

1 Sonication versus tissue sampling for diagnosis of prosthetic joint and other orthopaedic
2 device-related infections.

3 SUPPLEMENTARY APPENDIX

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Table S - 1 Summary of published studies comparing sonication and tissue culture for diagnosis of prosthetic joint infection (PJI) and other (Trampuz et al., 2006) orthopaedic device-related infections (DRI).

Author & Year (reference)	Case mix ^k	Definition of infection ^l	No. infected cases	No. aseptic cases	% early infection cases ^a	Antibiotics in 14 days prior to surgery, %	Methodology			Sensitivity, %		Specificity, %		
							Number of tissue specimens ^b	Automated liquid culture ^p	Sonication fluid concentrated	Sonication threshold (cfu/ml ^q)	Sonication culture	Tissue culture	Sonication culture	Tissue culture
Trampuz 2006 ¹	PJI	Clinical ²	24	54		54	≥2	Synovial only	No	2	75	54	87	98
Dora 2007 ³	PJI	Other clinical	14	55			mean 4		No	2	71	79	96	98
Trampuz 2007 ²	PJI	Clinical ²	79	252		56	≥2	Tissue	No	10	79	61	89	99
Esteban 2008 ⁴	PJI, DRI	Modified clinical	17 ^d	14 ^d			3 to 5		Yes	10 ^m	94	88	43	100
Piper 2009 ⁵	PJI	Clinical ²	33	101	^g	24	≥2		No/Yes	10	67	55	98	95
Sampedro 2010 ⁶	DRI	IDSA ⁷	36	76	82	>39	2 to 9		No/Yes	10 to 1000 ⁱ	91	73	97	93
Verdigis 2011 ⁸	PJI	IDSA ⁷	9	27	^g	33	≥2		Yes	0.1 to 2 ^j	89	55	100	93
Bjerkan 2012 ⁹	PJI	IDSA ⁷	18	36			5		Yes	1.6	82	100	100	100
Gomez 2012 ¹⁰	PJI	Clinical ²	135	231	76 ^h	51 ^e	≥2	Synovial only	Yes	2	73	70	98	99
Borens 2013 ¹¹	PJI, DRI	Modified MSIS	12	27	66		Not stated		No	10 ^m	83	100		
Evangelopoulos 2013 ¹²	PJI	MSIS ¹³	24	10		0	≥2		Not stated	Not stated	71	47		
Janz 2013 ¹⁴	PJI	Modified IDSA	37	65		0	2 to 6		No	Not stated	89	52	72	100
Esteban 2013 ¹⁵	PJI, DRI	Modified IDSA	70 ^d	33 ^d		46 ^f	3 to 5		Yes	100 ⁿ	68	60	94	98
Puig-Verdie 2013 ¹⁶	PJI	IDSA ⁷	109	208	85	6	≥5		No	50	90	67	99	100
Cazanave 2013 ¹⁷	PJI	Clinical ²	144	290		43	≥2	Synovial only	Yes	2	73	70	98	98
Portillo 2014 ¹⁸	PJI	Modified MSIS	69	162	65	48	5		No	2 to 50 ^{im}	81	61	99	100
Yano 2014 ¹⁹	DRI	Clinical ²	125	55		31	≥2, mean 2.9		Yes	0.1 to 5 ⁱ	90	57	91	96
Janz 2015 ²⁰	PJI	Modified IDSA	31	88			2 to 6		No	Not stated ^j	74	65	85	100
Portillo 2015 ²¹	PJI, DRI	Modified MSIS	69	162		56	Not stated	Sonication only	No	50	87	59	100	100
Puchner 2016 ²²	DRI	MSIS ¹³	23	8		61	Not stated		No	2 ^m	91	52	100	100
Hischebeth 2016 ²³	PJI	Histopathology	47	33			Not stated	Sonication only	Yes	Not stated	72	61	76	77
Rak 2016 ²⁴	PJI	MSIS ¹³	58	29	^g	28	5 to 10		No	Not stated	93	76	77	69
Grosso 2017 ²⁵	PJI	Modified clinical	25	28		0	2 to 8		No	2 to 20	56	96	93	75
Tani 2017 ²⁶	PJI	IDSA ⁷	61	53	^g	0	≥5		No	50	77	56	98	94
Van Diek 2017 ²⁷	PJI	MSIS ¹³	75	177	81	0	≥6		No	50	47	68	99	80
Renz 2017 ²⁸	PJI	EBJIS ³²	78	33		0	Not stated		No	10 to 50 ^l	58	51	100	100
Fernandez-Sampedro 2017 ²⁹	PJI	Modified IDSA	130	368	86	19	3 to 6		Not stated	10 ^m	85	62	100	100
Rothenberg 2017 ³⁰	PJI	MSIS ¹³	178	325			≥2		Yes	10 to 250	93	70	93	98

