Prosthetic Joint Infections: Diagnosis – Guideline Review

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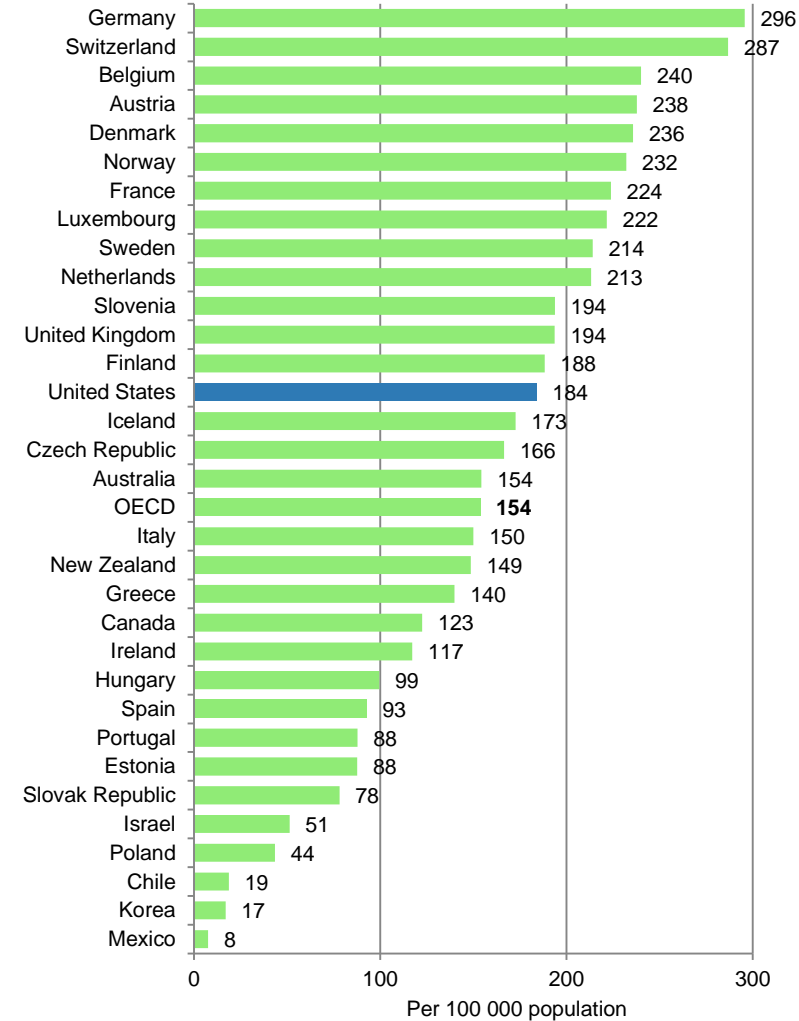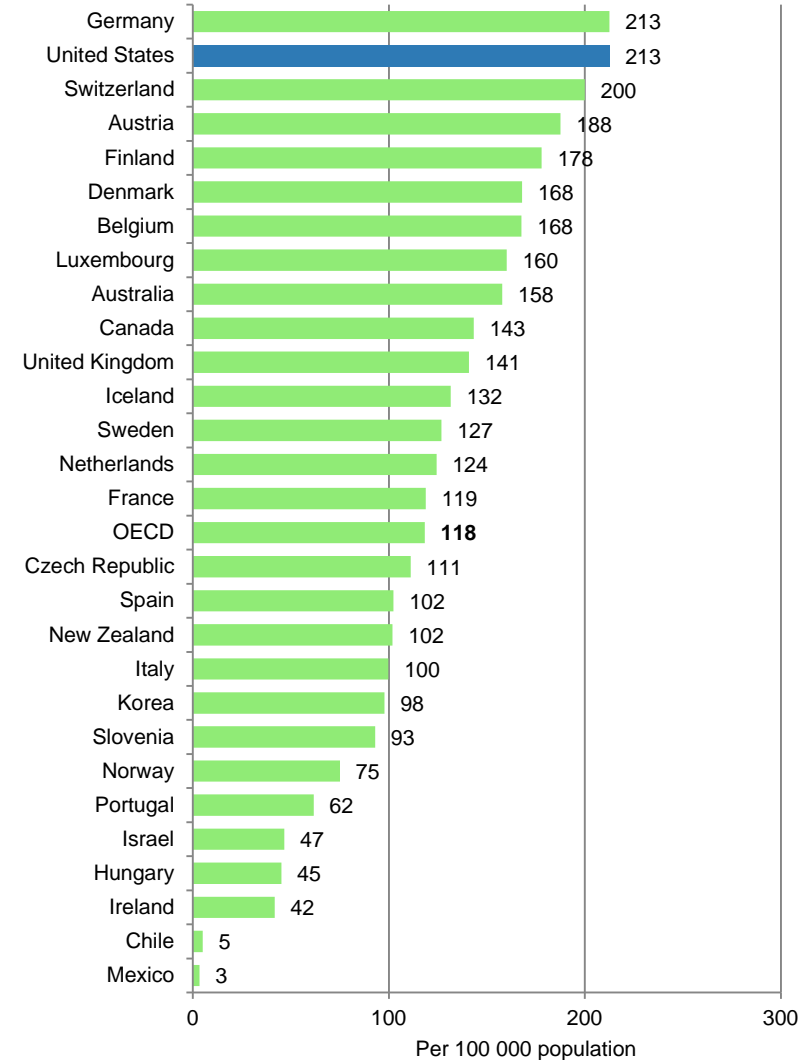**Mayo Clinic Infectious Diseases Subspecialties Update**

May 7th- 9th, 2015

TKA and THA Placements: OECD Countries

TKAs/100,000 population 2009

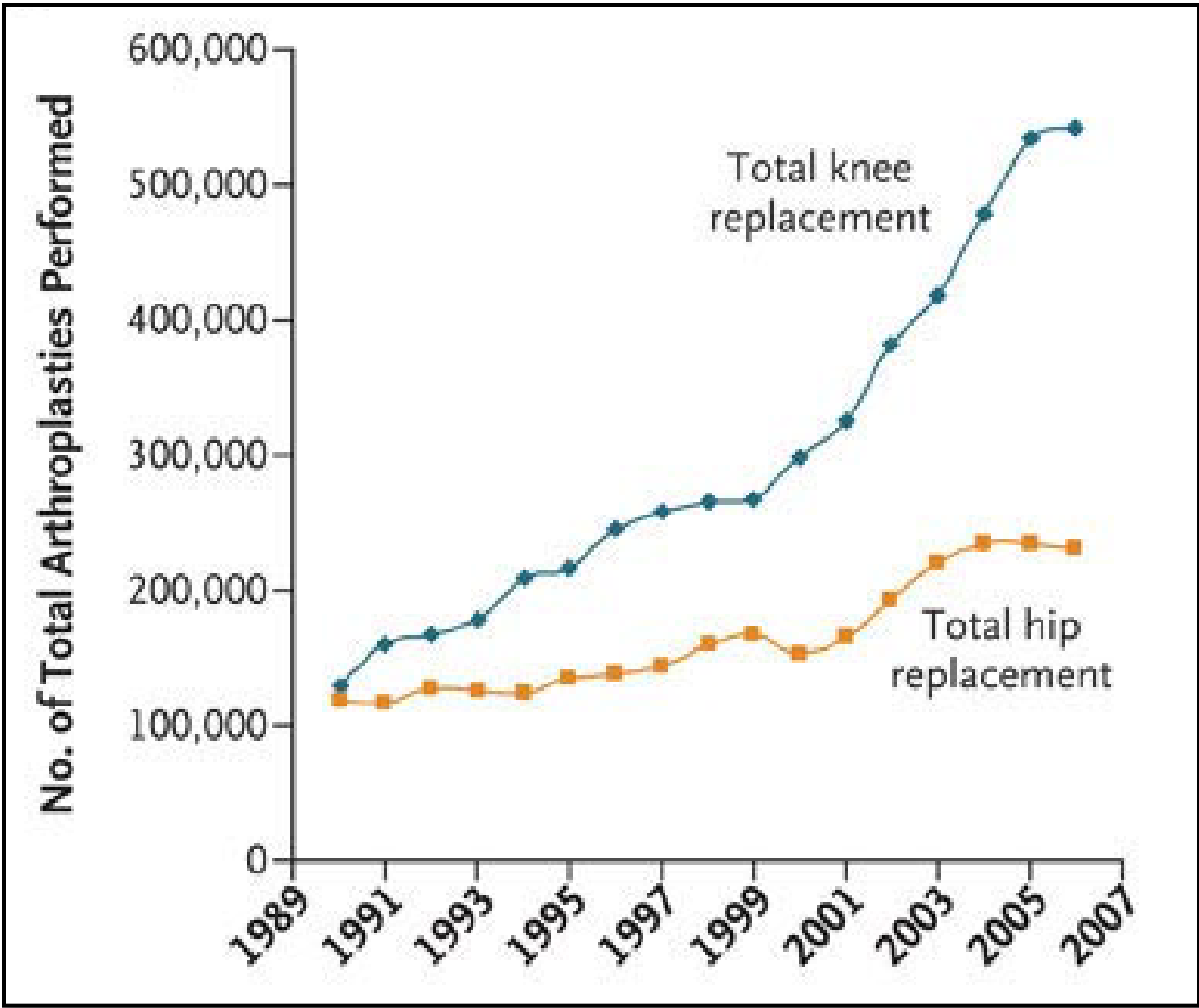| Country	Value
Germany	213
United States	213
Switzerland	200
Austria	188
Finland	178
Denmark	168
Belgium	168
Luxembourg	160
Australia	158
Canada	143
United Kingdom	141
Iceland	132
Sweden	127
Netherlands	124
France	119
OECD	118
Czech Republic	111
Spain	102
New Zealand	102
Italy	100
Korea	98
Slovenia	93
Norway	75
Portugal	62
Israel	47
Hungary	45
Ireland	42
Chile	5
Mexico	3

Per 100 000 population

THA/100,000 population 2009

Country	Value
Germany	296
Switzerland	287
Belgium	240
Austria	238
Denmark	236
Norway	232
France	224
Luxembourg	222
Sweden	214
Netherlands	213
Slovenia	194
United Kingdom	194
Finland	188
United States	184
Iceland	173
Czech Republic	166
Australia	154
OECD	154
Italy	150
New Zealand	149
Greece	140
Canada	123
Ireland	117
Hungary	99
Spain	93
Portugal	88
Estonia	88
Slovak Republic	78
Israel	51
Poland	44
Chile	19
Korea	17
Mexico	8

Per 100 000 population

OECD: Organization for Economic Co-operation and Development

http://www.oecd-ilibrary.org/

TKA trends 2000-2009: OECD Countries
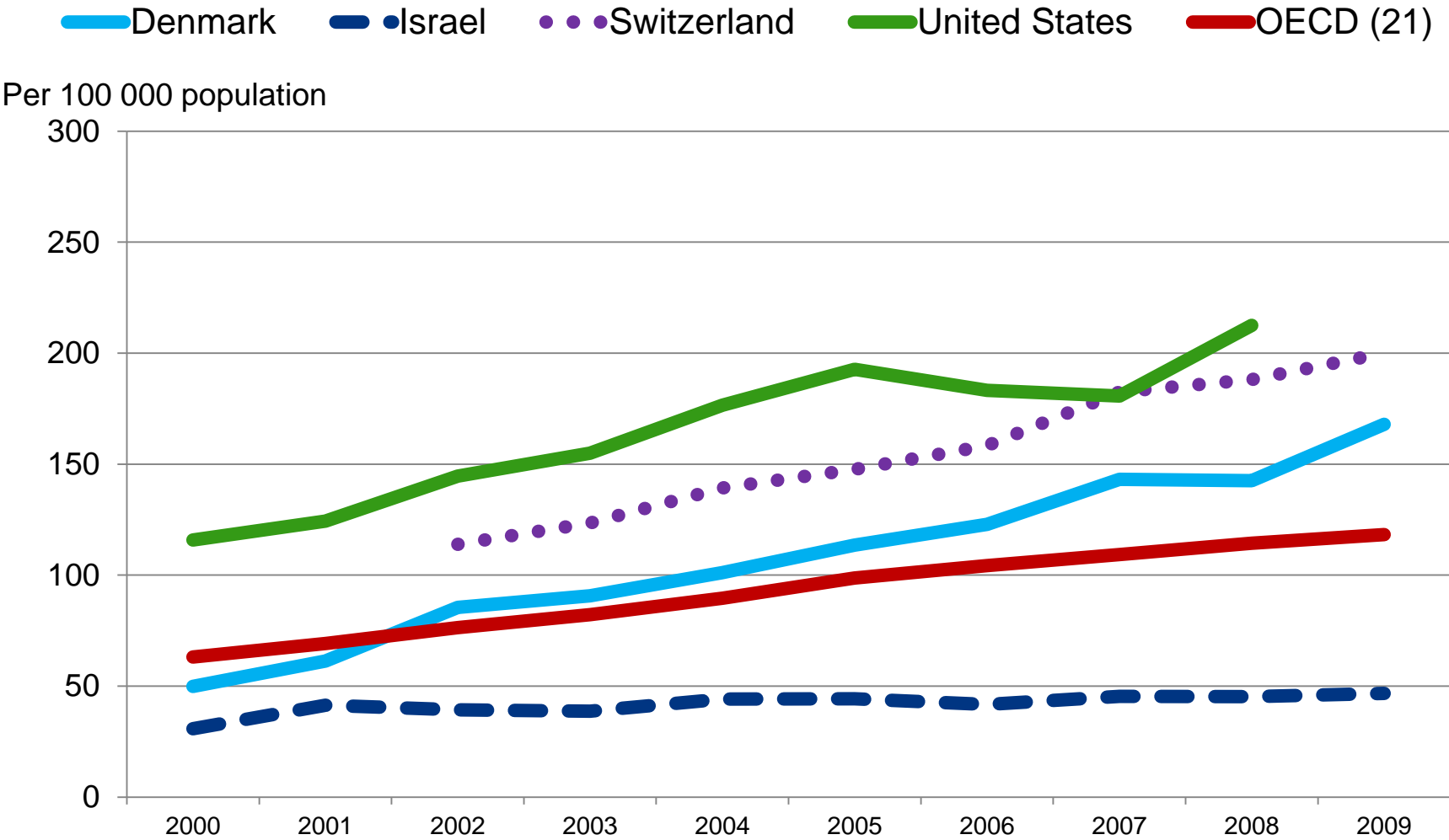
Prosthetic joint replacements TKA & THA by year: U.S.

Financial burden of PJI (USA)
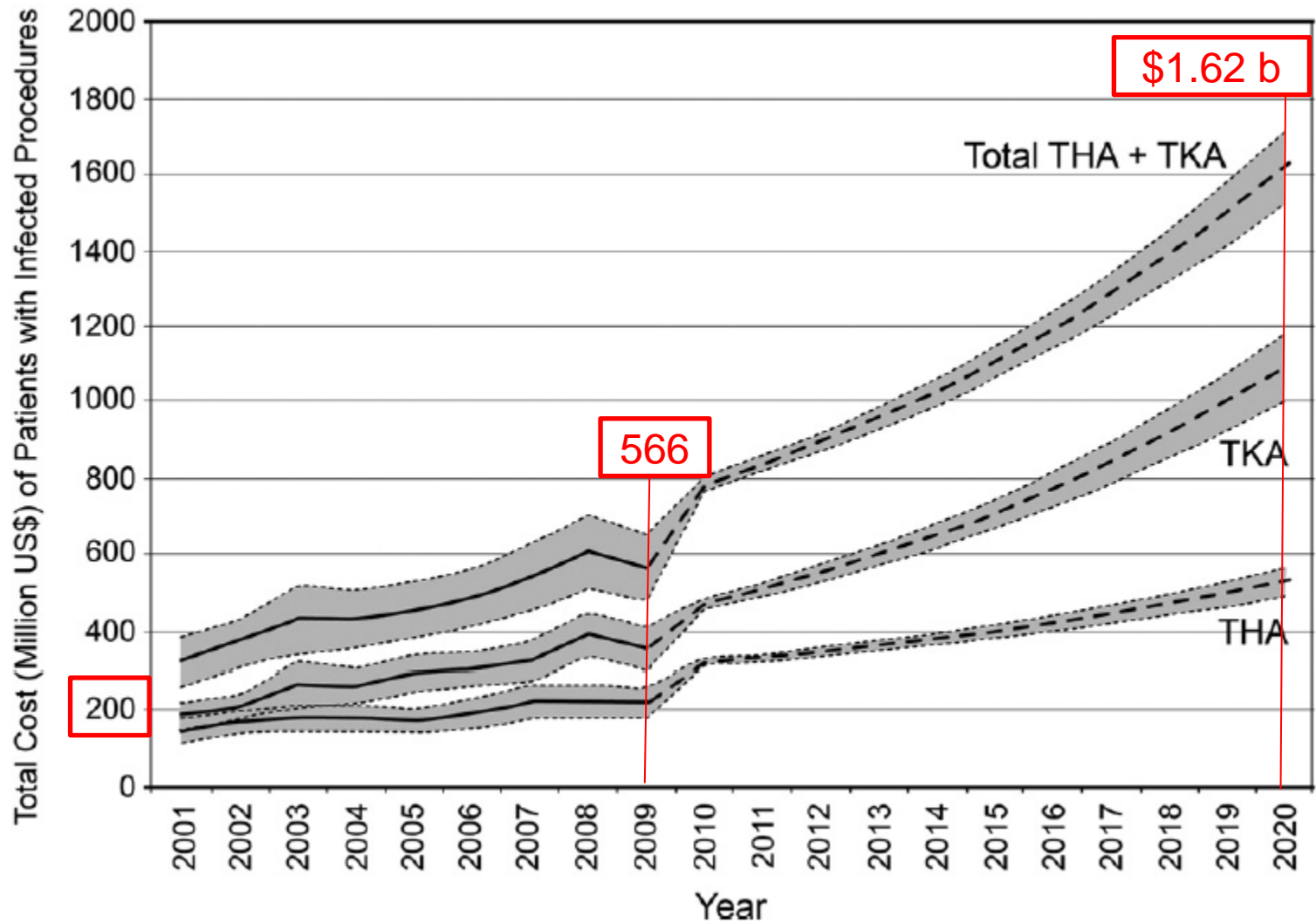
Epidemiology and Microbiology
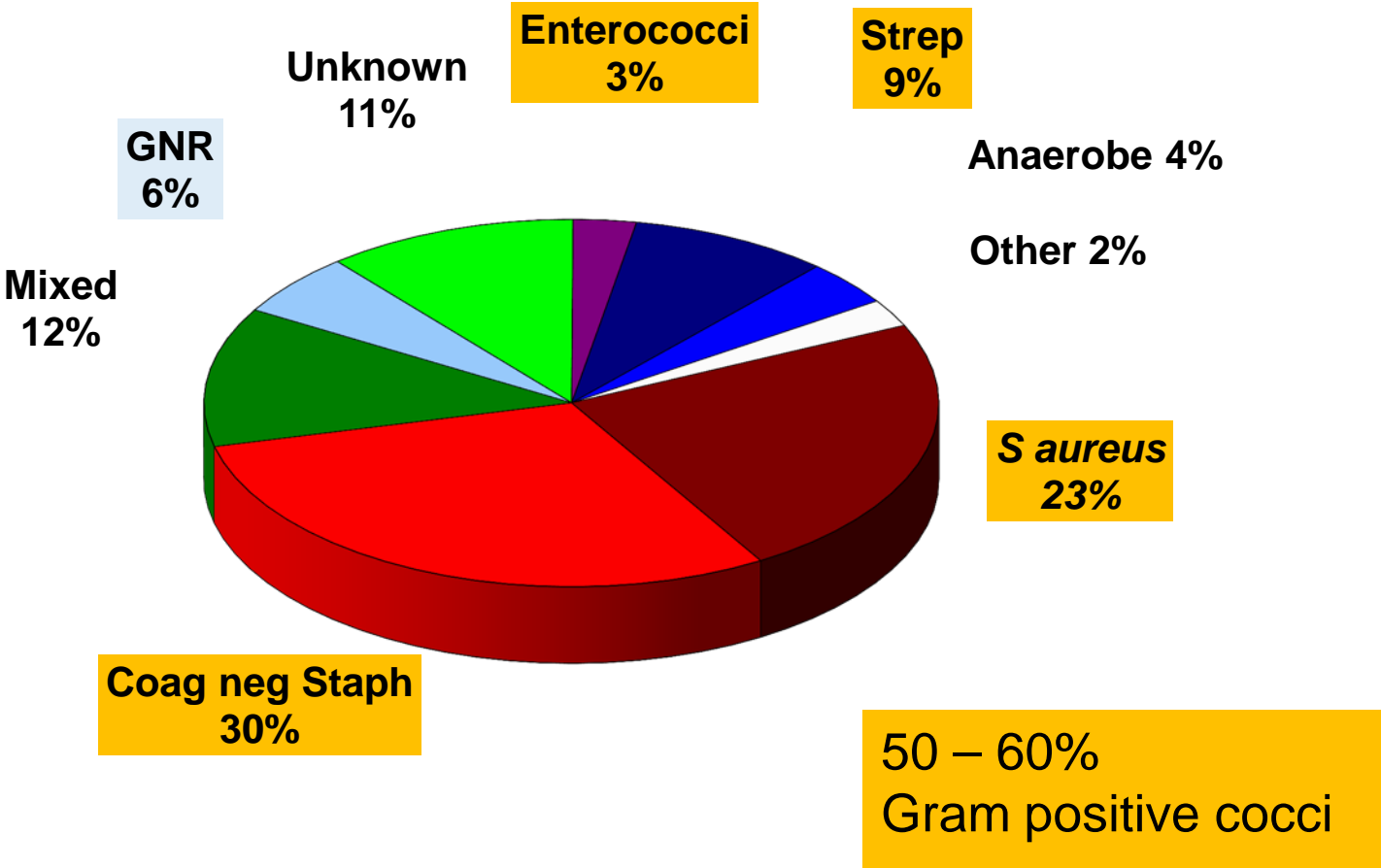## Incidence Rate of Prosthetic Joint Infection at Mayo Clinic 1969-1991
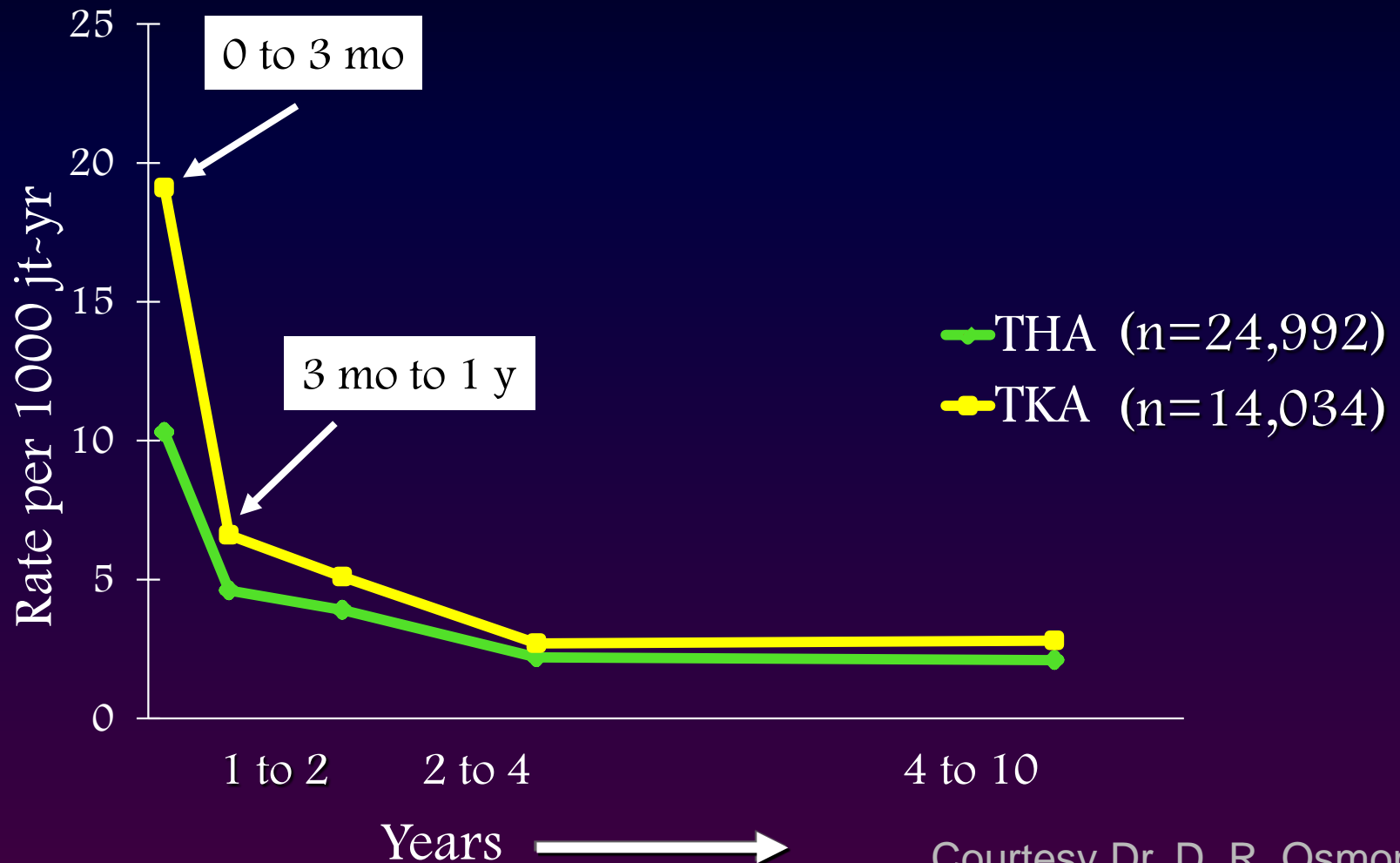
Courtesy Dr. D. R. Osmon

PJI Microbiology

Sia, Berbari, Karchmer. Infect Dis Clin N Am 19 (2005) 885–914

OBJECTIVES

- Identify the best methods to make the diagnosis of PJI

- Explain the principles of diagnostic testing

- Describe how to optimize microbiologic diagnosis in culture-negative situations

- Describe new tests that maybe helpful in PJI diagnosis

No single diagnostic test

Stack evidence **for** **or** **against** the diagnosis of PJI
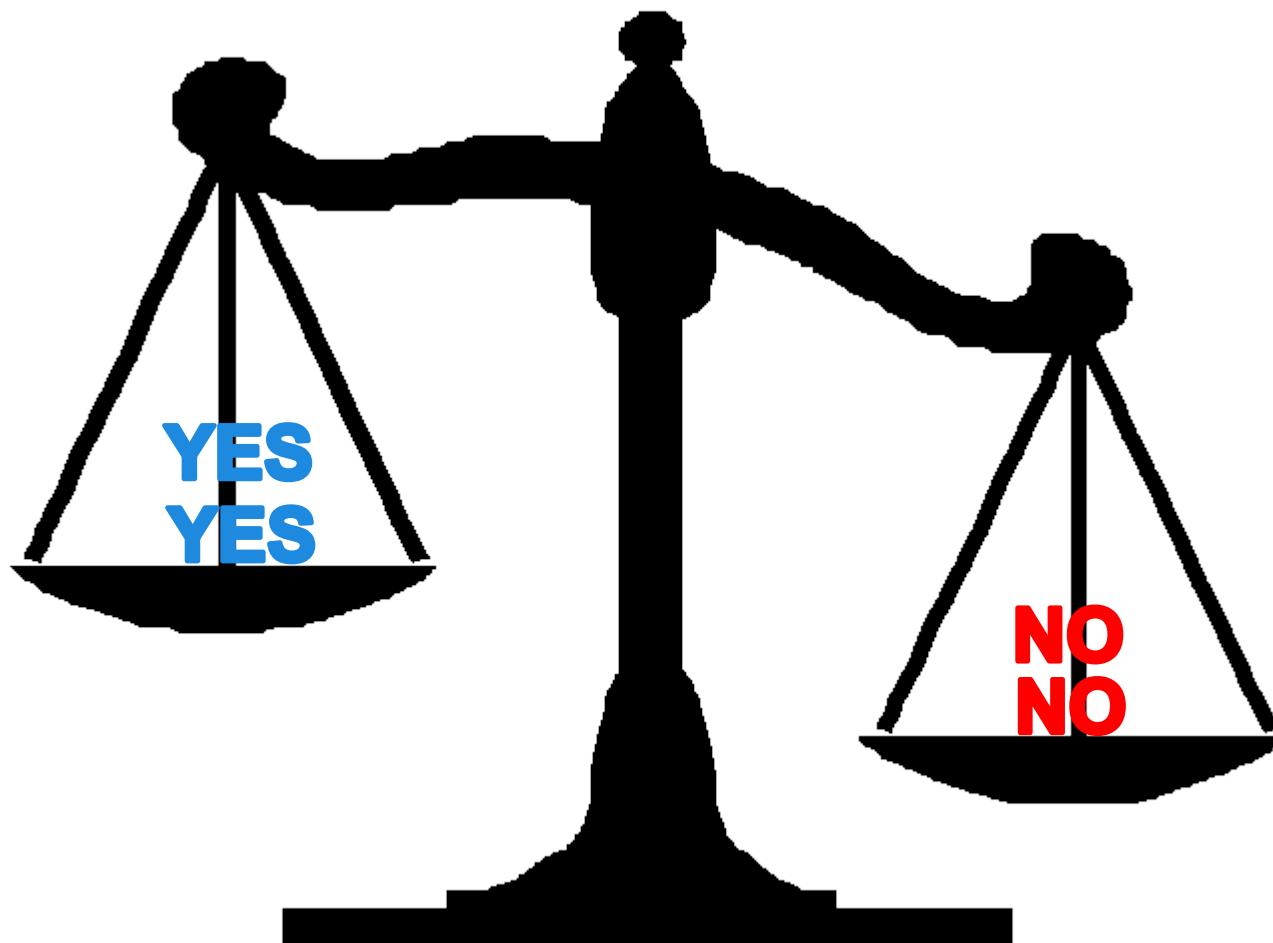
Table 1. Strength of Recommendation and Quality of Evidence

Category/Grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use.
B	Moderate evidence to support a recommendation for or against use.
C	Poor evidence to support a recommendation.
Quality of evidence	
I	Evidence from >1 properly randomized, controlled trial.
II	Evidence from >1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Assessment

Pre-operative

- Symptoms / signs
- Risk factor assessment
- Biomarkers
- Synovial assessment
- Imaging

Both pre and intraoperative

- Cultures
- Other methods for pathogen detection

Intraoperative

- Surgical findings
- Histopathology

Preoperative Diagnostic Approach

- **Clinical history and examination**
  - Symptoms and signs
  - Duration of prosthetic joint arthroplasty (PJA)
  - Specific joint differences – fewer symptoms in shoulders, elbows

- **Risk factors of PJI**

- **Serum Biomarkers**
  - May remain elevated for 30-60 days after PJA
  - Other concurrent illnesses may affect biomarkers

- **Synovial fluid analysis**
  - Acute versus late
    - Synovial WBC/PMN remain elevated for 90 days after PJA
      - Christensen et al. J Bone Joint Surg Am. 2013;95:2081-7
  - Specific joint fluid differences – lower cell count or biomarkers in shoulders
  - Culture positivity affected by biofilm, antibiotics etc

- **Imaging**
  - Limited but important role

Timing and definition of infection

- **Early postoperative infection**
  - Within 3 months

- **Late infection**
  - More than 3 months from surgery

- **Acute hematogenous seeding**
  - Late acute infections of previously stable/functional PJA
  - Often *Staphylococcus aureus*, GBS, GNB

- **Positive intra-operative cultures**
  - Incidental positive culture(s) at time of revision

Assessment of Risk factors for PJI

HOST RISK FACTORS

- Previous revision arthroplasty
- Previous arthroplasty infection
- Tobacco abuse
- Obesity
- Rheumatoid arthritis
- Malignancy
- Immunosuppression
- Diabetes mellitus
- Hemophilia
- Failed metal-on-metal prosthesis
- Skin disorders

SURGICAL RISK FACTORS

- Simultaneous bilateral arthroplasty
- A long operative time (>2.5 hours)
- Allogeneic blood transfusion

POSTOPERATIVE RISK FACTORS

- Wound healing complications (e.g., superficial infection, hematoma, delayed healing, wound necrosis, dehiscence)
- *S. aureus* bacteremia (~ 30%)
- Urinary tract infection
- Atrial fibrillation
- Myocardial infarction
- Prolonged hospital stay

Del Pozo, Patel, R. N Engl J Med 2009;361:787-94

Symptoms & signs: sinus tracks are uncommon

Symptoms & signs – C III	Percent
Pain	96%
Swelling	90%
Drainage	29%
Fever	9%
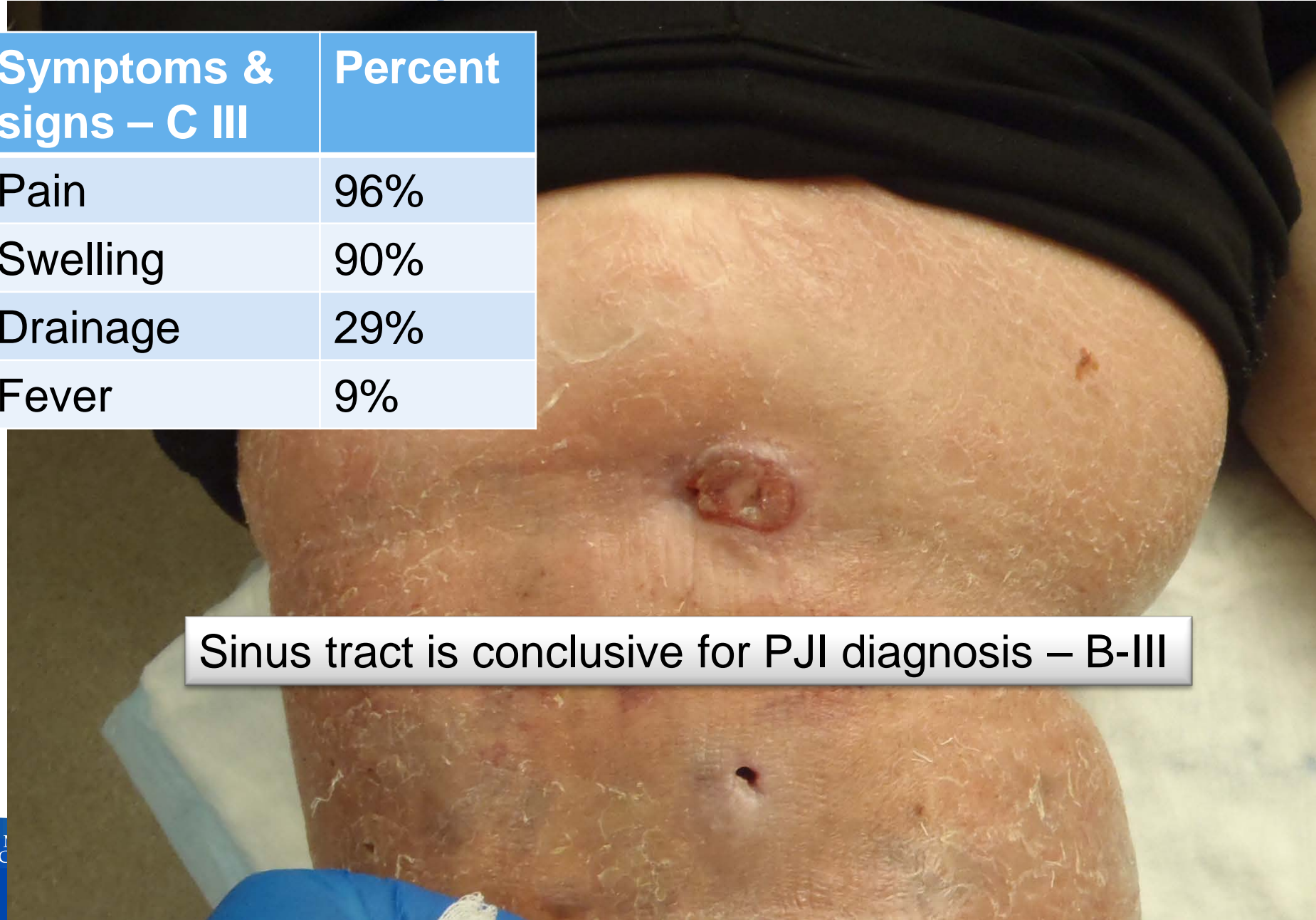
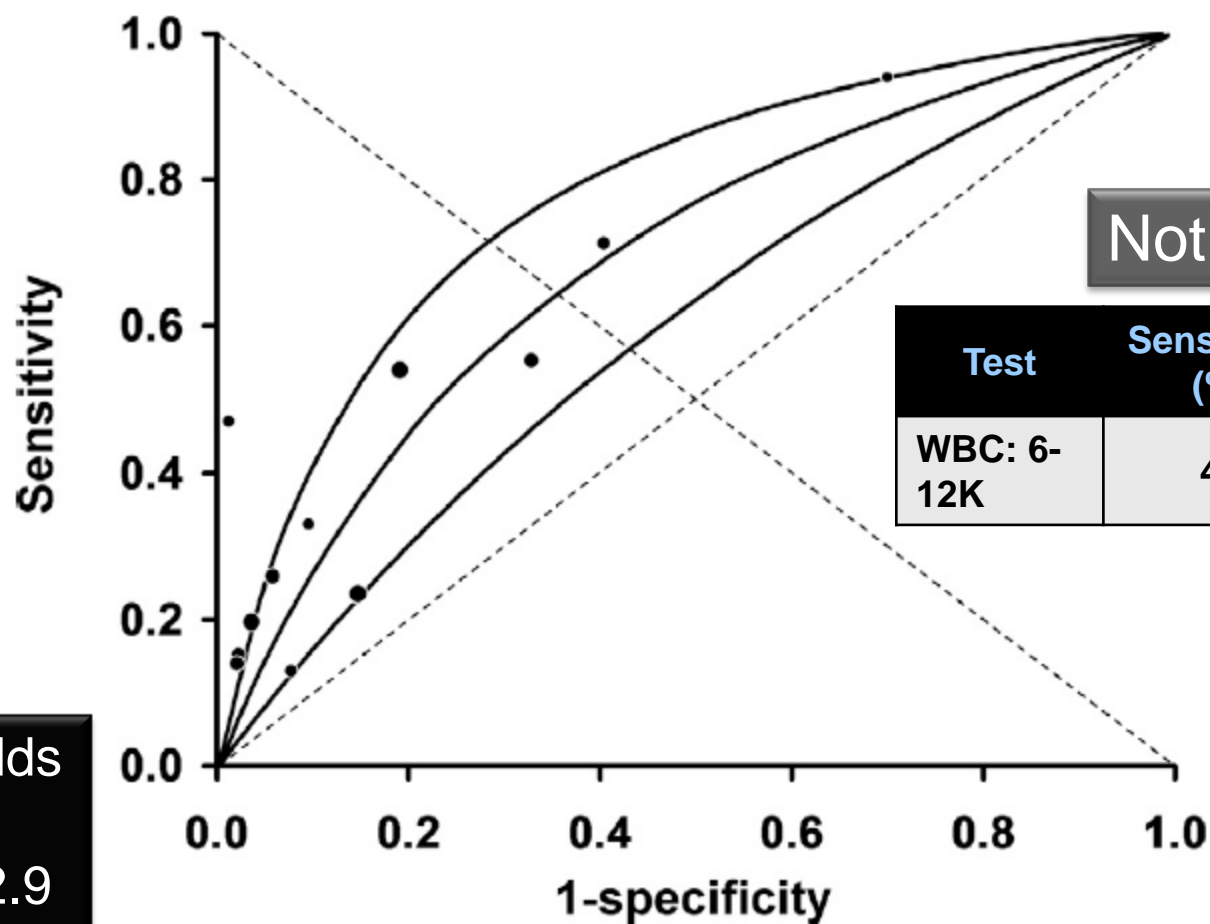

Sinus tract is conclusive for PJI diagnosis – B-III

Case 2: 70 year old with history of gout and DJD

- L THA 2011, uncomplicated

- 2013: pain, no other symptoms, good ROM

- No inciting infectious events

- No fevers, chills or sweats

Meta-analysis of **blood biomarkers** for PJI diagnosis
Summary Receiver Operator Curve: **WBC**

Not very helpful

Test	Sensitivity (%)	Specificity (%)
WBC: 6-12K	45	87

Diagnostic odds ratio:
4.4 (95% CI 2.9 – 6.6)

Berbari et al. J Bone Joint Surg Am. 2010;92:2102-9

Meta-analysis of **blood biomarkers** for PJI diagnosis
Summary Receiver Operator Curve: **Sed Rate**

Somewhat helpful

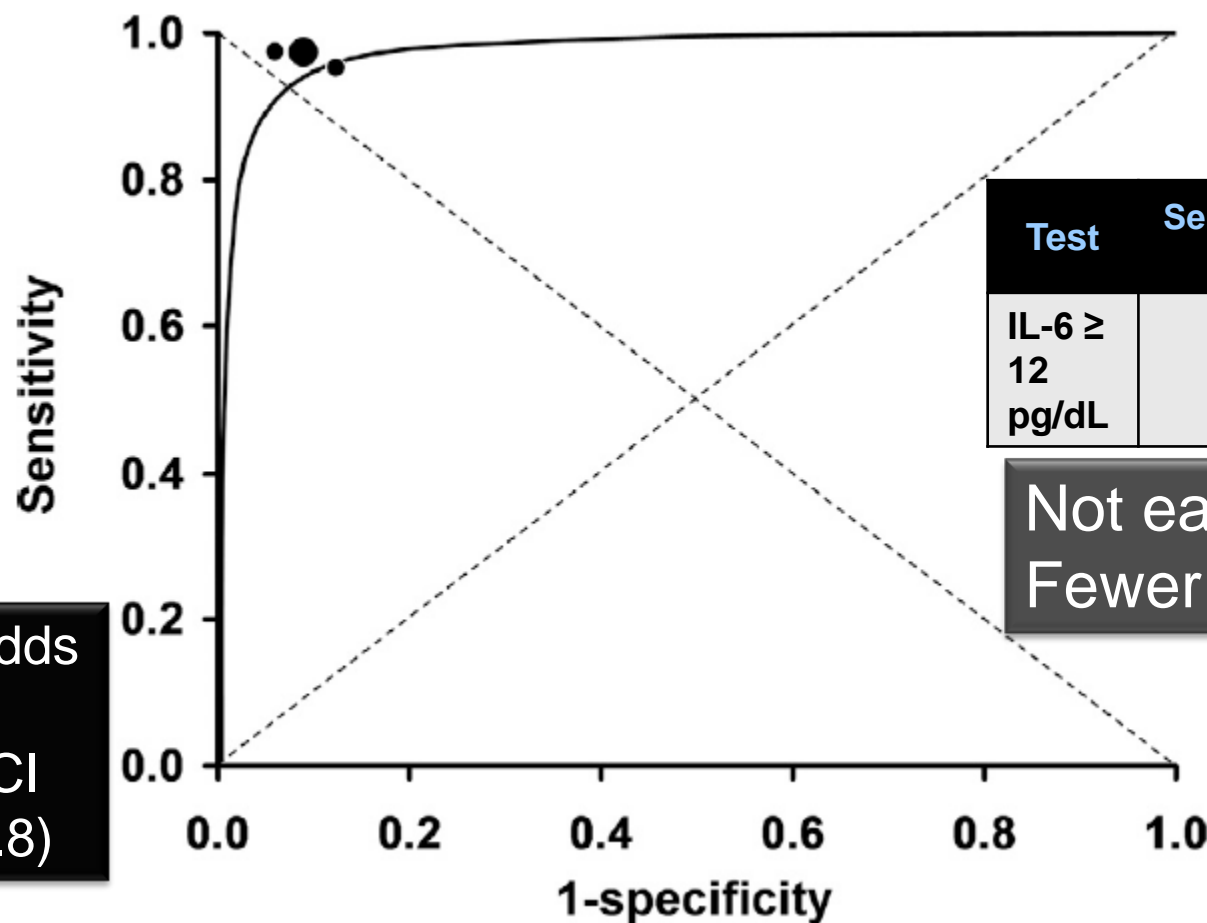| Test	Sensitivity (%)	Specificity (%)
ESR > 30mm/hr	75	70
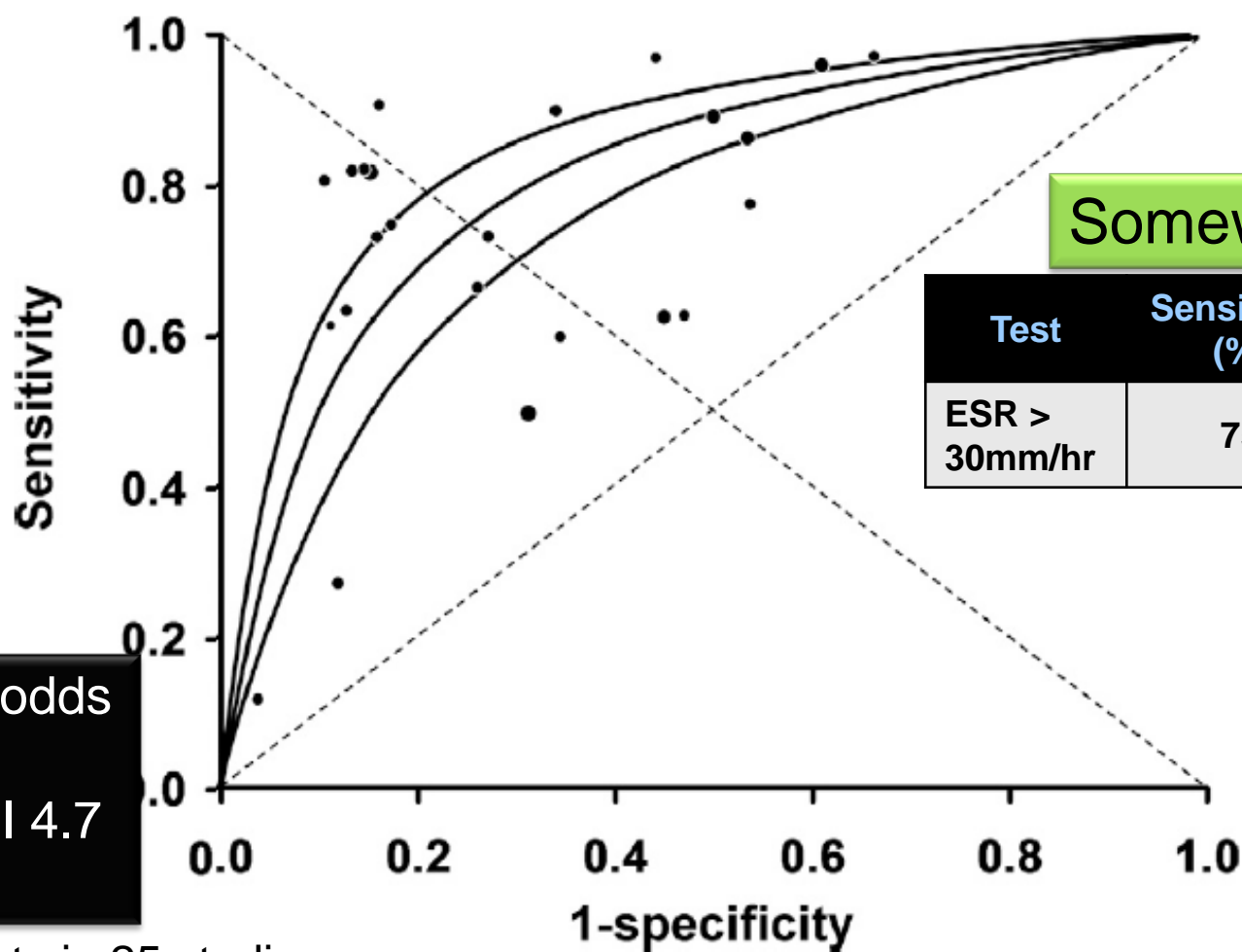
Diagnostic odds ratio:
7.2 (95% CI 4.7 - 10.9)

3,370 patients in 25 studies

A-III

Berbari et al. J Bone Joint Surg Am. 2010;92:2102-9

Meta-analysis of **blood biomarkers** for PJI diagnosis
Summary Receiver Operator Curve: **C-Reactive Protein**
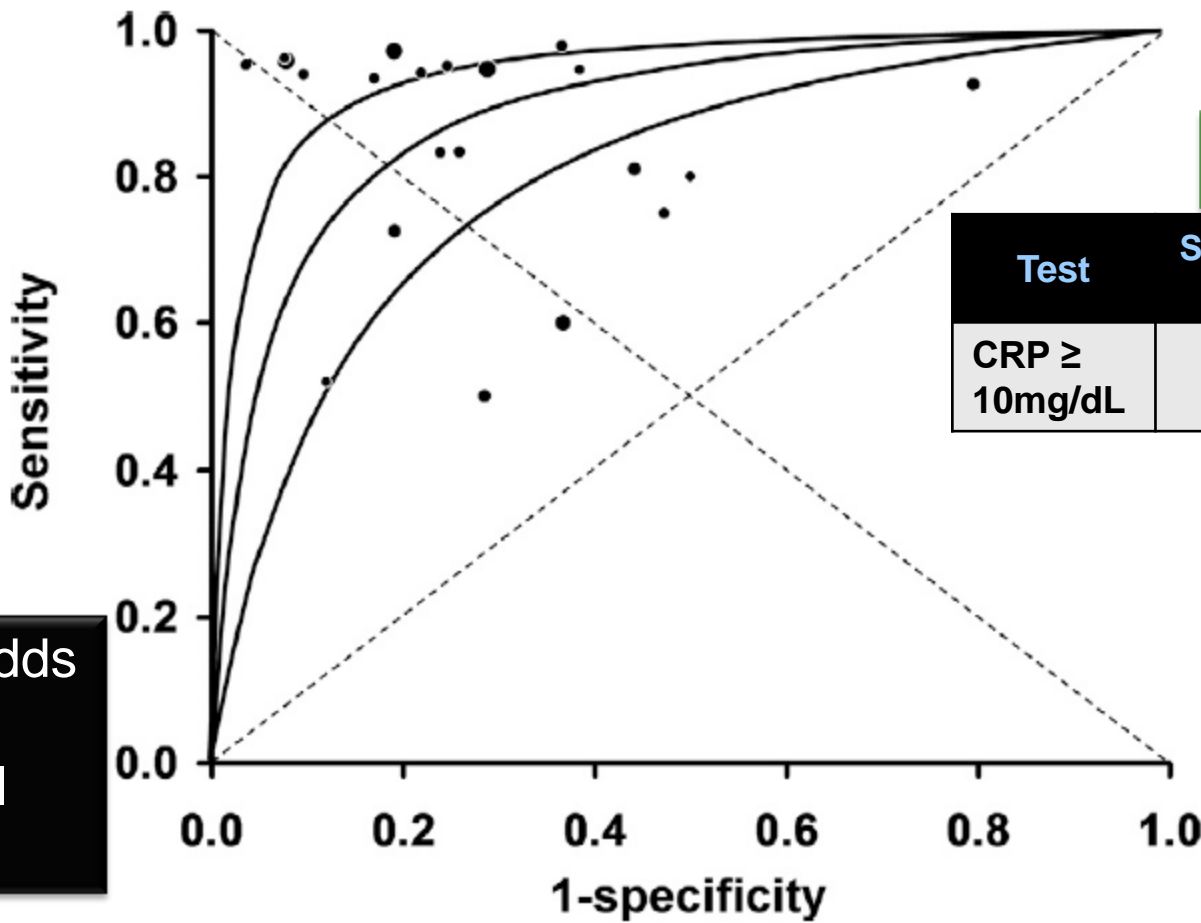
More helpful

Test	Sensitivity (%)	Specificity (%)
CRP ≥ 10mg/dL	88	74

Diagnostic odds ratio:
13.1 (95% CI 7.9 to 21.7)

3,225 patients in 23 studies

A-III

Berbari et al. J Bone Joint Surg Am. 2010;92:2102-9

Meta-analysis of **blood biomarkers** for PJI diagnosis
Summary Receiver Operator Curve: **IL-6**

Very helpful

Test	Sensitivity (%)	Specificity (%)
IL-6 ≥ 12 pg/dL	97	91

Not easily available
Fewer studies

Diagnostic odds ratio:
314.7 (95% CI 113.0 to 876.8)

Berbari et al. J Bone Joint Surg Am. 2010;92:2102-9
Di Cesare et al. JBJS:2005; 1921-1927

Probability of PJI Based on Combinations of Common Pre-operative Tests

[1]ESR	CRP	Aspiration [#]	Probability	Range
Neg	Neg	-----	0%*	0-4
Pos	Pos	----	83%	62-95
Neg	Neg	Neg	0%	0-4
Pos	Pos	Pos	89%	52-100

[2]ESR	CRP	Sensitivity	Specificity	PPV	NPV
Neg	Neg	95%	56%	58%	95%

[#] Defined as positive: At least one positive culture

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein

*Negative predictive value 0.97

1. Spangehl et al. J Bone Joint Surg Am 1999; 81; 672-683
2. Austin MS et al. J. Arthroplasty:2008 23:65–68

Other **blood biomarkers** for PJI diagnosis

Test	Sensitivity (%)	Specificity (%)
Procalcitonin > 0.3 ng/ml	33	98
TNF-α	43	94

Bottner F. JBJS: 2007;89-B,94-99

Preoperative Diagnostic Approach
Imaging: Important to do in all but not diagnostic
Poor sensitivity and specificity for PJI

- Plain x-rays (mostly normal)
  - Lucency at bone-prosthesis interface
  - Subperiosteal elevation, new bone formation
  - Early (within 5 years of prosthesis) loosening
  - Early osteolysis
  - Useful to understand complexity of prosthesis, diagnose mechanical problems, retained foreign material
  - Serial imaging for comparison

A-III

1. Sia et. al. et al. Infect Dis Clin N. Am. 2005:19,885
2. Fenandez Sampedro et al Infect Dis Clin North Am 2007; 21, 785
3. Parvizi et al. JBJS 2006; 88-A 138-146

MAYO CLINIC

Chronically infected prosthesis: lucency at the bone –prosthesis interface, periosteal new bone formation

Lucency: bone – prosthesis interface

Periosteal new bone formation

Lucency: bone – prosthesis interface
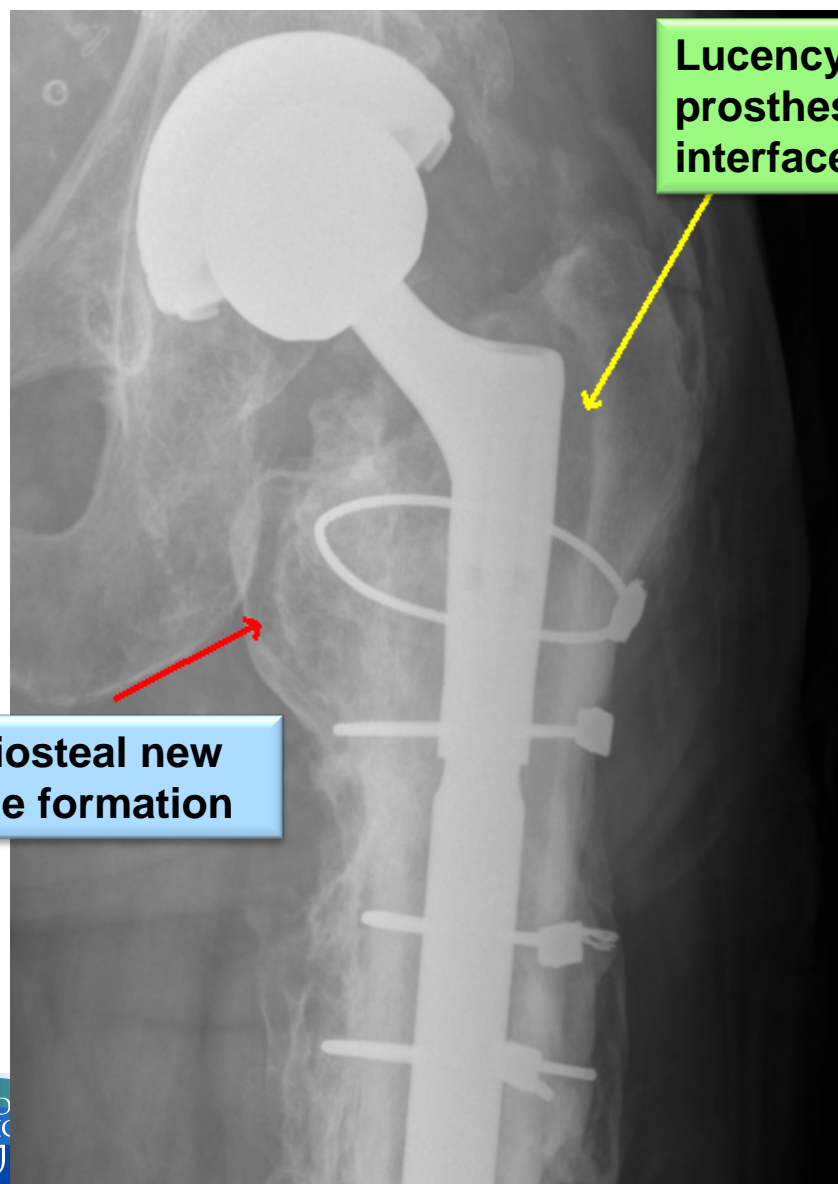
Understanding the complexity of reconstruction:
Chronic SCN re-infection of left custom THA
S/p 2 previous 2-stage exchanges for infection

# Diagnosis
Additional Imaging Studies – rarely needed

Legend:
- Sensitivity (green)
- Specificity (blue)

Test	Sensitivity	Specificity
X-ray	30	79
Tc99/Gallium	48	89
IWBC	90	72
Tc99/IWBC	94	97
IWBC IgG	92	88
PET	82	87

B-III

Spangehl MJ. *J Bone Joint Surg.* 1997; 47:285-295
Del Pozo, Patel. N Engl J Med 2009;361:787-94
Osmon, DR. et al. Clinical Infectious Diseases 2013;56(1):e1–25

