Prosthetic Joint Infection Update from the Laboratory

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Déclaration d'intérêts de 2012 à 2015

- **Conflict of interest:**
  - Nil to declare

- **Funding acknowledgement:**
  - Australian National Health & Medical Research Council

Background

- >1.4million arthroplasties in 2015 in US
  - >140,000 revisions
  - Will increase by >40% by 2020
    - Kurtz et al (JBJS 2014;96:624)
- Infections 1-3%
  - US$1.1billion
    - Kurtz et al (J Arthro 2012;27(S1):61)

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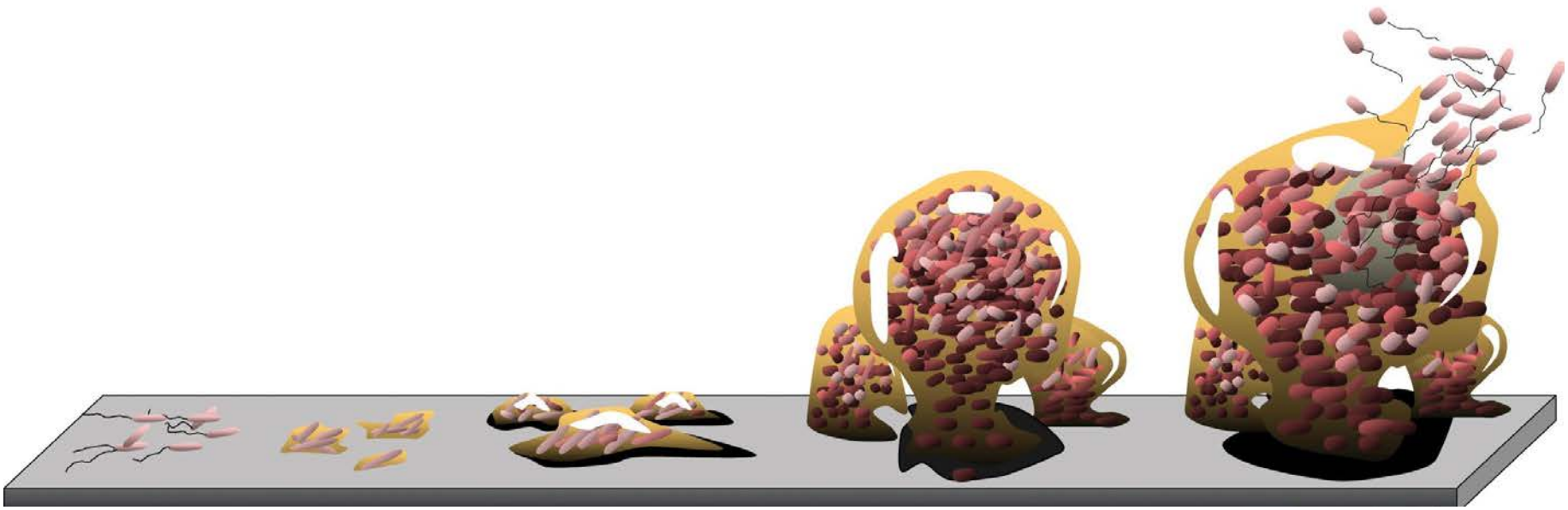
Challenges



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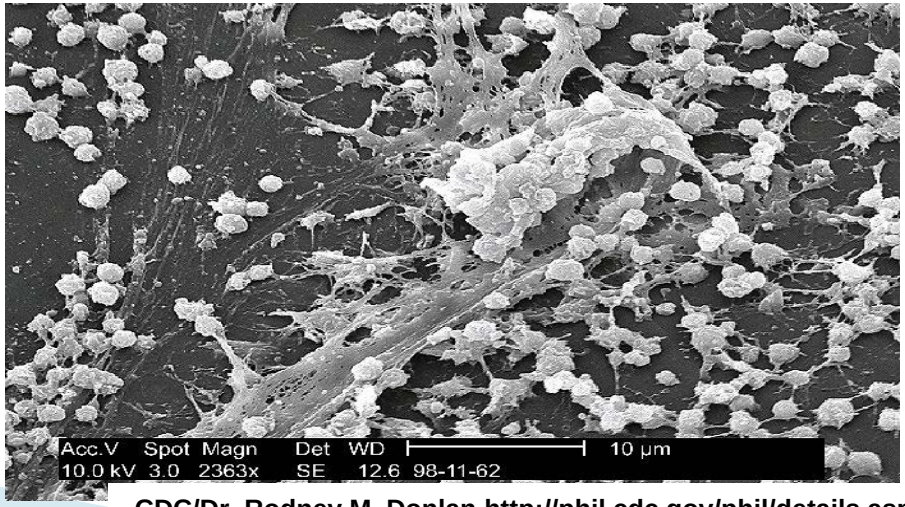

CDC/Dr. Rodney M. Donlan http://phil.cdc.gov/phil/details.asp

Challenges

- No gold standard
- Differentiating pathogen from contaminant
- Overlap in symptomatology
- Prompt diagnosis important (DAIR)
- Diagnosis of shoulder arthroplasty infections

Outline

- Diagnostic Criteria
- Pre-operative diagnosis
  - Inflammatory markers
  - Synovial Aspirate
  - New diagnostic tests
- Operative Diagnosis
  - Culture based
  - Non-culture based molecular techniques
  - Histopathology

Diagnostic Criteria

MSIS Criteria	
Major	1. ≥2positive cultures 2. Sinus tract
Minor	a. ↑CRP or ↑ESR b. ↑Synovial WCC or ++ leukocyte esterase strip c. ↑Synovial PMN% d. Positive histology e. Single positive culture
PJI = 1 major or 3/5 minor	

IDSA Criteria
1. ≥2positive cultures 2. Sinus tract 3. Positive histopathology 4. Intra-operative purulence
PJI = 1 or more present

Parvizi et al J Arthro 2014;29:1331
Osmon et al CID 2013;56:1

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Inflammatory Markers

The Journal of Arthroplasty 29 (2014) 1331

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Table 2
The Threshold for the Minor Diagnostic Criteria.

