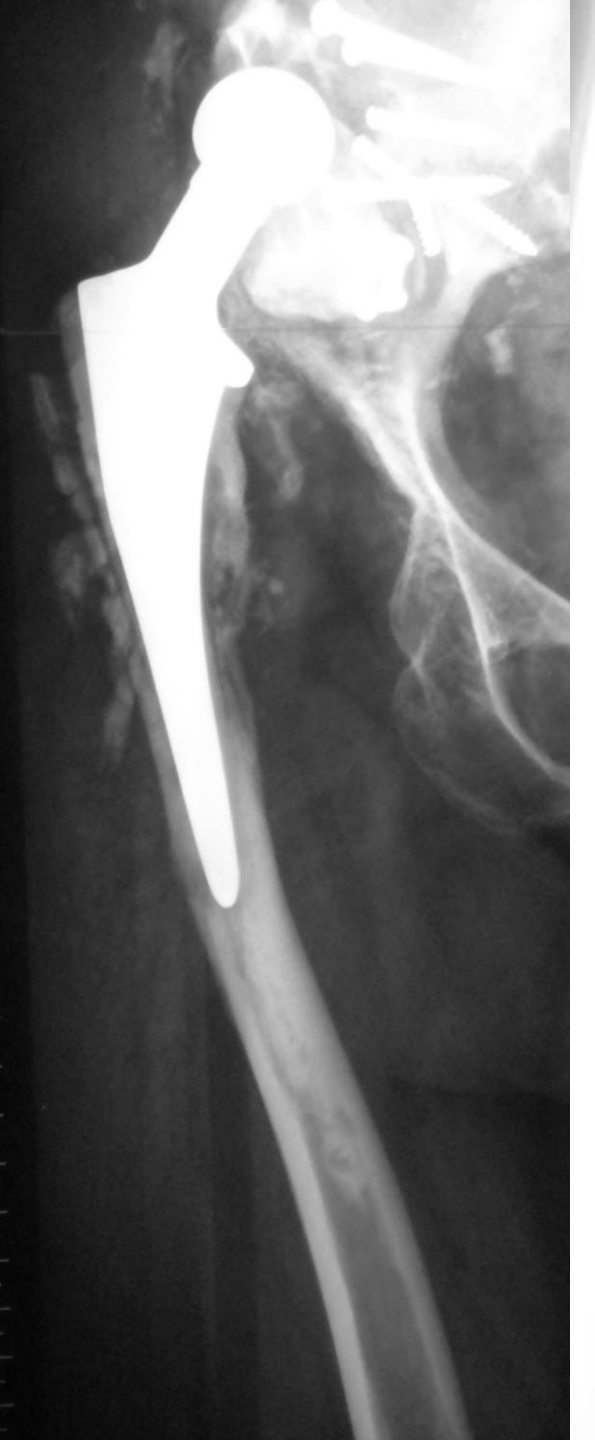


Periprosthetic Joint Infection
Update for 2023

Javad Parvizi MD, FRCS
Professor
Acibadem University, Istanbul

Disclosures

- Research support:
  - NIH
  - Department of Defense
  - OREF
  - 3M
  - Aesculap
  - AO Spine
  - Biomet
  - Cempra
  - CeramTec
  - DePuy
  - Integra
  - Lima
  - Myoscience
  - NDRI
  - Novartis
  - Pfizer
  - Rotation Medical
  - Simplify Medical
  - Smith and Nephew
  - Stelkast
  - Stryker Orthopedics
  - Synthes
  - TissueGene
  - Tornier
  - Orthospace
  - Zimmer Biomet

Disclosure

- **Consultant**
  - Becton Dickinson
  - Corentec
  - Convatec
  - Cardinal Health
  - Ethicon
  - G-21
  - KCI / 3M (Acelity)
  - Zimmer Biomet

- **Royalty**
  - Becton Dickenson
  - Corentec
  - Datatrace
  - Elsevier
  - Jaypee publishers
  - Slack
  - Wolters Kluwer

Equity Ownership

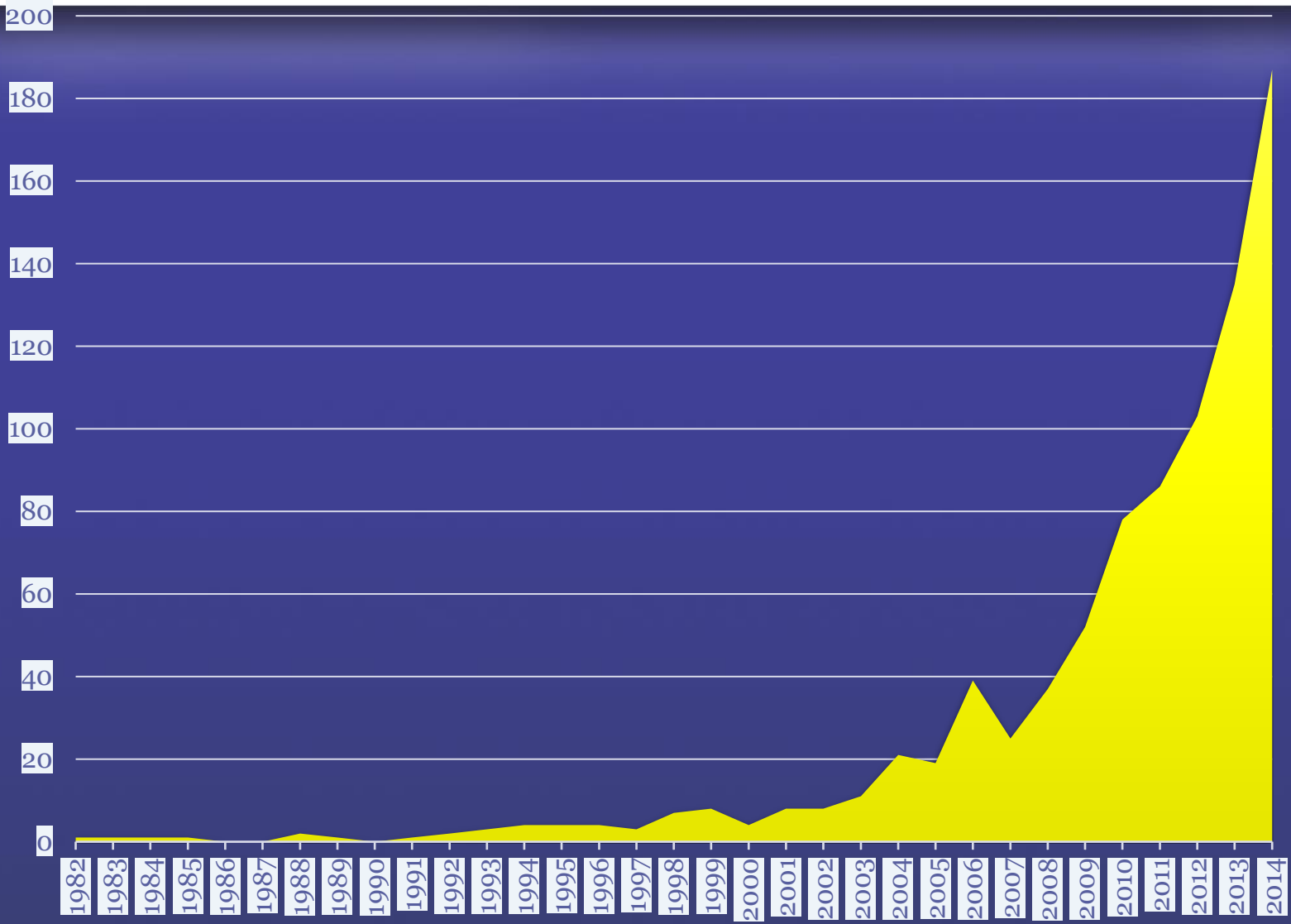
- Acumed
- Alphaeon/Strathsby Crown
- Ceribell
- Coracoid
- Corin
- Efferent
- Elute
- Hip Innovation Technology
- Illuminos
- Intellijoint
- Molecular Surface Tech.
- Nanooxygenic
- Optinutrium
- Osteal
- Parvizi Surgical Innovation and subsidiaries
- Peptilogic
- Plasmology4
- Sonata
- Sonogen
- Tangen

PJI

Fact

Infection is on the rise

Pubmed Publications for PJI by Year

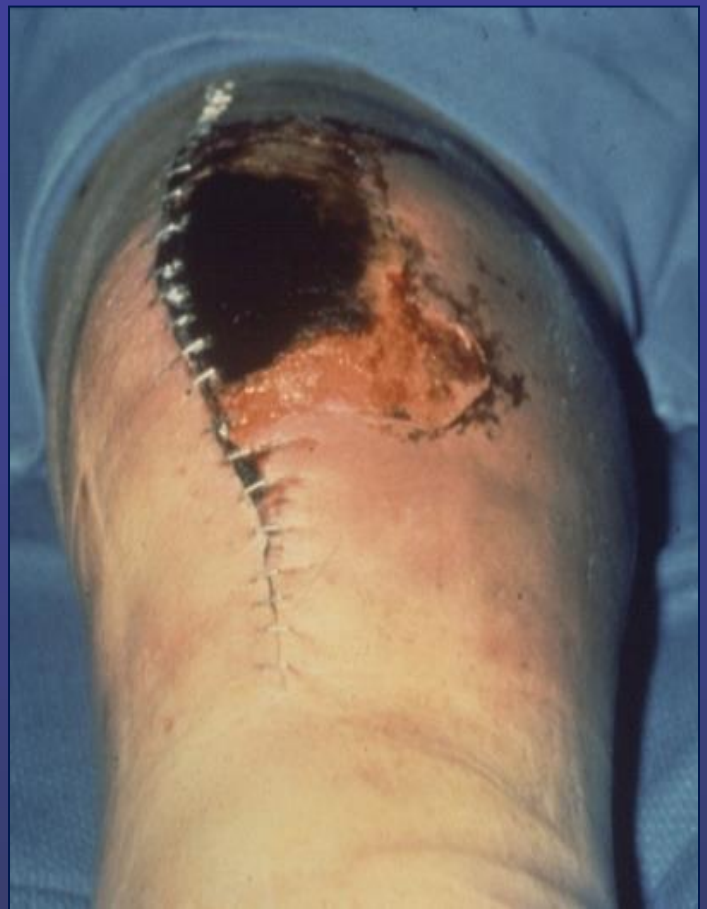


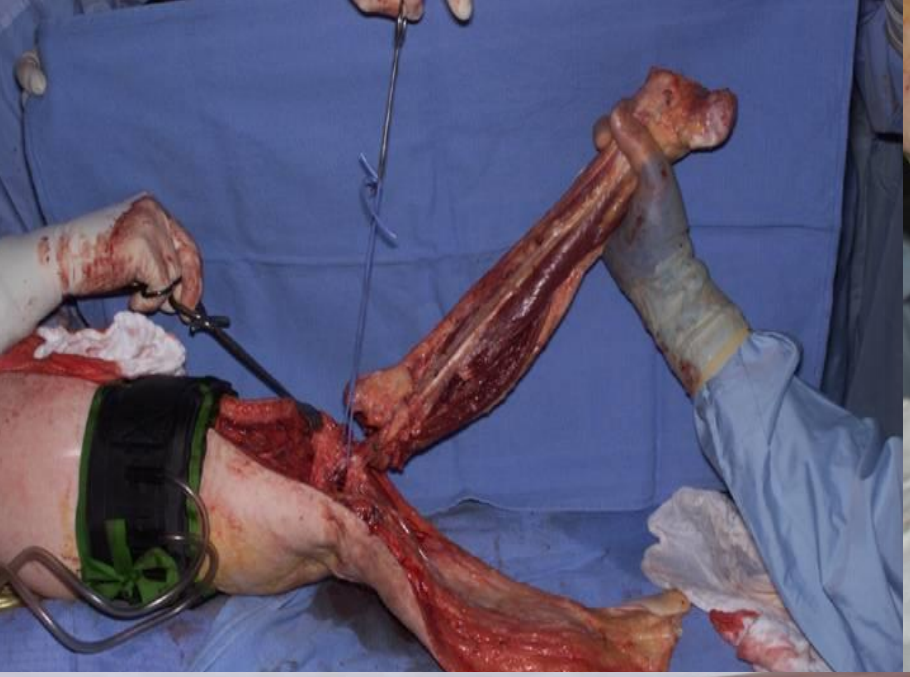
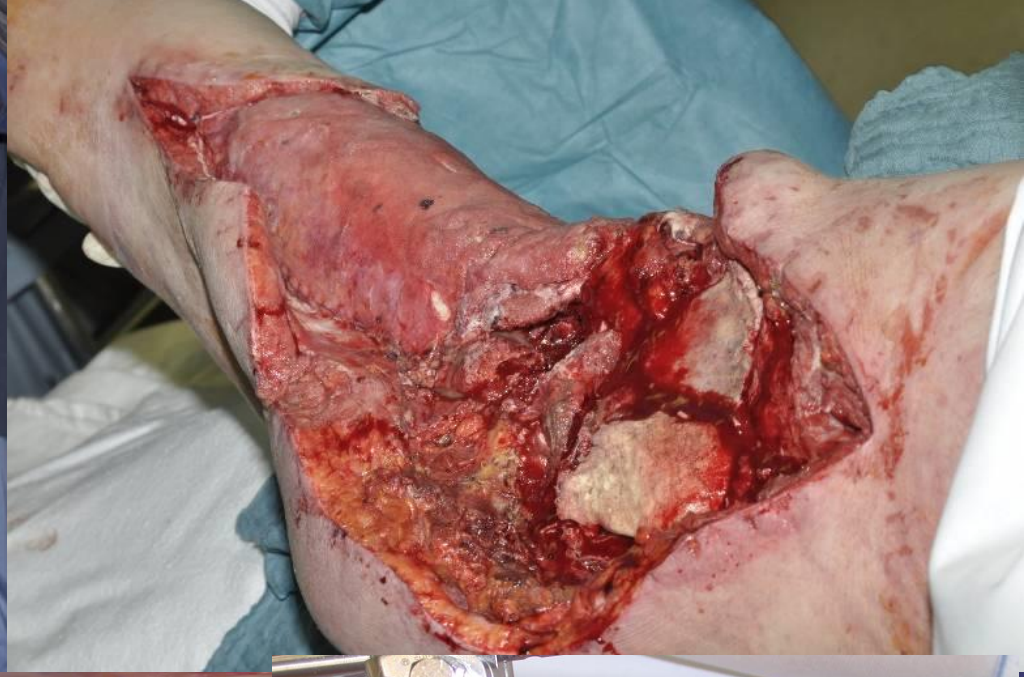
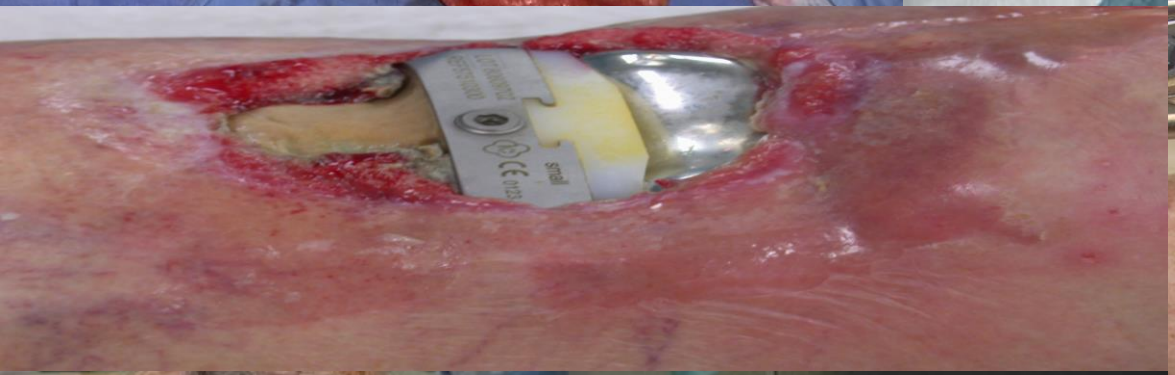
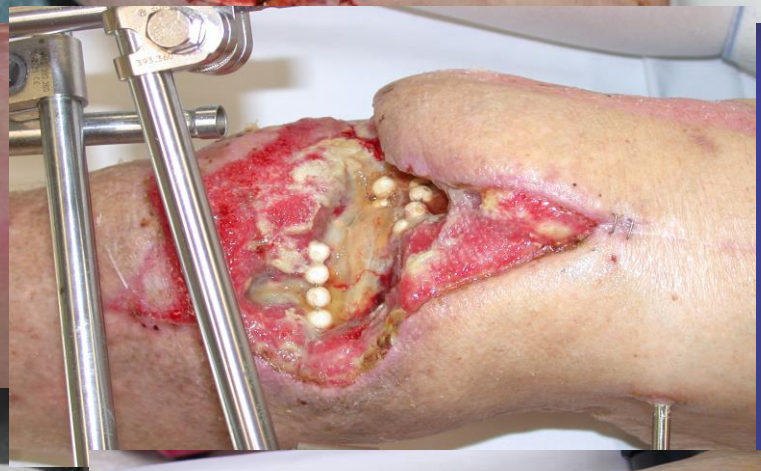
Obtained using the keyword “periprosthetic joint infection”

