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AMMI Canada – CACMID
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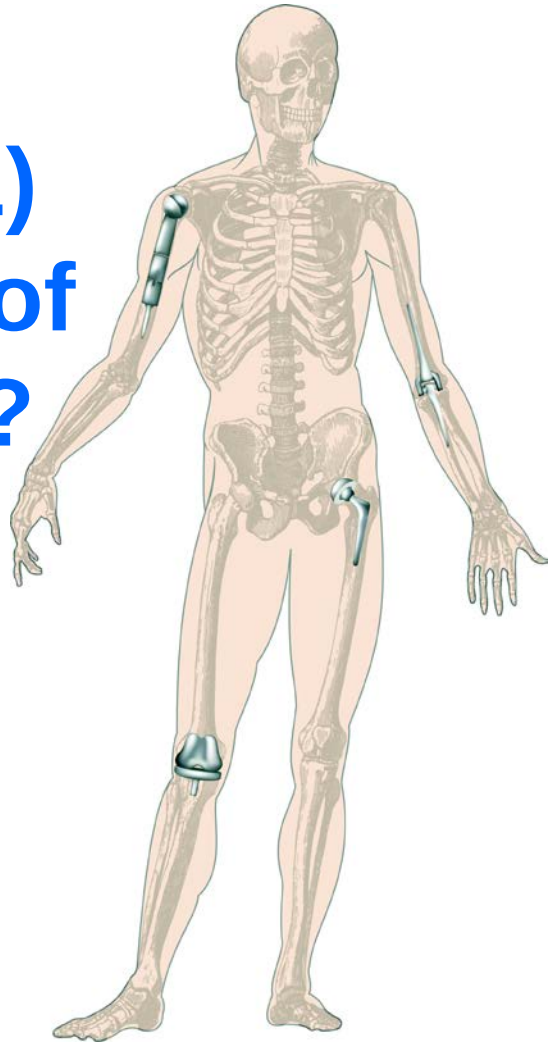
SHAKE'N BAKE (SHAKE, RATTLE AND ROLL) What's New in the Diagnosis of Device-Associated Infection?



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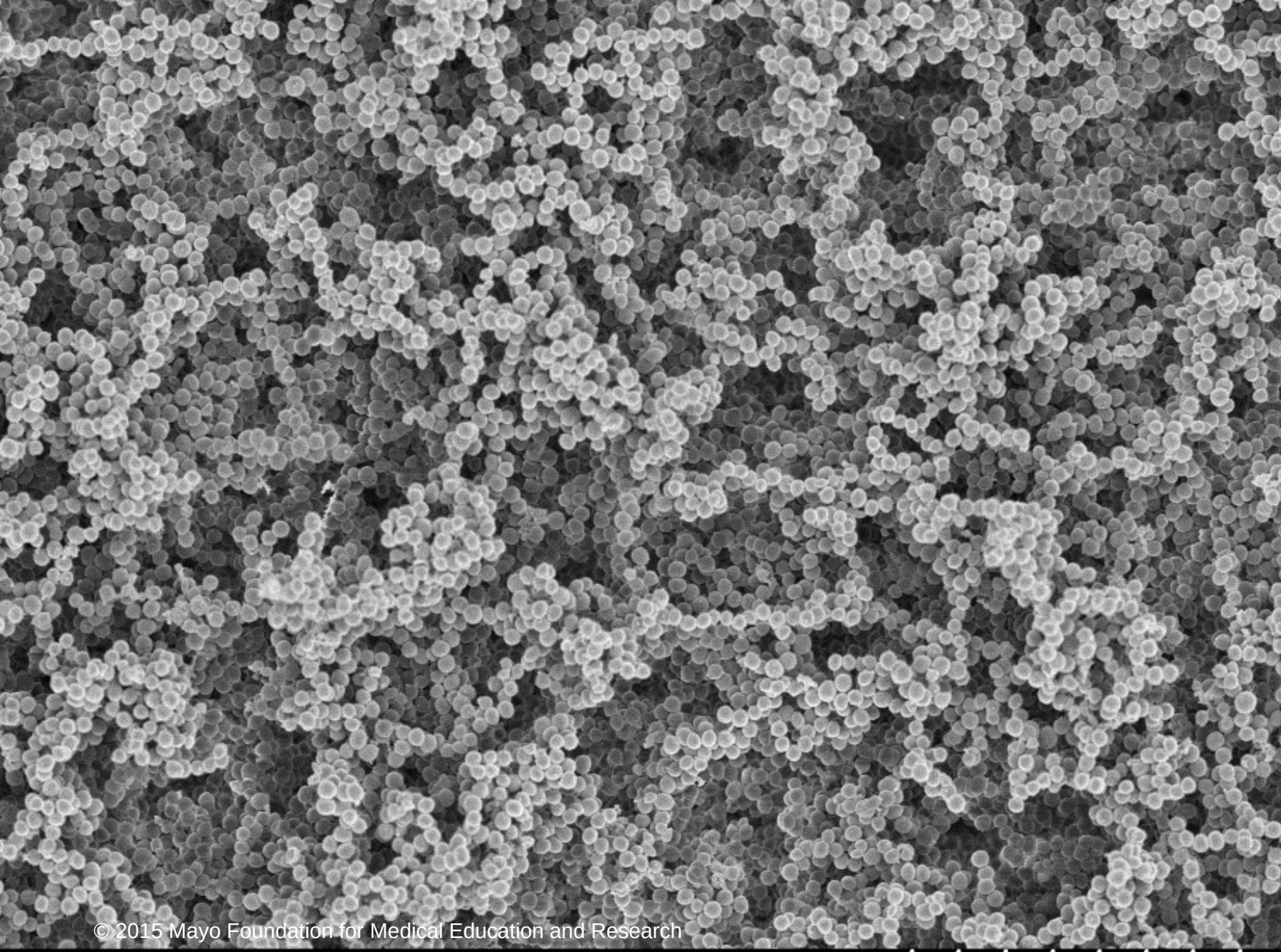
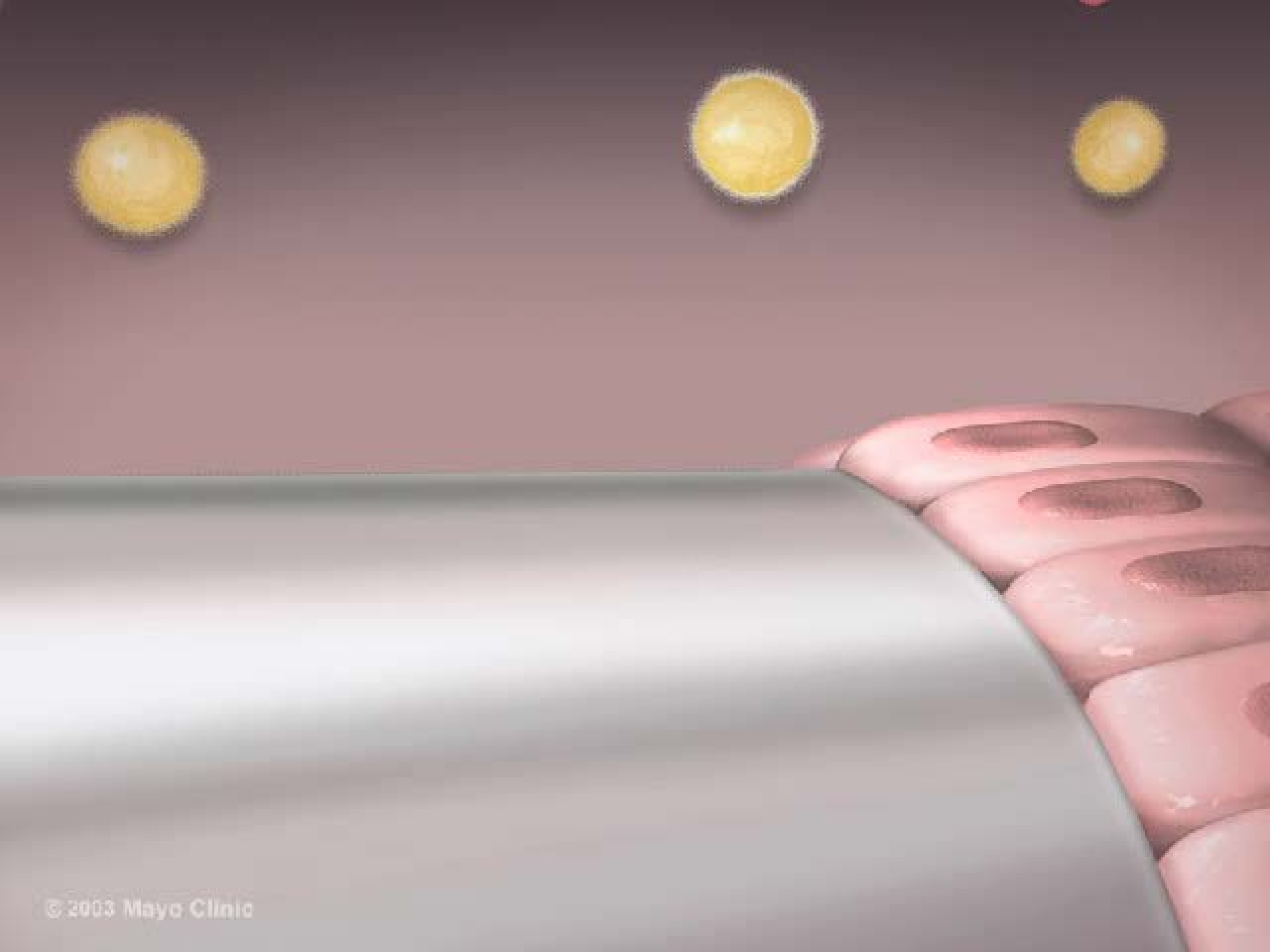
Objectives