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18 Table footnotes:

19 a Duration of symptoms < 3 months

20 b Synovial fluid included as a tissue specimen by most studies; median number of specimens not reported

21 c Colony-forming units per millilitre of unconcentrated sonication fluid

22 d More than one prosthetic component per patient submitted; number of components reported

23 e Proportion receiving antibiotics in preceding 4 weeks

24 f Proportion receiving antibiotics in preceding 7 days

25 g Mean duration of infection >12 months

26 h Proportion of infections of more than 12 months' duration

27 i Variable diagnostic threshold according to clinical or microbiologic criteria

28 j For non-clinical definitions of infection, positive culture led to inclusion of patients with no additional diagnostic criteria for infection

29 k PJI: Prosthetic Joint Infection; DRI: Device-related orthopaedic infection (other than prosthetic joints)

30 m Theoretical limit of detection

31 n Colony-forming units per millilitre of concentrated sonication fluid; concentration ratio not described

32 p Automated liquid mycobacterial culture not included in definition

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Reference standard definition of infection	Criteria for diagnosis of infection within each reference standard definition	
	Clinical Criteria	Microbiological Criteria
Clinical	Presence of a sinus OR Visible purulence OR Histology positive for infection	None
Consensus	Presence of a sinus OR <i>Three of the following minor criteria:</i> <i>Elevated serum CRP AND ESR</i> <i>Visible purulence¹</i> <i>Histology positive for infection</i> <i>Single positive periprosthetic culture</i>	OR Two positive (periprosthetic) tissue cultures with phenotypically indistinguishable organisms
IDSA	Presence of a sinus OR Visible purulence OR Histology positive for infection	OR Two positive (periprosthetic) tissue cultures with phenotypically indistinguishable organisms OR growth of virulent organism (e.g. <i>S. aureus</i>) in a single tissue specimen or synovial fluid ²
Composite	Presence of a sinus OR Visible purulence OR Histology positive for infection	OR Two positive periprosthetic cultures with phenotypically indistinguishable organisms OR Sonication culture positive

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37 Table footnotes:

38 1 Visible purulence at surgery was substituted for elevated synovial leucocyte count, ++ change on leucocyte esterase strip test, and elevated synovial fluid polymorphonuclear cell percentage; as these tests were
39 not routinely carried out in our centre.

40 2 For the purposes of our analyses using the IDSA criteria the only organism we included as evidence of infection if isolated from a single deep tissue biopsy was *S. aureus*.

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44 **Table S - 3. Anatomical location of explanted joint prostheses & components.**

Joint	No. (%)
Shoulder	2 (0.6)
Elbow	7 (2.0)
Hip	159 (45.8)
Knee	176 (50.7)
Ankle	3 (0.9)
Total	347

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46 **Table S - 4. Anatomical location of other orthopaedic devices.**

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Source	No. (%)
Clavicle	1 (0.6)
Humerus	13 (8.2)
Elbow	5 (3.2)
Forearm	5 (3.2)
Femur	47 (29.8)
Tibia	61 (38.6)
Ankle/foot	24 (15.2)
Spine	2 (1.2)
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Total	8

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Supplementary Table S-5. Regression coefficients (β), and adjusted odds ratio and 95% CI for variables included in multivariable logistic regression model of potential associations with tissue and sonication culture yield.

Variable	Tissue culture			Sonication culture		
	β	Odds ratio (95% CI)	p value	β	Odds ratio (95% CI)	p value
Antibiotic free days before surgery	0.012228	1.01 (0.95-1.08)	0.709	0.044472	1.05 (0.99-1.11)	0.119
Organism virulence	2.137526	8.48 (1.68-42.8)	0.010	- 0.335979	0.71 (0.21-2.40)	0.586
Months since device implantation	0.000060	1.00 (0.99-1.01)	0.993	- 0.006871	0.99 (0.99-1.00)	0.056
Presence of sinus	0.756216	2.13 (0.45-10.0)	0.338	0.160056	1.17 (0.40-3.44)	0.770
Visible purulence	0.892211	2.44 (0.56-10.6)	0.235	0.550222	1.73 (0.59-5.11)	0.318

Table S - 6 Clinical and microbiological characteristics of cases from which mixed infections were identified by tissue and/or sonication culture.