Criterion	Acute PJI (<90 days)	Chronic PJI (>90 days)
Erythrocyte Sedimentation Rate (mm/hr)	Not helpful. No threshold was determined	30
C-Reactive Protein (mg/L)	100	10
Synovia White Blood Cell Count (cells/μl)	10,000	3,000
Synovial Polymorphonuclear (%)	90	80
Leukocyte Esterase	+ Or ++	+ Or ++
Histological Analysis of Tissue	>5 neutrophils per high power field in 5 high power fields (×400)	Same as acute

Parvizi et al J Arthroplasty 2014;29:1331

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Inflammatory Blood Laboratory Levels as Markers of Prosthetic Joint Infection

A Systematic Review and Meta-Analysis

By Elie Berbari, MD, Tad Mabry, MD, Geoffrey Tsaras, MD, Mark Spangehl, MD, Pat J. Erwin, MLS, Mohammad Hassan Murad, MD, James Steckelberg, MD, and Douglas Osmon, MD

THE JOURNAL OF BONE & JOINT SURGERY · JBJS.ORG
VOLUME 92-A · NUMBER 11 · SEPTEMBER 1, 2010

	Sensitivity (95%CI)	Specificity (95%CI)
CRP	88% (86–90)	74% (71–76)
ESR	75% (72–77)	70% (68–72)
IL-6	97% (93–99)	91% (87–94)*
WCC	45% (41–49)	87% (85–89)

Inflammatory Markers

C-Reactive Protein, Erythrocyte Sedimentation Rate and Orthopedic Implant Infection

Kerryl E. Piper[1], Marta Fernandez-Sampedro[1], Kathryn E. Steckelberg[1], Jayawant N. Mandrekar[2], Melissa J. Karau[1], James M. Steckelberg[1], Elie F. Berbari[1], Douglas R. Osmon[1], Arlen D. Hanssen[4], David G. Lewallen[4], Robert H. Cofield[4], John W. Sperling[4], Joaquin Sanchez-Sotelo[4], Paul M. Huddleston[4], Mark B. Dekutoski[4], Michael Yaszemski[4], Bradford Currier[4], Robin Patel[1,3]*

February 2010 | Volume 5 | Issue 2 | e9358 PLoS ONE | www.plosone.org

Table 3. Sensitivity and specificity of CRP (>10 mg/l) and/or ESR (>30 mm/h) for the detection of infected knee, hip and shoulder arthroplasty and spinal instrumentation.

	Sensitivity	Specificity	PPV	NPV	Area Under the ROC Curve	p-value from Logistic Regression
Shoulder ESR >30 mm/h	16 (3/19)	98 (44/45)	75 (3/4)	73 (44/60)	0.57	0.0764
Shoulder CRP >10 mg/l	42 (8/19)	84 (38/45)	53 (8/15)	78 (38/49)	0.63	0.0269
Shoulder ESR >30 mm/h or CRP >10 mg/l	42 (8/19)	82 (37/45)	50 (8/16)	77 (37/48)	0.62	0.0455

- 'Normal' ESR & CRP in 23% of shoulder infections

Piper et al PLoS One 2010;5:e9358

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Synovial Aspirate

The Journal of Arthroplasty 29 (2014) 1331

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journal homepage: www.arthroplastyjournal.org

Definition of Periprosthetic Joint Infection

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Synovial Polymorphonuclear (%)	90	80
Leukocyte Esterase	+ Or ++	+ Or ++
Histological Analysis of Tissue	>5 neutrophils per high power field in 5 high power fields (×400)	Same as acute

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Synovial Aspirate

- Acute (≤42 days)
  - Paul et al THA
    - WCC 10000/µL
      - Sensitivity 95%
      - Specificity 91%
    - PMN 89%
      - Sensitivity 84%
      - Specificity 69%
  - Bedair et al TKA
    - WCC ≥12800/ µL
      - Sensitivity 89%
      - Specificity 100%
    - PMN 89%
      - Sensitivity 81%
      - Specificity 90%
- Chronic (>90days)
  - Cipriano et al THA and TKA
  - WCC 3450/µL
    - Sensitivity 91%
    - Specificity 93%
  - PMN 78%
    - Sensitivity 95.5%
    - Specificity 87.3%

Paul et al CORR 2014;472:424
Bedair et al CORR 2011;469:34
Cipriano et al JBJS 2012;94:594

Synovial Aspirate

- Most data based on lower limb arthroplasty
  - Less robust data for other joints
  - Most studies exclude inflammatory arthritis
  - Metal-on-metal falsely elevates cell count
    - Manual leucocyte counts more reliable

Tande & Patel CMR 2014;27:302
Parvizi et al J Arthro 2014;29:1331

Synovial Aspirate Culture

JCM Journals.ASM.org

Preoperative Aspiration Culture for Preoperative Diagnosis of Infection in Total Hip or Knee Arthroplasty