MAYO CLINIC
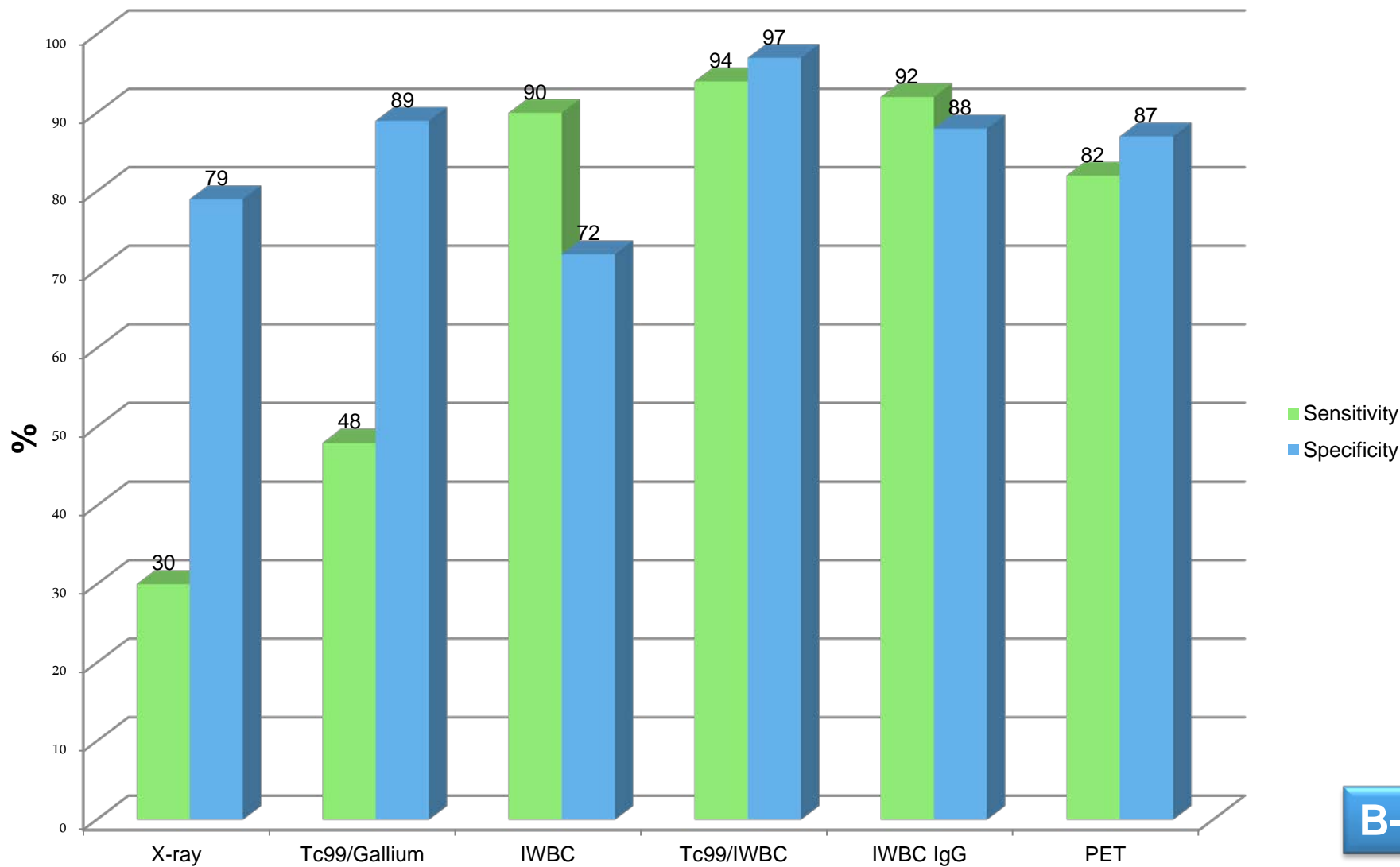
Synovial fluid assessment for diagnosis of PJI

- Should be done in all patients suspected to have a PJI **A-III**

- Ideally off antibiotics for 2 weeks – B-III

- Fluid should be sent for cell count, differential, cultures and crystals
  - Mostly aerobic and anaerobic bacterial cultures though may need to modify based on risk factors
  - Analysis varies based on acute versus chronic presentation
  - Presence of crystals does not exclude PJI

- Aspiration may be withheld in patients going for surgery imminently and intra-operative cultures will be obtained

- Blood cultures recommended for acutely ill – B-III

Osmon, DR. et al. Clinical Infectious Diseases 2013;56(1):e1–25

Synovial fluid in TKA PJI in TKAs > 6 months after implantation without underlying inflammatory joint disease

Trampuz et al. Am J Med. 2004;117:556 –562
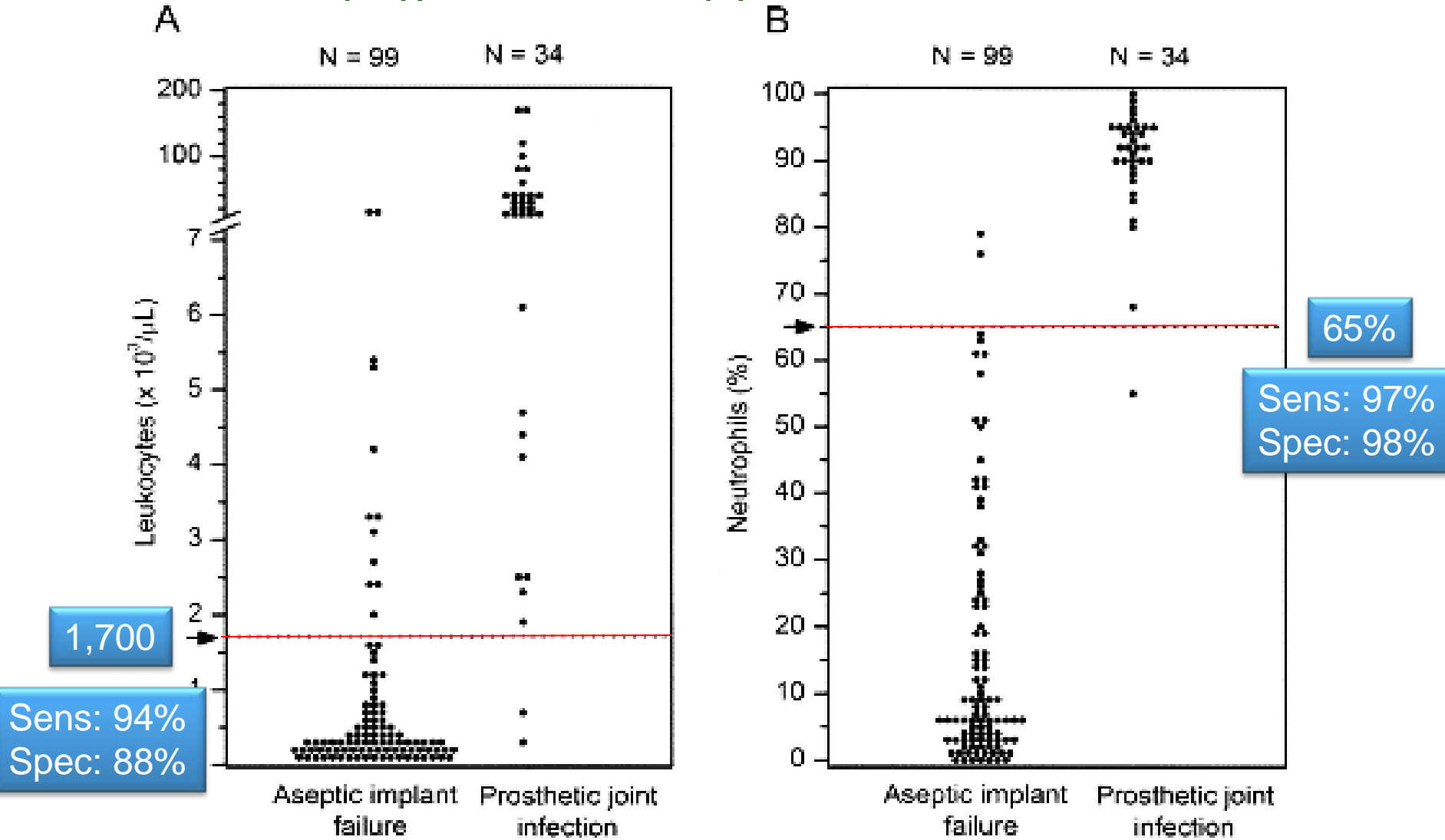
Synovial fluid analysis

Joint		Sensitivity %	Specificity %
TKA > 6 months after implantation			
TNC cells/µl[1]	**≥ 1700**	97	88
TNC cells/µl[2]	≥ 1100	91	88
%PMN[1]	**≥ 65%**	94	98
%PMN[2]	≥ 64%	95	95
TKA PJI **within 6 weeks after primary TKA** [3]			
TNC cells/µl	≥ 27,800	87	99
%PMN	≥ 89%	84	69
THA > 6 months after implantation [4]			
WBC cells/µl	≥ 4200	90	93
%PMN	≥ 80%	87	90
THA and TKA > 6 months after implantation [5]			
WBC cells/µl	≥ 3450	91	93
%PMN	≥ 78%	95	87

1. Trampuz et al. Am J Med. 2004;117:556 –562
2. Ghanem et al. JBJS 2008:90-A: 1637-1643
3. Bedair H et al. CORR 2011 Jan;469(1):34-40
4. Schinsky MF et al. J Bone Joint Surg Am. 2008. 90(9):1869-75
5. Cipriano CA et al. J Bone Joint Surg Am 94:594–600

Other causes for high synovial counts

- **Inflammatory diseases**
  - The specificity may be lower of the cell count

- **Metallosis**
  - Manual cell count and differential may be needed
    - Monocytes with phagocytosed metal may be read as WBC in automated machines
    - Discordance between WBC and PMN – high cell count, low PMN may suggest metallosis and need for manual check
  - 80% PMN more sensitive & specific: 100% and 97%

Synovial fluid analysis – The Holy Grail!

Table 2. Biomarkers listed and their fold-elevation in the infection group versus the aseptic group

Biomarker		Fold-elevation	p
IL–1b	Interleukin 1-beta	257.8	< 0.0001**
G-CSF	Granulocyte colony-stimulating factor	119.9	< 0.0001**
IL–17	Interleukin 17	112.5	< 0.0001**
IL–6	Interleukin 6	27.3	< 0.0001**
IL–1a	Interleukin 1-alpha	24.5	< 0.0001**
MIP–1B	Macrophage inflammatory protein 1-beta	18.0	< 0.0001**
IL–10	Interleukin 10	8.0	< 0.0001**
IL–8	Interleukin 8	6.2	< 0.0001**
GM-CSF	Granulocyte monocyte colony-stimulating factor	5.1	0.0678
MIP-1a	Macrophage inflammatory protein 1-alpha	4.9	< 0.0001**
TNF-a	Tumor necrosis factor alpha	4.1	0.0048
IL–5	Interleukin 5	2.5	0.001*
ENA-78	Epithelial cell-derived neutrophil-activating peptide 78	2.2	0.0048
SKALP	Skin derived antileukoproteinase	2.1	< 0.0001**
IFN-g	Interferon gamma	2.0	0.168
FGF-Basic	Fibroblast growth factor basic	1.9	0.0012*
IL–1ra	Interleukin 1 receptor antagonist	1.6	0.0054
IL–4	Interleukin 4	1.3	0.336
VEGF	Vascular endothelial growth factor	1.3	0.0302
Tpo	Thrombopoietin	1.2	0.1019
MCP-1	Monocyte chemotactic protein 1	0.8	0.3185
Rantes	Regulated upon Activation, Normal T-cell Expressed, and Secreted	0.7	0.4706
SLPI	Secretory leukocyte peptidase inhibitor	0.6	N/A

The p values listed are the raw p values based on the Mann-Whitney test; * = p value significant after Bonferroni adjustment for multiplicity; ** = p value highly significant after Bonferroni adjustment for multiplicity.

Deirmengian, et al. Clin Orthop Relat Res (2010) 468:2017–2023

Synovial fluid analysis – other tests

- ## Synovial fluid CRP
  - Similar sensitivity, specificity, PPV, NPV, as serum CRP assay

- ## Synovial leukocyte esterase
  - 80.6% sensitivity, 100% specificity
    - when result was ++
  - Positive predictive value - 100%
  - Negative predictive value - 93.3%
  - Many unreadable due to excessive blood, debris

1. Tetreault et al. Clin Orthop Relat Res. 2014 Dec;472(12):3997-4003
2. Parvizi et al. J Bone Joint Surg Am. 2011;93:2242-8

Synovial alpha-defensin (antimicrobial peptide from neutrophils) and C-reactive protein algorithm

TABLE II Relevant Laboratory and Clinical Findings for MSIS Definition		
Finding	Aseptic (N = 112)	Periprosthetic Joint Infection (N = 37)
Sinus (no. of patients)	0	5
≥1 positive culture (no. of patients)	5	24
Mean ESR (mm/hr)	21	83
Mean CRP level (mg/L)	8	160
Mean leukocyte count (cells/μL)	637	43,391
Mean neutrophil percentage	26	88

- Sensitivity 97%; Spec 100%

- Pending validation studies

- Single center study
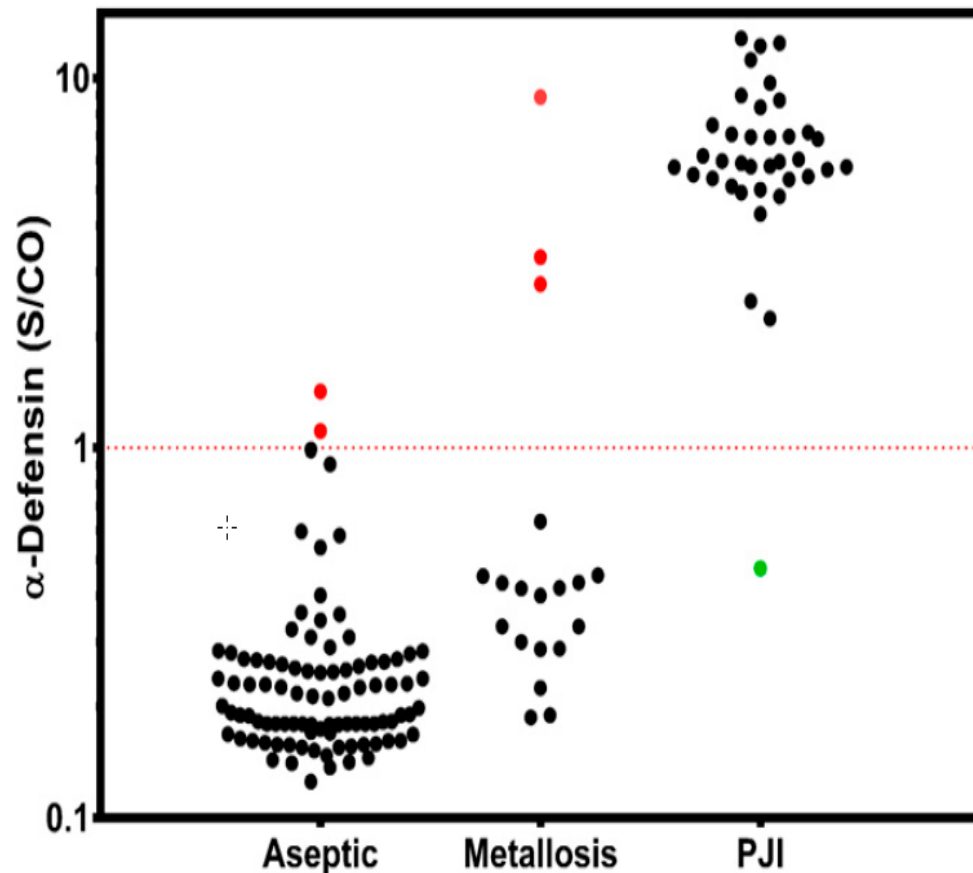
(S/CO): semiquantitative signal-to-cutoff ratio

Case 2: 70 year old with history of gout and DJD

- L THA 2011, uncomplicated

- 2013: pain, no other symptoms , good ROM

- Normal white count

- Sed rate 46, CRP 20.9

- Hip aspiration
  1,980 TNC, 91% PMN
  Cultures negative
  Crystals negative

- 2nd aspirate negative
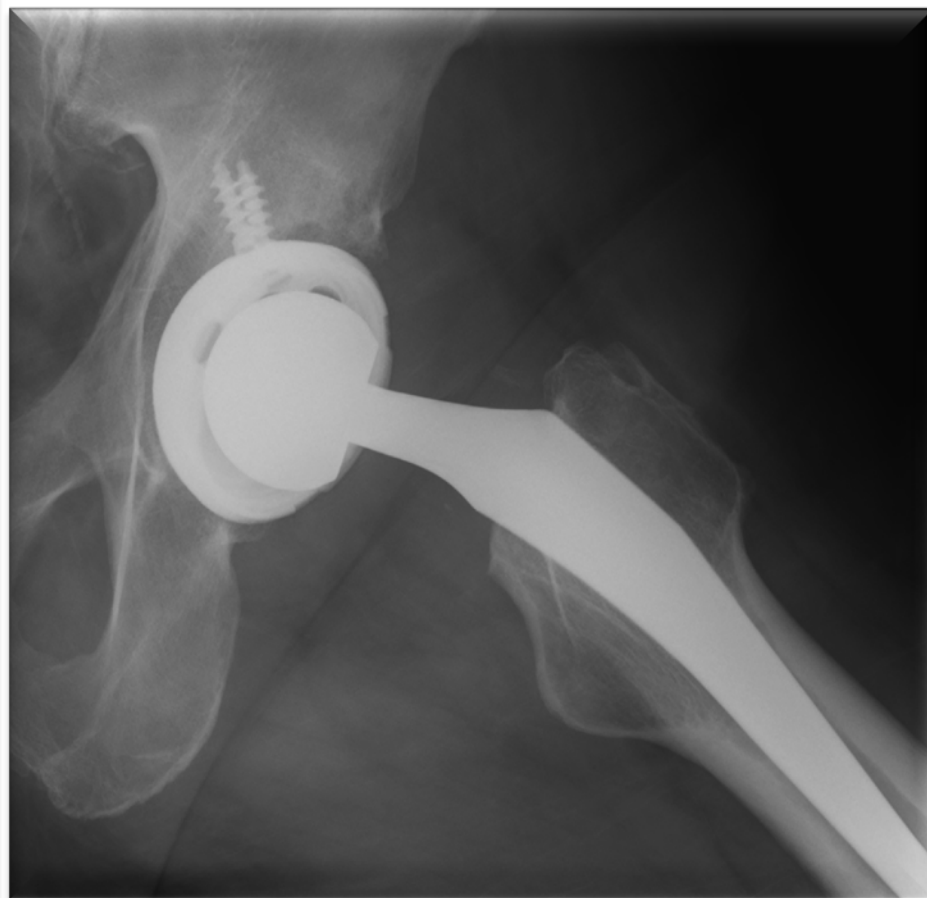
Surgery vs not?
Debridement/retention vs resection?
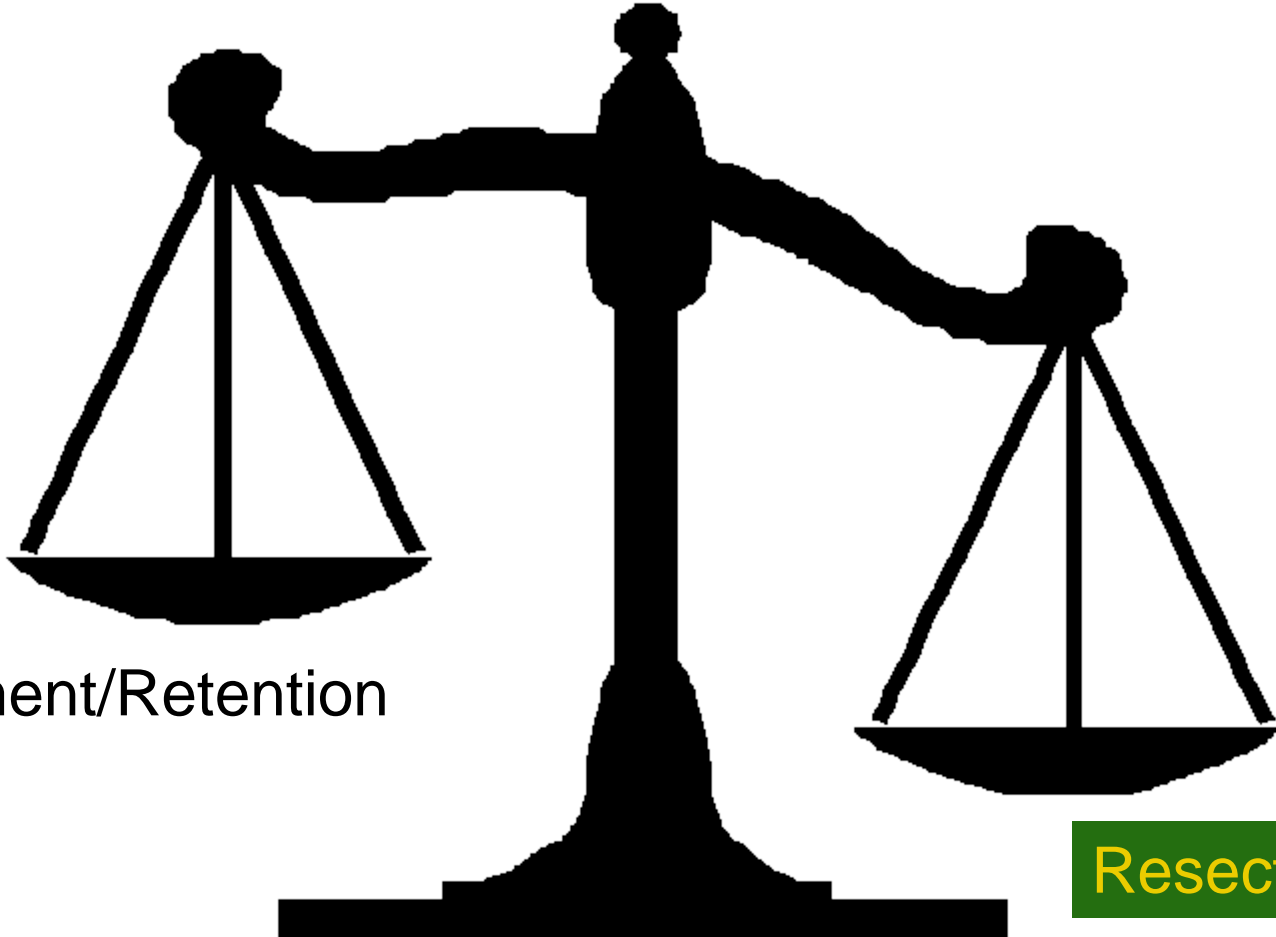
Debridement/Retention

Resection

Diagnosis: Intra and post-operative Tests

Test modality	Sensitivity (%)	Specificity (%)	Probability of infection (%)	
Histopathology incl frozen pathology (>5 PMN/hpf)	75-80	94	74	B-II
Gram stain	<30	98		
Tissue cultures				
3	66-80	99.6	94.8	B-II
2			20.4	
1			13.3	
0			3.4	

Tissue cx should be taken 2 weeks off antibiotics – A-II
Perioperative antibiotics should be held.
Incubation for 14 days to optimize *Propionibacterium* species and other anaerobes

No swab cultures – lower sensitivity

Tsaras et al. J Bone Joint Surg Br 2012;94:1700-11
Atkins BL. J Clin Micro. 1998; 36:2932-2939.
Spangehl et al. J Bone Joint Surg Am 1999;81:672-83
Qu X et al. Clin. Microbiol. 2013 51:3830–3834

MAYO
CLINIC

Prosthesis Sonication Provides Increased Sensitivity for Prosthetic Joint Infection

Add 400 ml Ringer's Solution (laboratory)

Prosthesis Placed in Container (operating room)

Vortex 30 sec

Sonicate 5 min

Vortex 30 sec

0.5 ml Aerobic & Anaerobic Culture Plates

Trampuz et al. NEJM 2007;357:654

Sonication Removes Bacterial Biofilms Scanning Electron Microscopy
S. epidermidis biofilm on polycarbonate coupons
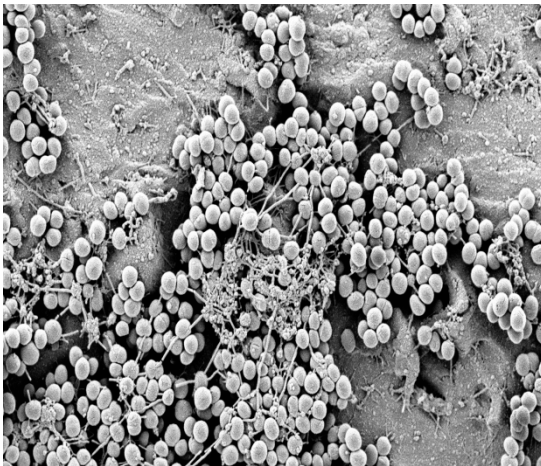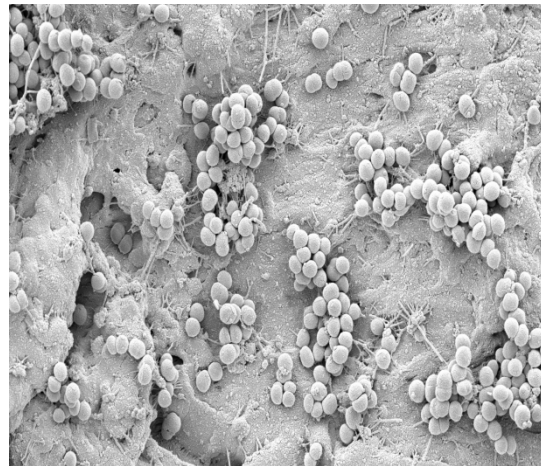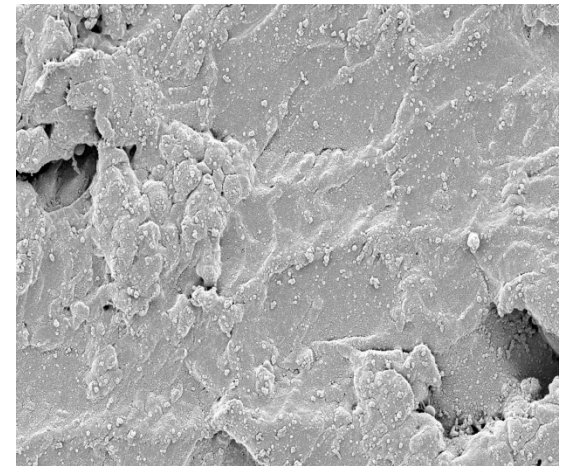
Soaking   **Scraping**   **Sonication**

Magnification x 4.00k, WD = 14.4mm

Courtesy of Robin Patel, MD, Mayo College of Medicine

Prospective Clinical Study

Tissue   **Sonicate***

***Positive defined as ≥ 5 CFU / culture plate**

Courtesy of Robin Patel, MD, Mayo College of Medicine
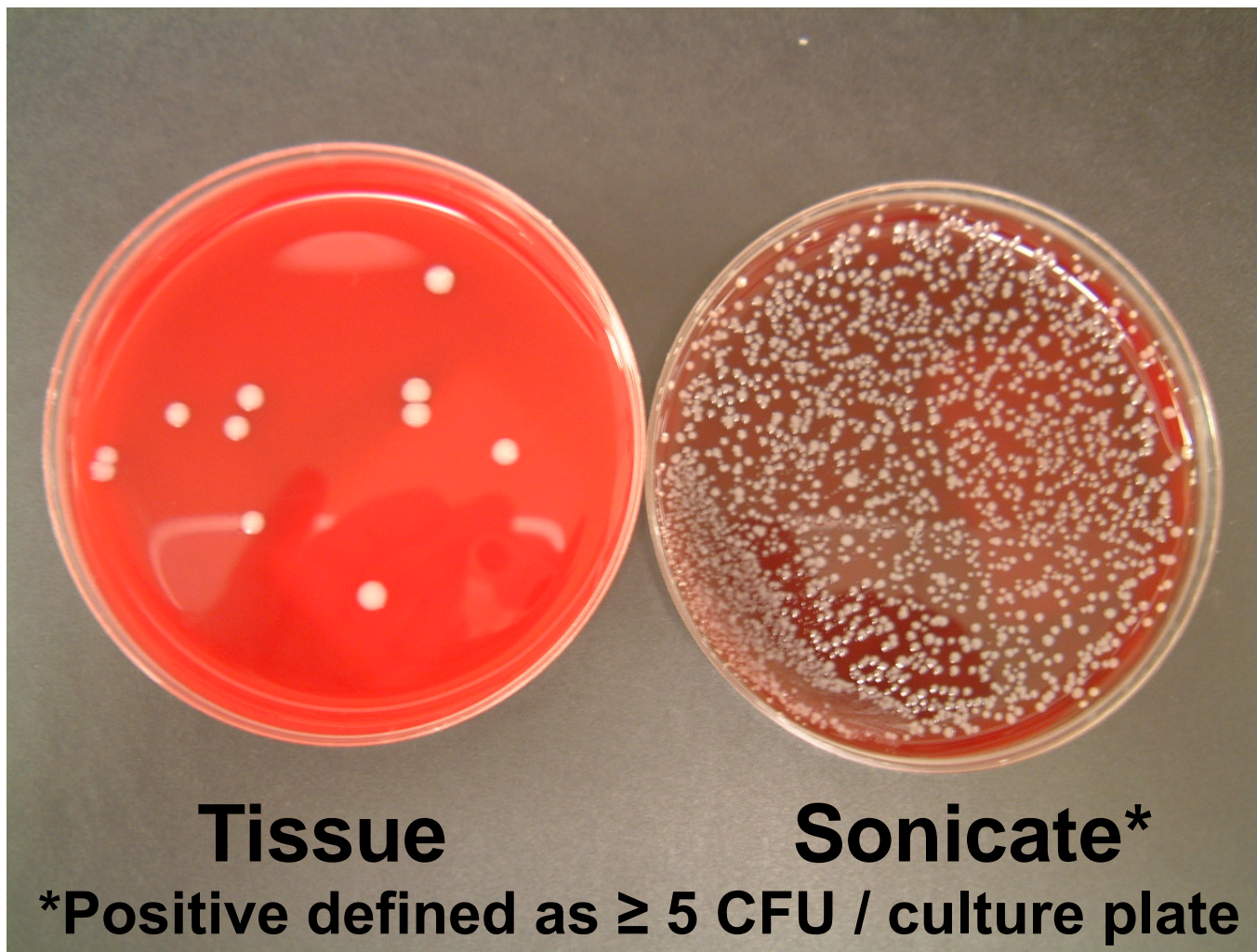
Diagnosis
Sonication and vortexing
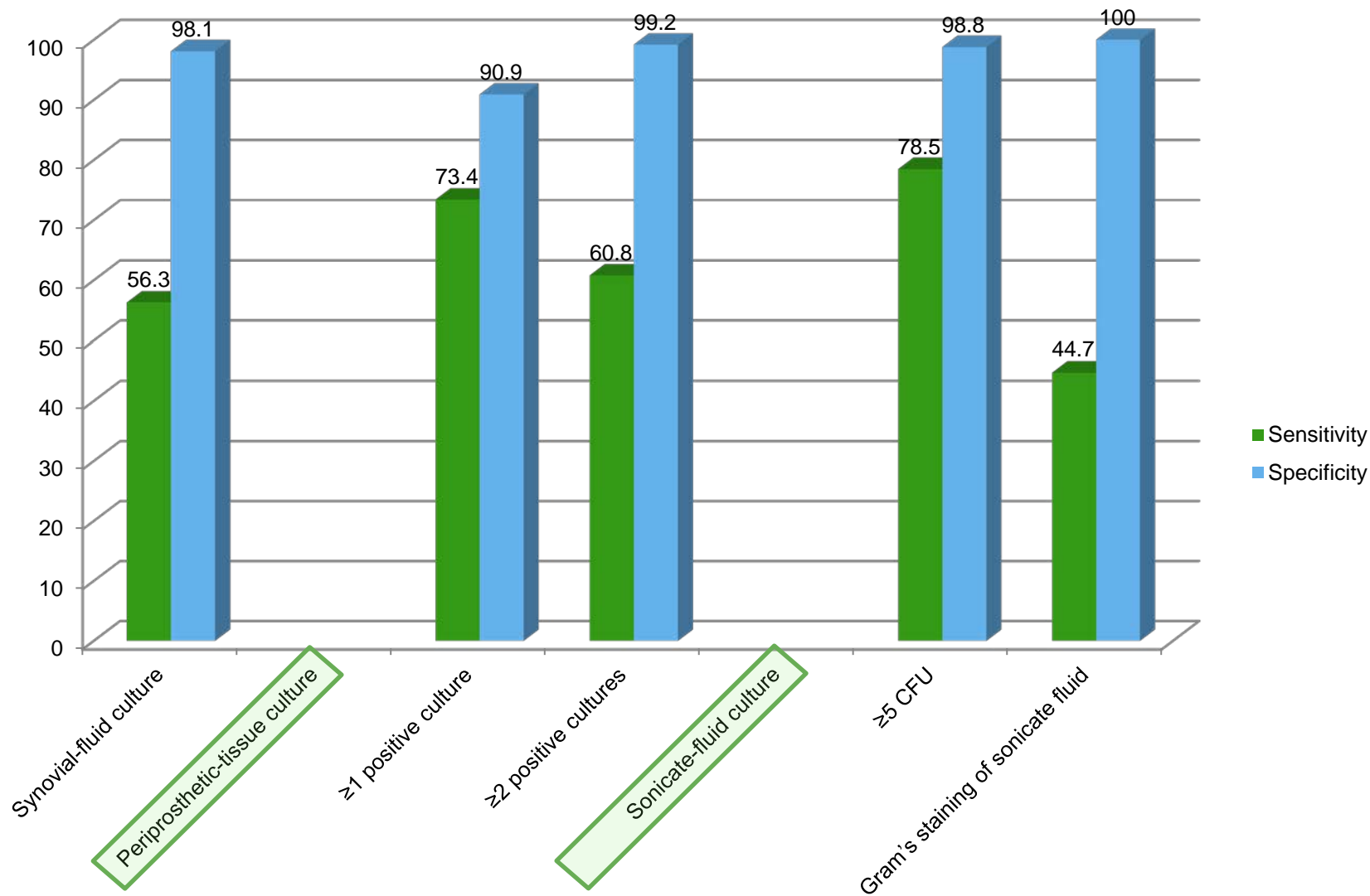
Effect of Preoperative Antimicrobial Therapy on Culture Sensitivity in Patients with Prosthetic-Joint Infection
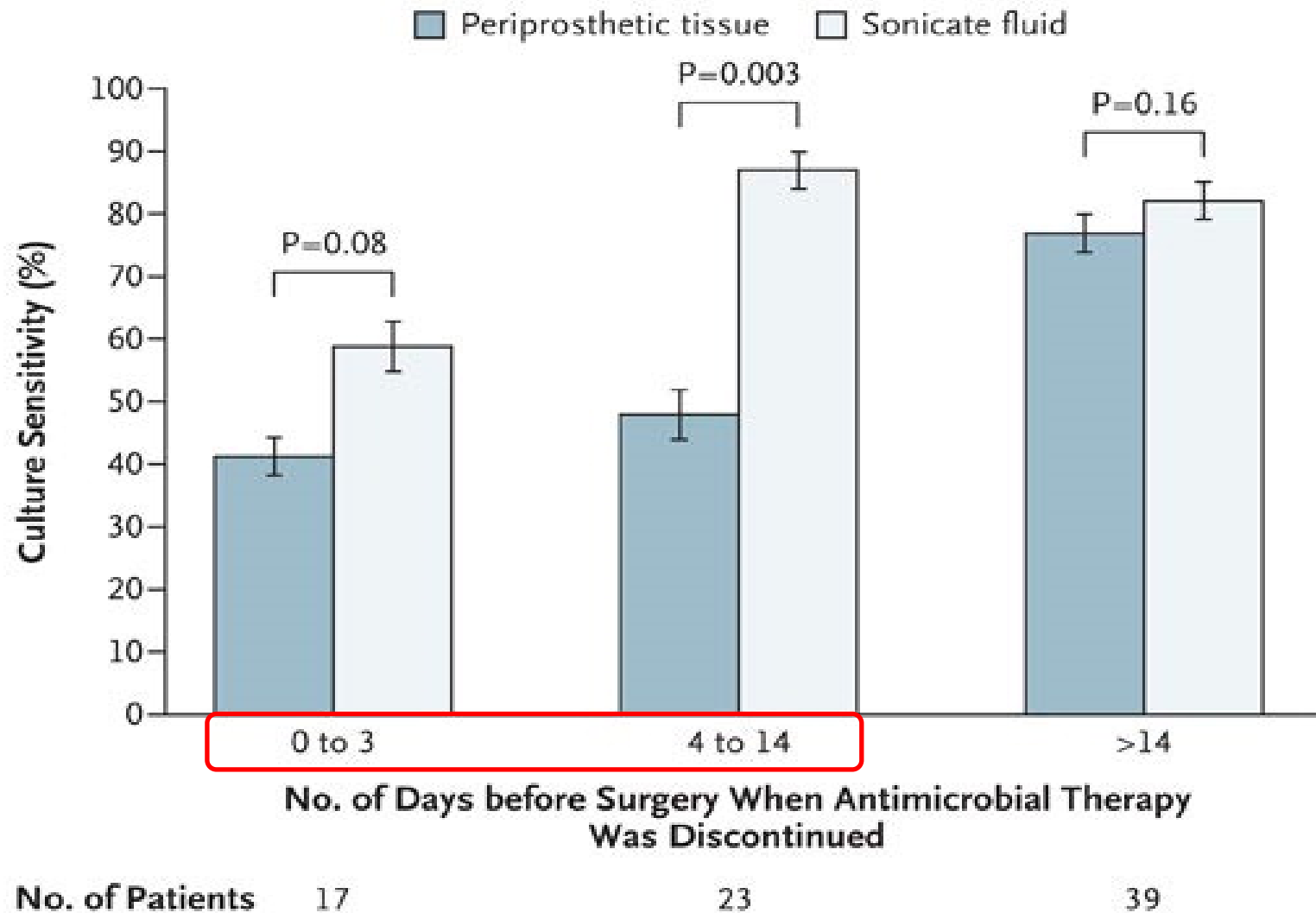
Trampuz A et al. N Engl J Med 2007;357:654-663

Molecular diagnosis of pathogens in PJI

- 16S rRNA gene PCR on tissue or synovial fluid
  - Risk of false-positives for various reasons
  - Difficult to assess
  - High sensitivity but poor specificity (0-100%)

- 16S rRNA gene PCR on sonicate fluid
  - Some studies show higher sensitivity but lower specificity (68%) compared to sonicate fluid cultures (89%)
  - No difference in sensitivity (70%) or specificity (98%) between real-time16Sr RNA gene PCR on sonicate fluid and culture of synovial fluid, periprosthetic tissue, or sonicate fluid

- Multiplex or multipanel PCR assays
  - Unclear utility yet

- More useful in patients with prior antibiotics

Cazanave et al. J Clin Microbiol. 2013 July; 51(7): 2280–2287
Aaron Tande, Robin Patel. Clin Microbiol Rev. 2014 April; 27(2): 302–345
Gomez et al. J. Clin. Microbiol. 2012.50:3501– 3508

Considerations in culture-negative PJI (7-15%)

- Exclude Inflammatory conditions, look for alternate source of elevated biomarkers

- If synovial fluid and other tests are suggestive of infection but multiple bacterial (aerobic/anaerobic) cultures are negative (without recent antibiotics)
  - Re-assess exposure history
  - Consider
    - Serologic diagnosis
      - Q fever, brucella, fungal serologies
    - Cultures for fungi and mycobacteria
      - Discuss with lab regarding special culture methods
        - Adding oil for *Malassezia furfur* etc
    - Add special stains on pathology specimens
    - Molecular tests – 16S PCR, specific organism PCR
    - Re-biopsy in some cases

Definition of PJI by Society / Consensus Statement

Musculoskeletal Infection Society (2011)

1) Sinus tract communicating with the prosthesis; or

2) A pathogen is isolated by culture from at least 2 separate tissue or fluid samples obtained from the affected prosthetic joint; or

3) Four of the following six criteria exist:
    a) Elevated serum erythrocyte sedimentation rate; serum C-reactive protein
    b) Elevated synovial leukocyte count
    c) Elevated synovial neutrophil percentage
    d) Isolation of a microorganism in one culture of periprosthetic tissue or fluid
    e) Purulence in the affected joint
    f) Greater than 5 neutrophils per high-power field in 5 high-power fields observed from histologic analysis of periprosthetic tissue at 9400 magnification

Diagnosis made if 1, 2 or 3 present

Infectious Diseases Society of America (2012)

1) A sinus tract that communicates with the prosthesis

2) Two or more intraoperative cultures or combination of preoperative aspiration and intraoperative cultures that yield the same organism (indistinguishable based on common laboratory tests including genus and species identification or common antibiogram)

3) The presence of acute inflammation on histopathologic examination of periprosthetic tissue at the time of surgical debridement or prosthesis removal as defined by the attending pathologist

4) The presence of purulence without another known etiology surrounding the prosthesis

Diagnosis made if any present

International Consensus Meeting (2013)

1) A sinus tract communicating with the joint, or

2) Two positive periprosthetic cultures with phenotypically identical organisms, or

3) Three of the following five criteria:
    a) Elevated CRP and ESR
    b) Elevated synovial fluid white blood cell (WBC) count OR ++change on leukocyte esterase test strip
    c) Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%)
    d) Positive histological analysis of periprosthetic tissue
    e) Single positive culture

Diagnosis made if 1, 2 or 3 present

Results

Total of records reviewed	603
Total of patients included	371

Diagnostic Criteria	PJI
MSIS	70 (18.8%)
IDSA	73 (19.7%)
ICM	73 (19.6%)

		MSIS	
		PJI	Aseptic Failure
IDSA	PJI	69	4
	AF	1	297

p= 0.56

		ICM	
		PJI	AF
IDSA	PJI	69	4
	AF	4	294

p= 0.9

		MSIS	
		PJI	AF
ICM	PJI	70	3
	AF	0	298

p= 0.65

- Concordant cases among the 3 diagnostic criteria combined: 363 (97.8%): 69 PJI, 294 AF
- Discordant cases among the 3 diagnostic criteria combined: 8 (2.2%)

Dante Melendez, Douglas R. Osmon, Kerryl E. Greenwood-Quaintance, Arlen D. Hanssen, Robin Patel
Presented at MSIS, Charleston, NC. August 2014

MAYO CLINIC

PJI Diagnostic Algorithm

- Sinus tract or persistent wound drainage
- Acute onset of painful prosthesis
- Chronic painful prosthesis

Orthopedic referral

- History and exam
- Plain film of prosthesis
- Sedimentation rate and CRP
- Blood cultures*

Infection suspected

No infection suspected

STOP

Arthrocentesis
- Cell count
- Differential
- Aerobic and anaerobic culture

Osmon, DR. et al. CID. 2013;56(1):e1–25
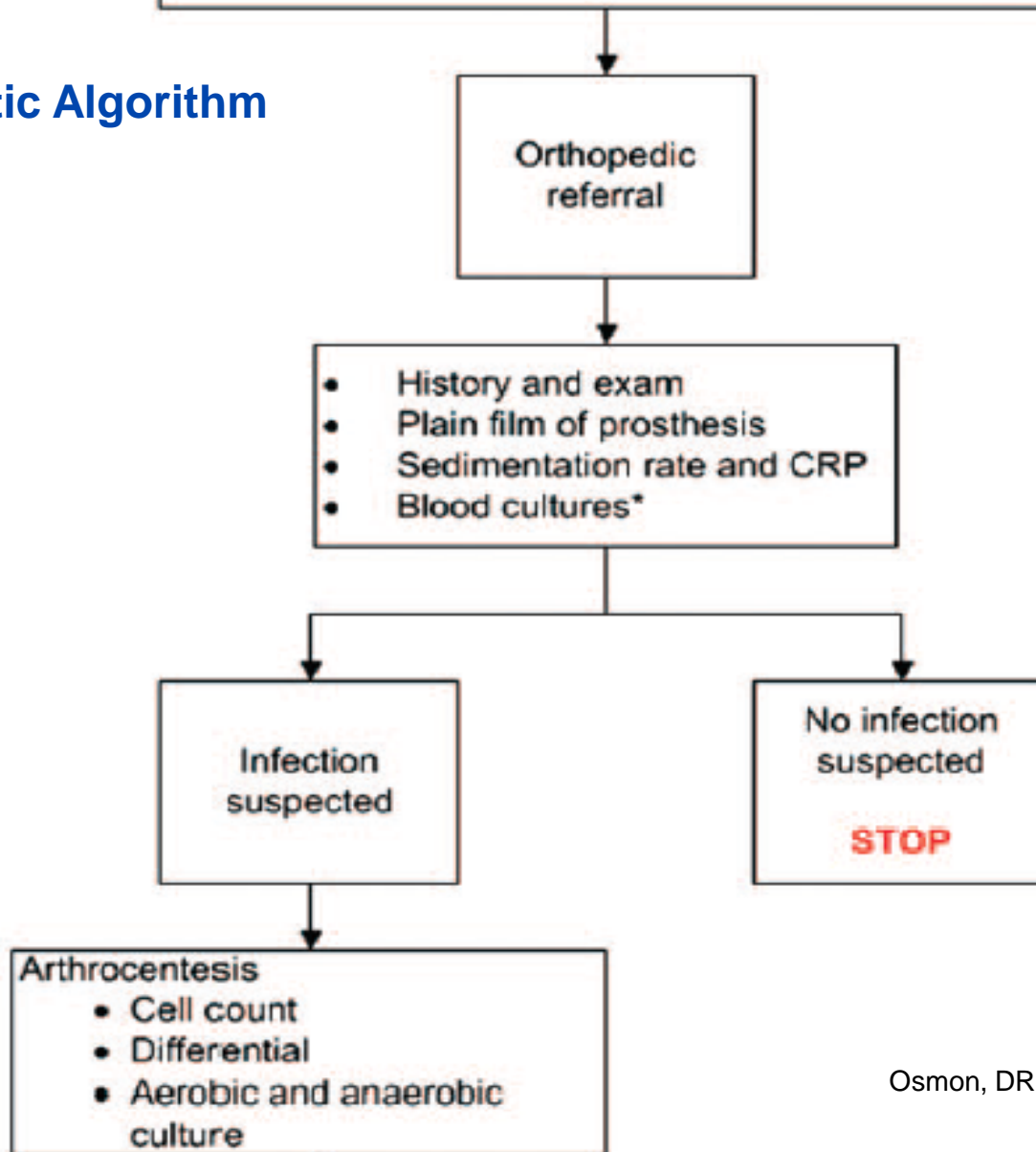
Continued PJI Diagnostic Algorithm

Infection suspected or confirmed and surgery planned

No infection suspected

STOP

- Intraoperative inspection
- Histopathology*
- 3 to 6 cultures or
- Ultrasonicate of prosthesis*

Osmon, DR. et al. CID. 2013;56(1):e1–25
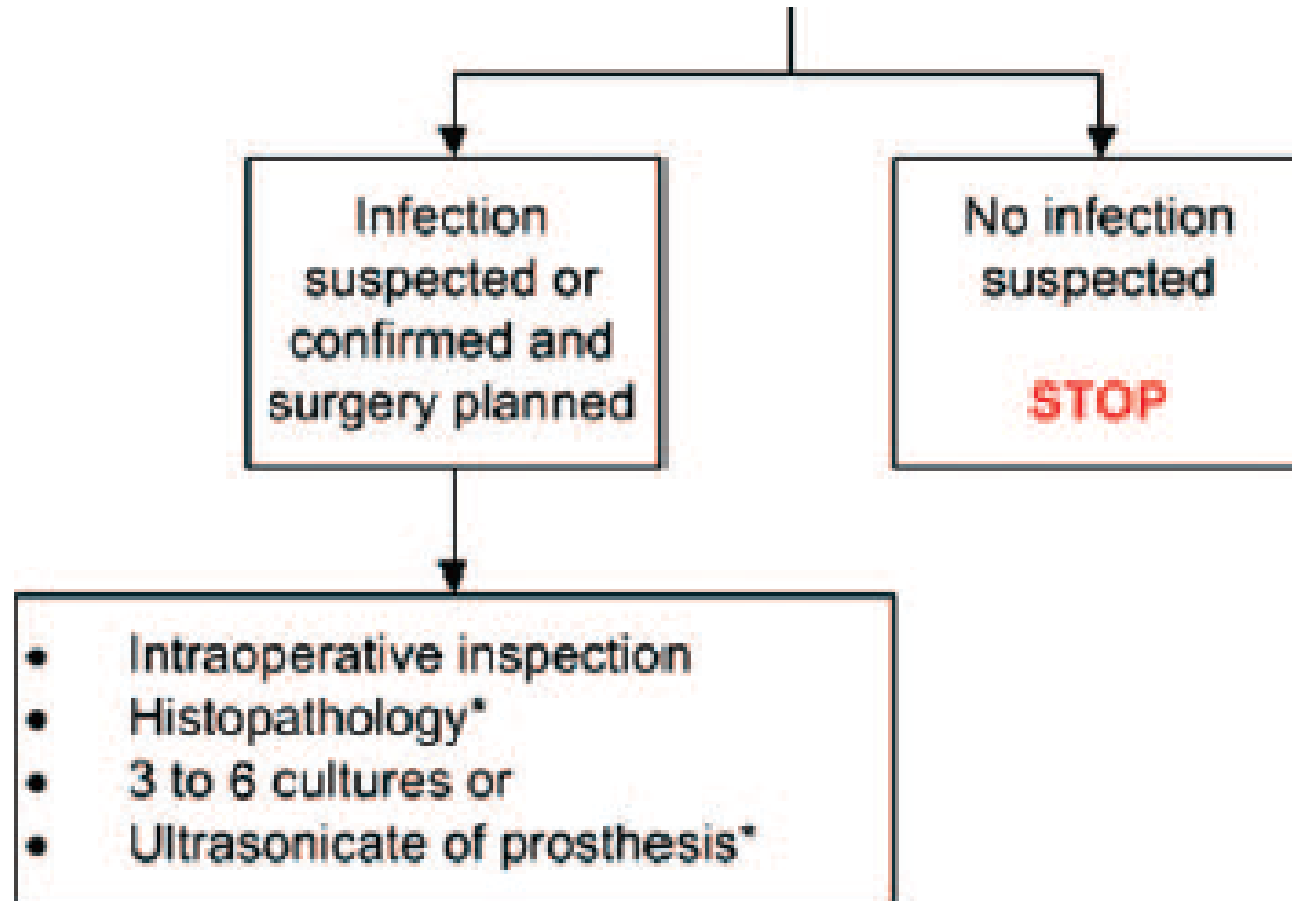
Case 1 outcome

- MDR MRSA

- Not very mobile

- Poor skin

- Co-morbidities

  - Resection without PMMA

  - ? No reimplantation

Case 2: L THA 2011

- 2013: pain, no other symptoms

- Normal white count

- Sed rate 46, CRP 20.9

- Hip aspiration
  1,980 TNC, 91% PMN
  Cultures negative
  Crystals negative

- 2nd aspirate negative

- Resected, PMMA

- All surgical cultures positive for viridans group strep.

- 2-stage exchange

Summary of PJI Diagnosis

- Multidisciplinary approach

- Sinus tracts and 2 positive cultures with same organism meets criteria for PJI

- For other patients, diagnosis is based on a combination of
  - Symptoms, signs, risk factors
  - Serum biomarkers especially sed rate, CRP, IL-6
  - Synovial fluid cell count, PMN differential, cultures

- Intraoperative ≥ 3 or more cultures

- Sonication cultures in select patients especially those with recent antibiotics

- MSIS, ICM and IDSA Guidelines - minor variations but concordant in assisting in diagnosis

Prosthetic Joint Infection Guideline Review: Management

Douglas R. Osmon MD, MPH

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Disclosure Information

- I will discuss off label use and/or investigational use of drugs and devices in my presentation.

- I have no financial relationships to disclose:

- EFB: UpToDate

Talking Points :IDSA PJI Guidelines 2013

- TJR is a highly effective intervention that significantly improves patients' quality of life

- PJI remains one of the most serious complications of TJR

- Diagnosis is difficult and no gold standard definition of PJI

- Management of PJI necessitates the need for surgery and prolonged courses of antimicrobial therapy

IDSA PJI Guidelines 2013

- An essential component of the care of patients with PJI is strong collaboration between all involved medical and surgical specialists

- It is anticipated that consideration of these guidelines may help reduce morbidity, mortality and the costs associated with PJI

- The panel realized that not all medical institutions have the necessary resources to implement all the recommendations in these guidelines

IDSA PJI Guidelines 2013

- Multidisciplinary committee from US and Europe

Elie F Berbari	Anthony R Berendt
Daniel Lew	Werner Zimmerli
James M Steckelberg	Nalini Rao
Arlen Hanssen	Walter R Wilson

- Each section begins with a specific clinical question and is followed by recommendations evidence in support of the recommendations.

- The Panel followed a process used in other IDSA guidelines which included a systematic weighting of the quality of the evidence and the grade of recommendation

IDSA PJI Guidelines 2013

Strength of Recommendation	Definition	Quality of Evidence	# of Recommendations
A	Good Evidence to support a recommendation for or against use	I II III	3 9 4
B	Moderate Evidence to support a recommendation for or against use	I II III	0 3 19
C	Poor Evidence to support a recommendation	I II III	0 0 13

Adapted : Minnassian,et al
JAC69 Suppl 1:i29-i35, 2014

I: Evidence from at least 1 randomized controlled trial
II: Evidence from >1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments.
III: Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Bleck TB. BMJ, 2000: EFB Editorial

Class 0: Things I believe

Class 0a: Things I believe despite the available data

Class 1: Randomized controlled clinical trials that agree with what I believe

Class 2: Other prospectively collected data

Class 3: Expert opinion

Class 4: Randomized controlled clinical trials that don't agree with what I believe

Class 5: What you believe that I don't

PJI: A Problem of the Elderly
2003 THA

Characteristic	Primary	Partial	Revision	All Surgical Patients
2003 est (N):	201,420	105,408	35,851	20,105,637
Age (yrs):				
>65	59%	93%	63%	36%
>85	5%	37%	8%	6%
Comorbidities				
None	25%	9%	20%	36%
>3	17%	42%	24%	23%

Zhan C. JBJS 2007:89: 526-533

Management Of PJI
Talking Points

- The goal is pain free functional joint

- Eradication of infection is often the most direct method to achieve this goal

Surgical Treatment Modalities of THA/TKA infection
Mayo Clinic- 1995-1999 (N=509)
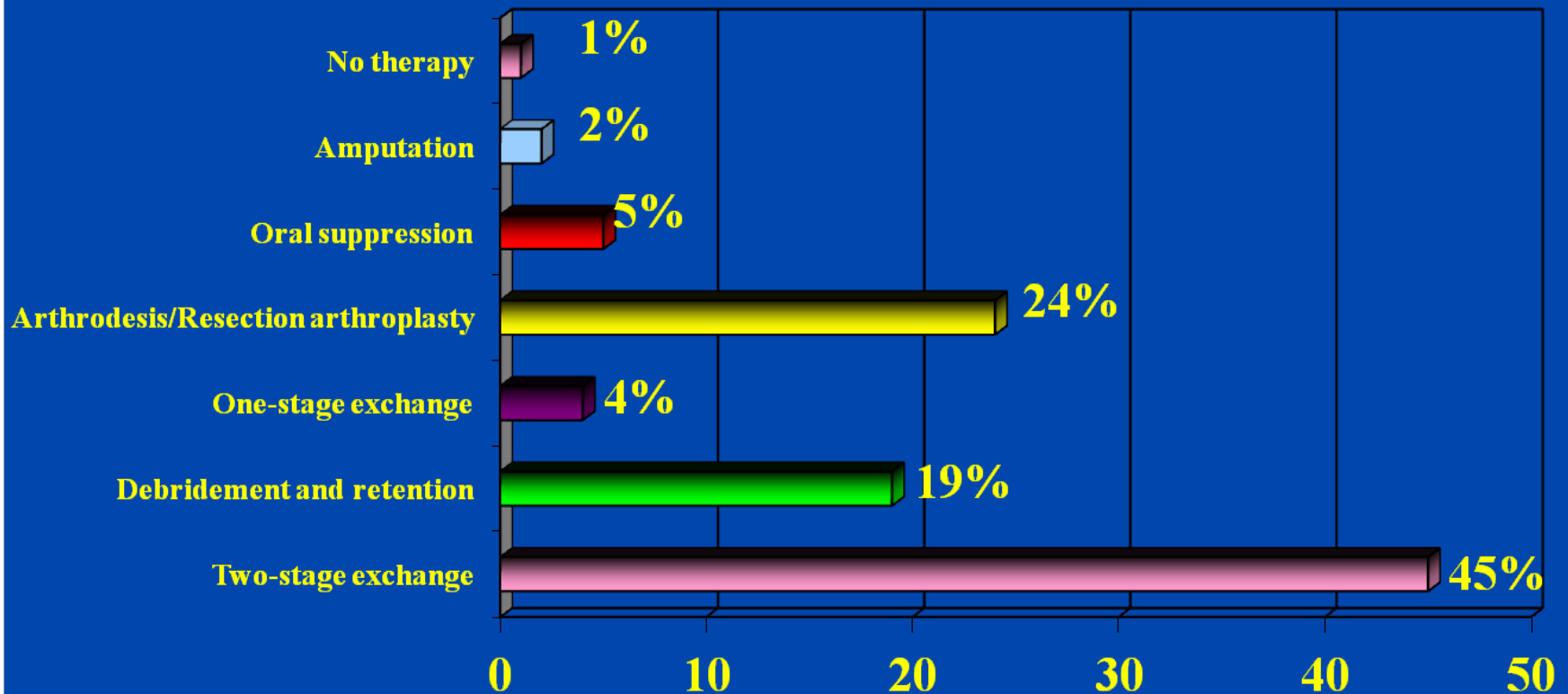
Case

A 75 year old male presents with acute pain, swelling and erythema of the right knee of 3 days duration. He had his primary R TKA performed 3 years ago and it has functioned well. There is no prior history of infection. He had right great toe paronychia treated with debridement and cephalexin 2 weeks ago. The patient's WBC 12,500, Sed rate 120, CRP 150. Synovial fluid aspiration reveals gross purulence (150,000 WBC: 95% PMN) and gram positive cocci on gram stain. Synovial fluid cultures grew MSSA. Blood cultures prior to antimicrobials are negative. X-rays reveal a well seated prosthesis.