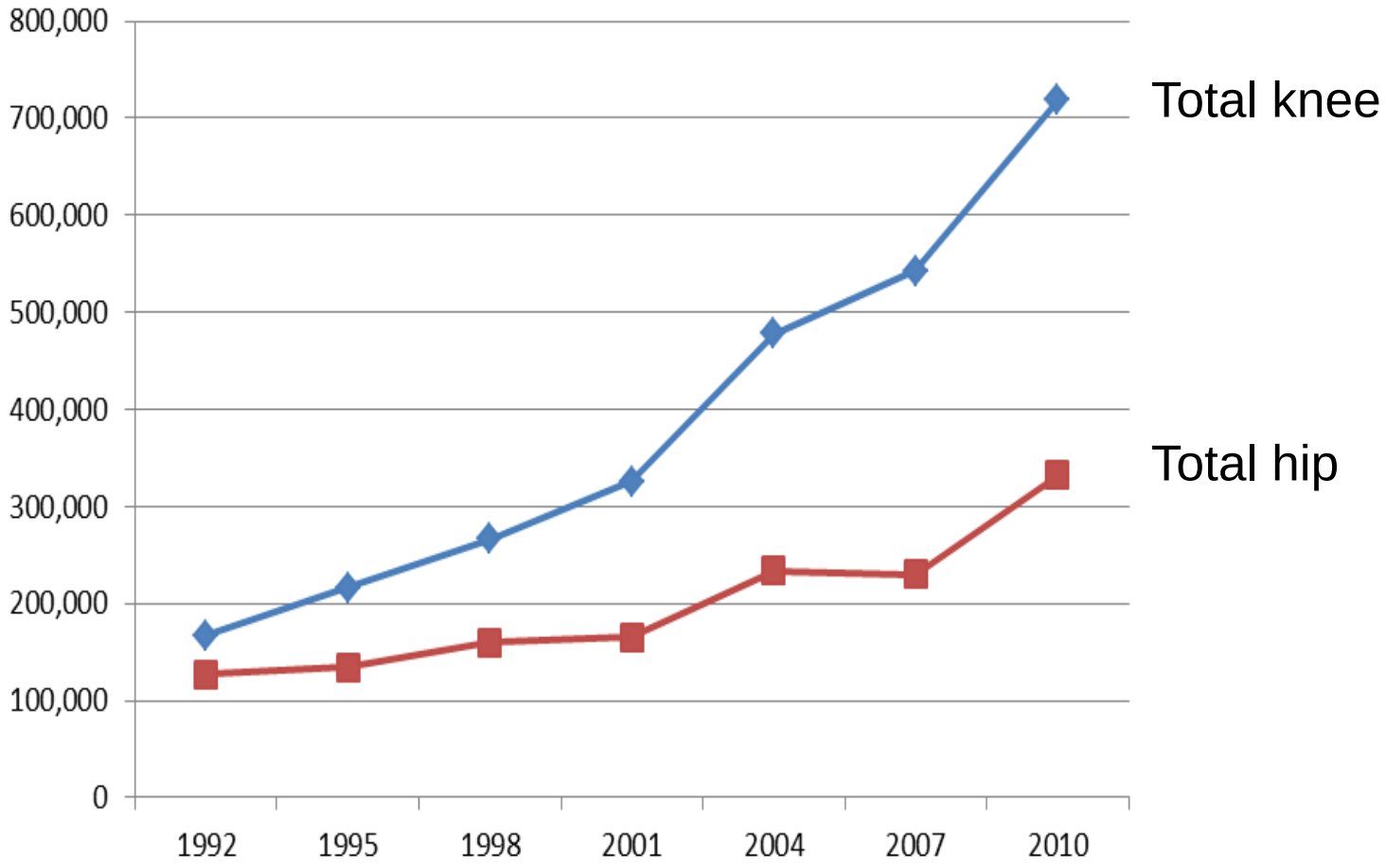
1. To review the epidemiology, pathogenesis, and microbiology of device-associated infection
2. To determine appropriate specimen types and methods for culture for diagnosing device-associated infection
3. To understand the role of molecular diagnostics in the diagnosis of device-associated infection





Total Hip & Knee Replacement Procedures United States

National Hospital Discharge Survey http://www.cdc.gov/nchs/about/major/hdasd/listpubs.htm



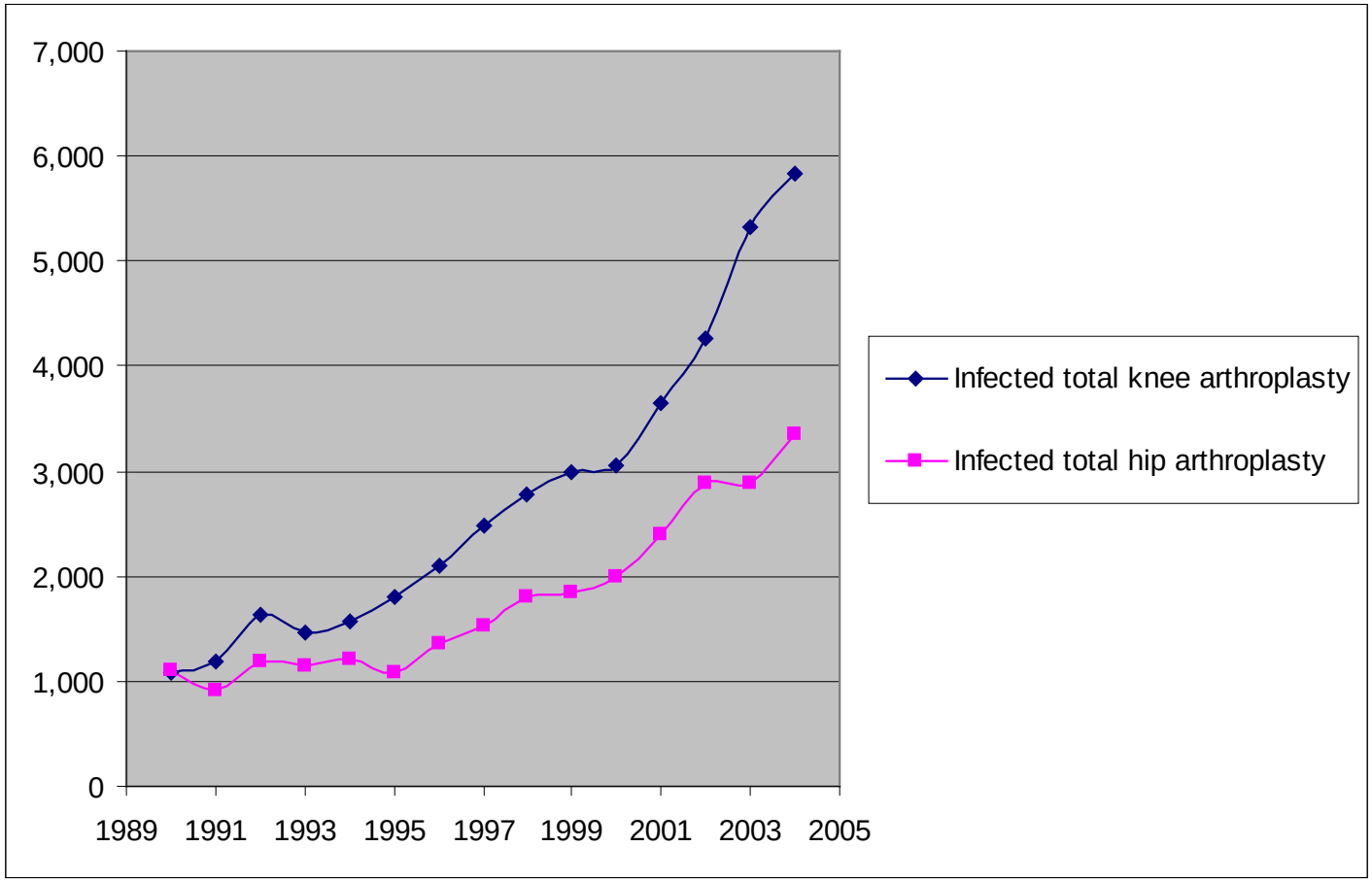
Prosthetic Joint Infection Rates

	Years*	
	0-2	2-10
Prosthetic knee infection	1.55%	0.46%
Prosthetic hip infection	0.78%	0.33%

*Medicare Population
Primary Elective Arthroplasty
1997-2006

Kurtz et al. Clin Orthop Relat Res 2010:468:52
Ong et al. J Arthroplasty 2009;24:105

Prosthetic Hip and Knee Infections United States



Kurtz et al. J Arthroplasty 2008;23:984

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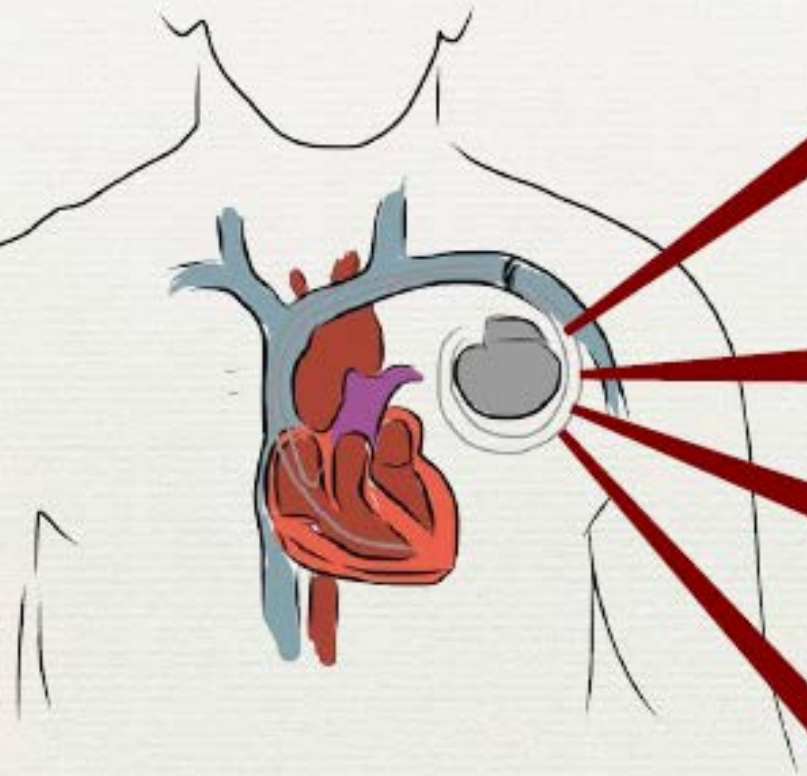