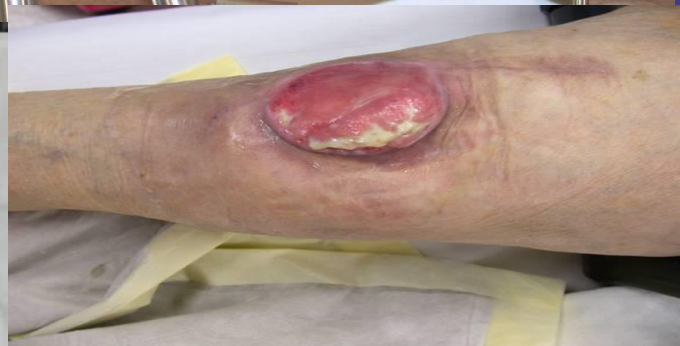
PJI

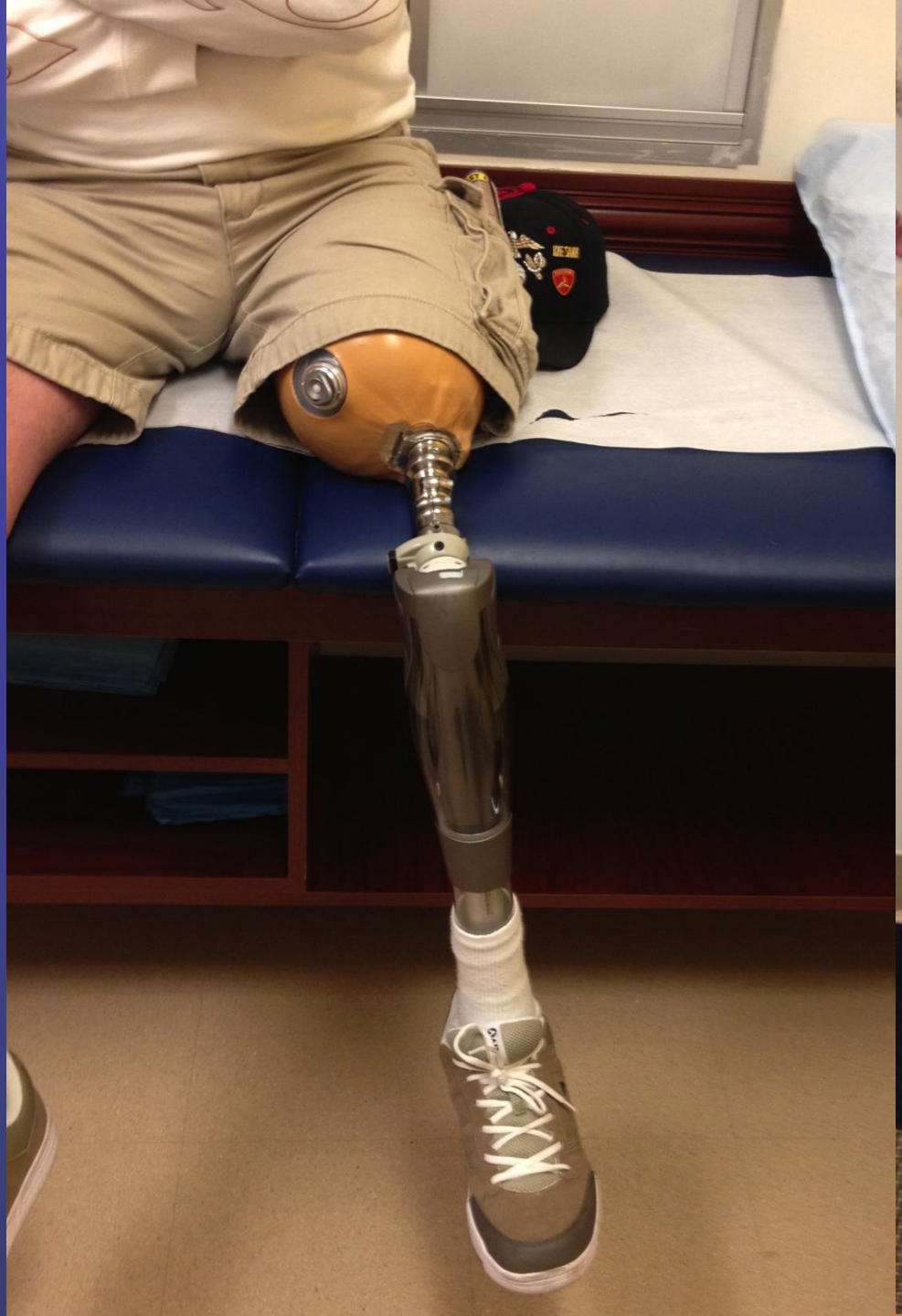
Fact

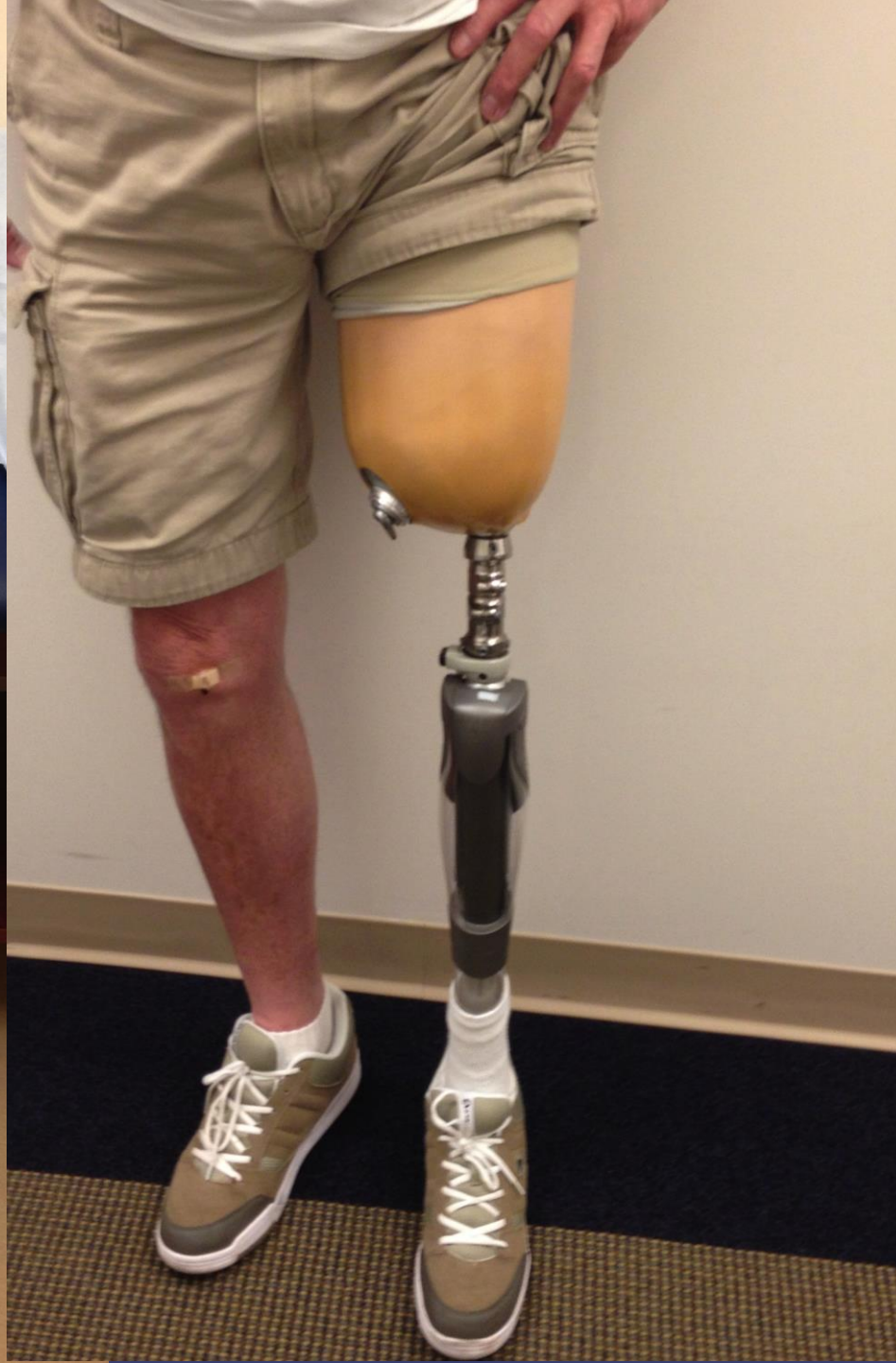
High morbidity





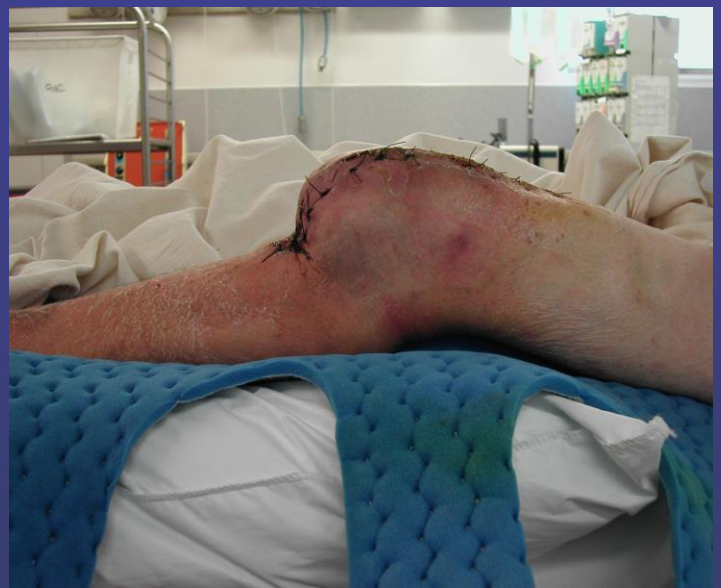




PJI

Fact

Infection kills

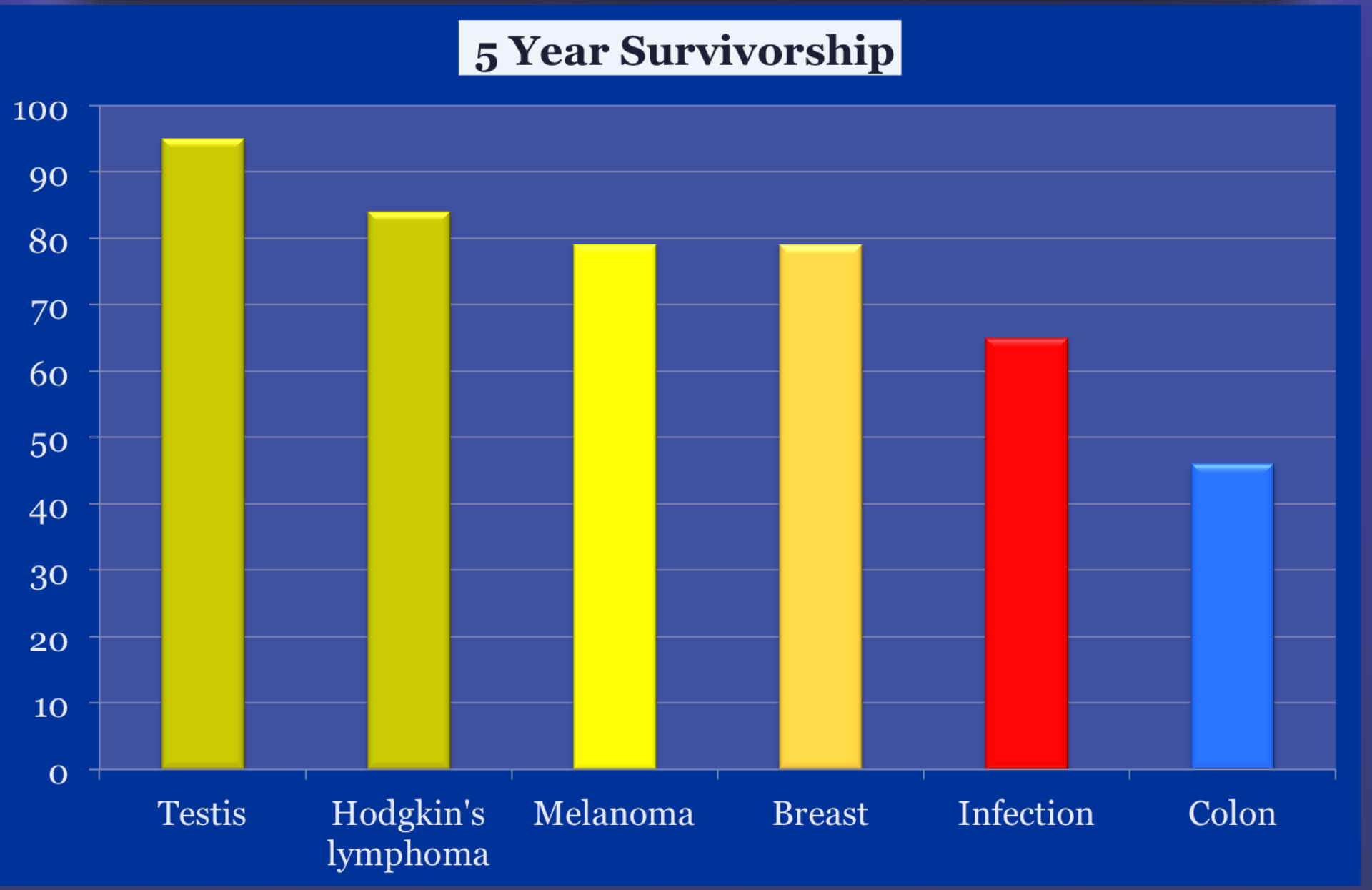


Rothman Study

- PJI is an independent predictor of mortality.
  - When adjusting for confounders, PJI is associated with a **4x** increased odds of one-year mortality compared to aseptic revision.

Zmistowski B et al JBJS 2013

PJI worse than Some Cancers



What is New?

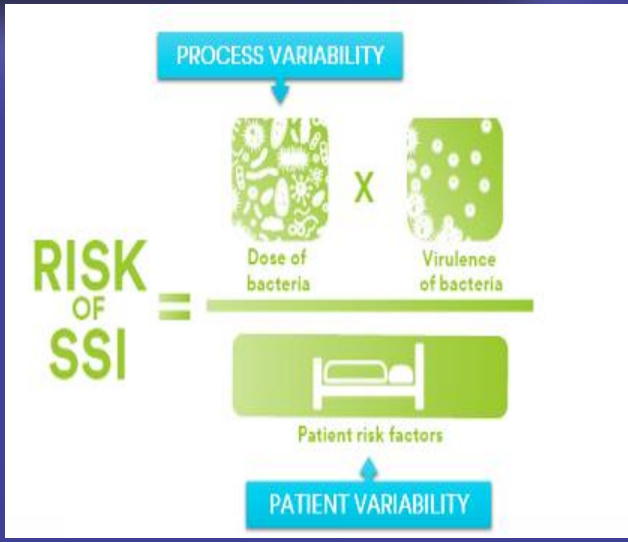
Prevention is a bundle

Risk of Infection

Conceptual Formula

- According to the CDC's conceptual formula for SSI Risk, SSIs are impacted by the number of microbes that contaminate an incision during surgery[1]

- Most surgical site infections are caused by contamination of an incision with microbes from the patient's own skin



Source: CDC

- The skin can contain over 1,000,000 bacteria per sq cm [2]

- It can take as few as 10 microbes per sq cm* to cause a surgical site infection[3]

If we can reduce the number of microorganisms, we can reduce the risk of infection

*
1. CDC Guideline For Prevention Of Surgical Site Infection, 1999 http://www.cdc.gov/ncidod/dhqp/gl_surgicalsite.html
2. Percival SL, Emanuel C, Cutting KF, Williams DW. Microbiology of the skin and the role of biofilms in infection. *Int Wound J*. 2012;9:14-32.
3. Feldman G, et al. Recent advances in the basic sciences: osteoarthritis, infection, degenerative disc disease, tendon repair and inherited skeletal diseases. In: Austin MS, Klein GR, ed. *Recent Advances in Orthopedics*. Philadelphia, PA Jaypee Medical Inc; 2014: 256.