Case (Continued)

- You recommend:
  1. Open arthrotomy or arthroscopic debridement or resection arthroplasty?
  2. 2, 4 or 6 weeks of IV antimicrobial therapy?
  3. Which one, nafcillin, cefazolin or ceftriaxone?
  4. The use of rifampin ?
  5. The use of chronic oral antimicrobial suppression?
  6. How long: "chronic oral antimicrobial suppression?

Therapy of Orthopedic Implant Infection
Debridement and retention

- Well-fixed prosthesis
- PJI $\leq$ 1 month
- *A*cute infection(< 2-3 weeks)
- Low virulence organism
- No sinus track

Debridement/
Polyethylene
Exchange

Diagnosis

4-6 weeks systemic antimicrobials

Chronic suppression
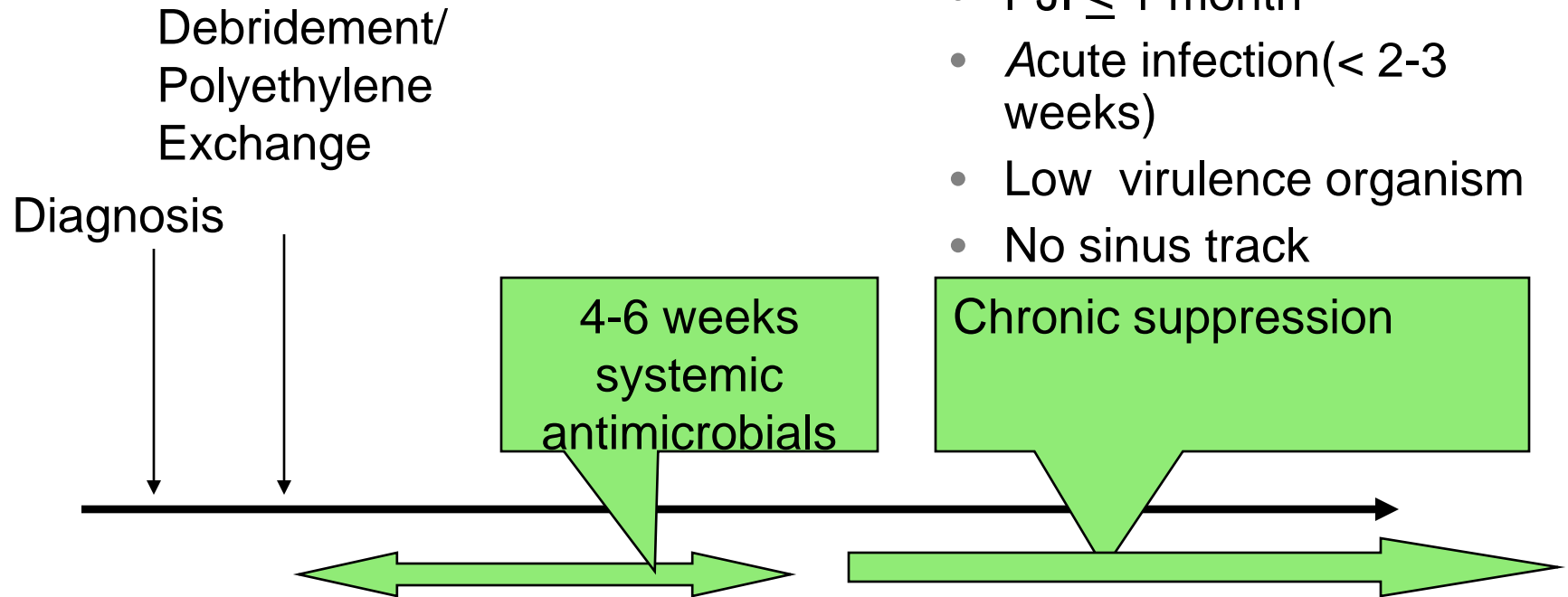
Overall Success in 99 Episodes of PJI Treated with Debridement and Retention at Mayo Clinic: 1995-1999

Kaplan-Meier Cumulative Survival Plot
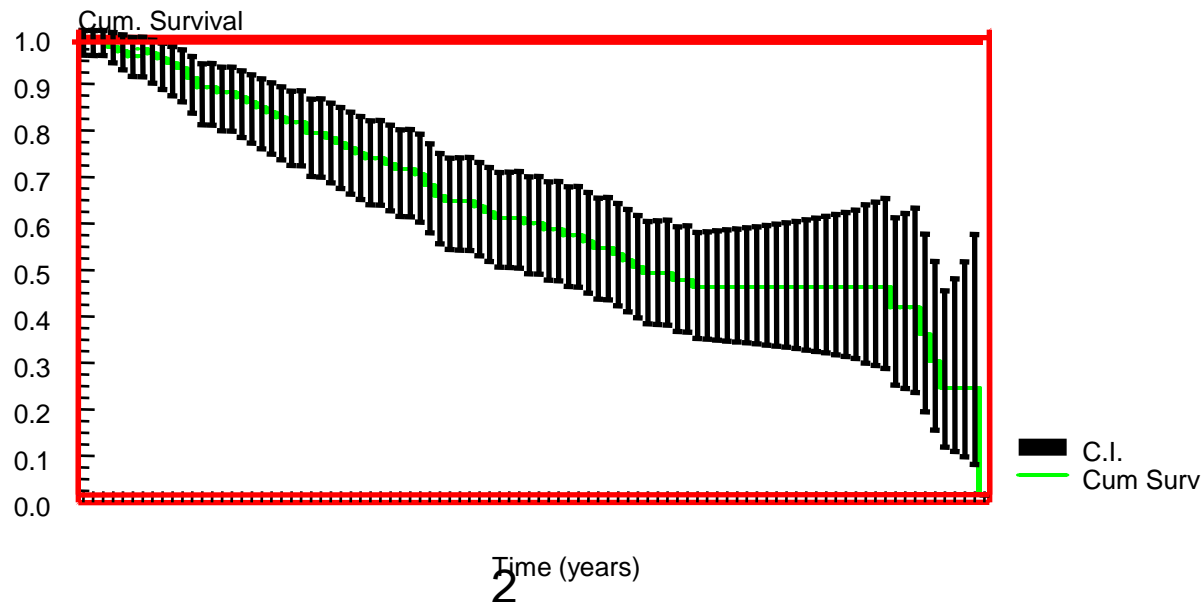
The 2-year cumulative probability of success: 60% (95%CI: 50-71%)

Marculescu, CE. Et. al. *CID 2006 Feb 15;42(4):471-8.*

Table 6. Univariate assessment of risk factors for treatment failure among patients with prosthetic joint infection treated with debridement and retention of prosthesis.

Variable	Hazard ratio (95% CI)	P
Infecting microorganism		
Staphylococcus aureus	5.14 (2.36–11.20)	<.001
Coagulase-negative staphylococci	0.43 (0.12–1.62)	.21
Streptococci	0.80 (0.30–2.12)	.65
Other[a]	1.0 (reference)	
Diabetes mellitus		
Present	1.13 (0.53–2.41)	.75
Absent	1.0 (reference)	
Sinus tract		
Present	2.85 (1.50–5.44)	.002
Absent	1.0 (reference)	
Duration of symptoms		
≥8 days	1.79 (1.04–3.09)	.04
<8 days	1.0 (reference)	
Joint age		
≥31 days	0.65 (0.25–1.65)	.36
<31 days	1.0 (reference)	
Rheumatoid arthritis		
Present	1.34 (0.42–4.34)	.61
Absent		
Joint location		
Total knee arthroplasty	1.09 (0.63–1.89)	.75
Total hip arthroplasty	1.0 (reference)	

[a] Includes infections due to gram-negative bacilli, gram-positive bacilli, enterococci, or anaerobes; culture-negative infections; polymicrobial infections; and fungal infections.

Multivariate Analysis:
1. Sinus Tract: HR: 2.84; 95% CI (1.48-5.44)
2. Duration of symptoms > 8 days HR: 1.77; 95% CI (1.02-3.07)

Marculescu, CE. Et. al. Outcome of prosthetic joint infections treated with debridement and retention of components. *Clinical Infectious Diseases 2006 Feb 15;42(4):471-8*

Antimicrobial Strategies-The Role of Rifampin

- **Randomized 33 patients**

- **Staphylococcal PJI**

- **Stable prosthesis or internal fixation device**

- **3-6 months of oral treatment with cipro plus rifampin or ciprofloxacin alone, after initial therapy with flucloxacillin or vancomycin**

- **24 were evaluated in an efficacy analysis***

  - **100% 12 patients treated rifampin-containing regimen**
  - **58% of the 12 who did not receive rifampin were cured without device removal**
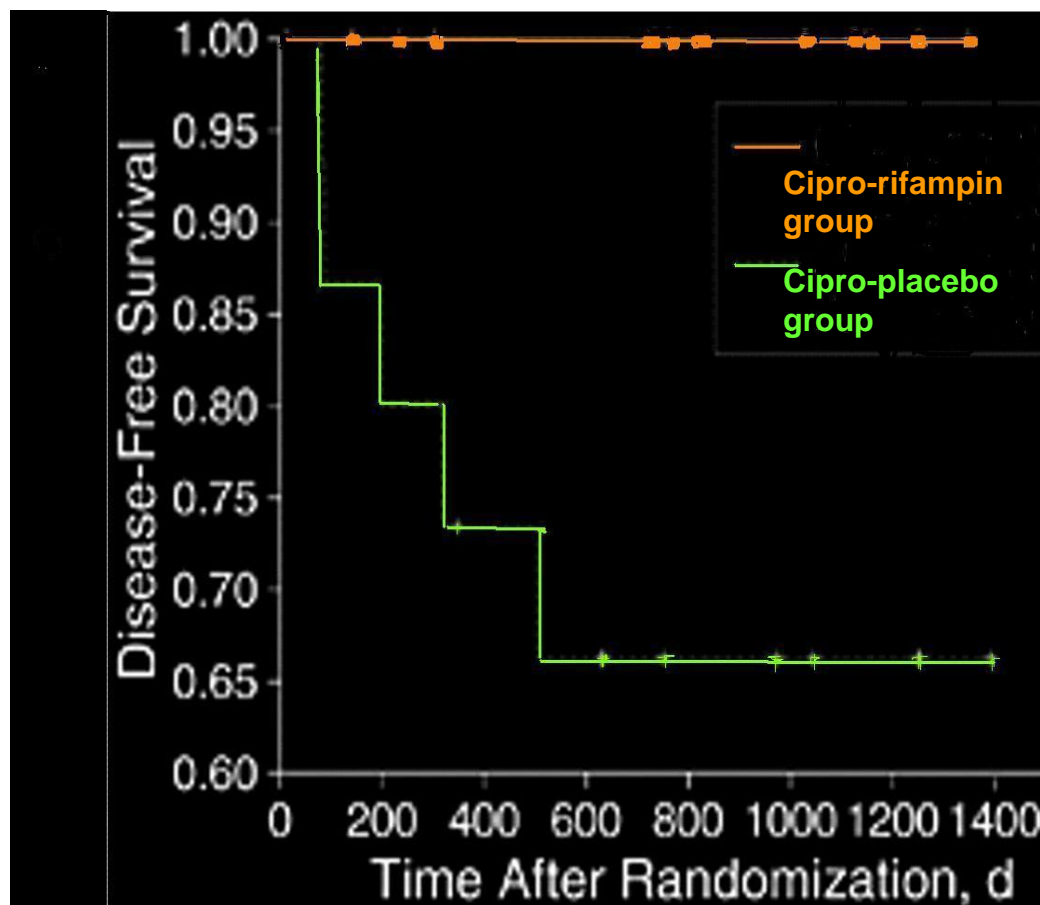
Zimmerli, W et al ; JAMA, 29(19): 1537-41, 1998

Risk Factors for Treatment Failure After DAIR (N=112)

Table 2. Multiple Cox regression model of significant factors from univariate analysis

	Hazard ratio	95% CI	P
Implant to debridement ≥90 days	1.1	0.31–3.8	0.89
Intravenous antibiotics ≥28 days	0.49	0.18–1.37	0.18
Arthroscopy versus open	4.2	1.5–12.5	0.008
S. aureus	2.9	1.0–8.4	0.050
Revised versus primary arthroplasty	3.1	1.2–8.3	0.008
Presence of co-morbidity	1.81	0.55–5.9	0.32

Goodness of fit: log likelihood $= -59.6$, $\chi^2 = 17.2$, $P = 0.0006$.

Byren et al.; J of Antimicrobial Chemotherapy. 2009;63;:1264-1271

IDSA PJI Guidelines (Chronic Suppression)

- The decision to offer chronic suppressive therapy must take into account the individual circumstances of the patient
  - including the ability to use rifampin in the initial phase of treatment
  - the potential for progressive implant loosening and loss of bone stock
  - the hazards of prolonged antibiotic therapy

- Reserved for patients who are unsuitable for, or refuse, further exchange revision, excision arthroplasty, or amputation

Can You Discontinue Chronic Antimicrobial Suppression after DAIR ? (N=112)
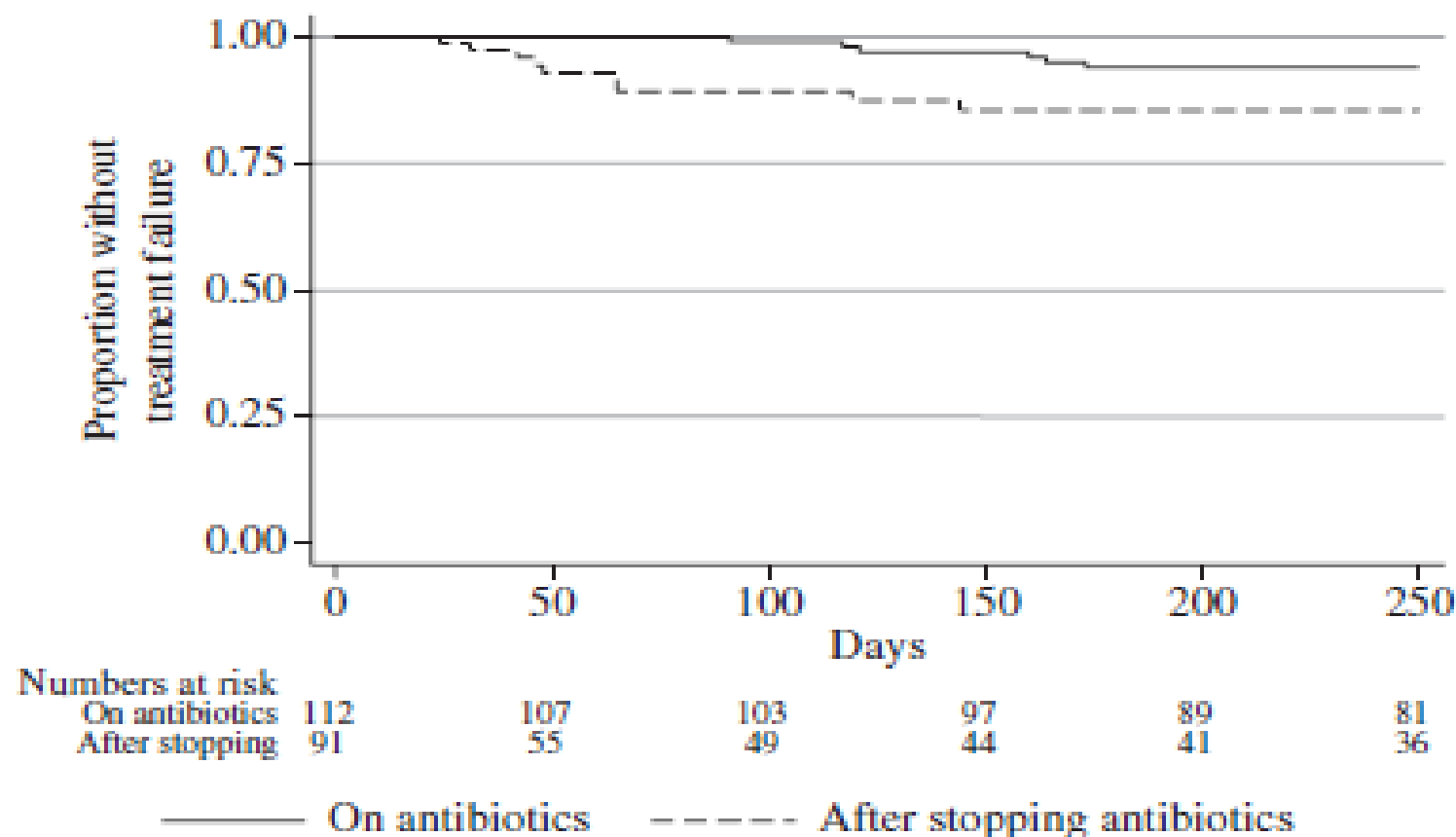
Figure 3. Kaplan–Meier plot of time to treatment failure for patients on oral antibiotics (HR=1) and patients stopping oral antibiotics (where day of stopping is day 0, HR=4.3, 95% CI 1.4–12.8, $P=0.01$).

Byren et al.; J of Antimicrobial Chemotherapy. 2009;63;:1264-1271

Debridement and Retention:
Current Medical Strategy
Mayo Clinic Rochester

- Staphylococci
  - 4-6 wks IV antimicrobial plus rifampin followed by
  - Quinolone / 1st generation cephalosporin / TMP-SMX / minocycline plus rifampin
    - 6-8 weeks THA
    - 20-22 weeks TKA

        followed by
  - Chronic oral suppression: 1st generation cephalosporin or TMP-SMX or minocycline

- Streptococci (B-hemolytic)
  - 4-6 weeks IV antimicrobial followed by
  - Chronic oral suppression with Penicillin VK/amoxicillin or 1st gen cephalosporin

Case (Continued)

- I would recommend in this case …..
  - Open arthrotomy or arthroscopic debridement?
  - 2, 4 or 6 weeks of IV antimicrobial therapy?
  - Cefazolin, ceftriaxone or nafcillin
  - The use of rifampin (yes or no)?
  - Chronic oral antimicrobial suppression?
  - (yes or no)
  - How long is "chronic oral antimicrobial suppression? 6 months, 1 year, Life long
  - Can chronic oral suppression ever be discontinued? Sometimes

Case

A 69 year old man presents with a painful right THA that was placed in 2008. It is lose on plain radiograph and there is significant bone loss. The sed rate is 45, CRP 20. Preoperative aspiration reveals 5100 cells and a PMN % of 95. The synovial fluid culture reveals an OX resistant SCN sensitive to TMP-SMX and minocycline and rifampin. The surgeon and patient want to know what you think about a one-stage exchange. The surgeon is not planning on using antibiotic loaded cement and will need to do extensive bone grafting in the acetabular region.

You recommend…..

Case (Con't)

A. A two-stage exchange

B. A one stage exchange

C. Debridement and retention

D. Chronic antimicrobial suppression

E. Another ID opinion

Management
Reimplantation-Controversies

- Direct Exchange vs. Staged Reimplantation
    - Time to reimplantation in staged procedures

- The role of antibiotic impregnated cement at time of reimplantation

- The need and type of antibiotic impregnated PMMA spacers in two-stage reimplantation

- Optimal type and duration of intravenous and oral antimicrobials

- Outcome of reinfection following reimplantation

IDSA Guidelines
1-Stage Exchange

- A 1-stage exchange associated with a success rate of 80%–90% in patients with THA infecttion

- Most series use antibiotic impregnated cement to fix the new prosthesis

- There are much fewer data for the use of this procedure for prosthetic joints other than a THA or without antibiotic impregnated cement and with bone graft

- There is more literature on the utilization of this procedure from European than US institutions for THA infection

IDSA Guidelines
1-Stage Exchange
Medical Management: Staphylococcal PJI

- 2 to 6 weeks of IV antimicrobial therapy+ rifampin 300–450 mg orally BID followed by rifampin plus a companion oral drug for a total of 3 months is recommended (CIII)
- Indefinite chronic oral antimicrobial suppression may follow the above regimen
- The recommendation regarding using suppressive therapy after rifampin treatment was not unanimous

Case (Con't)

A. A two-stage exchange

B. A one stage exchange

C. Debridement and retention
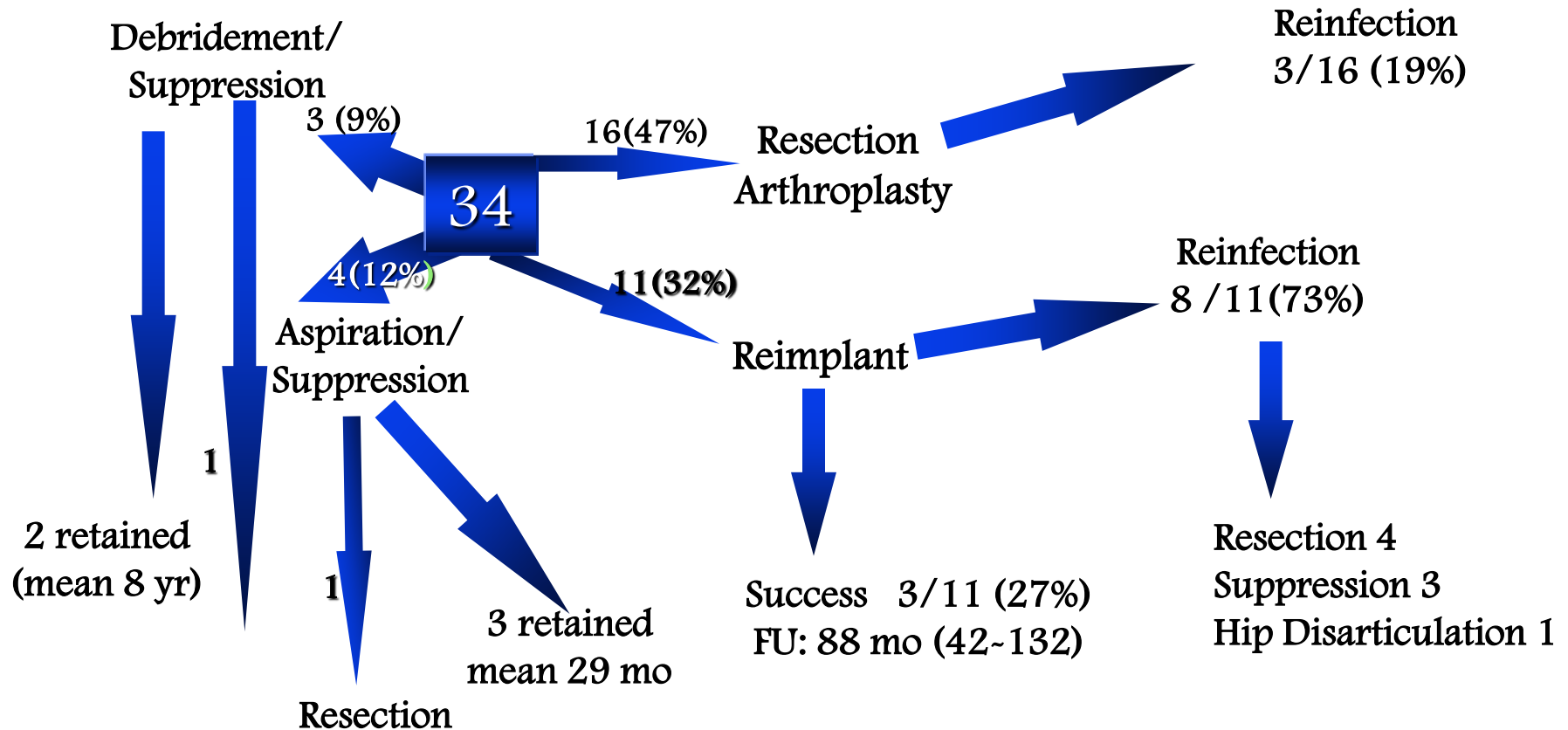
D. Chronic antimicrobial suppression

Management
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S. aureus Prosthetic Joint Infection Treated with Prosthesis Removal and Delayed Reimplantation Arthroplasty
Time to Reimplantation

- *38 S. aureus* PJI (22 THA and 16 TKA) 1980-1991

- Strict case definition

- Median follow-up of 7.4 years (0.9-16.4)

- Definite treatment failure occurred in 1/38 (2.6%) 1.4 years following reimplantation arthroplasty

Brandt et al.; Mayo Clin Proc. 1999;74:553-558.

S. aureus Prosthetic Joint Infection Treated with Prosthesis Removal and Delayed Reimplantation Arthroplasty
Time to Reimplantation: Median(Range)

THA: 222 days (36-4436)
TKA: 32 days (8-494)

Patients No. (y-axis, 0–20)

- 0-90: 42.1%
- 91-180: 18.4%
- 181-270: 13.2%
- 271-365: 7.9%
- >365: 18.4%

Time from prosthesis removal to reimplantation arthroplasty (days)
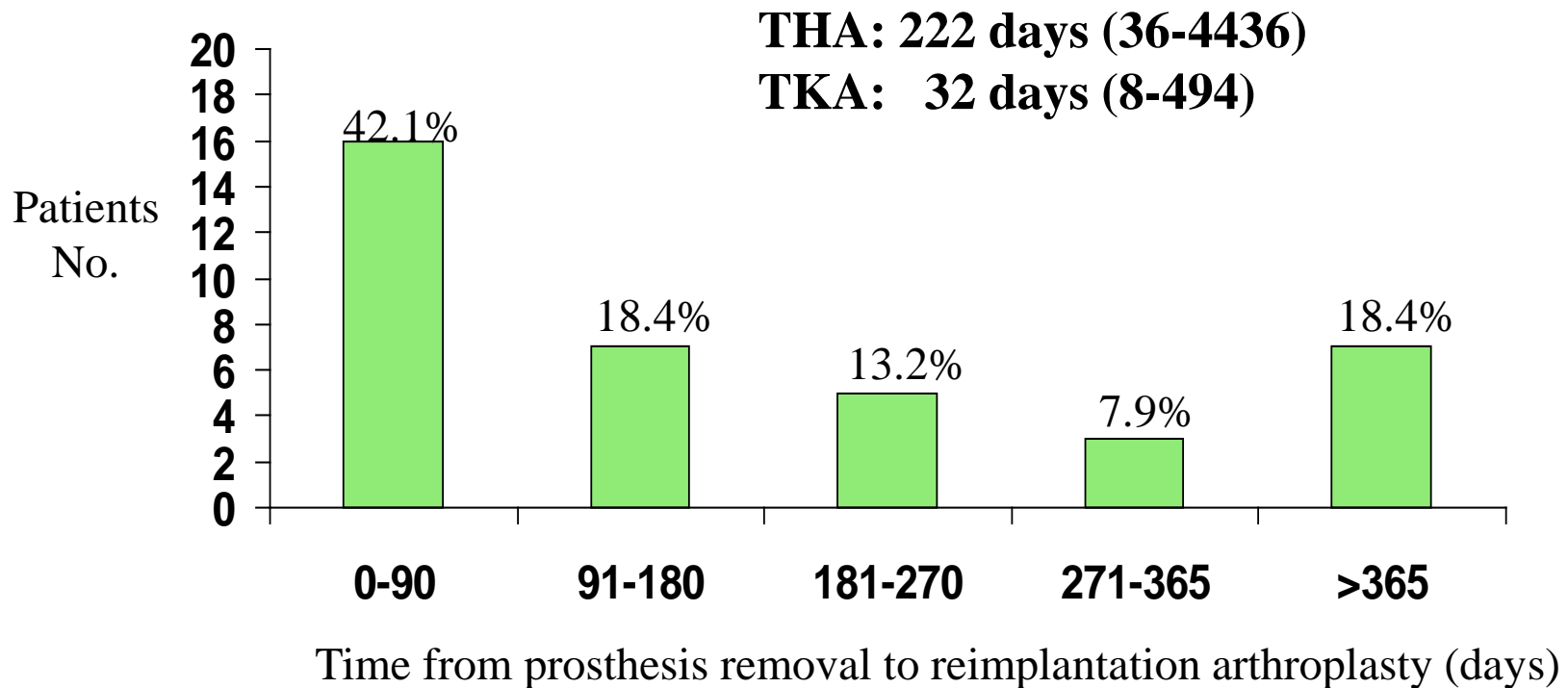
Brandt et al.; Mayo Clin Proc. 1999;74:553-558.

Current Delay Prior to Reimplantation Mayo Clinic Rochester

- 6-8 weeks delay for TKA reimplantation
  - Articulating spacer may increase interval

- 3 month delay for THA reimplantation

Management
Reimplantation-Controversies

- Direct Exchange vs. Staged Reimplantation
  - Time to reimplantation in staged procedures

- The role of antibiotic impregnated cement at the time of reimplantation

- The need and type of antibiotic impregnated PMMA spacers in two-stage reimplantation

- Optimal type and duration of intravenous and oral antimicrobials

- Outcome of reinfection following reimplantation

Antibiotic Loaded Cement and PJI Prevention: Fixation Cement

- Low-Dose :0.5-1.0 gram of antibiotic per 40 gram cement

- 6 FDA approved products:Approved for use in second stage of two-stage reconstruction for PJI

- Antibiotics include gentamicin or tobramycin

- Not vancomycin, cefuroxime unless used as clinician directed application

Jiranek et al. JBJS; 2006; 2487-2500

Survival Free of TKA Infection in 89 PJI Treated with Staged Reimplantation at the Mayo Clinic Between 1980-1990 Categorized by the Use of AbPMMA at the Time of Reimplantation
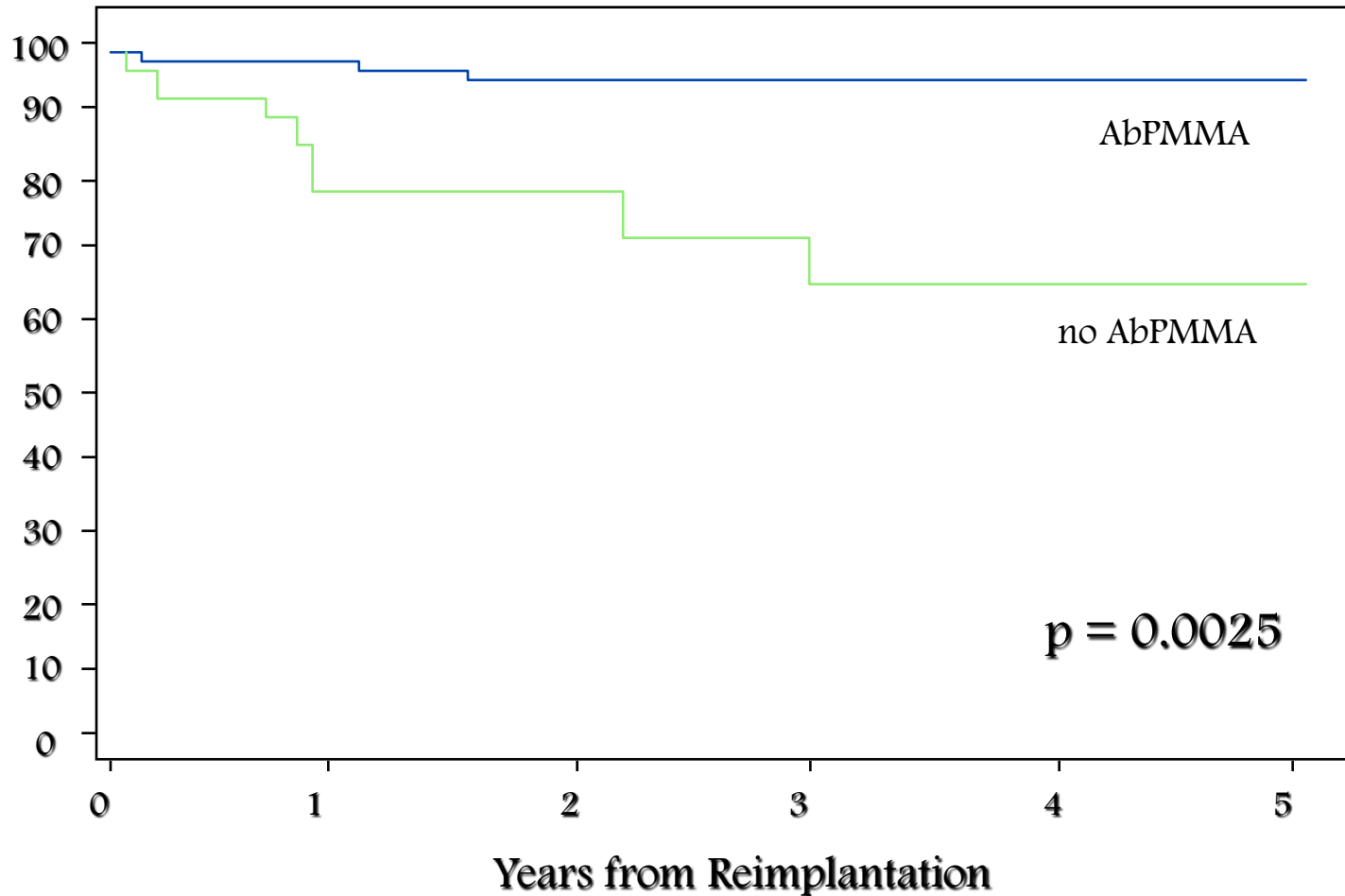
Hanssen et al. Clin Orthop. 1994;309:44-55.

Efficacy of ABLC in Preventing PJI Following Total Hip Replacement
Parvizi et al. Acta Orthopaedica 2008;79 (3) 335-341
2.3% vs. 1.2%

Citation	Lower	Upper	n (total)	P-value	Antibiotic	Non-antibiotic	Antibiotic cement	Non-antibiotic c.	Effect
Espehaug (1997)	0.158	0.634	10905	0.001	11 / 6043	28 / 4862			0.316
Josefsson (1990)	0.178	1.038	1409	0.053	7 / 711	16 / 698			0.430
Josefsson (1993)	0.290	1.564	1115	0.36	9 / 565	13 / 550			0.674
Lieberman (1994)	0.168	16.908	35	0.65	2 / 19	1 / 16			1.684
Lynch (1987)	0.020	1.779	303	0.10	1 / 194	3 / 109			0.187
Lynch (1987)	0.382	2.501	1075	0.96	7 / 424	11 / 651			0.977
McQueen (1987)	0.047	5.567	295	0.57	1 / 146	2 / 149			0.510
Random combined	0.341	0.751	15137	0.001	38 / 8102	74 / 7035			0.506

Weighted mean effect

Management
Antibiotic Impregnated Spacers

- Now considered to be standard of care in US for two-stage exchange

- Clinician directed applications and commercially available applications exist (i.e. Prostalac)

- Articulating and non-articulating spacers are utilized

- Aminoglycosides and/or vancomycin most commonly utilized antibiotics

- Other antibiotics elute from PMMA in vitro but much less if any clinical data on efficacy and safety

- Doses utilized are not uniform across institutions

Qui C, 2007: JBJS; 89-871

Two-stage Re-implantation for ORSA or OR-SCN TKA Infection (N=37)

- ORSA (25) or OR-SCN (12)

- Median F/U: 51 months

- Treatment
  - 35/37 treated with antibiotic loaded spacer
  - 36/37 treated with IV Vancomycin, median 6 weeks
  - Only 6 received rifampin

- Treatment failure
  - 4/37 relapses (1 ORSA, 3 OR-SCN)
  - 5/37 re-infections with different organism
  - 28/37 overall success (79%)

Mittal et al. 2007; JBJS;89:1227-31

Management
Reimplantation-Controversies

- Direct Exchange vs. Staged Reimplantation
  - Time to reimplantation in staged procedures

- The role of antibiotic impregnated cement

- The need for antibiotic impregnated PMMA beads and spacers in two-stage reimplantation

- Optimal type and duration of intravenous and oral antimicrobials

- Outcome of reinfection following reimplantation

Duration of Intravenous Antimicrobial Therapy

- No standard: from prior retrospective data

- Most investigators have reported outcome data on 6 weeks of intravenous antibiotic therapy

  Insall et al. J Bone J Surg. 65A:1087-1098, 1983.

  Lieberman et al. Clin Orthop. 301:205-212, 1994

  Tsukayama et al. J Bone J Surg. 78A:512-523, 1996.

  Segawa H., et al. J. Bone J Surg. 81(10):1434-45, 1999

S. aureus Prosthetic Joint Infection Treated with Prosthesis Removal and Delayed Reimplantation Arthroplasty
Duration of intravenous antibiotic therapy

Median duration: 29 days (9-63)
B-lactams = 74%

Duration of effective intravenous antimicrobial therapy (days)
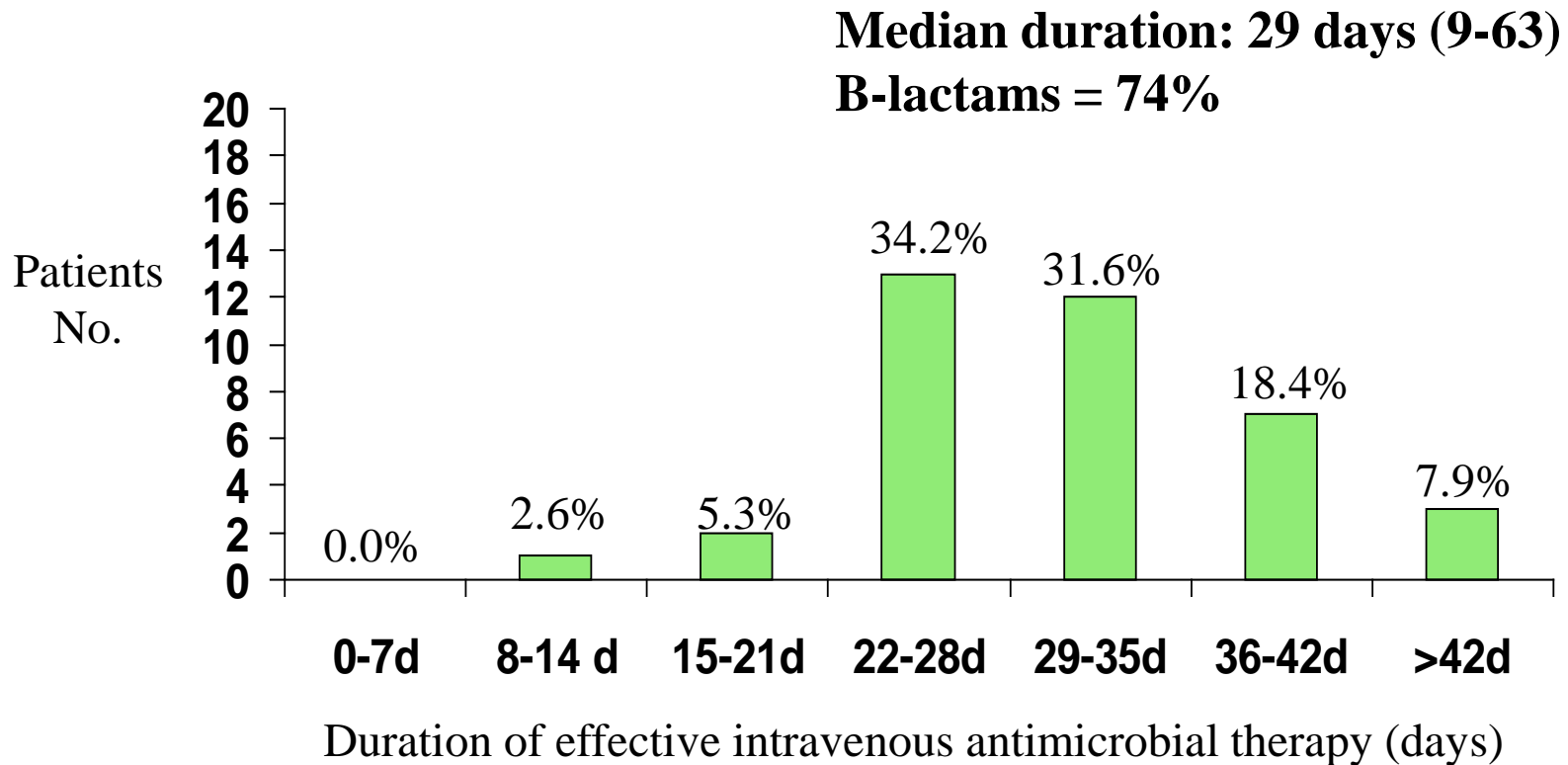
Brandt et al.; Mayo Clin Proc. 1999;74:553-558.

Adjusted Treatment Free Failure in 208 episodes of PJI Treated with Two Stage Exchange: Impact of duration of therapy Mayo Clinic 1995-1999
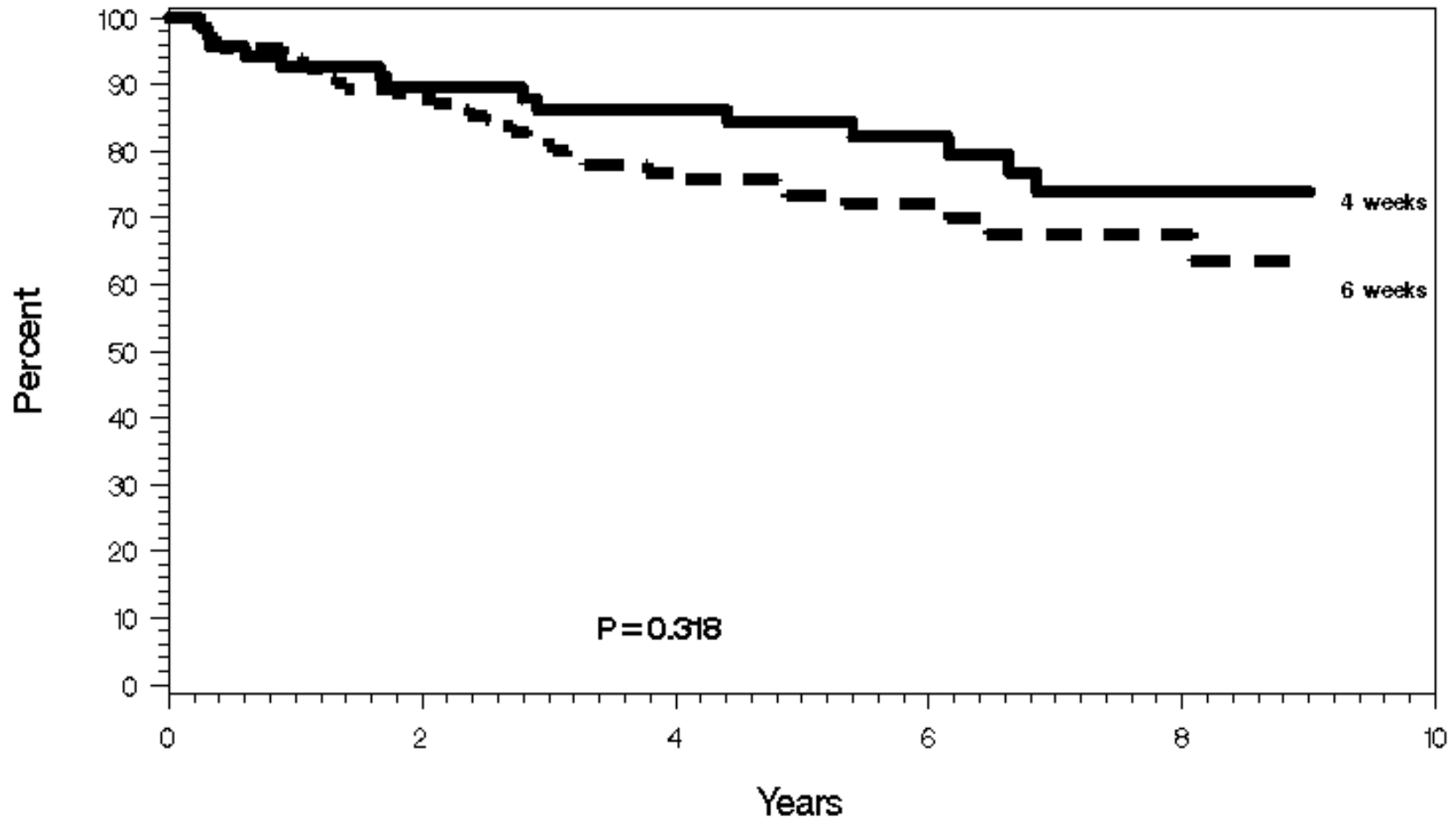
Management
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- The role of antibiotic impregnated cement at reimplantation

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- Outcome of reinfection following reimplantation

Final Outcome Following Reinfection After Staged Reimplantation for THA Infection at the Mayo Clinic 1976-1992

34

Debridement/ Suppression

3 (9%)

16(47%) Resection Arthroplasty

Reinfection 3/16 (19%)

4(12%)

11(32%)

Aspiration/ Suppression

Reimplant

Reinfection 8 / 11(73%)

1

2 retained (mean 8 yr)

1

Resection

3 retained mean 29 mo

Success   3/11 (27%)
FU: 88 mo (42~132)

Resection 4
Suppression 3
Hip Disarticulation 1

Functional Prosthesis: 11/34 (32%)

Pagnano et al. Clin Orthop. 1997;338:192-204.

Amputation for TKA Infection and Medical Therapy. The role of Residual Intramedullary Osteomyelitis

Special Thanks

- Douglas R Osmon, MD, MPH

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- Camelia Marculescu, MD

- Odette El Helou, MD

- Robin Patel, MD

- Jay Mandrekar, PhD

- Scott W Harmsen, MS

- Mary Duffy, RN

- Andre Trampuz, MD

Declarations of interest and context

- No commercial relationships
- Medical Director of an acute/specialist hospital (NHS, UK)
- Co-chair/co-author of a number of clinical guidelines on diabetic foot infection
- Consultant in Infectious Diseases with >15 years involvement in a multidisciplinary unit treating all manifestations of bone and joint infection

Oxford Bone Infection Unit, Nuffield Orthopaedic Centre, OUH

- 26 beds
- Multidisciplinary team; ID, orthopaedics, plastic surgery, OPAT, MSK imaging and pathology
- All manifestations of bone and joint infection

Oxford University Hospitals **NHS**

NHS Trust

Overview of presentation

- Introduction: why and what?

- Pathogenesis and pathophysiology

- Management, and guidelines

- Beyond guidelines….

- Conclusions

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Introduction: why

- A global public health problem

- Diabetic foot problems account for the majority of hospital bed days used by patients with diabetes

- A major cause of non-traumatic lower limb amputation, and infection a major proximate event

- In older patients, major amputation has significant impacts on the ability to maintain independence
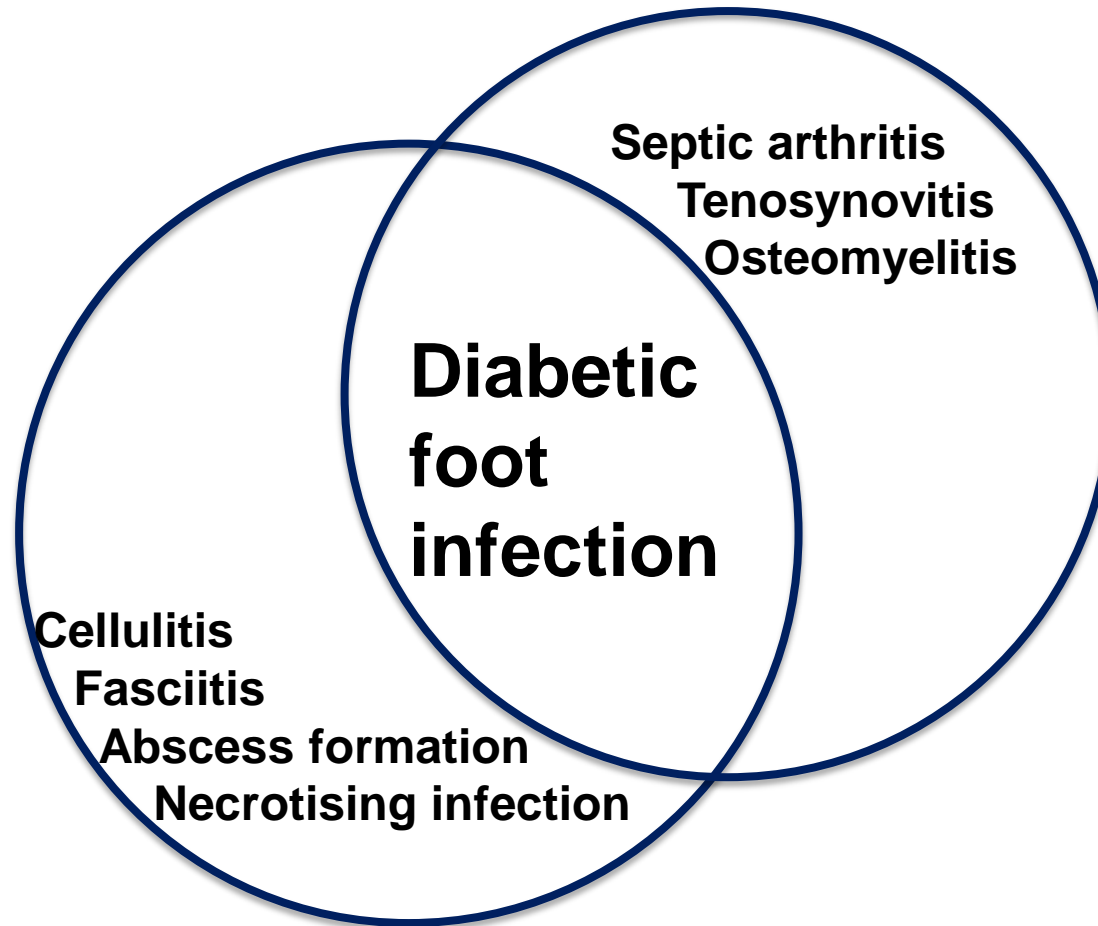
Introduction: why?