275,000 de novo implantations each year

x1% Infection rate for de novo devices

+

157,000 replacement devices each year

x3% Infection rate for replacement devices

+

3.1 MIL devices exist in patients

x0.8% Infection rate for existing devices

=

30,820

Total infections

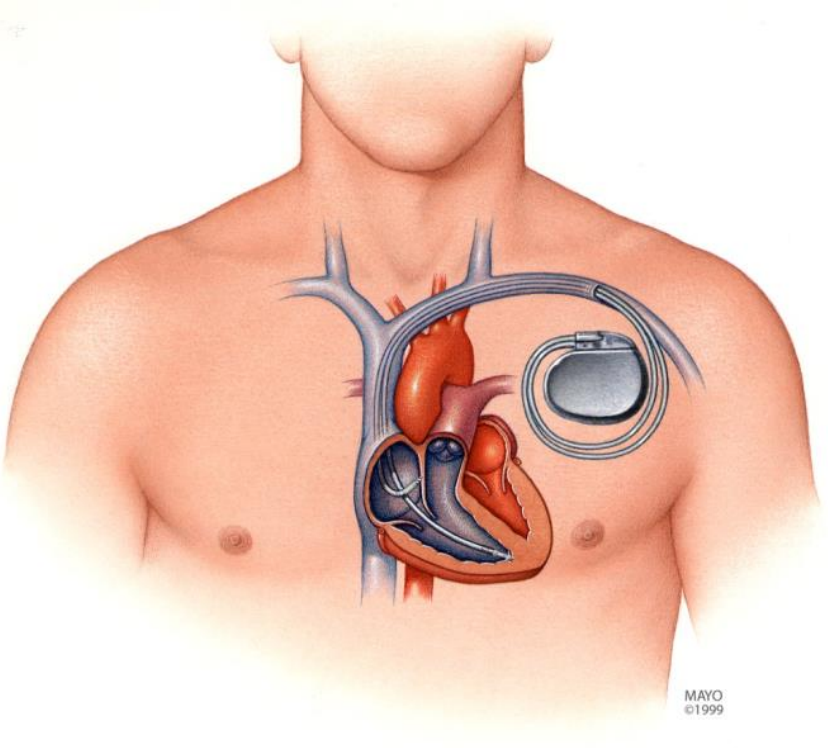
Slide courtesy of Rizwan Sohail

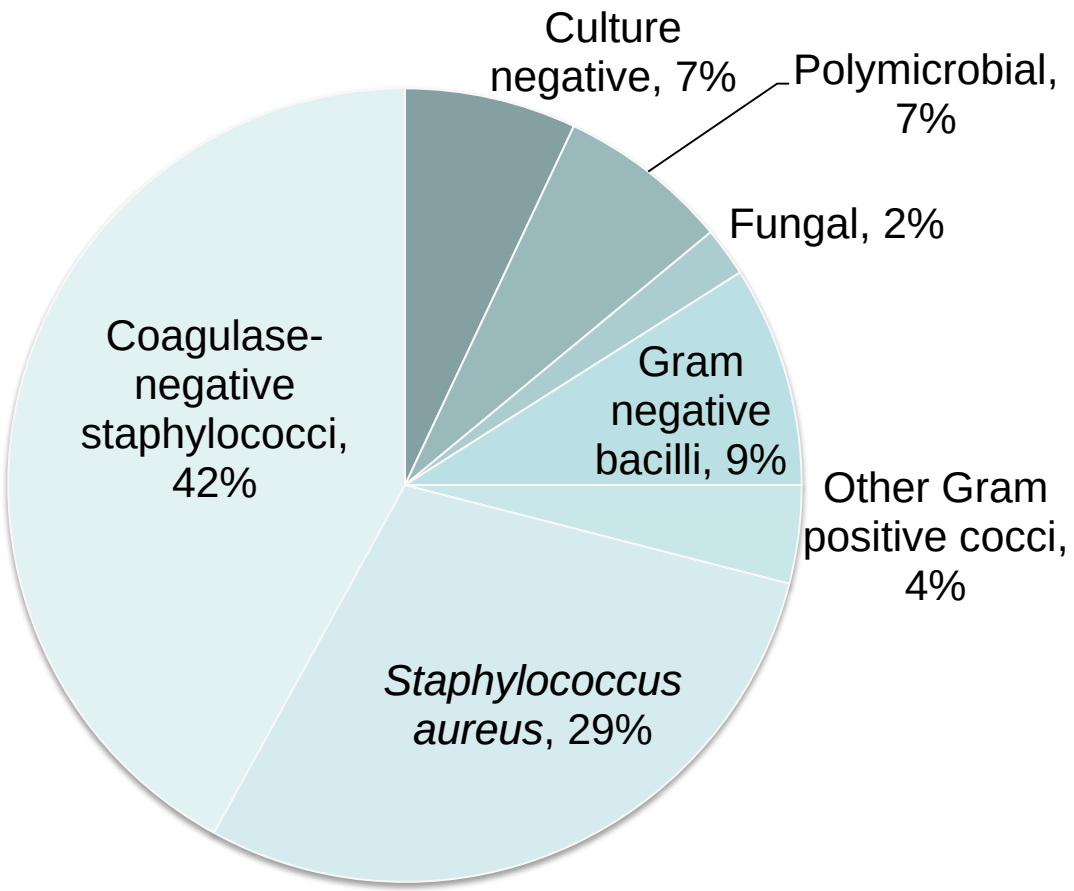
Prosthetic Joint Infection Microbiology

	Hip and Knee		Hip	Knee	Shoulder	Elbow
	All time periods	Early				
Number of joints	2435	637	1979	1427	199	110
Staphylococcus aureus	27	38	13	23	18	42
Coagulase negative staphylococci	27	22	30	23	41	41
***Streptococcus* species**	8	4	6	6	4	4
***Enterococcus* species**	3	10	2	2	3	0
Aerobic gram negative bacilli	9	24	7	5	10	7
Anaerobic bacteria	4	3	9	5		
Propionibacterium acnes					24	1
Other anaerobes					3	0
Culture negative	14	10	7	11	15	5
Polymicrobial	15	31	14	12	16	3
Other	3					

Tande and Patel. Clin Microbiol Rev 2014;27:302

Cardiovascular Implantable Electronic Device Infection - Microbiology





Sohail et al. J Am Coll Cardiol 2007;49:1861

PJI Definitions

	Definitions of Prosthetic Joint Infection					
	2011 Musculoskeletal Infection Society[1]		2013 Infectious Diseases Society of America[2]		2013 International Consensus[3]	
	Definitive evidence	Supportive evidence	Definitive evidence	Supportive evidence	Definitive evidence	Supportive evidence
Sinus tract communicating with the prosthesis	X		X		X	
Identical microorganism isolated from ≥2 cultures	X		X		X	
Purulence surrounding the prosthesis		X	X			
Acute inflammation of periprosthetic tissue		X		X		X
A single culture with any microorganism		X				X
A single culture with a virulent microorganism				X		
Elevated synovial fluid leukocyte count		X				X
Elevated synovial fluid neutrophil percentage		X				X
Elevated serum ESR and CRP		X				X

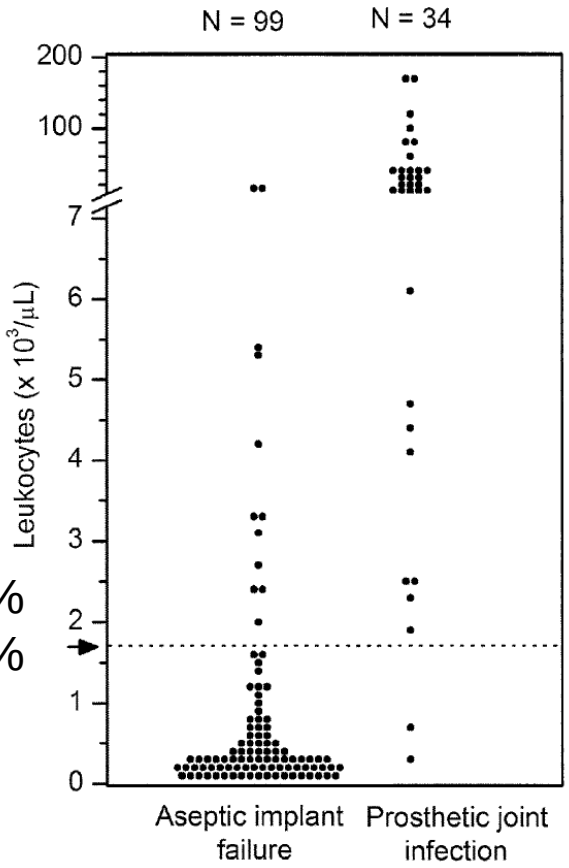
[1]Parvizi et al. Clin Orthop Relat Res 2011;469:2992
[2]Parvizi & Gehrke. Proceedings of the International Consensus Meeting on Periprosthetic Joint Infection 2013
[3]Osmon et al. Clin Infect Dis 2013:56:e1

Test Characteristics and Relative Costs of Preoperative Tests for PJI Diagnosis

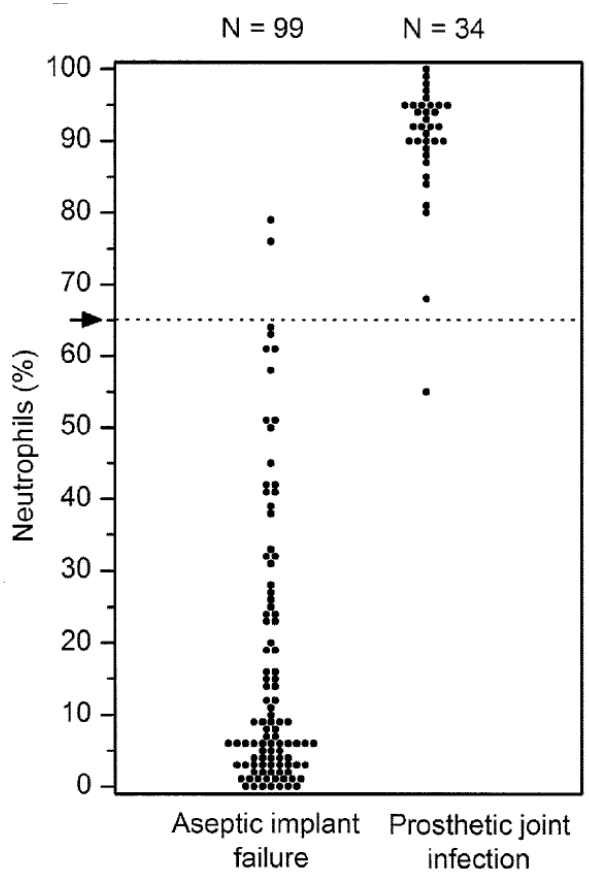
Test	Joint	Threshold value	Sensitivity	Specificity	+ LR	- LR	Cost	Comments
PERIPHERAL BLOOD								
WBC	Hip and knee	11,000 x 10^9/L	45	87	3.5	0.6	$	1796 patients in 15 studies
CRP		10 mg/L	88	74	3.4	0.2	$	3225 patients in 23 studies
ESR		30 mm/hr	75	70	2.5	0.4	$	3370 patients in 25 studies
IL-6		10 pg/mL	97	91	10.8	0.0	$	432 patients in 3 studies
Procalcitonin		0.3 ng/mL	33	98	16.5	0.7	$	78 patients in single study
IMAGING								
Plain radiograph	Hip	Lucency or periosteal new bone formation	75	28	1.0	0.9	$	65 patients in single study
Triple phase bone scan	Late hip	Increased uptake on all 3 phases	88	90	8.8	0.1	$$$	46 patients in single study
Bone scan/labeled leukocyte scan	Late hip and knee	Incongruent images	64	70	2.1	0.5	$$$	166 patients in single study
FDG-PET scan	Hip and knee		82	87	6.1	0.2	$$$$$	635 patients in 11 studies
SYNOVIAL FLUID								
Cell count	Knee	1100 cells/μL	91	88	7.6	0.1	$$	429 patients in single study
Neutrophil percentage		64%	95	95	17.9	0.1	$$	
Cell count	Hip	4200 cells/μL	84	93	12.0	0.2	$$	201 patients in single study
Neutrophil percentage		80%	84	82	4.7	0.2	$$	
Cell count	Knee (<6 weeks)	27,800 cells/μL	84	99	84.0	0.2	$$	146 patients in single study
Neutrophil percentage		89%	84	69	2.7	0.2	$$	
Culture	Hip and knee		72	95	14.4	0.3	$$	3332 patients in 34 studies

Tande and Patel. Clin Microbiol Rev 2014;27:302

Synovial Fluid Leukocyte/Differential Prosthetic Knee (>6 months from index surgery)



Sensitivity, 94%
Specificity, 88%



Sensitivity, 97%
Specificity, 98%

Trampuz et al. Am J Med 2004;117:556

Synovial Fluid Leukocyte/Differential

	WBC (cells/μl)	Sensitivity	Specificity	Neutrophil percentage	Sensitivity	Specificity	Joint type	Time from index surgery
Trampuz Am J Med 2004;117:556	**1,700**	94	88	**65**	97	98	Knee (133)	>6 months
Ghanem JBJS 2008;90:1637	**1,100**	91	88	**64**	95	95	Knee (429)	Varied
Schinsky JBJS 2008;90:1869	**4,200**	84	93	**80**	84	82	Hip (201)	Varied
Bedair CORR 2011;469:34	**10,700**	95	91	**89**	84	69	Knee (146)	<6 weeks
Cipriano JBJS 2012;94:594 **Non-inflammatory arthritis**	**3,450**	91	93	**78**	96	87	Hip/Knee (810)	Unknown
Cipriano JBJS 2012;94:594 **Inflammatory arthritis**	**3,444**	88	80	**75**	100	82	Hip/Knee (61)	Unknown
Zmistowski J Arthroplasty 2012;27:1589	**3,000**	93	94	**75**	93	83	Knee (150)	Unknown
Dinneen Bone & Joint J 2013;95:554	**1,590**	90	91	**65**	90	87	Hip/Knee (75)	Unknown