Xinhua Qu,[a] Zanjing Zhai,[a] Chuanlong Wu,[a] Fangchun Jin,[b] Haowei Li,[a] Lei Wang,[a] Guangwang Liu,[a,d] Xuqiang Liu,[a] Wengang Wang,[a] Huiwu Li,[a] Xiaoyu Zhang,[c] Zhenan Zhu,[a] Kerong Dai[a]

2013;51:3830

- Sensitivity 72% (65–78)
- Specificity 95% (93–97)
  - Less sensitive for THA than TKA
  - Marked heterogeneity
  - No comment on culture media or duration

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Synovial Aspirate Culture

Culture with BACTEC Peds Plus/F Bottle Compared with Conventional Methods for Detection of Bacteria in Synovial Fluid

JOHN G. HUGHES,[1] EMILY A. VETTER,[1] ROBIN PATEL,[1,2] CATHY D. SCHLECK,[3] SCOTT HARMSEN,[3] L. THOMAS TURGEANT,[2] AND FRANKLIN R. COCKERILL III[1,2]*

JCM 2001;39:4468

- Blood culture bottles
  - Increased yield cf agar
- Acute vs Chronic infection
  - Sensitivity 91% acute vs 79% chronic
  - Specificity 100% both
  - Font-Vizcarra et al (CORR;2010:468:2238)

https://c1.staticflickr.com/1/28/48025150_db0fa4b573.jpg

The Journal of Arthroplasty 29 (2014) 1331

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Parvizi et al J Arthroplasty 2014;29:1331

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Synovial Leucocyte Esterase

Diagnosis of Periprosthetic Joint Infection: The Utility of a Simple Yet Unappreciated Enzyme

Javad Parvizi, MD, FRCS, Christina Jacovides, BS, Valentin Antoci, MD, PhD, and Elie Ghanem, MD

- "Point of care"
- Measure of '+' or '++'
- Sensitivity
  - 80% – 92.9%
- Specificity
  - 89–100%
- Cellular debris
  - 10 – 29% unable to be read

https://upload.wikimedia.org/wikipedia/commons/6/68/Chemstrip1.jpg

Parvizi et al JBJS 2011;93:2242
Wetters et al J Arthro 2012;27(S1):8

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Synovial Leucocyte Esterase

Leukocyte esterase in the diagnosis of shoulder periprosthetic joint infection

Gregory N. Nelson, MD[a,*], E. Scott Paxton, MD[b], Alexa Narzikul, BS[c], Gerald Williams, MD[c], Mark D. Lazarus, MD[c], Joseph A. Abboud, MD[c]

J Shoulder Elbow Surg (2015) 24, 1421-1426

Table IV Accuracy of leukocyte esterase in Musculoskeletal Infection Society periprosthetic joint infection–positive revision shoulder arthroplasty

Variable	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PJI				
True	28.6	63.6	28.6	87.5
Potential	33.3	–	14.3	–
True + potential	30.0	66.7	42.9	83.3
"Bloody" results considered positive				
True PJI	57.1	63.6	66.7	87.5
Potential PJI	66.7	–	33.3	–
True + potential PJI	60.0	66.7	37.5	83.3

NPV, negative predictive value; *PJI*, periprosthetic joint infection; *PPV*, positive predictive value.

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https://i.ytimg.com/vi/Or7VTdnr8OI/maxresdefault.jpg

Synovial CRP

Diagnosis of Periprosthetic Joint Infection Using Synovial C-Reactive Protein

Javad Parvizi, MD, FRCS, James C. McKenzie, BS, and James P. Cashman, MD

- Sensitivity 85-87.1%
- Specificity 71-97.7%

- Threshold / cut-off not well established
  - Parvizi et al proposed 9.5mg/L
- Value unclear
  - Strongly correlates with serum CRP (r^2 0.72)
    - Parvizi et al
  - CRP manufactured in liver
    - Emerging evidence that other sites may produce CRP

Deirmengian et al CORR 2010;468:2017
Jacovides et al J Arthro 2011;26(S1):99
Parvizi et al J Arthro 2012;27(S1):12
Deirmengian et al JBJS 2014;96:1439

Synovial Alpha Defensin

Clin Orthop Relat Res (2014) 472:3254–3262

Diagnosing Periprosthetic Joint Infection

Has the Era of the Biomarker Arrived?

Carl Deirmengian MD, Keith Kardos PhD,
Patrick Kilmartin, Alexander Cameron, Kevin Schiller,
Javad Parvizi MD

- Synovial α-defensin
  - Sensitivity 97.3%
  - Specificity 95.5%
- Synvosure®
  - CD diagnostics
  - Not FDA approved
- Not widely studied

Synovial Alpha Defensin

J Shoulder Elbow Surg (2015) 24, 1021-1027

ELSEVIER

JOURNAL OF SHOULDER AND ELBOW SURGERY

www.elsevier.com/locate/ymse

Table III Diagnostic parameters of synovial fluid α-defensin

Parameter	α-Defensin
Optimized cutoff	0.48 S/CO
Area under the curve	0.78
Sensitivity (%)	63
Specificity (%)	95
Positive likelihood ratio*	12.1
Negative likelihood ratio†	0.38

* A value > 5 is considered useful for ruling in infection.

† A value < 0.2 is considered useful for ruling out infection.