- AND:

  - Interface between SSSI and MSK infection
  - Complex biology; host/pathogen/wound/biomechanics
  - (Simple)-Complex management; multiple inputs for optimal outcome
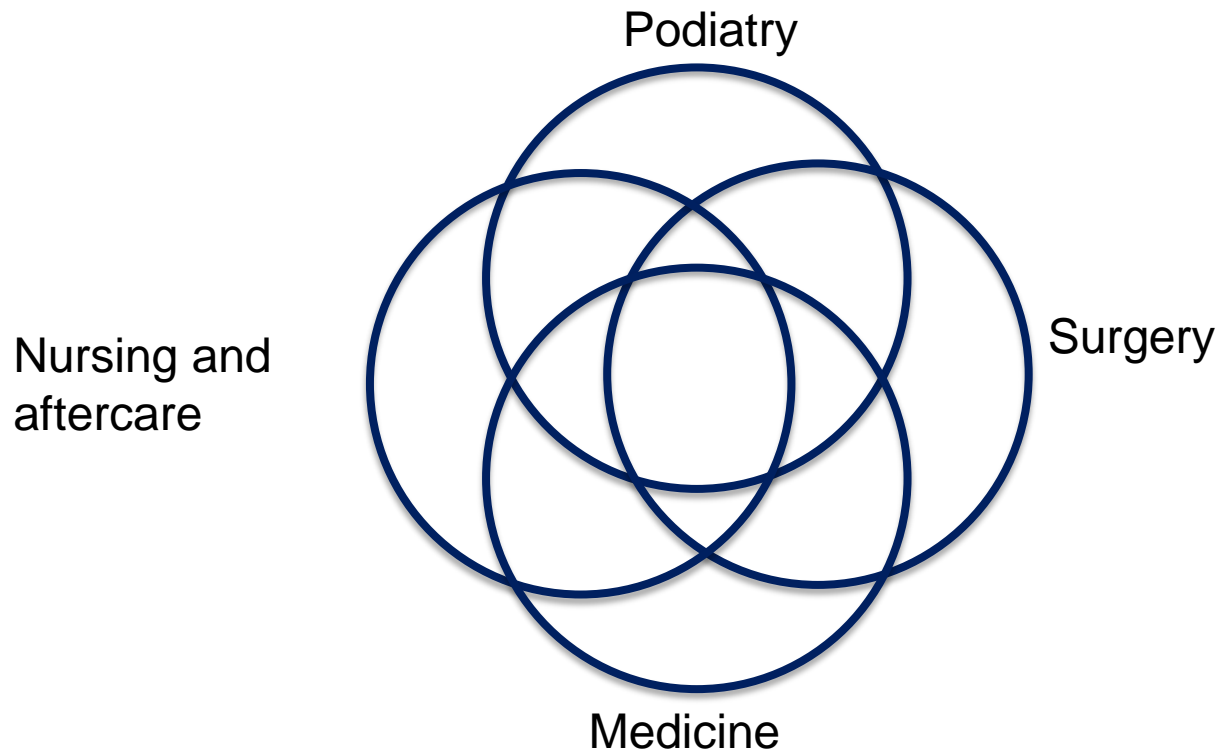
Pathogenesis: diabetic foot ulceration
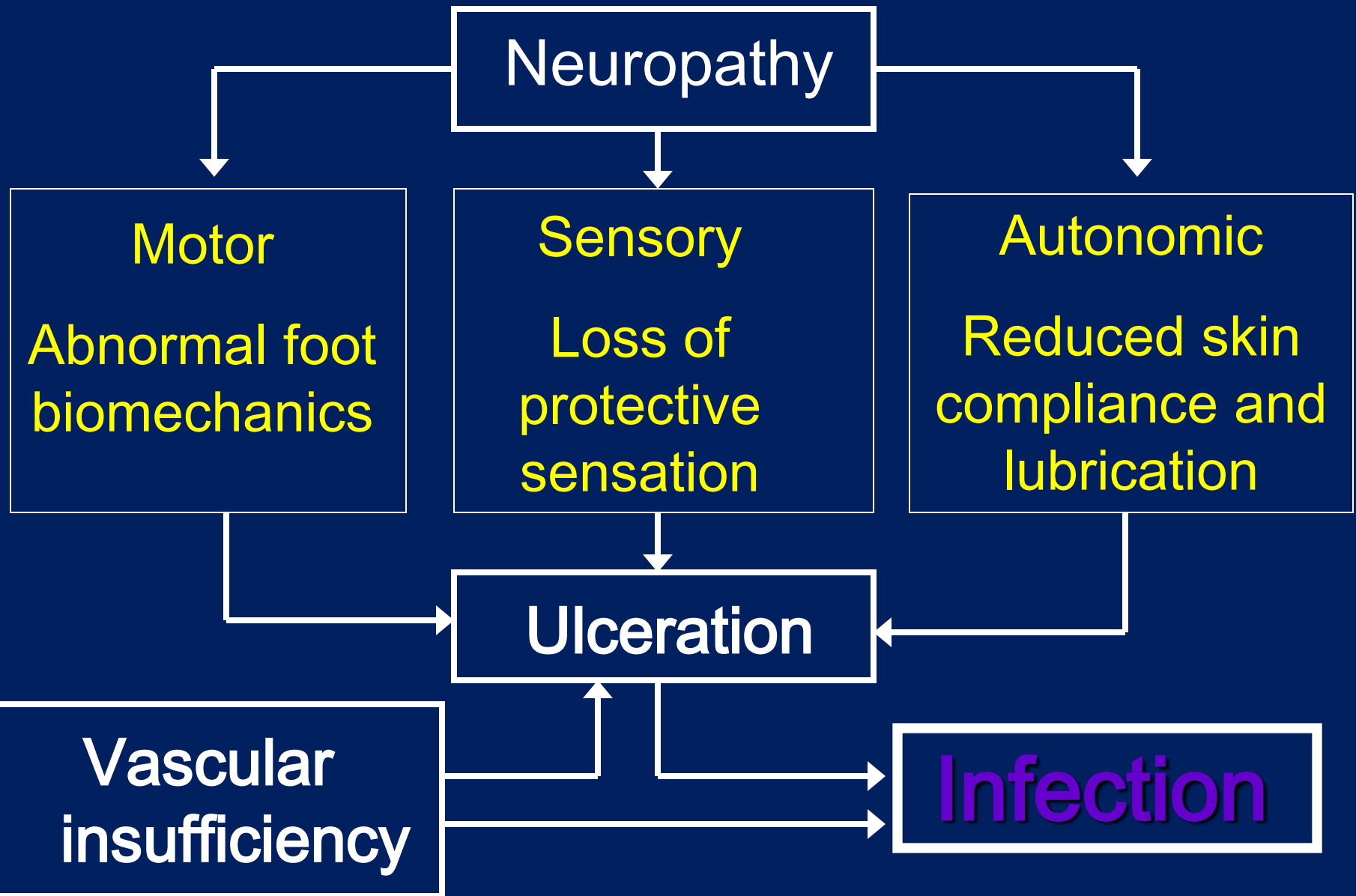
Pathogenesis

- Soft tissue loss leads to cortical death & infection
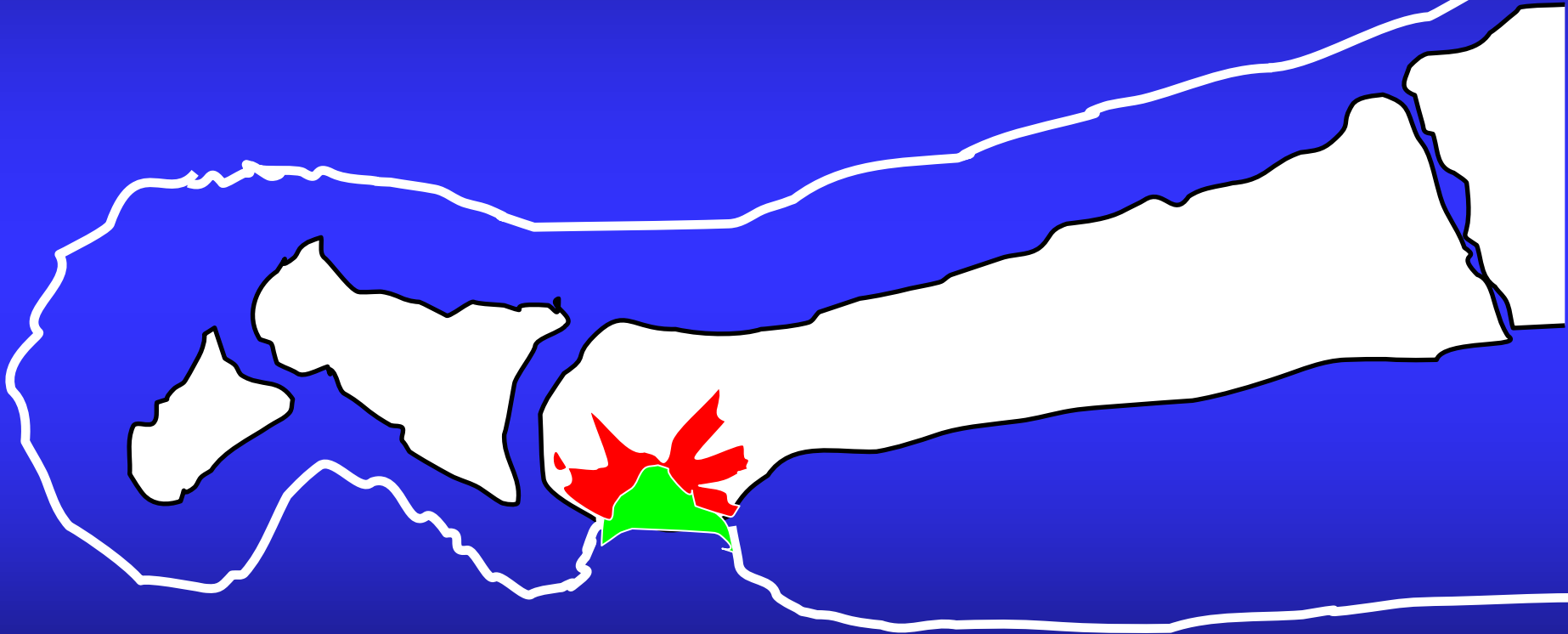
- *Staph. aureus* is the dominant pathogen

Pathogenesis

- Ulceration – colonisation – invasion (infection)
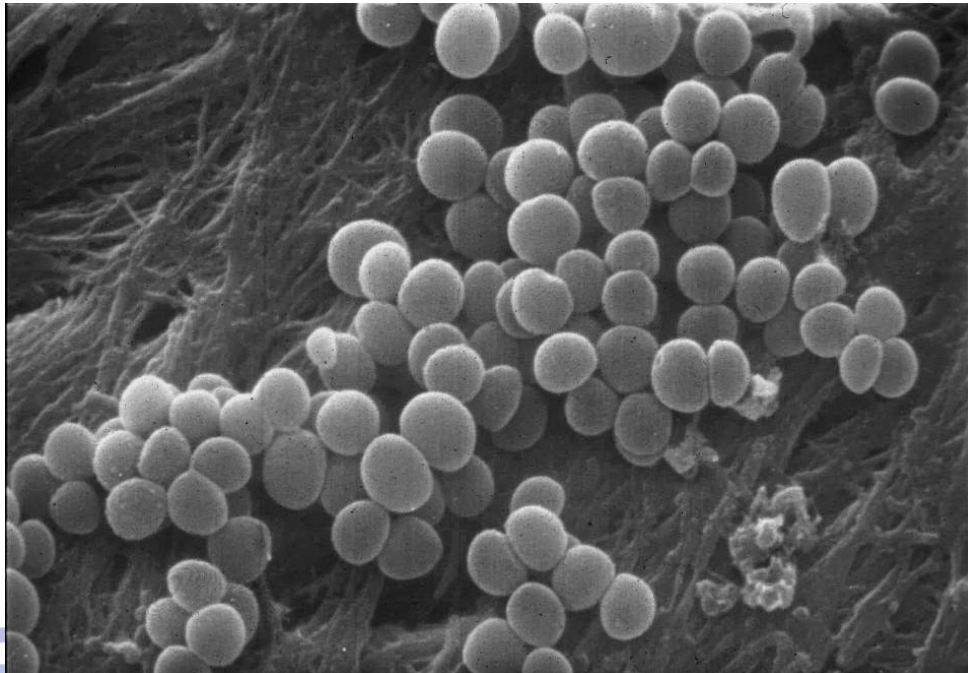
Progression

- Intramedullary spread of infection leads to more bone death
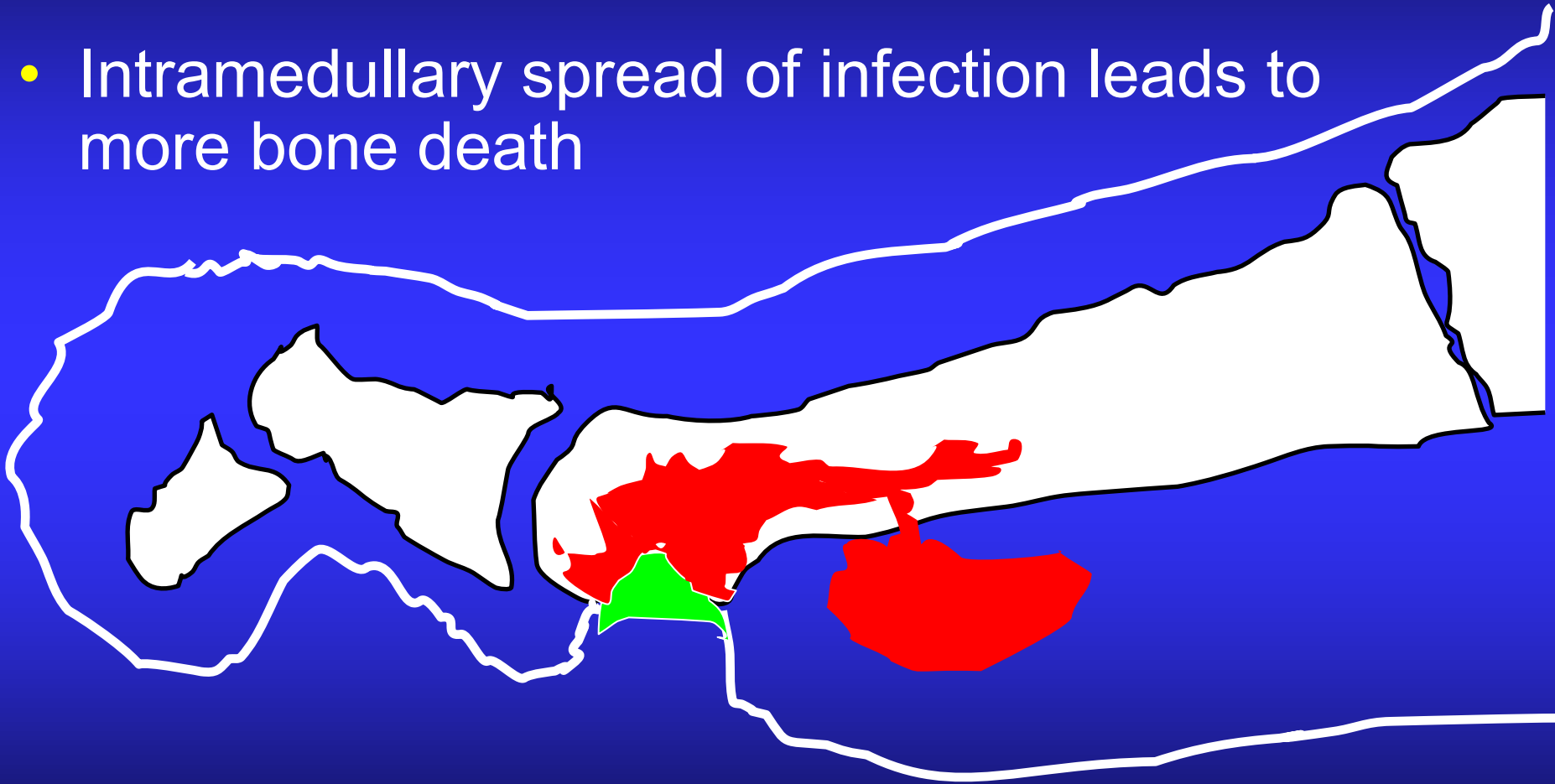
- Dead bone permits infection to persist

Pathophysiology of Contiguous and Hematogenous Osteomyelitis

HEMATOGENOUS

Initial Seeding to Bone Marrow

Extension Through Cortex Forms Subperiosteal Abscess

Periosteal Reaction, Involucrum, Cloaca, Draining Sinus

CONTIGUOUS FOCUS

Exposed Bone in Ulcer, Extensive Bone Involvement

Extension Into Bone As Soft Tissue Is Lost

Initial Contiguous Infection

ACUTE

TIME

ACUTE

TIME

HEMATOGENOUS
Bone Infection Early
Soft Tissue Involvement Late

Infected and Dead Bone
Soft Tissue Loss

CONTIGUOUS FOCUS
Bone Infection Late
Soft Tissues Involved Early

CHRONIC

Management, and guidelines

- What do you do?

Oxford University Hospitals **NHS**
NHS Trust

Introduction Pathogenesis Management Guidelines Beyond guidelines Conclusions

Guidelines

- Several…..

- IDSA 2004, updated 2012

- IWGDF via International Consensus on the Diabetic Foot (2004; 2008; 2012; new guidance May 2015)

- NICE in UK (CG 119 diabetic foot problems in hospital inpatients 2011, revised version to be published August 2015)

- Globally, various other country-specific guidelines

Case 1

You see this foot lesion in a 64 year man who has had diabetes for 15 years:

- On a home visit
- In your practice/surgery/office/clinic
- In the Emergency Department/Room
- On the medical take when admitted for an acute coronary syndrome
- On an ID consult

You are the first healthcare worker to see this

Is this lesion infected or not?

A. No

B. Yes

C. Unable to say

D. Refuse to say!

1. In which diabetic patients with a foot wound should I suspect infection, and how should I classify it?

- Diagnose infection clinically, suspected on the basis of cardinal signs

- Also suspect if chronic wound behaves surprisingly; odour, granulation tissue, drainage

- Classify using the IDSA/PEDIS scheme

How and why to assess severity?

- Dictates antibiotic choice

- Dictates pace and location of management

- Dictates urgency of involvement of others in the team

- Provides prognostic information

- Provides basis for audit and benchmarking

- Need a scheme……

Classification of DFI

A. I have not heard of the IDSA classification scheme for DFI

B. I have heard of it but am not familiar with it

C. I am familiar with it but don't like/want/need to use it/sprit is willing but.....

D. I use the scheme for any of research/clinical care/handover of cases to colleagues/assessment of outcomes

Clinical Classification

Clinical Manifestations of Infection   **Severity**   **PEDIS**

Wound w/o purulence or any mnfstns of inflammation

≥2 mnfstns inflammation (purulence or erythema, pain, tenderness, warmth or induration), but any cellulitis/erythema extends ≤2 cm around ulcer & infection limited to skin/superficial subQ tissues. No local complications or systemic illness

Infection in patient who is systemically well & metabolically stable but has ≥1 of cellulitis extending >2 cm; lymphangitis; spread beneath fascia; deep tissue abscess; gangrene; muscle, tendon, joint or bone involved

Infection in patient with systemic toxicity or metabolic instability (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, hyperglycemia, azotemia)

Validation of IDSA classification
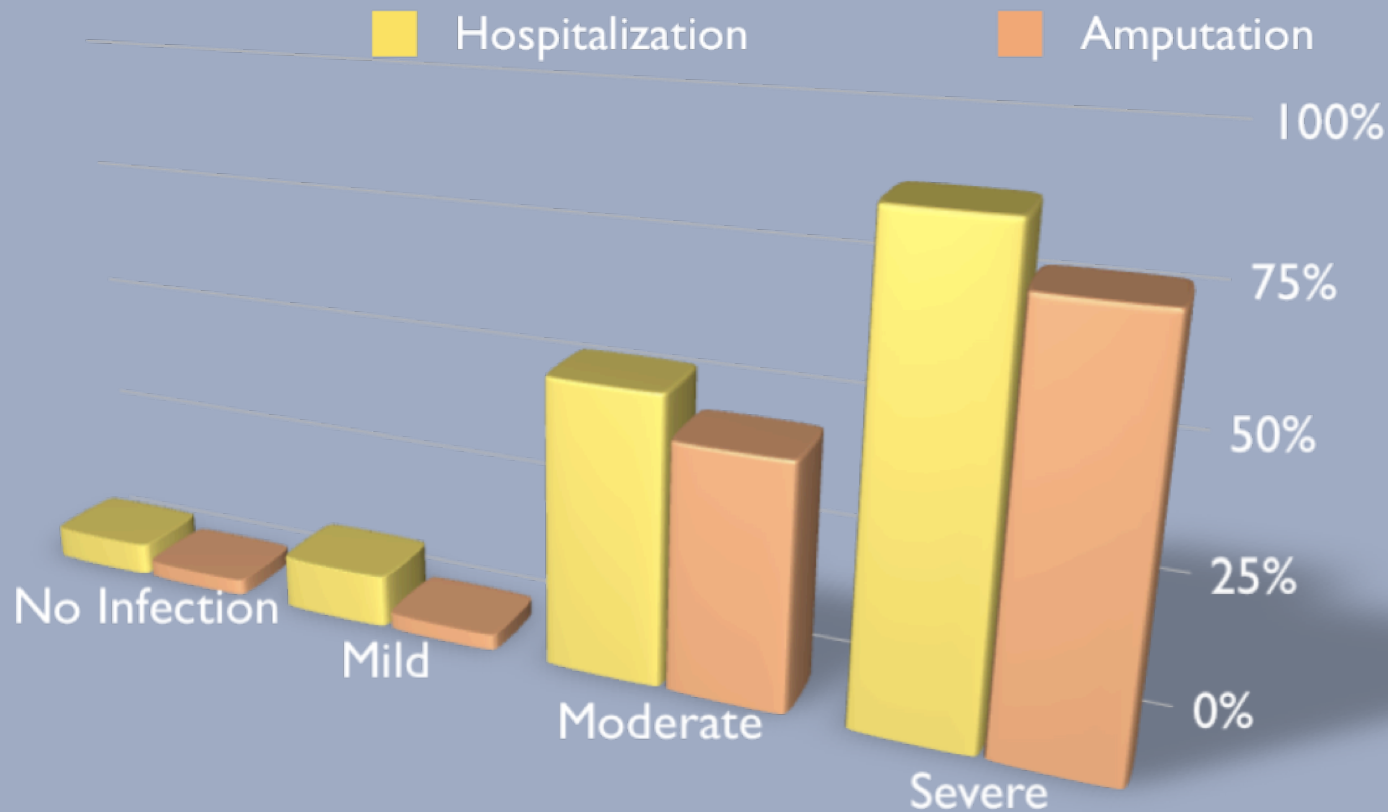
Lavery, Armstrong, et al, Clin Infect Dis, 2007

Slide courtesy of Dr W. Joseph

Slide courtesy of Dr W. Joseph

Slide courtesy of Dr W. Joseph

2. How should I assess a diabetic patient presenting with a foot infection?

- Treat the patient….

- ….attached to the leg…..

- ….attached to the foot….

- ….which has an infection….

- …usually as a result of a chronic wound

Standard ulcer care

- Evaluate for infection
- Debride ulcer, remove callosities
- Check for sensation (monofilament)
- Check for circulation (pulses, Dopplers)
- Probe to bone?
- Adequate offloading
- Antibiotics if infected
- Secondary prevention of ulcer and of major diabetes related events

PEDIS

Perfusion

Extent/size

Depth/tissue loss

Infection

Sensation

Schaper N. *Diab Med* 2004

Introduction Pathogenesis Management Guidelines Beyond guidelines Conclusions

Evaluating the Patient with a DFI

Patient

- – *Systemic response*
    - • Fever, chills, sweats, cardiovascular status
- – *Metabolic status*
    - • Hyperglycaemia, electrolyte imbalance, hyperosmolality, renal impairment
- – *Cognitive function*
    - • Delirium, depression, dementia, psychosis
- – *Social situation*
    - • Support, self-neglect
- **Limb/Foot**
- **Wound**
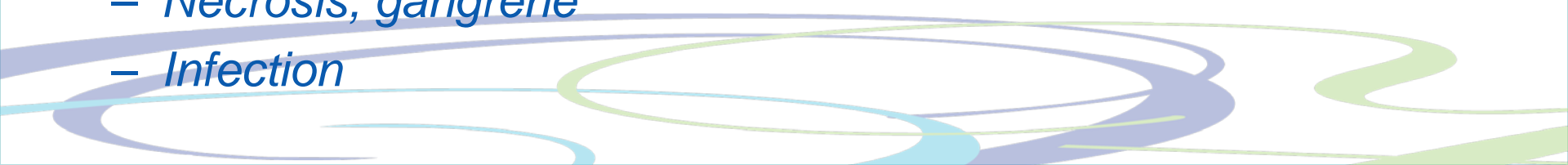
Evaluating the Patient with a DFI

Patient

Limb or Foot

- *Biomechanics*
- *Vascular*
  - Ischaemia
  - Venous insufficiency
- *Neuropathy*
- *Infection*

Wound

- *Size, depth*
- *Necrosis, gangrene*
- *Infection*

3. When and from whom should I request a consultation for a patient with a diabetic foot infection?

- Take a multi-disciplinary approach

- Identify your deficits in expertise and plan how you will fill them

- Will always need

Podiatry

Nursing and aftercare

Surgery

Medicine
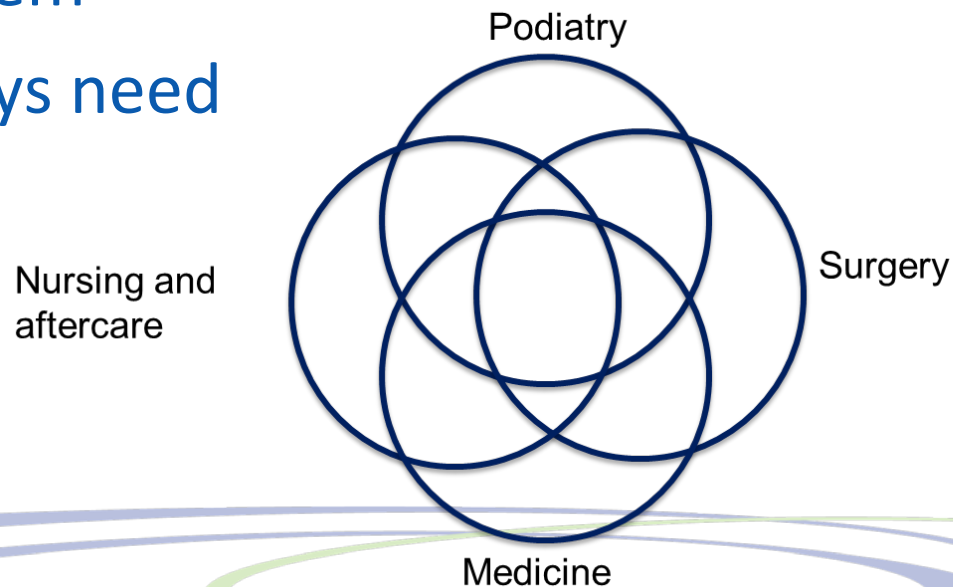
MDT support for DFI

A: I have no access to other specialists with an interest in DFI

B: I have access to some specialist support but not all I need

C: I work in a fully-functioning MDT when I provide care for patients with diabetic foot infection

D: I work in a functioning DFI MDT that regularly reviews protocols, outcomes and team effectiveness

4. Which patients with a diabetic foot infection should I hospitalize, and what criteria should they meet before I discharge them?

- All severe
- Some moderate
- Patients unable to adhere to treatment plan

5. When and how should I obtain specimen(s) for culture from a patient with a diabetic foot wound?

- All moderate or above

- Mild if particular concerns

- If failing to respond

- Tissue favoured >>> over swabs

6. How should I initially select, and when should I modify, an antibiotic regimen for a diabetic foot infection?

- Mild: start narrow and broaden up. Default initial = oral

- Severe: start broad and narrow, Default initial = parenteral

The Antibiotic Therapy Puzzle

Oxford University Hospitals NHS

NHS Trust

ANTIBIOTIC ISSUES
Safety profile
Dosing frequency
Availability
Efficacy/Approval
Cost
Drug interactions

INFECTION ISSUES
Clinical severity
Recent antibiotics
Bone infection
Vascular status

PATHOGEN ISSUES

Likely etiologic agent
Local resistance data

PATIENT ISSUES
Antibiotic allergies
Immune status
Renal/hepatic dz
GI absorption

Modified from: Pea & Viale, *Clin Inf Dis* 2006;42:1764;; Slide courtesy of Dr B Lipsky

Oxford University Hospitals — NHS Trust

Advised Route	Oral for Most	Oral or IV	Parenteral
Dicloxacillin	Yes		
Clindamycin	Yes		
Cephalexin	Yes		
TMP/SMX	Yes	Yes	
Amoxicillin/clavulanate	Yes	Yes	
Levofloxacin	Yes	Yes	
Cefoxitin		Yes	
Ceftriaxone		Yes	
Ampicillin/sulbactam		Yes	
Linezolid (± aztreonam)		Yes	
Daptomycin (± aztreonam)		Yes	
Ertapenem		Yes	
Cefuroxime (± metronidazole)		Yes	
Ticarcillin/clavulanate		Yes	
Piperacillin/tazobactam		Yes	Yes
Levo- or Cipro- floxacin + Clindamycin		Yes	Yes
Imipenem-cilastatin			Yes
Vanco + Ceftazidime ± metronidazole			Yes

Site	Severity	Route	Location	Duration
Soft tissue only	**Mild**	Topical or oral	Outpatient	7-14 days; extend up to 28 d if slow to resolve
	Moderate	Oral (or initial parenteral)	Outpatient/ inpatient	2-4 weeks
	Severe	Initial IV, switch to oral when possible	Inpatient, to outpatient	2-4 weeks
Bone or joint	Extent of surgery	*Route*		*Duration*
	No residual infected tissue (e.g. post amputation)	Parenteral or oral		2-5 days
	Residual infected soft tissue only	Parenteral or oral		2-4 weeks
	Residual infected (but viable) bone	Initial IV, then consider oral switch		4-6 weeks
	No surgery, or residual dead bone post-op.	Initial IV, then consider oral switch		>3 months

What to do with the culture results?

Aiming for narrowest spectrum possible with good clinical response

Infection responding

- If cultures permit, choose narrower spectrum drug
- If some organisms appear "missed" by empiric regimen, continue

Infection not responding

- Re-evaluate
- If some organisms appear "missed" by empiric regimen, broaden spectrum
- If all organisms covered by empiric regimen, challenge previous assessment of biology

Options for MRSA treatment

Vancomycin

Teicoplanin

Doxycycline

Rifampicin

Fusidic acid

Trimethoprim (-Sulphamethoxazole)

(Clindamycin/Erythromycin)

Newer agents (Linezolid, Daptomycin, ~~Tygecycline~~, others)

7. When should I consider imaging studies to evaluate a diabetic foot infection, and which should I select?

- Baseline evaluation

- Suspected osteomyelitis

- Suspected deep space infection
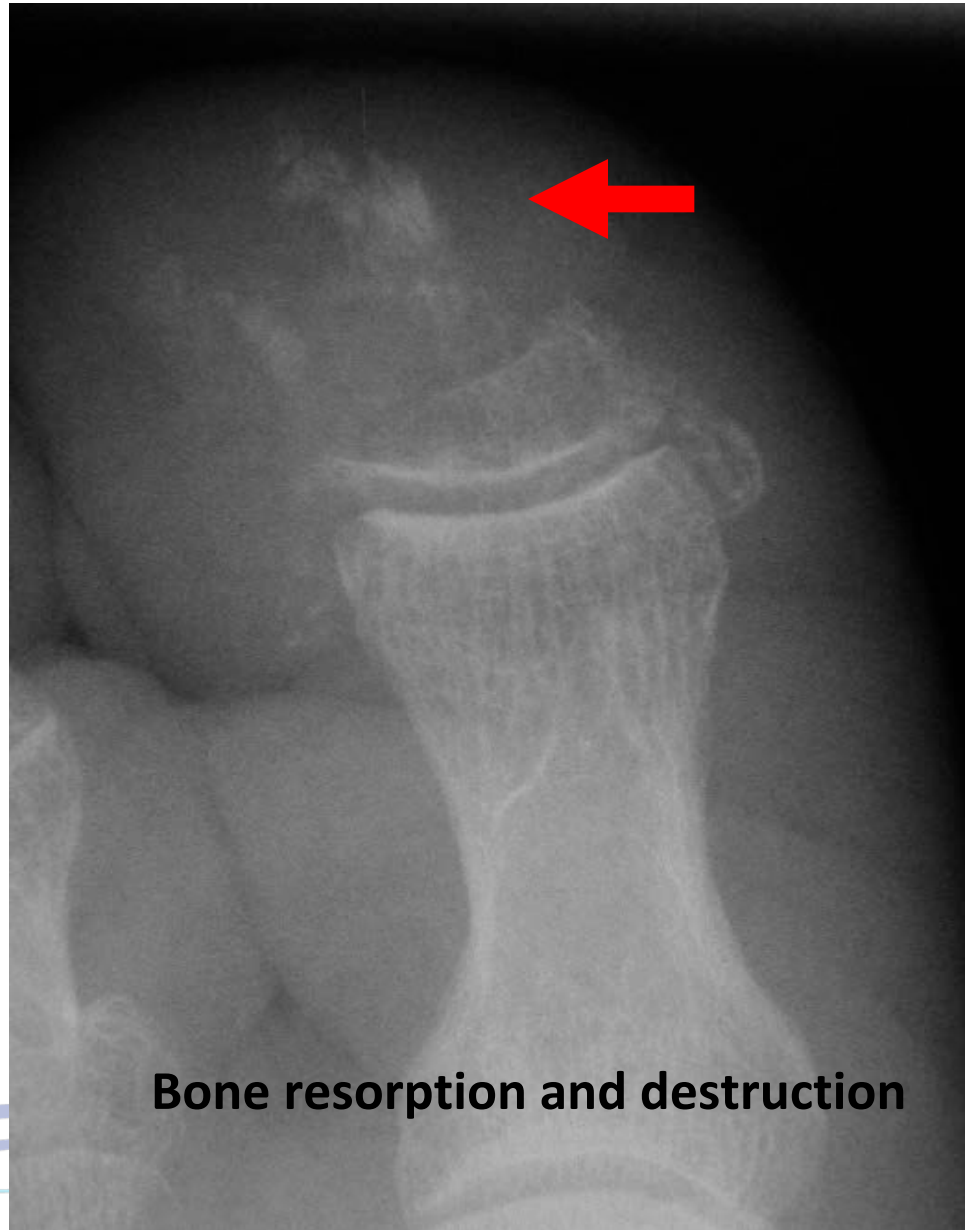
Bone resorption and destruction

8. How should I diagnose and treat osteomyelitis of the foot in a patient with diabetes?

- Criterion standard: discuss

- Clinical features

- ESR

- MRI

- XR particularly serial

- PTB test

Probe to bone test

A: I have never heard of the probe to bone test

B: I have heard of it but have no interest in using it/don't believe the evidence supports its use

C: I have heard of it but am not familiar with it/cannot get the probes

D: I use the probe to bone test

When should we suspect osteomyelitis?

Wound won't heal despite adequate perfusion and offloading

Ulcer that is deep or extensive

Visible, palpable or discharging bone

"Sausage toe"

Case 2

65 year old man

NIDDM

4 years ago, critical ischaemia, fem-pop bypass

Graft subsequently failed

Presents with episodes of recurrent infection involving second toe, spreading into mid-foot

Responds to antibiotics
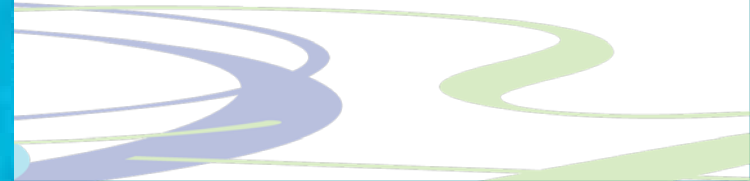
Infection or neuro-osteopathy?
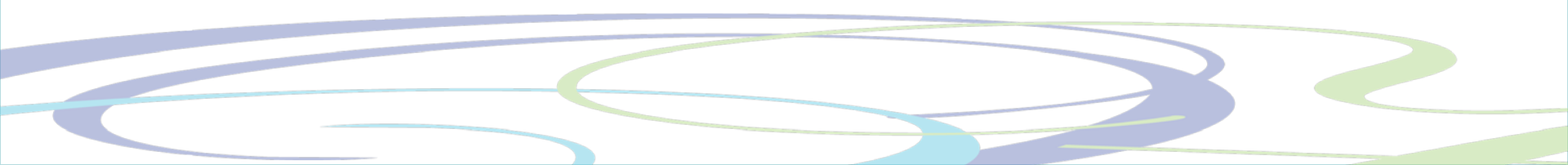
The diabetic foot: Charcot foot with "rocker bottom" deformity

Non-surgical treatment for osteomyelitis

- Several centres report series with success rates of antibiotic alone on 70-80%

- ? Selection as most retrospective

- ? Side effects on oral regimens

- ? Effect of podiatry on encouraging separation and discharge of sequestra

Jeffcoate and Lipsky (2004) Clin Inf Dis 39;s115

Surgery vs non-surgery for DFO

A: All my DFO patients are referred for consideration of surgery

B: Most of my DFO patients are referred for surgery

C: Some of my DFO patients are referred for surgery

D: I refer only a small minority of my patients for surgery

Bone resorption and destruction

Bone regeneration on antibiotic therapy
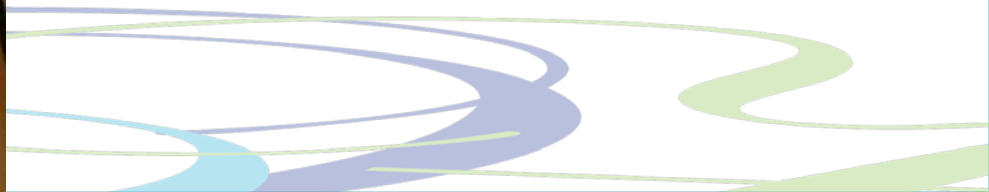
Diabetic foot

- 63 year old man with diabetes
- Previous L AKA
- Develops ulcer above and below R 5th MTPJ
- Cellulitis up to 2 cms from ulcer edge, purulence, superficial ulcer, no deep involvement, patient well
- Assessed on Infectious Diseases ward 8th May 2008....XR considered normal, and treated as for soft tissue infection

13th May 2008

8th May 2008

06.06.20

July 2008

11th Ju   08

R

R
120

RIGHT

Oxford University Hospitals NHS
NHS Trust

8th July 2008
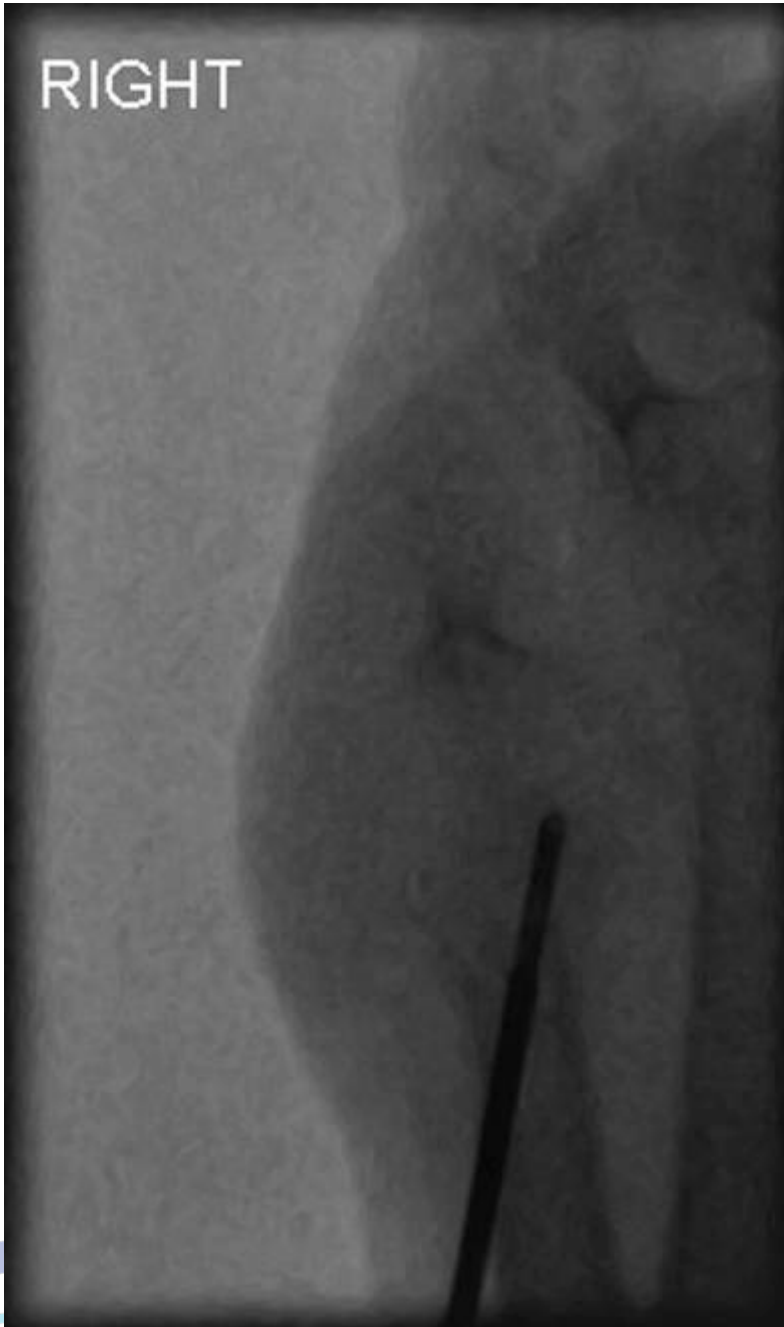
- Biopsy grew coagulase negative staph with histology suggesting osteomyelitis
- Treated with Teicoplanin for six weeks followed by Ciprofloxacin and Rifampin

Oxf

NHS

13th Nov 2008

5 year retrospective, n = 147

Game and Jeffcoate (2008)
Diabetologia; 51(6):962-7

Surgery, n = 34

Medical, n = 113

Major amput^{n}, n = 6

Minor amput^{n}, n = 28

Relapse, n = 35

Remission, n = 66

Major amput^{n}, n = 2

Minor amput^{n}, n = 6

2nd remission, n = 27

Major amputation, n = 8 (5%)

Minor amputation, n = 34 (23%)

Remission, n = 93 (63%)

Bone Infection Unit, Nuffield Orthopaedic Centre, Oxford

Introduction Pathogenesis Management Guidelines Beyond guidelines Conclusions

Probe-to-Bone

Oxford University Hospitals **NHS** NHS Trust
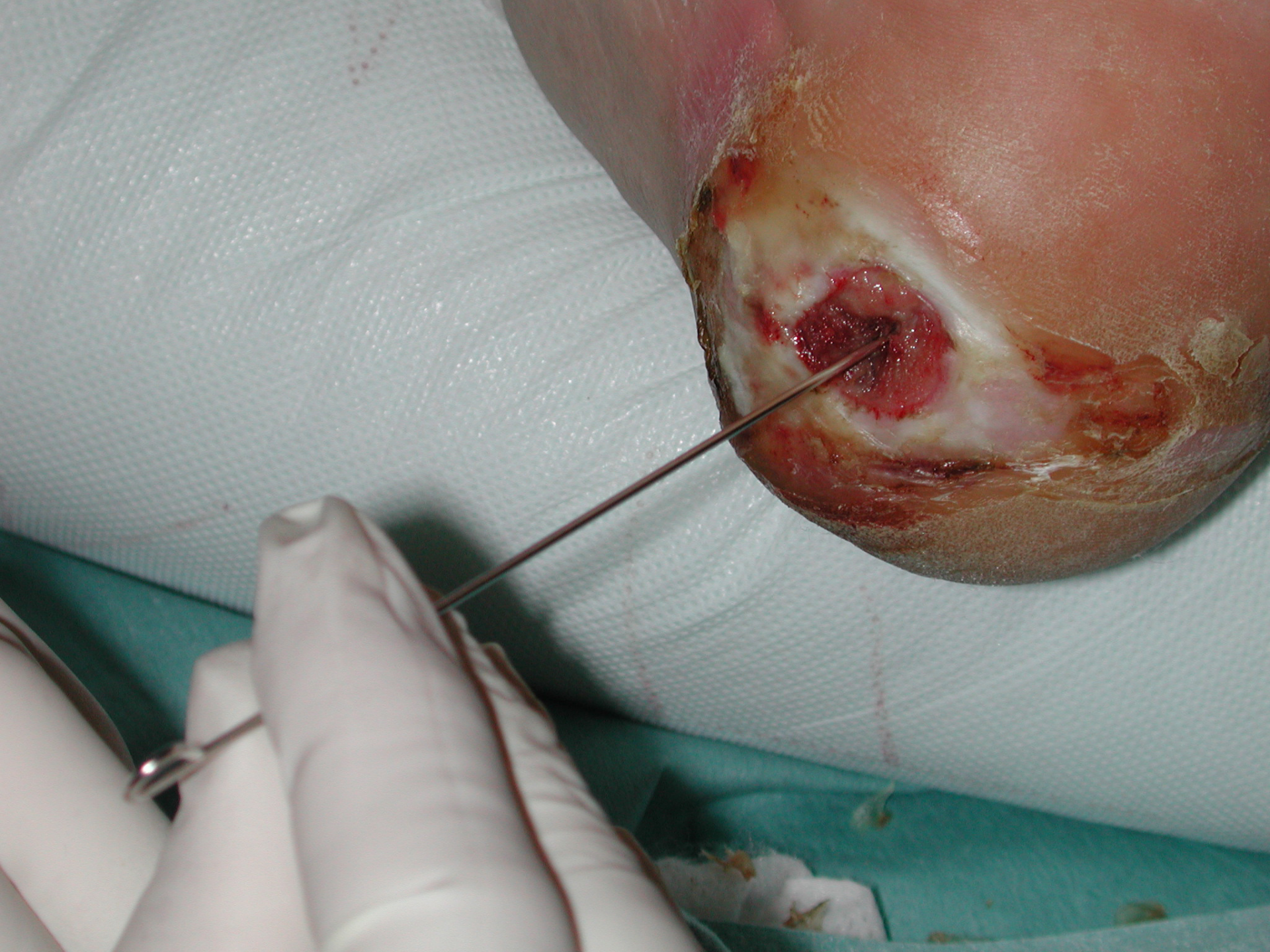
	Sensi-tivity	Speci-ficity	+LR Ratio	Pos PV	Neg PV	Osteo Prev.
*Grayson**(n=76)	66%	85%	4.04	89%	56%	**66%**
Lipsky[†] (n=283)	59%	86%	4.02	54%	88%	**21%**
Shone[‡] (n=104)	38%	91%	4.22	53%	85%	**20%**
Lavery[¶] (n=247)	87%	91%	9.67	57%	98%	**20%**

[*] Grayson et al. *JAMA* 1995;273:721
[†] Lipsky et al, Linezolid diabetic foot Infection study (unpublished data)
[‡] Shone et al, *Diabetes Care* 2006;29:945
[¶] Lavery, Armstrong, Lipsky et al, *Diabetes Care*

Introduction Pathogenesis Management Guidelines Beyond guidelines Conclusions

9. In which patients with a diabetic foot infection should I consider surgical intervention, and what type of procedure may be appropriate?

- All severe infections

- Abscess, fasciitis, necrosis, gas gangrene

- Ischaemia

- Major mechanical derangements

- When indications for amputation are met

- Choose a foot-sparing surgeon who understands about the need for a "shoeable foot"

10. What types of wound care techniques and dressings are appropriate for diabetic foot wounds?

- Offloading

- Moist wound healing

- Avoid magical thinking

- Indications and true cost effectiveness of HBOT remain unclear; no evidence it helps treat infection in DFI

After the guidelines…..
…..the hard work starts
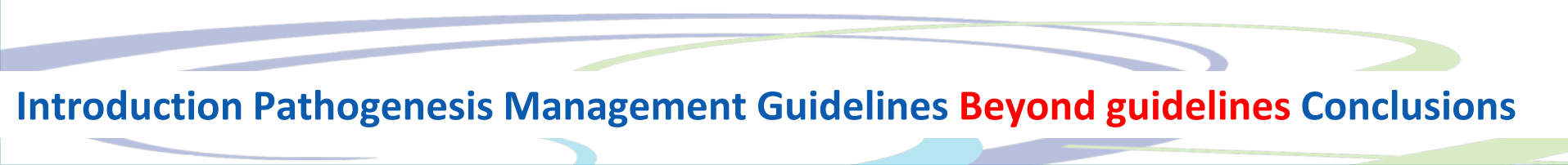
If you always do
What you've always done
You will always get
What you've always got
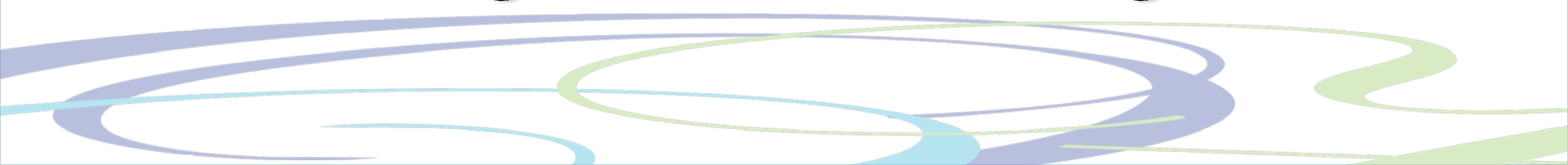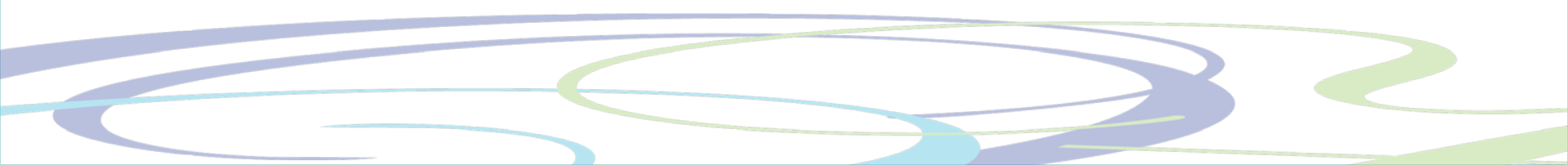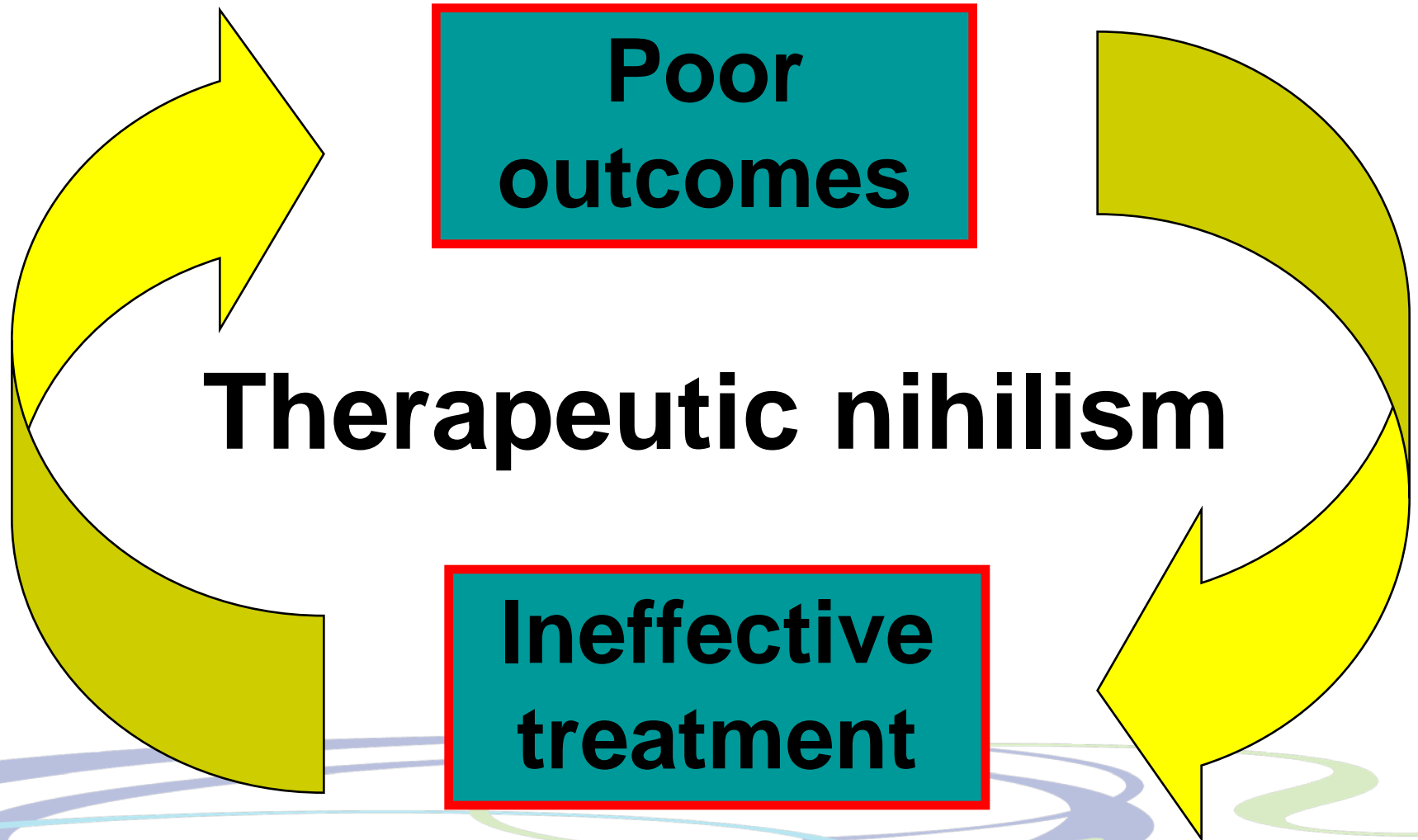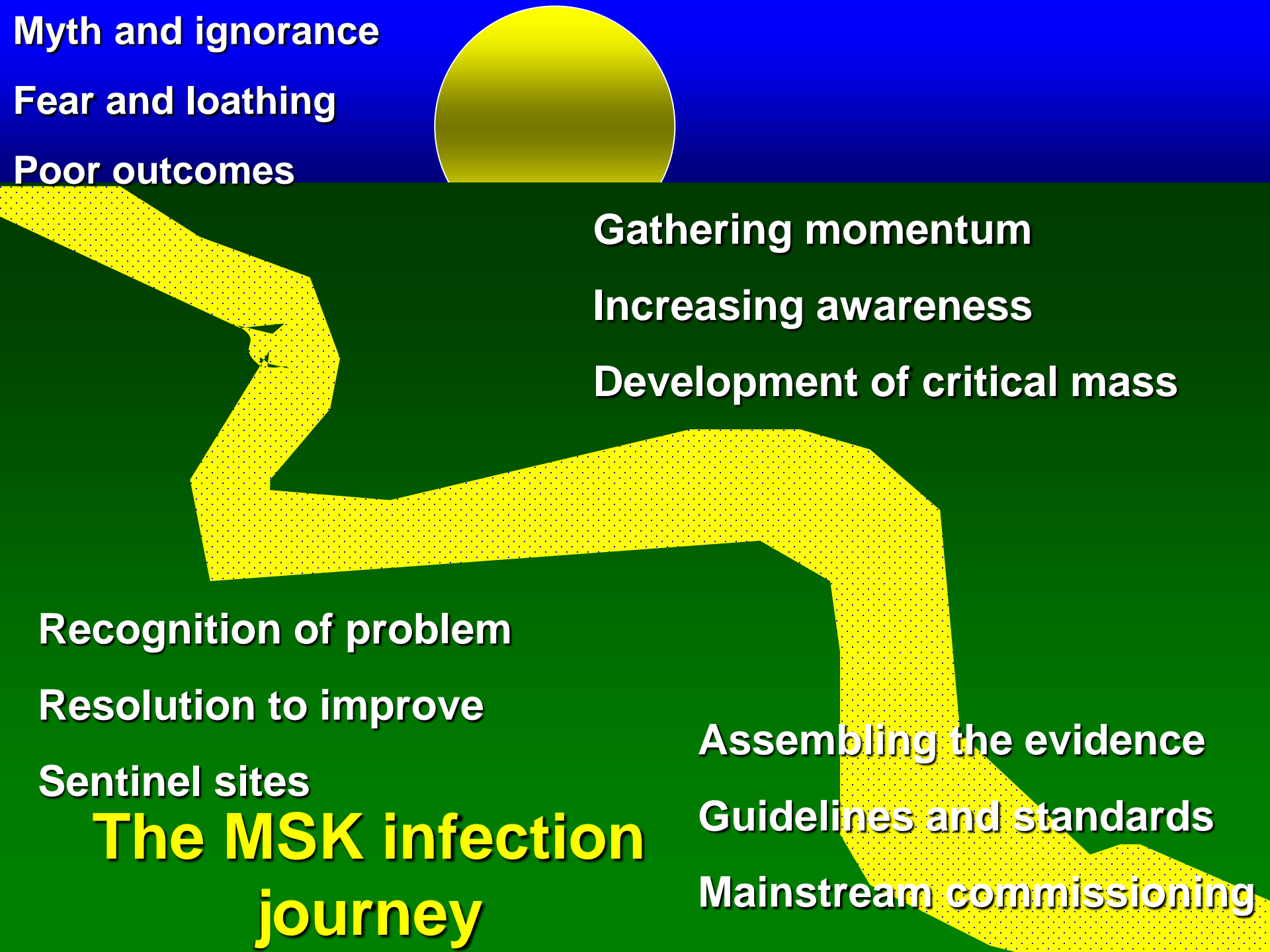
Conclusions

- We have raised expectations

- A methodical approach flows from guidance into patient management

- Guidelines point the way to standards

- Standards can be used to improve rapidly

- A key element is the MDT....critical that this is in place and functioning
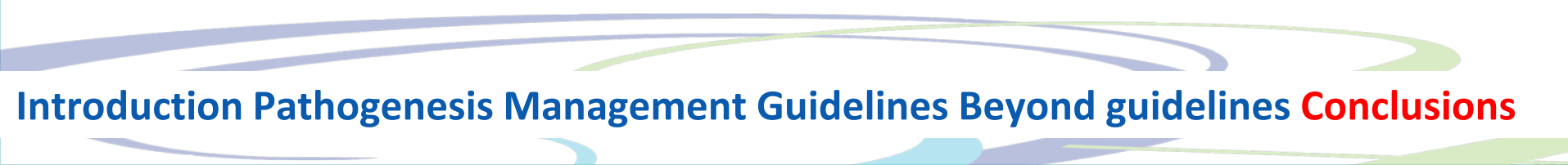
Who's in *your* team?

Vertebral Osteomyelitis – IDSA Workgroup Recommendations

Elie F Berbari, MD, FIDSA
Professor of Medicine
Section of Orthopedic Infectious diseases
Mayo Clinic College of Medicine
Berbari.elie@mayo.edu

Division of
INFECTIOUS DISEASES

Mayo Clinic Infectious Diseases Subspecialties Update
May 7-9, 2015

IDSA Vertebral Osteomyelitis Work Group Members

- Rabih Darouiche, MD

- Souha Kanj, MD

- Edward 'Ted' Hendershot, MD

- Paul Holtom, MD

- Todd Kowalski, MD

- Steven Schmitt, MD

- Andreas Widmer, MD

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- Paul Huddleston, MD

- Rodrigo Hasbun, MD

- Douglas Osmon, MD

- UpToDate Honorarium
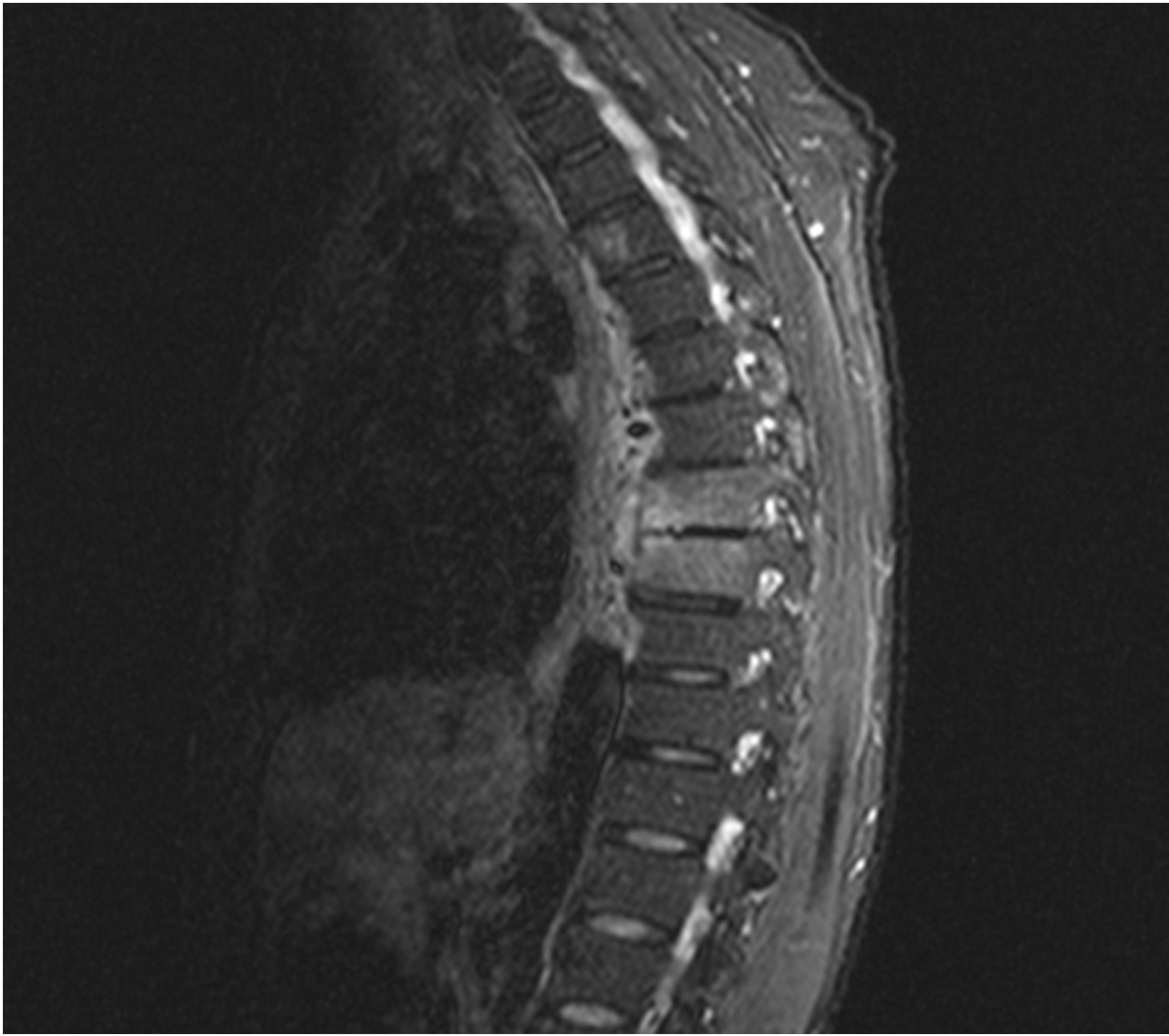
- 42 yo Female with DM presents with back pain for 2-3 weeks

- ESR = 75 mm/hr

- The patient recently finished a course of levofloxacin for a UTI

1. When should the diagnosis of NVO be considered?

2. What is the appropriate diagnostic evaluation of patients with suspected NVO?

3. When should an image-guided aspiration biopsy or additional work-up be performed ?

4. How long should antimicrobial therapy be withheld prior to an image-guided diagnostic aspiration biopsy ?

5. When is it appropriate to send fungal, mycobacterial, brucella cultures or other specialized testing following an image-guided aspiration biopsy?

6. When is it appropriate to send the specimens for pathologic examination following an image-guided aspiration biopsy ?

7. What is the preferred next step in patients with non-diagnostic image-guided aspiration biopsy ?

8. When should empiric antimicrobial therapy be started?

9. What is the optimal duration of antimicrobial therapy?

10. What are the indications for a surgical intervention?

11. How should failure of therapy be defined?

12. What is the role of systemic inflammatory markers and MRI in the follow-up of treated patients?

13. How do you approach a patient with NVO and suspected treatment failure?

What is the appropriate diagnostic evaluation of patients with suspected NVO?

