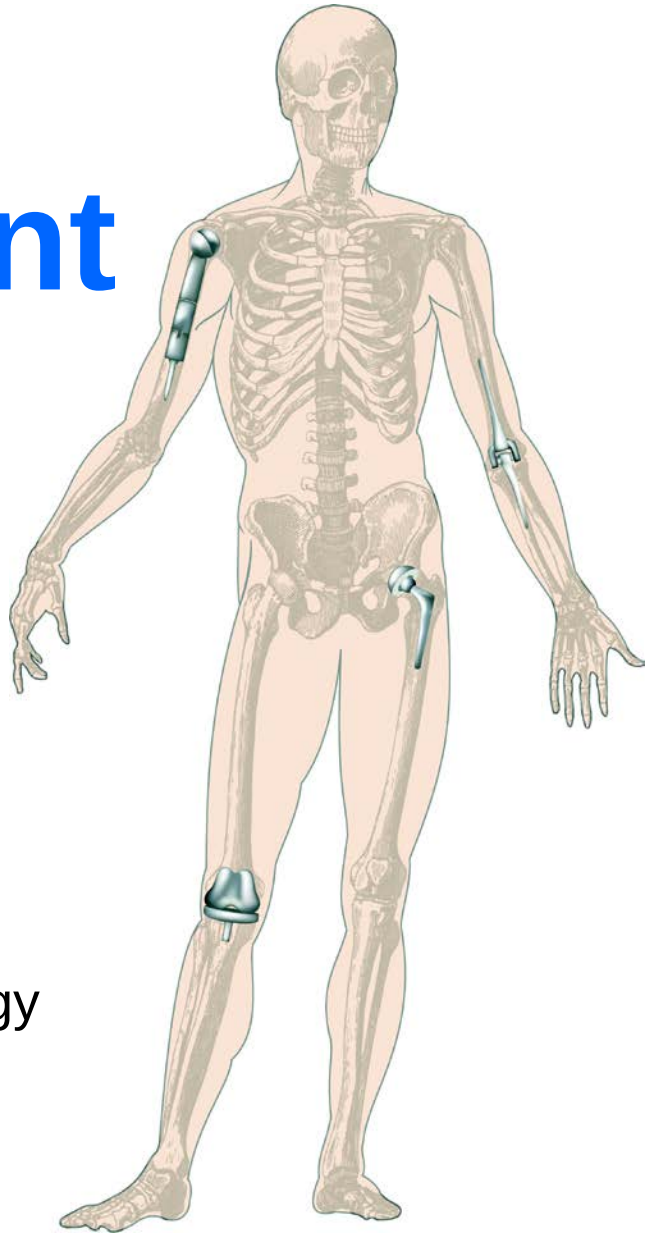
Prosthetic Joint Infection



Robin Patel, M.D.

Elizabeth P. and Robert E. Allen

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Professor of Medicine and Microbiology

Mayo Clinic College of Medicine

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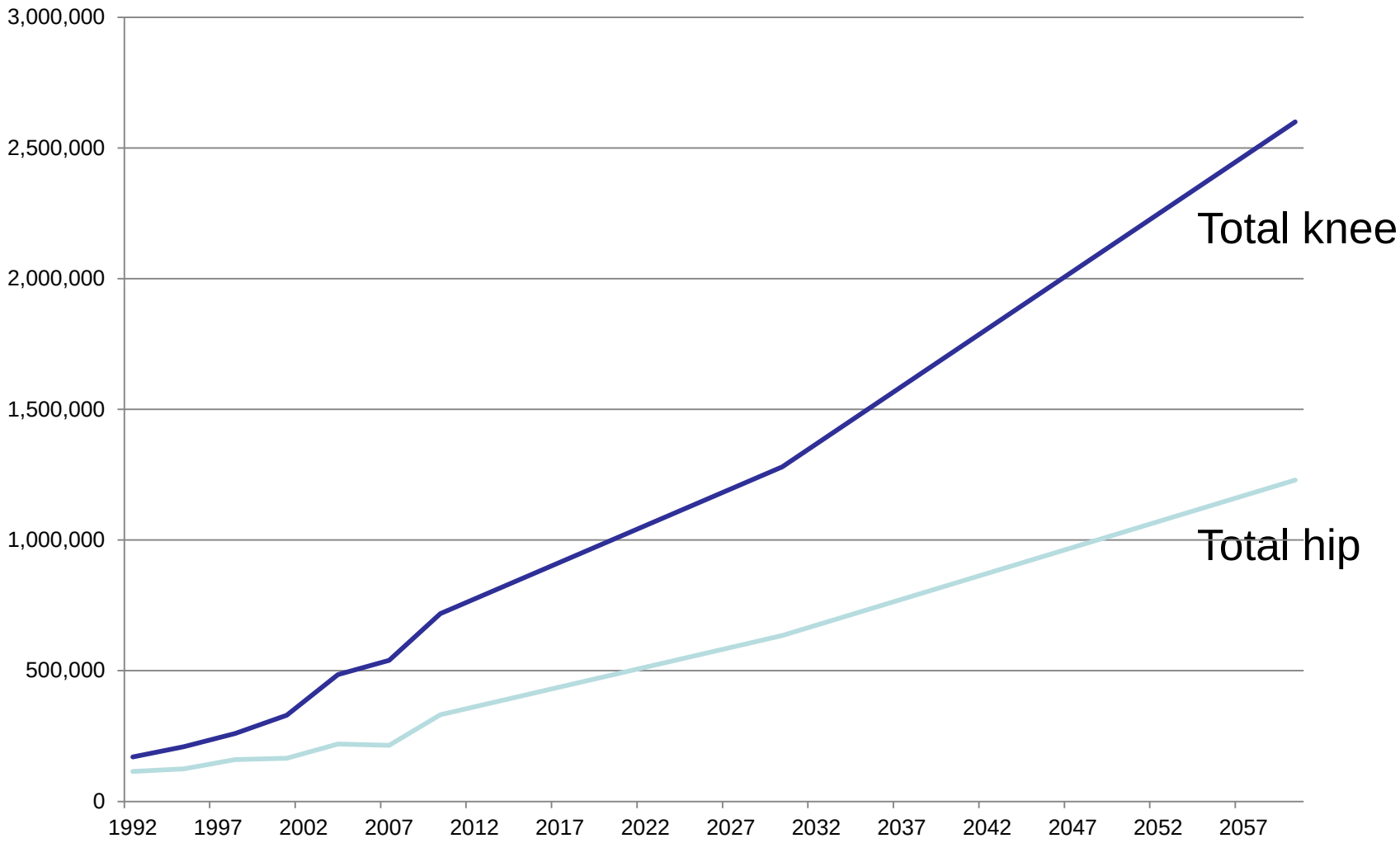
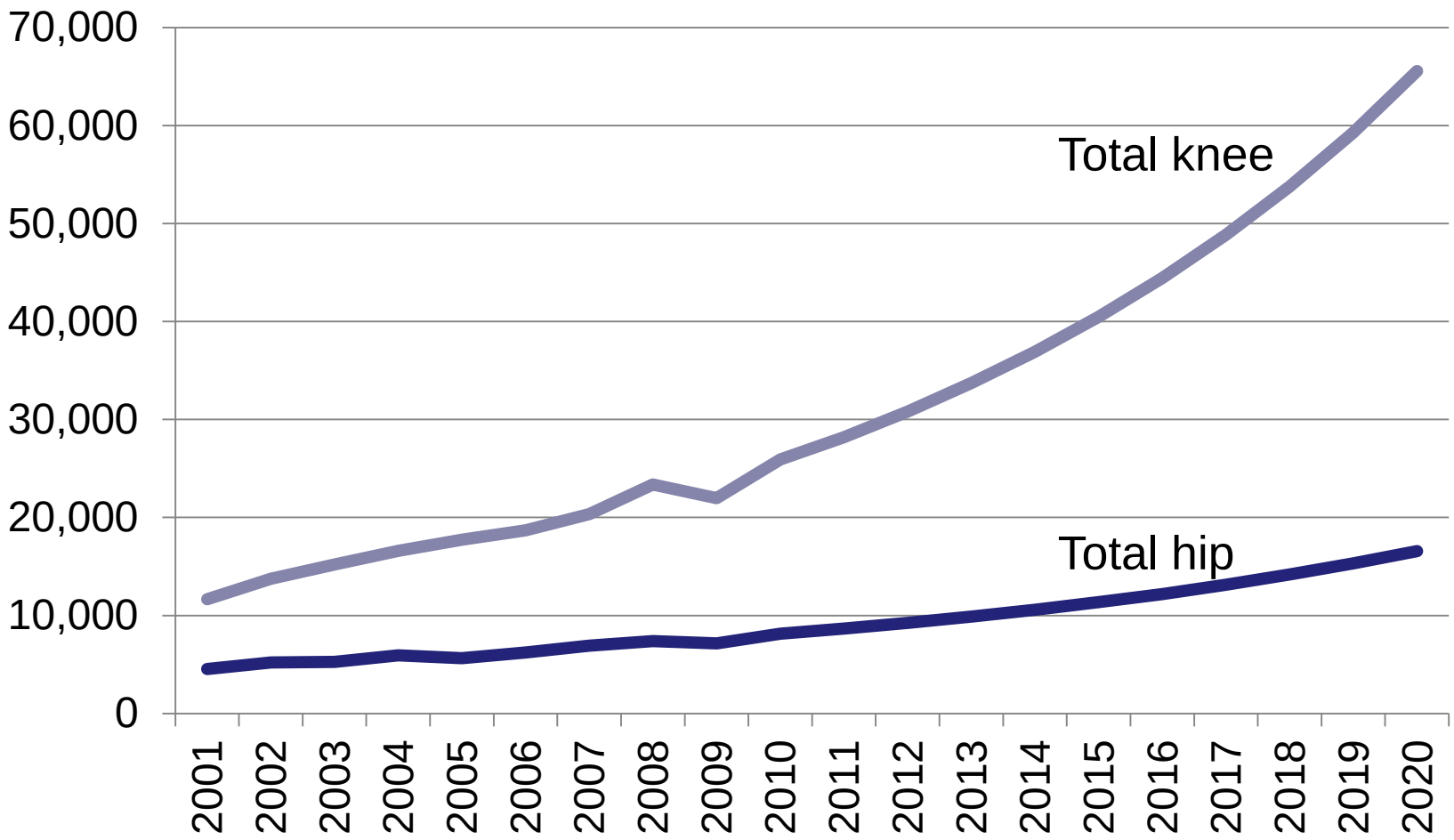
Total Hip & Knee Replacement - United States