Surgical Site Infection (SSI)

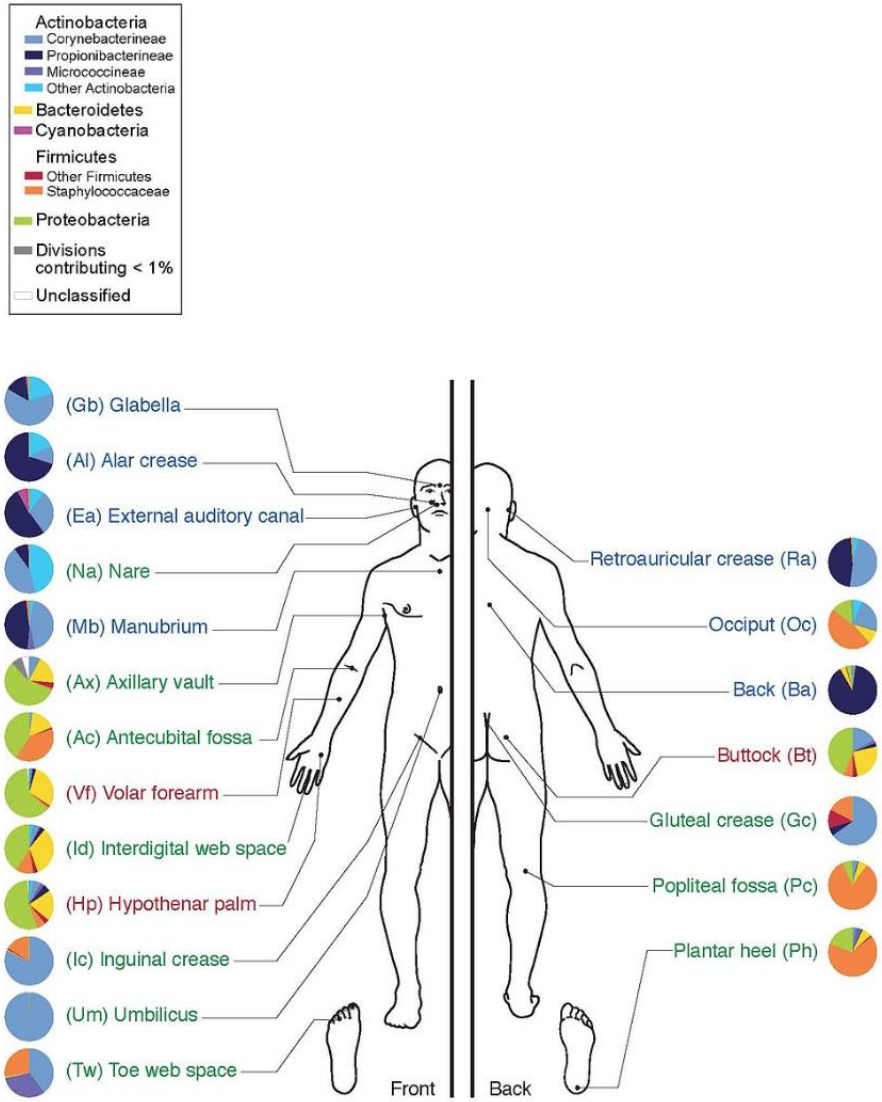
Patient Optimization

- Systemic or local infection
- Immunosuppressive state
- Uncontrolled Diabetes/hyperglycemia
- Chronic disease (anemia, liver, renal, etc.)
- Malnutrition
- Obesity
- Affective disorders
- Smoking
- Excessive Alcohol consumption
- IV drugs/HIV

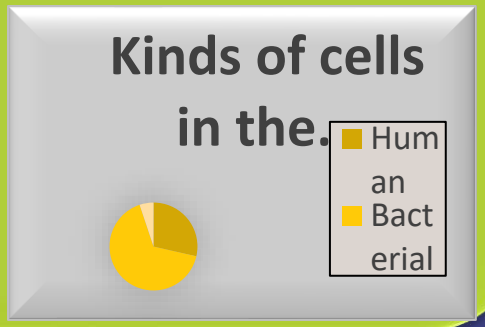
What is New?

Microbiome plays a role

Microbiome



37 Trillion
Human Cells
100 Trillion
Microbial Cells



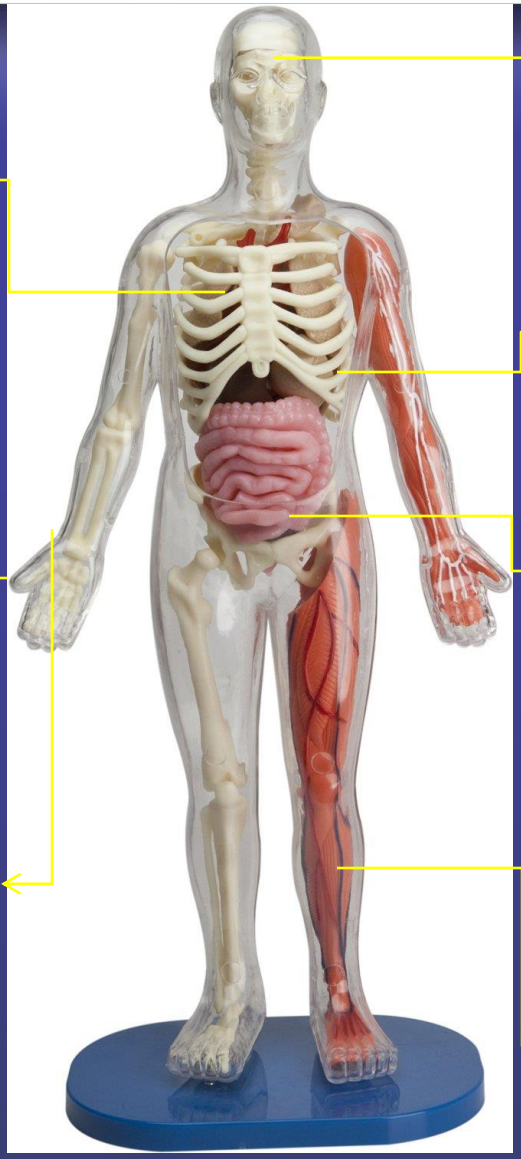
American Society for Microbiology Academy. FAQ: Human Microbiome 2014.Retrieved December 08, 2016, from https://www.asm.org/images/stories/documents/FAQ_Human

Symbiosis

The Story of Commensalism

1877: Heinrich Anton de Bary

Dysbiosis



Brain
Autism
Depression
CP
Alzheimer's

Heart
HTN
IHD

GI
Cancer
Biliary
IBD
Crohn;s
Fatty Liver

Vascular
PVD

Respiratory
Asthma
COPD

Skin
Cancer
Allergy

GU
Cancer
Polycystic ovarian syndrome

Shoulder microbiome

J Shoulder Elbow Surg (2018) 27, 1734–1739

ELSEVIER

JOURNAL OF SHOULDER AND ELBOW SURGERY

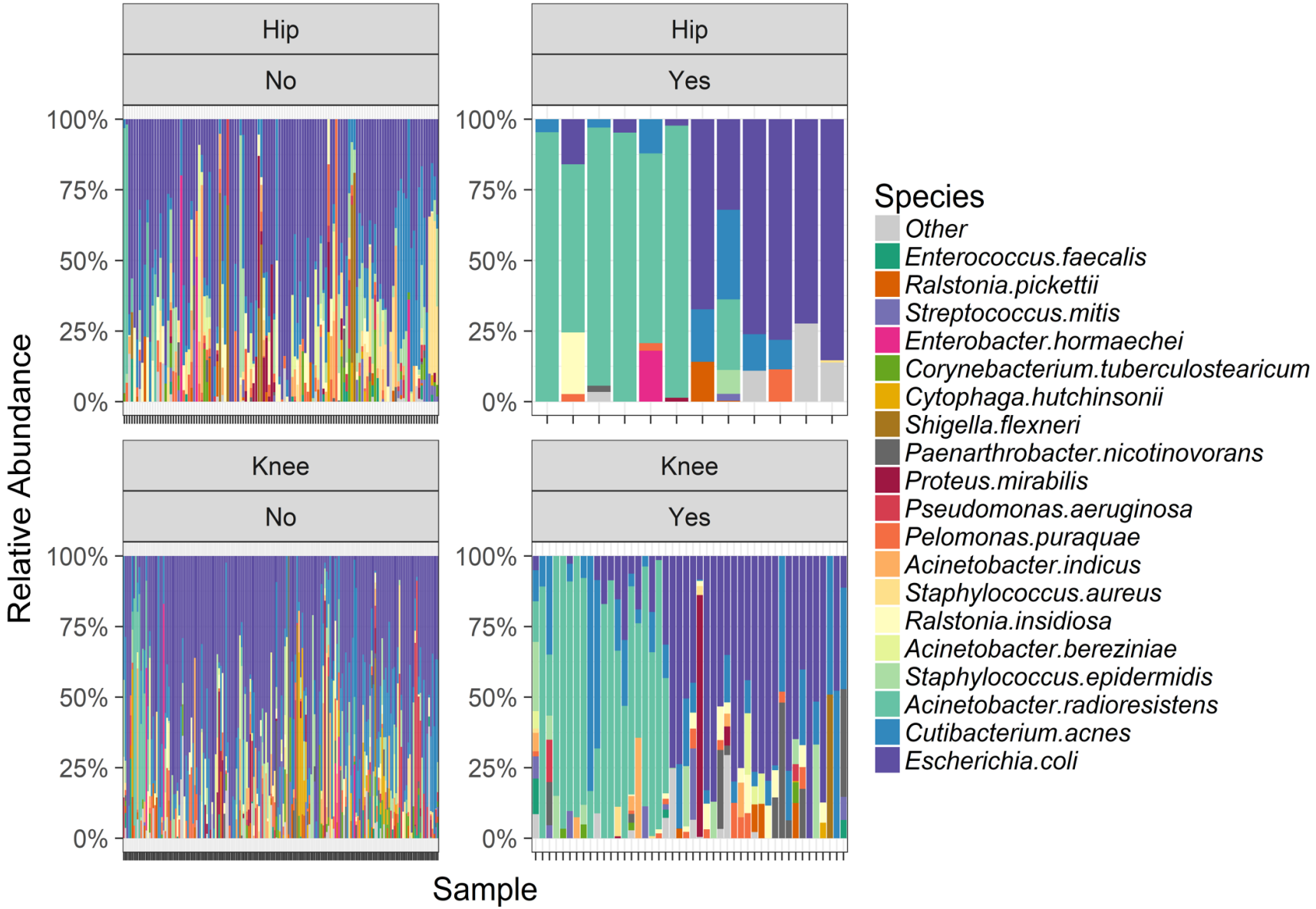
www.elsevier.com/locate/ymse

BASIC SCIENCE

Cutibacterium acnes and the shoulder microbiome

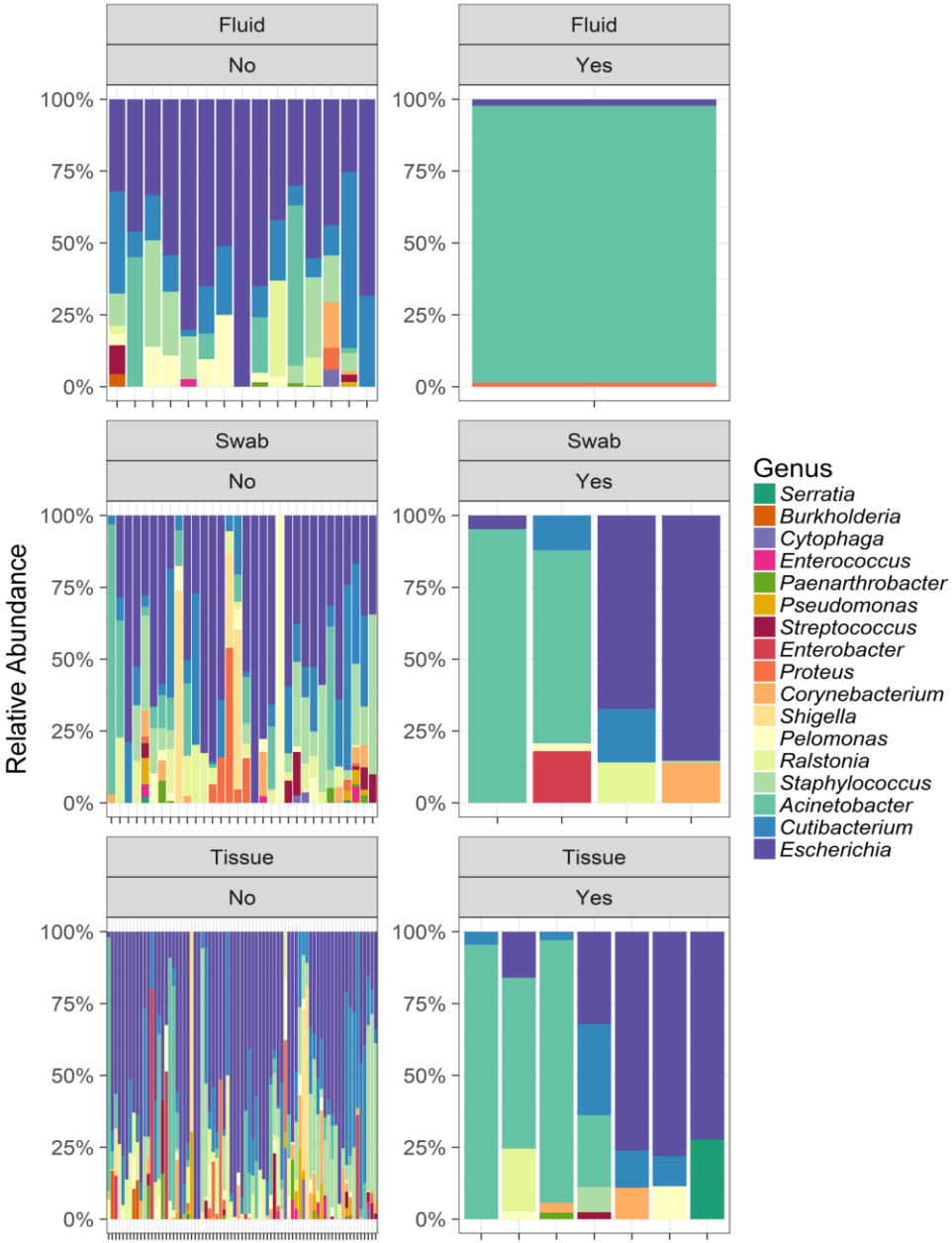
Boyang Qiu, BMedSc[a], Kait Al, BMedSc[b], Ana M. Pena-Diaz, MSc[c], George S. Athwal, MD[a,c], Darren Drosdowech, MD[a,c], Kenneth J. Faber, MD[a,c], Jeremy P. Burton, PhD[a,b], David B. O'Gorman, PhD[a,c,*]

Hip vs. Knee Microbiome:
99% overlap in composition



No injection vs. Prior injection

Acinetobacter enrichment (p<0.001)



The Mark Conventry Award

Human Knee Has a Distinct Microbiome: Implications for Periprosthetic Joint Infection

Javad Parvizi, MD

Human Knee Has A Distinct Microbiome: Implications for Periprosthetic Joint Infection

Diana Fernández-Rodríguez[1,2]; Colin M. Baker[1]; Saad Tarabichi[1]; Emma E. Johnson[1]; Michael G. Ciccotti[1]; Javad Parvizi[1]

[1] Rothman Orthopaedic Institute, Philadelphia, Pennsylvania, USA

[2] Plan de Estudios Combinados en Medicina (PECEM) MD/PhD, Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico City, Mexico.

Understanding Infection

Microbiome

- All knees with OA have a microbiome
- OA knee has different microbiome than non-OA knee
- Profile of organisms in PJI joint is similar to contralateral non-infected knee

Pre and Probiotics

ARTICLE

https://doi.org/10.1038/s41586-018-0616-y

Pathogen elimination by probiotic *Bacillus* via signalling interference

Pipat Piewngam[1,2], Yue Zheng[1,5], Thuan H. Nguyen[1,5], Seth W. Dickey[1], Hwang-Soo Joo[1,4], Amer E. Villaruz[1], Kyle A. Glose[1], Emilie L. Fisher[1], Rachelle L. Hunt[1], Barry Li[1], Janice Chiou[1], Sujiraphong Pharkjaksu[2], Sunisa Khongthong[3], Gordon Y. C. Cheung[1], Pattarachai Kiratisin[2] & Michael Otto[1]*

Probiotic nutrition is frequently claimed to improve human health. In particular, live probiotic bacteria obtained with food are thought to reduce intestinal colonization by pathogens, and thus to reduce susceptibility to infection. However, the mechanisms that underlie these effects remain poorly understood. Here we report that the consumption of probiotic *Bacillus* bacteria comprehensively abolished colonization by the dangerous pathogen *Staphylococcus aureus* in a rural Thai population. We show that a widespread class of *Bacillus* lipopeptides, the fengycins, eliminates *S. aureus* by inhibiting *S. aureus* quorum sensing—a process through which bacteria respond to their population density by altering gene regulation. Our study presents a detailed molecular mechanism that underlines the importance of probiotic nutrition in reducing infectious disease. We also provide evidence that supports the biological significance of probiotic bacterial interference in humans, and show that such interference can be achieved by blocking a pathogen's signalling system. Furthermore, our findings suggest a probiotic-based method for *S. aureus* decolonization and new ways to fight *S. aureus* infections.