Clinical Study

The utility of image-guided percutaneous needle aspiration biopsy for the diagnosis of spontaneous vertebral osteomyelitis: a systematic review and meta-analysis

Jakrapun Pupaibool, MD[a,*], Shawn Vasoo, MD[b], Patricia J. Erwin, MLS[c], Mohammad Hassan Murad, MD[d], Elie F. Berbari, MD[a]

[a]Division of Infectious Diseases, Department of Medicine, Mayo Clinic College of Medicine, 200 1st St SW, Rochester, MN 55905, USA

Forest Plot of Sensitivity and Specificity of Image-guided biopsy for Diagnosis of Vertebral Osteomyelitis

Sensitivity (95% CI)

Study	Sensitivity	(95% CI)
Chew et al., 2001	0.74	(0.57 - 0.88)
Chu et al., 2011	0.73	(0.45 - 0.92)
Fouquet et al., 1996	0.65	(0.50 - 0.78)
Kim et al., 2013	0.38	(0.30 - 0.47)
Michel et al., 2005	0.61	(0.36 - 0.83)

Pooled Sensitivity = 0.52 (0.46 to 0.58)
Chi-square = 24.63; df = 4 (p = 0.0001)
Inconsistency (I-square) = 83.8 %

Specificity (95% CI)

Study	Specificity	(95% CI)
Chew et al., 2001	1.00	(0.86 - 1.00)
Chu et al., 2011	1.00	(0.48 - 1.00)
Fouquet et al., 1996	0.94	(0.70 - 1.00)
Kim et al., 2013	1.00	(0.89 - 1.00)
Michel et al., 2005	1.00	(0.85 - 1.00)

Pooled Specificity = 0.99 (0.95 to 1.00)
Chi-square = 3.70; df = 4 (p = 0.4483)
Inconsistency (I-square) = 0.0 %

Forest Plot Of Diagnostic Odds Ratio Of Image-guided Percutaneous Biopsy For Diagnosis Of Spontaneous Vertebral Osteomyelitis
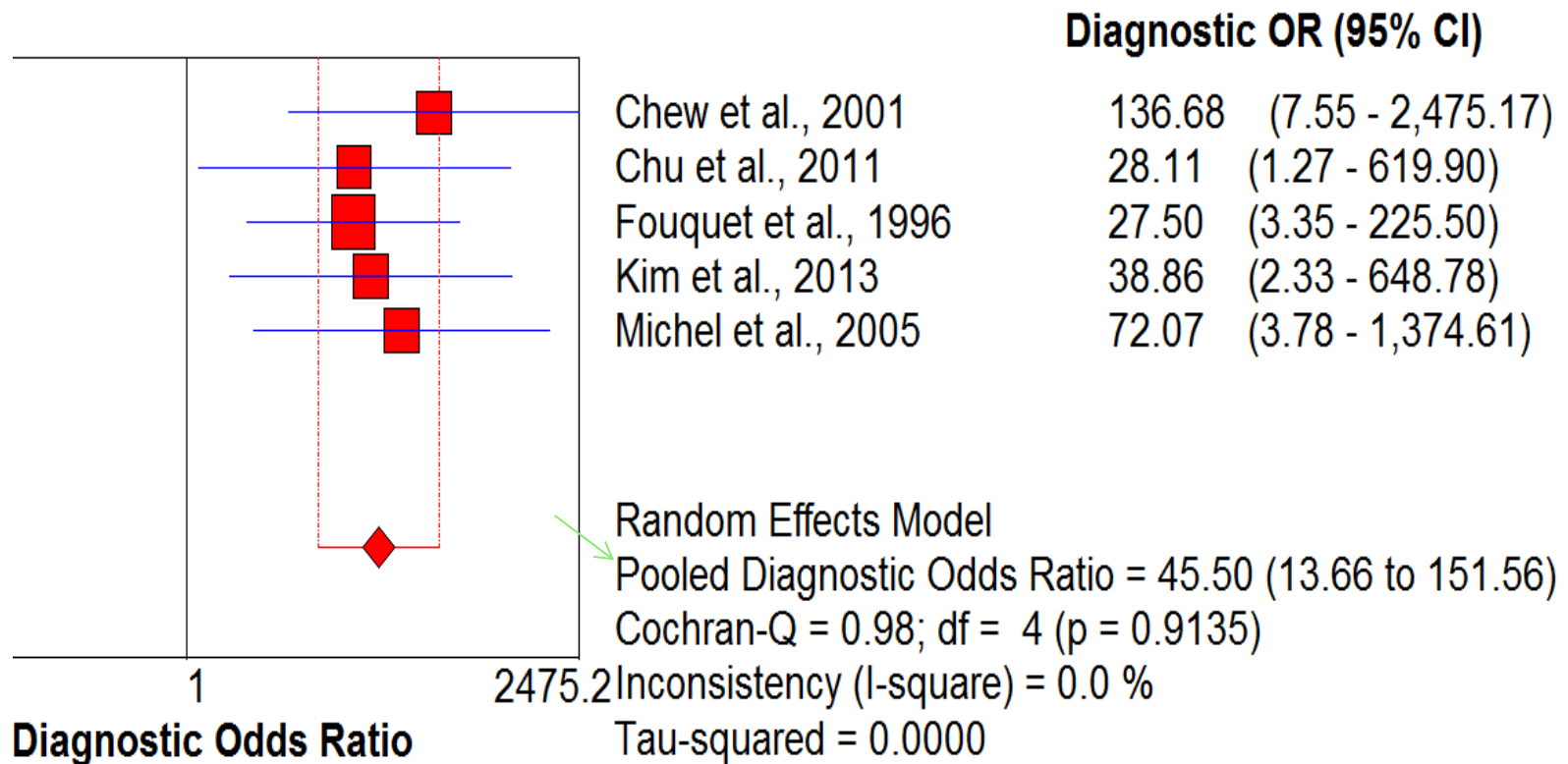
Diagnostic OR (95% CI)

Study	Diagnostic OR	(95% CI)
Chew et al., 2001	136.68	(7.55 - 2,475.17)
Chu et al., 2011	28.11	(1.27 - 619.90)
Fouquet et al., 1996	27.50	(3.35 - 225.50)
Kim et al., 2013	38.86	(2.33 - 648.78)
Michel et al., 2005	72.07	(3.78 - 1,374.61)

Random Effects Model
Pooled Diagnostic Odds Ratio = 45.50 (13.66 to 151.56)
Cochran-Q = 0.98; df = 4 (p = 0.9135)
Inconsistency (I-square) = 0.0 %
Tau-squared = 0.0000

1   2475.2

Diagnostic Odds Ratio

How long should antimicrobial therapy be withheld prior to an image-guided diagnostic aspiration biopsy in patients with suspected NVO?

Microbiologically and Clinically Diagnosed Vertebral Osteomyelitis: Impact of Prior Antibiotic

Multivariate analysis of factors associated with culture positivity in patients with PVO[a]

Factor	Adjusted OR (95% CI)	P value
L–spine involved	0.27 (0.04–1.80)	0.177
Paravertebral abscess	5.91 (1.49–23.4)	0.011
Duration of antibiotic exposure		
None[b]	1.00	
1–3 days	0.09 (0.01–1.49)	0.092
4 or more days	0.05 (0.01–0.24)	<0.001
WBC (1,000/mm^3)	1.06 (0.88–1.29)	0.518
PMN (%)	1.02 (0.96–1.09)	0.471
CRP (mg/dl)	1.07 (0.95–1.21)	0.267

Kim et al, AAC 2012

How Long Should Antimicrobial Therapy be Withheld Prior to a CT guided Diagnostic Aspiration?
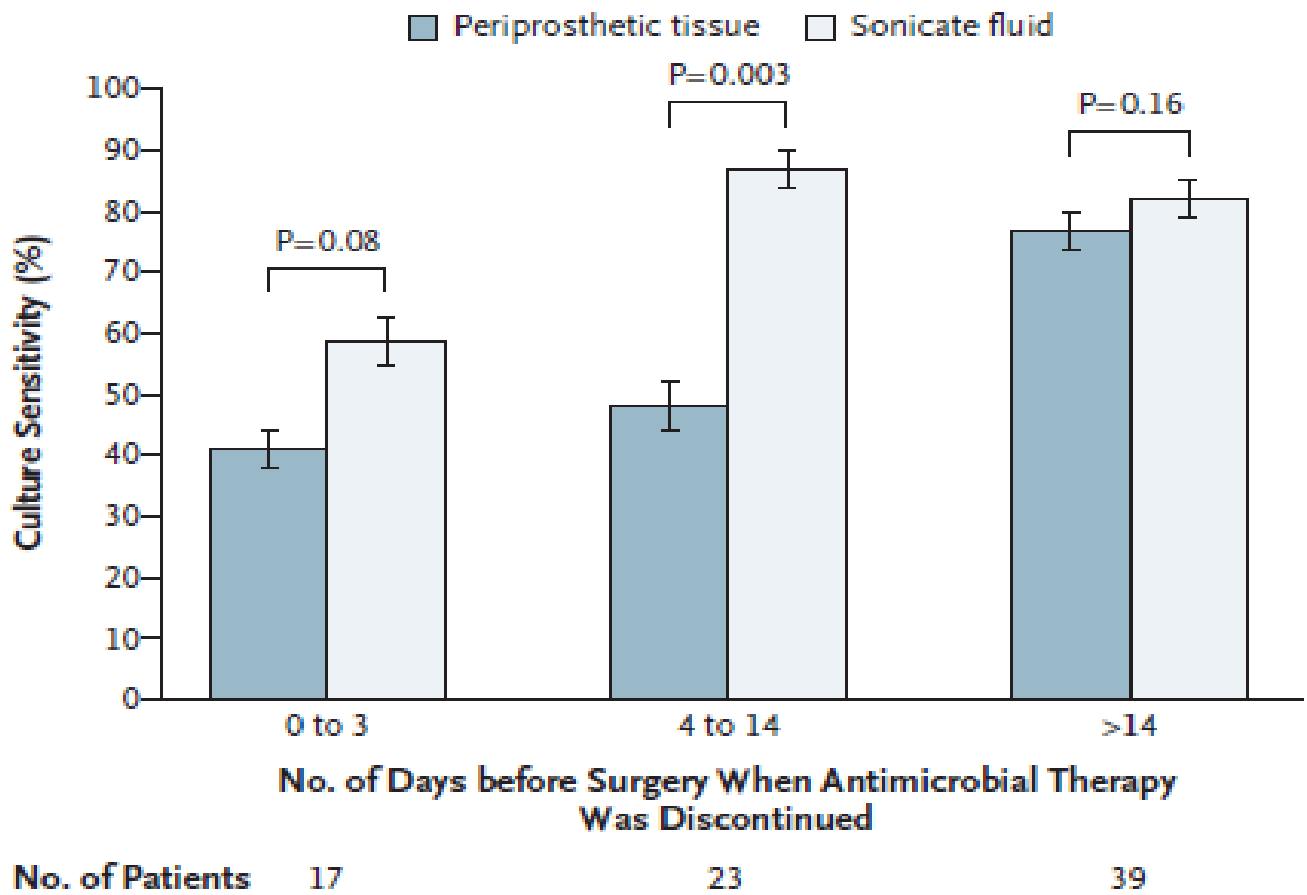
Trampuz et al NEJM, 2007

What is the preferred next step in patients with non-diagnostic image-guided aspiration biopsy and suspected NVO?

What is the optimal duration of antimicrobial therapy in patients with NVO?

Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial

Louis Bernard, Aurélien Dinh, Idir Ghout, David Simo, Valerie Zeller, Bertrand Issartel, Vincent Le Moing, Nadia Belmatoug, Philippe Lesprit, Jean-Pierre Bru, Audrey Therby, Damien Bouhour, Eric Dénes, Alexa Debard, Catherine Chirouze, Karine Fèvre, Michel Dupon, Philippe Aegerter, Denis Mulleman, on behalf of the Duration of Treatment for Spondylodiscitis (DTS) study group*

	6-week regimen	12-week regimen	Difference in proportion of patients*	95% CI
Intention-to-treat analysis, n	176	175		
Cured	160 (90·9%)	159 (90·9%)	+0·1	−6·2 to 6·3
Cured and alive†	156 (88·6%)	150 (85·7%)	+2·9	−4·2 to 10·1
Cured without further antibiotic treatment‡	142 (80·7%)	141 (80·6%)	+0·1	−8·3 to 8·5
Per-protocol analysis, n	146	137		
Cured	137 (93·8%)	132 (96·4%)	−2·5	−8·2 to 2·9
Cured and alive†	133 (91·1%)	126 (92·0%)	−0·9	−7·7 to 6·0
Cured without further antibiotic treatment‡	NA	NA	NA	NA

Optimal Duration of Antibiotic Therapy in Vertebral Osteomyelitis
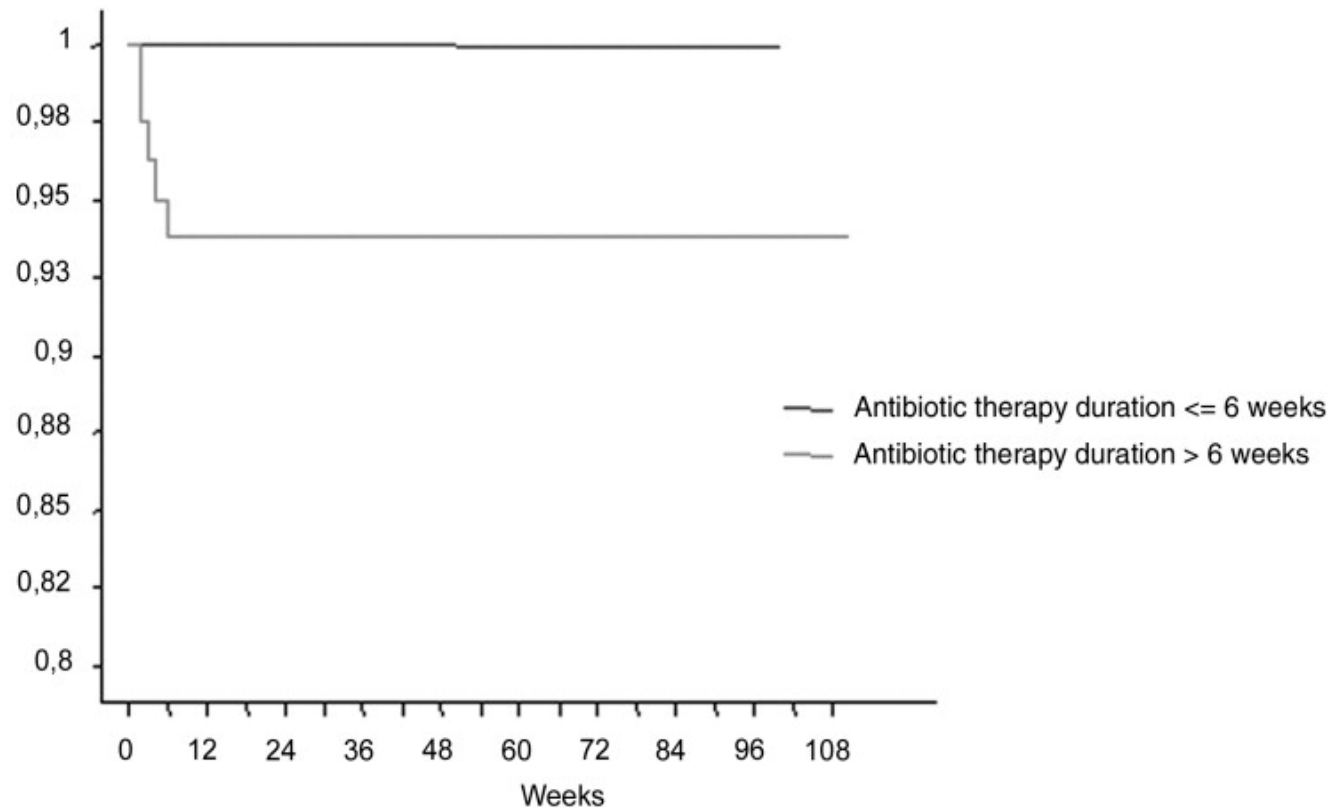
Oral step-down therapy is comparable to intravenous therapy for *Staphylococcus aureus* osteomyelitis

Naval G. Daver [a], Samuel A. Shelburne [a], Robert L. Atmar [a], Thomas P. Giordano [a], Charles E. Stager [b], Charles A. Reitman [c], A. Clinton White Jr. [a,*]

Table 2 Apparent cure rates for methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA) comparing IV and switch groups

Organism	Cured (N)	Relapsed (N)	Total	% Cured
MSSA	29	6	35	83
IV	12	4	16	75[a]
Switch	17	2	19	89
MRSA	24	13	37	65
IV	13	7	20	65[b]
Switch	11	6	17	65

[a] $P = 0.26$ for IV versus switch group for MSSA.
[b] $P = 0.99$ for IV versus switch group for MRSA.

Oral Therapy for NVO

- 48 patients with vertebral osteomyelitis (65% MSSA)

- Levofloxacin 500 mg PO Q 12/Rifampin600 mg PO daily

- 15.1 weeks (range 7.7–26.6 weeks)

- Till 2 consecutive CRP normalization one week apart

- Plasma levels measured

- 96.3% Success among those receiving targeted therapy

Viale, P. et al. International journal of antimicrobial agents, 2009.

Surgical Indications and Options for Vertebral Osteomyelitis
Dr. Ahmad Nassr
Associate Professor of Orthopedics, Mayo Clinic College of Medicine

What is the role of systemic inflammatory markers and MRI in the follow-up of treated patients with NVO?

How do you approach a patient with NVO and suspected treatment failure?

Kaplan Meier Survival Curve in 252 Patients with Pyogenic Vertebral Osteomyelitis at the Mayo Clinic, Rochester, 1994-2002
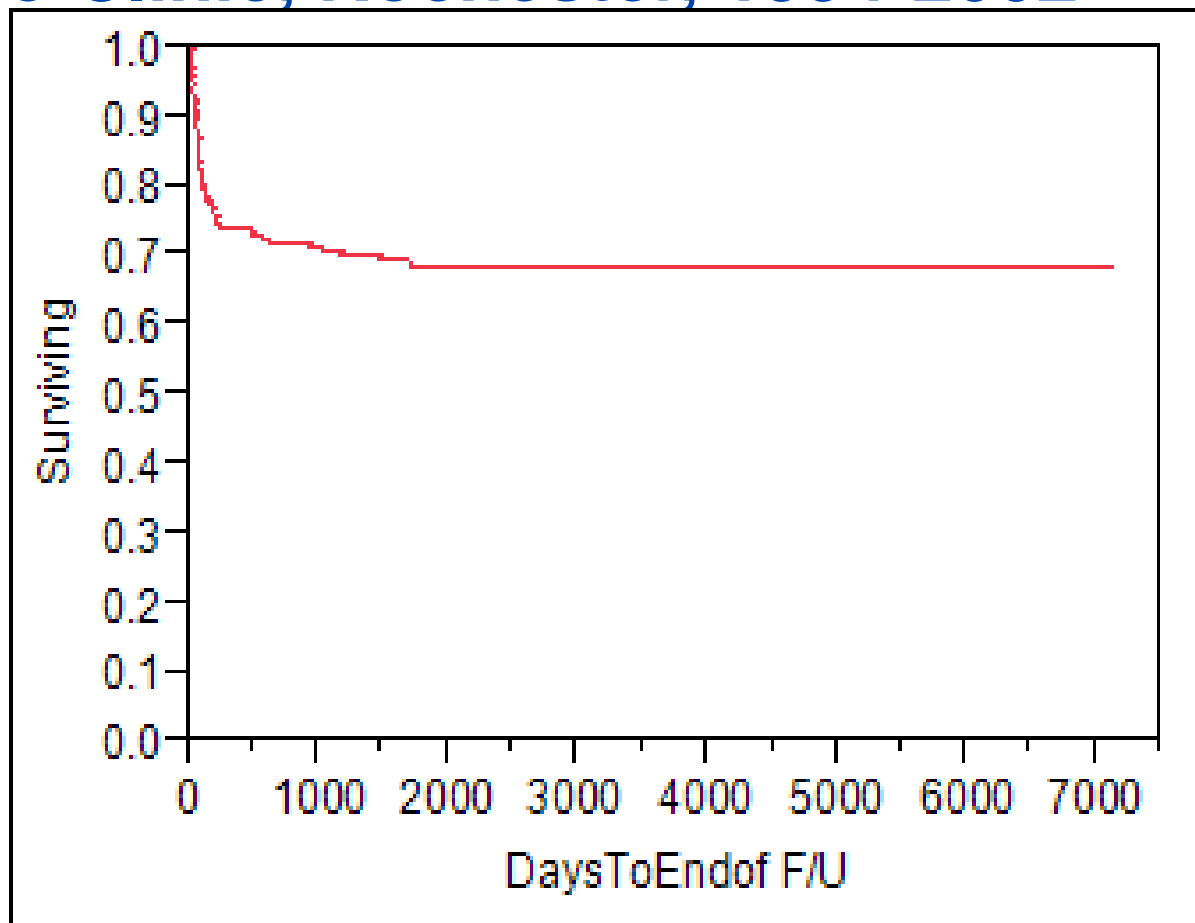
Table 4. Follow-up imaging examination findings, by clinical status.

Follow-up imaging finding	Follow-up clinical status			Total
	Improved	Equivocal	Worse	
Improved	26 (33)	1 (1)	0 (0)	27 (34)
Equivocal	21 (27)	14 (18)	3 (4)	38 (48)
Worse	5 (6)	4 (5)	5 (6)	14 (18)
Total	52 (66)	19 (24)	8 (10)	…

NOTE. Data are no. (%) of patients.
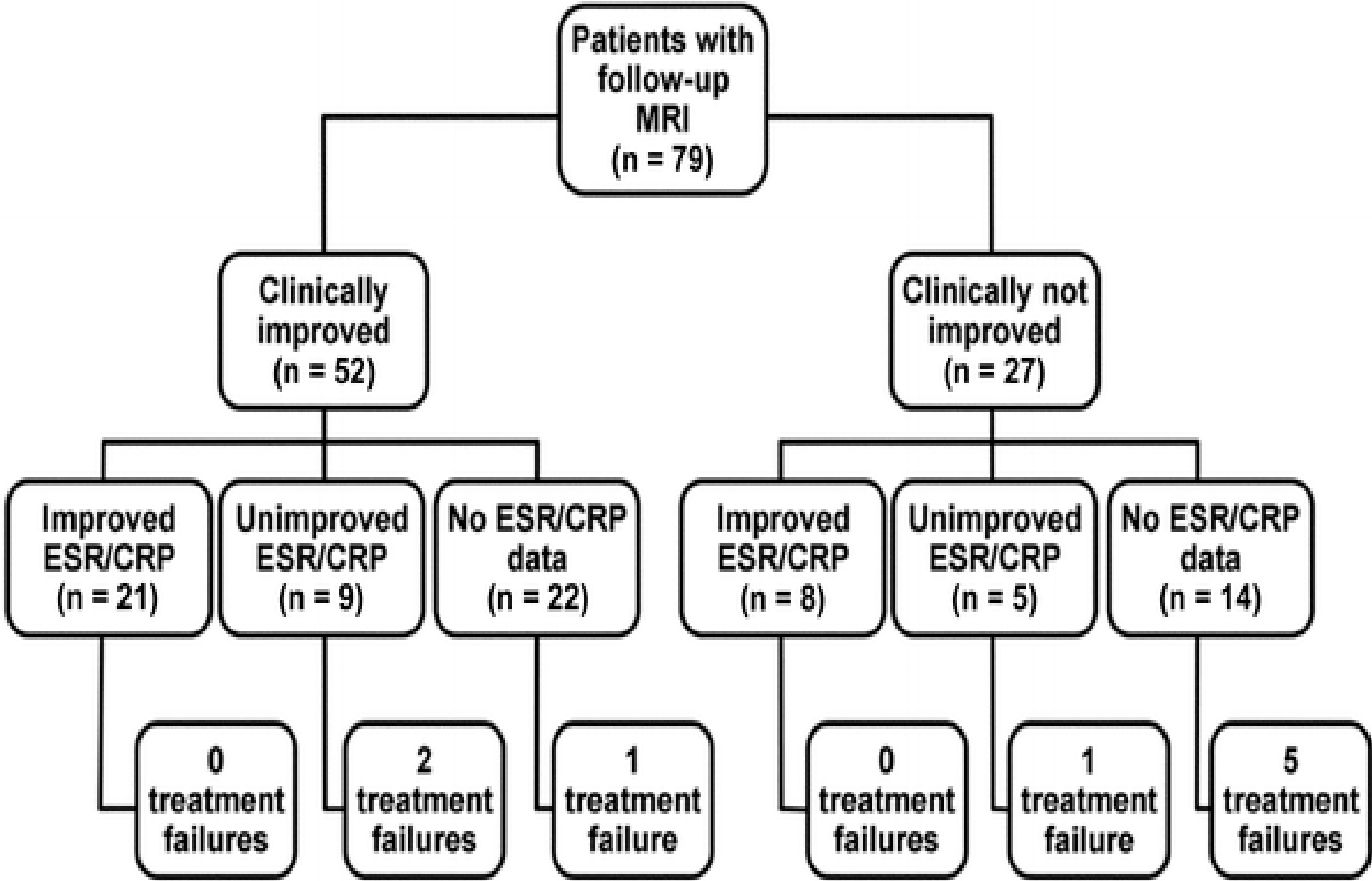
Kowalski et al, CID , 2006

Follow up MRI in Vertebral Osteomyelitis: Take home points

- No
  - If the patients is clinically improving and has improvement of ESR and CRP from baseline

- Yes
  - Lack of improvement

- Maybe
  - Discordant improvement (Labs vs clinical)

Follow up ESR in Patients with Vertebral Osteomyelitis

In conclusion

- Image-guided aspiration biopsy in patients with suspected NVO when a microbiologic diagnosis for a known associated organism (S. aureus, S. lugdunensis, and Brucella sp.) has not been established by blood cultures or serologic tests (Strong, Low)

- In patients with neurologic compromise, we recommend immediate surgical intervention and initiation of empiric antimicrobial therapy (Strong, Low). (2 week wait period)

- We recommend obtaining a second aspiration biopsy in patients with suspected NVO in whom the original image-guided aspiration biopsy specimen grew a skin contaminant (Strong, Low)

- We recommend a total duration of 6 weeks of parenteral or highly bioavailable oral antimicrobial therapy for most patients with bacterial NVO (Strong, Low)

- We suggest monitoring systemic inflammatory markers (ESR and or CRP) in patients with NVO after approximately 4 weeks of antimicrobial therapy, in conjunction with a clinical assessment (Weak, Low)

- We recommend against routinely ordering follow-up MRI in patients with NVO in whom a favorable clinical and laboratory-based response to antimicrobial therapy was observed (Strong, Low)

Antibiotic Treatment of Hardware Associated Vertebral Osteomyelitis

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- 81 Yo male underwent spinal lumbar fusion for degenerative spine disease

- 2 weeks later he presented with wound drainage

- Surgical debridement revealed deep purulence

- Cultures grew Coagulase negative Staphylococcus

Questions

- How to prevent such an infection?

- How long would you treat this patient?

- What is the role of oral antimicrobial therapy?

- Would you retain hardware?

- Would you suppress with antimicrobial therapy?

Lumbar laminectomy and fusion with routine local application of vancomycin powder: Decreased infection rate in instrumented and non-instrumented cases

Russell G. Strom [a,*], Donato Pacione [a], Stephen P. Kalhorn [b], Anthony K. Frempong-Boadu [a]

[a] Department of Neurosurgery, NYU Langone Medical Center, New York, USA
[b] Department of Neurosciences, Division of Neurosurgery, Medical University of South Carolina, Charlestown, USA

Infection rate among patients undergoing lumbar laminectomy and fusion before versus after routine application of vancomycin powder.

	Untreated: # infections/pts (%)	Vancomycin powder: # infections/pts (%)	p value
All cases	11/97 (11%)	0/156 (0%)	0.0000182
Instrumented cases	9/77 (12%)	0/88 (0%)	0.000806
Non-instrumented cases	2/20 (10%)	0/68 (0%)	0.0496

Clinical Study

Reduced surgical site infections in patients undergoing posterior spinal stabilization of traumatic injuries using vancomycin powder

Kevin R. O'Neill, MD[a], Jason G. Smith, BS[b], Amir M. Abtahi, BS[b], Kristin R. Archer, PhD, DPT[a], Dan M. Spengler, MD[a], Matthew J. McGirt, MD[c], Clinton J. Devin, MD[a,*]

[a]Department of Orthopaedics, Vanderbilt University Medical Center, Nashville, TN 37232, USA
[b]Vanderbilt University School of Medicine, Nashville, TN 37232, USA
[c]Department of Neurosurgery, Vanderbilt University Medical Center, Nashville, TN 37232, USA

SSI yearly rates among 5 adult spine surgeons at the Mayo Clinic: 2006-2012
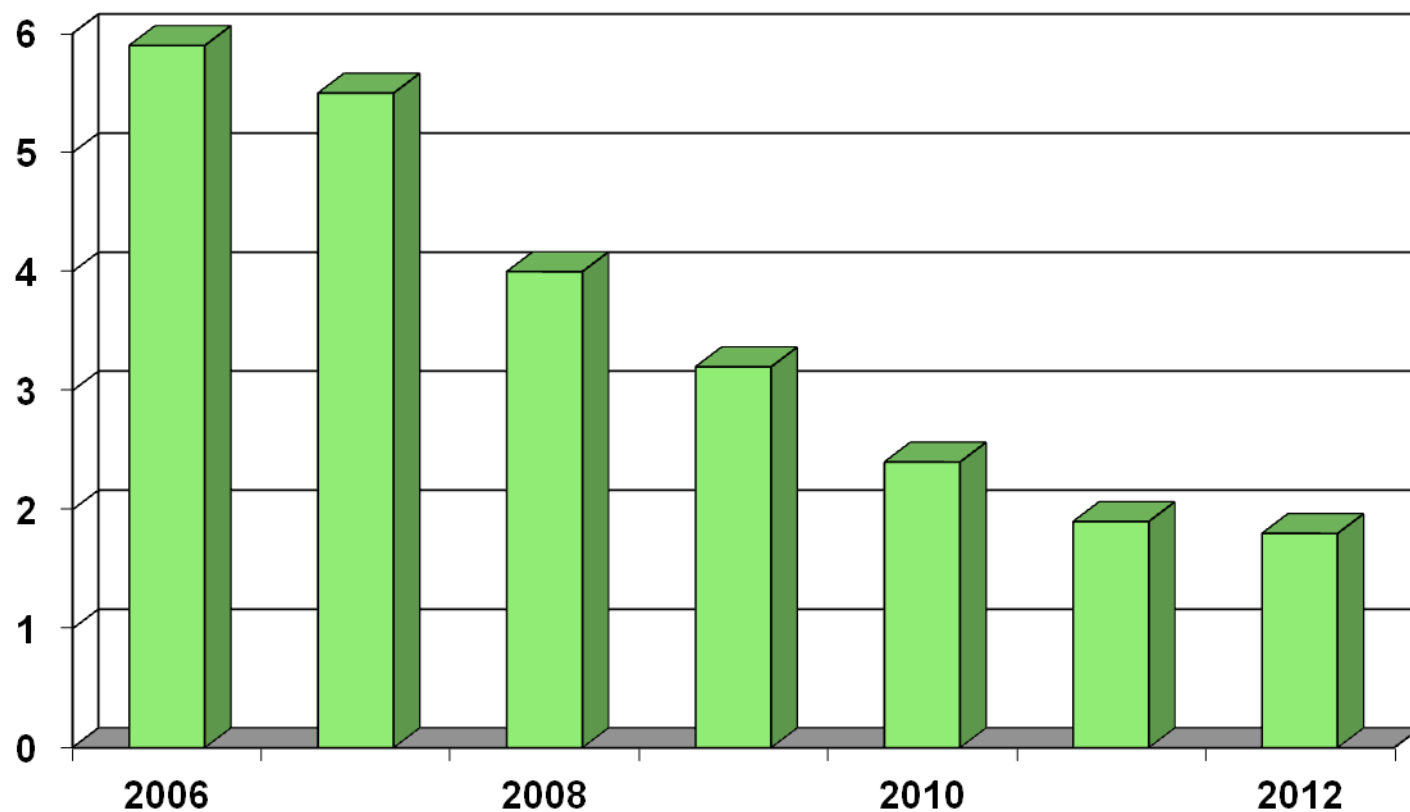
- Tod Kowlaski, MD

- Studied more than 500 episodes of vertebral osteomyelitis between 1994-2002

- Looked at the outcome, therapeutic modalities, and need for inflammation markers and imaging in the follow up of treated patients

Management of 81 Patients With Spinal Implant Infection at The Mayo Clinic 94-02

- Retrospective cohort study 1994-2002

- 30 patients with early onset spinal implant infection

- 51 patients with late onset spinal implant infection

Kaplan-Meier Plot Of Patients With Early-onset Infection By Use Of Oral Suppression Therapy
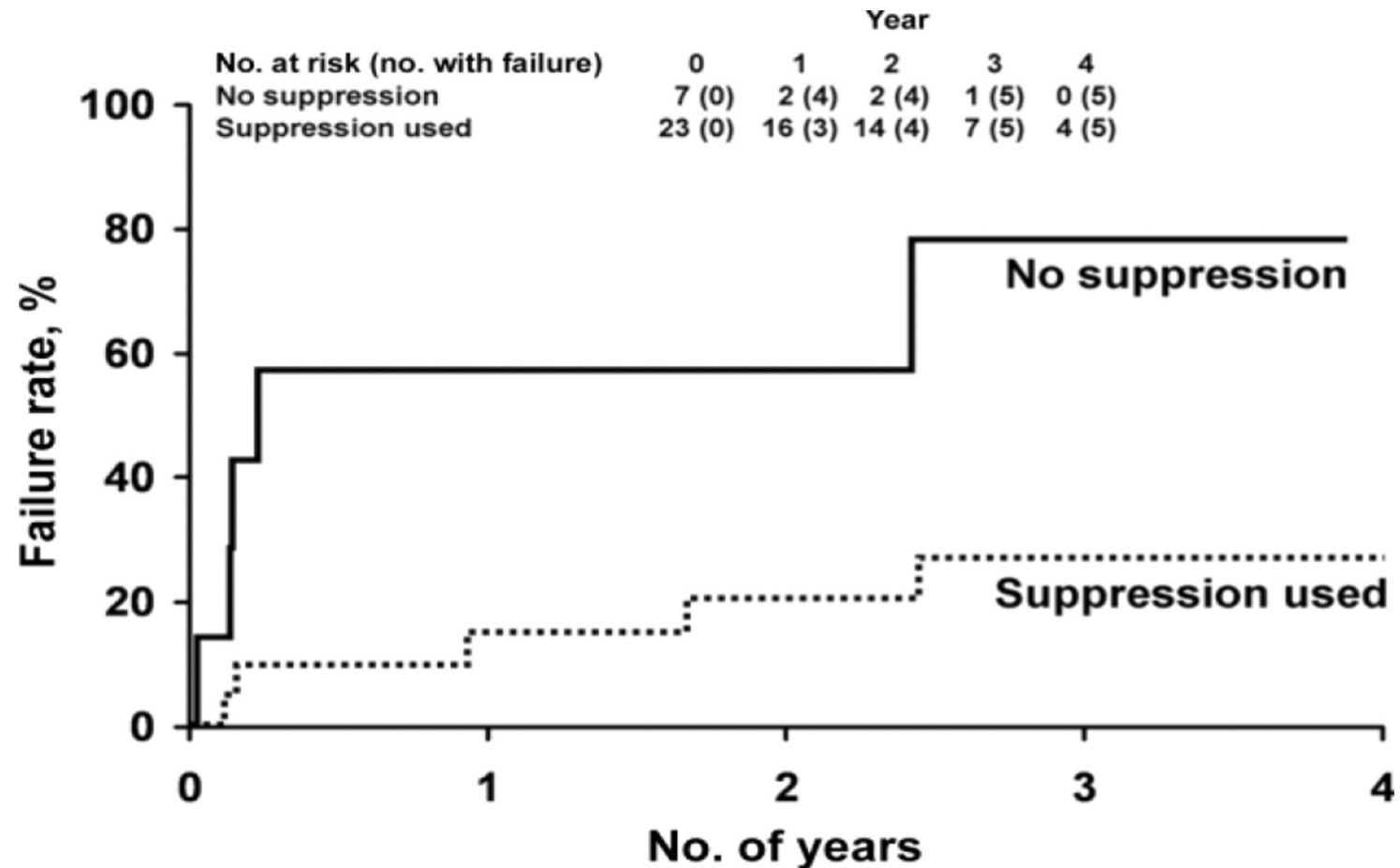
Kowalski T J et al. Clin Infect Dis. 2007;44:913-920

Antimicrobial Therapy Duration (days) Among 81 Patients with Spinal Implant Infections at the Mayo Clinic, Rochester, 1994-2002

	Early Infection(30)	Late Infection(51)
Parenteral therapy	41 (27 – 43)	42 (36 – 44)
Oral therapy	30 (26 – 33)	39 (20 – 50)
Suppressive Rx	303 (147 – 672)	410 (61 – 667)

Kaplan-Meier failure plot of late-onset infection by implant removal
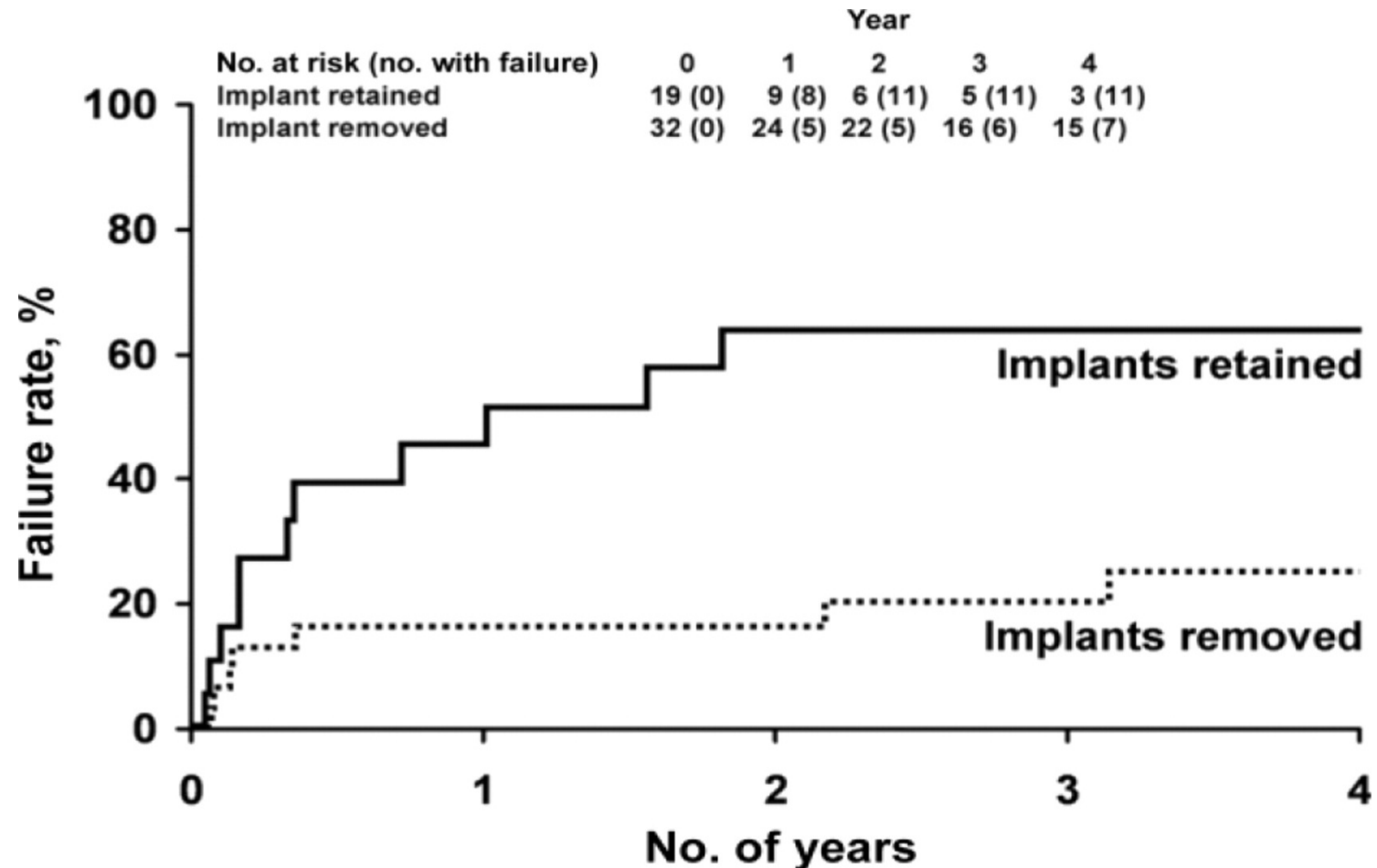
Kowalski T J et al. Clin Infect Dis. 2007;44:913-920

Conclusion

- Use of prophylactic Vancomycin in the wound is likely beneficial but more data is needed regarding its safety and development of resistance

- Early hardware associated spine infection:
  - Retention of hardware
  - Surgical debridement
  - Chronic antimicrobial suppression

- Late hardware infection:
  - Hardware removal if stability of the spine not jeopardized

Financial Disclosures

None
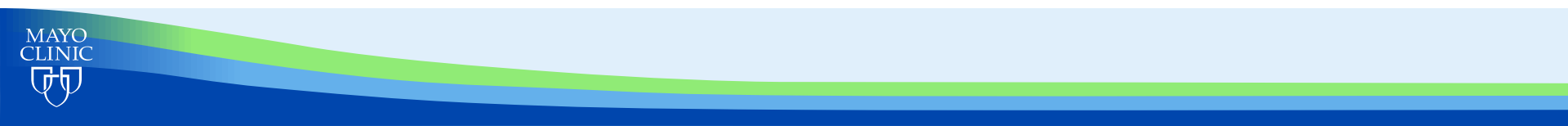
Objectives

- Describe the need for the development of the profession

- Understand how incorporating APPs can impact the delivery of care to the infectious disease patient

- Explore the collaborative team approach

- Examine key elements to the APP role in the hospital/clinic setting

History of the Professions

- 1961 Dr. Charles Hudson proposed, at a AMA meeting, that individuals be trained to perform routine clinical tasks. He pointed out that the Army and Navy had used corpsmen in similar roles.

Dr. Charles Hudson

History of the Professions

- 1965 The first PA class enters Duke University

- 1965 The first NP program at University of Colorado is developed

History of the Professions

- 1966 President Johnson-Allied Health Professions personnel Act (PL-751) promotes development of programs to train new primary care providers through grants
    - Federal grants for construction and rehabilitation of allied health training centers at universities, colleges and junior colleges.

History of the Professions

- 1971 AMA recognizes the PA profession

- 1973 NCCPA is established and NBME administers first certifying exam

- 1975 Nurse training Act of 1975-first legislation act to financially support NP training

- 1977 Rural Health Clinic Services ACT (PL-95-210) provides medicare reimbursements to PA/NP services in rural clinics

History of the Professions

- 1986 Medicare Part B grant coverage to PA/NP in hospitals, nursing homes and as surgical assistants

- 1990 Direct reimbursement for PA/NP in healthcare professional shortage areas, rural areas and long term care facilities

- 1997 Prescription authority granted in all 50 states

What is an Advanced Practice Provider (APP)?

- Umbrella title
  - Physician Assistant
  - Nurse Anesthetists
  - Midwifery
  - Clinical Nurse Specialist
  - Nurse Practitioner

- Requires completion of an advanced formal education AND certification

  >400,000 APPs in
  USA

APP Role

- Key member of the Patient-Centered Team
  - Patient direct contact
    - Inpatient
    - Outpatient
  - Patient non-direct contact
    - Phone/email
    - Patient online services

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Patient Centered Team-Inpatient
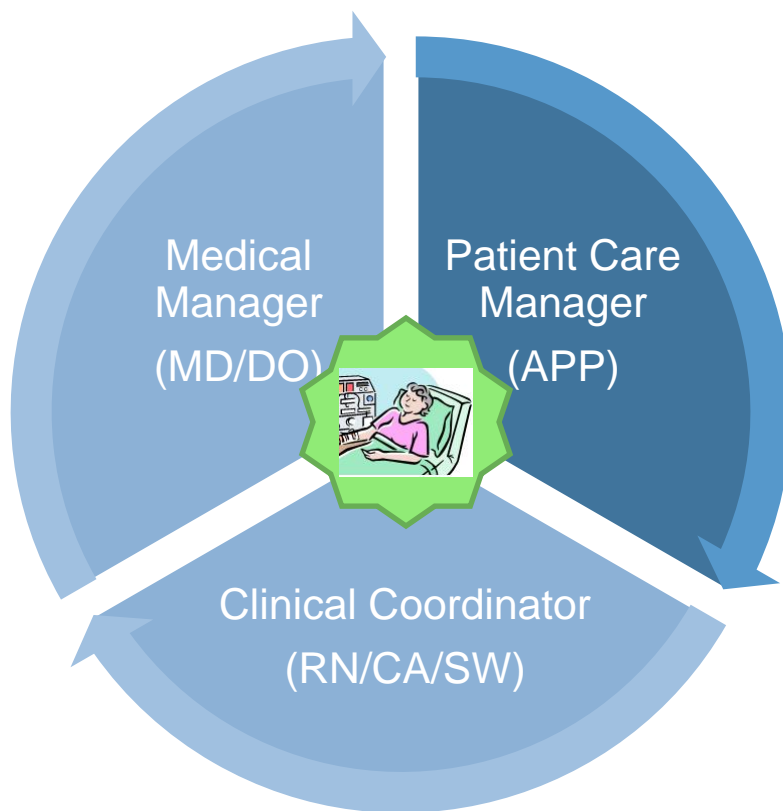
Patient Centered Team-Inpatient

Medical
Manager
(MD/DO)
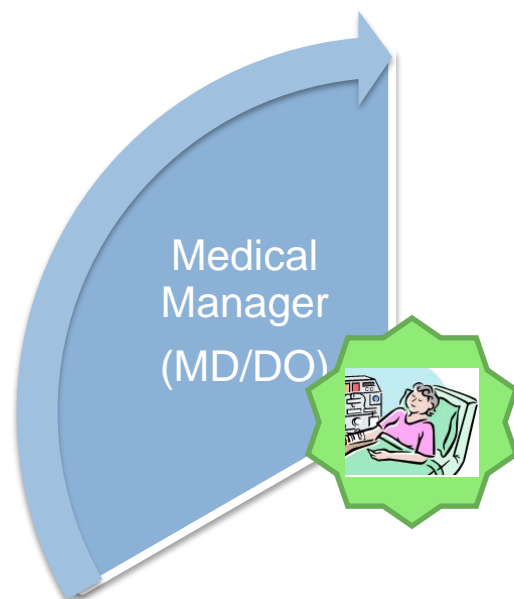
- Makes key medical decisions
- Follows progress
- Establishes Sign-off plan

Patient Centered Team-Inpatient

Patient Care Manager

(APP)

- Implements decisions
  - (dependent and independent)
- Monitors care
- Executes sign off plan

Patient Centered Team-Inpatient

- Attend rounds
- Order and interpret tests
- New consults
- Follow patient progress
- Author sign-off note
- Provide discharge orders/prescriptions
- Educate patients and families

Patient Care Manager

(APP)

Patient Centered Team-Inpatient

- Coordinates the processes of discharge
  - Home
  - Skilled care facility
- Arranges follow up

Clinical Coordinator

(RN/CA/SW)

Patient Centered Team-Outpatient

Patient Centered Team-Outpatient

Medical Manager (MD/DO)
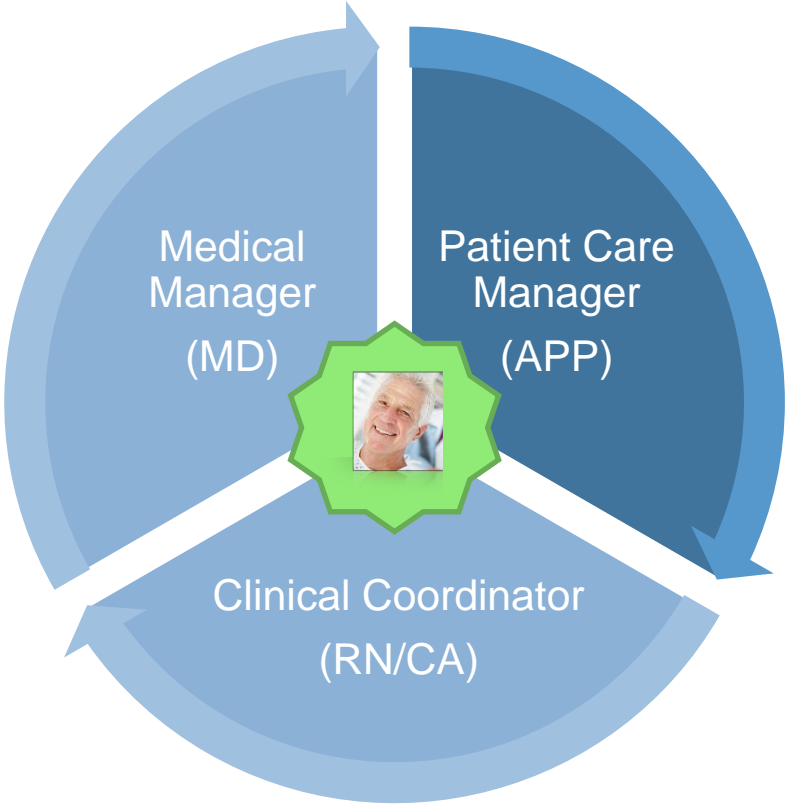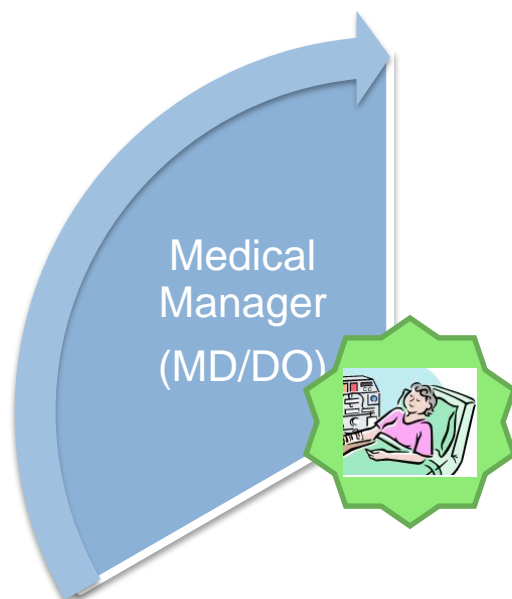
- See new out-patients
- Develops plan
- Pre-surgical evaluations

Patient Centered Team-Outpatient

- Hospital follow-up
- New patients
- Pre-surgical evaluations
- OPAT
- Late cultures
- Phone Calls
- Rx refills

Patient Care Manager

(APP)

Patient Centered Team-Outpatient

- Hospital follow-up
  - Examine wounds/PICC
    - Coordinate PICC removal
  - Post hospital testing
    - TEE/blood cultures
  - Minor procedures
    - Wound debridement
  - Possibly modify therapy
    - Discontinue/change antibiotics
    - Discharge or re-admission if necessary

Patient Centered Team-Outpatient

- Outpatient Parenteral Antibiotic Therapy (OPAT)

- ~150 patients discharged on OPAT per month
  - Infectious Disease Society OPAT guidelines for lab monitoring for toxicities
  - >200 patients with weekly labs faxed to ID
    - Team of RNs receive each lab
      - Will track down missing labs
    - RN lab protocol
      - Standardized labs for each antimicrobial
        - Normal
        - Abnormal-acceptable
        - Abnormal-unacceptable—Sent to APP for review

Outpatient Parenteral Antibiotic Therapy

- Outpatient Parenteral Antibiotic Therapy (OPAT)

  - APP reviews abnormal labs and determines next step
  - ~275 abnormal lab reviewed per month
    - Continue to monitor closely/repeat labs
    - Change antimicrobial therapy
    - Evaluate patient/possible re-admit

Patient Centered Team-Outpatient

- Late cultures
  - Discharge before cultures are finalized
  - Some up to 60 days incubation
  - Approximately 500 cultures are reviewed daily
    - Nurse review-roll to APP if culture not addressed in notes
      - April 2015
        - 115 cultures had new data reviewed
          - Document new finding
          - Modify therapy

Mayo Clinic ID APPs

- 6+ focus Groups
  - Orthopedic ID
  - Transplant ID
  - Hematology/Oncology ID
  - General ID
  - ICU/Neurosurgery ID
  - Pre-Travel/Post-Travel ID

  - New 2015- Non-Tuberculosis Mycobacteria Clinic (NTM)

Mayo Clinic ID APPs

- 4 Physician Assistants

- 1 Nurse Practitioner

- 1 Certified Nurse Specialist

- 2 Open APP positions

Advantages of APPs

- Cost less than physician F.T.E.