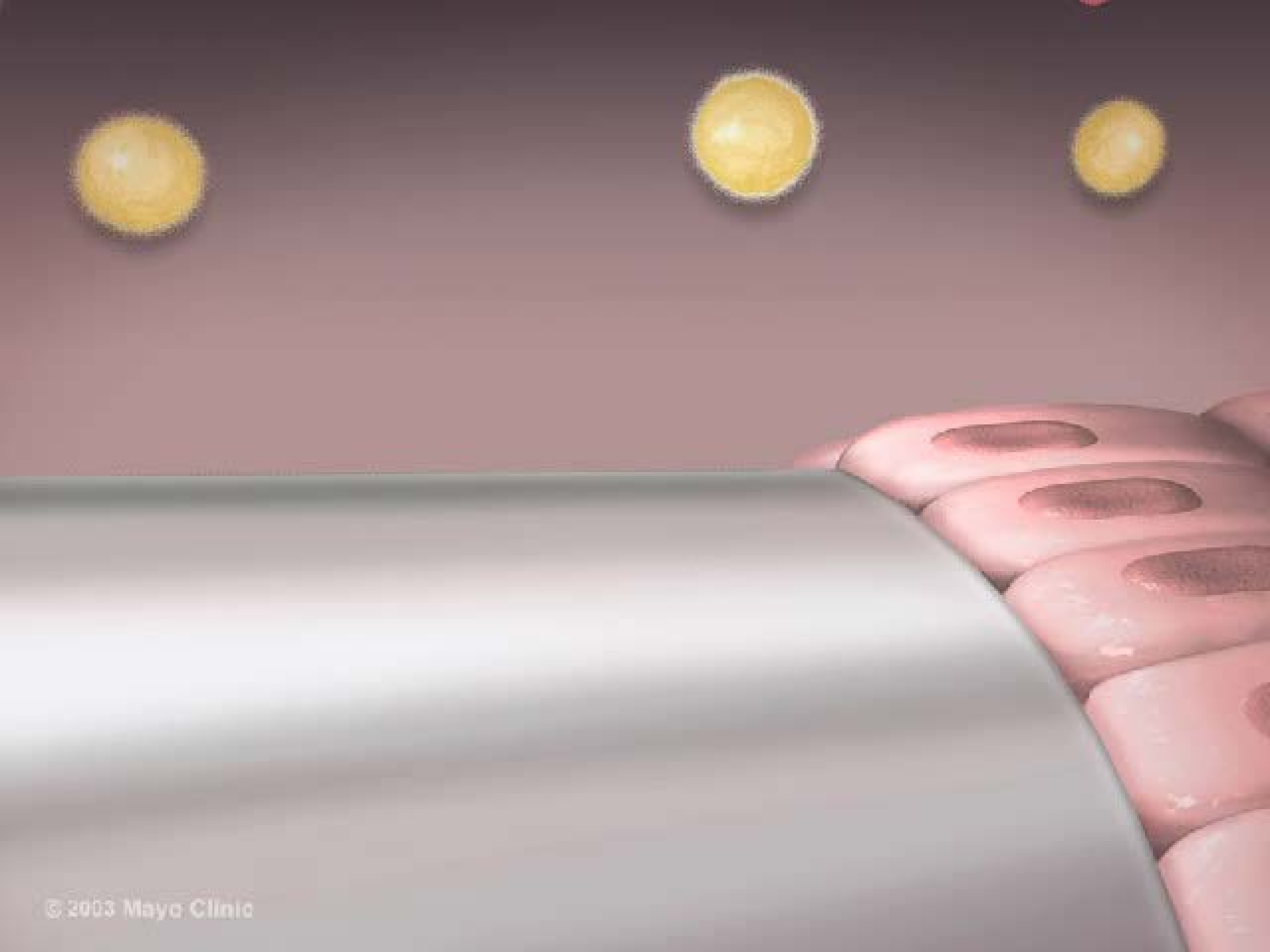


National Hospital Discharge Survey www.cdc.gov/nchs/about/major/hdasd/listpubs.htm and Sloan & Sheth – AAOS Annual Meeting 2018

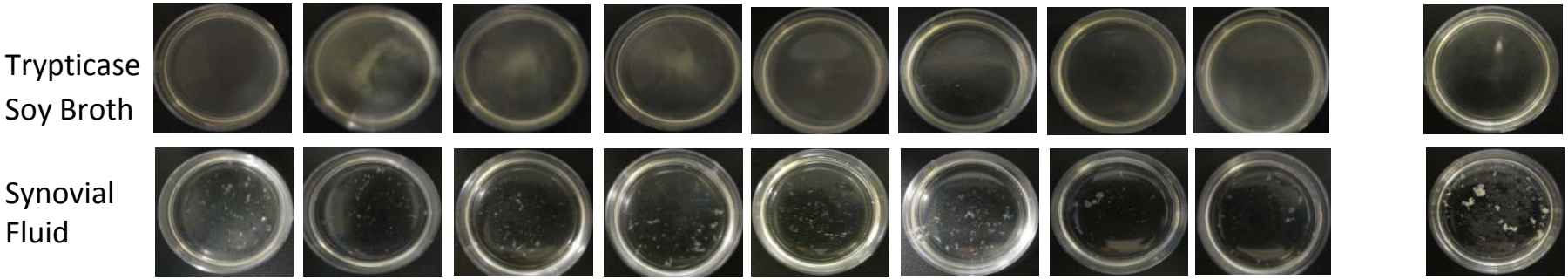
Prosthetic Hip & Knee Infection - United States