Natural Progression of Synovial Fluid Leukocytes in TKA

WBC, Neutrophil Percentage and Total Neutrophil Count by Time Period*				
	First 45 Days	Days 46 to 90	3 Months to 1 Year	1 to 2 Years
WBC count/µL	3037±3786	1119 ±1325†	474 ±894‡	428±706
Neutrophil %	69±27	49±23†	41±27	28±32‡
Neutrophils µL	2533±3483	649±871†	270±598‡	241±552

*Values are means and standard deviations
†Significantly different from the first 45 days ($p<0.05$)
‡Significantly different from days 46 to 90 ($p<0.05$)

Christensen et al. JBJS 2013;95:2081

Novel Synovial Fluid Biomarkers

Biomarker	Cutoff	Sensitivity (%)	Specificity (%)	
α-Defensin	4.8 µg/mL	100	100	Deirmengian et al. Clin Orthop Rel Res 2014;472:3254 (95 subjects; 29 PJI; hip/knee)
Neutrophil elastase 2	2.0 µg/mL	100	100	
Bactericidal/permeabiity-increasing protein	2.2 µg/mL	100	100	
Neutrophil gelatinase-associated lipocalin	2.2 µg/mL	100	100	
Lactoferrin	7.5 µg/mL	100	100	
IL-8	6.5 ng/mL	100	95	
CRP	12.2 mg/L	90	97	
Resistin	340 ng/mL	97	100	
α-Defensin	5.2 mg/L	97	96	Deirmengian et al. JBJS 2014;96:1439 (149 subjects; 37 PJI; hip/knee; did not report WBC)
CRP	3 mg/L	97	79	
α-Defensin → if positive, CRP		97	100	
α-Defensin	5.2 mg/L	100	100	Deirmengian et al. CORR 2015;473:198 (46 subjects; 23 PJI; hip/knee; did not report WBC performance)
α-Defensin	7720 ng/mL	95	100	Bingham et al. CORR 2014;472:4006 (57 subjects; 19 PJI; hip/knee; did not report %neutrophils)
α-Defensin	0.48 S/CO	63	95	Frangiamore et al. J Shoulder Elbow Surg 2015 In Press (33 cases; 11 PJI; shoulder)
IL-6	359.3 pg/mL	87	90	Frangiamore et al. J Bone Joint Surg Am 2015:97:63 (35 subjects; 15 PJI; shoulder)

Intraoperative Frozen Section Histopathology

Reference	Specimen	Joint	#PMN*	n	Sensitivity	Specificity	PPV**
Feldman et al. JBJS(Am) 1995;77:1807	JC, IM	Hip/knee	5	33	100	100	100
Athanasou et al. JBJS(Br) 1995;77:28	JC, IM	Hip/knee	1	106	90	96	88
Lonner et al. JBJS(Am) 1996;78:1553	JC, IM, ASPI	Hip/knee	5	175	84	96	70
			10		84	99	89
Pace et al. J Arthroplasty 1997;12:64	JC, IM	Hip/knee	5	18	82	93	82
Abdul-Karim et al. Mod Pathol 1998;11:427	IM, ST, UDT	Hip/knee	5	64	43	97	60
Banit et al. CORR 2002;401:230	JC, ASPI	Knee	10	55	100	96	82
		Hip	10	63	45	92	55
Musso et al. Postgrad Med J 2003;79:590	JC, IM, ASPI	Hip/knee	5	45	50	95	60
Wong et al. J Arthroplasty 2005;20:1015	JC, IM, SS	Hip/knee	5	33	93	77	68
			10		86	85	75
Ko et al. J Arthroplasty 2005;20:189	JC, IM, ASPI	Hip/knee	5	40	67	97	86
Frances Borrego et al. Int Orthop 2007;31:33	PST	Hip	10	63	67	90	80
		Knee		83	50	100	100
Nunez et al. Acta Orthop 2007;78:226	JC, IM, ASPI	Hip	5	136	86	87	79
Tohtz et al. CORR 2010;468:762	IM	Hip	10	52	87	200	100

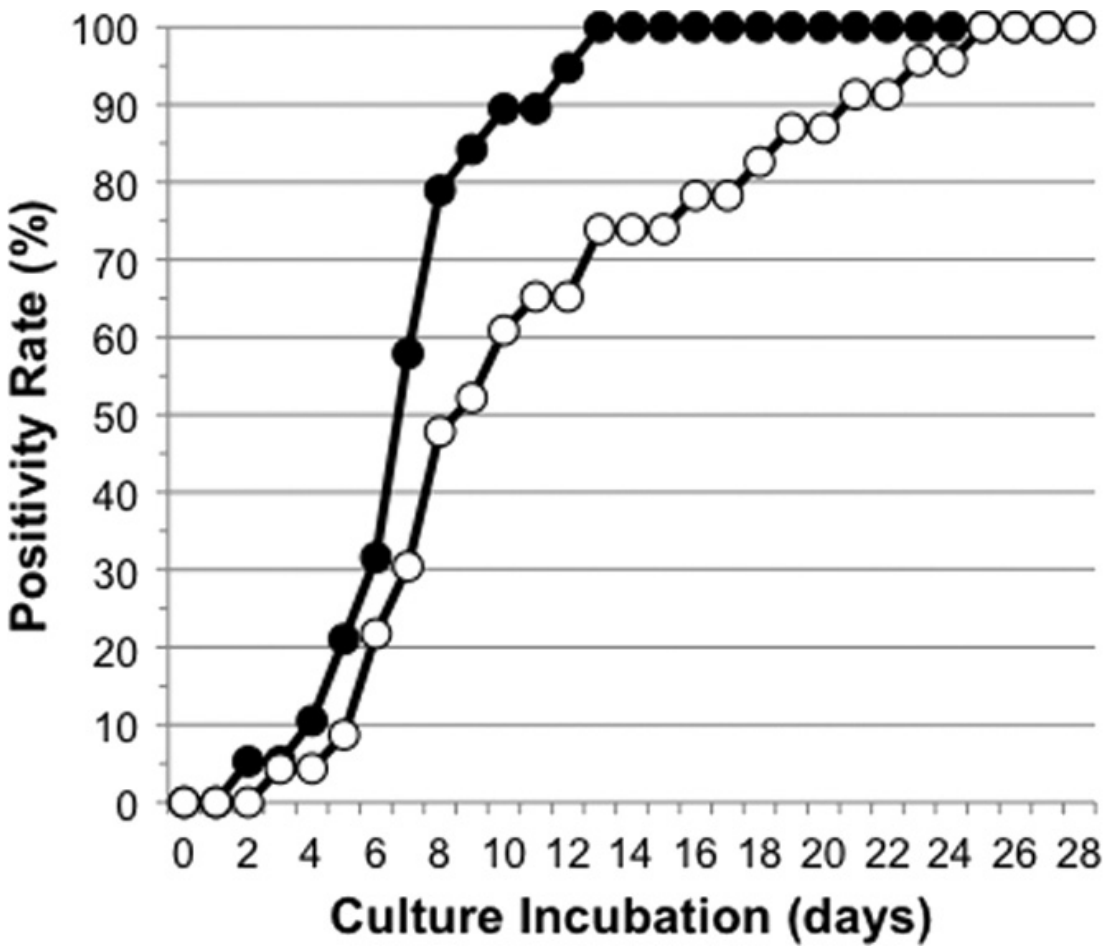
*Some studies used >, others ≥ the number shown, **Positive predictive value
JC, joint pseudocapsule; IM, interface membrane; ASPI, any area that appears suspicious for possible infection; ST, synovial tissue; SS, synovial surface; UDT, unusually discolored tissue; PST, periprosthetic soft tissue

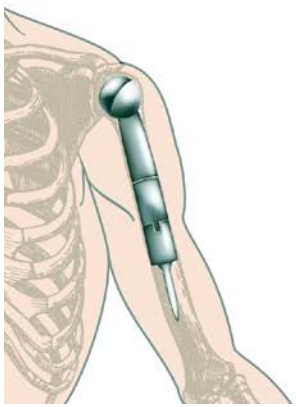
Propionibacterium acnes PJI

Histopathology	≥2 Cultures positive for *P. acnes*
Positive	6
Negative	9
All	15

Butler-Wu et al. J Clin Microbiol 2011;49:2490

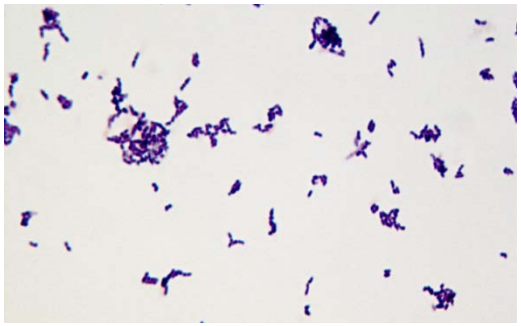
Propionibacterium acnes PJI





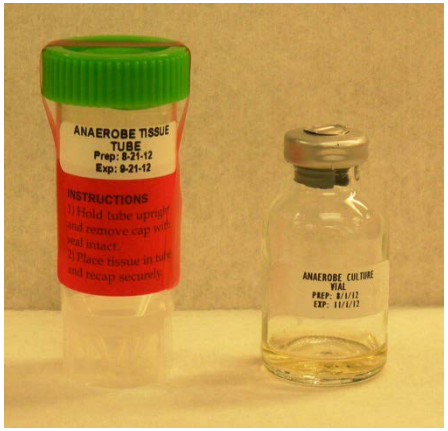
Infected Events

Non-Diagnostic Events



Butler-Wu et al. J Clin Microbiol 2011;49:2490

Propionibacterium acnes PJI



- ~6 month period, 2011
- Fluids and tissues placed in anaerobic fluid or tissue vials in operating room
- Tissues homogenized in 3 ml brain heart infusion broth
  - 0.1 ml tissue homogenate/fluid onto CDC anaerobic sheep blood agar, incubated anaerobically @ 37°C for 14 days
    - Examined Monday, Wednesday, and Friday for first week, then on days 7 and 14 or until positive
  - 1 ml tissue homogenate/fluid inoculated into **anaerobically prereduced thioglycolate broth**, closed, incubated @ 37°C for 14 days
    - Examined daily or until positive

Shannon et al. J Clin Microbiol 2013;51:731

Propionibacterium acnes PJI

- 14 subjects ≥2 shoulder bone/joint culture *P. acnes*
- 72 anaerobic plate or broth cultures (3 to 13/event)
- *P. acnes* growth
  - 28 plates (27 within 7 days)
  - 53 broths (52 within 7 days)

- All events 2 positive broth cultures by 7 days, but 3 negative plate cultures and another 3 single positive plate cultures even with 14 days of incubation
- No events plate positive only
- Broth more likely to be positive than plate culture by day 7 and overall (*P*, 0.0001)