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- Microbiological culture is paramount
  - Confirmation of diagnosis
  - Allows susceptibility testing
    - Guide therapy
    - Avoid unnecessarily broad-spectrum antimicrobials
    - Epidemiology / Infection Control

- Disadvantages
  - Slow
  - Low sensitivity
  - Challenges differentiating pathogen vs contaminant

Operative Culture

Clin Orthop Relat Res (2013) 471:3196–3203
DOI 10.1007/s11999-013-2974-y

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

SYMPOSIUM: 2012 MUSCULOSKELETAL INFECTION SOCIETY

Swab Cultures Are Not As Effective As Tissue Cultures

Table 3. Sensitivity, specificity, PPV, NPV, and likelihood ratios for tissue and swab cultures

Number of positive cultures considered diagnostic	Intraoperative test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Positive diagnostic likelihood ratio	Negative diagnostic likelihood ratio
≥ 1	Tissue culture	93.3 (79–98)	97.7 (92–99)	93.3 (79–98)	97.7 (92–99)	40.6 (10.2–160.3)	0.07 (0.02–0.26)
	Swab culture	70.0 (52–83)	88.5 (80–93)	67.7 (50–81)	89.5 (81–94)	6.1 (3.2–11.4)	0.34 (0.20–0.59)
≥ 2	Tissue culture	63.3 (46–78)	97.7 (92–99)	90.5 (71–97)	88.5 (81–94)	27.6 (6.8–111.4)	0.38 (0.23–0.60)
	Swab culture	53.3 (36–70)	97.7 (92–99)	88.9 (67–97)	85.9 (78–91)	23.2 (5.6–95.0)	0.48 (0.33–0.70)

The 95% CIs are reported in parentheses; PPV = positive predictive value; NPV = negative predictive value.

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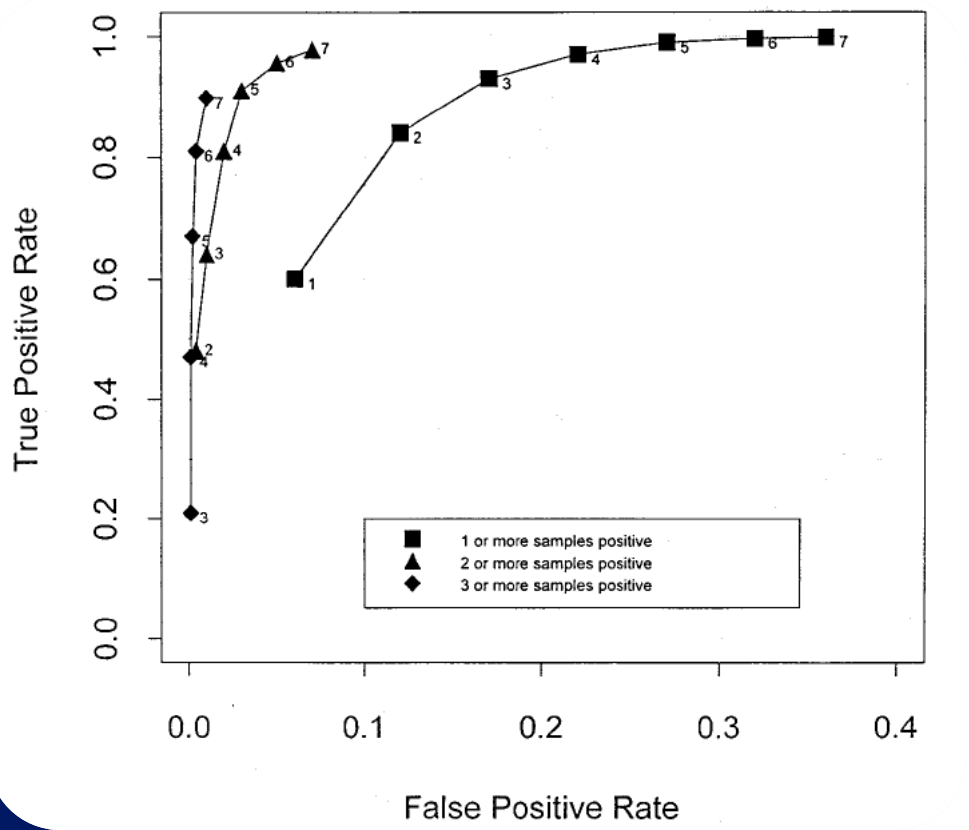
Optimal Number of Specimens

Prospective Evaluation of Criteria for Microbiological Diagnosis of Prosthetic-Joint Infection at Revision Arthroplasty

BRIDGET L. ATKINS,[1,2] NICHOLAS ATHANASOU,[3,4] JONATHAN J. DEEKS,[5] DERRICK W. M. CROOK,[2] HAMISH SIMPSON,[4,6] TIMOTHY E. A. PETO,[2] PETER McLARDY-SMITH,[4] ANTHONY R. BERENDT,[2,4]* AND THE OSIRIS COLLABORATIVE STUDY GROUP†

Public Health Laboratory,[1] Department of Pathology,[3] Nuffield Department of Orthopaedic Surgery,[6] and Bone Infection Unit,[4] Nuffield Orthopaedic Centre, Academic Unit of Microbiology and Infectious Diseases, John Radcliffe Hospital,[2] and Centre for Statistics in Medicine, Institute of Health Sciences,[5] Oxford, United Kingdom

JCM 1998;36:2692



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Culture Media

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RESEARCH ARTICLE

TABLE 2 Sensitivity and specificity of periprosthetic tissue culture techniques using Bayesian latent class modeling and Infectious Diseases Society of America criteria for prosthetic joint infection diagnosis as gold standards[a]