Kurtz et al. J Arthroplasty 2012;27:61


© 2003 Mayo Clinic

Biofilm-Like Aggregation in Synovial Fluid



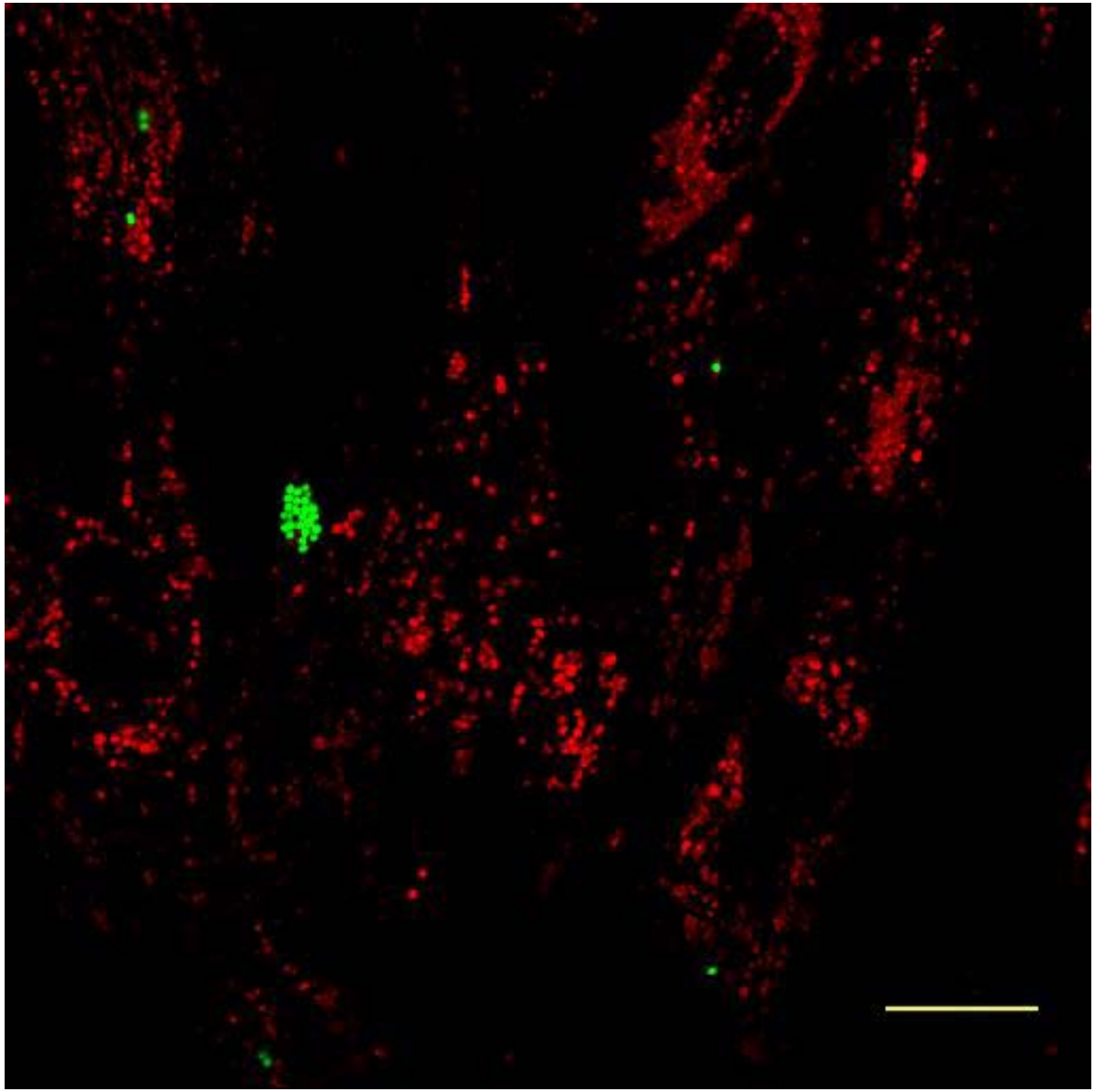
Staphylococcus epidermidis

RP62A-7073 IDRL-8873 IDRL-8933 IDRL-8934 IDRL-8864 IDRL-8866 IDRL-8849 IDRL-8850

Staphylococcus aureus USA 300

Perez and Patel. J Inf Dis 2015;212:335

Intracellular Survival/Growth



Human fibroblasts infected with *Staphylococcus aureus* USA300-GFP
Lysosomes visualized with LAMP-2 antibody with Alexa Fluor 594
Images collected starting 4 hours post infection.
One image acquired every 10 minutes for 4 hours

Perez and Patel. Infect and Immun 2018;86;e00237-18

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		
Cutibacterium acnes					24	1
Other anaerobes					3	0
Culture negative	14	10	7	11	15	5
Polymicrobial	15	31	14	12	16	3
Other	3					

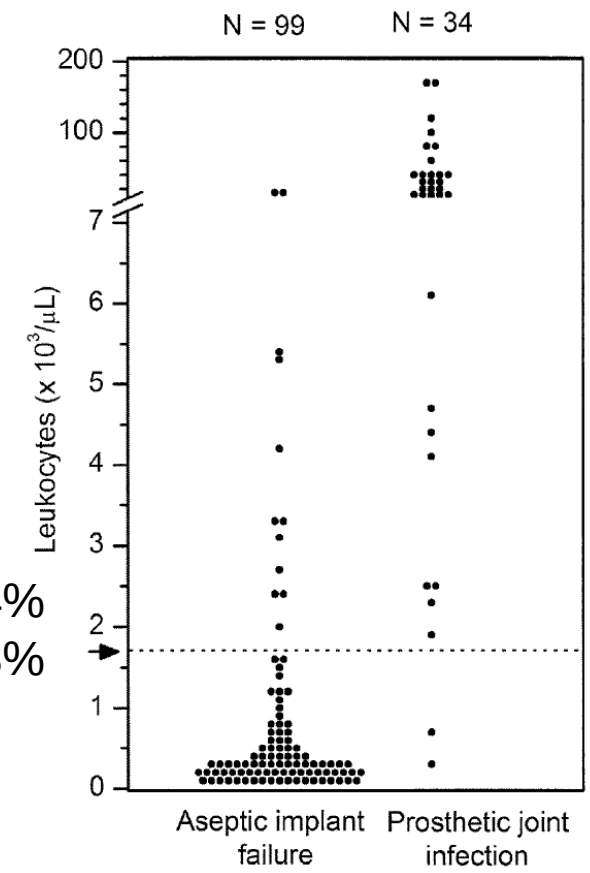
Tande and Patel. Clin Microbiol Rev 2014;27:302

Monomicrobial *versus* Polymicrobial Hip and Knee Prosthetic Joint Infection

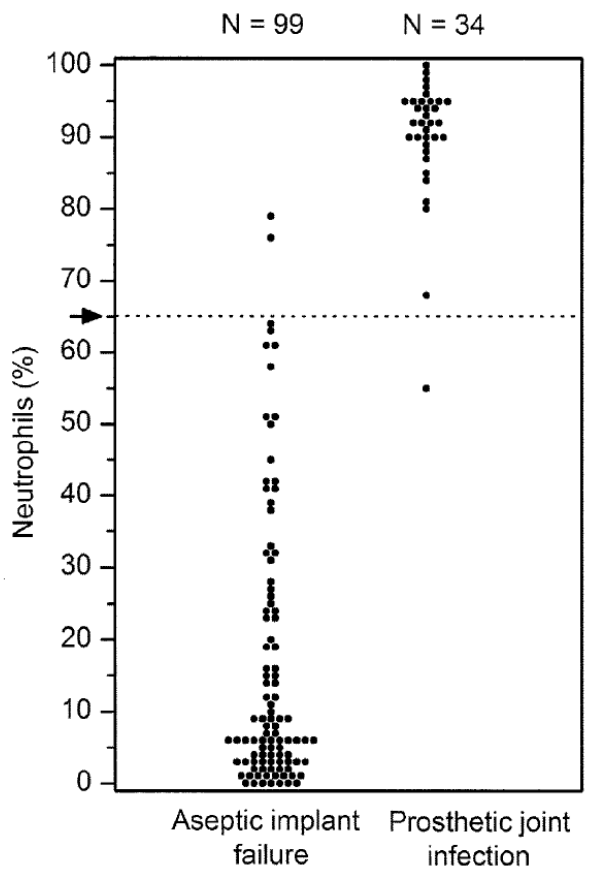
MICROORGANISM	MONOMICROBIAL	POLYMICROBIAL	p value
Staphylococcus epidermidis	97 (35%)	19 (59%)	0.007
Staphylococcus aureus	58 (21%)	7 (22%)	0.9
Other *Staphylococcus* species	17 (6%)	8 (25%)	0.0002
***Enterococcus* species**	16 (6%)	9 (28%)	<0.0001
***Corynebacterium* species**	8 (3%)	5 (16%)	0.0007
Gram negative bacilli	21 (8%)	3 (9%)	0.7
***Streptococcus* species**	31 (11%)	2 (6%)	1
Granulicatella adiacens	6 (2%)	0 (0%)	-
Finegoldia magna	4 (1%)	6 (19%)	<0.0001
Cutibacterium acnes	9 (3%)	3 (9%)	0.1
Others	11 (4%)	4 (12%)	-

Flurin, Greenwood-Quaintance and Patel. Diagn Microbiol Infect Dis. 2019;94:255

Synovial Fluid Leukocyte/%Neutrophils Knee Arthroplasty



Sensitivity, 94%
Specificity, 88%



Sensitivity, 97%
Specificity, 98%

AAOS. www.aaos.org/pjiguideline. 2019
Moderate ***

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

Synovial Fluid Leukocyte Esterase

Study	Hip/Knee Arthroplasties	Sensitivity (%)	Specificity (%)
Parvizi et al. (2011, Chemstrip 7 urine test strip)	0/108	81	100
Shafafy et al. (2015, Multistix 8 SG)	30/79	81	93
Koh et al. (2017, multiple)	0/60	84	100
Sharma et al. (unpublished, Siemens Multistix 10 SG)	14/93	90	84
Sharma et al. (unpublished, Chemstrip 10 MD)	14/93	81	95

AAOS. www.aaos.org/pjiguideline. 2019
Moderate ***

Synovial Fluid C-Reactive Protein

Study		Hip/Knee Arthroplasty	Threshold	Sensitivity (%)	Specificity (%)
Vanderstappen et al. (2013)	Preoperative	0/44	2.8 mg/L	91	94
Tetreault et al. (2014)		59/60	6.6 mg/L	88	85
Omar et al. (2015)		89/0	2.5 mg/L	96	93
Sharma et al. (unpublished)		14/93	5.7 mg/L	80	92
Sousa et al. (2017)	Intraoperative	15/30	6.7 mg/L	78	94