Shannon et al. J Clin Microbiol 2013;51:731

Periprosthetic Tissue Culture

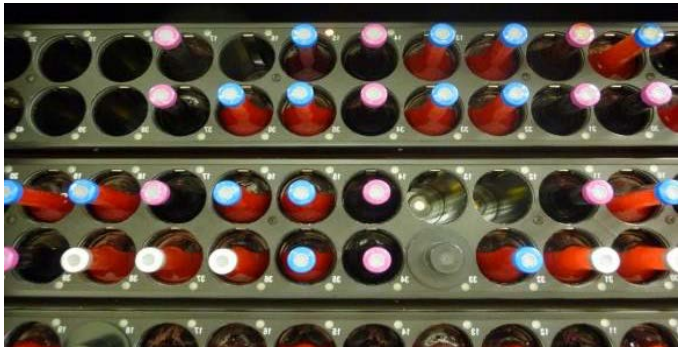
- Multiple (5 or 6) specimens cultured
- ≥ or >2 operative specimens indistinguishable organism

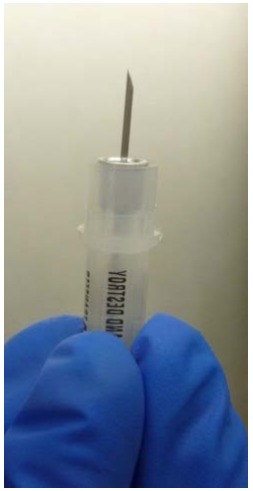
Atkins et al. J Clin Microbiol 1998;36:2932

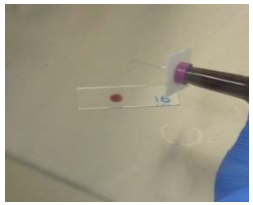
- IDSA Guideline - At least 3 and optimally 5 or 6 periprosthetic intraoperative tissue samples or the explanted prosthesis itself should be submitted for aerobic and anaerobic culture at the time of surgical débridement or prosthesis removal to maximize the chance of obtaining a microbiologic diagnosis (B-II).

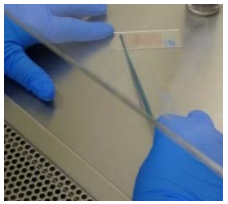
Osmon et al. Clin Infect Dis 2013:56:1

Periprosthetic Tissue Culture
Blood Culture Bottles









Periprosthetic Tissue Culture Blood Culture Bottle Study (Oxford #1)

- Tissue + sterile glass beads (Ballotini) 5 ml saline (shaking)
  - 1 ml each into Robertson's cooked meat broth, fastidious anaerobic broth, BACTEC Anaerobic/F & Aerobic/F bottles
  - 0.25 ml each onto chocolate, aerobic & anaerobic (2) blood agars
  - 5 day incubation
  - 141 elective joint revisions (mean, 4.9 specimens/case)
  - 23 PJI cases

Sensitivity/ Specificity (≥2 positive)	Direct plates	Fastidious anaerobic broth	Cooked meat broth	BACTEC blood culture bottles
Sensitivity, %	39	57	83	87
Specificity, %	100	100	97	98

Hughes et al. Clin Microbiol & Infect 2011;10:1528

Periprosthetic Tissue Culture Blood Culture Bottle Study (Oxford #2)

- Tissue + 3 ml saline + sterile glass beads → vortexed 15 sec
  - 0.5 ml BACTEC Lytic/10 Anaerobic/F and Plus Aerobic/F bottles
  - 14 day incubation
- 322 patients (mean, 4 specimens/case)
- 66/79 PJI culture-positive (sensitivity, 84%)
  - All positive within 3 days of culture except 1 (detected at 8 days)
- 7/243 non-PJI culture-positive (specificity, 97%)
- *Propionibacterium* species, 30 isolates
  - 67 samples positive
  - 6 patients - 2 PJI, detected at 3 and 8 days
  - Detected, median of 5 days (1 day for other bacterial species)
  - Sub-culturing negative bottles after 14-days' incubation detected only a single (clinically insignificant) additional *Propionibacterium* isolate from 1000 bottles

Minassian et al. BMC Infect Dis 2014;14:233

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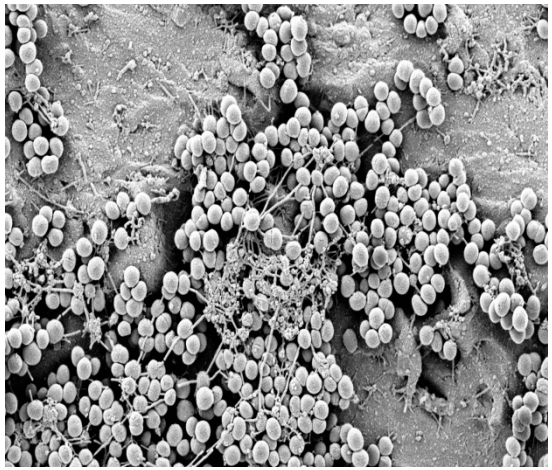
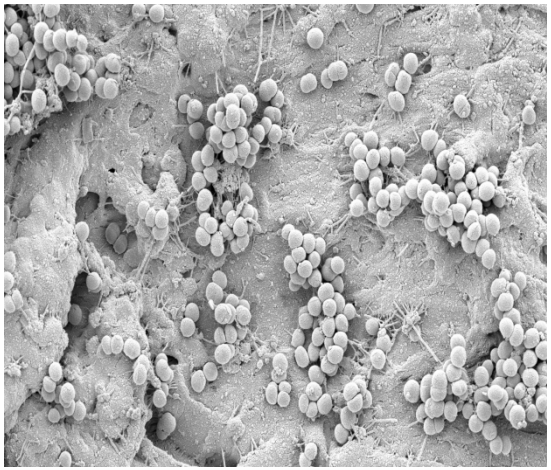
MALDI TOF MS and Prosthetic Joint Infection

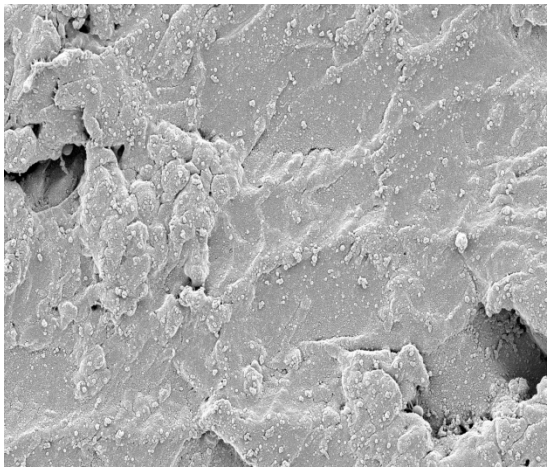
- **May 2012 - May 2013**
- **178 PJI, 82 aseptic failure (AF) cases with positive cultures**
- **770 organisms**
  - **Median 3/subject**
  - **MALDI TOF MS used to identify 455 organisms (59%)**
    - **89% identified to species level**
- ***Staphylococcus aureus*, *Staphylococcus caprae* always associated with infection**
- ***Staphylococcus epidermidis*, *Staphylococcus lugdunensis* pathogens or contaminants**
- **All other coagulase-negative staphylococci more frequent as contaminants**
- **Most streptococcal & *Corynebacterium* isolates pathogens**

Peel et al. Diagn Microbol Infect Dis 2015;81:163

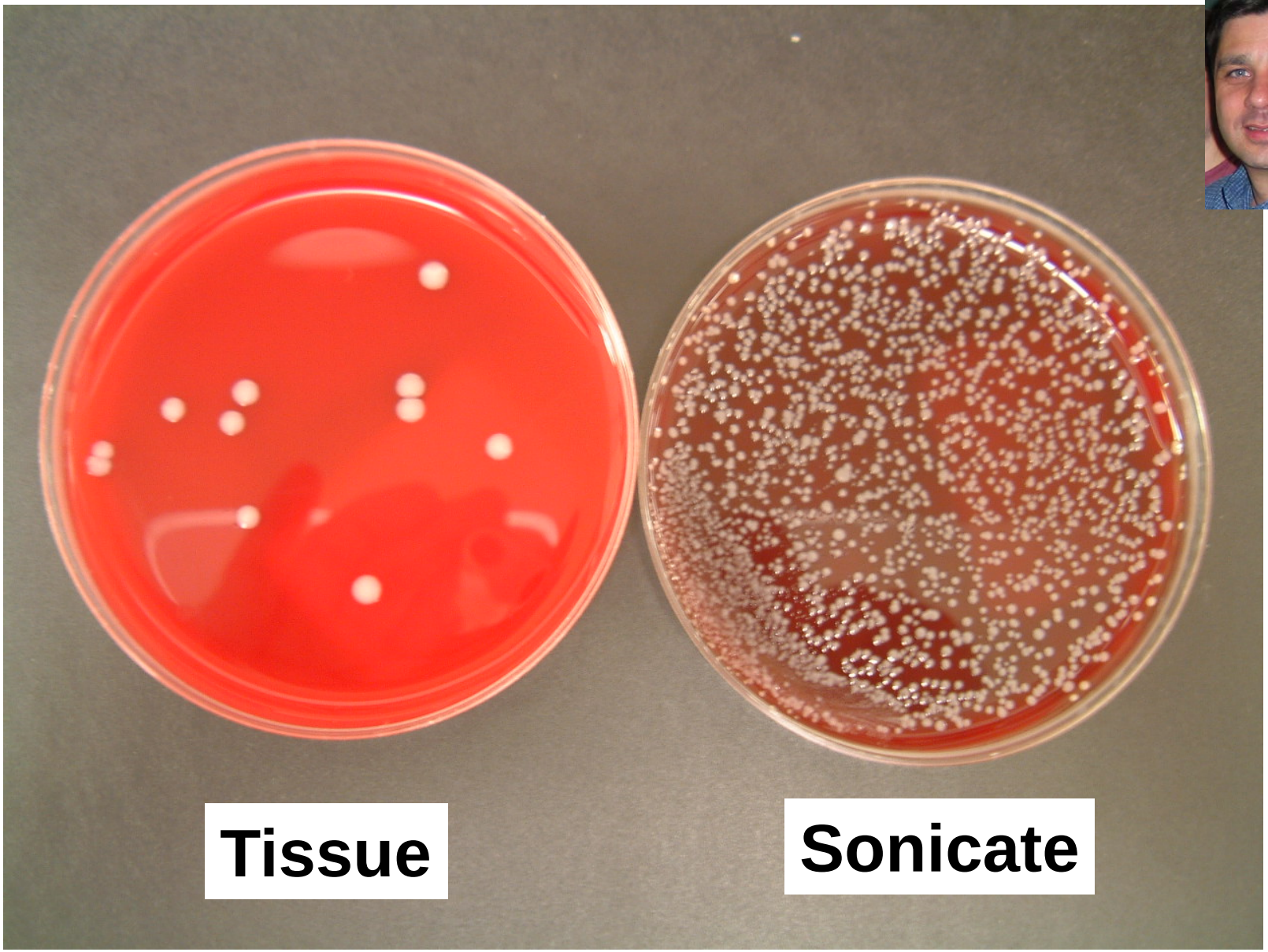
Staphylococcus epidermidis Biofilm on Polycarbonate Coupons Scanning Electron Microscopy







Soaking	Scraping	Sonication



Current Orthopaedic Implant Processing - Mayo Clinic

Prosthesis Placed in Container (Operating Room)