Treating Infection

Microbiome Manipulation

Articles

Probiotic for pathogen-specific *Staphylococcus aureus* decolonisation in Thailand: a phase 2, double-blind, randomised, placebo-controlled trial

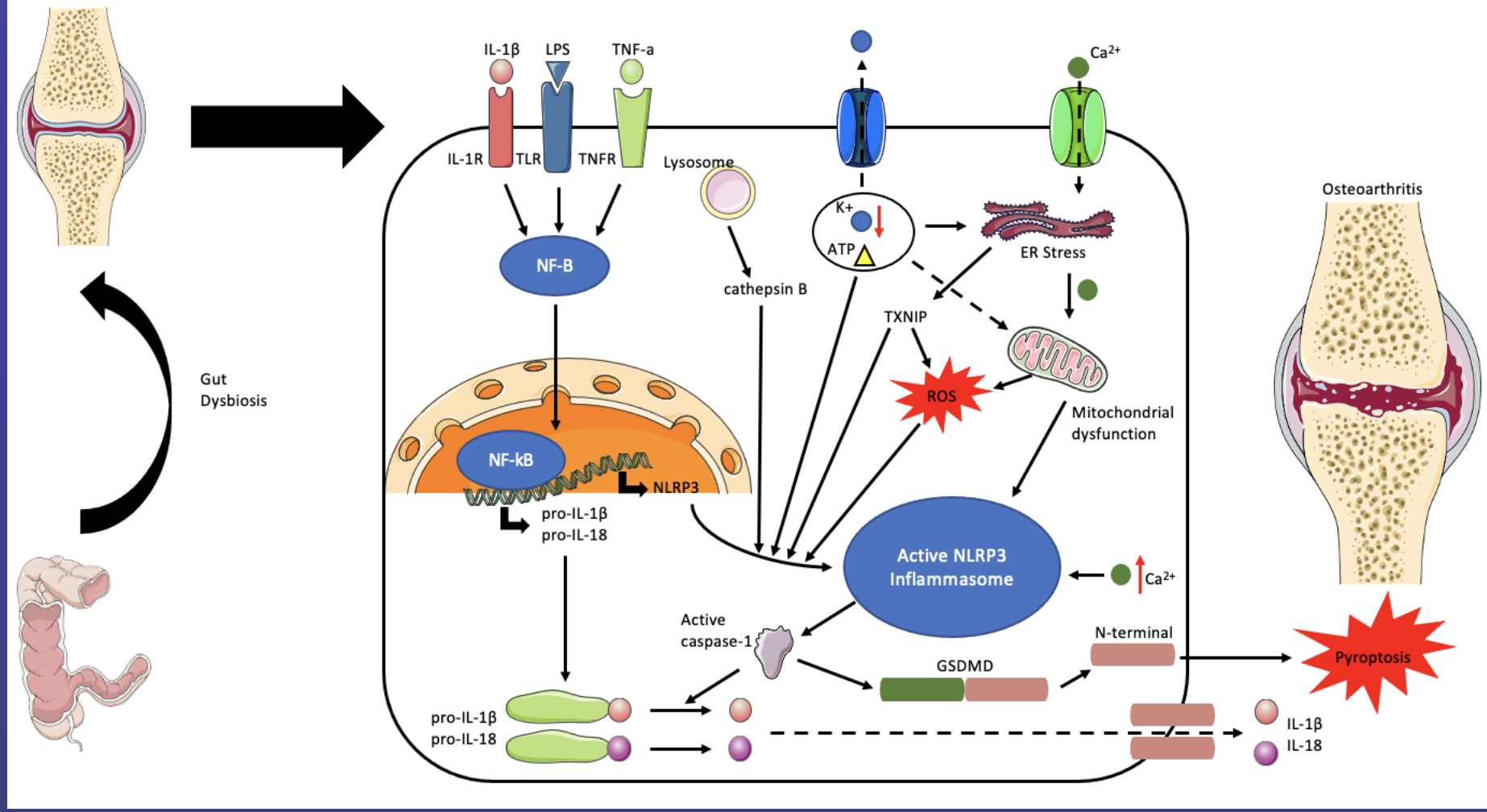
Pipat Piewngam, Sunisa Khongthong*, Natthrit Roekngam, Yongyuth Theapparat, Somkiat Sunpaweravong, Damrongsak Faroongsarng, Michael Otto*

Interpretation *B subtilis* probiotic eliminated more than 95% of the total *S aureus* colonising the human body without altering the microbiota. This probiotic strategy offers several key advantages over presently used decolonisation strategies for potential use in people with chronic or long-term risk of *S aureus* infection. Furthermore, by establishing a defining role of the intestinal colonisation site, our findings call for revisiting fundamental notions about *S aureus* colonisation.

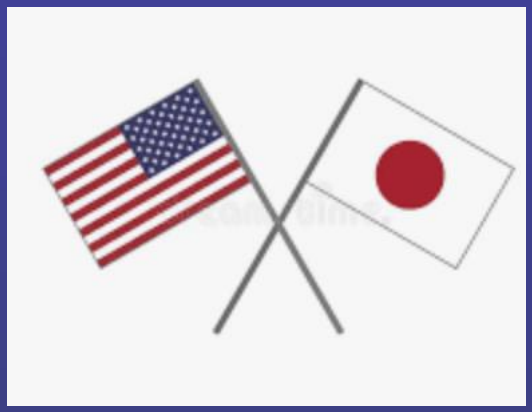
What is New?

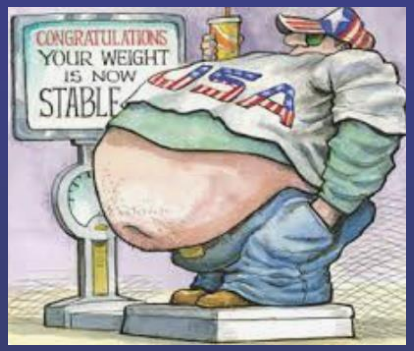
Epithelial barrier of GI tract is important

Osteoarthritis and Microbiome

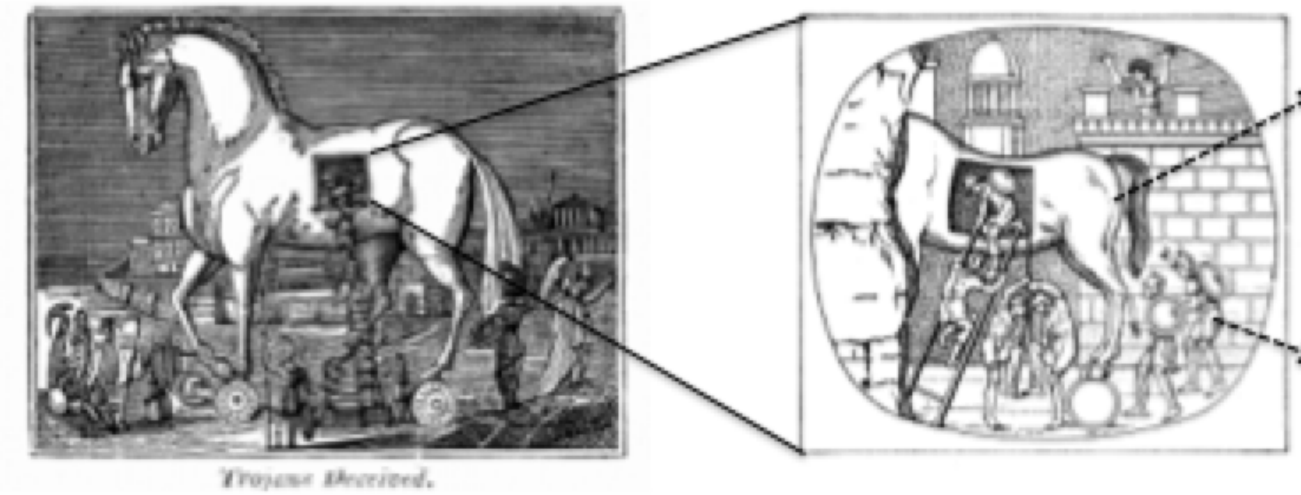


Microbiome and Genetics



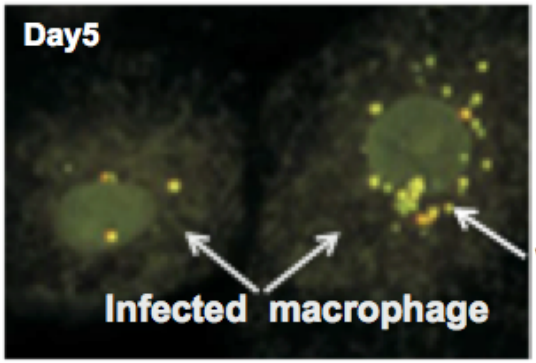


How does *S. aureus* translocate from the surgical site to internal organs?



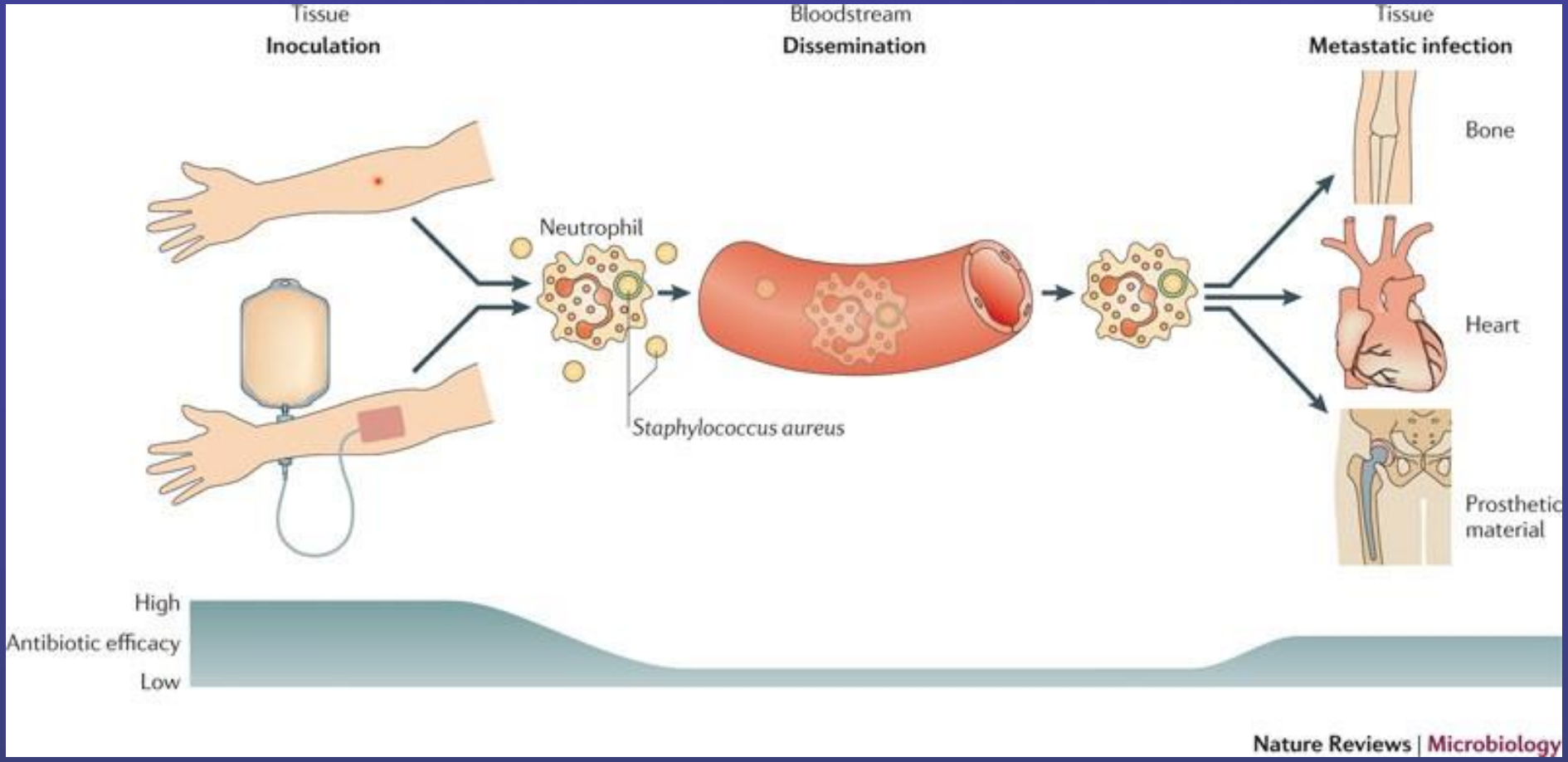
- ***S. aureus* persists inside macrophages for several days without affecting the viability of these mobile cells**

  → Serve as vehicles for the dissemination of infection



Kubica M et al. *PLoS One* 2008
Hamaza T et al. *BMC Microbiology* 2014

Trojan-Horse hypothesis?



Trojan-Horse hypothesis?

ARTICLE IN PRESS

The Journal of Arthroplasty xxx (2022) 1–6

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

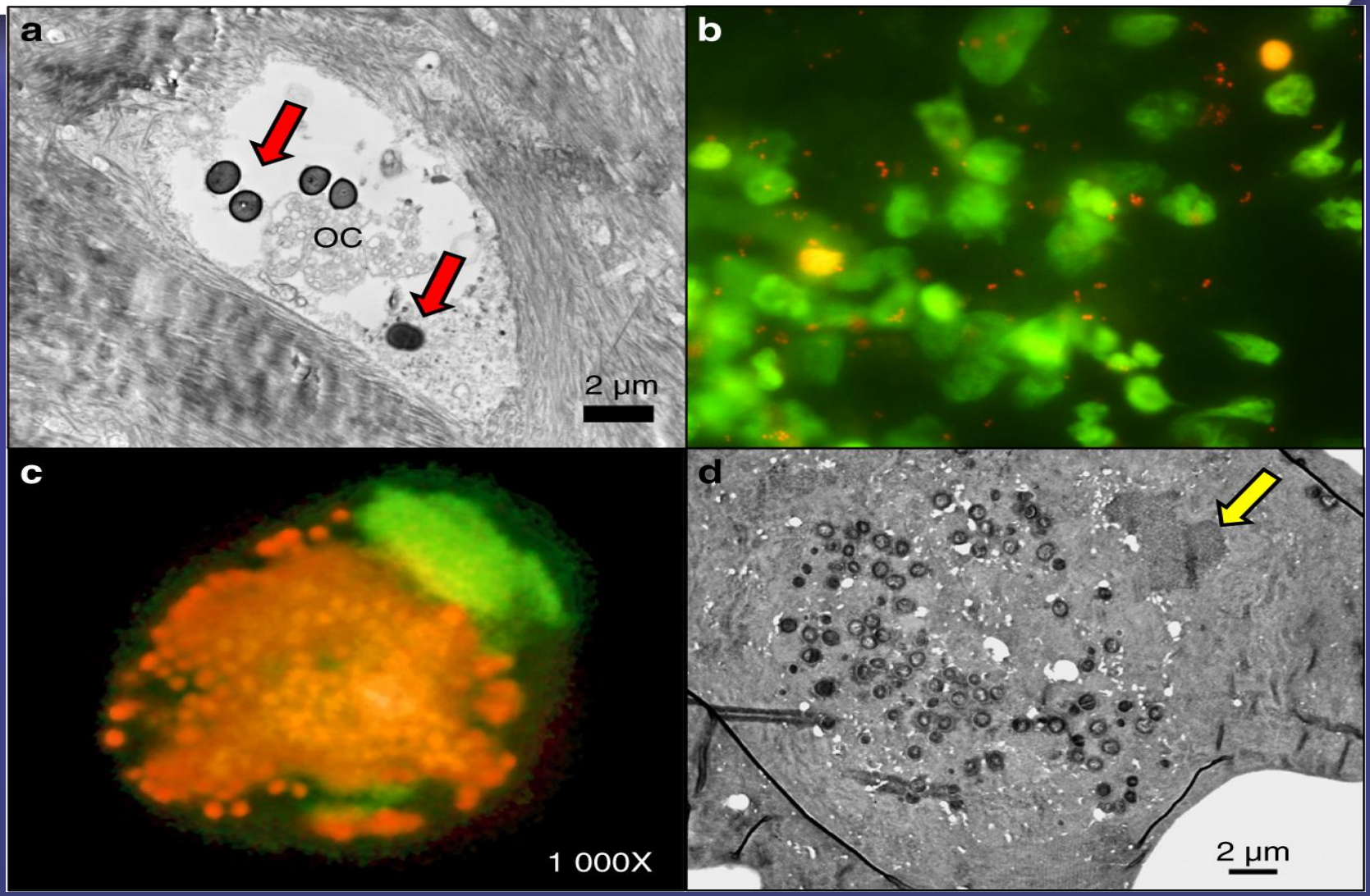
Periprosthetic Joint Infection and the Trojan Horse Theory: Examining the Role of Gut Dysbiosis and Epithelial Integrity

Emanuele Chisari, MD [a, b], Jeongeun Cho, BS [a], Marjan Wouthuyzen-Bakker, MD, PhD [b], Javad Parvizi, MD, FRCS [a, *]

[a] *Rothman Orthopaedic Institute at Thomas Jefferson University, Philadelphia, PA*
[b] *Department of Medical Microbiology and Infection Prevention, University of Groningen, University Medical Center Groningen, Groningen, Netherlands*

Conclusion: In our study, we report the first clinical evidence of the translocation of bacteria from the gut to the joint in patients with PJI. In particular, when evaluating the microbiological profile of the NGS signal, a great number of known gut commensals were seen in patients with a highly permeable dysbiotic gut. Manipulation of the gut microbiome may become part of an essential and comprehensive approach for management of patients with PJI.