AAOS. www.aaos.org/pjiguideline. 2019
Moderate ***

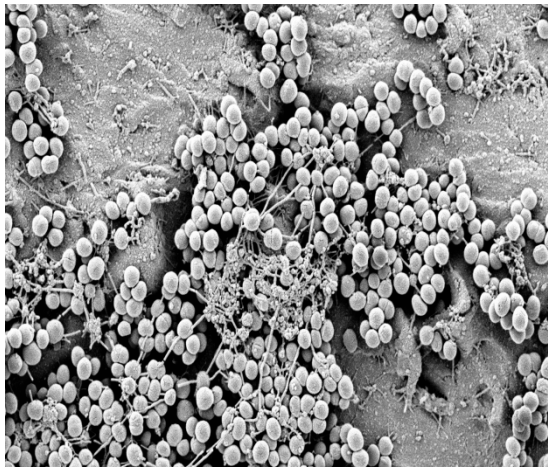
Synovial Fluid Alpha-Defensin

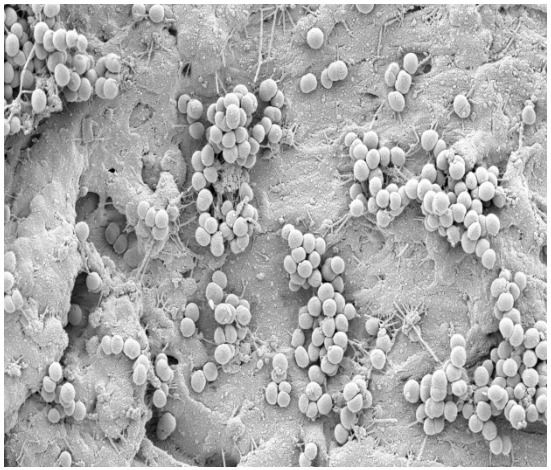
Assay	Knee/Hip Arthroplasty	Sensitivity (%)	Specificity (%)
ELISA			
Deirmengian et al. (2014)	84/11	100	100
Deirmengian et al. (2015)	43/3	100	100
Deirmengian (2014)	116/33	97	96
Frangiamore et al. (2016)	78* 38**	100* 67**	98* 97**
Bonanzinga et al. (2017)	65/91	97	97
Kelly et al. (2018)	33/6	82	82
Sigmund et al. (2018)	54/17	85	98
Stone et al. (2018)	121/62	81	96
Ivy et al. (unpublished)	106/25	94	97
Lateral Flow			
Bingham et al. (2014)	61**	100	95
Kasparek et al. (2016)	29/11	67	93
Sigmund et al. (2017)	17/30*	69	94
Okroj et al. (2017)	0/26	100	68
Balato et al. (2017)	51/0	88	97
Berger et al. (2017)	85/36	97	97
Suda et al. (2017)	19/11	77	82
Gehrke et al. (2018)	99/96	92	100
Renz et al. (2018)	151/61	84	96
Sigmund et al. (2018)	54/17	77	98
Ivy et al. (unpublished)	106/25	91	93

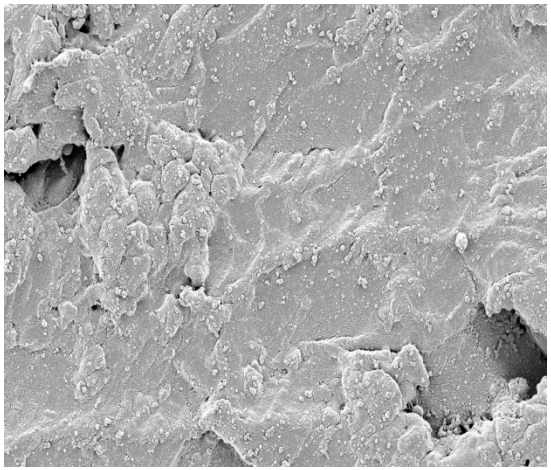
AAOS. 2019
Moderate ***
www.aaos.org/pjiguideline

*Analysis of first or single-stage revision; **Analysis of second-stage revision (i.e., re-implantation)

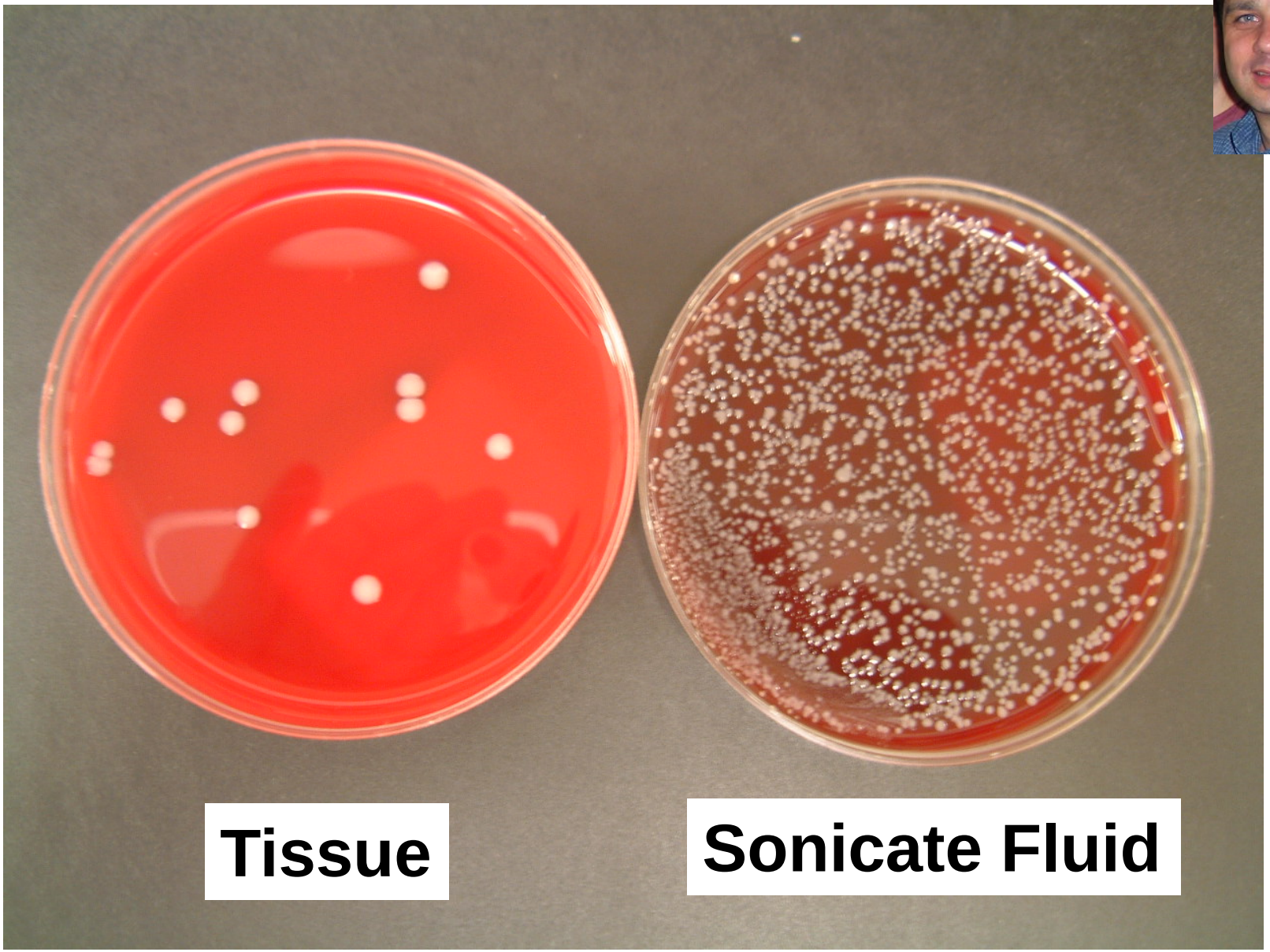
Staphylococcus epidermidis Biofilm (on Polycarbonate Coupons)







Soaking	Scraping	Sonication



Sonicate Fluid *versus* Tissue Culture Orthopedic Foreign Body Infection Diagnosis

Implant type		Sonicate fluid	Periimplant tissue	p value	Reference
Hip/knee arthroplasties	Sensitivity	79%	61%	<0.001	Trampuz et al, NEJM 2007 Vol 357;654
	Specificity	99%	99%		
Shoulder arthroplasties	Sensitivity	67%	55%	0.046	Piper et al, JCM 2009 Vol 47:1878
	Specificity	98%	95%		
Spine implants	Sensitivity	91%	73%	0.046	Sampedro et al, Spine 2010 Vol 25:1218
	Specificity	97%	93%		
Elbow arthroplasties	Sensitivity	89%	55%	0.18	Vergidis et al, JSES 2011 Vol 20;1275
	Specificity	100%	93%		
Hip/knee/shoulder arthroplasties, mega-prostheses, osteosyntheses, spine implants	Sensitivity	83%	61%	0.034	Holinka et al. J Orthop Res 2011 Vol 29:617
	Specificity	95%	95%		
Hip/knee arthroplasties, tibial inserts, acetabular components, fixation devices, spinal devices, etc.	Sensitivity	90%	67%	<0.001	Puig-Verdie et al. Bone Joint J 2013;95-B(2):244-9
	Specificity	99%	99.5%		
Hip arthroplasties	Sensitivity	75%	69%		Bogut et al. Polish J Microbiol 2014:63:299
	Specificity	97%	100%		
Hip/knee arthroplasties, internal device	Sensitivity	77%	34%	<0.002	Scorzolini et al. New Microbiol 2014;37:321
Fracture fixation implant (plate, screws, spine implant, intramedullary nail)	Sensitivity	90%	57%	<0.001	Yano et al. J Clin Microbiol 2014;52:4176
	Specificity	91%	96%		
Hip/knee/shoulder/elbow arthroplasties	Sensitivity	81%	61%	<0.01	Portillo et al. J Infect 2014:69:35e41
	Specificity	99%	100%		
Hip/knee arthroplasties	Sensitivity	97%	70%	<0.001	Rothenberg et al. Clin Orthop Relat Res 2017;475:1827
	Specificity	90%	97%		
Modular megaprostheses	Sensitivity	91%	52%	0.004	Puchner et al. J Orthop Res 2017
	Specificity	100%	100%		
Hip/knee/other arthroplasties	Sensitivity	47%	68%		Van Diek et al. Acta Orthopaedica, 2018 Vol 88;294-299
	Specificity	99%	80%		
Hip/knee arthroplasties	Sensitivity	77%	56%	0.012	Tani et al. Eur J Orthop Surg Trauma 2018 Vol 28:51
	Specificity	98%	94%		
Shoulder arthroplasties	Sensitivity	56%	96%		Grosso et al. J Shoulder Elbow Surg 2018 Vol 27; 211
	Specificity	99%	75%		
Hip/knee arthroplasties	Sensitivity	93%	67%	0.02	Sebastian et al. J Microbiol Meth 2018 Vol 146:51
	Specificity	100%	100%		
Hip/knee/shoulder arthroplasties	Sensitivity	70%	53%	0.001	Prieto-Borja et al. Eur J Clin Microbiol Infect Dis 2018 Vol 37;715
	Specificity	98%	91%		
Multiple	Sensitivity	57%	69%		Dudareva et al. J Clin Microbiol 2018 Vol 56:1
	Specificity	94%	97%		
Megaprostheses	Sensitivity	98%	86%	<0.001	Sambri et al. Orthopedics 2019 Vol 42;28
	Specificity	94%	100%		
Spine implants	Sensitivity	94%	66%	0.002	Bürger et al. Eur Spine J 2019 Vol 28;768
	Specificity	99%	96%		
Hip/knee/ankle/elbow arthroplasties	Sensitivity	71%	29%	0.02	Ueda et al. J Arthroplasty 2019 Vol 34:1189
	Specificity	100%	100%		
Hip/knee arthroplasties	Sensitivity	71%	47%	<0.001	El-Khier et al. Egyptian J Basic and Applied Sci 2019