- Manage the care of patients not requiring direct physician care time

- Provide high-quality care

- Facilitate and coordinate care processes

- Enhance efficiency

- Augment practice productivity

Thank you

- Dr. Virk

- Dr. Baddour

- Dr. Berbari

- Dr. Osmon

- Dr. Razonable

- Dr. Steckelberg

- Dr. Wilson

- Dr. Walker

- Dr. Tande

- Dr. Sia

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Thank you

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Rapid Diagnostics in Clinical Practice

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Division of
INFECTIOUS DISEASES

Mayo Clinic Infectious Diseases Subspecialties Update
May 7-9, 2015

Disclosure of Relevant Financial Relationships

Nature of Relevant Financial Relationship	Name of Company(s)
Consultant	St. Jude, Thermo Fisher Scientific, Curetis
Grant/Research Support	Pfizer, Pradama, Tornier, Astellas, Pocared, ECI Biotech, nanoMR, BioFire, Curetis, Check-Points, National Institutes of Health, 3M, Cubist/Merck, Hutchison Biofilm Medical Solutions, Accelerate Diagnostics, Actavis (Instrument Evaluations: bioMérieux, Bruker, Abbott, Nanosphere, Siemens, BD)
Full-time/part-time Employee	Mayo Clinic; Associate Editor's Stipend for Journal of Clinical Microbiology; Vice Chair/Chair ICAAC Program Planning Committee (volunteer)
Patents	*B. pertussis* PCR, anti-biofilm substance, device/method for sonication
Off–label use	Biotyper

MAYO CLINIC

Objectives

Upon completion of this session, participants should be better able to:

- State the applications of matrix-assisted laser desorption ionization time-of-flight mass spectrometry in clinical microbiology

- Appraise the potential value of laboratory automation and rapid antimicrobial susceptibility testing

- Recognize how rapid panel-based and broad-range molecular diagnostics work

Outline

1. Rapid bacterial identification
2. Laboratory automation
3. Rapid antimicrobial susceptibility testing
4. Rapid panel-based molecular diagnostics for direct detection of microorganisms in clinical specimens
5. Broad-range microbial diagnostics

Outline

1. Rapid bacterial identification
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Matrix-Assisted Laser Desorption Ionization Time-of-Flight (MALDI TOF) Mass Spectrometry (MS)
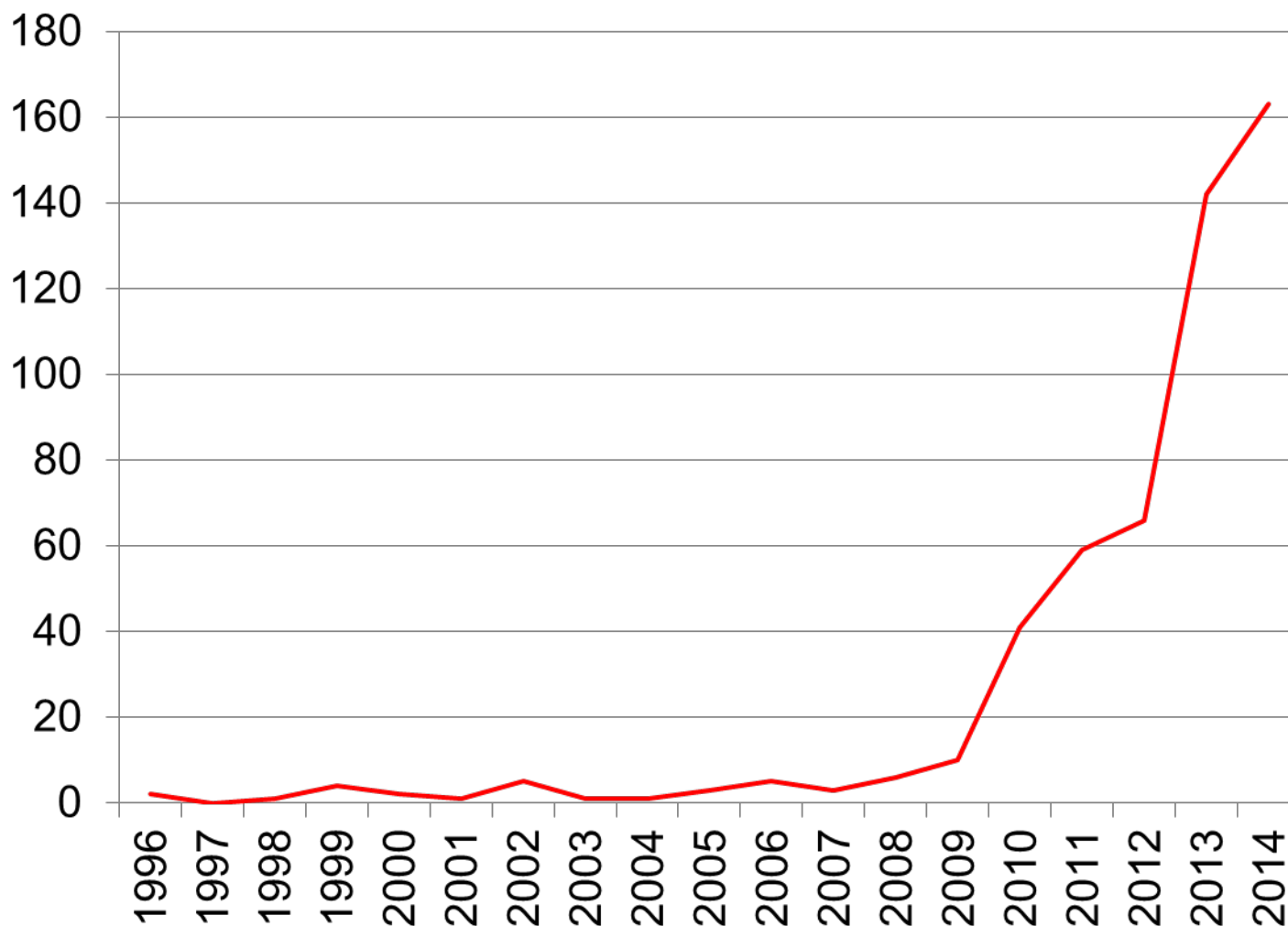
Workflow with MALDI TOF MS
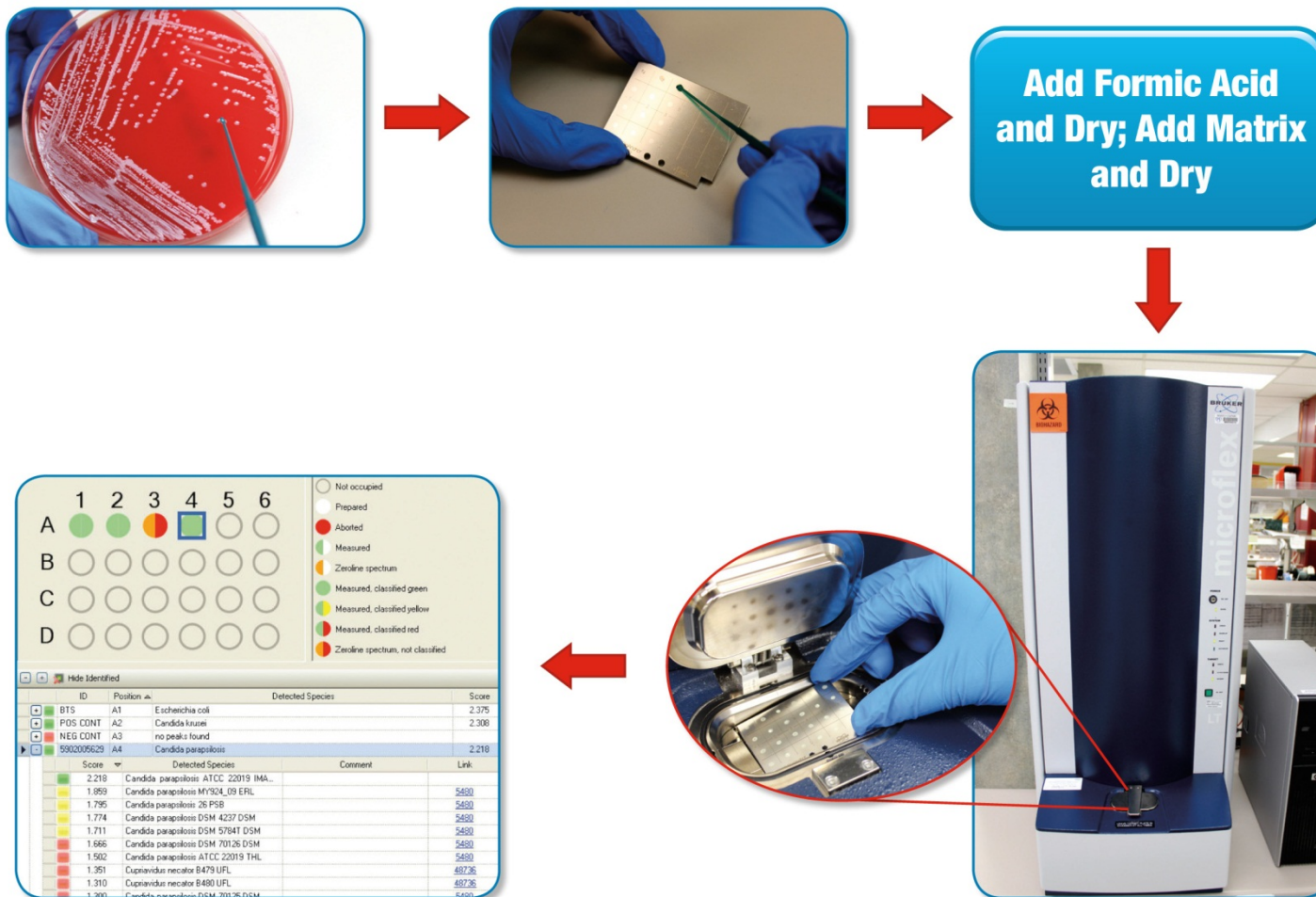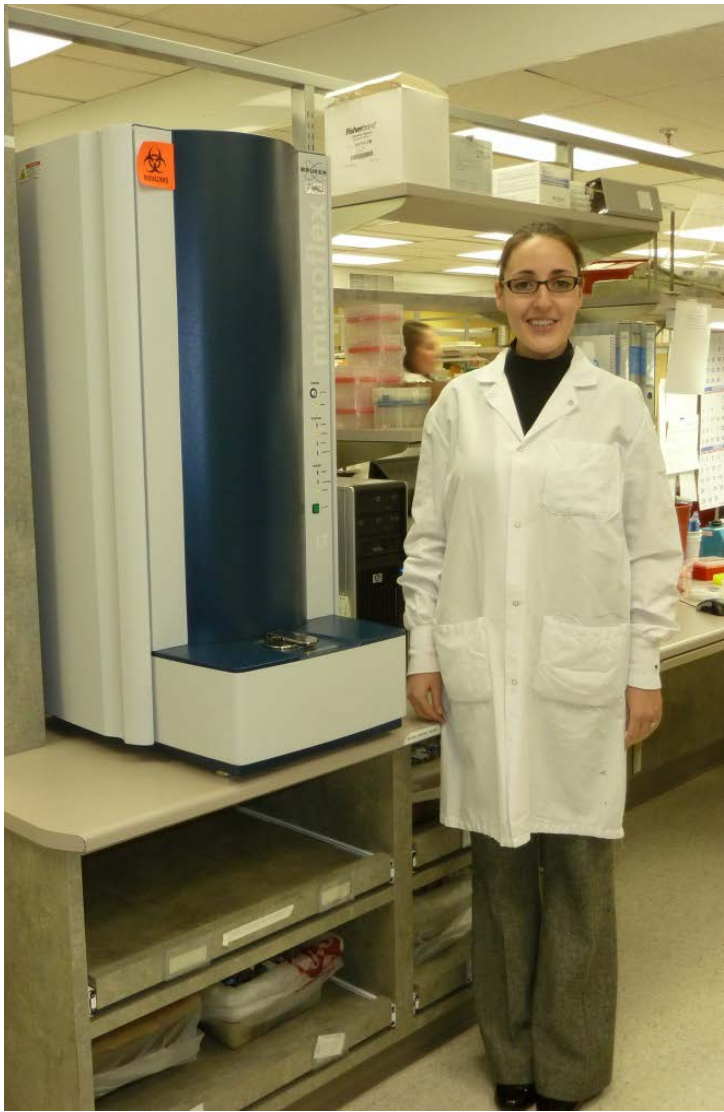
MALDI TOF MS

1. **70% formic acid (1 µl)**

2. **Add colony**

3. **Add matrix (1-2 µl)**

$$HC=C-COOH$$
CN
OH
α-cyano-4-hydroxycinnamic acid
(CHCA)
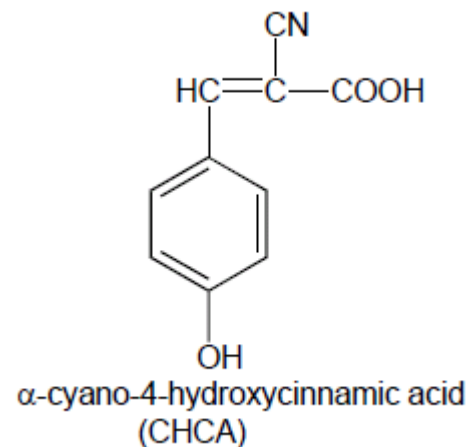
Dissolved in acetonitrile (50%) & 2.5% trifluoroacetic acid

4. **Dry – room air 5 min**
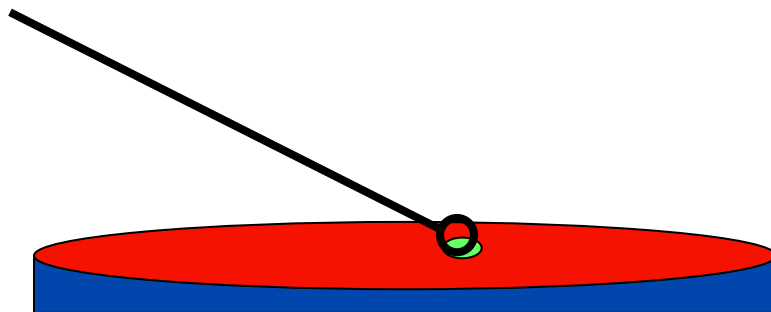
MALDI TOF MS
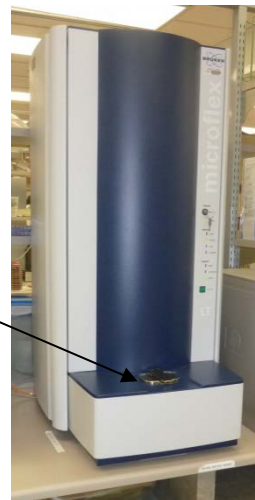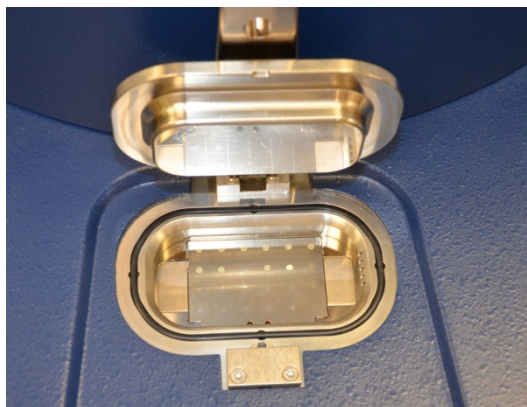
MALDI TOF Mass Spectrometer
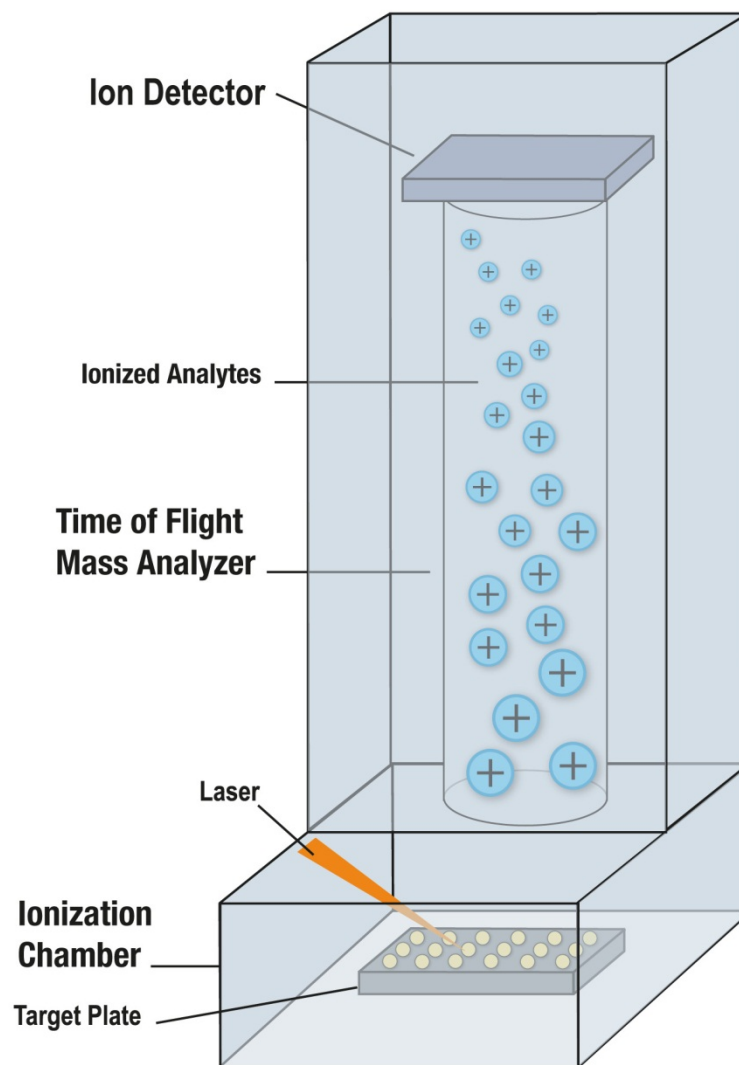
Matrix-Assisted Laser Desorption Ionization

Matrix

Analyte

Target plate
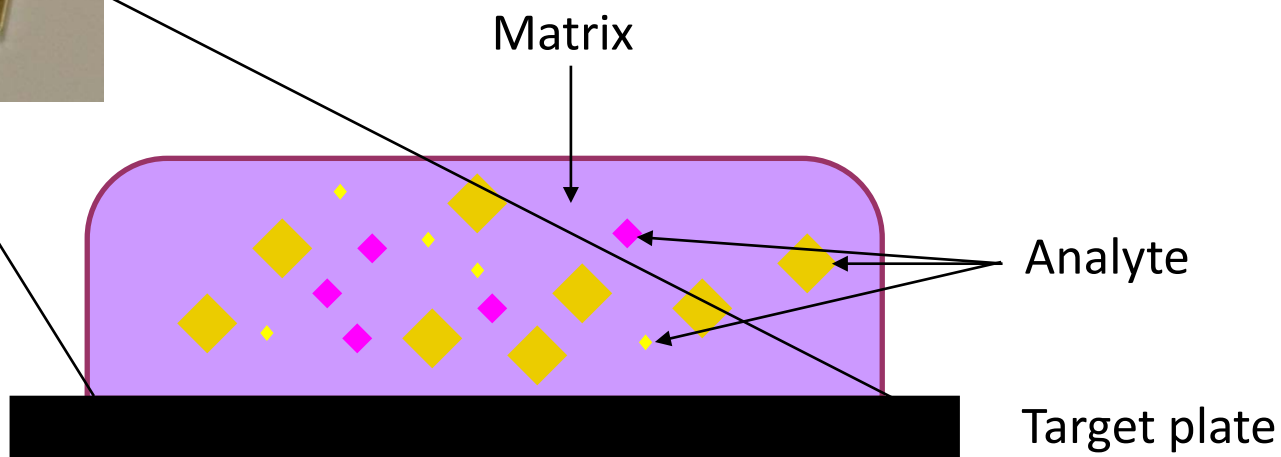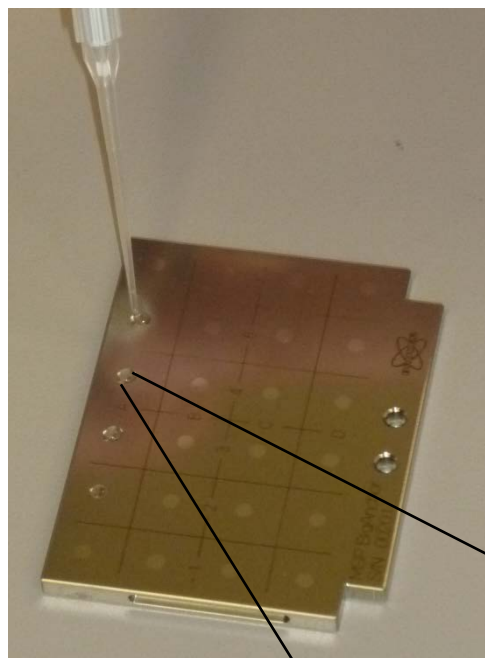
Matrix-Assisted **L**aser Desorption Ionization
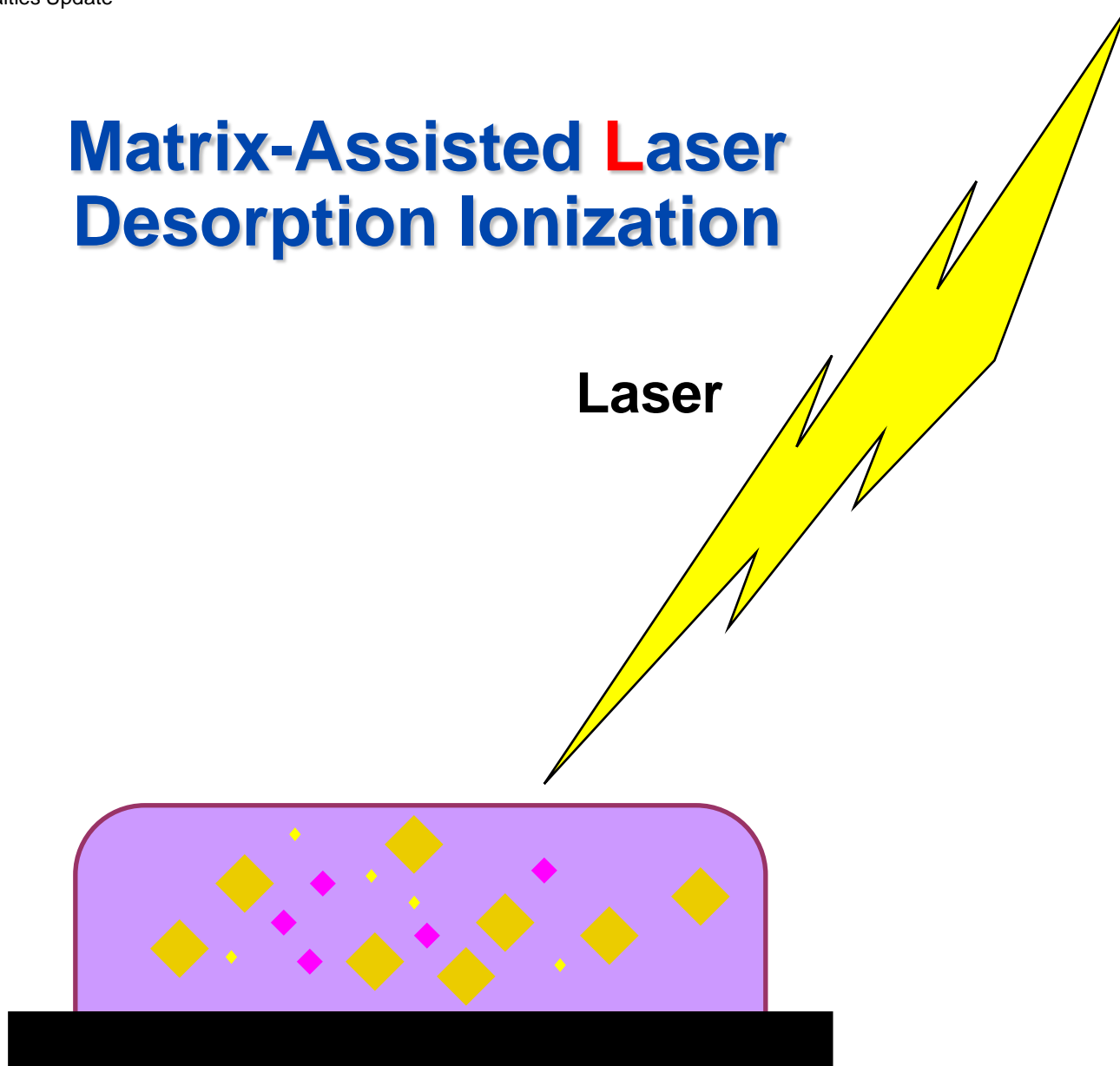
Laser

Matrix-Assisted Laser Desorption Ionization
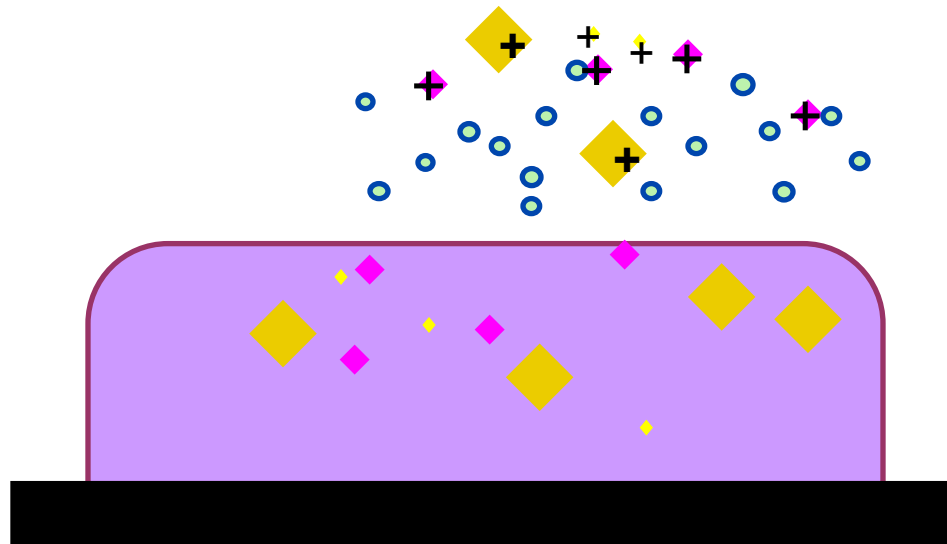
Time of Flight

Detector

Drift region

Accelerating potential
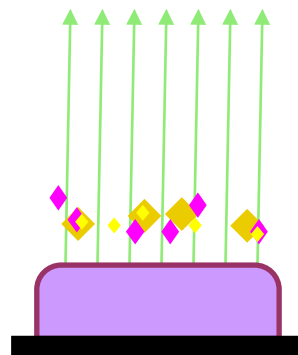
Mass Spectrum Generated Compared with Library (Database)
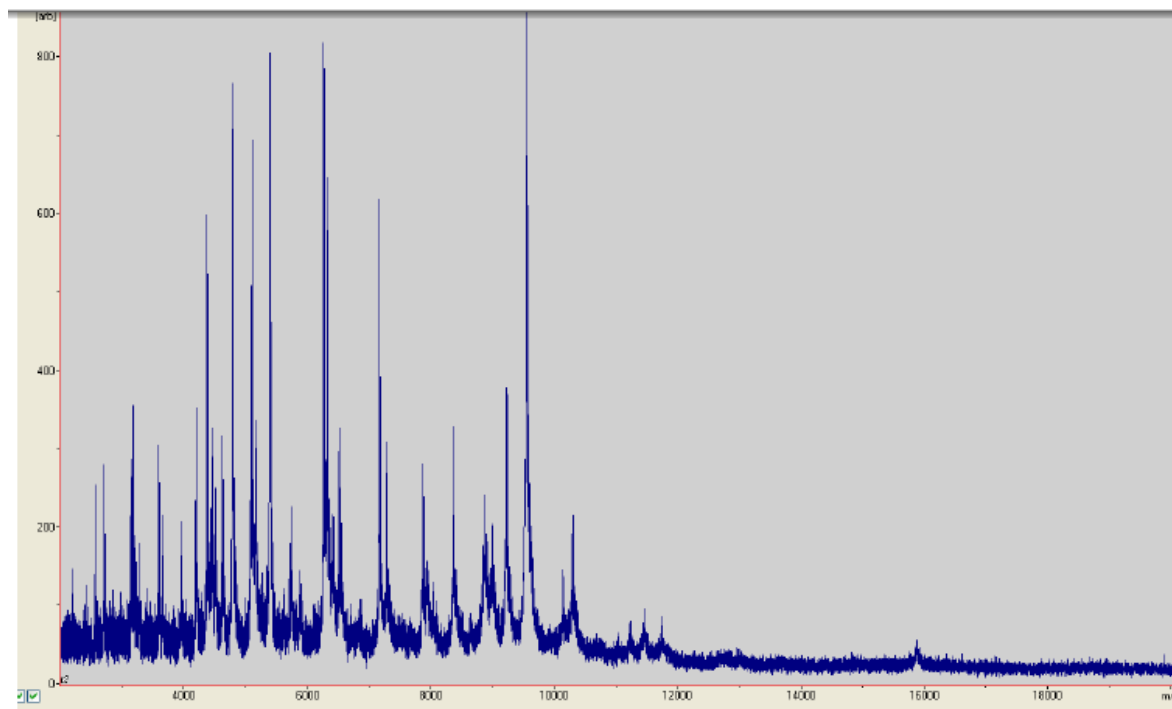
Routine Identification of Bacteria by MALDI TOF MS

- ## Routine MALDI TOF MS vs. conventional identification
  - Aerobes, anaerobes; multiple sources; 16 weeks
  - Vitek 2 and API ANA identification strip
  - Discrepant resolution - 16S rRNA gene, *rpoB* sequencing
  - Bruker Biotyper database, version 2.0 complemented with local database

- ## Mean time MALDI TOF MS identification - 1 isolate in 6 min

MALDI TOF identification	Routine phenotypic identification, no. of isolates			
	Species identification	No identification	Misidentification	Total
Species identification	1392	4	1	1397
Genus identification	185	2	2	189
No identification	18	26	2	46
Misidentification	27	0	1	28
Total	1622	32	6	1660

Seng et al. Clin Infect Dis 2009;49:543

Bruker Biotyper MALDI TOF Mass Spectrometry
versus
BD Phoenix Automated Microbiology System Identification of Gram Negative Bacilli

```
              Common
            Gram negative
            bacilli*- 308
           /              \
     Phoenix          Mass Spectrometry
                          (Bruker)
      /    \              /        \
  Genus   Species     Genus     Species
294 (95%) 285 (93%)  296 (96%)  286 (93%)
```
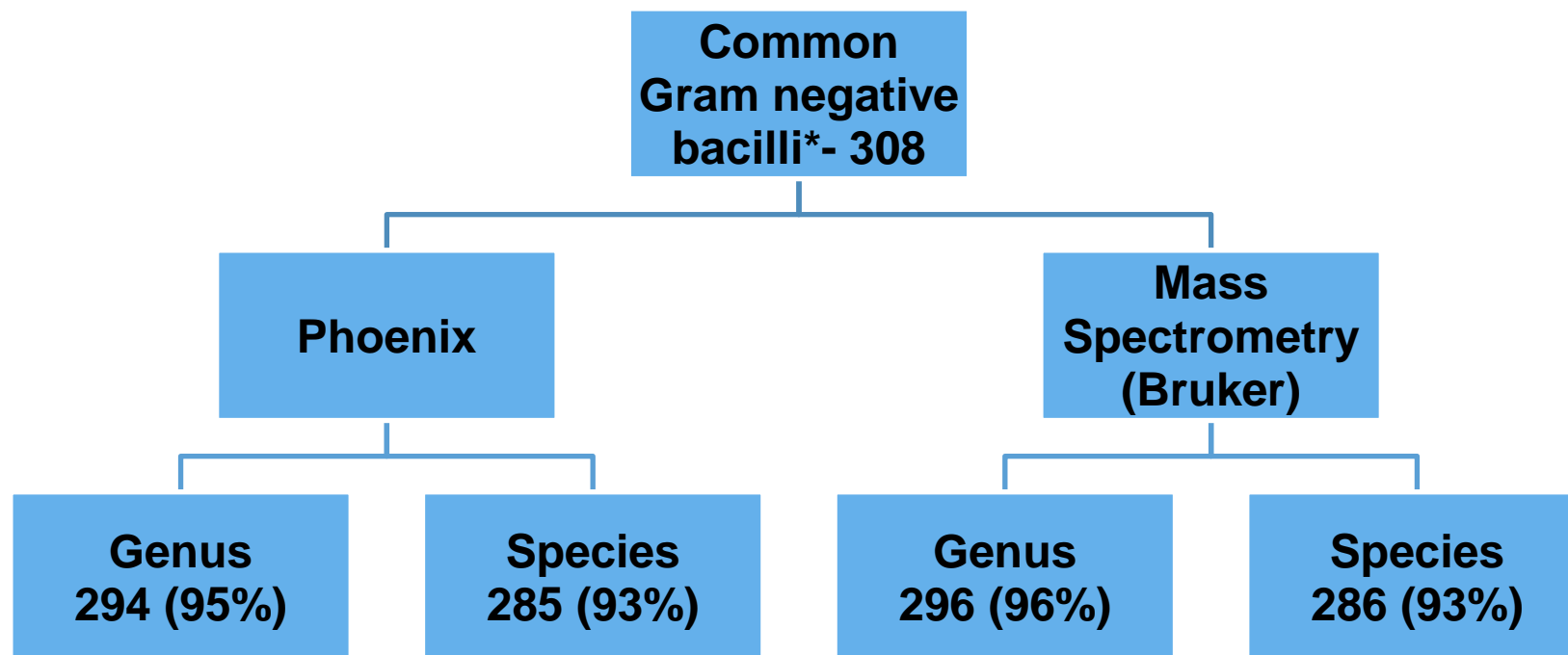
*>1 isolate/week: *Acinetobacter* species, *Acinetobacter ureae*, *Citrobacter freundii* complex, *Citrobacter koseri*, *Escherichia coli*, *Enterobacter aerogenes*, *Enterobacter cloacae* complex, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Klebsiella* species, *Morganella morganii*, *Pantoea agglomerans*, *Proteus mirabilis*, *Providencia rettgeri*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Stenotrophomonas maltophilia*

Saffert et al. J Clin Microbiol 2011;49:887

Bruker Biotyper MALDI TOF Mass Spectrometry
versus
BD Phoenix Automated Microbiology System Identification of Gram Negative Bacilli

Saffert et al. J Clin Microbiol 2011;49:887
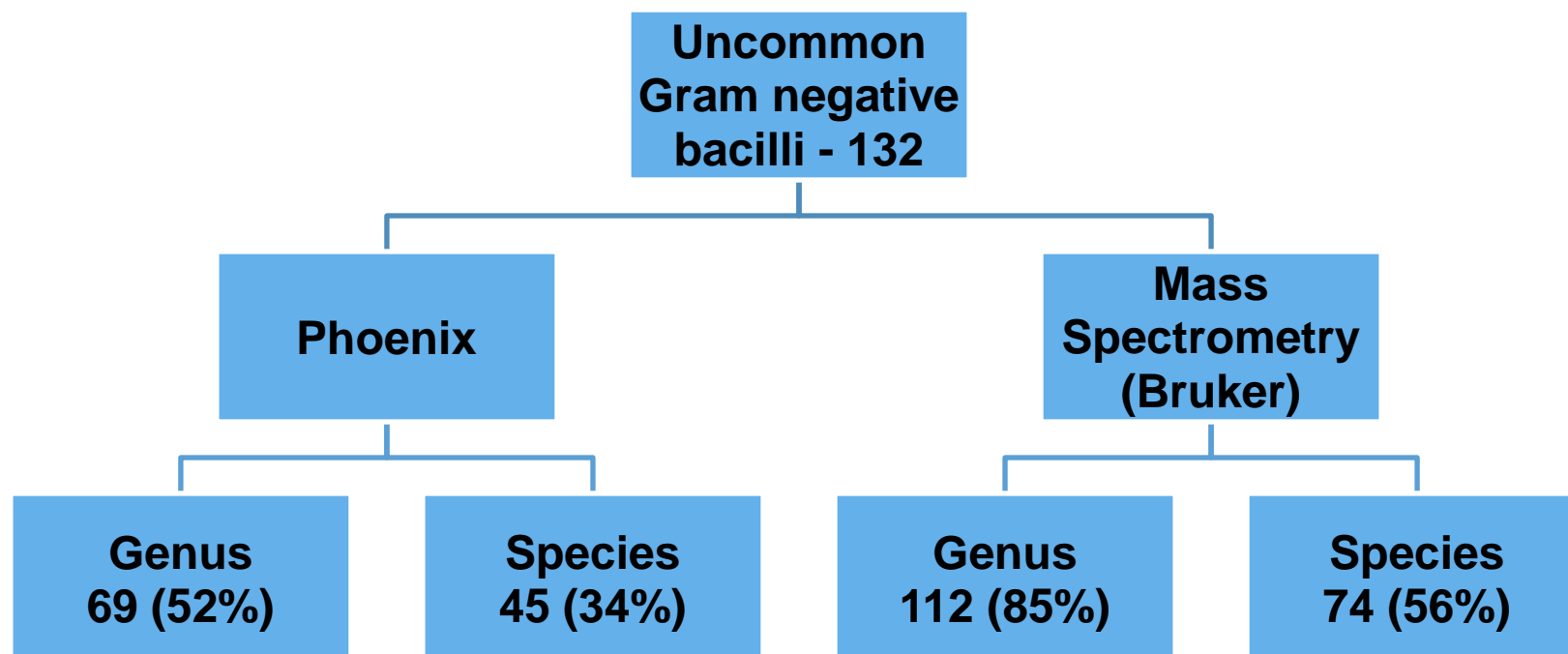
Bruker Biotyper MALDI TOF Mass Spectrometry Gram Positive Cocci

Alatoom et al. J Clin Microbiol 2011;49:2868
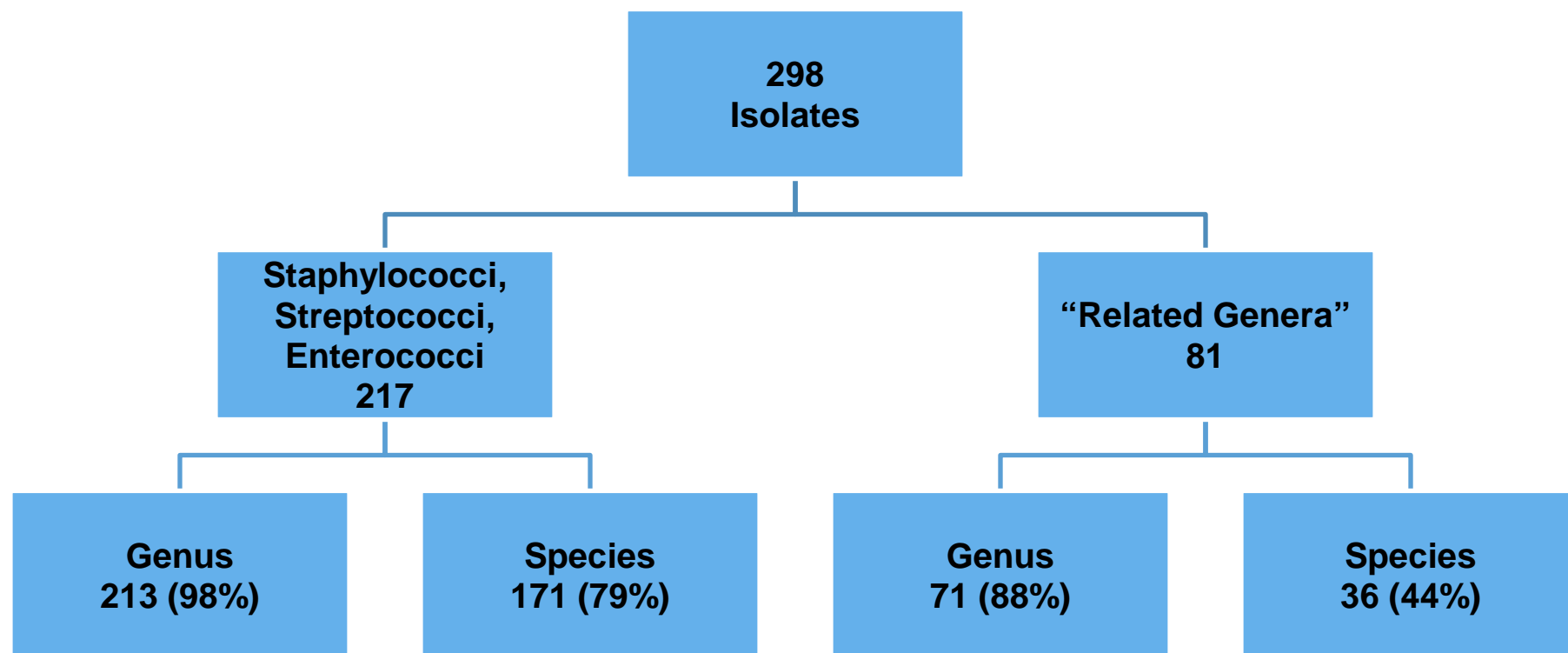
Cost Comparisons Bacterial Identifications (*Estimated*)

	Time/ test (hour)	FTE Cost/test*	Supply Cost/test	Total Cost
Rapid Biochemicals	0.10	$4.14	$0.29	$4.43
Automated Biochemicals	0.14	$5.79	$9.59	$15.38
Long Biochemicals	0.33	$13.65	$5.32	$18.97
Sequencing	0.73	$30.19	$20.02	$50.21
MALDI TOF MS	**0.05**	**$2.07**	**$0.24**	**$2.31**

*FTE cost/hour $41.35

MALDI TOF MS
Time-to-Identification, Cost-Effectiveness

• Improves turnaround-time for bacterial and fungal identification by 1.45 days (average)

• ~87% isolates identified on 1st day (compared with 9% with standard techniques)

- Final identifications 1 day earlier for most organisms
- Several days earlier for biochemically inert, fastidious, or slow-growing organisms
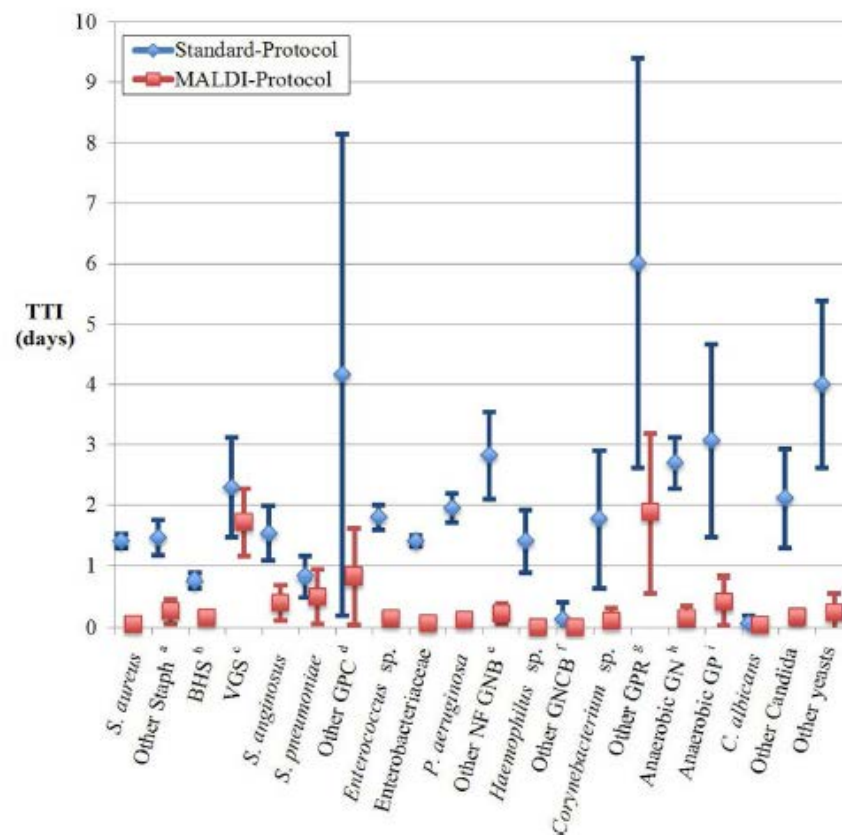
Tan et al. J Clin Microbiol 2012;50:3301-8.

Historical Bacteriology Laboratory Workflow

Accessioning

Culture to appropriate media

Rapid Biochemical   Automated Instruments   Long Biochemicals   Sequencing

Phoenix 100 Automated Microbiology System   Fluorescence Microscopy

Workflow with MALDI TOF MS

Receiving and accessioning

Culture to appropriate media

MALDI TOF MS/Quick biochemicals   Sequencing

Outline

1. Rapid bacterial identification
2. Laboratory automation
3. Rapid antimicrobial susceptibility testing
4. Rapid panel-based molecular diagnostics for direct detection of microorganisms in clinical specimens
5. Broad-range microbial diagnostics
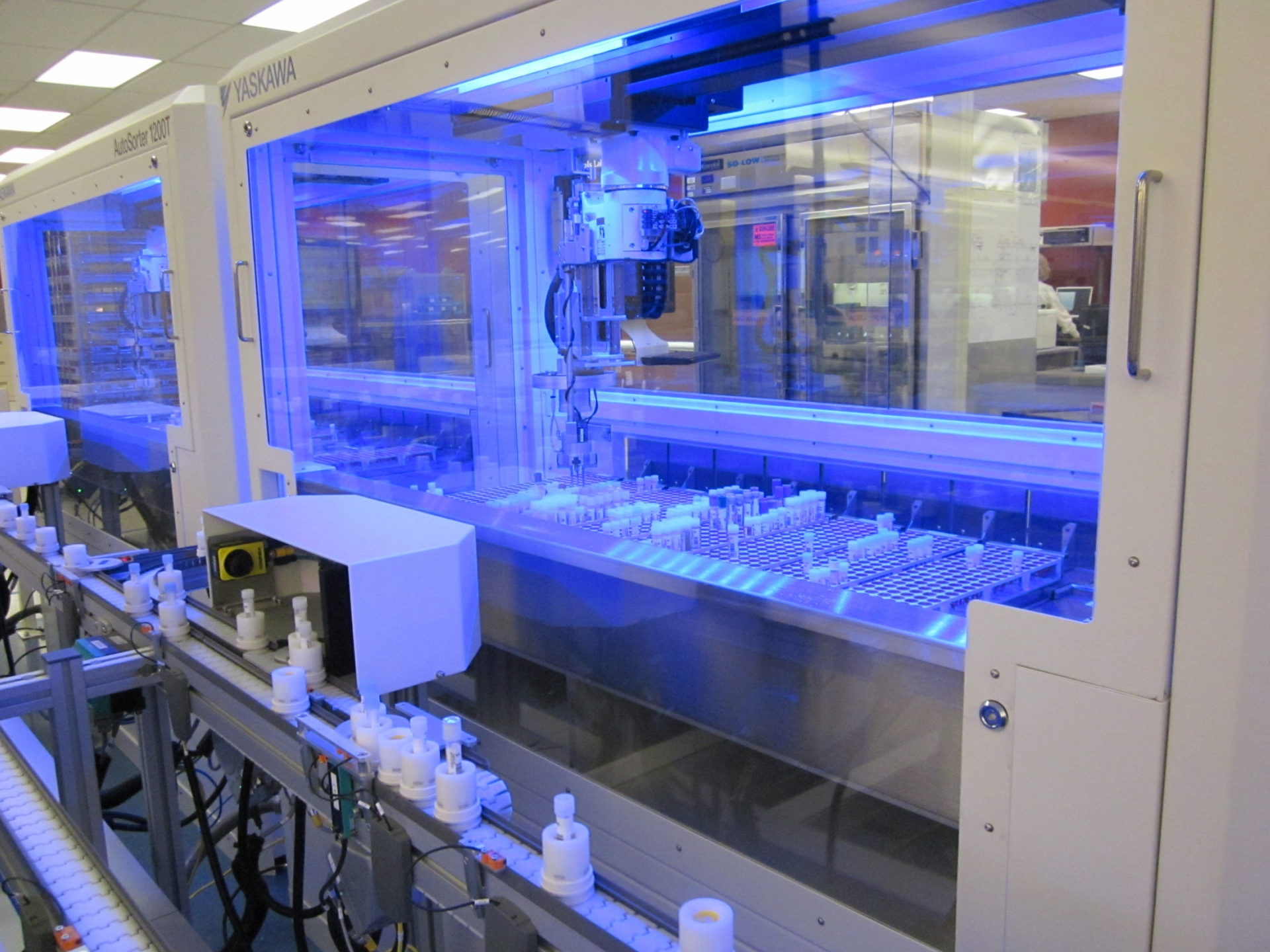
Automated Specimen Processing

Instrument	Specimen type	Inoculation technique	Capacity (plates inoculated/h)
Innova **BD**	Liquid based specimen	Loop	180
InoquIA FA/MI (Full Automation/Manual Interaction) **BD-Kiestra**	Liquid based specimen (FA) Swab (MI)	Bead	400
PREVI Isola **bioMérieux**	Liquid based specimen	Comb	180
WASP™ (Walk away specimen processor) **Copan**	Liquid based specimen	Loop	180

Total Laboratory Automation

Wasp Lab

BD-Kiestra

bioMérieux FMLA (Full Microbiology Lab Automation)
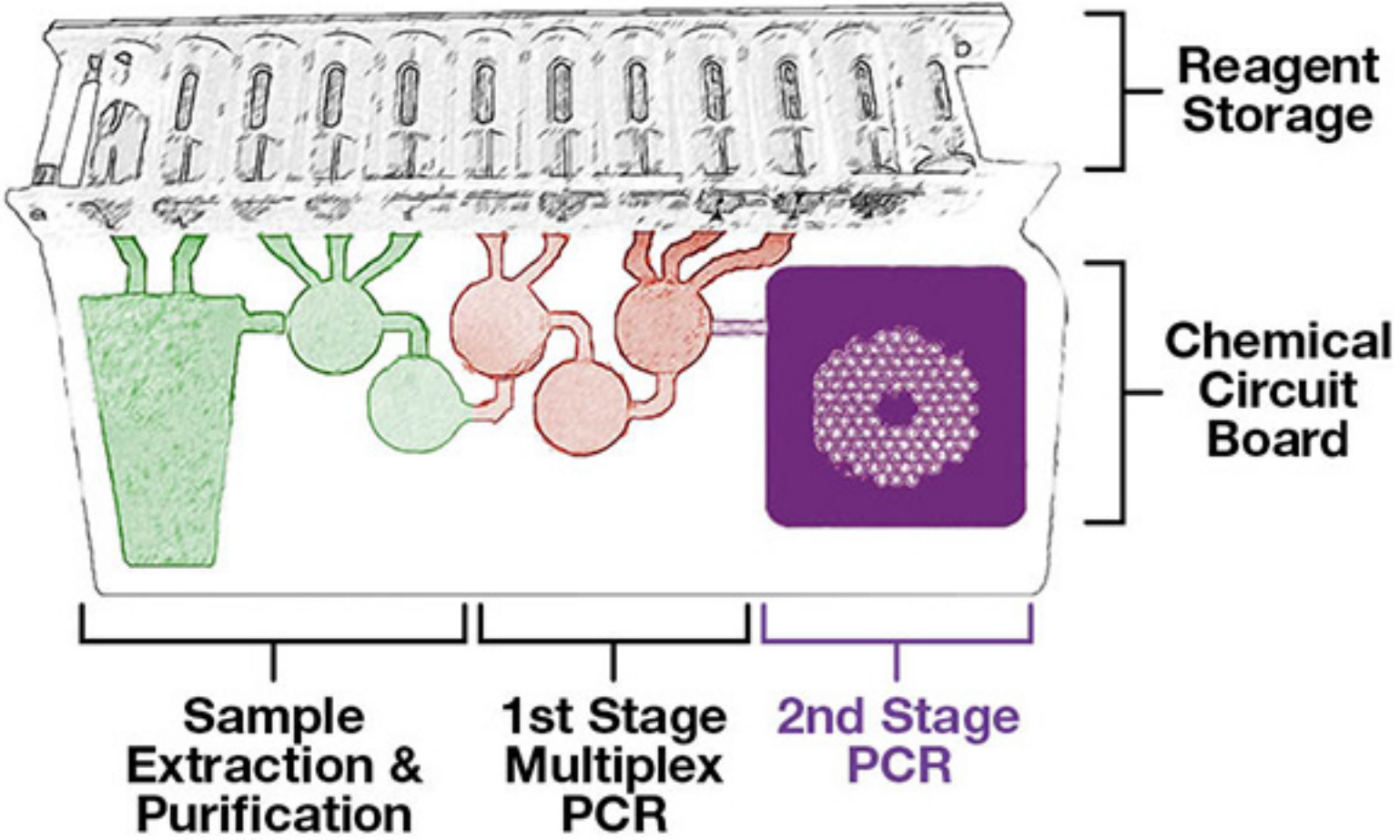
Digital Imaging
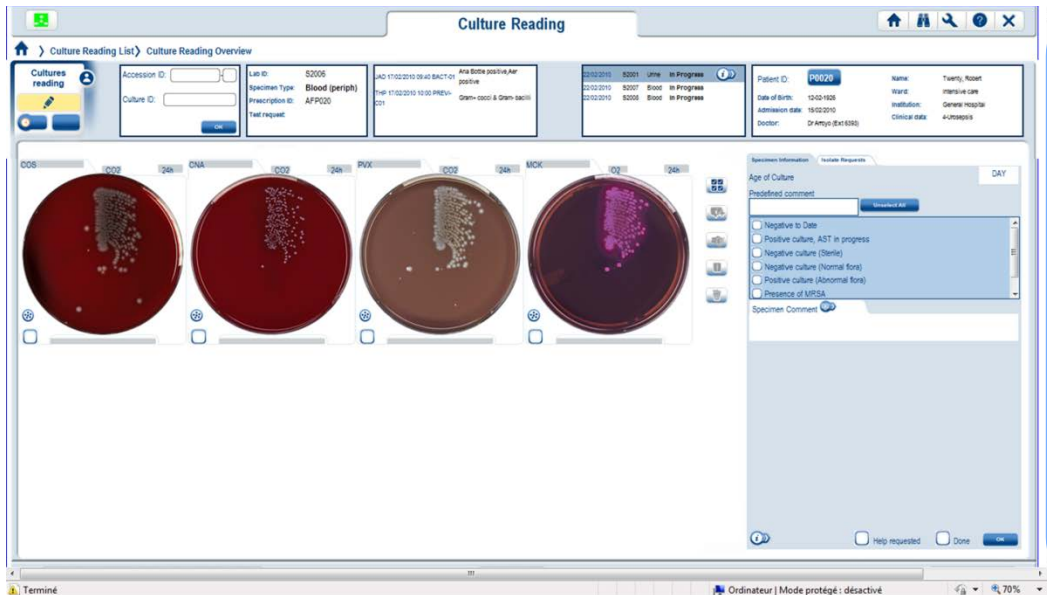
bioMérieux

BD

Outline

1. Rapid bacterial identification
2. Laboratory automation
3. **Rapid antimicrobial susceptibility testing**
4. Rapid panel-based molecular diagnostics for direct detection of microorganisms in clinical specimens
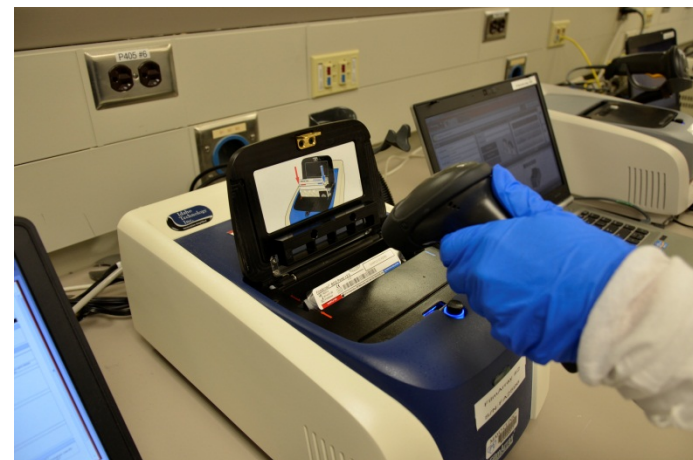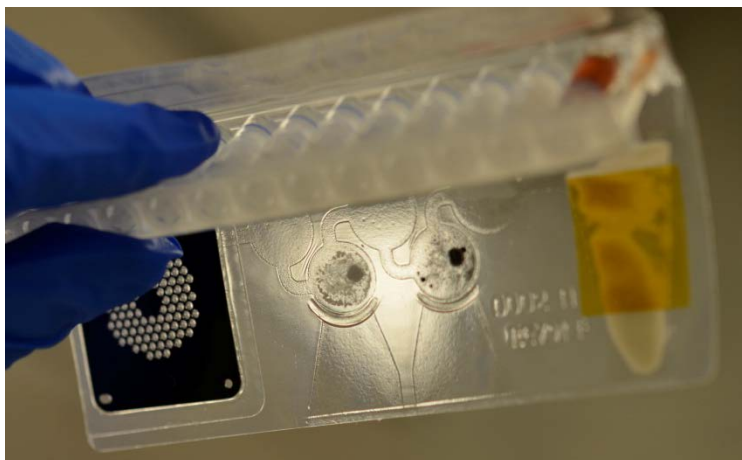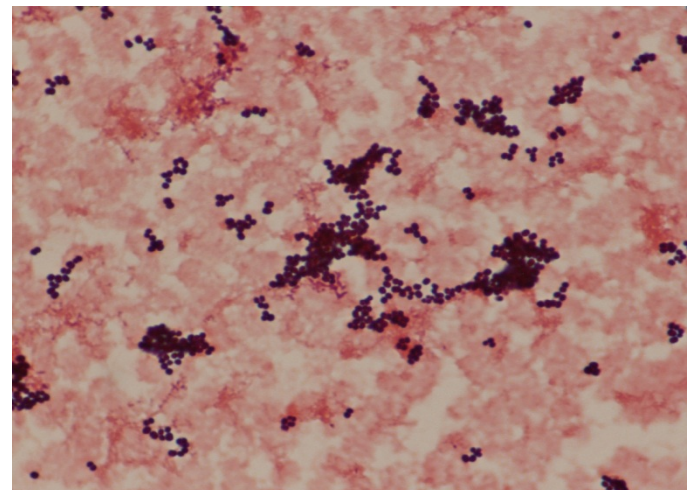5. Broad-range microbial diagnostics

MAYO CLINIC

Rapid Phenotypic Susceptibility Testing Accelerate ID/AST

- Positive blood culture bottle
- 1 hour Identification
  - Polymicrobial infection detection
  - Universal probe to detect, or rule-out, non-target organisms
- 5 hour susceptibilities
  - MIC determination and SIR interpretation
  - Polymicrobial ASTs
- Automated
  - Scalable, sample-to-answer system

How Does It Work?

Positive blood culture bottle → Electro-filtration → Immobilization → Identification → Antimicrobial susceptibility testing

Sample → Gel electrofiltration → Electrokinetic concentration → Automated imaging and data analysis
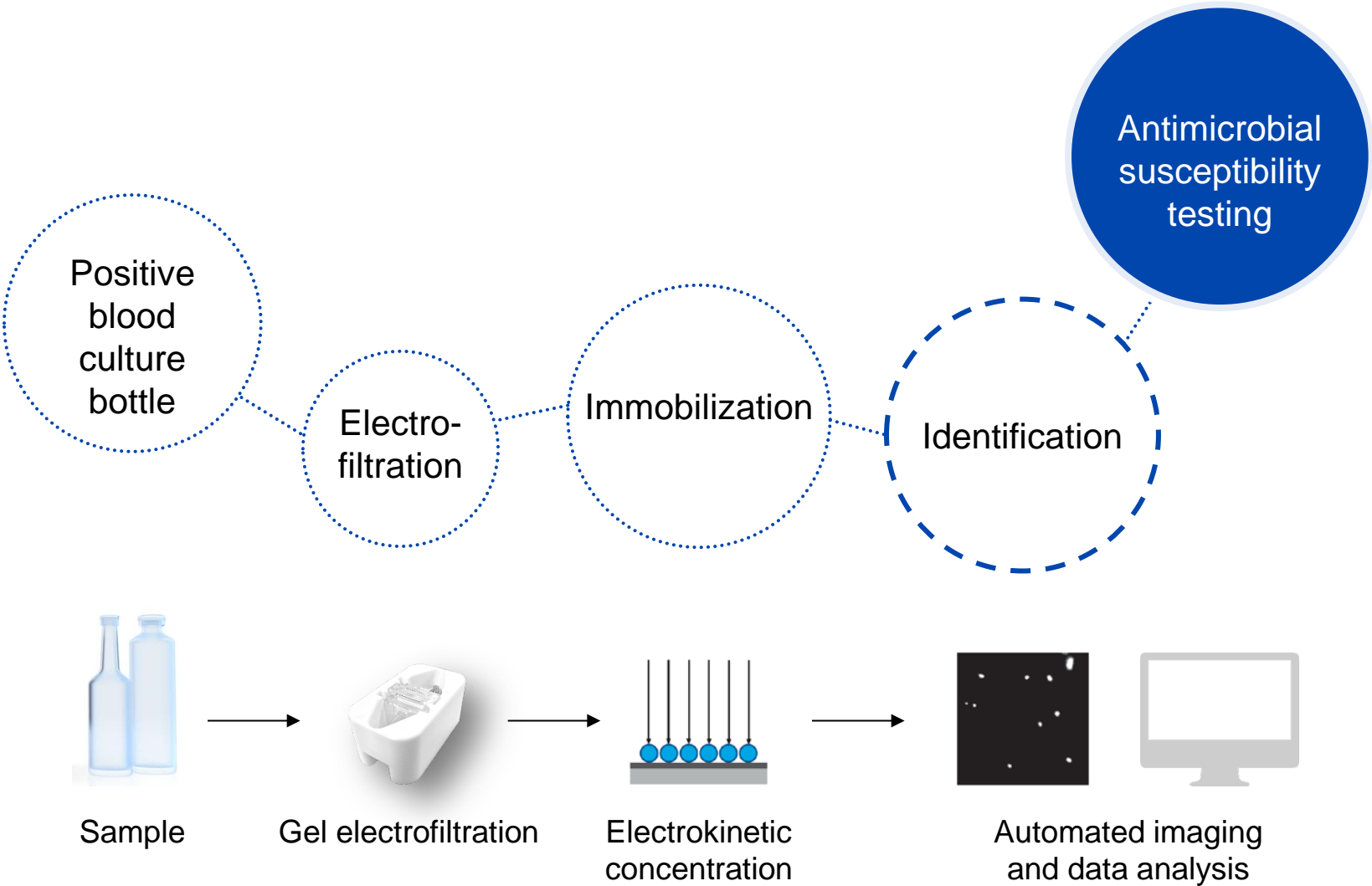
Sample Prep - Gel Electrofiltration

- Blood cells lysed
- Sample added to gel electrofiltration well (contains gel with pores smaller than bacteria)
- Positive charge applied $\rightarrow$ debris migrates into gel leaving bacteria behind.
- Negative charge applied $\rightarrow$ bacteria move to center of well for ease of retrieval.

