What is the clinican's interest in improving the etiologic diagnosis of PJI

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- Introduction
- Microorganisms causing PJI
- Definition and classification of PJI
- Culture-negative PJI
- Treatment concepts
- Aseptic loosening vs low-grade infection
- Conclusions

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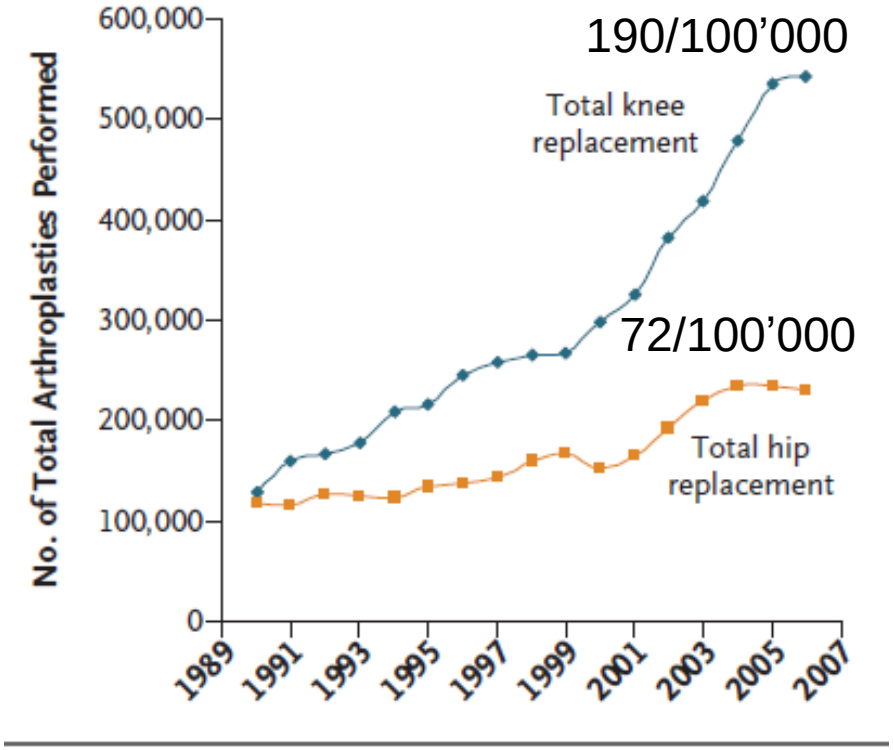
INTRODUCTION
Number of TJAs in USA and Germany



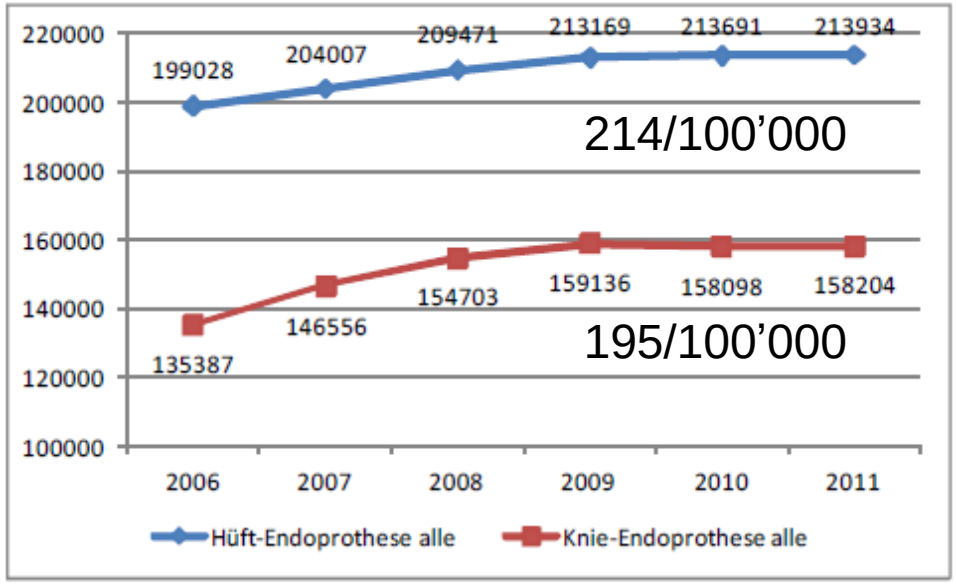
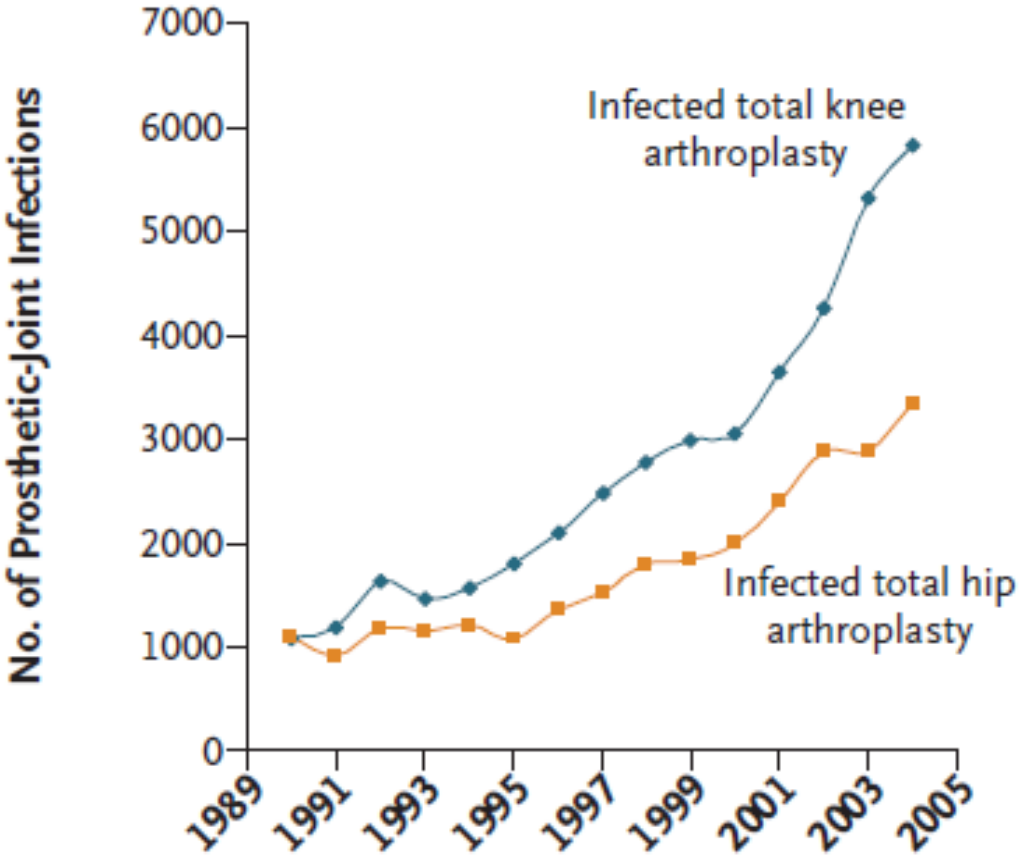