Mayo Clinic Orthopedic Implant Processing

Prosthesis Placed in Container (Operating Room)

400 ml Ringer's Solution Added

Vortex 30 sec

Sonicate 5 min

Vortex 30 sec

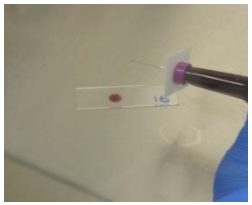
Centrifuge 5 min

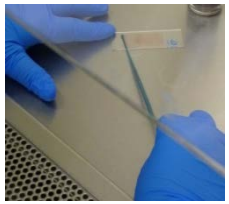
Aspiration

Plating

AAOS. www.aaos.org/pjiguideline. 2019 Moderate ***

Periprosthetic Tissue Culture*
Blood Culture Bottles





AAOS. www.aaos.org/pjiguideline. 2019
Moderate ***

Periprosthetic Tissue Blood Culture Bottle Study

- Patients undergoing revision arthroplasty, Mayo Clinic, 8/2013–4/2014
  - 369 subjects - 138 hip, 160 knee, 49 shoulder, 22 elbow arthroplasties
  - 117 (32%) IDSA diagnostic criteria for PJI

Peel et al. mBio 2016;7:e01776

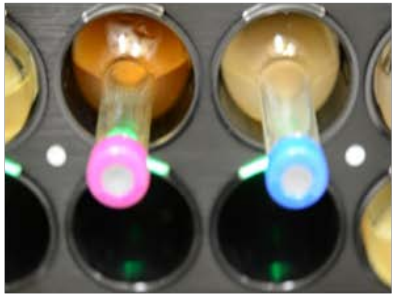
Peri-prosthetic tissue sample

Tissue sample homogenized

Conventional Culture Technique:
Homogenate inoculated onto agars and broth

Media manually checked daily for growth and sub-cultured if growth detected

New Technique:
Homogenate inoculated into blood culture bottles and placed onto the semi-automated machine



Bottles continuously monitored for growth and sub-cultured if flagged positive

Periprosthetic Tissue Blood Culture Bottle Study Bayesian Latent Class Modeling

Media Combination	Sensitivity	Specificity
Aerobic and anaerobic agars	48.9	99.7
Aerobic and anaerobic agars and thioglycollate broth	62.6	98.1
Aerobic and anaerobic blood culture bottles	92.1	99.7
Aerobic and anaerobic blood culture bottles and thioglycollate broth	92.1	98.8
Aerobic and anaerobic blood culture bottles and aerobic agar	94.6	99.7
Aerobic and anaerobic blood culture bottles and anaerobic agar	96.8	99.8
Aerobic and anaerobic blood culture bottles and aerobic and anaerobic agars	99.1	99.7
All media combined	99.1	97.3

Peel et al. mBio 2016;7:e01776

Tissue Cultures in Blood Culture Bottles: Laboratory Staff Time

Peel et al. J Clin Microbiol 2017;55:2817

Periprosthetic Tissue Culture

- 499 consecutive patients undergoing revision arthroplasty (August 2013 through April 2014)
- 1,437 periprosthetic tissue samples
- **Conventional culture techniques** (aerobic and anaerobic sheep blood agars, thioglycolate broth)
  - Greatest accuracy with **four specimens** (91%; 95% Credible Interval: 77-100%)
- Inoculation of tissues into aerobic and anaerobic **blood culture bottles**
  - Greatest accuracy with **three specimens** (92%; 95% Credible Intervals: 79-100%)

Peel et al. J Clin Microbiol 2017;55:234

Periprosthetic Tissue Blood Culture Bottle BioFire FilmArray BCID

- Positive blood culture bottles inoculated with periprosthetic tissue:
  - Tested with BioFire FilmArray BCID assay
    - *Staphylococcus* species, *Staphylococcus aureus, mecA*
- 22 clinical specimens (+ 4 spiked bottles*) → 100% accuracy
  - *S. epidermidis* (8), *S. aureus* (8), *S. capitis* (1), *S. hominis* (1), *S. lugdunensis* (2)
  - *S. agalactiae* (1), *E. faecalis* (2)*, *E. faecium* (1)*, *E. durans* (1)*

Tissue Culture in Blood Culture Bottles *versus* Sonication

	IDSA PJI criteria as gold standard				Bayesian latent class modeling		
	Subjects with		Sensitivity	Specificity	Prevalence	Sensitivity	Specificity
	PJI	Aseptic failure	% (95% confidence interval)		% (95% credible interval)		
	104	125			37.2 (31.1, 43.5)		
Tissue	69	5	66.4 (56.4, 75.3)	96.0 (90.9, 98.7)		86.3 (78.3, 92.4)	99.6 (97.7, 100.0)
Sonicate fluid	76	0	73.1 (63.5, 81.3)	100.0 (97.1, 100.0)		88.7 (81.0, 94.3)	99.6 (97.7, 100.0)
Combination	80	5	76.9 (67.6, 84.6)	96.0 (90.9, 98.7)		99.1 (95.7, 100.0)	99.5 (97.6, 100.0)

Yan et al. J Clin Microbiol 2018:56(6)

Sonication and 16S rRNA Gene PCR Hip/Knee Prostheses

Test	Sensitivity 135 PJI	Specificity 231 Aseptic Failure	Accuracy
	% (95% Confidence Interval)		
Sonicate fluid culture	72.6 (66.8-78.4)	98.3 (96.6-100)	88.8 (84.7-92.9)
Sonicate fluid 16S rRNA gene PCR	70.4 (64.5-76.3)	97.8 (95.9-99.7)	87.7 (83.5-91.9)
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

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Sonication Fluid – PJI PCR Panel Hip/Knee Prostheses

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				
Cutibacterium 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

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Sonicate Fluid Shotgun Metagenomic Sequencing *versus* Culture

	Samples	Identical Findings	Organisms Not Identified by Metagenomics	New Organisms Detected by Metagenomics
Aseptic Failures	195	188 (96.4%)	N/A	7 (3.6%)
Culture-Positive PJIs	115	99 (86.1%)	6 (5.2%)	11 (9.6%)
Culture-Negative PJIs	98	55 (56.1%)	N/A	43 (43.9%)