	No gold standard (Bayesian LCM)		IDSA PJI criteria as gold standard	
Culture medium[b]	Sensitivity (95% credible interval)	Specificity (95% credible interval)	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)
Individual culture media				
Aerobic agar	59.4 (45.3, 72.5)	99.5 (98.3, 100.0)	26.5 (18.8, 35.5)	100.0 (98.6, 100.0)
Anaerobic agar	32.2 (20.8, 45.7)	99.5 (98.3, 100.0)	14.5 (8.7, 22.2)	100.0 (98.6, 100.0)
Thioglycolate	74.8 (61.5, 85.8)	99.4 (98.1, 99.9)	33.3 (24.9, 42.6)	100.0 (98.6, 100.0)
Aerobic blood culture bottle	82.0 (69.5, 91.1)	97.1 (94.8, 98.6)	42.7 (33.6, 52.2)	100.0 (98.6, 100.0)
Anaerobic blood culture bottle	90.2 (79.4, 96.5)	96.3 (93.7, 98.1)	47.9 (38.5, 57.3)	99.6 (97.8, 100.0)
Combinations of culture media				
Aerobic and anaerobic agars	48.9 (38.3, 59.7)	99.7 (98.7, 100.0)	33.3 (24.9, 42.6)	100.0 (98.6, 100.0)
Aerobic and anaerobic agars and thioglycolate	62.6 (51.7, 72.5)	98.1 (96.1, 99.3)	44.4 (35.3, 53.9)	98.8 (96.6, 99.8)
Aerobic and anaerobic BCBs	92.1 (84.9, 97.0)	99.7 (98.7, 100.0)	60.7 (51.2, 69.6)	98.8 (96.6, 99.8)
Aerobic and anaerobic BCBs and thioglycolate	92.1 (84.9, 97.0)	98.8 (97.0, 99.6)	63.3 (53.8, 72.0)	98.8 (96.6, 99.8)
Aerobic and anaerobic BCBs and aerobic agar	94.6 (88.1, 98.6)	99.7 (98.7, 100.0)	62.4 (53.0, 71.2)	98.8 (96.6, 99.8)
Aerobic and anaerobic BCBs and anaerobic agar	96.8 (91.3, 99.3)	99.8 (98.7, 100.0)	62.4 (53.0, 71.2)	98.0 (95.4, 99.4)
Aerobic and anaerobic BCBs and aerobic and anaerobic agars	99.1 (95.7, 100.0)	99.7 (98.7, 100.0)	64.1 (54.7, 72.8)	98.0 (95.4, 99.4)
All media combined	99.1 (95.7, 100.0)	97.3 (94.8, 98.7)	67.5 (58.2, 75.9)	96.8 (93.8, 98.6)

Peel et al mBIO 2016

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RESEARCH ARTICLE

Improved Diagnosis of Prosthetic Joint Infection by Culturing Periprosthetic Tissue Specimens in Blood Culture Bottles

TABLE 3 Time to detection of microorganisms with different culture media[a]

Culture medium	Median time (h) to detection (IQR)			
	Complete cohort (n = 369)	Met IDSA criteria for PJI		
		No (n = 252)	Yes (n = 117.0)	P value[b]
Aerobic agar	41 (21, 63)	49 (45, 95)	33 (21, 62)	0.003
Anaerobic agar	62 (43, 144)	144 (50, 163)	52 (43, 140)	0.3
Thioglycolate	65 (43, 92)	160 (65, 195)	64 (43, 90)	0.01
Aerobic blood culture bottle	21 (14, 45)	27 (21, 42)	21 (13, 45)	0.8
Anaerobic blood culture bottle	23 (16, 47)	52 (24, 147)	22 (14.5, 38.5)	0.02