Case no.	Specimen type	Time since implantation (months)	Antibiotics in preceding 14 days	Clinically infected	Prosthetic joint infection	Sonication culture	Tissue culture
<i>Identical isolates from tissue and sonication culture</i>							
18	bone		yes	yes	no	Staphylococcus aureus, Streptococci	Staphylococcus aureus, Streptococci (Group G)
49	prosthesis (± hardware)	2		yes	yes	Coagulase negative Staphylococci, Enterococcus spp	Enterococcus spp, Staphylococcus epidermidis
51	hardware only	59	no	yes	no	Citrobacter koseri, Enterococcus faecalis, Streptococci	Citrobacter koseri, Enterococcus faecalis, Streptococci (Group B)
185	prosthesis (± hardware)	34	no	yes	yes	Enterococcus faecalis, Klebsiella oxytoca	Enterococcus faecalis, Klebsiella oxytoca
224	bone	9	yes	yes	no	Corynebacterium spp, Staphylococcus aureus	Corynebacterium striatum, Staphylococcus aureus
248	hardware only	7	yes	yes	no	Enterococcus faecalis, Escherischia coli	Escherischia coli, Enterococcus faecalis
257	components (± hardware)	9	no	yes	yes	Enterococcus faecalis, Staphylococcus aureus	Enterococcus faecalis, Staphylococcus aureus
278	components (± hardware)	4	no	yes	yes	Enterococcus faecalis, Escherischia coli, Klebsiella pneumoniae	Enterococcus faecalis, Escherischia coli, Klebsiella pneumoniae
325	prosthesis (± hardware)	53	yes	yes	yes	Enterococcus faecalis, Pseudomonas aeruginosa	Enterococcus faecalis, Pseudomonas aeruginosa
326	hardware only	4		yes	no	Enterobacter cloacae, Pseudomonas otitidis	Enterobacter cloacae, Pseudomonas otitidis
424	components (± hardware)	0	no	yes	yes	Coagulase negative Staphylococci	Staphylococcus epidermidis, Staphylococcus lugdunensis
440	hardware only	56	yes	no	no	Aeromonas hydrophila, Staphylococcus aureus	Aeromonas spp, Pseudomonas aeruginosa, Staphylococcus aureus
523	components (± hardware)	423	no	yes	yes	Escherischia coli, Proteus mirabilis	Escherischia coli, Proteus mirabilis
553	prosthesis (± hardware)	107	yes	yes	yes	Coagulase negative Staphylococci, Pseudomonas aeruginosa	Coagulase negative Staphylococci, Pseudomonas aeruginosa
<i>At least one but not all tissue and sonication culture isolates the same</i>							
54	prosthesis (± hardware)	35	yes	yes	yes	Staphylococcus aureus	Enterobacter cloacae, Staphylococcus aureus
127	hardware only	25		yes	no	Propionibacterium avidum	Actinomyces neuui, Propionibacterium avidum
144	components (± hardware)	2	no	yes	yes	Enterococcus faecalis, Pseudomonas aeruginosa	Enterococcus faecalis, Morganella morganii, Pseudomonas aeruginosa, Streptococci (Group B)
153	prosthesis (± hardware)	120	no	yes	yes	Streptococci	Streptococcus dysgalactiae, Streptococcus equisimilis
166	hardware only	68	no	yes	no	Staphylococcus aureus	Escherischia coli, Staphylococcus aureus
177	prosthesis (± hardware)	2	yes	yes	yes	Anaerobes, Enterobacter cloacae	Enterobacter cloacae, Enterococcus faecium
196	hardware only	9	yes	yes	no	Staphylococcus aureus	Klebsiella pneumoniae, Staphylococcus aureus
247	prosthesis (± hardware)	55		yes	yes	Pasteurella multocida	Enterococcus faecalis, Pasteurella multocida
260	hardware only	85	no	yes	no	Coagulase negative Staphylococci	Corynebacterium propinquum, Staphylococcus lugdenensis