400 ml Ringer's Solution Added

Vortex 30 sec

Sonicate 5 min

Vortex 30 sec

Centrifuge 5 min

Aspiration

Plating


Comparison of Sonicate Fluid and Tissue Culture for Diagnosis of Infection Associated with Orthopedic Implants


Implant type		Sonicate fluid	Periimplant tissue	p value	Reference
Our studies					
Prosthetic hip/knee joint	Sensitivity	79%	61%	<0.001	Trampuz et al, NEJM 2007 Vol 357;654
	Specificity	99%	99%		
Prosthetic shoulder joint	Sensitivity	67%	55%	0.046	Piper et al, JCM 2009 Vol 47:1878
	Specificity	98.0%	95%		
Prosthetic elbow joint	Sensitivity	89%	55%	0.18	Vergidis et al, JSES 2011 Vol 20;1275
	Specificity	100%	93%		
Spine implant	Sensitivity	91%	73%	0.046	Sampedro et al, Spine 2010 Vol 25:1218
	Specificity	97%	93%		

Sonication *versus* Vortexing for Prosthetic Joint Infection Diagnosis

- 135 removed prostheses
  - 35 PJI
  - 100 aseptic failure
- Using cut-off of 50 CFU/ml
  - Sonication more sensitive than vortexing (60% versus 40%)
- Specificity was 99% for both methods

Portillo et al. J Clin Microbiol 2013:51:591

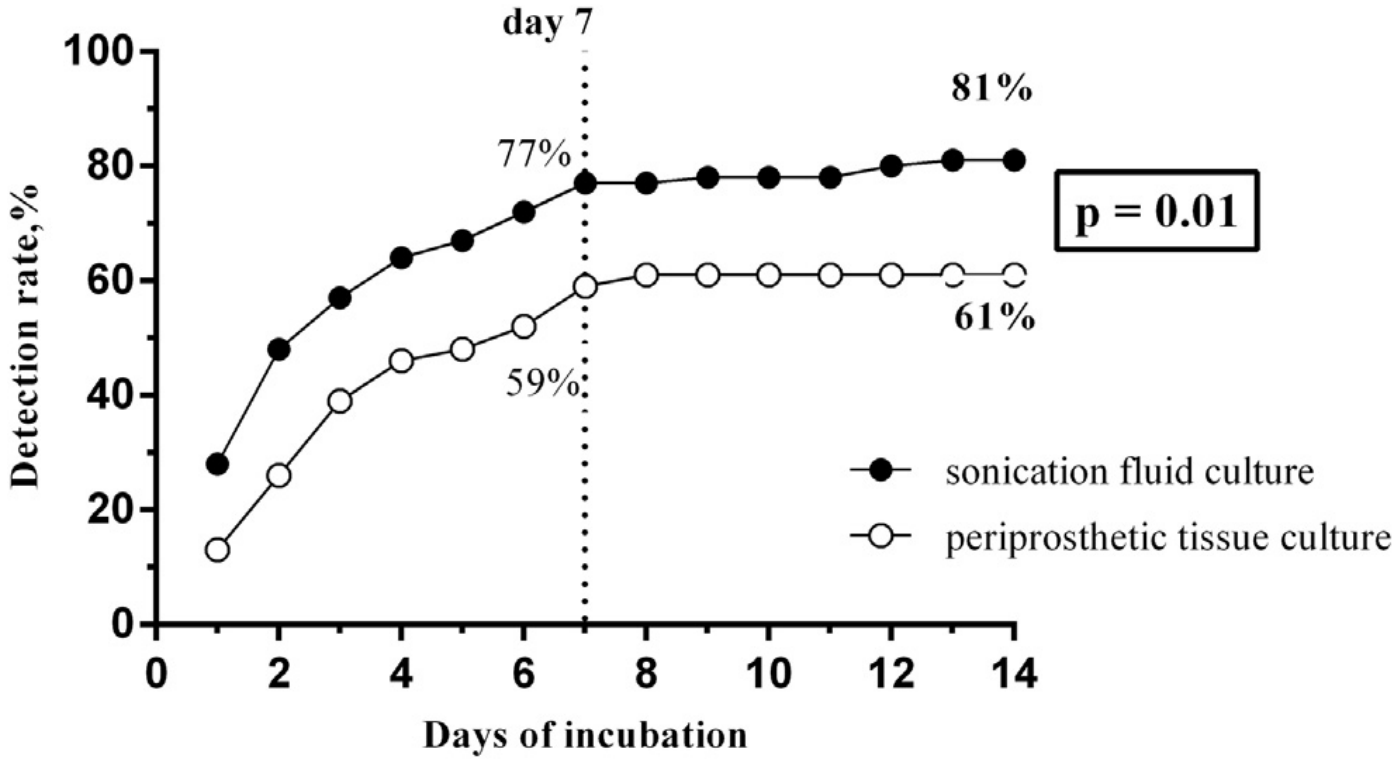
Sonication of Orthopedic Implants Particularly Helpful for Delayed Implant Infection

Type of failure	Sensitivity			Specificity		
	Sonicate	Tissue	p-value	Sonicate	Tissue	p-value
Overall (n = 317)	90	67	<0.001	99	99.5	1
Suspected septic failure (n = 79)	86	76	0.057	100	100	1
Unsuspected septic failure (n = 238)	100	49	<0.001	99	99.5	1
p-value	0.032	0.007		0.864	1	
Early (<3 months) (n = 43)	93	85	0.625	94	100	1
Delayed (>3 months) (n = 240)	88	68	<0.001	99	100	1
p-value	0.723	0.013		0.169	1	

Puig-Veridié et al. Bone Joint J 2013;95-B:244-9.

Sonication Provides “Rapid” Results

- 231 explanted prostheses (AF, 162; PJI, 69)
  - Sensitivity/specificity
    - Sonicate fluid culture 81/99%, tissue culture 61/100%



Portillo et al. J Infect 2014;69:35-41

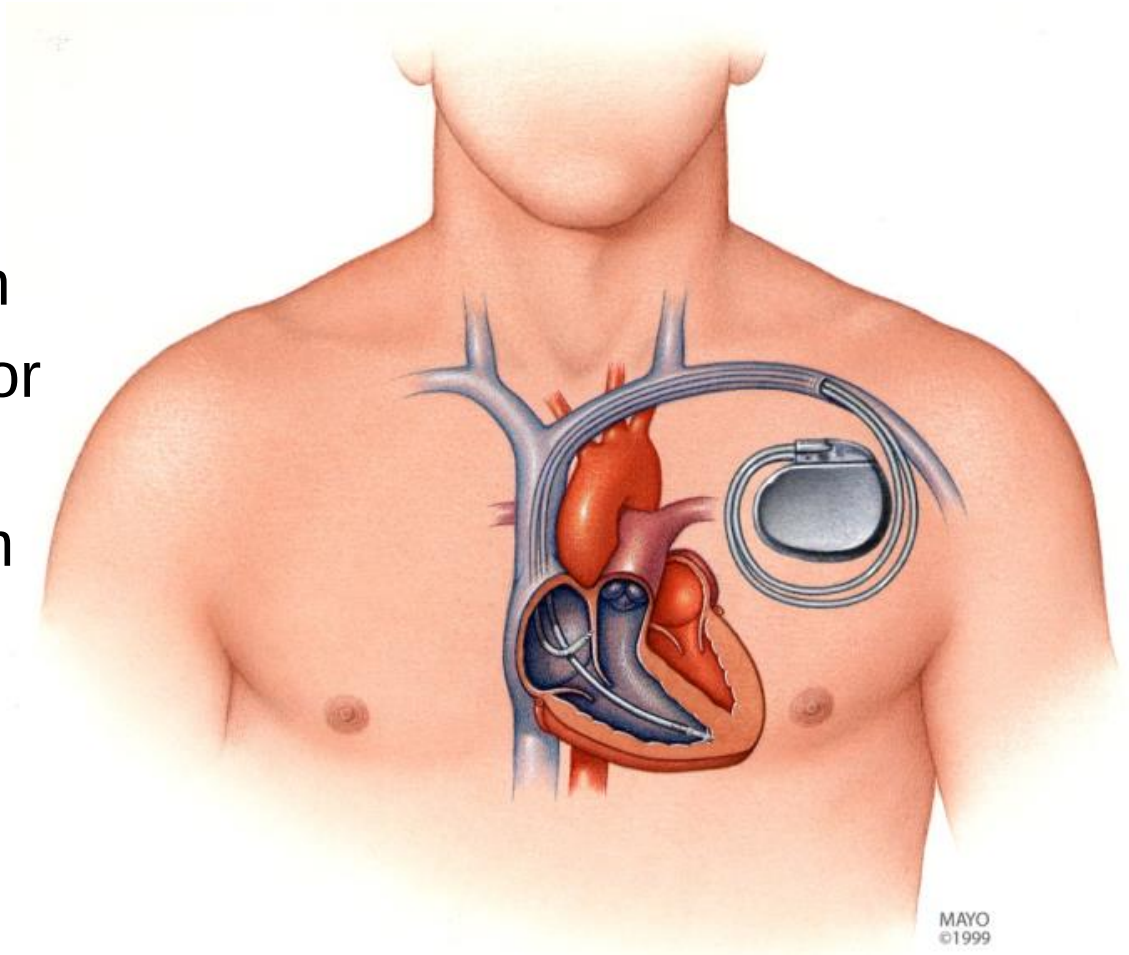
Cardiovascular Implantable Electronic Device Infection

Sohail et al. Expert Rev Anti-infect Ther 2010;7:831

Dababneh and Sohail Cleveland Clinic J Med 2011;8:529

Cardiovascular Implantable Electronic Device Cultures

- High degree of device colonization and/or culture contamination in absence of infection
  - 33-42% of generator pockets positive[1,2]
- Negative cultures from those with device infection
  - 31%[1]



[1]Dy Chua J, et al. Pacing Clin Electrophys. 2005;28:1276
[2]Kleemann T, et al. Europace. 2010;12:58-63

Cardiovascular Implantable Electronic Device Infection Guidelines for Diagnosis*

	Blood Cultures	Generator Pocket				Lead tip culture	Device culture
		Tissue Gram stain	Tissue culture	Swab	Pus or fluid****		
American Heart Association[1]	√	√**	√			√	
British Society for Antimicrobial Chemotherapy[2]***	√	√	√		√	√ (ideally distal and proximal) and lead vegetation	Merits further study