Peel et al mBIO 2016

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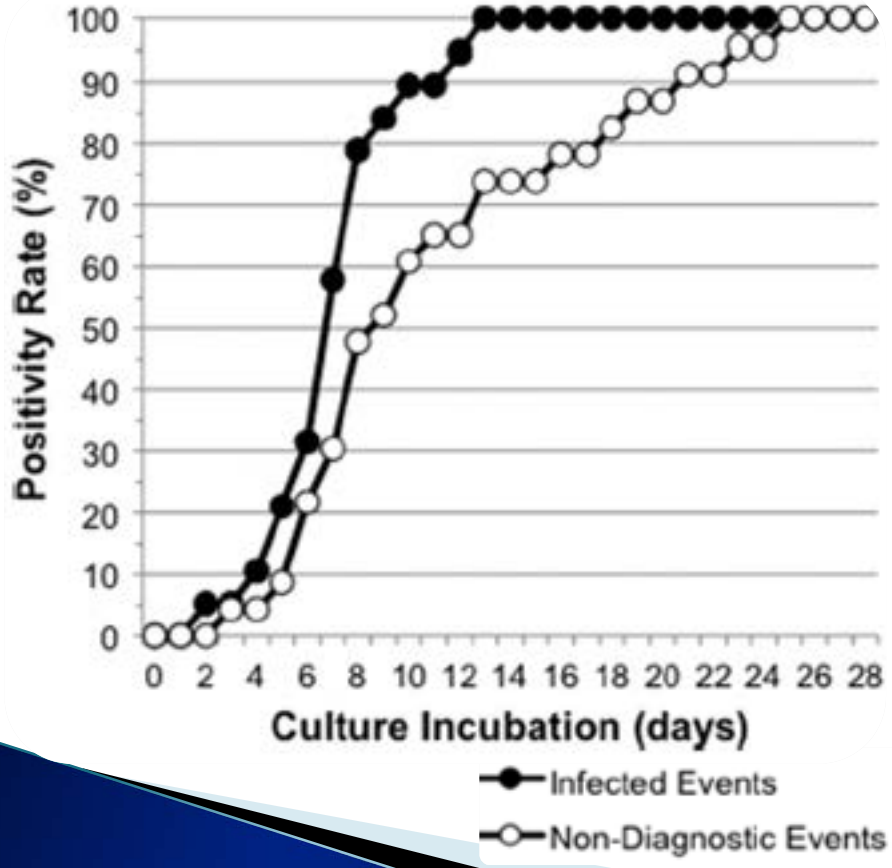
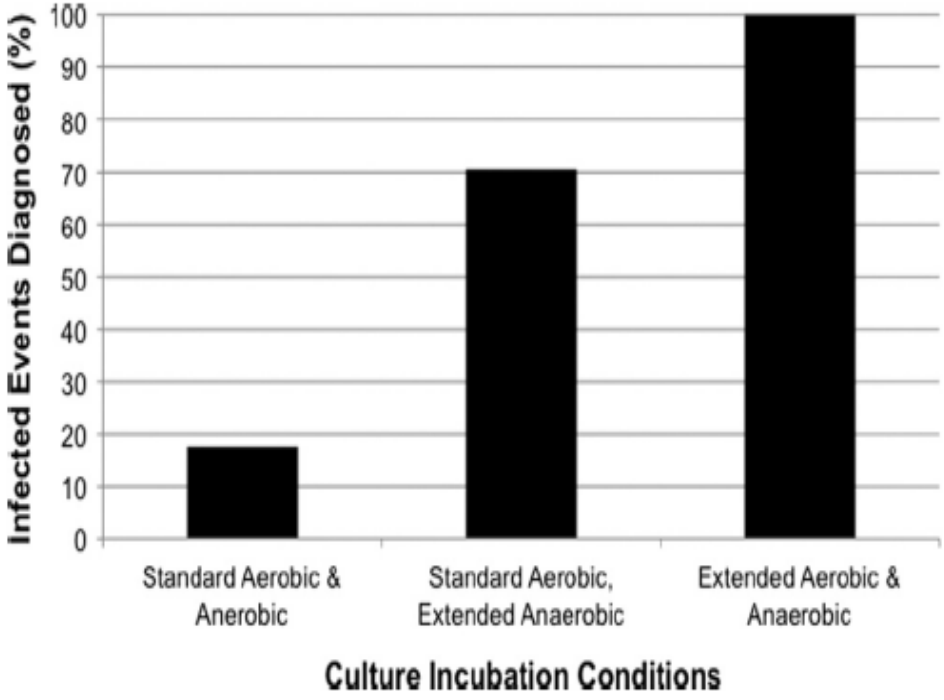
Culture Duration

Optimization of Periprosthetic Culture for Diagnosis of *Propionibacterium acnes* Prosthetic Joint Infection[▽]

Susan M. Butler-Wu,[1]* Erica M. Burns,[2]† Paul S. Pottinger,[3] Amalia S. Magaret,[1] Jennifer L. Rakeman,[1]‡ Frederick A. Matsen III,[2] and Brad T. Cookson[1,4]

Department of Laboratory Medicine,[1] Department of Orthopaedics and Sports Medicine,[2] Department of Medicine,[3] and Department of Microbiology,[4] University of Washington, Seattle, Washington





JCM 2011;49:2490

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Sonication

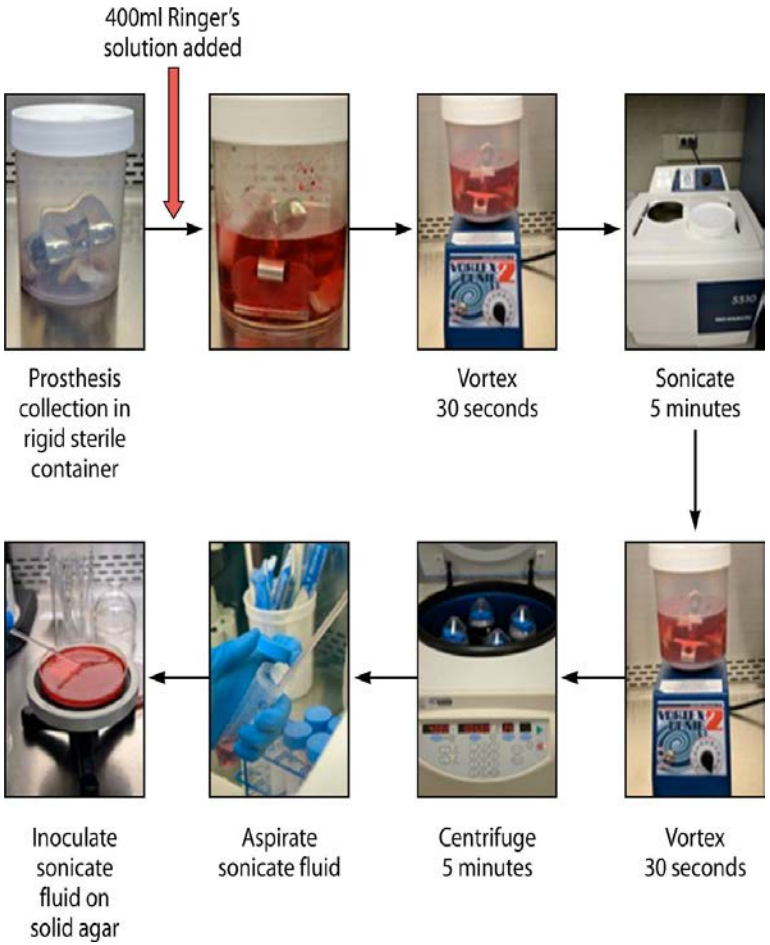

Photo courtesy of David Lynch, Mayo Clinic MN
From Tande & Patel Clin. Microbiol. Rev. 2014;27:302