Thoendel et al. Clin Infect Dis. 2018:67:1333

MAYO CLINIC

Organisms Detected by Shotgun Metagenomic Sequencing in Culture-Negative PJIs

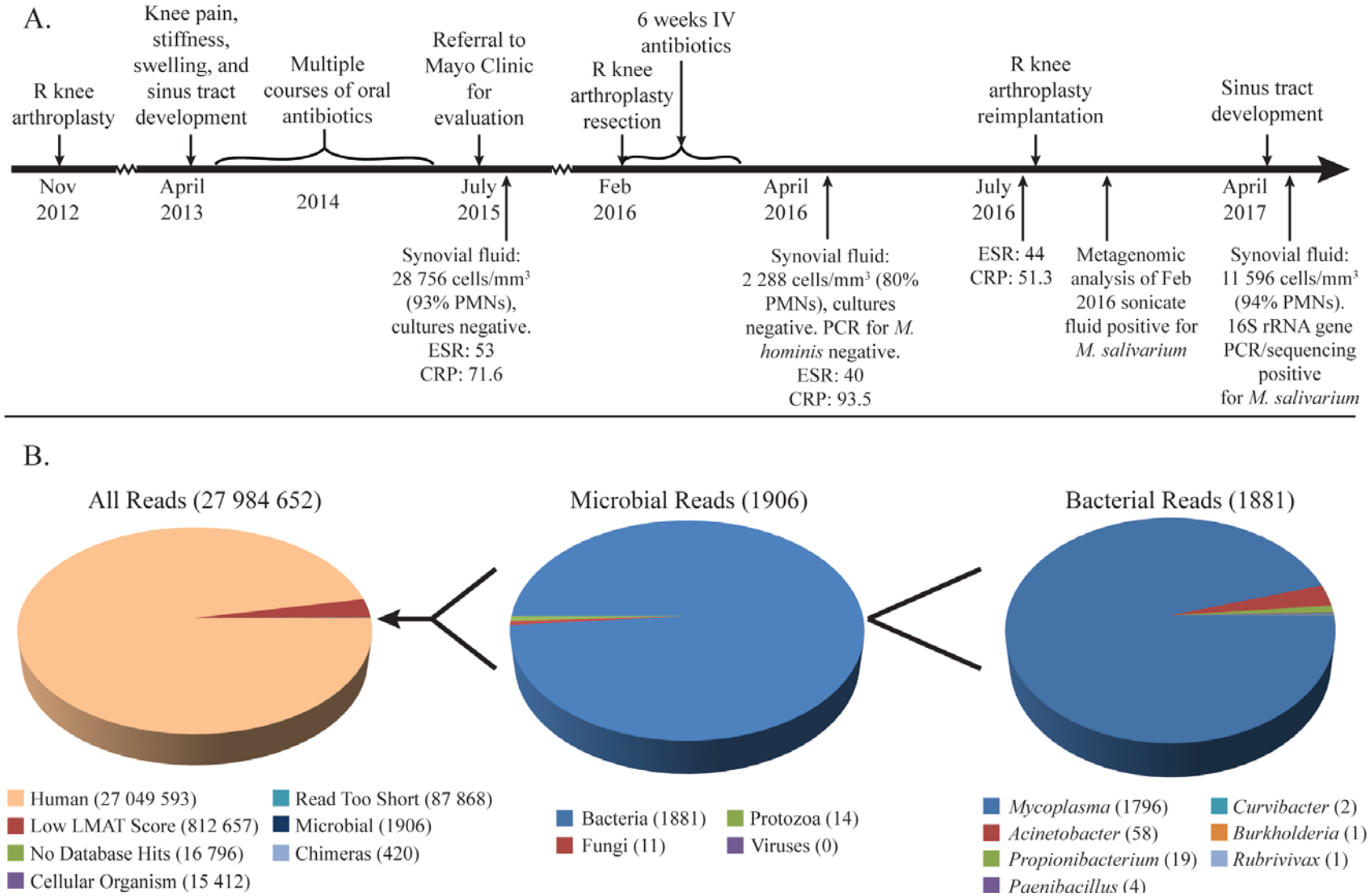
Anaerococcus urinae	*Metamycoplasma salivarium*
Candida albicans (2)*	*Peptoniphilus* species
*Candida parapsilosis**	*Pasteurella multocida**
Clostridium perfringens	*Staphylococcus aureus* (10)*
Corynebacterium pseudogenitalium	*Staphylococcus epidermidis* (5)*
Cutibacterium acnes	*Staphylococcus haemolyticus* (2)*
Enterococcus faecalis (3)*	*Staphylococcus lugdunensis*
Enterobacter cloacae (2)*	*Streptococcus agalactiae* (4)
Facklamia languida	*Streptococcus dysgalactiae* (4)*
Granulicatella adiacens (2)*	*Streptococcus oralis**
Mycobacterium bovis BCG*	

*Indicates organism identified in cultures other than sonicate fluid

Thoendel et al. Clin Infect Dis. 2018:67:1333

MAYO CLINIC

53 yo Man – Right Knee PJI

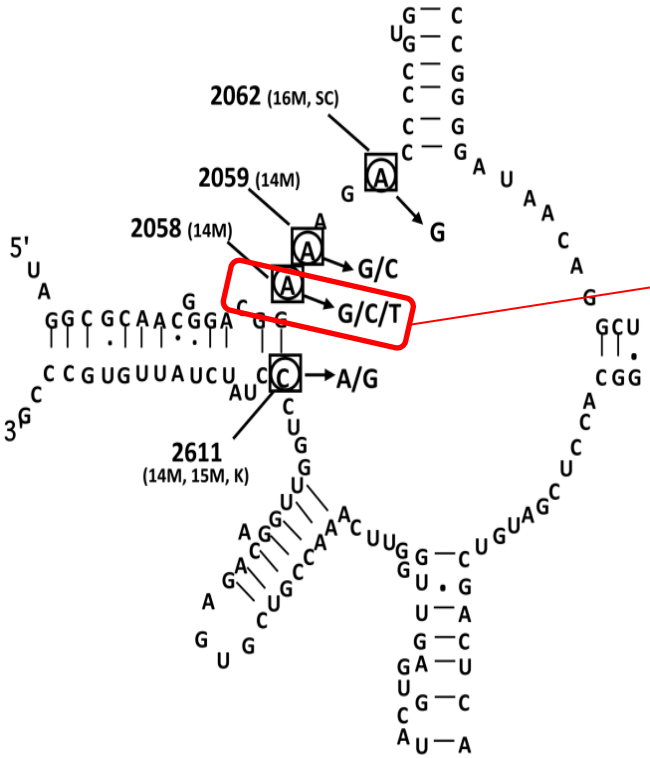


Thoendel et al. Clin Infect Dis 2017;65:332.