283	cement	28	no	yes	no	Pseudomonas aeruginosa	Pseudomonas aeruginosa, Staphylococcus aureus, Streptococci (Group B)
303	hardware only	16	no	yes	no	Escherischia coli	Enterococcus faecalis, Escherischia coli
313	components (± hardware)	79	yes	yes	yes	Staphylococcus aureus	Pseudomonas aeruginosa, Staphylococcus aureus
387	hardware only			no	no	Enterobacter cloacae	Enterobacter cloacae, Klebsiella pneumoniae
406	hardware only	7	no	yes	no	Enterobacter cloacae, Pseudomonas aeruginosa	Enterobacter cloacae, Pseudomonas aeruginosa, Staphylococcus epidermidis
419	components (± hardware)	0	no	no	yes	Coagulase negative Staphylococci	Enterococcus avium, Staphylococcus epidermidis
426	components (± hardware)	0	yes	yes	yes	Staphylococcus aureus	Staphylococcus aureus, Streptococcus dysgalactiae,
430	hardware only	331	yes	yes	no	Enterobacter cloacae, Staphylococcus aureus	Staphylococcus aureus, Streptococcus dysgalactiae
449	prosthesis (± hardware)	45	no	yes	yes	Staphylococcus aureus	Corynebacterium striatum, Escherischia coli, Staphylococcus aureus
465	hardware only	52	no	yes	no	Streptococci	Enterobacter cloacae, Staphylococcus aureus, Streptococci (Group B)
530	components (± hardware)	53	yes	yes	yes	Enterobacter cloacae	Enterobacter cloacae, Escherischia coli
547	components (± hardware)	1	no	yes	yes	Enterococcus faecalis	Enterococcus faecalis, Staphylococcus epidermidis
<i>Mixed isolates from sonication culture but tissue culture negative</i>							
9	components (± hardware)	44	no	no	yes	Coagulase negative Staphylococci, Propionibacterium acnes	
50	prosthesis (± hardware)	59	yes	yes	yes	Enterococcus faecalis, Streptococci	
109	hardware only	5	yes	yes	no	Coagulase negative Staphylococci, Escherischia coli	
187	components (± hardware)	2	yes	yes	yes	Escherischia coli, Proteus mirabilis	
232	prosthesis (± hardware)	64	yes	yes	yes	Staphylococcus aureus, Staphylococcus condimenti	
391	prosthesis (± hardware)	21		yes	yes	Arcanobacterium haemolyticum, Enterococcus faecalis	
410	prosthesis (± hardware)	16	yes	yes	yes	Coagulase negative Staphylococci, Enterococcus faecalis	
418	components (± hardware)	13	yes	yes	yes	Coagulase negative Staphylococci, Enterobacter cloacae	
429	hardware only	3	no	no	no	Bacillus spp, Coagulase negative Staphylococci	
<i>Mixed isolates from tissue culture but sonication culture negative</i>							
163	prosthesis (± hardware)	22	no	yes	yes		Enterococcus faecalis, Staphylococcus epidermidis
394	components (± hardware)	37	no	yes	yes		Campylobacter ureolyticus, Fingoldia magna, Peptoniphilus harei
471	hardware only	10	no	yes	no		Staphylococcus aureus, Pseudomonas aeruginosa
517	hardware only		no	yes	no		Staphylococcus aureus, Pseudomonas aeruginosa
<i>Isolates from tissue and sonication culture completely discordant</i>							
142	hardware only	6	no	yes	no	Coagulase negative Staphylococci	Klebsiella oxytoca, Pseudomonas aeruginosa
212	cement	2		yes	no	Propionibacterium acnes	Bacteroides fragilis, Escherischia coli
309	hardware only	234	no	yes	no	Streptococci	Bacillus fragilis, Escherischia coli, Pseudomonas aeruginosa

Clinical Features:

- Peri-prosthetic loosening
- No soft tissue inflammation
- Usually indolent presentation
- Marked soft tissue inflammation
- Purulence ± sinus formation
- Presentation may be more acute

ANATOMICAL & BIOLOGICAL SPECTRUM



Microbiology:

- Usually less virulent organisms
- Mainly biofilm
- Often more virulent organisms
- Biofilm and planktonic bacteria

58 **Supplementary references**

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