Does it happen?



Microbiome:
Organ Chip technology

Science News *from research organizations*

Human gut microbiome physiology can now be studied in vitro using Organ Chip technology

Date: May 13, 2019

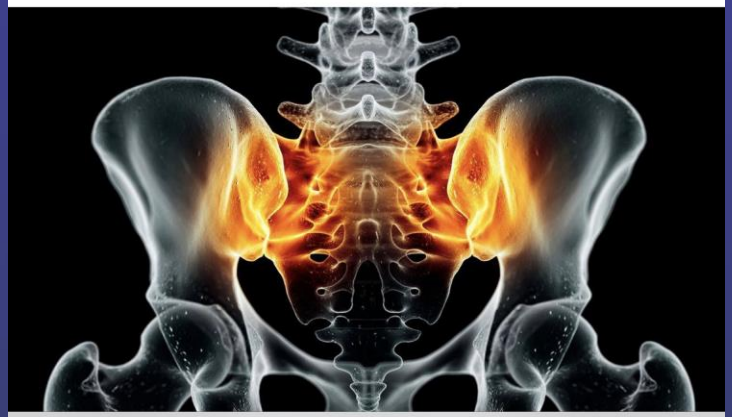
Source: Wyss Institute for Biologically Inspired Engineering at Harvard

Summary: A research team has developed an approach to co-culture a complex human gut microbiome in direct contact with intestinal tissue for at least five days using 'organ-on-a-chip' (Organ Chip) microfluidic culture technology.

THE FUTURE OF EVERYTHING

A KNEE OR HIP 'REPLACEMENT' WITHOUT SURGERY? IT'S ON THE HORIZON

With better drugs and stem-cell therapies, researchers hope to repair cartilage—or prevent damage—before osteoarthritis sets in or an operation is needed



Helicobacter pylori

Press Release

3 October 2005

The Nobel Assembly at Karolinska Institutet has today decided to award The Nobel Prize in Physiology or Medicine for 2005 jointly to

Barry J. Marshall and **J. Robin Warren**

for their discovery of **"the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease"**

Osteoarthritis and Microbiome

PLOS ONE

RESEARCH ARTICLE

The relation between the gut microbiome and osteoarthritis: A systematic review of literature

Emanuele Chisari[1,2]*, Marjan Wouthuyzen-Bakker[2], Alex W. Friedrich[2], Javad Parvizi[1]

1 Rothman Orthopaedic Institute at Thomas Jefferson University, Philadelphia, Pennsylvania, United States of America, **2** Department of Medical Microbiology and Infection Prevention, University of Groningen, University Medical Center Groningen, RB, Groningen, Netherlands

Osteoarthritis and Microbiome

nature

Environmental factors

Disrupts gut microbiome

Prevent changes

High-sugar diet

High-fat diet

Obesity

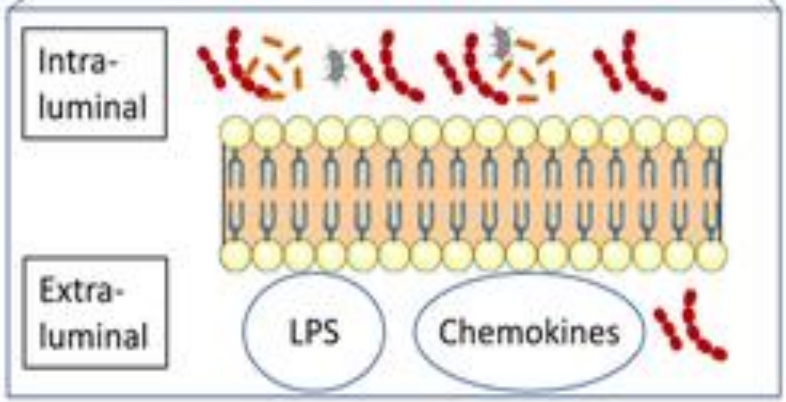
Probiotics (e.g. Lactobacilli)

Prebiotics (e.g. FOS)

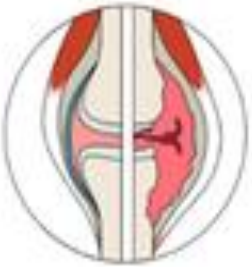
Dysbiosis and Intestinal Villi damage

Increased permeability to bacteria and bacterial product (e.g. LPS)

Increased Firmicutes/Bacteroides ratio



Joint inflammation and OA



Synovitis and joint effusion

Osteoarthritis symptoms and severity

What is New?

Diagnosis

The Problem

- No test with absolute accuracy exists
  - i.e. no gold standard

Definition of PJI

The Journal of Arthroplasty 33 (2018) 1309–1314

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria

Javad Parvizi, MD [a,*], Timothy L. Tan, MD [a], Karan Goswami, MD [a], Carlos Higuera, MD [b], Craig Della Valle, MD [c], Antonia F. Chen, MD, MBA [a], Noam Shohat, MD [a,d]

[a] Rothman Institute, Thomas Jefferson University, Philadelphia, PA
[b] Cleveland Clinic, Cleveland, OH
[c] Rush University Medical Center, Chicago, IL
[d] Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

2018 Definition of PJI

- Evidence-Based
- Validated (multi-instituional data)
- Pretest-probability
- Step-wise approach
- Preoperative diagnosis is possible

- **Parvizi J . et al. JOA May 2018**

Preoperative Diagnosis		Minor criteria	Score	Decision
	Serum	Elevated CRP *or* D-Dimer	2	≥6 Infected
		Elevated ESR	1	
	Synovial	Elevated Synovial WBC *or* LE	3	**2-5 Possibly Infected***
		Positive Alpha-defensin	3	0-1 Not Infected
		Elevated Synovial PMN (%)	2	
		Elevated Synovial CRP	1	

Intraoperative Diagnosis	*Inconclusive pre-op score *or* dry tap	Score	Decision
	Preoperative Score	-	≥6 Infected
	Positive Histology	3	**4-5 Inconclusive****
	Positive Purulence	3	≤3 Not Infected
	Single Positive Culture	2	

2018 Definition of PJI

Validation results of the "2018" definition of PJI compared to the original MSIS/ICM criteria

	PJI Cohort (n=222)			Aseptic Cohort (n=200)			Sensitivity (95% CI)	Specificity (95% CI)
	True positives	False Negatives	Inconclusive	True Negative	False positives	Inconclusive		
MSIS (2011)	176 (79.3%)	46 (20.7%)	-	199 (99.5%)	1 (0.5%)	-	79.3% (73.4-84.4)	99.5% (97.3-99.99)
ICM (2013)	193 (86.9%)	29 (13.1%)	-	199 (99.5%)	1 (0.5%)	-	86.9% (81.8-91.1)	99.5% (97.3-99.99)
New Criteria	212 (95.5%)	5 (2.3%)	5 (2.3%)	195 (97.5%)	1 (0.5%)	4 (2.0%)	97.7% (94.7-99.3)	99.5% (97.2-99.99)

Background

Increasing knowledge
has led to many
official diagnostic recommendations

IDSA

MSIS

AAOS

ICM

Opportunities in Management of PJI

Era of Biomarkers is here

The Journal of Arthroplasty Vol. 26 No. 6 Suppl. 1 2011

Molecular Markers for Diagnosis of Periprosthetic Joint Infection

Christina L. Jacovides, BS, Javad Parvizi, MD, FRCS, Bahar Adeli, BA, and Kwang Am Jung, MD

Molecular Markers
Protein Analysis

Category	Proteins
Cytokines	IL-1α, IL-1β, IL1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 subunit p40, IL-12 subunit p70, IL-15, IL-17, IL-23, IFN-γ, TNF-α, TNF-β, TNF receptor-like 2
Adhesion Molecules	ICAM-1, Vascular Cell Adhesion
Growth Factors	VEG-F, BDNF
Acute-phase reactants	CRP
Complement cascade	Complement C3, α-2 macroglobulin, Beta-2-Microglobulin, von Willebrand Factor, Fibrinogen, Factor VII
Chemotactic proteins	Monocyte Chemotactic Protein 1, Eotaxin-1
Metalloproteinase compounds	MMP-2, MMP-3, MMP-9, TIMP-1
Lysis/Destruction	Alpha-1-Antitrypsin, Granulocyte-Macrophage Colony-Stimulating Factor, Macrophage Inflammatory Protein-1 alpha Macrophage Inflammatory Protein-1 beta
Other	Ferritin, Haptoglobin, Stem Cell Factor, T-Cell-Specific Protein, RANTES, Molecule-1, Vitamin D-Binding Protein

Synovial CRP- 2011

Clin Orthop Relat Res
DOI 10.1007/s11999-011-1991-y

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

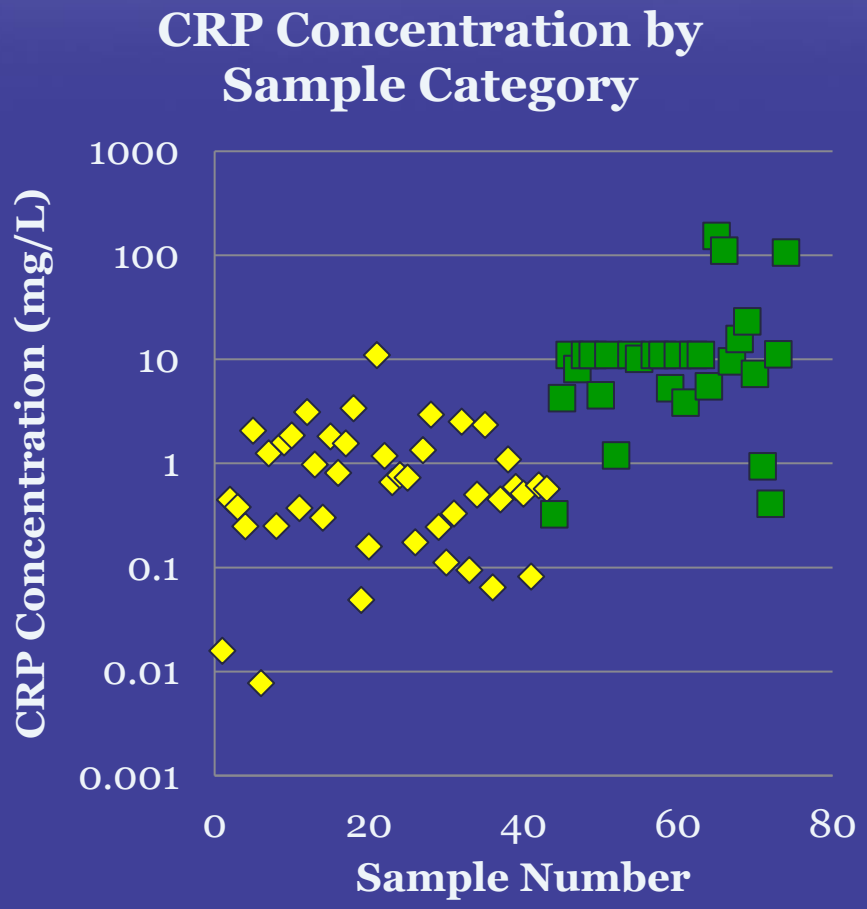
SYMPOSIUM: PAPERS PRESENTED AT THE ANNUAL MEETINGS OF THE KNEE SOCIETY

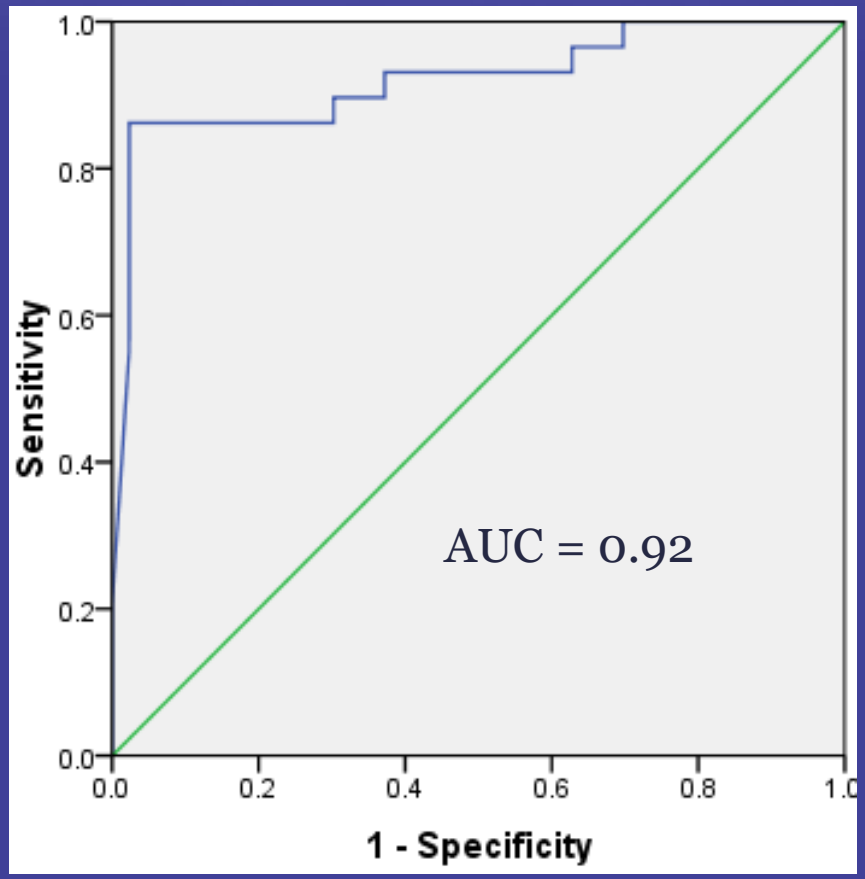
Mark B. Coventry Award

Synovial C-reactive Protein: A Prospective Evaluation of a Molecular Marker for Periprosthetic Knee Joint Infection

Javad Parvizi MD, FRCS, Christina Jacovides BS, Bahar Adeli BA, Kwang Am Jung MD, William J. Hozack MD

C-Reactive Protein (CRP)