- Meta-analysis Zhai et al
  - Pooled data
    - Sensitivity 80%
    - Specificity 95%
    - Moderate quality studies
  - Best cut-off ≥5CFU/mL
    - (unconcentrated)
    - Not taking in account organism
  - Better results with
    - Ringer's solution
    - Containers
    - Extended cultures to 14 days
- Useful if prior antibiotics

Zhai et al JCM 2014;52:1730

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Vortex Only

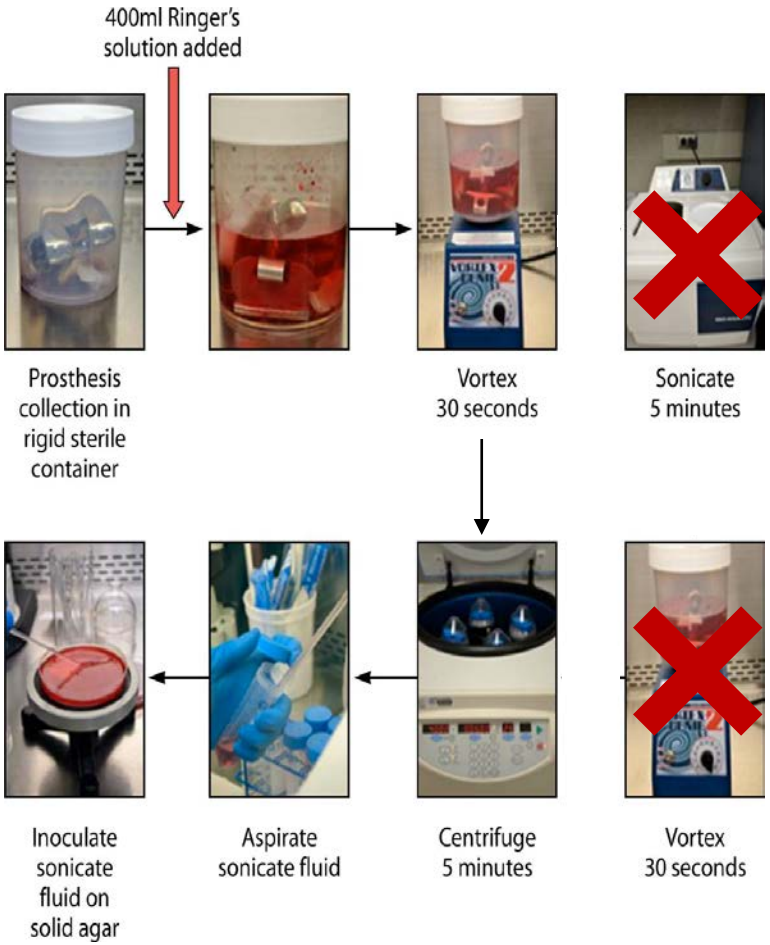

Photo courtesy of David Lynch, Mayo Clinic MN
From Tande & Patel Clin. Microbiol. Rev. 2014;27:302

- Portillo et al compared
  - Vortex + Sonication
  - Vortex alone
- Cut-off ≥1CFU/mL
  - Similar sensitivity (71 v 69%)
  - Sonication more sensitive with chronic PJI (58 vs 33%; p=0.2)
- Cut-off ≥50CFU/mL
  - Sonication more sensitive
    - 60% vs 40% (p=0.2)
- Vortex alone
  - Reasonable if sonication not available

Portillo et al JCM 2013;51:591

Definition of Periprosthetic Joint Infection

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Parvizi et al J Arthroplasty 2014;29:1331

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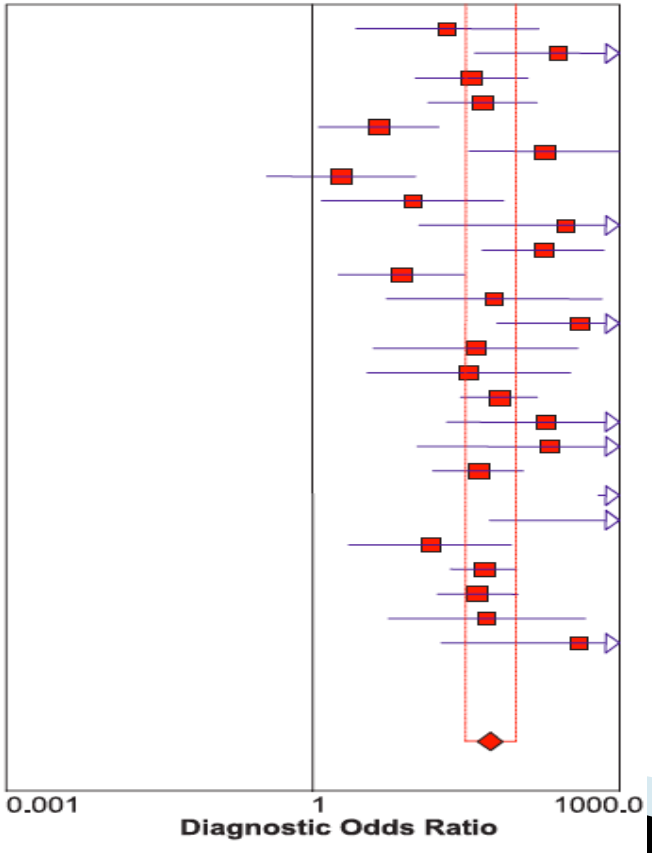
Utility of Intraoperative Frozen Section Histopathology in the Diagnosis of Periprosthetic Joint Infection

