i.v.
	for 1-2 weeks, followed by:		
	Fluconazole	1 x 400 mg	p.o.
	(suppression for ≥1 year)		
- Fluconazole-resistant	Suppression (e.g. voriconazole, posaconazol) or removal of implant		
Culture-negative	Ampicillin/sulbactam[c]	3 x 3 g	i.v.
	+/- Vancomycin	2 x 1g	i.v.
	for 2 weeks, followed by:		
	Rifampin[e] +	2 x 450 mg	p.o.
	Levofloxacin	2 x 500 mg	p.o.

[a] **Total duration** of therapy: **12 weeks**, usually 2 weeks intravenously, followed by oral route.

[b] Laboratory testing 2x weekly: leukocytes, CRP, creatinine/eGFR, liver enzymes (AST/SGOT and ALT/SGPT). Dose-adjustment according to renal function and body weight (<40/>100kg)

[c] **Penicillin allergy** of NON-type 1 (e.g. skin rash): cefazolin (3 x 2 g i.v.). In case of anaphylaxis (= type 1-allergy such as Quincke's edema, bronchospasm, anaphylactic shock) or cephalosporin allergy: vancomycin (2 x 1 g i.v.) or daptomycin (1 x 8 mg/kg i.v.). Ampicillin/sulbactam is equivalent to amoxicillin/clavulanic acid (3 x 1.2 g or 3 x 2,2 g i.v.).

[d] Fosfomycin (if available): cumulative daily dose 12-24 g i.v. divided into 2-3 single doses.

[e] **Rifampin** administer only after the prosthesis is reimplanted. Add to intravenous treatment when wounds are dry and drains removed; in patients >75 years, rifampin 2 x 300 mg p.o.

[f] Check **Vancomycin** through concentration at least 1x/week; therapeutic range: 15-20 µg/ml

[g] Give only, if **gentamicin high-level (HL)** is tested susceptible (consult the microbiologist). In gentamicin HL-resistant *E. faecalis*: gentamicin is exchanged with ceftriaxone (1 x 2 g i.v.).

[h] **Add i.v. treatment** (piperacillin/tazobactam 3 x 4.5 g or ceftriaxone 1 x 2 g or meropenem 3 x 1 g i.v. or fosfomycin 2 x 8 g i.v.) in the first postoperative days (until wound is dry).

[i] Rifampin recommended for *Cutibacterium* spp., optional for other anaerobes (little data).

[j] Loading dose 70 mg on the first day, then reduce dose to 1 x 50 mg for patients <80 kg.

LOCAL ANTIMICROBIALS IN BONE CEMENT (PMMA)

(Supporting systemic antimicrobial treatment – not replacing it)

Situation	Antimicrobials	Fixation cement	Spacer cement
		Dose: per 40 g PMMA cement Black: industrially admixed antimicrobials Red: manually admixed antimicrobials	
Standard situation • susceptible or unknown pathogen(s)	Gentamicin + Clindamycin	1 g 1 g	1 g 1 g (+2 g vancomycin)
Special situations • Oxacillin-/methicillin-resistant staphylococci (MRSE/MRSA) or enterococci	Gentamicin + Vancomycin or + Daptomycin	0.5 g 2 g 2 g	0.5 g 2 g (+2 g[a]) 3 g
• Vancomycin-resistant enterococci (VRE)	Gentamicin + Linezolid or Daptomycin or Fosfomycin-sodium[b]	0.5 g 1 g 2 g 2 g[a]	0.5 (or 1 g) 2 g 3 g 2-4 g
• Resistant gram-negative pathogens (e.g. *E. coli, Klebsiella, Enterobacter, Pseudomonas* spp.)	Gentamicin + Colistin[c] or Fosfomycin-sodium[b] or Meropenem or Ciprofloxacin[e]	0.5 g 5-10 Mio IU 2 g[a] 2 g 2 g	0.5 (or 1 g) 10-20 Mio IU 2-4 g 3 g[d] 3 g
• Yeasts (*Candida* spp.) or molds (e.g., *Aspergillus* spp.)	Gentamicin + Amphotericin B liposomal or Voriconazol	0.5 g 0.2 g[e] 0.2 g	0.5 (or 1 g) 0.4 g[a,e] 0.4 g[a]

[a] These antimicrobial concentrations do not fulfill the mechanical ISO requirements for fixation cement.
[b] Fosfomycin-sodium is preferred over fosfomycin-calcium due to better mechanical properties of PMMA.
[c] Available as colistin-sodium or colistin-sulfate (equal efficacy).
[d] Improved efficacy and antimicrobial release in combination with gentamicin 1 g and clindamycin 1 g, which can be used as basis for admixing additional antimicrobials.
[e] Literature is still controversial regarding minimal effective concentrations.

General considerations:

- When additional antimicrobials are admixed, industrially impregnated cements are preferred over plain cements (better mechanical properties and elution due to synergistic release).
- Antimicrobial susceptibility testing results are applicable for systemic antimicrobial application and might not be valid for local antimicrobial application due to high local concentrations and synergistic activity.
- Side effects and interactions of local antimicrobials are rare. However, serum concentrations of vancomycin and gentamicin should be monitored in patients with kidney insufficiency (eGFR <60ml/min) and/or intravenous application.
- Only use sterile antimicrobials in powder form. Liquid antimicrobials are not recommended due to inhomogeneous distribution in PMMA. Do not use antibiotics that interfere with polymerization process (e.g., rifampin, metronidazol) or are thermolabile or sensitive to oxidation (e.g., some beta-lactams).
- Data on mechanical stability are not available for combinations of >2 antimicrobials. If possible, the total amount of antimicrobials should not exceed 10% of the PMMA powder weight (= 4 g per 40 g).
- Recommendations are based on studies with PALACOS®/COPAL® PMMA cements and literature data. Elution data and mechanical stability depend on the PMMA cement basis used.
- Use hand mixing (not vacuum) for preparation of cement spacer (higher porosity → better elution).

Video-tutorial about admixing of antimicrobials in bone cement:

- Preparation of an PMMA hip spacer: https://www.youtube.com/watch?v=DovF7TzMgcA
- Antibiotic admixing to bone cement: https://www.youtube.com/watch?v=3-qj8ZYc7fk