***Routine microbiologic studies should not be performed on devices removed for non-infectious reasons**

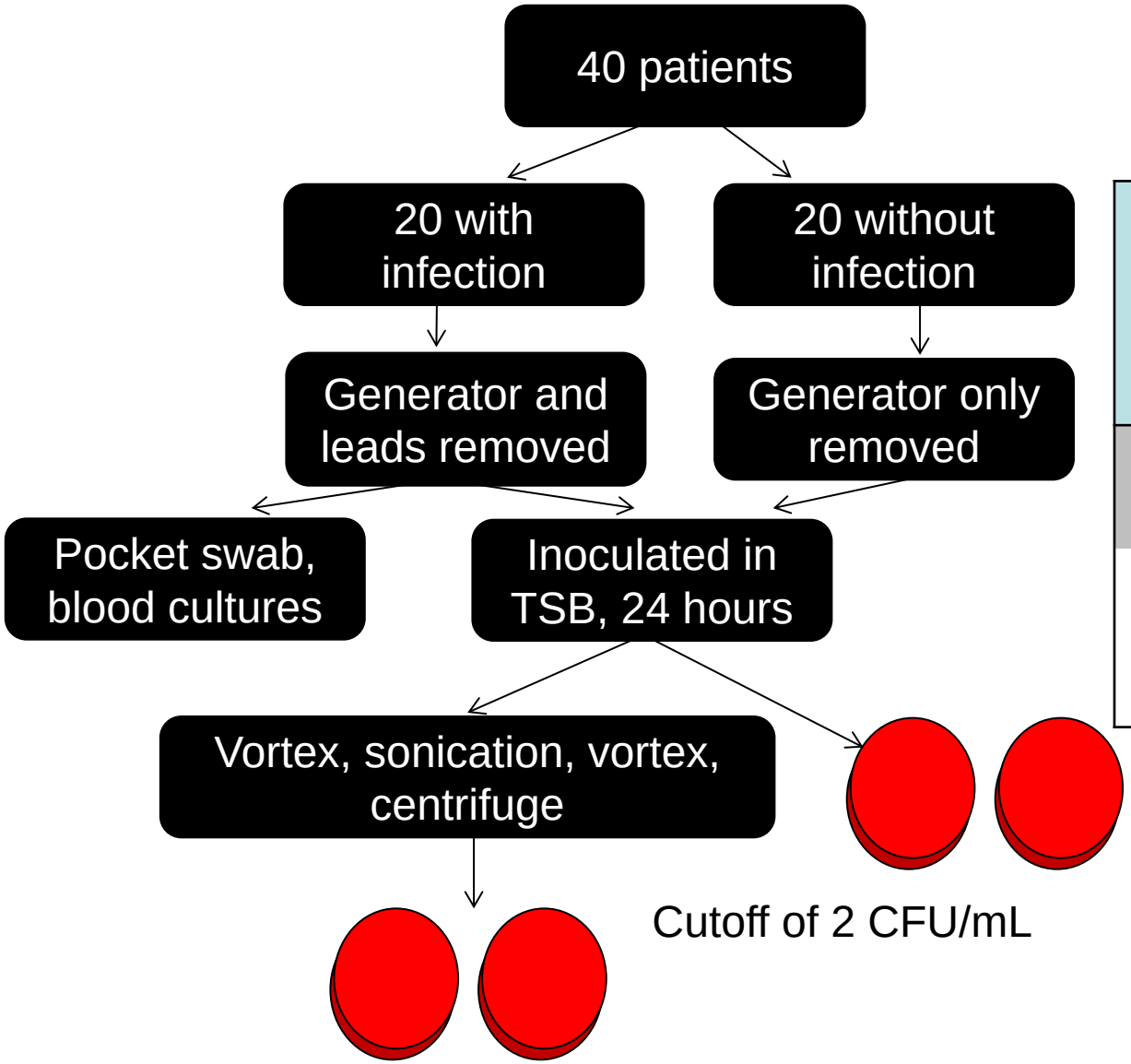
**Tissue and lead tip should be cultured for fungi and mycobacteria if the initial Gram stain is negative

***British Heart Rhythm Society, British Cardiovascular Society, British Heart Valve Society, British Society for Echocardiography

****Collected via syringe +/- needle from a discharging wound

[1]Baddour et al. Circulation 2010;121:458
[2]Sandoe et al. J Antimicrob Chemother 2015;70:325

Cardiovascular Implantable Electronic Device Sonication (Sapienza Università Study)



	Positive sonicate fluid culture, n(%)	Positive broth incubation culture, n(%)
Non-infected components (n=20)	8 (40)	4 (20)
Infected components (n=60)	46 (77)	36 (60)

p=0.001

Oliva et al. J Clin Microbiol 2013;51:496

Sonication, Swab and Blood Cultures 17 Subjects With Infected Cardiovascular Implantable Electronic Devices (Swiss Study)

CIED	Site of Infection	Echocardiography	Sonication (CFU/mL)	Swab Culture (Growth of Bacteria)	Blood Cultures (Positive Bottles)
PM	Pocket and definite IE	TTE: vegetations on lead and valve	MSSA (>1,000)	MSSA (strong)	MSSA (8/8)
CRT	Pocket and possible IE	TTE: no vegetation	MSSA (>1,000)	MSSA (strong)	MSSA (3/4)
PM	Pocket and possible IE	TTE: no vegetation	MSSA (>1,000), *P. aeruginosa* (>1,000)	MSSA (strong), *P. aeruginosa* (strong)	MSSA (10/10)
PM	Pocket and possible IE	TEE: no vegetation	*S. lugdunensis* (710)	*S. lugdunensis* (few)	*S. lugdunensis* (6/6)
PM	Pocket	TTE: no vegetation	MSSA (>1,000)	MSSA, 2 MT (strong)	Sterile
PM	Pocket	TTE: no vegetation	MSSA (>1,000)	MSSA (moderate)	Sterile
ICD	Pocket	No echocardiography	MSSA (>1,000, >1,000), P. acnes (750)	MSSA (few)	Sterile
PM	Pocket	TEE: no vegetation	CNS (50)	CNS (few)	Sterile
PM	Pocket	No echocardiography	*P. acnes* (700)	*P. acnes* (few)	Sterile
PM	Pocket	No echocardiography	CNS (>1,000)	Sterile	CNS (1/2)
PM	Definite IE	TTE: vegetation on lead and valve	MSSA (790)	Sterile	MSSA (4/4), *S. mitis* (1/4)
PM	Pocket and definite IE	TTE: vegetation on lead	*B. cereus* (>1,000)	Not performed	MSSA (10/10)
PM	Pocket	No echocardiography	*P. acnes* (>1,000), CNS (110)	Sterile	Sterile
PM	Pocket	TEE: no vegetation	*P. acnes* (700)	Sterile	Sterile
PM	Pocket	No echocardiography	CNS (>1,000)	Sterile	Sterile
PM	Pocket	TTE: no vegetation	MSSA (>1,000)	Sterile	Sterile
ICD	Pocket	TTE: no vegetation	Sterile	Sterile	Sterile

Rohacek et al. PACE 2015:38:247

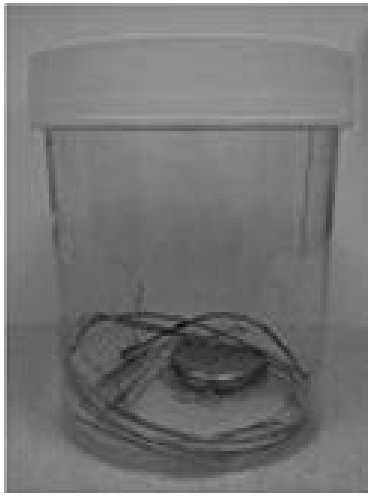
Sonication and Swab Cultures 115 Subjects With Non-Infected Cardiovascular Implantable Electronic Devices (Swiss Study)

- ≥10 CFU/mL of sonication fluid from 21 devices (18%)
- Pocket swab cultures positive 30 of 112 devices cultured (27%)
  - Moderate in 2 cultures
  - Few in 20 cultures
  - After enrichment in 7 cultures
- *Propionibacterium acnes* and CNS most common
- 6 subjects with >150 CFU/mL in sonication fluid (4 *Propionibacterium acnes*, 2 CNS) → 100% concordance with swabs
- 2 subjects with detection of CNS in sonication and swab culture developed clinical infection with CNS 3 weeks and 4 months later

Rohacek et al. Circulation 2010;121:1691

Cardiovascular Implantable Electronic Device Sonication (Mayo Clinic Study)

- Determine whether device vortexing-sonication followed by culture of resulting sonicate fluid enhances microbial detection compared with swab or pocket tissue cultures
  - 42 subjects with noninfected + 35 with infected devices enrolled over 12 months
  - One swab each from device pocket & device surface, pocket tissue & device per patient
  - Swabs, tissues cultured using routine methods
  - Device processed in Ringer's solution using vortexing-sonication → resultant fluid semiquantitatively cultured



Nagpal et al. American Journal of Cardiology, 2015;115:912

Sensitivity and Specificity of Culture For Cardiovascular Implantable Electronic Device Infection by Specimen Type (Mayo Clinic Study)

Test	Proportion	Sensitivity (95% CI)	P-value*	Proportion	Specificity (95% CI)	P-value*
Device Swab (≥2+)	3/35	9 (2-23%)	<0.001	41/42	98 (87-100%)	0.317
Pocket Swab (≥2+)	7/35	20 (8-37%)	0.001	41/42	98 (87-100%)	0.317
Tissue (≥2+)	3/35	9 (2-23%)	<0.001	40/42	95 (84-99%)	1.000
Sonicate Fluid (≥20 CFU/10 ml)	19/35	54 (37-71%)		40/42	95 (84-99%)	
Device Swab (any)	10/35	29 (15-46%)	<0.001	40/42	95 (84-99%)	<0.001
Pocket Swab (any)	15/35	43 (26-61%)	0.008	39/42	93 (81-99%)	<0.001
Tissue (any)	16/35	46 (29-63%)	0.004	28/42	67 (50-80%)	0.366
Sonicate Fluid (any)	26/35	74 (57-88%)		25/42	60 (43-74%)	

*p-value testing for a difference in performance rate relative to sonicate fluid culture via McNemar's test

Nagpal et al. American Journal of Cardiology, 2015;115:912

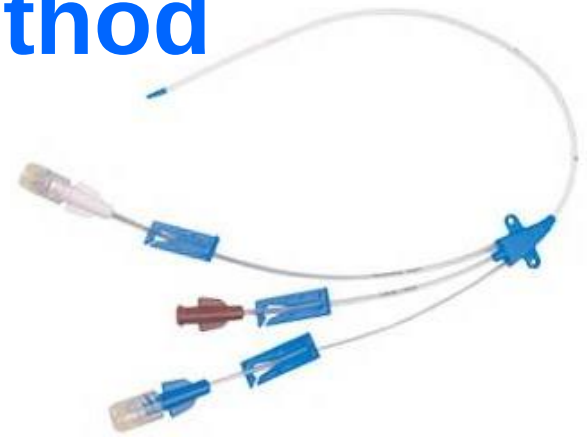
Culture Sensitivity Based on Specimen Types Studied Among Patients With Cardiovascular Implantable Electronic Device Infection (Mayo Clinic Study)

	Proportion	Rate, % (95% CI)	P-value*
Device Erosions/Pocket Infections (n=16)			
Device Swab	2/16	13 (2-38%)	0.003
Pocket Swab	5/16	31 (11-59%)	0.034
Tissue	2/16	13 (2-38%)	0.003
Sonicate Fluid	11/16	69 (41-89%)	
Lead or Valve associated Endocarditis (n=19)			
Device Swab	1/19	5 (0-26%)	0.008
Pocket Swab	2/19	11 (1-33%)	0.014
Tissue	1/19	5 (0-26%)	0.008
Sonicate Fluid	8/19	42 (20-67%)	

*p-value testing for a difference in performance rate relative to sonication via McNemar's test.