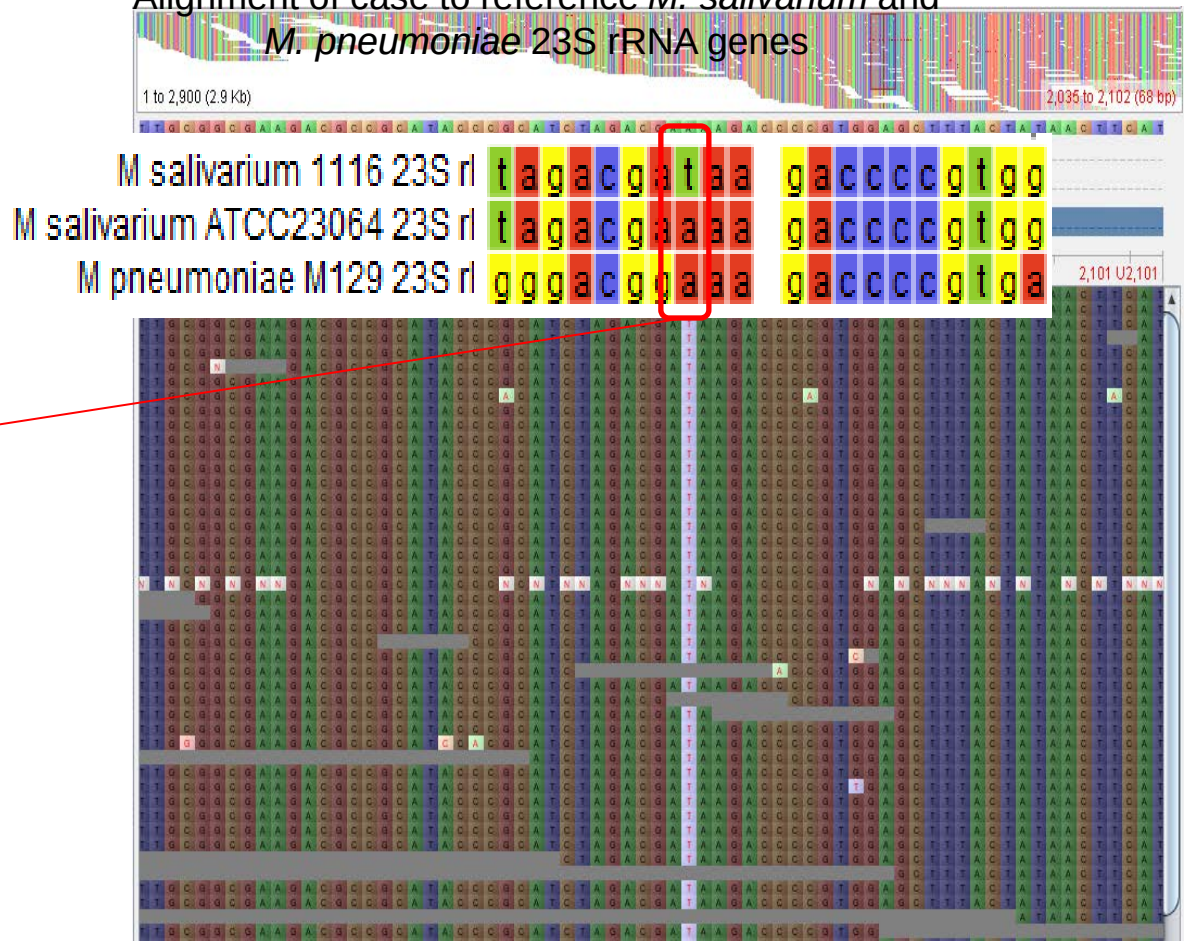
MAYO CLINIC

Antibiotic Resistance Prediction

Macrolide resistance-associated mutations in 23S rRNA gene of *M. pneumoniae*



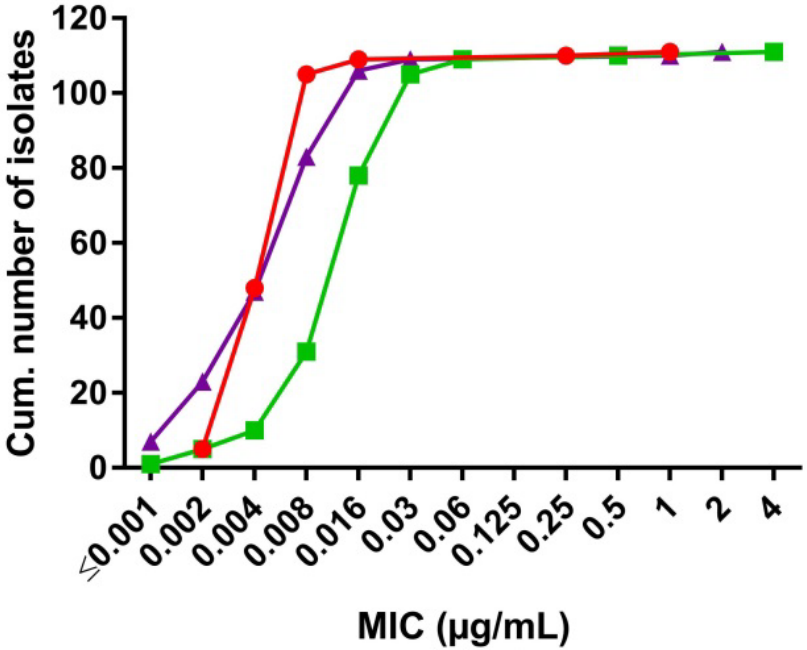
Alignment of case to reference *M. salivarium* and *M. pneumoniae* 23S rRNA genes



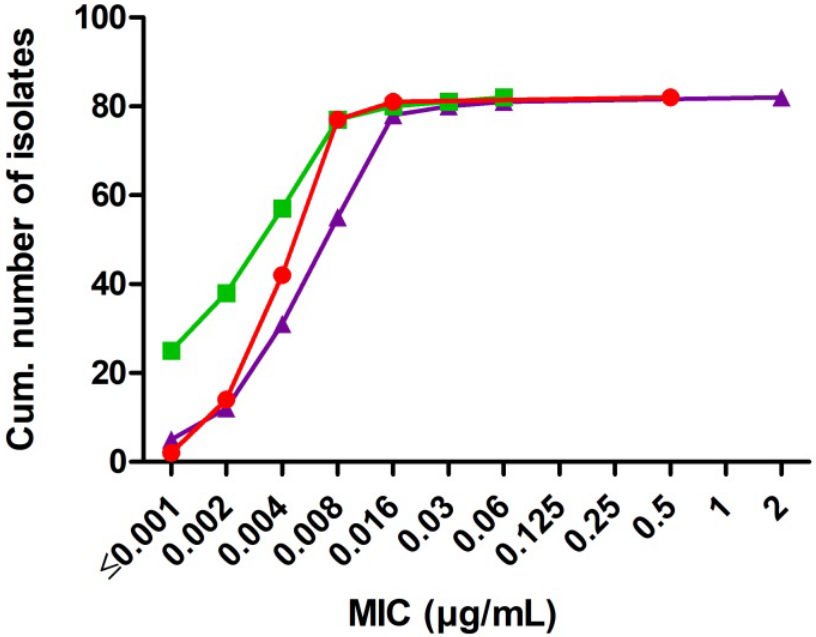
Pereyre, et al. Frontiers in Microbiology 2016.

Thoendel et al. Clin Infect Dis 2017;65:332

Staphylococcus aureus



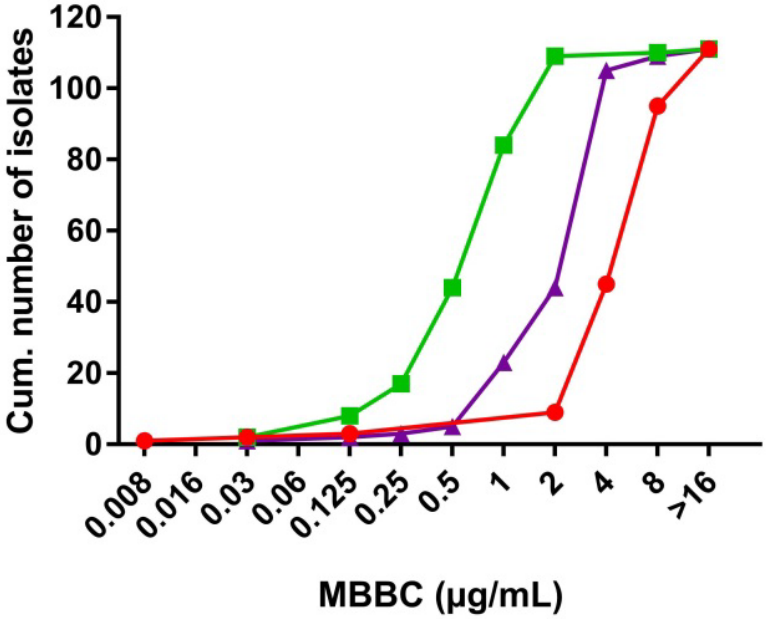
Staphylococcus epidermidis



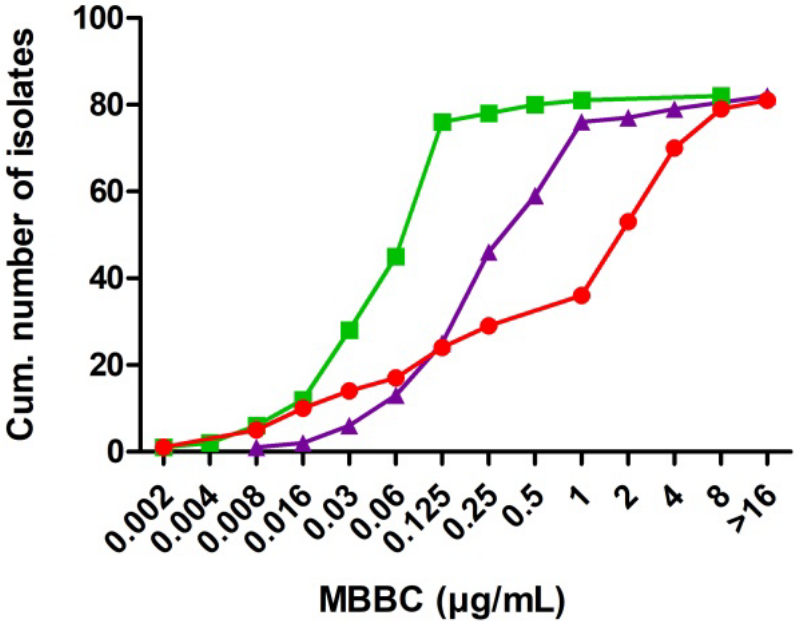
Rifampin Rifabutin Rifapentine

Albano et al. Antimicrob Ag Chemother. In Press.