A Systematic Review and Meta-Analysis

Geoffrey Tsaras, MBChB, MPH, Awele Maduka-Ezeh, MBBS, MPH, Carrie Y. Inwards, MD, Tad Mabry, MD, Patricia J. Erwin, MLS, M. Hassan Murad, MD, MPH, Victor M. Montori, MD, MSc, Colin P. West, MD, PhD, Douglas R. Osmon, MD, MPH, and Elie F. Berbari, MD

JBJS 2012;94:1700



- 26 studies THA and TKA
- DOR 54.7 (31.2–95.7)
  - LR+12.0 (8.4–17.2)
  - LR– 0.23 (0.15–0.35)
- Significant heterogeneity
- Majority small studies
- Diagnostic thresholds vary

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Sensitivity of Frozen Section Histology for Identifying *Propionibacterium acnes* Infections in Revision Shoulder Arthroplasty

J Bone Joint Surg Am. 2014;96:442-7

Matthew J. Grosso, BS, Salvatore J. Frangiamore, MD, Eric T. Ricchetti, MD, Thomas W. Bauer, MD, PhD, and Joseph P. Iannotti, MD, PhD

TABLE V Frozen Section Histopathology*

	P. acnes Infection Group (N = 18)	Other Infection Group (N = 12)	Total (N = 30)
Sensitivity			
Institutional guidelines	50% (9)	67% (8)	57% (17)
Periprosthetic Joint Infection AAOS Guideline #1[8]	50% (9)	58% (7)	53% (16)
Periprosthetic Joint Infection AAOS Guideline #2[8]	39% (7)	58% (7)	47% (14)
Morawietz et al. (2009)[19]	56% (10)	67% (8)	60% (18)
ROC cutoff	72% (13)	75% (9)	73% (22)
Specificity†			
Institutional guidelines	100% (15)	100% (15)	100% (15)
Periprosthetic Joint Infection AAOS Guideline #1[8]	100% (15)	100% (15)	100% (15)
Periprosthetic Joint Infection AAOS Guideline #2[8]	100% (15)	100% (15)	100% (15)
Morawietz et al. (2009)[19]	100% (15)	100% (15)	100% (15)
ROC cutoff	100% (15)	100% (15)	100% (15)

*The values are given as the percentage of positive results on culture, with the number of patients in parentheses. †Specificity was derived from the non-infection group (n = 15). As there were no false positives, the specificity was the same (100%) for all groups.

Molecular Diagnosis

- PCR
  - Specific PCR
    - Targets a single bacteria eg *Staphylococcus aureus*
  - Broad-range PCR
    - Bacterial ribosome (16S rDNA)
      - Highly conserved region
      - Allows detection of DNA from many bacteria species

JCM Journals.ASM.org

PCR-Based Diagnosis of Prosthetic Joint Infection

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- 14 studies (11 16sRibosomal PCR)
  - Sensitivity 86%
  - Specificity 91%
- Challenges
  - High false positive rate
  - Requires specific expertise
  - Expensive
  - Issues with polymicrobial infections
    - Comprise 10-30% of infections

Qu et al JCM 2013;51:2742

NCAS

Molecular Diagnosis

- Species specific and multiplex PCR
  - Septifast© (Roche Diagnostics)
  - Portillo et al
    - Performed on sonicate
    - PCR more sensitive 96% compared to:
      - Periprosthetic tissue culture 71% (p=0.03)
      - Sonicate culture 67% (p=0.02)*
    - 50% patients had received antibiotics in 14 days prior
      - PCR was positive in 96% cf 50% culture
    - Limitations
      - Probe for specific pathogen needs to be included
        - Eg *Propionibacterium acnes*

Portillo et al J Infect 2012;65:541

SUMMARY

Pre-operative Summary

- ESR and CRP aid clinical judgment
  - IL-6 promising but not widely in use
- Synovial aspirate
  - Synovial WCC, PMN% and culture (BCB)
  - Role of leukocyte esterase and CRP unclear
  - α-defensin promising but further studies required

Operative Work-Up Summary

- Peri-prosthetic tissue samples
  - Ideally 5-6 specimens
    - NOT swabs
  - Inoculation into blood culture bottles
  - Culture for 14 days
- Specimen for frozen section
- Sonication of the prosthesis
  - If aspiration is negative or recent antibiotics
- Consider additional specimen for PCR
  - Multiplex / species specific
  - If recent antibiotics and culture negative

Acknowledgements

THE UNIVERSITY OF MELBOURNE

Department of Surgery
Prof Peter Choong
Dr Michelle Dowsey
Dr Tim Spelman

MAYO CLINIC

Department of Clinical Microbiology
Prof Robin Patel
David Lynch
Brenda Dylla
Infectious Diseases Research Laboratory
Kerryl Greenwood Quaintance

Australian Government
National Health and Medical Research Council
NHMRC

Early Career Fellowship APP106973

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NHMRC Centre for Research Excellence
National Centre for Antimicrobial Stewardship