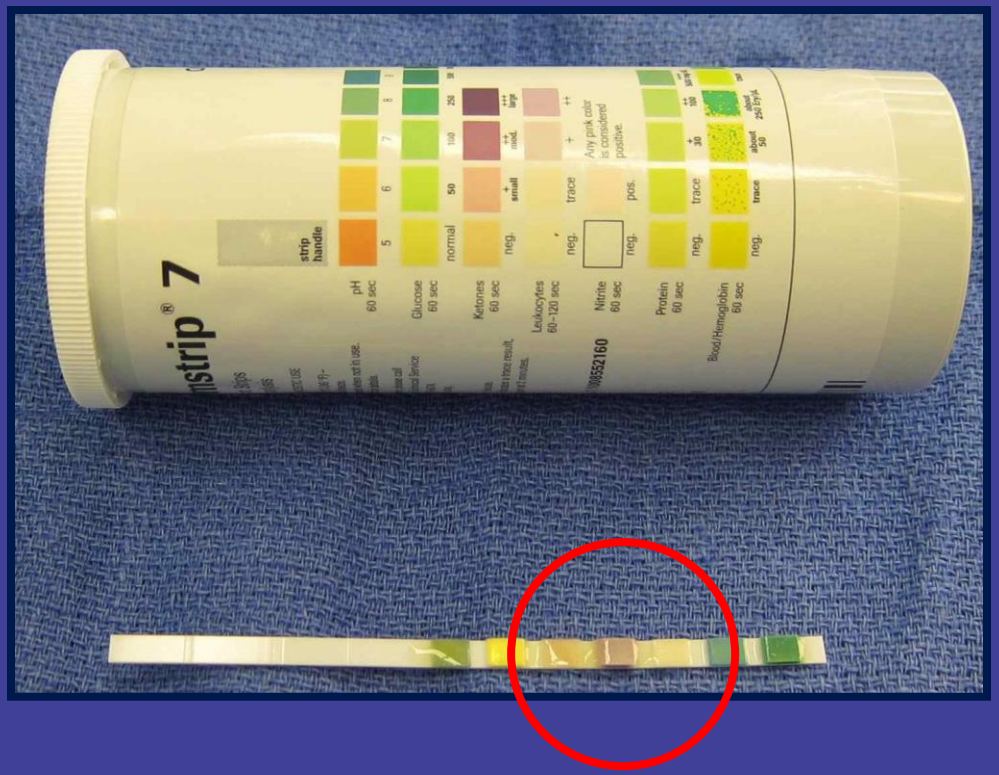




* P = 0.0009

Diagnosis of PJI
Simple Test

- UA strips for leukocyte esterase

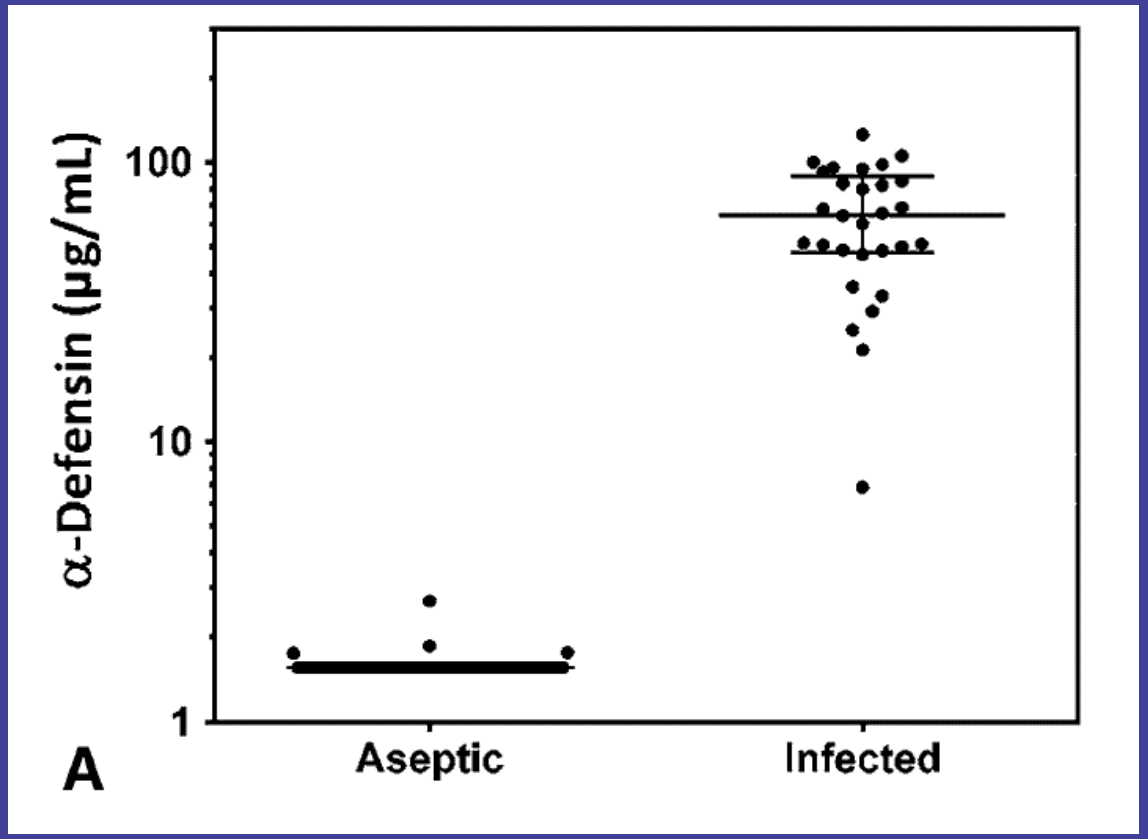


Diagnosing Periprosthetic Joint Infection

Has the Era of the Biomarker Arrived?

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

2014
Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®



95 Patients

43 Biomarkers Screened

MSIS definition of PJI

Alpha-Defensin
Specificity 100% (95–100)
Sensitivity 100% (88–100)

What is New?

Alpha Defensin is not needed routinely

The Journal of Arthroplasty 36 (2021) 1746–1752

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Complications - Infection

Alpha-Defensin Offers Limited Utility in Routine Workup of Periprosthetic Joint Infection

Lindsay T. Kleeman-Forsthuber, MD [a, *], Roseann M. Johnson, BS [a], Anna C. Brady, BS [a], Aviva K. Pollet, BS [a], Douglas A. Dennis, MD [a, b, c, d], Jason M. Jennings, MD, DPT [a, d]

[a] Colorado Joint Replacement, Denver, CO
[b] Department of Bioengineering, Colorado Joint Replacement, University of Tennessee, Knoxville, TN
[c] Department of Orthopaedics, Colorado Joint Replacement, University of Colorado School of Medicine, Denver, CO
[d] Department of Bioengineering, University of Denver, Denver, CO

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Keywords:
periprosthetic joint infection
alpha-defensin
false-positive
false-negative
diagnostic criteria
treatment

ABSTRACT

Background: Alpha-defensin (AD) is a synovial biomarker included as a minor criterion in the scoring system for diagnosing periprosthetic joint infection (PJI). The purpose of this study is to study the impact of AD on diagnosis and management of PJI.

Methods: Synovial fluid from 522 patients after total knee and hip arthroplasty was retrospective reviewed. Synovial white blood cell count, percentage of neutrophils, and culture from the AD immunoassay laboratory were reviewed with serum erythrocyte sedimentation rate and C-reactive protein values from our institution. A modified version of the 2018 scoring system for diagnosis of PJI was used, *only scoring* white blood cell count, percentage of neutrophils, erythrocyte sedimentation rate, and C-reactive protein. AD was then analyzed with these scores to determine if AD changed diagnostic findings or clinical management.

Results: Eight-two patients were categorized as "infected" (score ≥6), of which 76 patients had positive AD. Of the 6 "infected" patients with negative AD, 2 had positive cultures (*Staphylococcus epidermidis*). Two-hundred thirteen patients were diagnosed as "possibly infected" (score 2-5). Fourteen of these patients had positive AD, of which 5 had positive cultures assisting with the diagnosis. The AD test changed the diagnosis from "possibly infected" to "infected" in 8 patients (1.5%) but only altered treatment plan in 6 patients (1.1%). A score <2 (not infected) was calculated in 227 patients with no patients having positive AD.

Conclusion: AD may be beneficial in some cases where laboratory values are otherwise equivocal; however, its routine use for the diagnosis of PJI may not be warranted.

M. I. Ivy,
K. Sharma,
K. E. Greenwood-Quaintance,
A. J. Tande,
D. R. Osmon,
E. F. Berbari,
J. Mandrekar,
C. P. Beauchamp,
A. D. Hanssen,
M. P. Abdel,
D. G. Lewallen,
K. Perry,
D. R. Block,
M. R. Snyder,
R. Patel

THE BONE & JOINT JOURNAL EST. 1948

■ ARTHROPLASTY

Synovial fluid α defensin has comparable accuracy to synovial fluid white blood cell count and polymorphonuclear percentage for periprosthetic joint infection diagnosis

Conclusion

The diagnostic accuracy of synovial AD for PJI diagnosis is comparable and not statistically superior to that of synovial WBC count plus PMN% combined.

Cite this article: *Bone Joint J* 2021;103-B(6):1119–1126.

Draw synovial fluid into pipette

Mix with buffer solution

Deposit onto device

Read results in 10 minutes.

Qualitative α-defensin test (Synovasure) for the diagnosis of periprosthetic infection in revision total joint arthroplasty

50 patients (22M\28F)

- 13 septic \ 36 aseptic [according to MSIS criteria]

Sensitivity	**69%**
Specifity	94 %

Sigmund et al., Bone Joint J, Jan 2017

The Journal of Arthroplasty 36 (2021) 2150–2157

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Complications - Infection

What is the Clinical Utility of Synovial Alpha Defensin Testing of Antibiotic Spacers Before Reimplantation?

Christopher N. Carender, MD [a], David E. DeMik, MD, PharmD [a], Jesse E. Otero, MD, PhD [b], Nicolas O. Noiseux, MD [a], Timothy S. Brown, MD [a], Nicholas A. Bedard, MD [a, *]

[a] Department of Orthopedics and Rehabilitation, University of Iowa Hospitals and Clinics, Iowa City, IA
[b] OrthoCarolina Hip and Knee Center, Charlotte, NC

ARTICLE INFO

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Available online 5 February 2021

Keywords:
alpha defensin
two-stage
periprosthetic joint infection
total knee arthroplasty
total hip arthroplasty

ABSTRACT

Background: The purpose of this study was to evaluate the diagnostic performance of standalone alpha defensin (AD) testing of antibiotic spacers during two stage exchange and to determine if the addition of AD testing to other commonly used laboratory tests improves the ability to detect persistent infection in an antibiotic spacer.

Methods: Cases of two-stage exchange for periprosthetic joint infection from 2016 to 2019 at a single institution were retrospectively reviewed. Cases were classified as persistently infected or not infected in accordance with 2014 and 2018 Musculoskeletal Infection Society criteria to determine if AD provided any clinical utility beyond the other commonly used tests that make up both criteria. Delphi Consensus criteria at 1 year were used as the gold standard for determining recurrent periprosthetic joint infection.

Results: Fifty-two spacers (25 hips and 27 knees) in 51 patients were included for analysis. Five spacers were persistently infected based on Musculoskeletal Infection Society criteria. One spacer underwent reresection and the remaining 4 underwent reimplantation with no subsequent infectious complications. All 48 patients who were categorized as not infected underwent reimplantation; at 1 year post-operatively, 7 (13%) had failed due to infection. Three spacers (6%) had a positive AD test. Two spacers with positive AD tests underwent reimplantation, neither had failed at 1 year postoperatively. Sensitivity of standalone AD testing was 0%, and specificity was 96%.

Conclusion: Standalone AD testing for the purpose of predicting repeat infection after two-stage exchange arthroplasty exhibits sensitivity of 0% and low predictive value. Addition of synovial AD testing did not increase the diagnostic performance of commonly used synovial and serologic markers of infection.

Level of Evidence: IV—retrospective cohort study.

What is New?

Serum biomarkers for diagnosis and timing of reimplantation

Biomarker Screen

Biomarkers Failing Prescreen

- PCT
- TGFa
- LL-37, Human, ELISA kit
- LBP
- CGRP
- Orsomucoid
- Nibrin
- TSG6
- Plekstrin
- SOD2
- Urokinase
- MIF
- PAI-1 (total)
- sFas
- sFasL
- sICAM-1
- sVCAM-1
- Granzyme B
- HSP70
- IL-1α
- IL-10
- IL-17
- MIP-1α
- MIP-1β
- MMP-8

45 Markers Screened

Biomarkers Passing Prescree

- IL-1b
- IL-6
- IL-8
- TNFa
- G-CSF
- IL-1a
- VEGF
- IP-10
- BFGF (aka FGF2)
- CRP
- a2M
- SKALP
- Alpha-2 MG
- Lactoferrin
- Lipocalin-2/NGAL
- Neutrophil Elastase-2 (ELA2)
- Resistin
- Thrombospondin-1 (TSP-1)
- HNP1-3,
- BPI
- D-dimer
- Fibrinogen

D-dimer Story

Serum D-Dimer Test Is Promising for the Diagnosis of Periprosthetic Joint Infection and Timing of Reimplantation

Alisina Shahi, MD, Michael M. Kheir, MD, Majd Tarabichi, MD, Hamid R.S. Hosseinzadeh, MD, Timothy L. Tan, MD, and Javad Parvizi, MD, FRCS

Investigation performed at the Rothman Institute at Thomas Jefferson University, Philadelphia, Pennsylvania

What is New?

Detection of PJI pathogen from blood/serum

Direct Detection of Bacteria in Synvoial Fluid

Journal of Clinical Microbiology

Direct Detection of Staphylococcus Osteoarticular Infections by Use of Xpert MRSA/SA SSTI Real-Time PCR

Anne Dubouix-Bourandy, Aymard de Ladoucette, Valerie Pietri, Nazim Mehdi, David Benzaquen, Régis Guinand and Jean-Marc Gandois

J. Clin. Microbiol. **2011, 49(12):4225. DOI: 10.1128/JCM.00334-11.**
Published Ahead of Print 12 October 2011.

Blood Tests

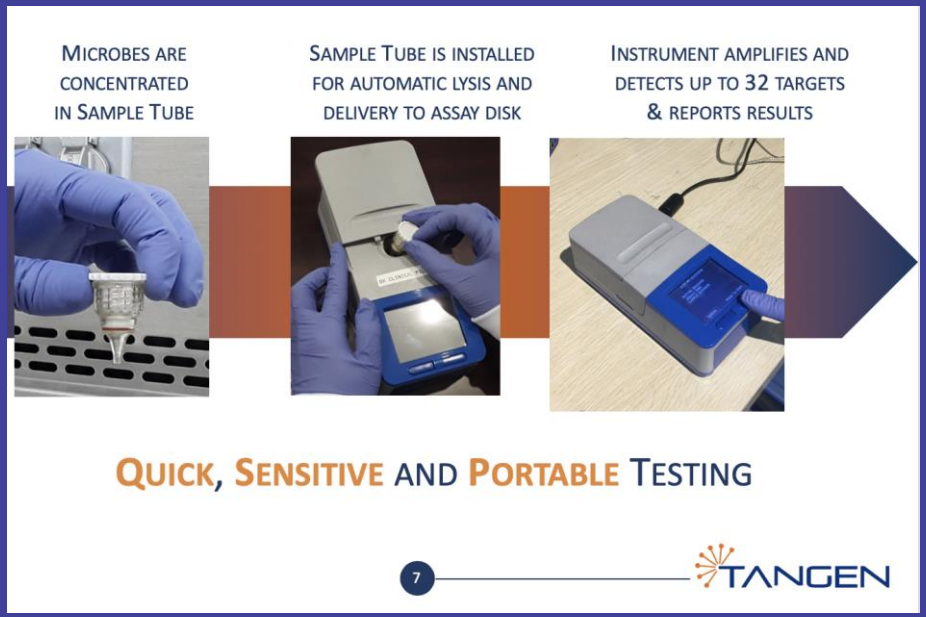
BIOFIRE®

GENEWEAVE™ biosciences

IQuum

T2Biosystems®

- Ability to isolate organisms from blood (2/ml)



J Bone Joint Surg Am. 2021 Sep 15;103(18):1705-1712. doi: 10.2106/JBJS.20.02229.

Sequencing of Circulating Microbial Cell-Free DNA Can Identify Pathogens in Periprosthetic Joint Infections

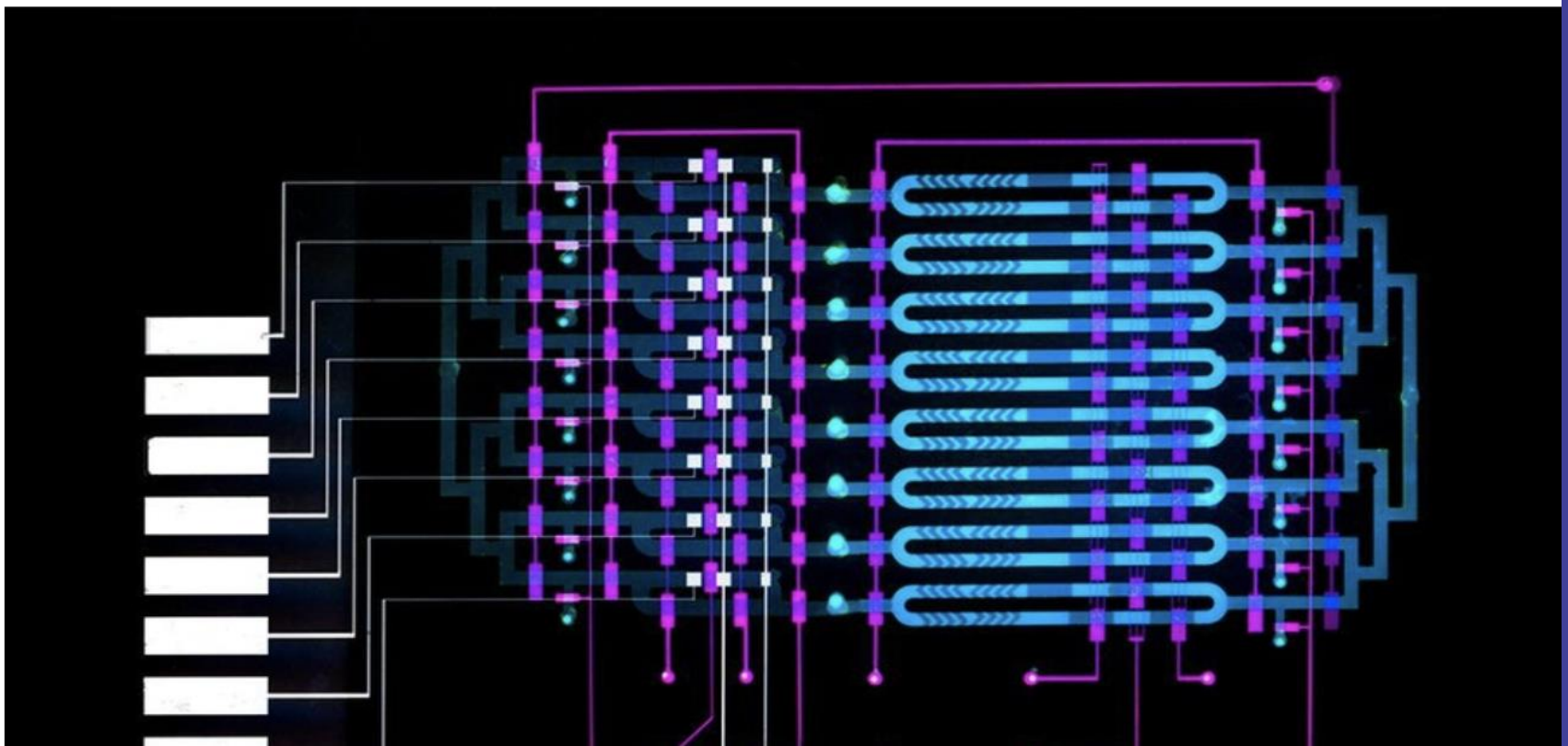
Adriana P Echeverria [1], Ian S Cohn [1], David C Danko [2], Sara Shanaj [1], Lily Blair [3], Desiree Hollemon [3], Alberto V Carli [4 5], Peter K Sculco [4 5], Carine Ho [3], Galit Meshulam-Simon [3], Christine Mironenko [4], Lionel B Ivashkiv [1 5], Susan M Goodman [5 6], Alexandra Grizas [7], Geoffrey H Westrich [4 5], Douglas E Padgett [4 5], Mark P Figgie [4 5], Mathias P Bostrom [4 5], Thomas P Sculco [4 5], David K Hong [3], Matthew S Hepinstall [8 9], Thomas W Bauer [5 7], Timothy A Blauwkamp [3], Barry D Brause [5 10], Andy O Miller [5 10], Mi[illegible] Henry [5 10], Asim A Ahmed [3], Michael B Cross [4 5], Christopher E Mason [2 11 12 13 14], Laura T Donlin [1 5 11]

Microfluidics device helps diagnose sepsis in minutes

When time matters in hospitals, automated system can detect an early biomarker for the potentially life-threatening condition.