Electrokinetic Concentration
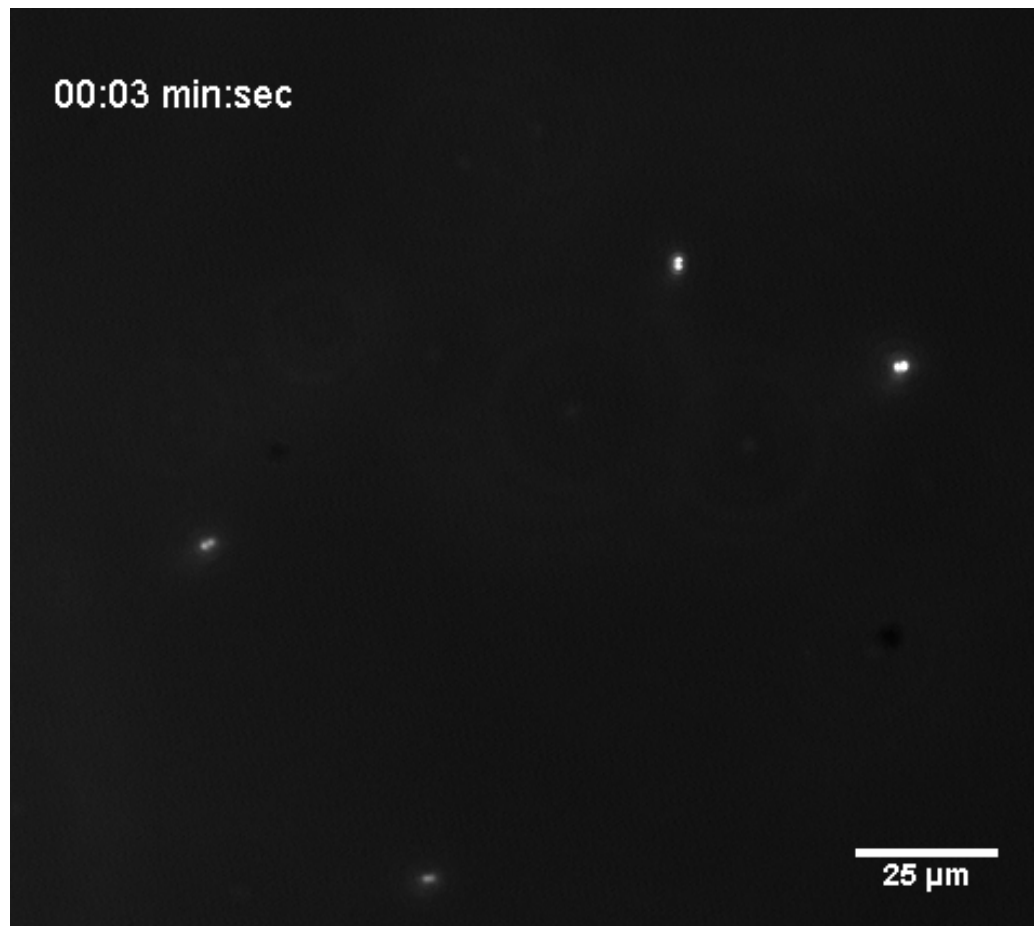
TIME-LAPSE IMAGE OF SURFACE CAPTURE IN LESS THAN 5 MINUTES

Cassette

- 19 flowcell channels for ID
- 29 flowcell channels for AST
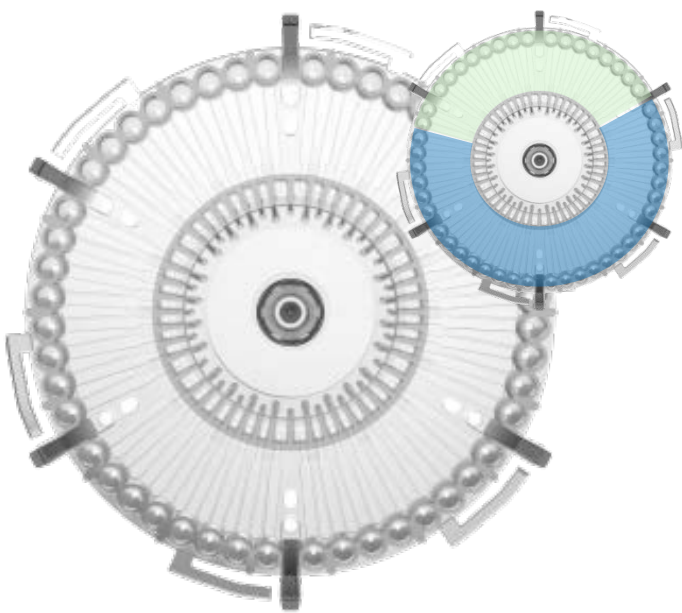
Reagent Cartridge

- 100 pipette tips
- >150 wells for antimicrobials, growth media, reagents, probes, waste
- 2 gel electrofiltration wells for sample prep

Antibiotics

Gel electrofiltraton

Sample Vial

Tips

Probes & Reagents

Gel electrofiltration
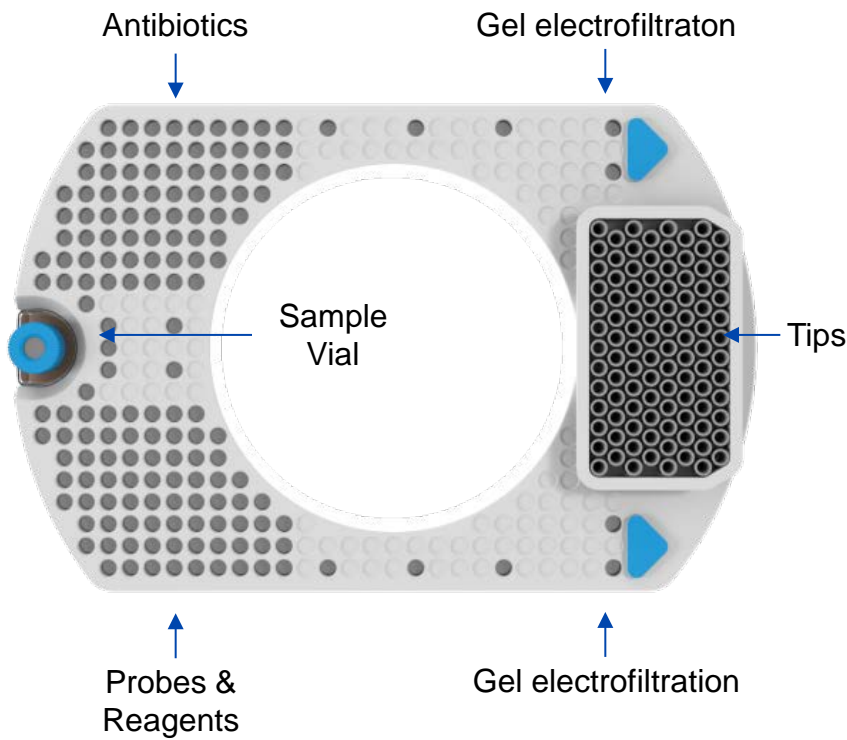
1 Hour Quantitative Identification

- Fluorescence *In Situ* Hybridization
  - 17 targets covering organisms responsible for 85-90% sepsis
  - Polymicrobial detection/identification
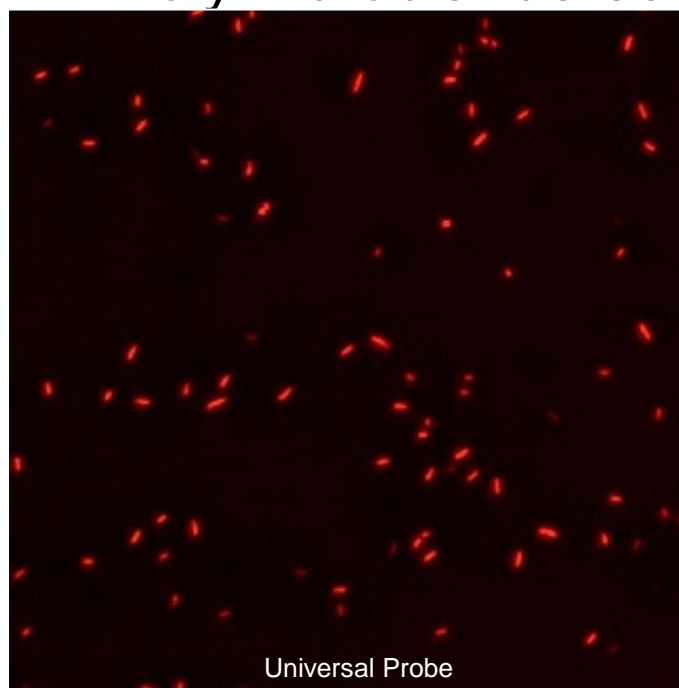
Universal Probe

Detection
Universal bacteria probe distinguishes bacteria from debris
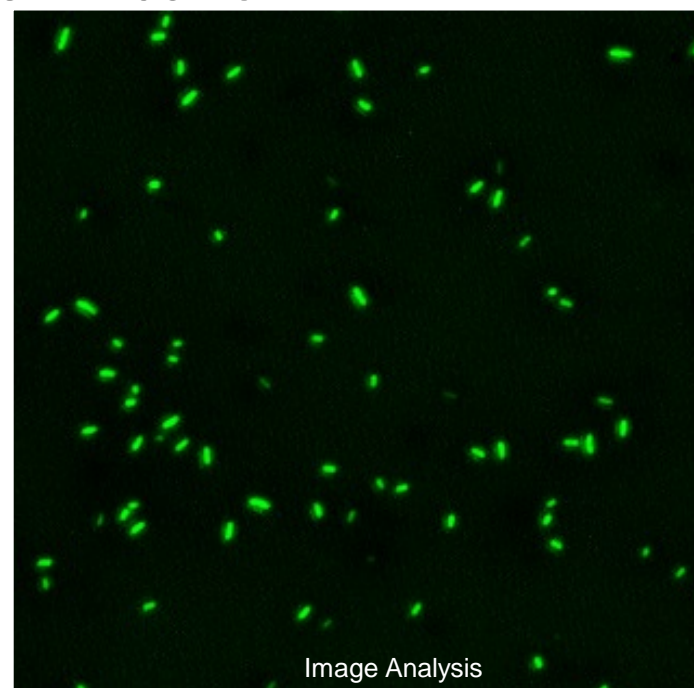
Image Analysis

Identification
Target probe identifies specific bacteria

5 Hour Antimicrobial Susceptibility Testing

- Time-lapse imaging and analysis of bacterial growth
  - Individual bacteria response to single concentration antibiotics over time
    - MIC determination and breakpoint interpretation
    - Polymicrobial susceptibility results

E. coli vs. 4 µg/mL piperacillin-tazobactam

MIC=8(S)

MIC=128(R)
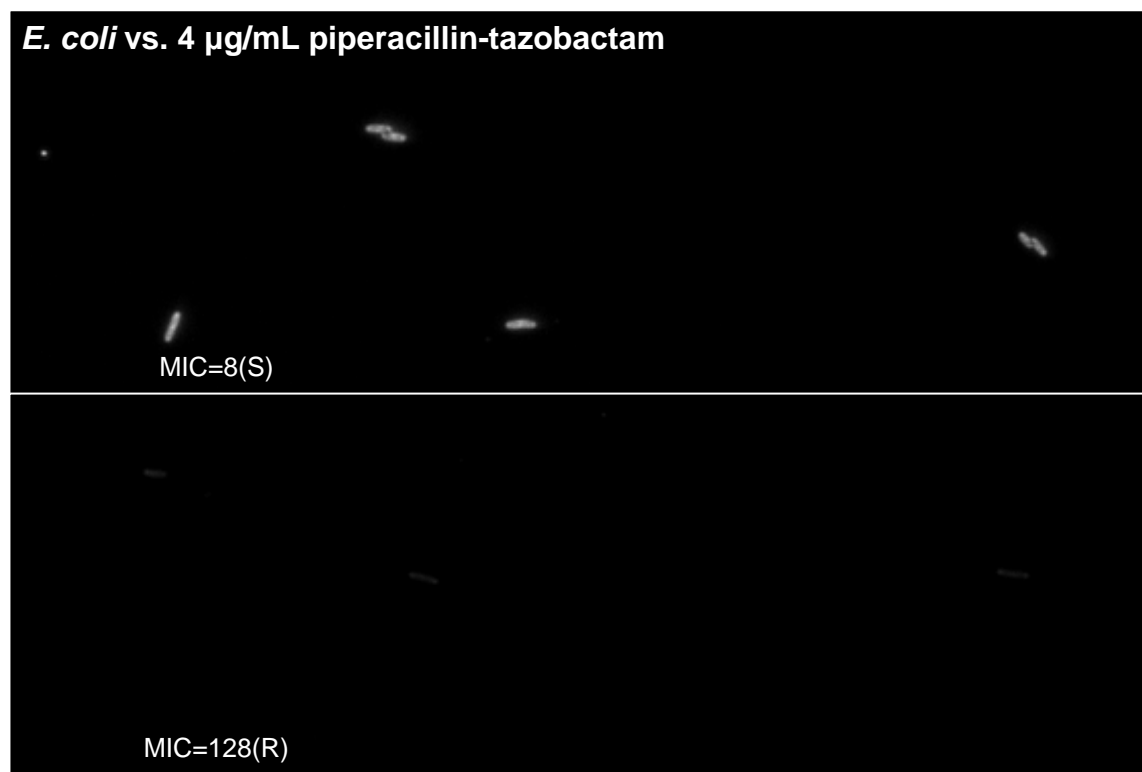
Cell Morphology Image Analysis

Species recognition - polymicrobial infection

Enables assignment of an MIC to each species
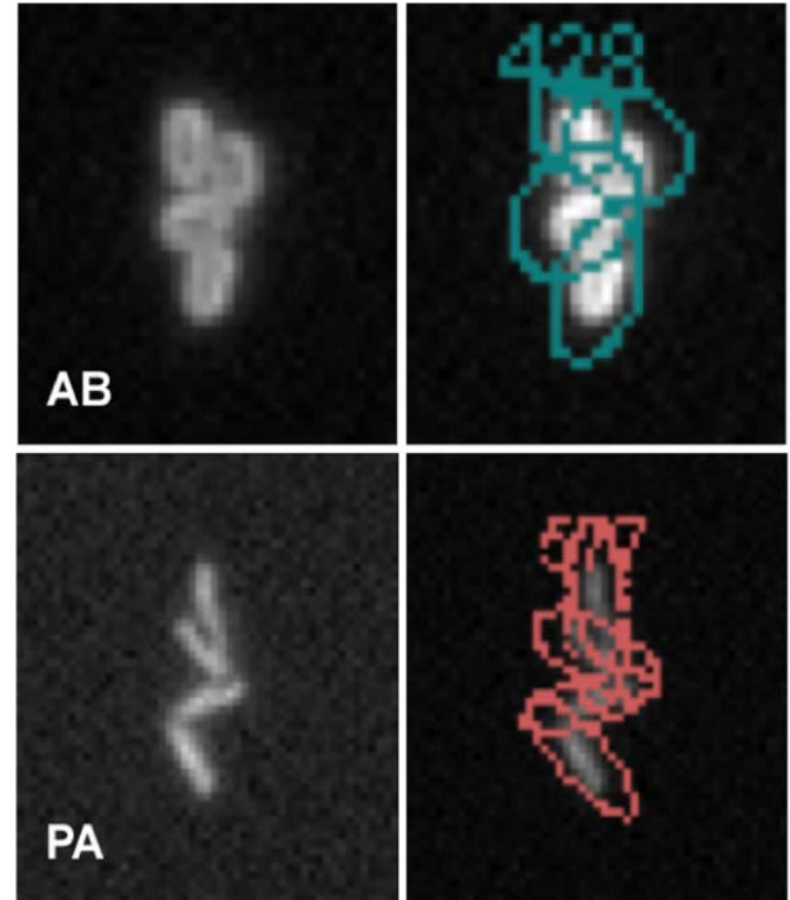
Polymicrobial Susceptibility Testing
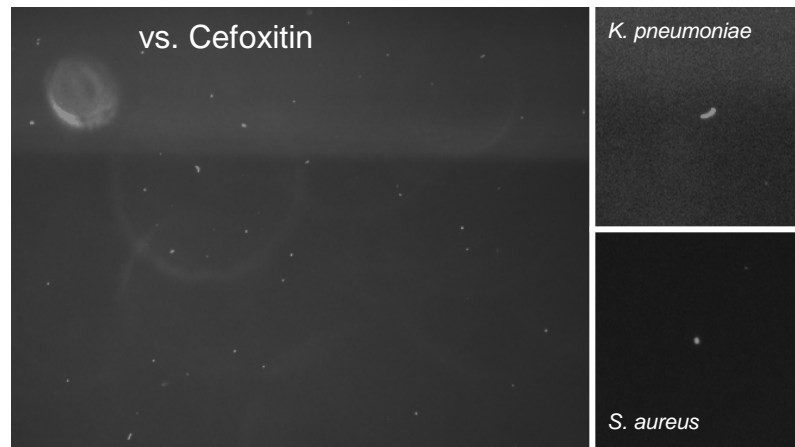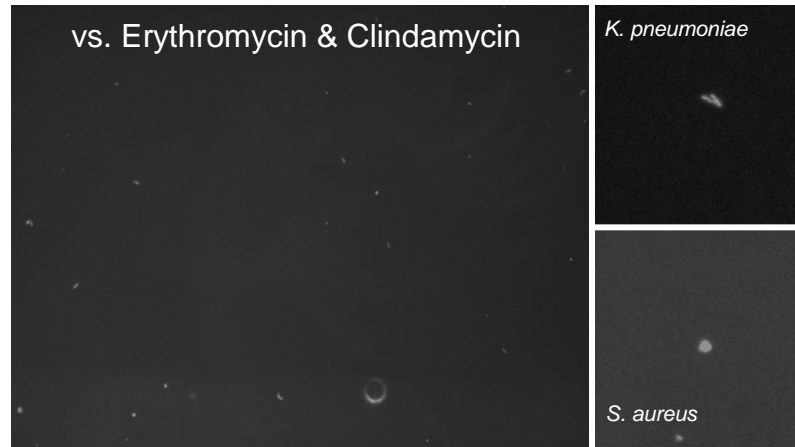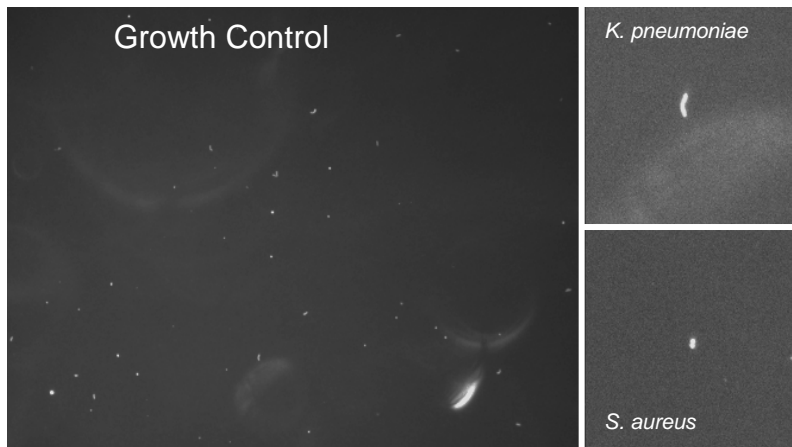
Morphology, division rates, growth patterns, signal intensity distinguish bacteria

Outline

1. Rapid bacterial identification
2. Laboratory automation
3. Rapid antimicrobial susceptibility testing
4. Rapid panel-based molecular diagnostics for direct detection of microorganisms in clinical specimens
5. Broad-range microbial diagnostics

Automated Molecular Platforms

- GeneXpert™ (Cepheid)

- BD Max™ (Becton Dickinson)

- 3M™ Integrated Cycler (Quest)

- Panther® and Tigris ® DTS ® (Gen-Probe)

- BD Viper® (Becton Dickinson)

- COBAS® AMPLICOR® (Roche Molecular Diagnostics)

- Verigene (Nanosphere)

- FilmArray (BioFire)

- Unyvero (Curetis)

FilmArray® Panels

Reagent Storage

Chemical Circuit Board

Sample Extraction & Purification

1st Stage Multiplex PCR

2nd Stage PCR

FilmArray® Blood Culture Identification Panel (BioFire)

FilmArray® Blood Culture Identification Panel
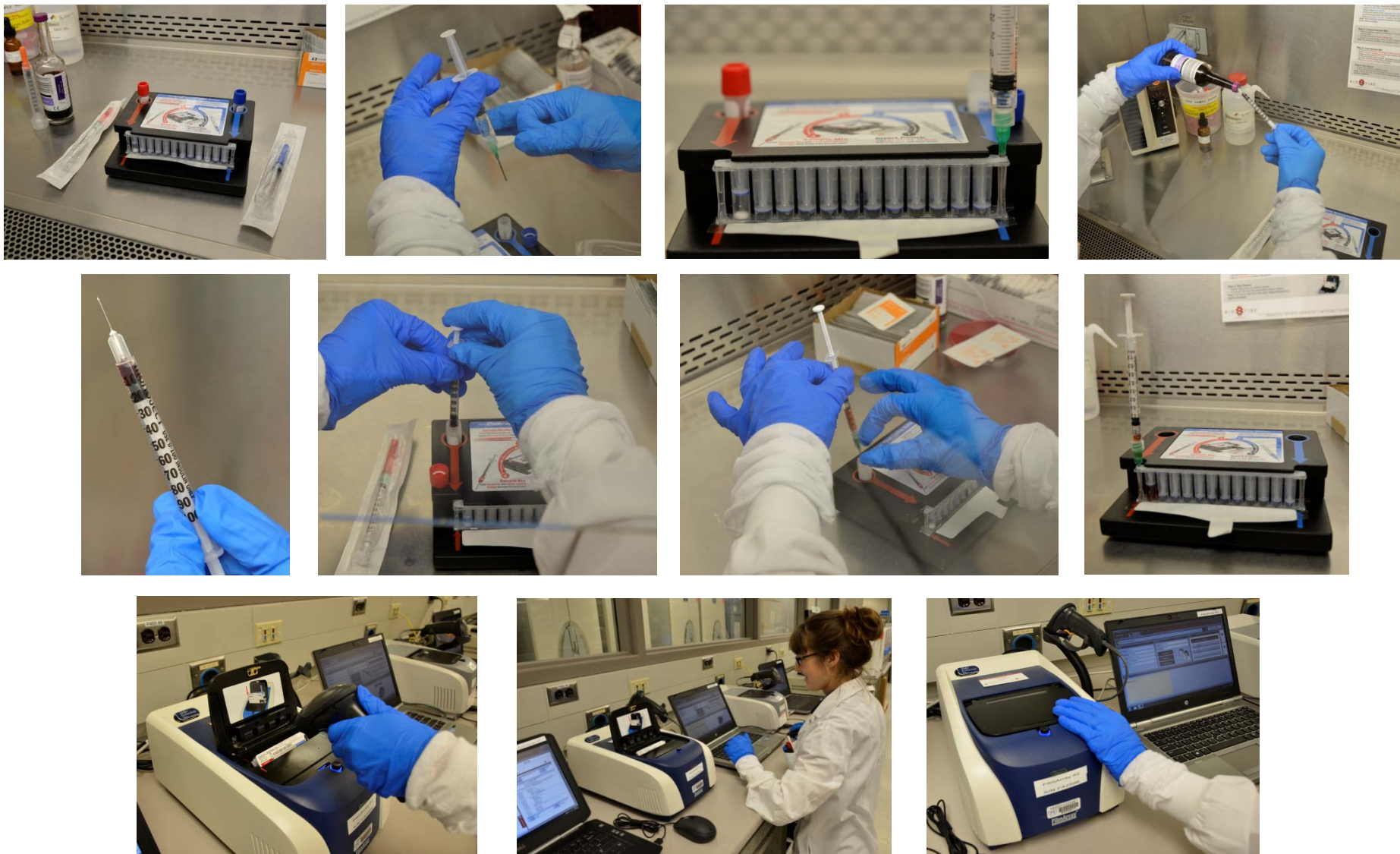
Banerjee et al. Clin Infect Dis IN PRESS

FilmArray® Blood Culture Identification Panel (BioFire)

Gram Positive Bacteria	Gram Negative Bacteria	Fungi	Resistance Genes
Staphylococcus	*Klebsiella oxytoca*	*Candida albicans*	
Staphylococcus aureus	*Klebsiella pneumoniae*	*Candida glabrata*	bla_{KPC}
Streptococcus	*Serratia*	*Candida krusei*	*mecA*
Streptococcus agalactiae	*Proteus*	*Candida parapsilosis*	*vanA/vanB*
Streptococcus pyogenes	*Acinetobacter baumannii*	*Candida tropicalis*	
Streptococcus pneumoniae	*Haemophilus influenzae*		
Enterococcus	*Neisseria meningitidis*		
Listeria monocytogenes	*Pseudomonas aeruginosa*		
	Enterobacteriaceae		
	Escherichia coli		
	Enterobacter cloacae complex		

Objectives

1. Rapid bacterial identification
2. Laboratory automation
3. Rapid antimicrobial susceptibility testing
4. Rapid panel-based molecular diagnostics for direct detection of microorganisms in clinical specimens
5. Broad-range microbial diagnostics

PCR–Electrospray Ionization Mass Spectrometry - History

1. "Triangulation identification for the genetic evaluation of risks" (TIGER)

2. Ibis T5000 Biosensor System prototype

3. Abbott Molecular acquired Ibis technology, 2008 - PLEX-ID

4. Abbott Molecular, 2014 - Iridica

MAYO CLINIC

PCR–Electrospray Ionization Mass Spectrometry Nucleic Extraction, Broad Range PCR
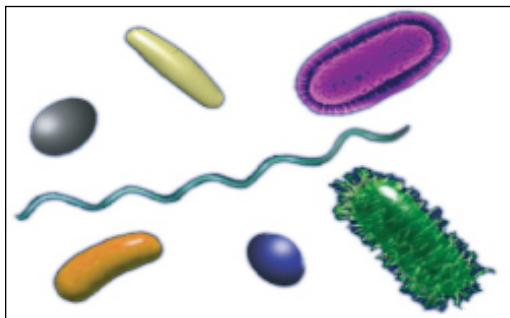
Slide courtesy of Ranga Sampath; Ecker et al. JALA 2006;11:341.
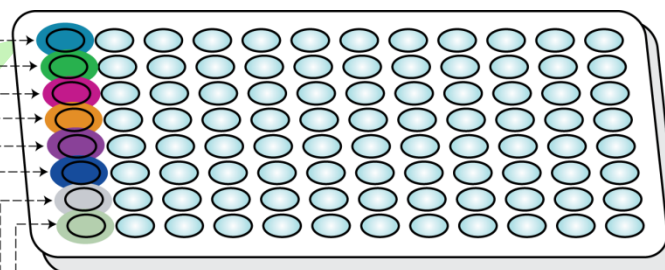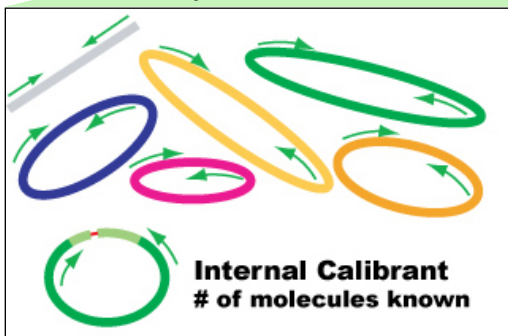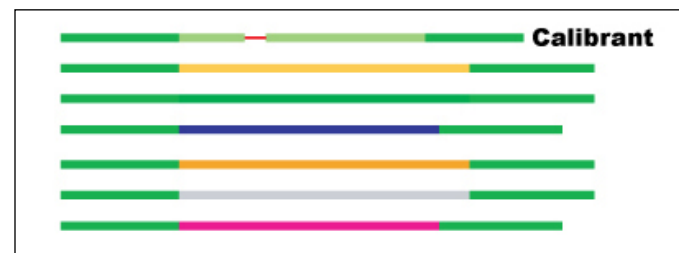
PCR–Electrospray Ionization Mass Spectrometry
Mass Spectrometry Analysis & Signal Processing

Mass Spectrometer

Sample → ESI needle
Capillary
Ion Store
Reflectron
Electron Multiplier
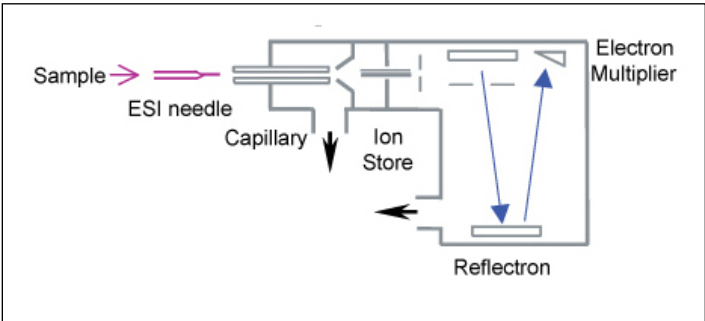
Spectral Signal
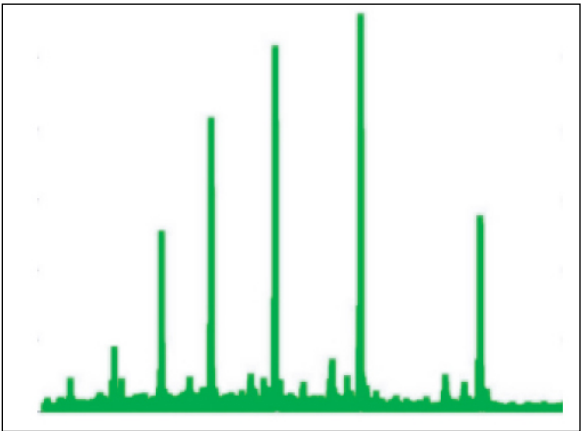
Signal Processing
Masses to Base Compositions

#	Mass	Base Count	Quantity
1	35875.03	$A_{25}G_{35}C_{30}T_{26}$	4260
2	35297.70	$A_{29}G_{33}C_{27}T_{25}$	1948
3	35619.87	$A_{26}G_{36}C_{29}T_{24}$	1555
4	36196.21	$A_{23}G_{37}C_{31}T_{26}$	1306
5	35297.70	$A_{29}G_{33}C_{27}T_{26}$	1949

Base Compositions Mapped
to Microbes

Slide courtesy of Ranga Sampath; Ecker et al. JALA 2006;11:341.

Metagenomics
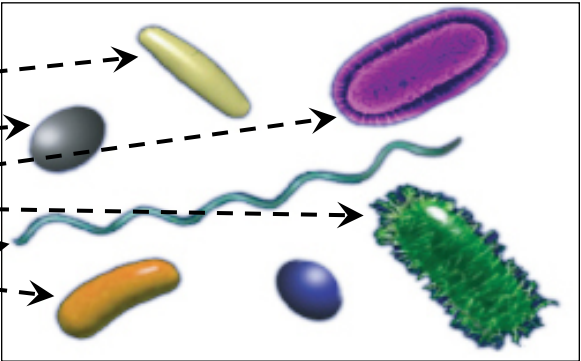
A Clinical Laboratory Workflow for NGS
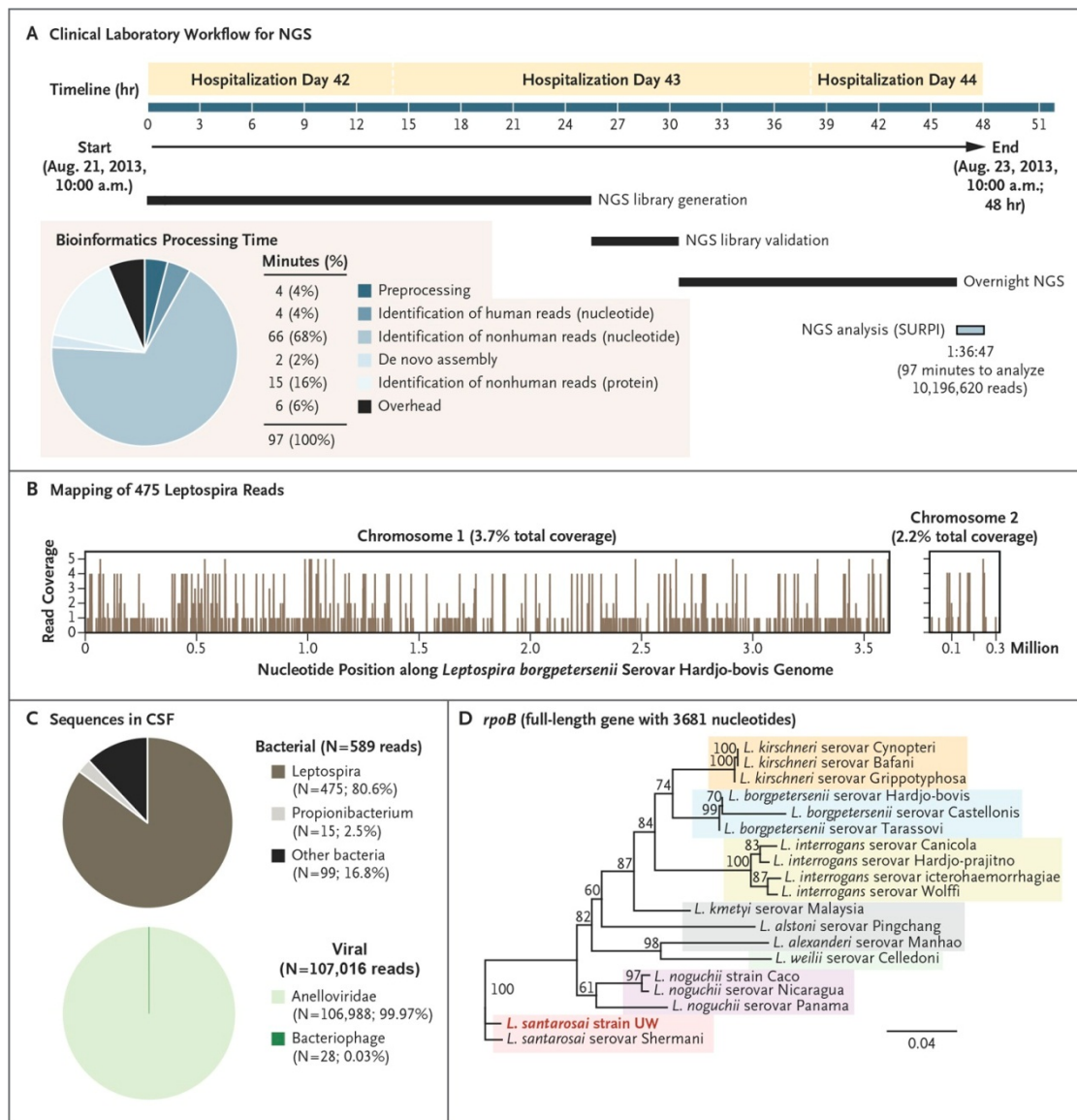
Best-case situation:
1) Any *Leptospira* species should be pathogenic in spinal fluid;
2) Clinical features were consistent with leptospirosis; and
3) Treatment was obvious (penicillin resistance not reported in *Leptospira* species)

Wilson et al. N Engl J Med 2014;370:2408
Relman. Clin Chem 2015;61:38

Broad-Range Microbial Diagnostics

- Sensitivity and specificity
  - Abundance relative to host & background organisms
  - Sequences must be identifiable

- Sequence data may not provide actionable information about drug susceptibility

- Data interpretation

- Timeliness

- Cost-effectiveness

- Clinical utility

Relman. Clin Chem 2015;61:38

Summary

1. Rapid bacterial identification
   - MALDI TOF MS

2. Laboratory automation
   - Coming soon

3. Rapid antimicrobial susceptibility testing
   - Under development

4. Rapid panel-based molecular diagnostics for direct detection of microorganisms in clinical specimens
   - Blood culture bottles, GI, respiratory (upper, lower), spinal fluid, orthopedic infection, transplant, etc.

5. Broad-range microbial diagnostics
   - Under development (PCR/ESI MS, metagenomics)

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Brenda Dylla

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Mary Jones

David Lynch

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Christine Teng, Pharm.D.

Bruker Daltonics

BioFire

Abbott

Accelerate Diagnostics

Curetis

bioMérieux

Copan

BD Diagnostics

Multiplex Molecular Testing for Viral Infections

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Division of
INFECTIOUS DISEASES

Mayo Clinic Infectious Diseases Subspecialties Update
May 7-9, 2015

Disclosures

- No corporate or financial conflicts of interest to disclose

Learning Objectives

- Review the advances that have been made in the laboratory diagnosis of viral infections

- Discuss the advantages and limitations of various diagnostic methods

- Introduce the FDA-cleared multiplex platforms for the detection of viruses in clinical samples

- Review data on the performance of multiplex tests in comparison to conventional methods

The Evolution of Viral Diagnostics

Gleaves and Smith
"Rapid" detection of
CMV using shell
vial cell culture
1985

Kimura and Morishima
EBV viral-load by real-
time PCR
1999

1948
Weller and Enders
First growth of
pathogenic human
viruses in
"tissue culture"

1988
Murakawa and Rossi
Direct detection of
HIV-1 RNA
from clinical samples
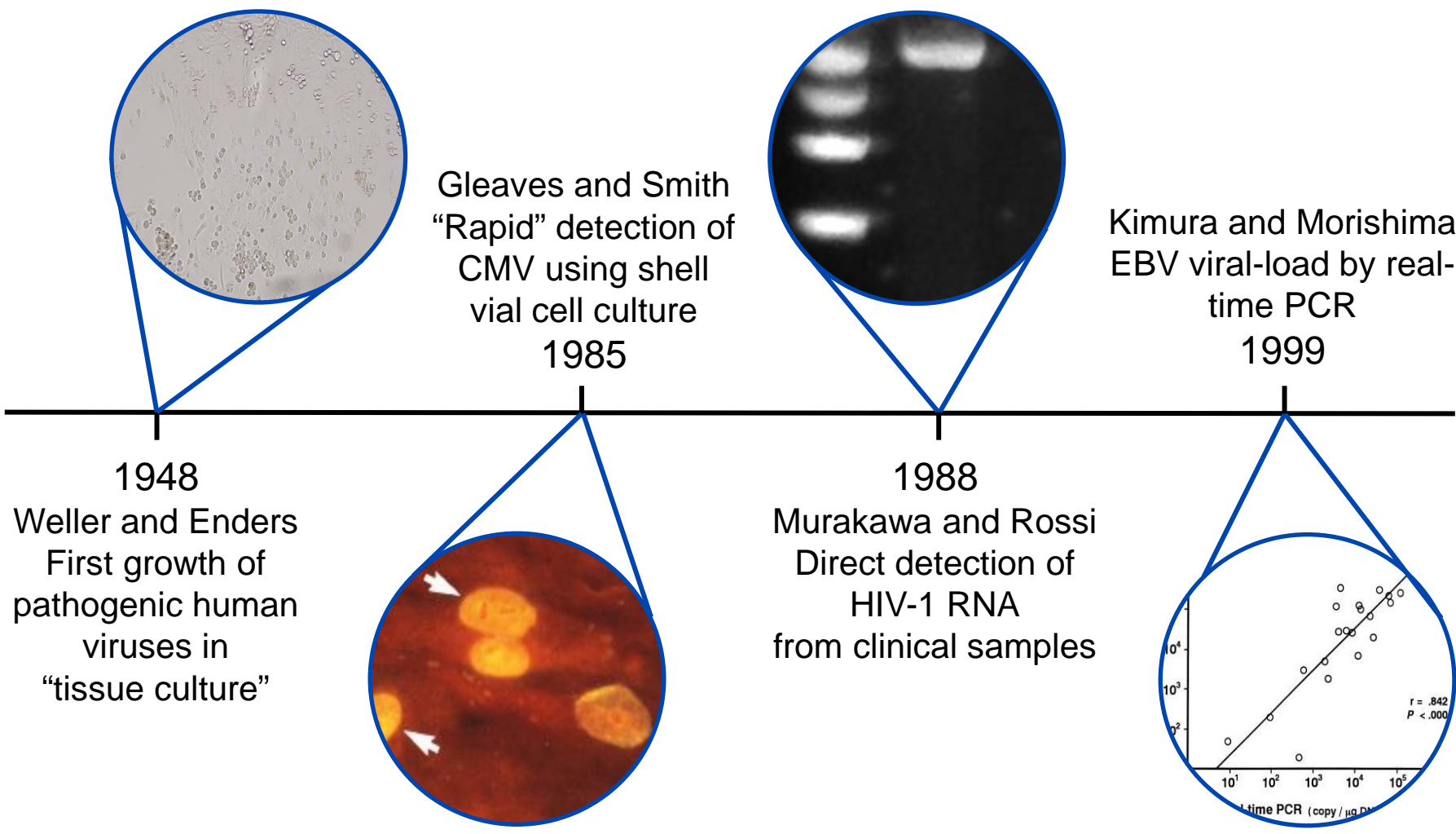
Advantages & Limitations of Conventional Methods

Viral cell culture

- Casts a "broad" net

- Isolates can be used for antiviral resistance testing (e.g., HSV)

- Prolonged turnaround time (1 day [HSV] → 14 days [CMV])

- Limited number of viruses grow in culture!
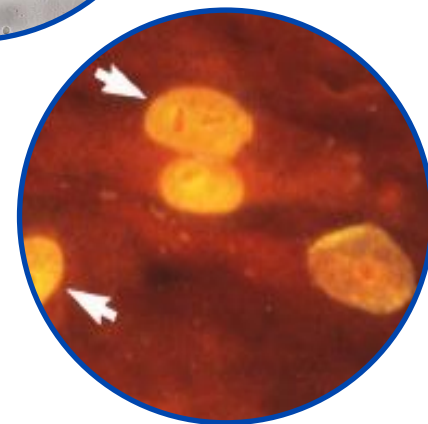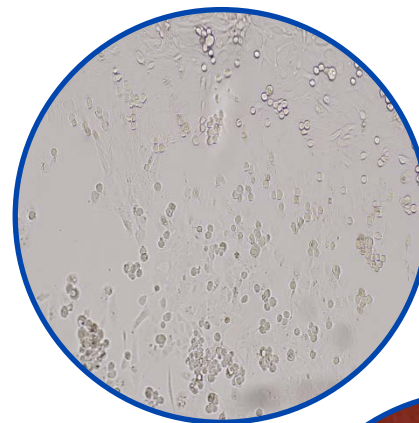
Advantages & Limitations of Conventional Methods

PCR & Real-Time PCR

- High sensitivity/specificity

- Rapid results

- Standard PCR prone to contamination

- No isolate recovered

- Historically, 1 test = 1 virus
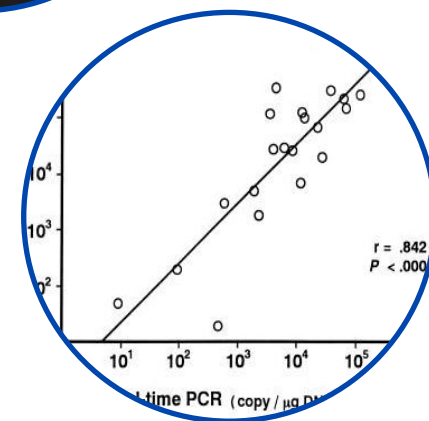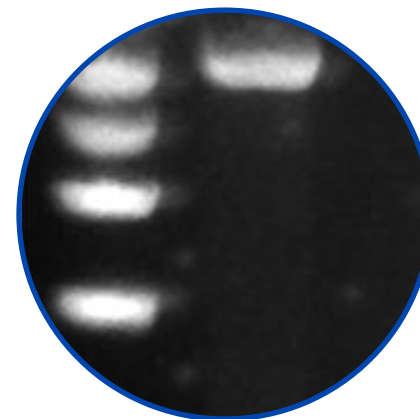
Multiplex Molecular Diagnostics – The Next Generation in Viral Diagnostics?

- Goal: Can we detect multiple (e.g., 10-20) pathogens in a single test?

- Several platforms for multiplex detection have been FDA-cleared

Luminex MAGPIX®

BioFire FilmArray®

Nanosphere Verigene®

GenMark eSensor®

Multiplex Molecular Diagnostics – The Next Generation in Viral Diagnostics?

- Two general lab protocols for multiplex testing:

1. Open system

   DNA/RNA extraction → End-point PCR → Detection

   Examples include: Luminex, GenMark eSensor

2. Sample-to-Result (Closed system)

   DNA/RNA extraction, PCR and Detection are

   automated in a closed reaction vessel

   Examples include: BioFire FilmArray, Nanosphere

How do Multiplex Assays Perform Compared to Conventional Tests?

Respiratory Viral Panel vs. Conventional Tests

- Hammond et al. (*J Clin Microbiol* 2012, 50:3216-3221)

- Compared the BioFire FilmArray RVP to conventional methods (i.e., cell culture/DFA, individual real-time PCR) using 90 samples (BAL, NP swab) from 87 ICH

Viruses
- Adenovirus
- Coronavirus HKU1
- Coronavirus NL63
- Coronavirus 229E
- Coronavirus OC43
- Human Metapneumovirus

- Human Rhinovirus/ Enterovirus
- Influenza A
- Influenza A/H1
- Influenza A/H1-2009
- Influenza A/H3

- Influenza B
- Parainfluenza 1
- Parainfluenza 2
- Parainfluenza 3
- Parainfluenza 4
- Respiratory Syncytial Virus
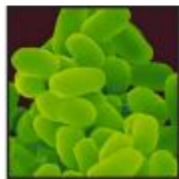
Bacteria
- *Bordetella pertussis*
- *Chlamydophila pneumoniae*
- *Mycoplasma pneumoniae*
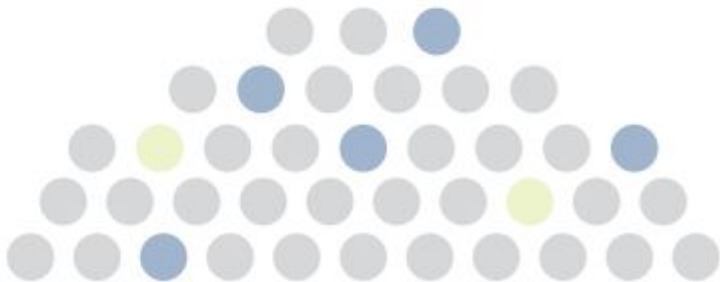
Respiratory Viral Panel vs. Conventional Tests

- Hammond et al. (*J Clin Microbiol* 2012, 50:3216-3221)

- Conventional testing (A) was positive in 16/90 (17.8%) samples

- FilmArray (B) detected viral pathogens in 30/90 (33.3%) of samples
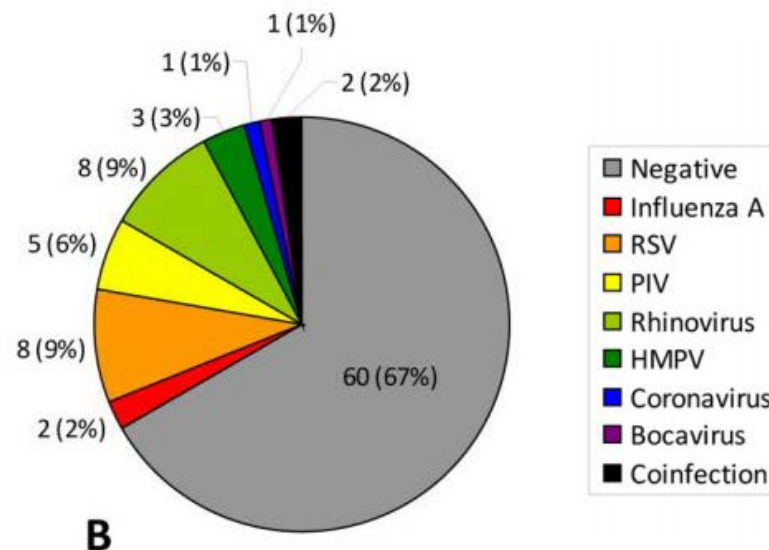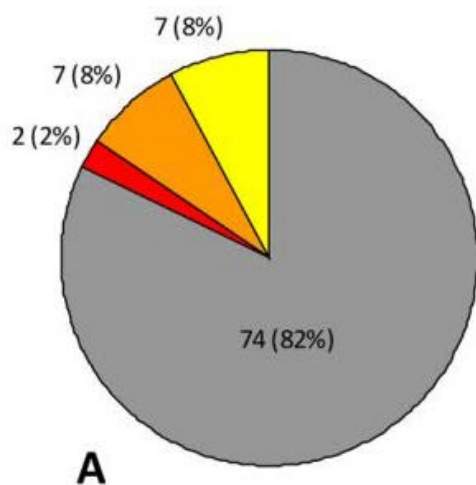
Gastrointestinal Panel vs. Conventional Tests

- Khare et al. (*J Clin Microbiol* 2014, 52:3667-3673)

- Compared the BioFire FilmArray and Luminex GI panels to conventional methods (i.e., culture, microscopy, antigen testing, individual real-time PCR) using 500 stool samples in Cary-Blair media

Bacteria

Aeromonas
* Campylobacter
* Clostridium difficile (Toxin A/B)
Plesiomonas shigelloides
* Salmonella
* Yersinia enterocolitica
* **Vibrio**
   Vibrio cholerae
Diarrheagenic E. coli/Shigella
   Enteroaggregative E. coli (EAEC)
   Enteropathogenic E. coli (EPEC)
* Enterotoxigenic E. coli (ETEC) lt/st
* Shiga-like toxin-producing E. coli (STEC) stx1/stx2
*   E. coli O157
* Shigella/Enteroinvasive E. coli (EIEC)

Protozoa

* Cryptosporidium
Cyclospora cayetanensis
* Entamoeba histolytica
* Giardia lamblia

Viruses

* Adenovirus F 40/41
Astrovirus
* Norovirus GI/GII
* Rotavirus A
Sapovirus
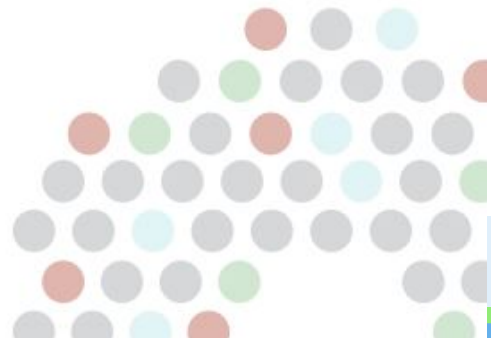
* Target also on Luminex Panel

Gastrointestinal Panel vs. Conventional Tests

- Khare et al. (*J Clin Microbiol* 2014, 52:3667-3673)

- Among 230 prospective stool samples, conventional testing was positive for ≥1 pathogen in 19 (8.3%) samples

- The FilmArray GI panel was positive in 76 (33.0%) samples

- The Luminex GI panel was positive in 69 (30%) samples

Gastrointestinal Panel vs. Conventional Tests

- Khare et al. (*J Clin Microbiol* 2014, 52:3667-3673)

- Distribution of pathogens detected by FilmArray (A) and Luminex (B) among prospective samples (n=230)
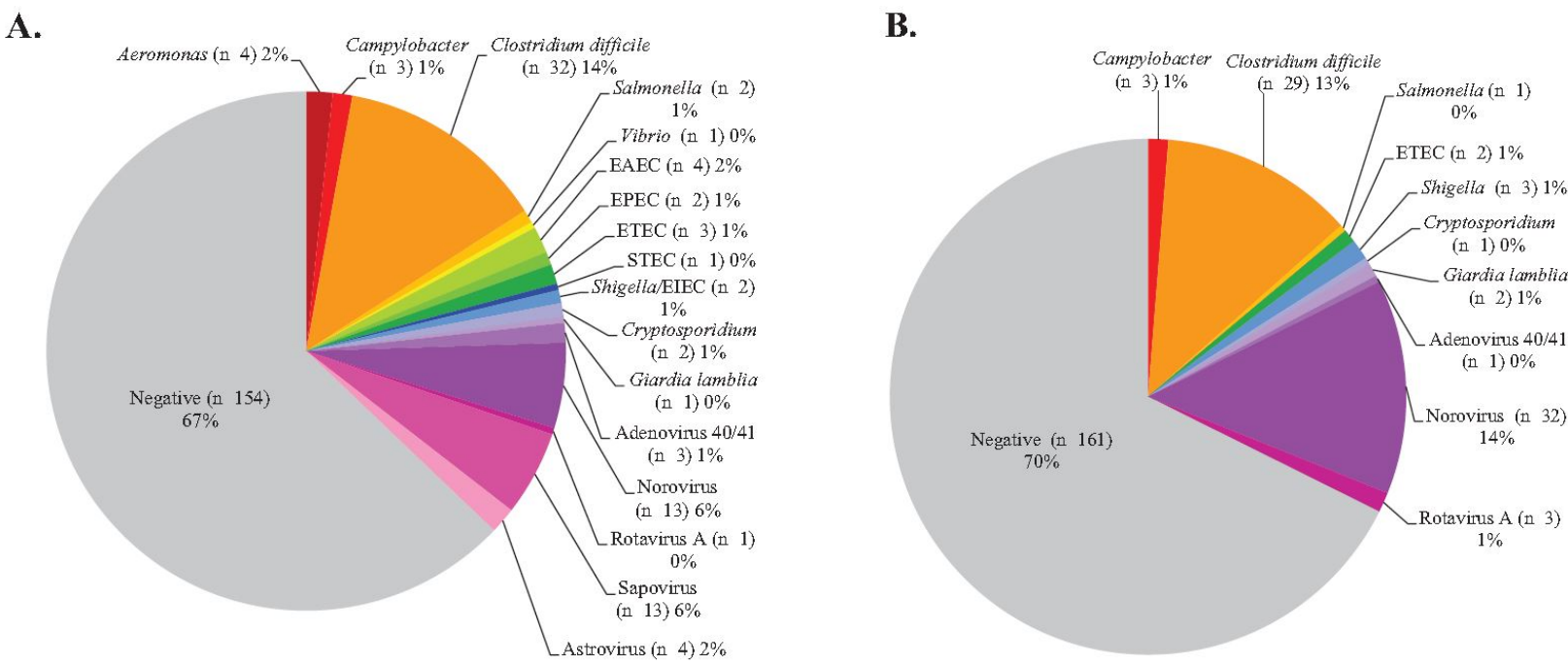
Gastrointestinal Panel vs. Conventional Tests

- Khare et al. (*J Clin Microbiol* 2014, 52:3667-3673)

- Multiplex assays showed higher rate of detection of mixed infections (≥2 pathogens/sample):

- Routine methods: 19 (8.3%) samples

- FilmArray: 86 (27%) samples

- Luminex: 44 (14.1%) samples

- Organisms most commonly detected in mixed infections: EAEC, *Y. enterocolitica*, Norovirus, *C. difficile*

Multiplex Tests: "Is More Better?"

- Cost-Effectiveness: The jury is still out

- Garcia-Garcia *Pediatr Infect Dis J* 2012; 31(8):808-13
  - Compared with conventional virology, diagnosis of respiratory viruses using PCR reduced antibiotic usage

- Oosterheert *Clin Infect Dis* 2004; 41(10):1438-44
  - Use of real-time PCR increased diagnostic yield from 21% to 43%; however, no statistically significant reduction in antibiotic usage, additional testing, or length of hospital stay was found.

Multiplex Tests: "Is More Better?"

- Cost-Effectiveness: The jury is still out

- Mahony JB *J Clin Microbiol* 2009; 47(9):2812-7
  - Cost analysis study (multiplex versus conventional viral diagnostic assays for respiratory infections)
  - Multiplex testing alone most cost-effective algorithm

Testing Algorithm	Cost per case* (Canadian Dollars)
DFA	$3911
DFA + culture	$3914
DFA + molecular multiplex	$3849
Molecular Multiplex	$3623

Inpatient savings of $291/case and $529,620/yr (1820 patients)

Multiplex Tests: "Is More Better?"

- Special population management

- Immunocompromised patients
  - Respiratory viruses have a high rate (20-40%) of progression to pneumonia in severely immunosuppressed, with associated mortality of 30-50%

- Kumar *Transplantation* 2010; 89(8):1028-33
  - Increased risk of acute rejection following respiratory virus infection (33.3% in infected cohort vs. 6.7% in non-infected)

- Rapid detection may allow for:
  - Appropriate infection control measures
  - Patient management decisions

Multiplex Tests: Additional considerations

- Who to test?
  - All-comers *versus* Immunocompromised hosts only
  - High cost to patient

- How often to test?
  - Nucleic acid amplification tests may remain positive despite therapy
  - Important to restrict duplicate orders if within 7 days

- How to interpret "unexpected" results
  - What to do with all the information?
  - Will the results of this test alter the management of my patient?

Summary

- Multiplex molecular tests offer a promising new tool in the diagnosis of infectious diseases

- Questions still remain regarding the cost-effectiveness of multiplex assays

- Interpretation of results, including the detection of co-infections, may be difficult

The Utility of Interferon Gamma Release Assays Compared to the Tuberculin Skin Test

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Mayo Clinic Infectious Diseases Subspecialties Update
May 7-9, 2015

Learning Objectives

- Review the advances that have been made in the laboratory diagnosis of tuberculosis

- Discuss the principle of interferon gamma release assays (IGRAs)

- Review data on the performance of IGRAs in:
  - HIV infected
  - Patients with IMIDs
  - HCWs

- Highlight potential pitfalls in the interpretation of IGRA results

Tuberculosis – A Continuing Global Health Threat

- One-third of the world's population is infected

- 9 million new cases and 1.5 million deaths in 2013

- One-third of HIV-infected are coinfected with TB
  - ~50% of deaths among HIV infected are attributed to TB

- In the U.S., 10-15 million are infected (LTBI)
  - 9,582 new cases (3 cases per 100,000 persons) reported in the United States

http://www.cdc.gov/tb/statistics/default.htm

Laboratory Diagnosis of TB: "Slow going…"
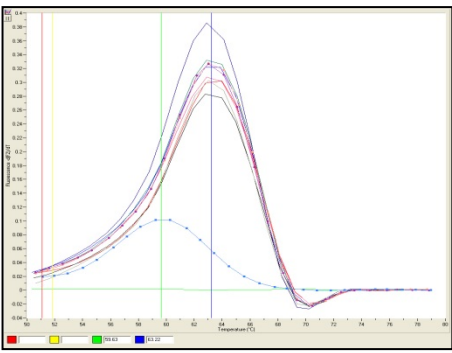
Image courtesy of N.L.Wengenack

1901	1910	2000	2000-2015
"Koch's Bacillus"	Tuberculin Skin Test	Still relying on: TST Culture (4-6 weeks) Direct smear	Probe ID Sequencing PCR IGRAs

http://phil.cdc.gov/phil/quicksearch.asp

Interferon Gamma Release Assays (IGRAs)

- Principle:
  - Persons infected with TB have "primed" T-cells.
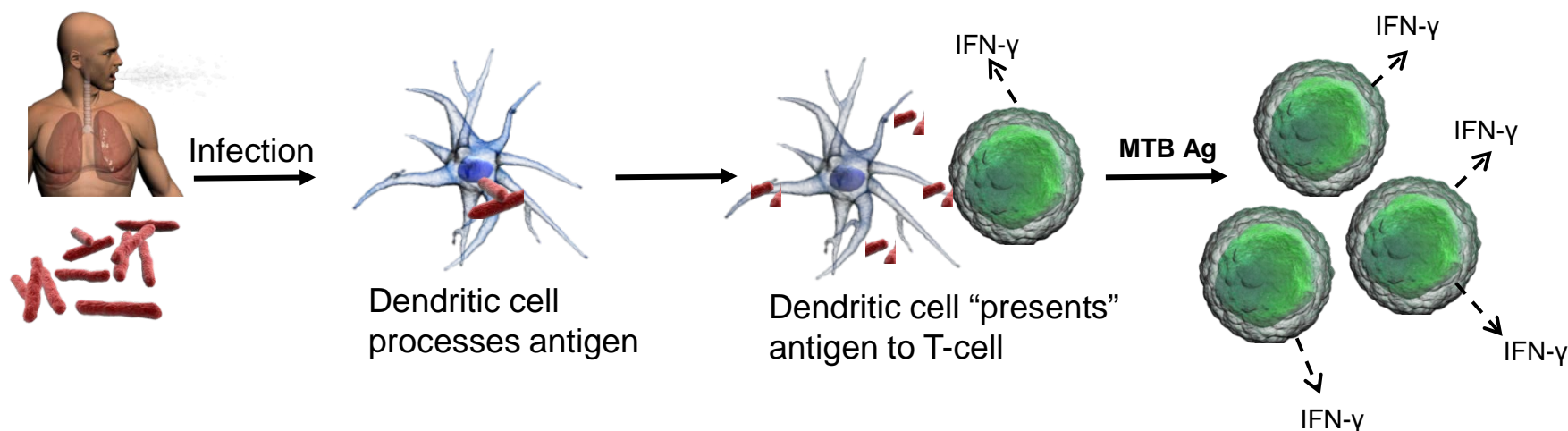
- IGRAs measure the ability of primed T-cells to produce IFN- γ in response to stimulation with antigens specific to *M. tuberculosis* complex.