Nagpal et al. American Journal of Cardiology, 2015;115:912

Intravascular Catheter Roll Plate Culture Method

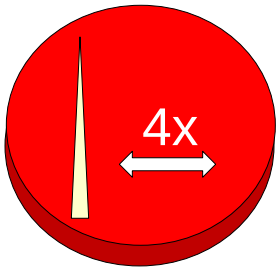


- Most commonly used method is semiquantitative roll plate method
  - o Peripheral (Maki 1977)
  - o Pediatric umbilical catheters (Adam 1982)
  - o Short term/long-term CVCs (Bouza 2005)
  - o Dialysis catheters (Brodersen 2007)
- Simple, requires no special equipment
  - o May not detect intraluminal colonization?

Intravascular Catheter Culture Comparative Methods Evaluation

975 nontunneled central venous catheters cut into 2 equal 5 cm-sized segments (subcutaneous/tip); 217 had significant colonization

Randomized order



Likelihood of detection of catheter colonization, using 15 cfu/tip (roll plate method) and 100 cfu/tip (sonication and vortex)

Roll plate method	Sonication
88	85

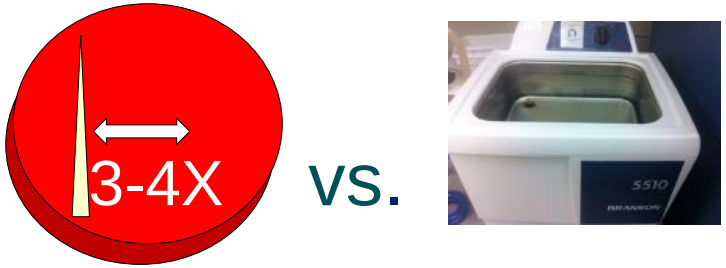
Erb S, et al. Clin Infect Dis 2014;59:514

Long Term Intravascular Catheters

- Random order of roll plate vs sonication
  - 313 Hickman catheters
    - Roll plate 21%/sonication 17%
    - 89 CRBSI sensitivity roll plate 35%/sonication 45%

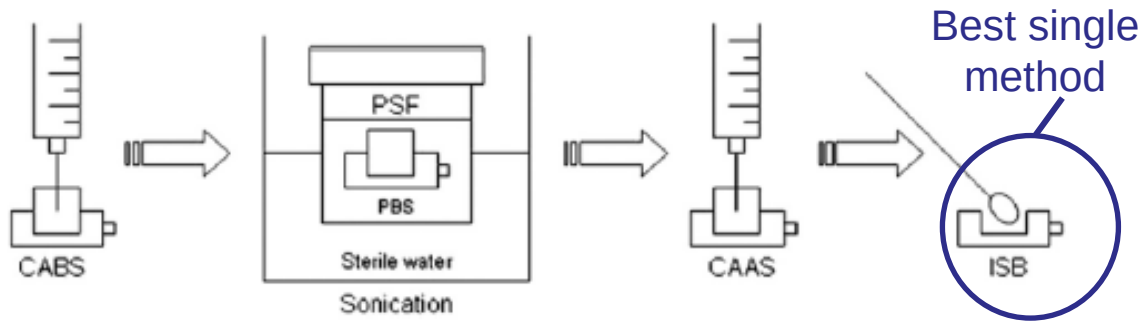
      Slobbe et al. J Clin Microbiol 2009;47:885
  - 149 tunneled long term catheters
    - 39 colonized
    - Roll plate 95%/sonication 44% (p<0.001)

      Guembe et al. J Clin Microbiol 2012;50:1003



Vascular Access Ports (VAP)

- 223 Port-A-Caths
  - 53 colonized
  - 17 bloodstream infection (BSI)



Bouza et al. Diagn Microbiol Inf Dis 2014;78:162

	Method	Sensitivity (port colonization)	Sensitivity/ specificity (VAP-associated BSI)
Tip	Roll plate	57	59/90
Tip	Sonication	32	47/96
Port	Aspirate (before sonication)	36	53/95
Port	Sonication fluid	57	77/92
Port	Aspirate (after sonication)	51	59/92
Port	Internal surface swab	**70**	**94/90**
Tip + Port	Roll plate + sonication + internal surface swab	94	100/84

Molecular Diagnostics

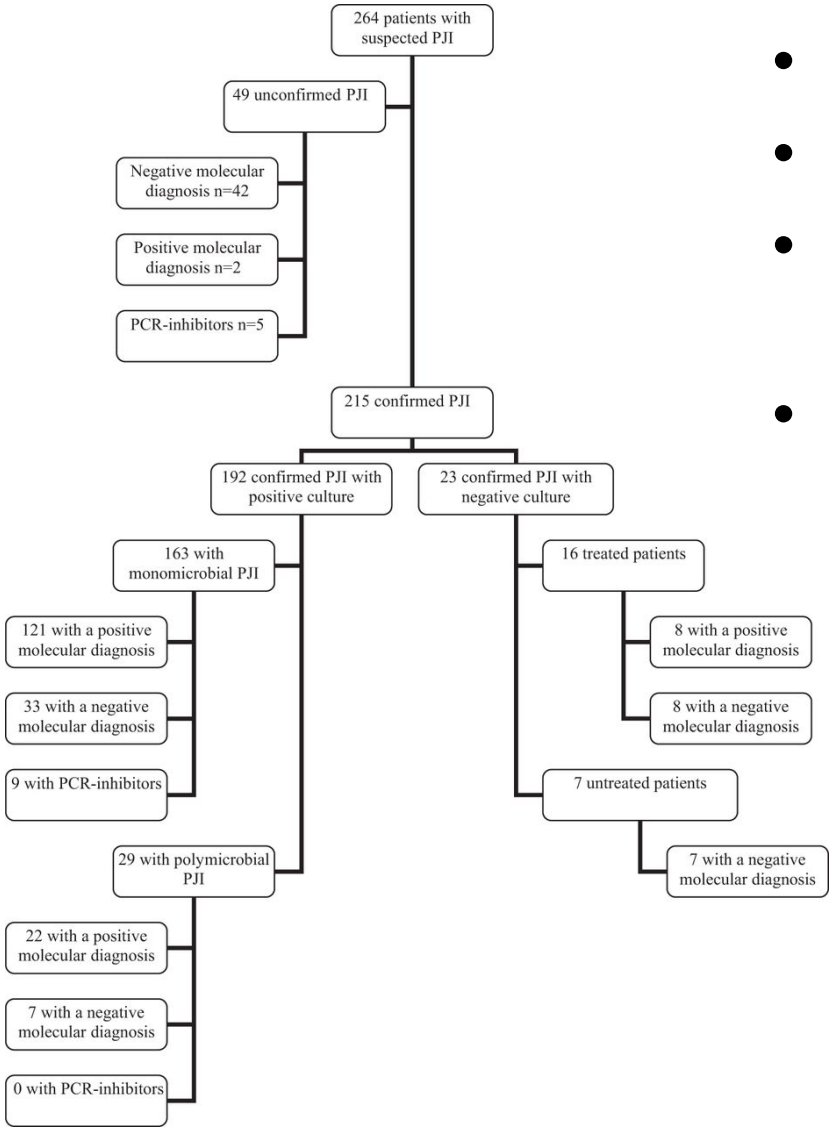
- Promises:
  - Increased diagnostic yield (e.g., in setting of prior antimicrobial therapy)
  - Rapid
- Broad range (e.g., 16S rRNA gene) PCR
  - Lack of specificity; requires sequencing or additional step for identification; difficult to detect polymicrobial infection
- Panel PCR
  - Limited to organisms included in panel

Prosthetic Joint Sonication and Broad-Range PCR - No Improvement Over Culture

Test	Sensitivity 135 PJI	Specificity 231 Aseptic Failure	Accuracy
	% (95% Confidence Interval)		
Tissue culture	70.4 (64.5-76.3)	98.7 (97.2-100)	88.3 (84.2-92.4)
Sonicate fluid culture	72.6 (66.8-78.4)	98.3 (96.6-100)	88.8 (84.7-92.9)
Sonicate fluid broad-range PCR	70.4 (64.5-76.3)	97.8 (95.9-99.7)	87.7 (83.5-91.9)
Combination of two tests above	83.0 (78.2-87.8)	95.7 (93.1-98.3)	91.0 (87.3-94.7)
Sonicate fluid culture plus PCR	78.5 (73-2-83.8)	97.0 (94.8-99.2)	90.2 (86.4-94.0)
Synovial fluid culture	64.7 (56.5-72.9)	96.9 (93.9-99.9)	84.1 (77.8-90.4)
Sonicate fluid PCR - lower cutoff (CP <27.59 cycles)	80.0 (74.8-85.2)	90.9 (87.2-94.6)	86.8 (82.5-91.3)

Gomez et al. J Clin Microbiol 2012:50:3501

Lack of Sensitivity of Periprosthetic Tissue Broad-Range PCR



- 2-year period
- 5 tissues/patient
- Culture, 16S rRNA gene PCR/sequencing
- 264 suspected cases of PJI
  - PJI confirmed (215)
    - Culture positive, 192 (89%)
    - PCR positive, 151 (73%)
  - Non-PJI (49)
    - PCR positive, 2 (specificity, 96%)

Bémer et al. J Clin Microbiol 2014:52:3583

Prosthetic Joint Sonication – PJI PCR Panel

Test	Aseptic failure (290)	PJI (144)	Sensitivity	Specificity	PPV	NPV
	No. of patients with positive specimens		% (95% confidence interval)			
Synovial-fluid culture	5/161	59/89	66.3 (55.5-76.0)	96.9 (92.9-99.0)	92.2 (82.7-97.4)	83.9 (77.8-88.8)
Tissue culture						
Any growth	45	119	82.6 (75.4-88.4)	84.5 (79.8-88.5)	72.6 (65.1-79.2)	90.7 (86.6-93.9)
≥2 positive tissues (same organism)	6	101	70.1 (62.0-77.5)	97.9 (95.6-99.2)	94.4 (88.2-97.9)	86.9 (82.7-90.3)
Sonicate fluid culture	5	105	72.9 (64.9-80.0)	98.3 (96.0-99.4)	95.5 (89.7-98.5)	88.0 (83.9-91.3)
Sonicate fluid PCR (10 assay panel)			77.1 (69.3-83.7)	97.9 (95.6-99.2)	94.9 (89.2-98.1)	89.6 (85.7-92.7)
Any positive result	6	111				
Staphylococcus sp	2	75				
S. aureus	0	28				
Coagulase-negative staphylococci	2	47				
Streptococcus sp	3	11				
Enterococcus/*Granulicatella*/*Abiotrophia* sp	0	11				
Enterobacteriaceae	1	8				
Gram-positive anaerobic cocci	0	8				
Propionibacterium sp	0	8				
P. aeruginosa	0	5				
Corynebacterium sp	0	4				
C. jeikeium/*urealyticum*	0	0				
Non-*jeikeium* sp	0	4				
Proteus sp	0	1				
B. fragilis group	0	0				

Cazanave et al. J Clin Microbiol 2013;51:2280

Summary

"Device-Related Infections Require Device-Specific Diagnostics"

- **Prosthetic joint infection**
  - Cultures – synovial fluid and periprosthetic tissue (blood culture bottles), sonicate fluid
  - Novel synovial fluid markers?
  - Panel PCR
- **Cardiovascular implantable electronic device infection**
  - Avoid culturing devices removed for non-infectious reasons
  - Vortexing-sonication with semiquantitative aerobic/anaerobic culture
  - Tissue Gram stain?
- **Intravascular catheter and port infection**
  - Roll plate method (intravascular catheter tips)
  - Culture both tip and port (vascular access ports)

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