Rob Matheson | MIT News Office

July 23, 2019

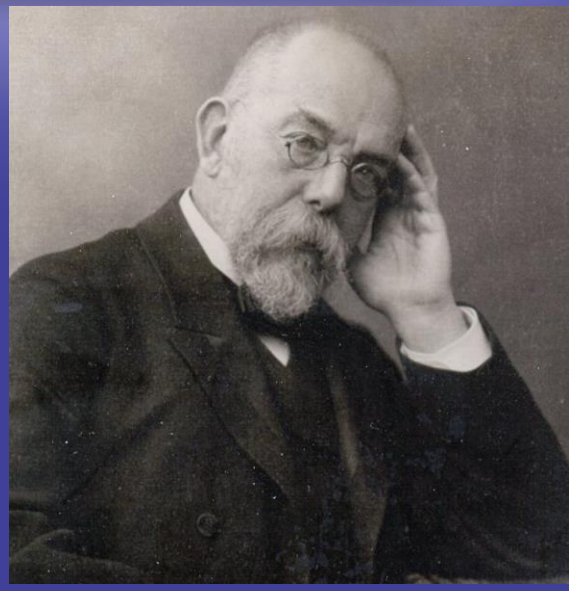


What is New?

Molecular Techniques for Culture Negative infections

Culture Technique

- Koch- 1886
- Anthrax
- Little has changed



ROTHMAN

Genomics and Infection Diagnosis

Jefferson

AMERICAN SOCIETY FOR MICROBIOLOGY

A report from the AMERICAN ACADEMY OF MICROBIOLOGY
RECOGNIZING SCIENTIFIC EXCELLENCE

Next-generation sequencing (NGS) has the potential to dramatically revolutionize the clinical microbiology laboratory by replacing current time-consuming and labor-intensive techniques with a single, all-inclusive diagnostic test. Traditional methods for identifying organisms such as mycobacteria, some bacterial species, and fungi in particular are often slow, specialized, and organism specific. Culturing, Gram staining, and biochemical and molecular tests are traditional assays that consume the manpower of the clinical microbiology laboratory. From this battery of tests, relevant treatment guidance for the clinician is not always produced. This has been described elsewhere as a "diagnostic odyssey" or a guessing game for the diagnosis and identification of infectious diseases. Executing diverse clinical tests can waste precious time for a patient and might be the difference between life and death. In the groundbreaking neuroleptospirosis case described by Wilson *et al* (2014), 38 different diagnostic tests on various sample types

NGS Isolates the Infecting Organism

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

BACTERIOLOGY

Reassessment of Routine Midstream Culture in Diagnosis of Urinary Tract Infection

Sanchutha Sathiananthamoorthy,[a] James Malone-Lee,[a] Kiren Gill,[a] Anna Tymon,[b] Trang K. Nguyen,[a*] Shradha Gurung,[a*] Linda Collins,[a*] Anthony S. Kupelian,[a*] Sheela Swamy,[a] Rajvinder Khasriya,[a*] David A. Spratt,[b] Jennifer L. Rohn[a]

[a]Centre for Nephrology, Division of Medicine, University College London, London, United Kingdom
[b]EDI Department of Microbial Diseases, University College London, London, United Kingdom

- NGS detects many uropathogens that MSU misses

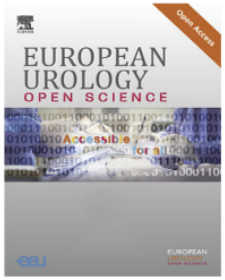
ROTHMAN

NGS Treated Patients Do Better

Jefferson

EUROPEAN UROLOGY OPEN SCIENCE 57 (2023) 74–83

available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com



European Association of Urology

Infections

Comparative Effectiveness Randomized Clinical Trial Using Next-generation Microbial Sequencing to Direct Prophylactic Antibiotic Choice Before Urologic Stone Lithotripsy Using an Interprofessional Model

Michael A. Liss [a,†,*], *Kelly R. Reveles* [b,c,†], *Craig D. Tipton* [d,e], *Jonathan Gelfond* [f], *Timothy Tseng* [a]

[a] *Department of Urology, University of Texas Health San Antonio, San Antonio, TX, USA;* [b] *College of Pharmacy, University of Texas, Austin, TX, USA;* [c] *Pharmacotherapy Education & Research Center, University of Texas Health San Antonio, San Antonio, TX, USA;* [d] *RTL Genomics, MicroGen DX, Lubbock, TX, USA;* [e] *Department of Biological Sciences, Texas Tech University, Lubbock, TX, USA;* [f] *Department of Population Sciences, University of Texas Health San Antonio, San Antonio, TX, USA*

NGS Isolates the Infecting Organism

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical Metagenomic Sequencing for Diagnosis of Meningitis and Encephalitis

M.R. Wilson, H.A. Sample, K.C. Zorn, S. Arevalo, G. Yu, J. Neuhaus, S. Federman, D. Stryke, B. Briggs, C. Langelier, A. Berger, V. Douglas, S.A. Josephson, F.C. Chow, B.D. Fulton, J.L. DeRisi, J.M. Gelfand, S.N. Naccache, J. Bender, J. Dien Bard, J. Murkey, M. Carlson, P.M. Vespa, T. Vijayan, P.R. Allyn, S. Campeau, R.M. Humphries, J.D. Klausner, C.D. Ganzon, F. Memar, N.A. Ocampo, L.L. Zimmermann, S.H. Cohen, C.R. Polage, R.L. DeBiasi, B. Haller, R. Dallas, G. Maron, R. Hayden, K. Messacar, S.R. Dominguez,

CONCLUSIONS

Routine microbiologic testing is often insufficient to detect all neuroinvasive pathogens. In this study, metagenomic NGS of CSF obtained from patients with meningitis or encephalitis improved diagnosis of neurologic infections and provided actionable information in some cases. (Funded by the National Institutes of Health and others; PDAID ClinicalTrials.gov number, NCT02910037.)

Multicenter study:
Microbiome of OA

ROTHMAN

Jefferson

HSS HOSPITAL FOR SPECIAL SURGERY

HEALTH UNIVERSITY OF UTAH

Colorado Joint Replacement
Centura Health Physician Group

UNIVERSITY OF LOUISVILLE

Cleveland Clinic

AORI

Penn Medicine

BOSTON MEDICAL CENTER

UPMC | ORTHOPAEDIC CARE

UF Department of Orthopaedics and Rehabilitation

UCSF Department of Orthopaedic Surgery

DukeHealth

NORTHSIDE HOSPITAL

MIDWEST ORTHOPAEDICS at RUSH

Diagnosis of Periprosthetic Joint Infection: The Potential of Next-Generation Sequencing

Majd Tarabichi, MD, Noam Shohat, MD, Karan Goswami, MD, Abtin Alvand, MD, PhD, FRCS, Randi Silibovsky, MD, Katherine Belden, MD, and Javad Parvizi, MD, FRCS

Investigation performed at The Rothman Institute at Thomas Jefferson University, Philadelphia, Pennsylvania

- Prospective Study
- 65 Revisions (17 Primary joints)
- 28 PJI cases
- Culture positive in 60%
- NGS isolated organism in 89%
- 11 Culture negative (NGS isolated organism in 9 cases)

NGS and PJI

Issues That Remain

- PJI (and others infections) may be polymicrobial…

……

Bonnie Bassler

Bacteria Can Talk

NGS and PJI

Issues That Remain

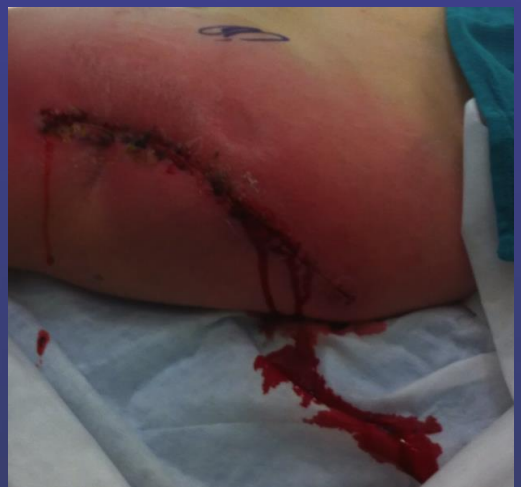
- Signal that NGS isolated organisms (ignored) may result in later failure

Management of PJI

- Treatment

Surgical Treatment
Acute PJI

- Irrigation and debridement
- One –stage exchange
- Two-stage exchange



Clin Orthop Relat Res (2011) 469:3043–3048
DOI 10.1007/s11999-011-1910-2

SYMPOSIUM: PAPERS PRESENTED AT THE 2010 MEETING OF THE MUSCULOSKELETAL INFECTION SOCIETY

Infection Control Rate of Irrigation and Débridement for Periprosthetic Joint Infection

Loukas Koyonos MD, Benjamin Zmistowski BS, Craig J. Della Valle MD, Javad Parvizi MD, FRCS

- Success rates:

37%	*our experience*
17%	*Salgado et al, CORR 2007*
29%	*Barberán et al, Am J Med 2006*
11%	*Kilgus et al, CORR 2002*

- Average success rate:

24%

Surgical Treatment

Acute PJI

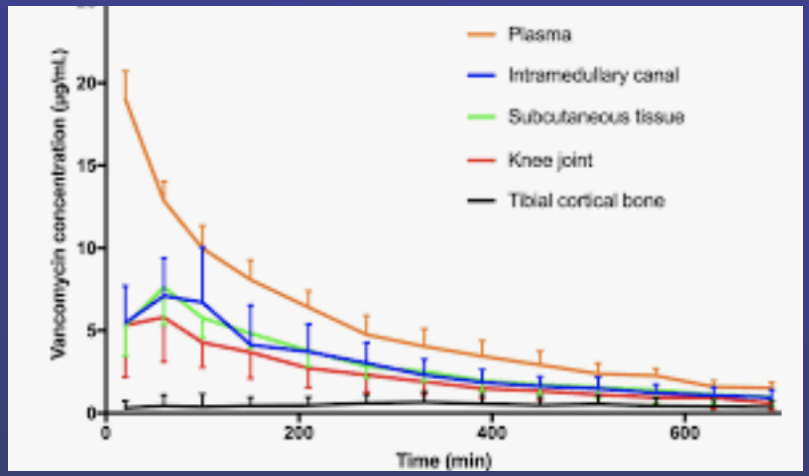
Irrigation and Debridement is technique dependent

Surgical Treatment
Acute PJI

- Repeat I and D (Tom Fehring)
- Chemical and mechanical debridement

Surgical Treatment
Local ABX

- Intraosseous delivery of antibiotics

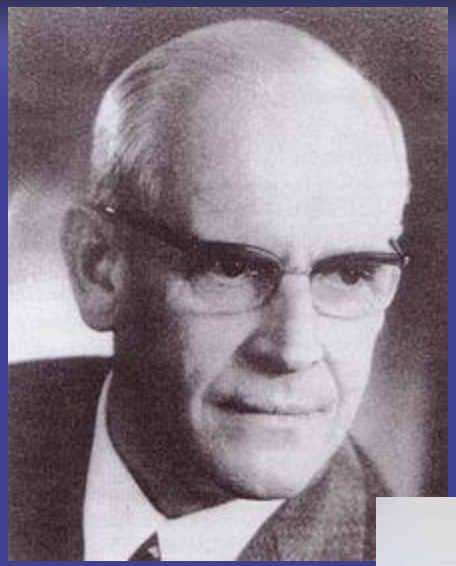


What is New?

One Stage Exchange is gaining popularity

One-Stage Exchange

- **One stage exchange arthroplasty** initially described by Bucholz in 70’ s
- Classically, procedure done with use of antibiotic laden bone cement
- Cementless fixation is the preferred technique for THA/rev THA in the USA
- Little has been published on the cementless technique for one stage exchange arthroplasty



One stage vs Two Stage

Clinical and cost effectiveness of single stage compared with two stage revision for hip prosthetic joint infection (INFORM): pragmatic, parallel group, open label, randomised controlled trial

Ashley W Blom,[1,2] Erik Lenguerrand,[1] Simon Strange,[1] Sian M Noble,[3] Andrew D Beswick,[1] Amanda Burston,[1] Kirsty Garfield,[3,4] Rachael Gooberman-Hill,[1,2] Shaun R S Harris,[3,4] Setor K Kunutsor,[1,2] J Athene Lane,[3,4] Alasdair MacGowan,[5] Sanchit Mehendale,[6] Andrew J Moore,[1] Ola Rolfson,[7] Jason C J Webb,[1] Matthew Wilson,[8] Michael R Whitehouse,[1,2] on behalf of the INFORM trial group

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The primary outcome :

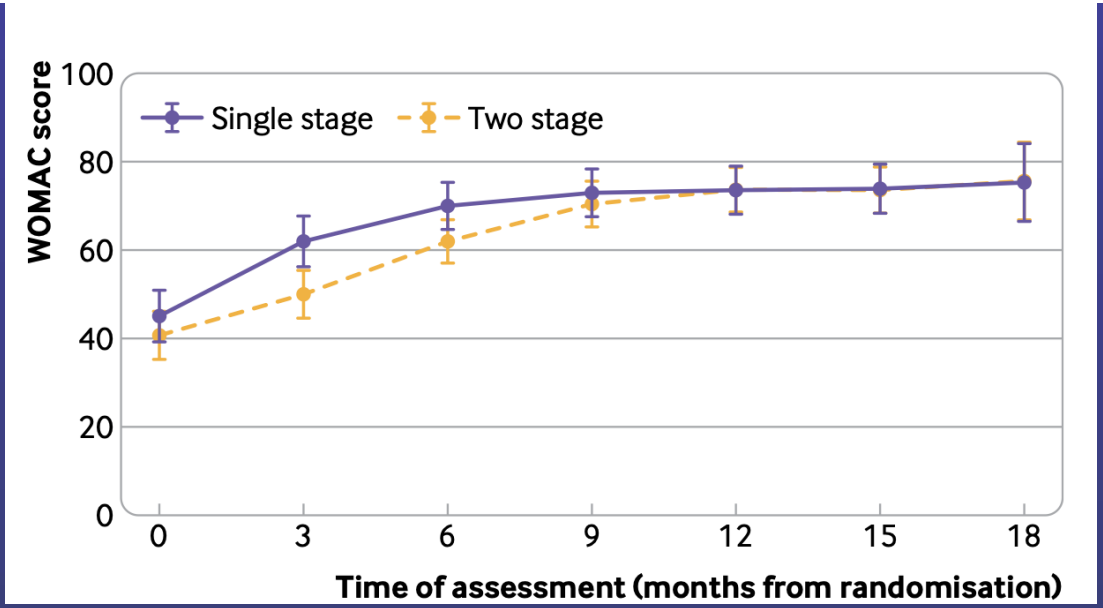
- pain, stiffness, and functional limitations (WOMAC)

Secondary outcomes

- Complications
- Recurrent infection
- Cost effectiveness

Clinical and cost effectiveness of single stage compared with two stage revision for hip prosthetic joint infection (INFORM): pragmatic, parallel group, open label, randomised controlled trial

Ashley W Blom,[1,2] Erik Lenguerrand,[1] Simon Strange,[1] Sian M Noble,[3] Andrew D Beswick,[1] Amanda Burston,[1] Kirsty Garfield,[3,4] Rachael Gooberman-Hill,[1,2] Shaun R S Harris,[3,4] Setor K Kunutsor,[1,2] J Athene Lane,[3,4] Alasdair MacGowan,[5] Sanchit Mehendale,[6] Andrew J Moore,[1] Ola Rolfson,[7] Jason C J Webb,[1] Matthew Wilson,[8] Michael R Whitehouse,[1,2] on behalf of the INFORM trial group