IGRAs *versus* TST

IGRAs

- *In vitro* test (routine phlebotomy)
- Results in 24-48 hours
- Single patient visit
- Objective interpretation
- "Boost" response?
- Not affected by BCG or *most* NTM infection

TST

- *In vivo* test
- Results in 48-72 hours
- Return visit required
- Subjective interpretation
- "Boost" response
- False-positives possible due to BCG or NTM infection

Limitations of IGRAs

- Cross-reactivity possible with some NTM infections
  - *M. kansasii*
  - *M. szulgai*
  - *M. marinum*

- Testing logistics
  - Specimen transport time

- Result interpretation may be challenging (e.g., conversion and reversion)

- Similar to TST, IGRAs can NOT distinguish between active and latent TB

IGRAs

Two commercially-available, FDA-cleared tests:

1. IFN-γ ELISA (QuantiFERON® TB-Gold In-Tube; Cellestis, Carnegie, Australia)

Three tubes:
1. **Nil** (negative)
2. **TB Ag** (CFP-10, ESAT-6, TB7.7)
3. **Mitogen** (Positive)

1. Collection tubes mixed and incubated at 37° C

2. Plasma harvested and IFN-gamma measured by ELISA

1. Antigen presenting cell (APC) takes up mycobacterial antigen

2. APC processes antigen

3. APC presents antigen to antigen-specific T cell

4. T cell produces IFN-γ
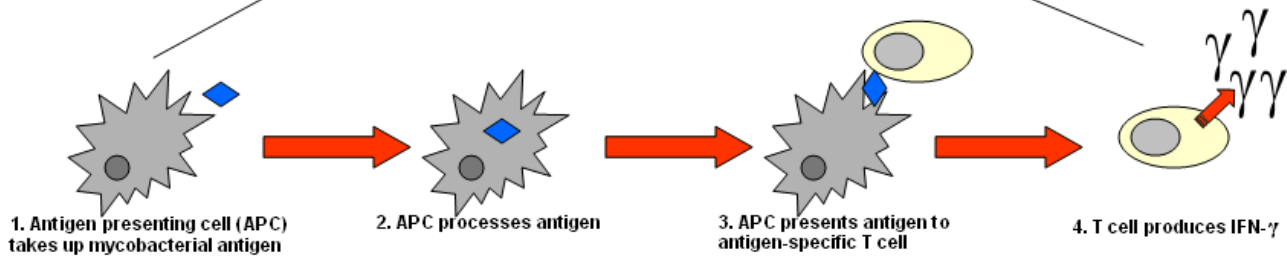
IGRAs

Two commercially-available, FDA-cleared tests:

2. ELISpot (T.SPOT®-*TB*; Oxford Immunotec, Abingdon, UK)

Nil Control

ESAT-6

CFP-10

Positive Control
(Phytohemagglutinin)

One tube of blood, aliquoted into 4 wells
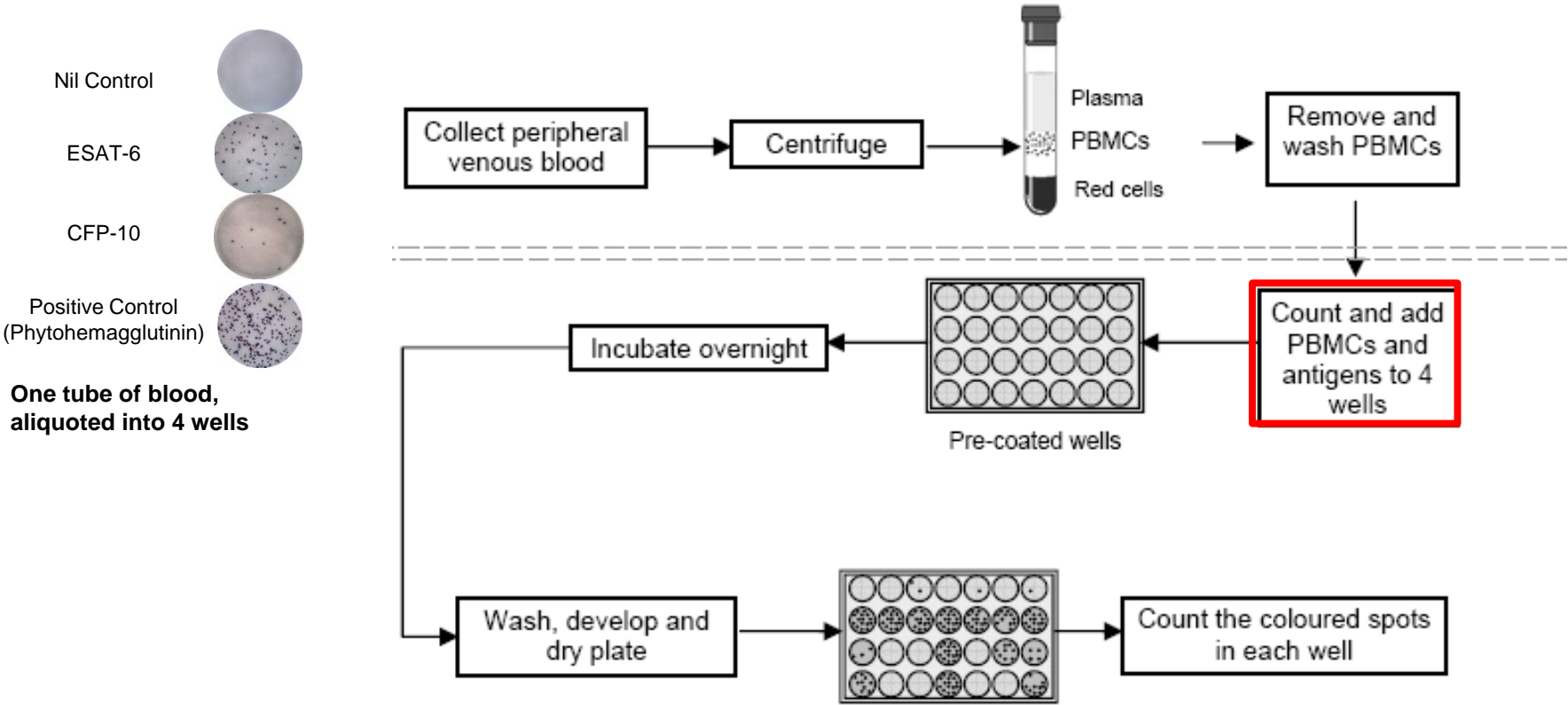
Interferon Gamma Release Assays: Frequently Asked Questions

How do IGRAs perform compared to TST?

- Pai M. *et al*: Systematic Review: T-cell-Based Assays for the Diagnosis of Latent Tuberculosis Infection: An Update. *Ann Intern Med* 2008;149:177-184

  - Performed meta-analysis of 38 studies assessing performance of IGRAs and TST

  - Sensitivity was assessed using microbiologically confirmed TB cases

  - Specificity was assessed using healthy, low-risk individuals without known exposure to TB

How do IGRAs perform compared to TST? A view from 30,000 feet

Table 1. Pooled sensitivity of IGRAs and TST.

	Pooled sensitivity	95% C.I.
TST	0.77	0.71 - 0.82
ELISA[1]	0.70	0.63 – 0.78
ELISpot [2]	0.90	0.86 – 0.93

[1] QFT-G In-Tube

[2] TSPOT.TB

Pai *et al*. Ann Intern Med 2008;149:177-184

How do IGRAs perform compared to TST? A view from 30,000 feet

Table 2. Pooled specificity of IGRAs and TST in BCG- and non-BCG vaccinated persons.

	Pooled specificity (95% CI) BCG-vaccinated	Pooled specificity (95% CI) non-BCG
TST	0.59 (0.46-0.73)	0.97 (0.95-0.99)
ELISA[1]	0.96 (0.94-0.98)	0.99 (0.98 – 1.0)
ELISpot[2]	0.93 (0.86-1.0)	

[1] QFT-G In-Tube

[2] TSpot.TB

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How do IGRAs perform in certain patient populations?

Individuals with Suspected TB Disease

- Metcalfe *et al* (*J Infect Dis* 2011) – meta analysis to assess diagnostic performance of IGRAs among adults with suspected or confirmed active pulmonary TB in low to middle-income countries.

- Pooled sensitivity:

  HIV-positive
  T-Spot.TB = 76% (45-92%)
  QFT = 60% (34-82%)

  HIV-negative
  T-Spot.TB = 88% (81-95%)
  QFT = 84% (78-91%)

- Pooled specificity (all participants HIV + and HIV -)
  - T-Spot.TB = 61% (40-79%)
  - QFT = 52% (41-62%)

- 2011 WHO policy: Neither IGRAs nor TST should be used for the diagnosis of active TB

HIV-infected Patients

- Cattamanchi *et al* (*J Acquir Immune Defic Syndr* 2011) – systematic review of HIV-infected persons with active TB.

- Pooled sensitivity:
  - T-Spot.TB = 72% (95% C.I., 62-81%)
  - QFT = 61% (47-75%)

- Neither IGRA was consistently more sensitive than TST. Potential role of combination (IGRA and TST) testing in severely ICH.

- Santin *et al* (PLoS One 2012) – meta-analysis that assessed impact of HIV on rate of indeterminate results
  - T-Spot.TB = 5.9%
  - QFT = 8.2%

Patients with Immune-Mediated Inflammatory Disease

- Chang *et al* (*Korea Clin Rheumatol* 2011) – prospective, longitudinal study comparing TST and QFT in 107 patients being treated with TNF-α inhibitors

- QFT was indeterminate in 7 (6.5%) patients

- QFT and TST were discordant for 33 (33%) patients
  - 16 (TST Positive, QFT Negative)
  - 17 (TST Negative, QFT Positive)

- None of these patients developed active TB

- A dual testing strategy (TST + IGRA) has been proposed to increase sensitivity in these patients

Health Care Workers

- Serial testing for LTBI is indicated for HCWs in high-risk settings.

- Higher rate of conversions/reversions with IGRAs compared to TST

- U.S. CDC TB Epidemiologic Studies Consortium (assessed 2,563 HCWs undergoing TB screening at 4 U.S. hospitals)
  - T-Spot.TB = 8.3% (177/2,137) conversion rate
  - QFT = 6.1% (138/2,263)
  - TST = 0.9% (21/2,293)

- IGRAs have also shown reversion rates of 20-60%, even without LTBI treatment
  - Most common in patients with IGRA results near borderline for Positive result (e.g., TB antigen value 0.35 – 1.0 IU/mL)

Health Care Workers

- Four phenotypes identified among HCWs undergoing serial testing
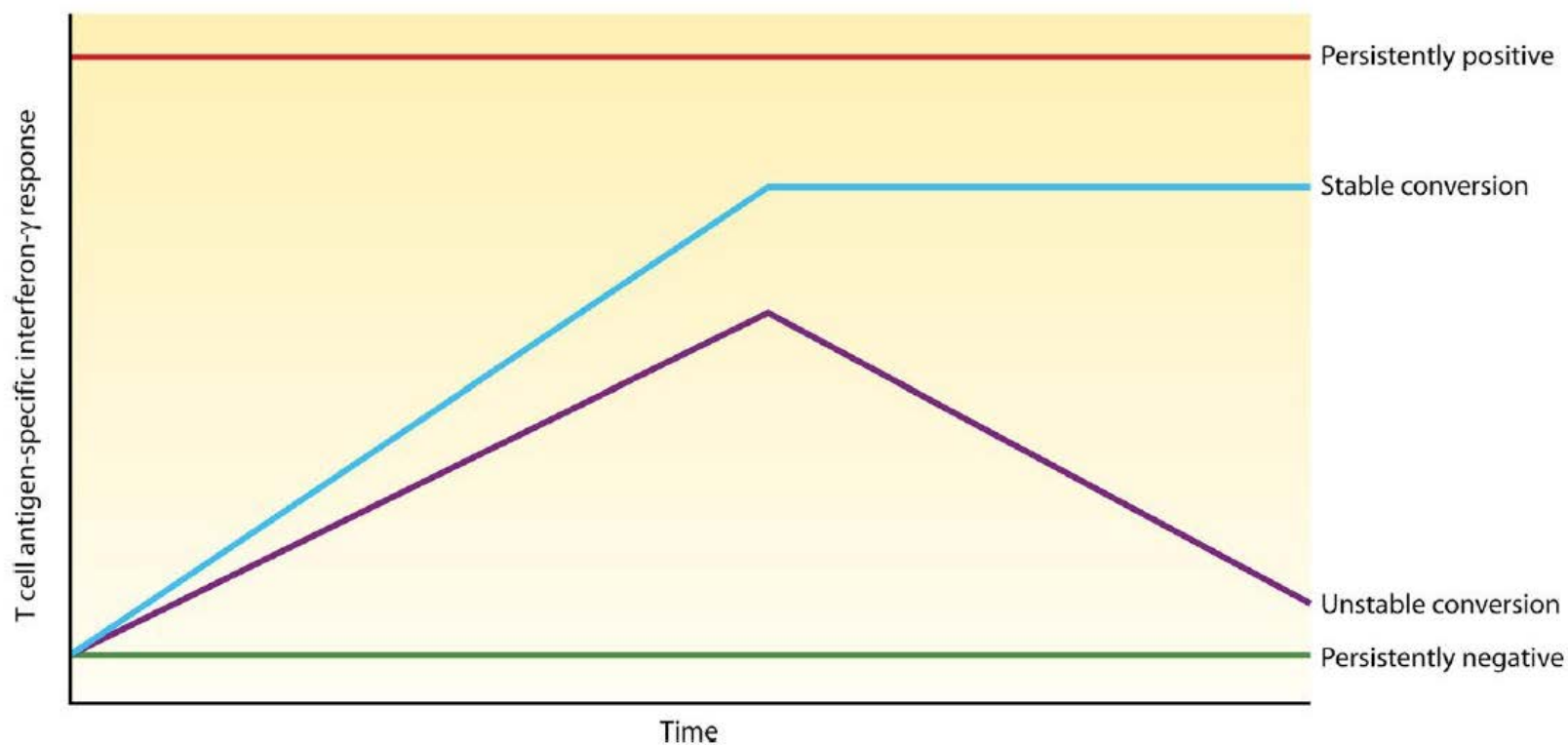
Pai, M. 2010. *Nat Rev Microbiol* 8:242

Additional Considerations

- Can IGRAs be used to monitor response to therapy?
  - Data are inconsistent, but current conclusion is that "monitoring IGRA changes over time seems to have only speculative value." (Chiappini et al., *Clin Ther* 2012)

- Can IGRAs be used to predict progression to active TB?
  - Predictive value of IGRAs is low and slightly (but not significantly) better than TST
  - IGRA conversion may be more predictive than a single positive result

Summary

- There is no perfect screening test for TB

- IGRAs are being increasingly favored in low-incidence settings, due to:
  - Increased specificity in comparison to TST
  - Logistical improvements (i.e., one patient visit, lab workflow)

- IGRAs may be preferable in populations with high rate of BCG vaccination

- TST may be preferable for serial testing of HCWs

- Neither TST nor IGRAs should be used to diagnose active TB.

Online TST/IGRA Interpreter

- www.tstin3d.com

- Estimates the risk of active TB based on results of TST and/or IGRA and clinical profile.

Pay for Performance and the ID Physician
It <u>is</u> all about the money, money, money………

Priya Sampathkumar, MD

Mayo Clinic, Rochester

Division of
INFECTIOUS DISEASES

Mayo Clinic Infectious Diseases Subspecialties Update
May 7-9, 2015

Objectives

- Provide an overview of the pay for performance programs: Value based purchasing (VBP) and Healthcare associated Conditions (HAC), hospital readmission reduction programs

- Understand the impact of these programs on the practicing ID physician

- Identify ways that ID physicians can reduce HAIs and make a financial impact on pay for performance

Started with: Pay for Reporting

Required CMS Measures for Inpatient Program
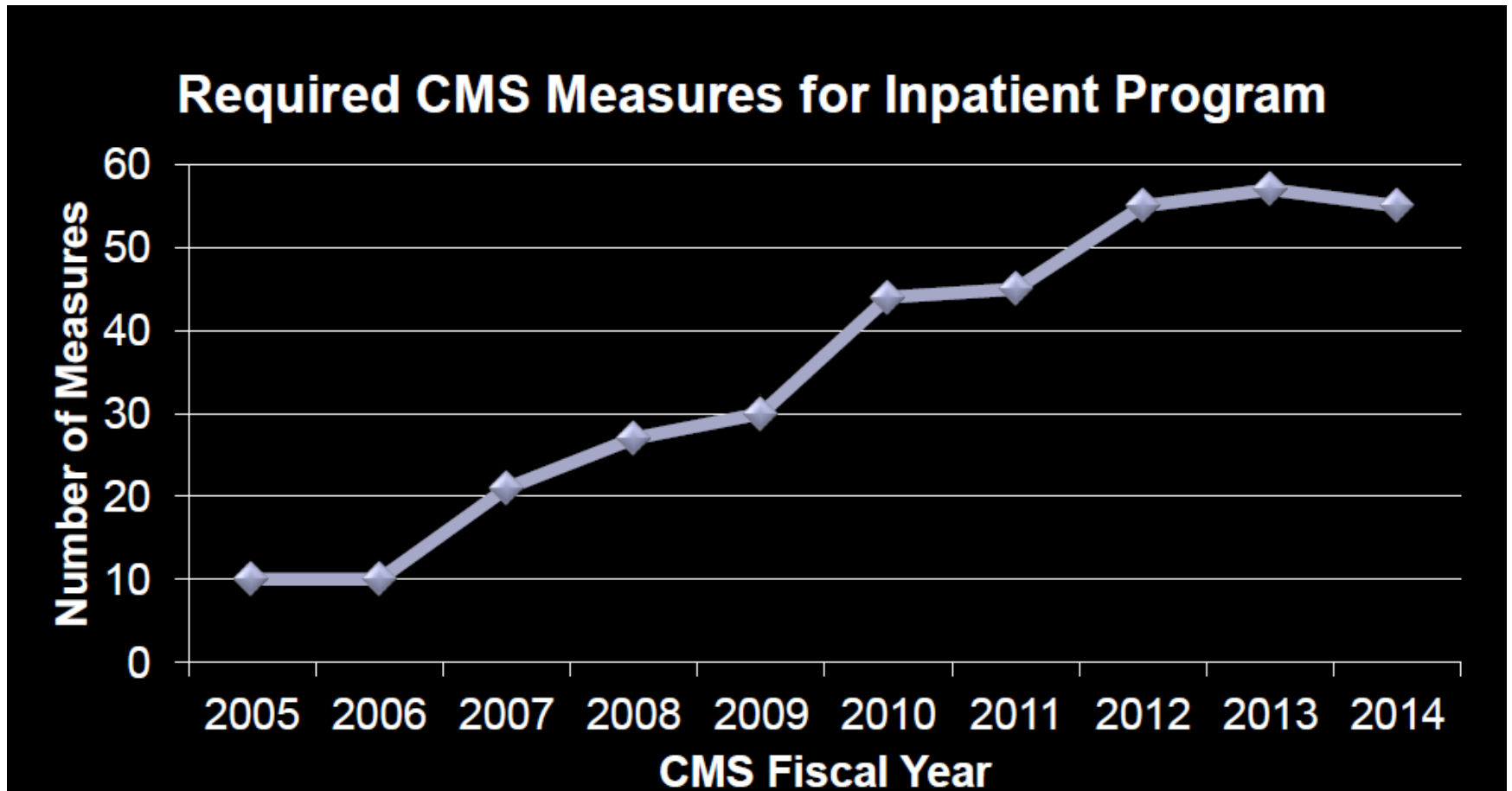
Inpatient Quality Reporting Program: Introduced through the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003, today 99% of US hospitals participate

Value Based Purchasing

What is VBP?

All hospitals · **Percentage of DRG withheld**

Hospitals above the median TPS

Hospitals below the median TPS

VBP withholds	
FY 2013	1.00%
FY 2014	1.25%
FY 2015	1.50%
FY 2016	1.75%
FY 2017	2.00%

"Instead of payment that asks, *How much did you do?*, the Affordable Care Act clearly moves us toward payment that asks, *How well did you do?*, and more importantly, *How well did the patient do?*"
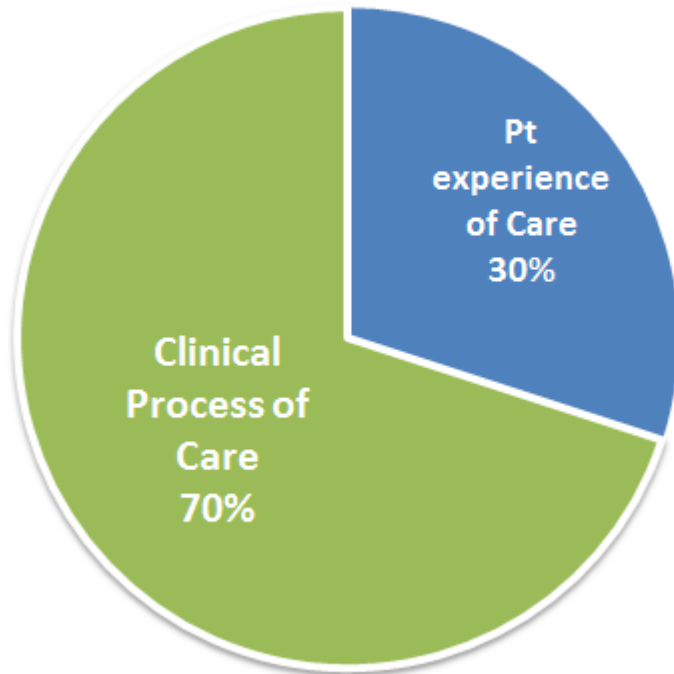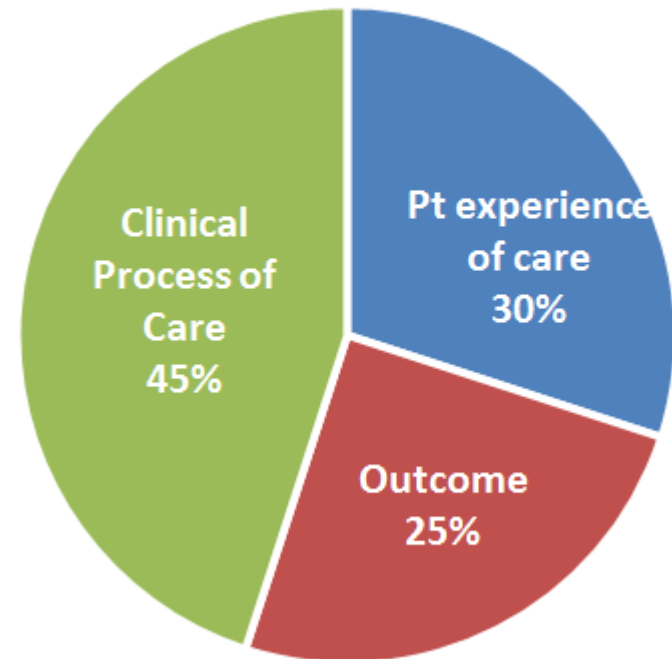
Don Berwick

Evolution of VBP Domains

FY 2013 VBP

Pt experience of Care 30%

Clinical Process of Care 70%

FY 2014 VBP

Clinical Process of Care 45%

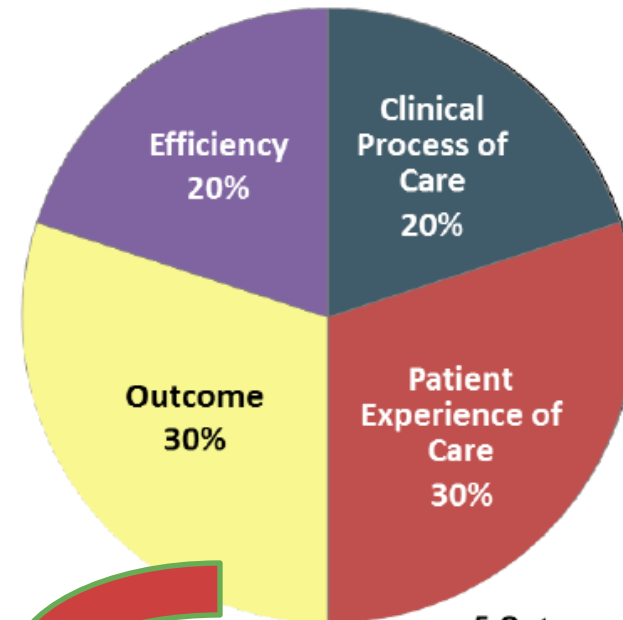Pt experience of care 30%

Outcome 25%

FY 2015 VBP Program

12 Clinical Process of Care Measures

1. AMI-7a Fibrinolytic Therapy Received within 30 Minutes of Hospital Arrival
2. AMI-8 Primary PCI Received within 90 Minutes of Hospital Arrival
3. HF-1 Discharge Instructions
4. PN-3b Blood Cultures Performed in the ED Prior to Initial Antibiotic Received in Hospital
5. PN-6 Initial Antibiotic Selection for CAP in Immunocompetent Patient
6. SCIP-Inf-1 Prophylactic Antibiotic Received within One Hour Prior to Surgical Incision
7. SCIP-Inf-2 Prophylactic Antibiotic Selection for Surgical Patients
8. SCIP-Inf-3 Prophylactic Antibiotics Discontinued within 24 Hours After Surgery
9. SCIP-Inf-4 Cardiac Surgery Patients with Controlled 6 a.m. Postoperative Serum Glucose
10. SCIP–Inf–9 Postoperative Urinary Catheter Removal on Postoperative Day 1 or 2
11. SCIP-Card-2 Surgery Patients on a Beta Blocker Prior to Arrival That Received a Beta Blocker During the Perioperative Period
12. SCIP-VTE-2 Surgery Patients Who Received Appropriate Venous Thromboembolism Prophylaxis within 24 Hours

Domain Weights

- Efficiency 20%
- Clinical Process of Care 20%
- Outcome 30%
- Patient Experience of Care 30%

8 Patient Experience of Care Dimensions

1. Nurse Communication
2. Doctor Communication
3. Hospital Staff Responsiveness
4. Pain Management
5. Medicine Communication
6. Hospital Cleanliness & Quietness
7. Discharge Information
8. Overall Hospital Rating

5 Outcome Measures

1. MORT-30-AMI – Acute Myocardial Infarction (AMI) 30-day mortality rate
2. MORT-30-HF – Heart Failure (HF) 30-day mortality rate
3. MORT-30-PN – Pneumonia (PN) 30-day mortality rate
4. **PSI-90 – Patient safety for selected indicators (composite)** ⭐
5. **CLABSI – Central Line-Associated Bloodstream Infection** ⭐

1 Efficiency Measure

1. MSPB-1 Medicare Spending per Beneficiary measure ⭐

⭐ **Represents a new measure for the FY 2015 program that was not in the FY 2014 program.**

7

VBP Roadmap through 2019

Metric	2016	2017	2018	2019
PSI	X	X	X	X
CLABSI	X	X	X	X
CAUTI	X	X	X	X
SSI: colon and TAH	X	X	X	X
Lab ID MRSA bloodstream infection		X	X	X
Lab ID CDI		X	X	X
Complication rate after elective primary THA/TKA				X

MAYO CLINIC

FY 2017 VBP Domain Weighting
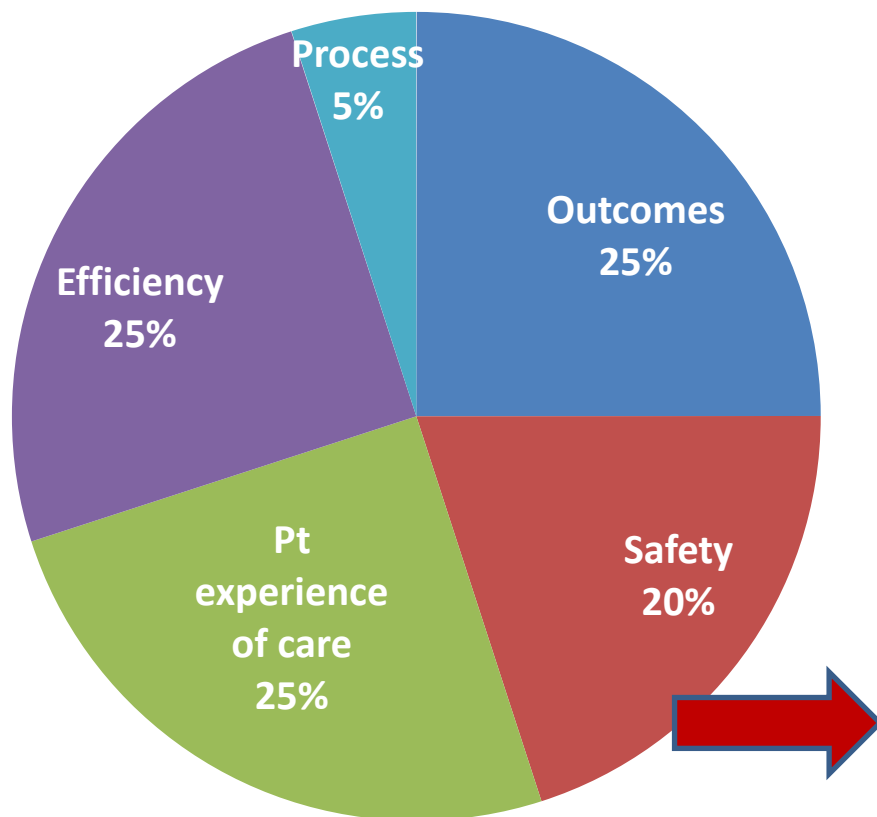
SAFETY		
Complication/Patient Safety for Selected Indicators		
Baseline Period	**Performance Period**	
October 1, 2010 – June 30, 2012	October 1, 2013 – June 30, 2015	
Measure	**Threshold (%)**	**Benchmark (%)**
AHRQ PSI 90 composite	.777936	.547889
Healthcare-Associated Infections		
Baseline Period	**Performance Period**	
January 1, 2013 – December 31, 2013	January 1, 2015 – December 31, 2015	
Measure	**Threshold (†)**	**Benchmark (†)**
CLABSI	0.457	0.0000
CAUTI	0.845	0.0000
SSI Colon‡	0.751	0.0000
SSI Abdominal Hysterectomy‡	0.698	0.0000
New! C. difficile	0.750	0.0000
New! MRSA	0.799	0.0000

Standardized Infection Ratio

SIR = <u># of observed Infections</u>

　　　# of expected Infections

- Expected infections calculated based on risk adjustment
- A SIR **above 1.0** means that the infection rate is higher than that found in the "standard population"
- The standard population comes from data reported by all NHSN Hospitals

HO-CDI	Expected	Patient Days	SIR	SIR pvalue	SIR 95% CI
46	74.082	80015	0.621	0.0005	0.460, 0.821

Metric	Achievement Threshold	Benchmark
CAUTI	0.845	0.0000
CLABSI	0.457	0.0000
C. difficile	0.750	0.0000
MRSA bacteremia	0.799	0.0000
SSI Colon	0.751	0.0000
SSI TAH	0.698	0.0000

SIR Risk adjustment

CLABSIs and CAUTIs	Hospital- onset C. difficile and MRSA	SSIs
- Bed size - Affiliation with a medical school - Type of patient care location	- Bed size - Affiliation with a medical school - Community-onset cases - The type of test the laboratory uses to identify C. difficile	- Duration of surgery - Surgical wound class - Use of endoscopes - Re-operation status - Patient age - Patient assessment at time of anesthesia

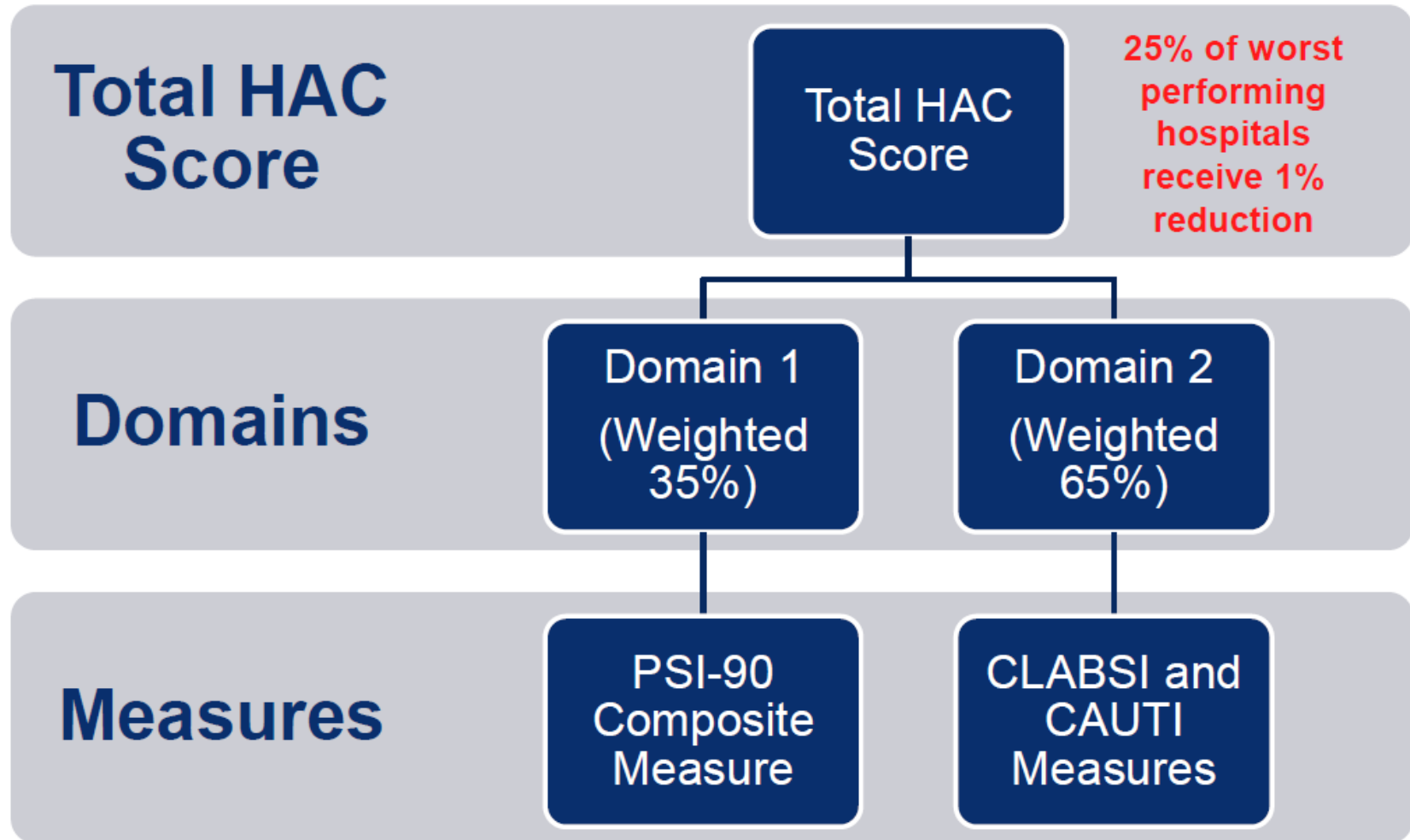# Healthcare associated Conditions Program

HAC: Present on Admission

- Implemented FY 2008
- Eliminates any additional payments for selected complications that are considered reasonably preventable
  - Mediastinitis after CABG
  - Vascular catheter related infection
  - CAUTI
  - SSI after orthopedic surgery (spine, neck, elbow, shoulder)
  - SSI after bariatric surgery
  - SSI after CIED
- Based on claims data

HAC Reduction Program Framework Finalized for FY 2015

Total HAC Score

Total HAC Score

25% of worst performing hospitals receive 1% reduction

Domains

Domain 1 (Weighted 35%)

Domain 2 (Weighted 65%)

Measures

PSI-90 Composite Measure

CLABSI and CAUTI Measures

HAC Reduction Program

Domain 1
(Claims Data)

Weighted 35%

AHRQ PSI-90 Composite

PSI-3:   pressure ulcer

PSI-6:   Iatrogenic pneumothorax

PSI-7:   **central venous catheter-related blood stream infection rate**

PSI-8:   hip fracture rate

PSI-12: postoperative PE/DVT rate

PSI-13: **sepsis rate**

PSI-14: **wound dehiscence rate**

PSI-15: accidental puncture

Domain 2
(NHSN reported data)

Weighted 65%

2015
CAUTI
CLABSI

2016 *(1 additional measure):*
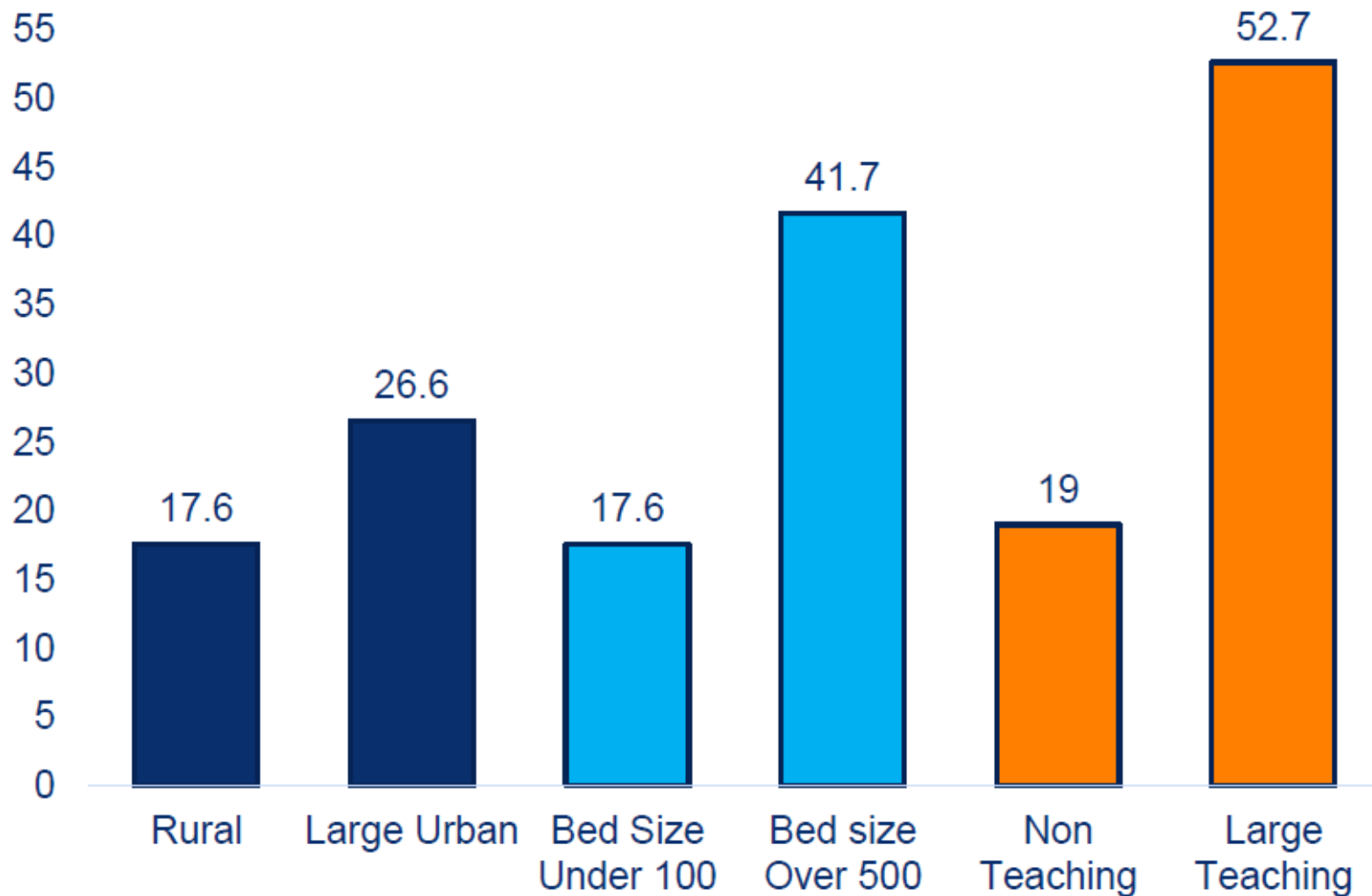Surgical Site Infection (Colon Surgery and Abdominal Hysterectomy)

2017 *(2 additional measures):*
MRSA
C Diff

In FY 2016, Domain 2 weight will be 75%

Percent of Hospitals Penalized by Type for FY 2015

Bar chart showing:
- Rural: 17.6
- Large Urban: 26.6
- Bed Size Under 100: 17.6
- Bed size Over 500: 41.7
- Non Teaching: 19
- Large Teaching: 52.7

Hospital Readmission Reduction Program

Hospital Readmission Reduction Program

FY 2013:

CMS payments to hospitals with excess readmissions reduced by 1%

- 30 day Readmissions Acute Myocardial Infarction (AMI)

- 30 day Readmissions Heart Failure (HF)

- 30 day Readmissions Pneumonia (PN)

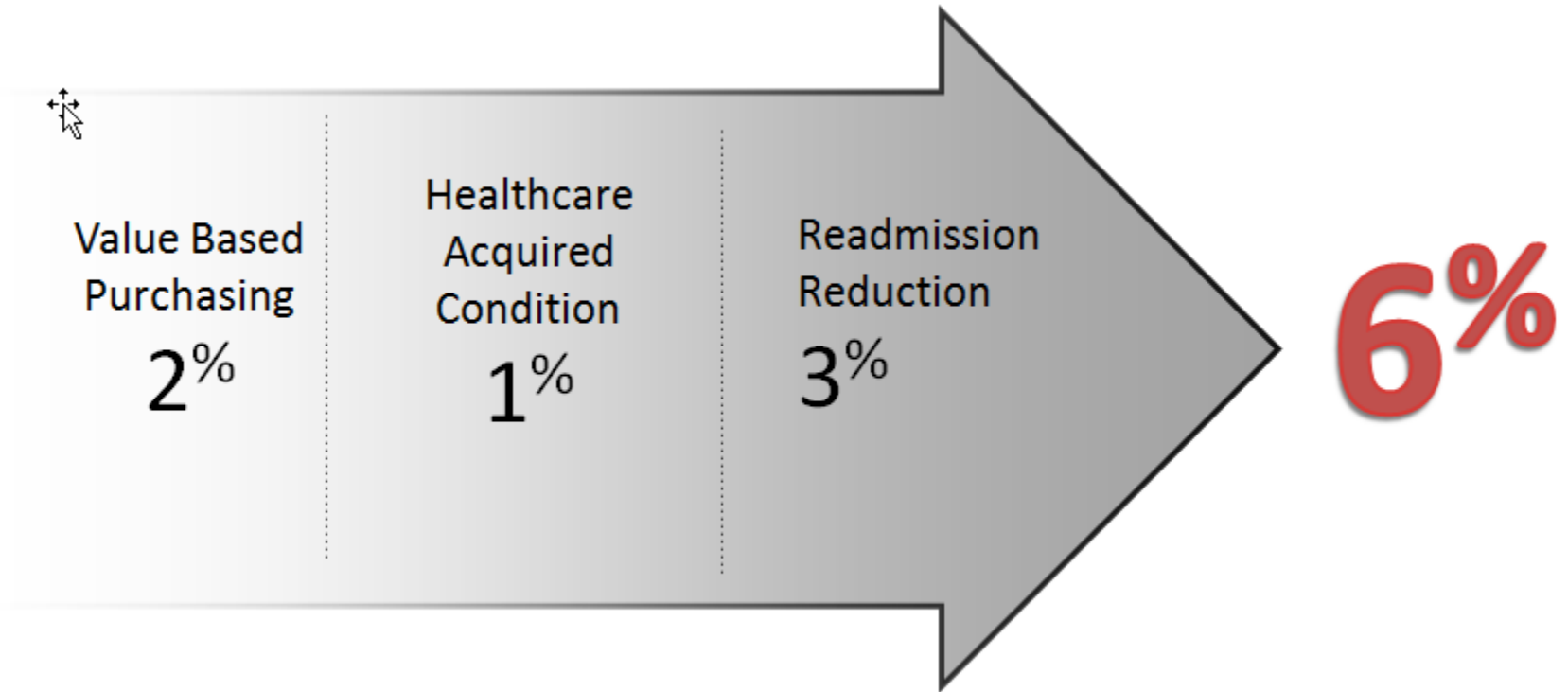**FY2014: No additions, 2% penalty**

FY 2015: Additions, 3% penalty

- 30 day Readmissions COPD

- 30 day Readmissions elective THA and total knee arthroplasty TKA

FY 2016 No Additions

FY 2017 Additions

- 30 day Readmissions CABG surgery

Percent of CMS Dollars at Stake by FY 2017

Value Based Purchasing 2%

Healthcare Acquired Condition 1%

Readmission Reduction 3%

6%

Impact of an HAI on reimbursement?

- **HAC Present on admission:** Additional costs for CLABSI not reimbursed

- **VBP:** Outcomes Domain - CLABSI included in PSI 90

- **VBP:** Outcomes Domain - CLABSI specific line item

- **VBP**: Efficiency Domain - CLABSI can potentially elevate Medicare spending per beneficiary

- **VBP:** Patient Experience of Care Domain **-** Potential Impact to Patient Satisfaction

- **2015 HAC Program:** Domain 1 – PSI 90

- **2015 HAC Program:** Domain 2 – CLABSI

- **Readmission Program**

NATIONAL

HEALTHCARE ASSOCIATED INFECTIONS PROGRESS +

Healthcare-associated infections (HAIs) are infections patients can get while receiving medical treatment in a healthcare facility. Working toward the elimination of HAIs is a CDC priority. The standardized infection ratio (SIR) is a summary statistic that can be used to track HAI prevention progress over time; lower SIRs are better. The infection data are collected through CDC's National Healthcare Safety Network (NHSN). HAI data for nearly all U.S. hospitals are published on the Hospital Compare website.

CLABSIs ↓ 46% LOWER COMPARED TO NAT'L BASELINE*

CENTRAL LINE-ASSOCIATED BLOODSTREAM INFECTIONS

When a tube is placed in a large vein and not put in correctly or kept clean, it can become a way for germs to enter the body and cause deadly infections in the blood.

- ☐ U.S. hospitals reported a significant decrease in CLABSIs between 2012 and 2013.

- **9%** Among the 2,389 hospitals in U.S. with enough data to calculate an SIR, 9% had an SIR significantly worse than the national SIR of 0.54.

CAUTIs ↑ 6% HIGHER COMPARED TO NAT'L BASELINE*

CATHETER-ASSOCIATED URINARY TRACT INFECTIONS

When a urinary catheter is not put in correctly, not kept clean, or left in a patient for too long, germs can travel through the catheter and infect the bladder and kidneys.

- ☐ U.S. hospitals reported a significant increase in CAUTIs between 2012 and 2013.

- **12%** Among the 2,781 U.S. hospitals with enough data to calculate an SIR, 12% had an SIR significantly worse than the national SIR of 1.06.

MRSA Bacteremia ↓ 8% LOWER COMPARED TO NAT'L BASELINE*

LABORATORY IDENTIFIED HOSPITAL-ONSET BLOODSTREAM INFECTIONS

Methicillin-resistant *Staphylococcus aureus* (MRSA) is bacteria usually spread by contaminated hands. In a healthcare setting, such as a hospital, MRSA can cause serious bloodstream infections.

- ☐ U.S. hospitals reported a significant decrease in MRSA Bacteremia between 2012 and 2013.

- **7%** Among the 2,002 U.S. hospitals with enough data to calculate an SIR, 7% had an SIR significantly worse than the national SIR of 0.92.

SSIs

SURGICAL SITE INFECTIONS   *See page 3 for additional procedures*

When germs get into an area where surgery is or was performed, patients can get a surgical site infection. Sometimes these infections involve only the skin. Other SSIs can involve tissues under the skin, organs, or implanted material.

SSI: Abdominal Hysterectomy ↓ 14% LOWER COMPARED TO NAT'L BASELINE*

- ☐ U.S. hospitals reported no significant change in SSIs related to abdominal hysterectomy surgery between 2012 and 2013.

- **6%** Among the 765 U.S. hospitals with enough data to calculate an SIR, 6% had an SIR significantly worse than the national SIR of 0.86.

SSI: Colon Surgery ↓ 8% LOWER COMPARED TO NAT'L BASELINE*

- ☐ U.S. hospitals reported a significant increase in SSIs related to colon surgery between 2012 and 2013.

- ☐ Several changes to the NHSN 2013 SSI protocol likely contributed to an increase in the national and some state-specific colon surgery SIRs compared to 2012.

- **7%** Among the 2,030 U.S. hospitals with enough data to calculate an SIR, 7% had an SIR significantly worse than the national SIR of 0.92.

C. difficile Infections ↓ 10% LOWER COMPARED TO NAT'L BASELINE*

LABORATORY IDENTIFIED HOSPITAL-ONSET *C. DIFFICILE* INFECTIONS

When a person takes antibiotics, good bacteria that protect against infection are destroyed for several months. During this time, patients can get sick from *Clostridium difficile* (*C. difficile*), bacteria that cause potentially deadly diarrhea, which can be spread in healthcare settings.

- ☐ U.S. hospitals reported a significant decrease in *C. difficile* infections between 2012 and 2013.

- **13%** Among the 3,557 U.S. hospitals with enough data to calculate an SIR, 13% had an SIR significantly worse than the national SIR of 0.90.
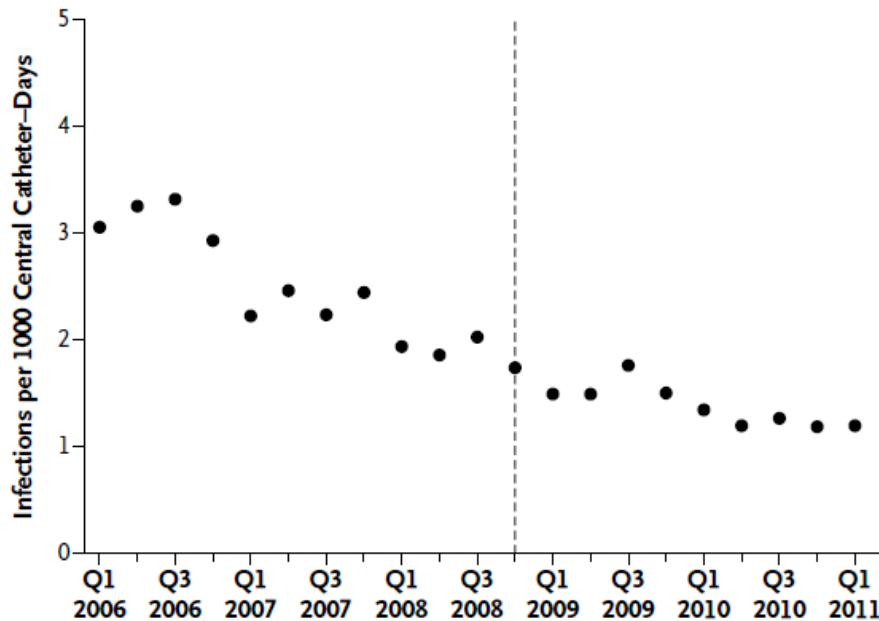
*Statistically significant.
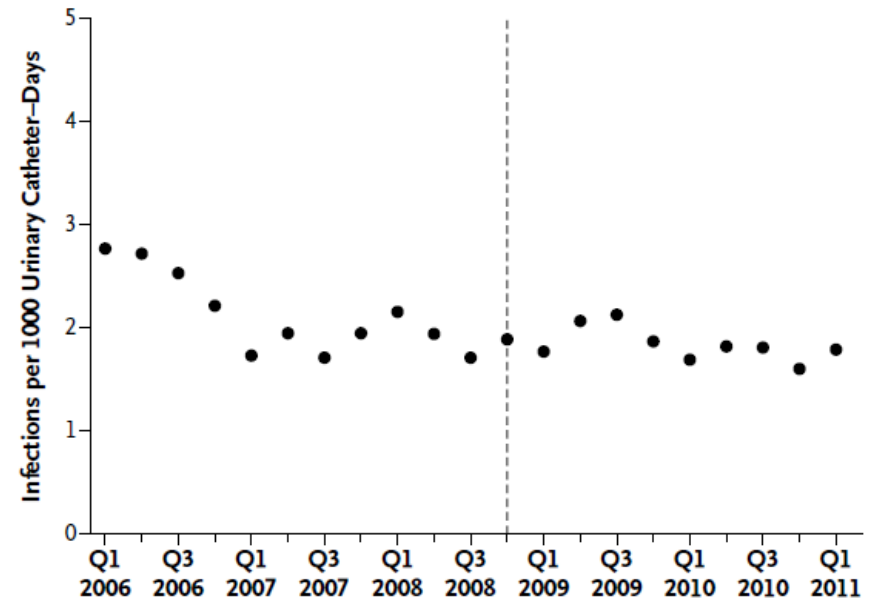
THIS REPORT IS BASED ON 2013 DATA, PUBLISHED JANUARY 2015

CDC

Effect of Nonpayment for Preventable Infections in U.S. Hospitals

A Central Catheter–Associated Bloodstream Infections

B Catheter-Associated Urinary Tract Infections
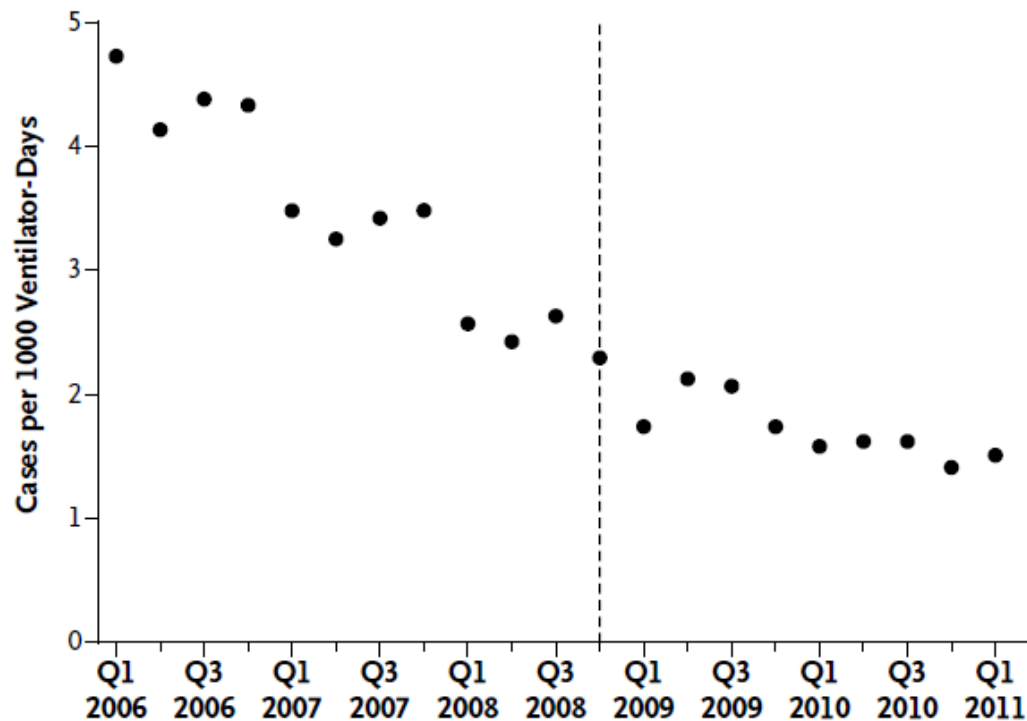
Effect of Nonpayment for Preventable Infections in U.S. Hospitals

C Cases of Ventilator-Associated Pneumonia

Suppose you are an auto mechanic…..paid on the basis of how many cars you fix and what work you do. You encourage drivers to bring their cars in for routine maintenance but you aren't always successful……….drivers bring in their cars when something goes wrong

Now suppose you are being paid on the basis of outcomes …..the number of breakdowns or accidents that occur in the cars ………. mostly affected by factors you can't control, like the weather, road conditions and drivers who are young or old or DUI.

The only way to protect yourself is to avoid these high-risk drivers and conditions. You may decline to fix older cars, cars of teenage or elderly drivers, or drivers that don't follow routine maintenance.
Eventually you may even close up shop because you are in an area that simply is prone to accidents.

Thomas Guastavino, MD

What's an ID Physician to do?

- Know your hospital infection rates
  - CLABSI
  - CAUTI
  - C. difficile infections
  - MRSA bacteremia
  - SSI – colon, TAH, TKA, THA, CABG

- Implement reduction measures
  - Hand hygiene
  - Isolation precautions
  - Monitor and reduce device utilization
  - Partner with stakeholders
  - Antimicrobial stewardship

Resources

- SHEA: Compendium of Strategies to Prevent Infection in Acute Care Hospitals 2014 Update

http://www.shea-online.org/View/ArticleId/289/Compendium-of-Strategies-to-Prevent-Healthcare-Associated-Infections-in-Acute-Care-Hospitals-2014-Up.aspx

- IDSA: Value Based Payments

http://www.idsociety.org/Value_Based_Payments/