Staphylococcus aureus



Staphylococcus epidermidis



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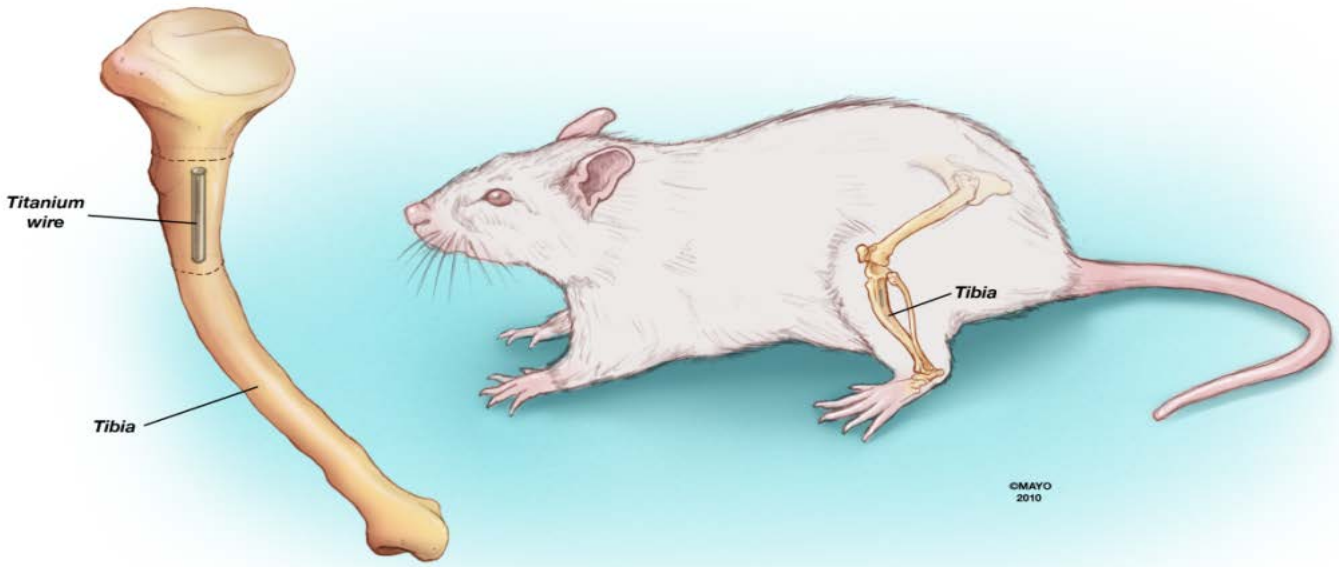
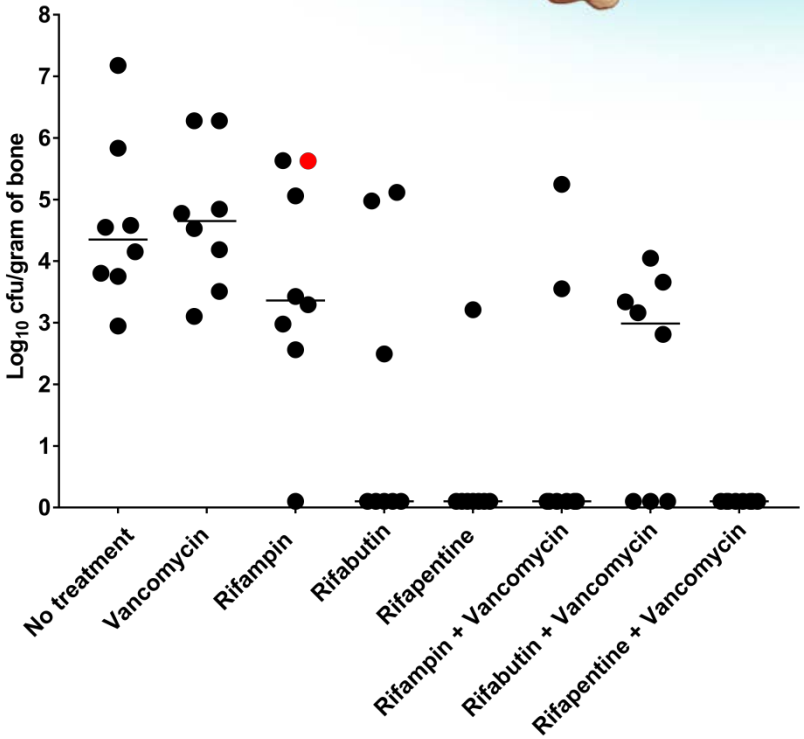
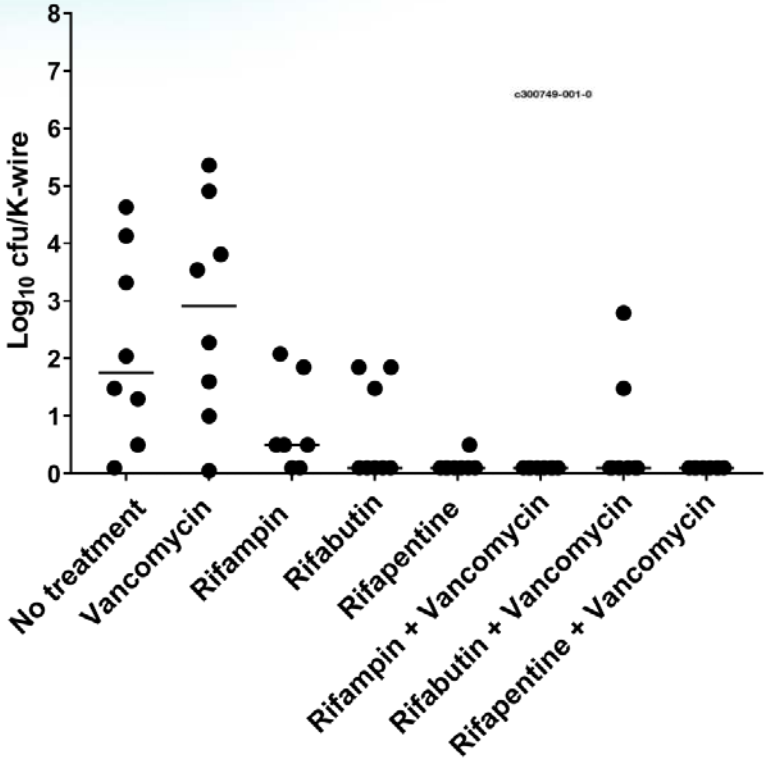
Albano et al. Antimicrob Ag Chemother. In Press.

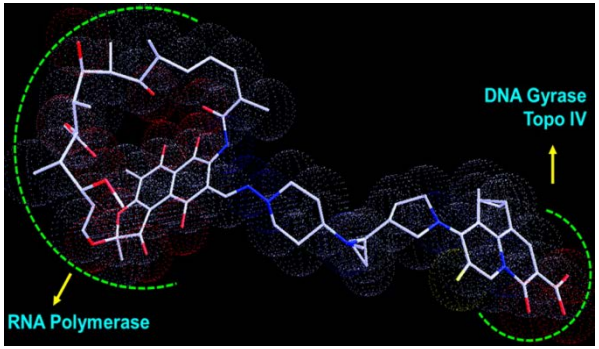




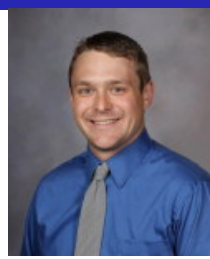


● Rifampin-resistant

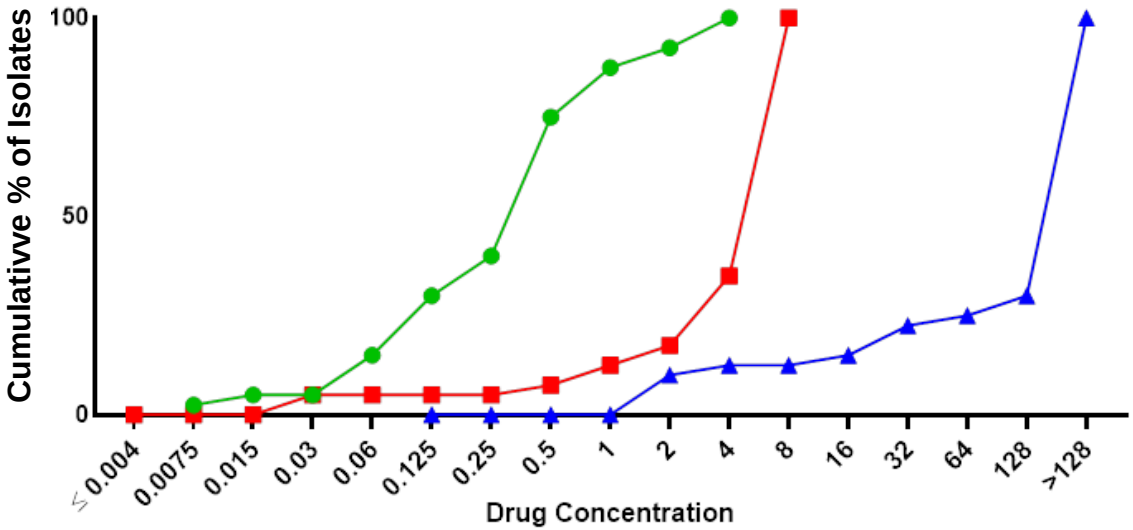
MAYO CLINIC



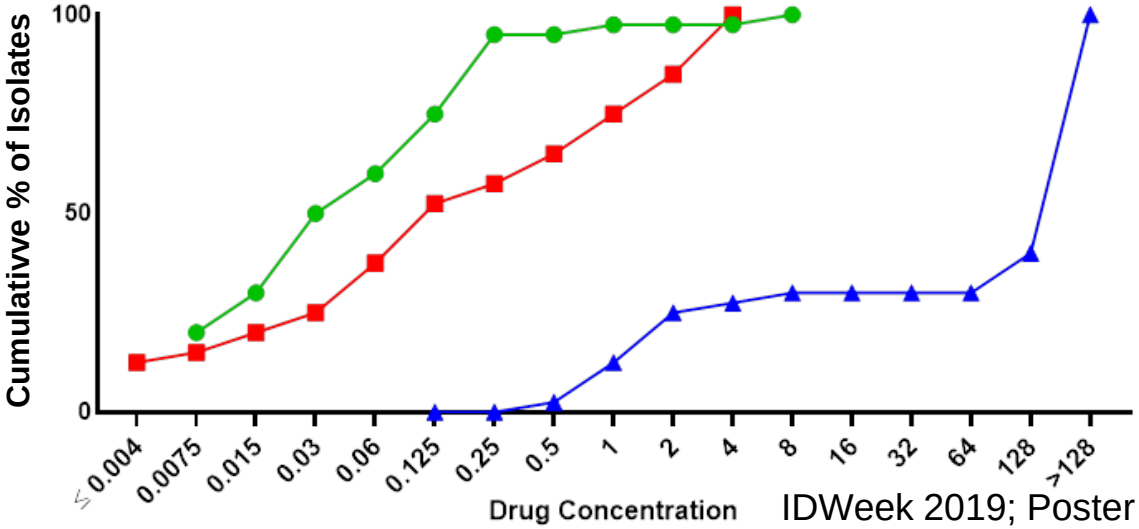
TNP-2092 MBBCs



S. aureus



S. epidermidis



IDWeek 2019; Poster 691

Summary

- **Arthroplasty cultures**
  - Site of biofilms
- **Improved tissue culture method**
  - Blood culture bottles
- **Molecular diagnostics**
  - Challenging cases
    - 16S rRNA gene PCR/sequencing, panel PCR, shotgun metagenomic sequencing
- **Non-rifampin rifamycins**
  - Rifampin alternative in staphylococcal PJI?

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