Clinical and cost effectiveness of single stage compared with two stage revision for hip prosthetic joint infection (INFORM): pragmatic, parallel group, open label, randomised controlled trial

Ashley W Blom,[1,2] Erik Lenguerrand,[1] Simon Strange,[1] Sian M Noble,[3] Andrew D Beswick,[1] Amanda Burston,[1] Kirsty Garfield,[3,4] Rachael Gooberman-Hill,[1,2] Shaun R S Harris,[3,4] Setor K Kunutsor,[1,2] J Athene Lane,[3,4] Alasdair MacGowan,[5] Sanchit Mehendale,[6] Andrew J Moore,[1] Ola Rolfson,[7] Jason C J Webb,[1] Matthew Wilson,[8] Michael R Whitehouse,[1,2] on behalf of the INFORM trial group

Complication	Single stage revision surgery (n=65)	Two stage revision surgery (n=75)	P value
Death	2 (3)	5 (7)	0.45
Serious adverse event	11 (17)	16 (21)	0.51
Complication of surgery	27 (42)	43 (57)	0.04
Intraoperative event	5 (9)	20 (27)	0.01
Readmission to hospital	22 (34)	31 (41)	0.47
Reoperation	10 (15)	20 (27)	0.08
Readmission to hospital owing to prosthetic joint infection	10 (15)	17 (23)	0.33
Reoperation owing to prosthetic joint infection	6 (9)	9 (12)	0.55
Possible prosthetic joint infection at 15-18 months	9 (14)	8 (11)	0.62
Prescribed antibiotics at 15-18 months	4 (6)	4 (5)	—

Clinical and cost effectiveness of single stage compared with two stage revision for hip prosthetic joint infection (INFORM): pragmatic, parallel group, open label, randomised controlled trial

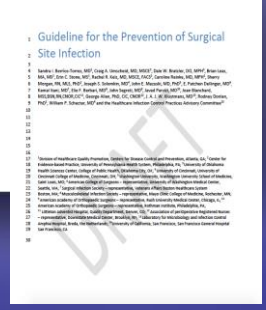
Ashley W Blom,[1,2] Erik Lenguerrand,[1] Simon Strange,[1] Sian M Noble,[3] Andrew D Beswick,[1] Amanda Burston,[1] Kirsty Garfield,[3,4] Rachael Gooberman-Hill,[1,2] Shaun R S Harris,[3,4] Setor K Kunutsor,[1,2] J Athene Lane,[3,4] Alasdair MacGowan,[5] Sanchit Mehendale,[6] Andrew J Moore,[1] Ola Rolfson,[7] Jason C J Webb,[1] Matthew Wilson,[8] Michael R Whitehouse,[1,2] on behalf of the INFORM trial group

£36 256 versus £46 312
a cost difference of – £10 055

What is New?

Shorter Length of Antibiotics

CDC Guidelines for SSI Prevention



- **Core Section**

Antibiotic Prophylaxis

- 1E. In Clean-contaminated procedures, **do not administer additional prophylactic antimicrobial agent** doses after surgical incision is closed in the operating room, even in the presence of a drain. (Category 1A)(Key Question)

Shorter Duration of Abx

Clin Orthop Relat Res (2019) 00:1-14
DOI 10.1097/CORR.0000000000000619

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

2018 Musculoskeletal Infection Society Proceedings

Is There a Difference in Infection Risk Between Single and Multiple Doses of Prophylactic Antibiotics? A Meta-analysis

Sean P. Ryan MD, Beau J. Kildow MD, Timothy L. Tan MD, Javad Parvizi MD, FRCS, on behalf of the American Association of Hip and Knee Surgeons Research Committee, Michael P. Bolognesi MD, Thorsten M. Seyler MD, PhD

A commentary by James A. Keeney, MD, is linked to the online version of this article at jbjs.org.

Perioperative Antibiotic Prophylaxis in Total Joint Arthroplasty

A Single Dose Is as Effective as Multiple Doses

Timothy L. Tan, MD, Noam Shohat, MD, Alexander J. Rondon, MD, MBA, Carol Foltz, PhD, Karan Goswami, MD, Sean P. Ryan, MD, Thorsten M. Seyler, MD, PhD, and Javad Parvizi, MD, FRCS

Investigation performed at The Rothman Institute at Thomas Jefferson University, Philadelphia, Pennsylvania

One vs Three

- Multicenter study
- Duke Team (>2000 patients)
- Please consider joining the study

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AMERICAN ASSOCIATION OF HIP AND KNEE SURGEONS

Oral vs IV Abx

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

H.-K. Li, I. Rombach, R. Zambellas, A.S. Walker, M.A. McNally, B.L. Atkins, B.A. Lipsky, H.C. Hughes, D. Bose, M. Kümin, C. Scarborough, P.C. Matthews, A.J. Brent, J. Lomas, R. Gundle, M. Rogers, A. Taylor, B. Angus, I. Byren, A.R. Berendt, S. Warren, F.E. Fitzgerald, D.J.F. Mack, S. Hopkins, J. Folb, H.E. Reynolds, E. Moore, J. Marshall, N. Jenkins, C.E. Moran, A.F. Woodhouse, S. Stafford, R.A. Seaton, C. Vallance, C.J. Hemsley, K. Bisnauthsing, J.A.T. Sandoe, I. Aggarwal, S.C. Ellis, D.J. Bunn, R.K. Sutherland, G. Barlow, C. Cooper, C. Geue, N. McMeekin, A.H. Briggs, P. Sendi, E. Khatamzas, T. Wangrangsimakul, T.H.N. Wong, L.K. Barrett, A. Alvand, C.F. Old, J. Bostock, J. Paul, G. Cooke, G.E. Thwaites, P. Bejon, and M. Scarborough, for the OVIVA Trial Collaborators*

- Multicenter study
- Rothman (25 patients)

THE KNEE SOCIETY
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What is New?

Alternative Treatment is emerging

Opportunities in Management of PJI

Biofilm Disruption Technologies

Int. J. Mol. Sci. **2013**, *14*, 18488-18501; doi:10.3390/ijms140918488

OPEN ACCESS
International Journal of
Molecular Sciences
ISSN 1422-0067
www.mdpi.com/journal/ijms

Review

Novel Strategies for the Prevention and Treatment of Biofilm Related Infections

Meng Chen [1], Qingsong Yu [2] and Hongmin Sun [3,*]

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[2] Department of Mechanical and Aerospace Engineering, University of Missouri, Columbia, MO 65211, USA; E-Mail: yuq@missouri.edu
[3] Division of Cardiovascular Medicine, Department of Internal Medicine, University of Missouri, Columbia, MO 65212, USA

* Author to whom correspondence should be addressed; E-Mail: sunh@health.missouri.edu; Tel.: +1-573-884-1964; Fax: +1-573-884-7743.

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Antimicrobial Peptides

www.nature.com/scientificreports

OPEN

Elimination of Antibiotic Resistant Surgical Implant Biofilms Using an Engineered Cationic Amphipathic Peptide WLBU2

Received: 7 August 2017
Accepted: 28 November 2017
Published online: 22 December 2017

Jonathan B. Mandell[1], Berthony Deslouches[2], Ronald C. Montelaro[2], Robert M. Q. Shanks[3], Yohei Doi[4] & Kenneth L. Urish[1,5,6,7,8]

Use Nature to Fight Nature

ARTICLE

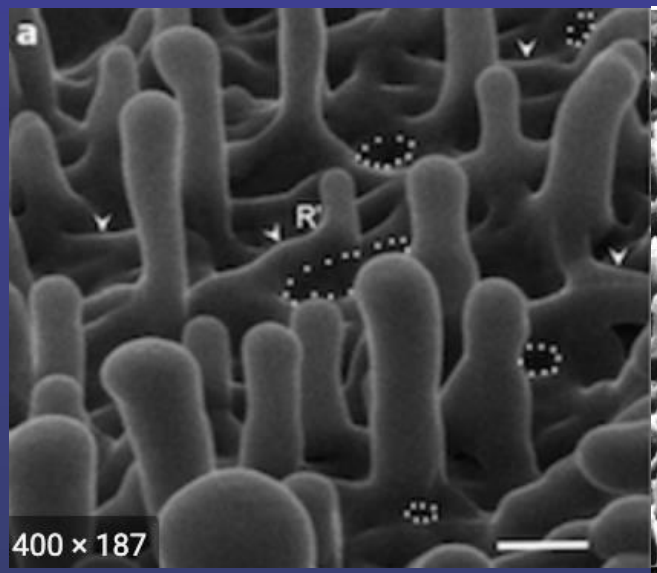
doi:10.1038/nature1863

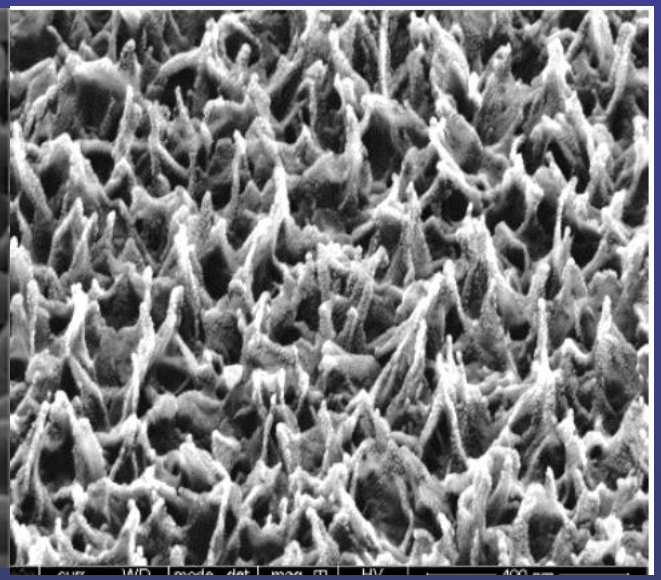
Human commensals producing a novel antibiotic impair pathogen colonization

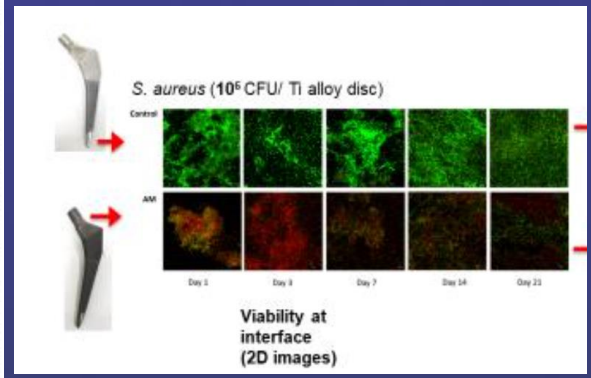
Alexander Zipperer[1,2]*, Martin C. Konnerth[3]*, Claudia Laux[1,2], Anne Berscheid[4], Daniela Janek[1,2]†, Christopher Weidenmaier[2,5], Marc Burian[6], Nadine A. Schilling[3,7], Christoph Slavetinsky[1,2], Matthias Marschal[5], Matthias Willmann[2,5], Hubert Kalbacher[7], Birgit Schittek[6], Heike Brötz-Oesterhelt[2,4], Stephanie Grond[3], Andreas Peschel[1,2] & Bernhard Krismer[1,2]

- *Staphylococcus lugdunensis* produce lugdunin (a thiazolidine-cyclic peptide) that inhibits S aureus colonization of nares

Surface Modification







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J Orthop Sci. 2012; 17(5): 595–604.
Published online 2012 Jul 18. doi: 10.1007/s00776-012-0247-3

PMCID: PMC3462916
PMID: 22806173

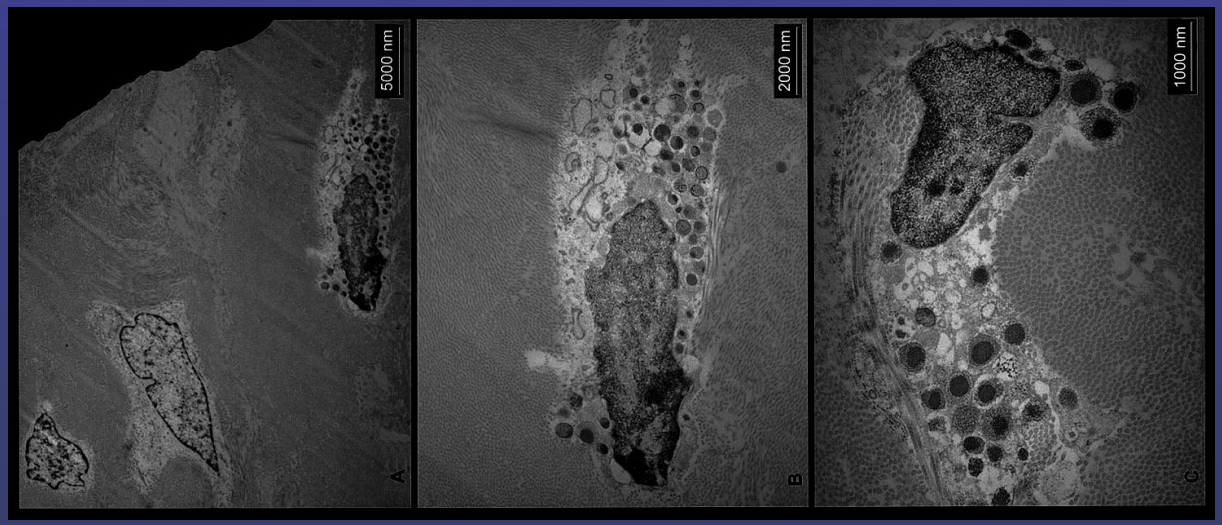
Innovative antimicrobial coating of titanium implants with iodine

Hiroyuki Tsuchiya,[✉] Toshiharu Shirai, Hideji Nis on Kabata, Norio Yamamoto, Koji Watanabe, and Junsuke Nakase

Author information ▸ Article notes ▸ Copyrigh PMC Disclaimer

New Antibiotics

- Target-sensors
- Akin to cancer therapy
- Receptor “switch”



Probiotics

ARTICLE

https://doi.org/10.1038/s41586-018-0616-y

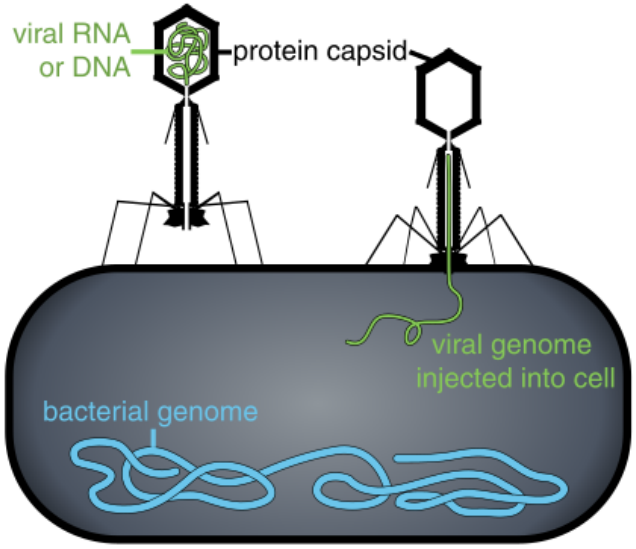
Pathogen elimination by probiotic *Bacillus* via signalling interference

Pipat Piewngam[1,2], Yue Zheng[1,5], Thuan H. Nguyen[1,5], Seth W. Dickey[1], Hwang-Soo Joo[1,4], Amer E. Villaruz[1], Kyle A. Glose[1], Emilie L. Fisher[1], Rachelle L. Hunt[1], Barry Li[1], Janice Chiou[1], Sujiraphong Pharkjaksu[2], Sunisa Khongthong[3], Gordon Y. C. Cheung[1], Pattarachai Kiratisin[2] & Michael Otto[1]*

Probiotic nutrition is frequently claimed to improve human health. In particular, live probiotic bacteria obtained with food are thought to reduce intestinal colonization by pathogens, and thus to reduce susceptibility to infection. However, the mechanisms that underlie these effects remain poorly understood. Here we report that the consumption of probiotic *Bacillus* bacteria comprehensively abolished colonization by the dangerous pathogen *Staphylococcus aureus* in a rural Thai population. We show that a widespread class of *Bacillus* lipopeptides, the fengycins, eliminates *S. aureus* by inhibiting *S. aureus* quorum sensing—a process through which bacteria respond to their population density by altering gene regulation. Our study presents a detailed molecular mechanism that underlines the importance of probiotic nutrition in reducing infectious disease. We also provide evidence that supports the biological significance of probiotic bacterial interference in humans, and show that such interference can be achieved by blocking a pathogen's signalling system. Furthermore, our findings suggest a probiotic-based method for *S. aureus* decolonization and new ways to fight *S. aureus* infections.

Bacteriophage

- Virus injecting DNA into bacteria
- Specific to the strain of bacterium
- Harmless to host and other bacteria



Phage injecting its genome into bacterial cell

Phage Therapy

- Fredrick Twort 1915
- 1940s Eli Lilly– USA
- Military use- very effective
- Discovery of Penicillin
- Abandoned Phage
- Russia, Georgia and Poland

Courtesy of Dr Vincent Fischetti, Rockefeller University, NY

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