Abbildung 1: Entwicklung der Anzahl von Knie- und Hüft-Endoprothesen in Deutschland 2006 bis 2011 (eigene Zusammenstellung nach Statistisches Bundesamt 2007-2012)

Del Pozo & Patel. NEJM 361:787-94,2009

Hkk Gesundheitsreport 2013

INTRODUCTION
Number of periprosthetic joint infection in USA



Del Pozo & Patel. NEJM 361:787-94,2009

INTRODUCTION
Pathogenesis (1)

Risk of PJI (knee and hips) is 0.5-2% despite clean surgery, because of a local immunodeficiency:

- **Local granulocyte defect due to frustrated phagocytosis (non-phagocytosable surface)**
- **Presence of biofilm compromizes bacterial killing by granulocytes**

[Zimmerli W, Sendi P. Semin Immunopathol 33:295-306, 2011
Zimmerli W, Moser C. FEMS Immunol Med Microbiol 65:158-68,2012]

INTRODUCTION
Pathogenesis (2)

Exogenous Infection (65%)

- Perioperatively during or within some days after surgery
- Late exogenous superinfection in patients with sinus tract

Hematogenous Infection (35%)

- Infection via bloodstream at any time after surgery
- Most frequent during *S. aureus* sepsis
- Most frequent primary foci: cardiovascular > skin/soft tissue > urogenital > oral cavity

[Laffer RR et al. Clin Microbiol Infect 12:433-9,2006
Banderet F et al. Clin Microbiol Infect 17:1098-1100, 2011
Rakow A et al. Clin Microbiol Infect 25:845-50 2019]

SPECIMENS FOR MICROBIOLOGY

Preoperative samples

- Synovial fluid (sensitivity for culture: 86% [50-93%])

[Widmer AF. Clin Infect Dis 33 (suppl 2):S94-106, 2001]

- Blood cultures (sensitivity: 81% in hematogenous PJI)

[Rakow A et al. Clin Microbiol Infect 25:845-50, 2019]

Note: Sinus tract swabs are inadequate specimens

Intraoperative samples

- Tissue homogenate (at least 3 samples)
- Sonicate fluid from removed devices

Note: Intraoperative swabs are inadequate specimens

MOST FREQUENT MICROORGANISMS IN PJI

(data from 1130 episodes)

- ***Staphylococcus aureus*** **21-43%**
- **Coagulase-negative staphylococci** **17-39%**
- ***Streptococcus spp*** **7-12%**
- **Gram-negative aerobic bacilli** **5-12%**
- **Enterococci** **1-8%**
- **Anaerobic bacteria (mainly *Cutibacterium* spp.)** **2-6%**
- **Polymicrobial (mainly in patients with sinus tract)** **15%**
- **No growth (>50% had prior antibiotics)** **4-15%**

Zimmerli & Sendi, in: Mandell, Douglas, Bennett's PPID 9th ed. 2020

RARE MICROORGANISMS IN PJI (published case reports)

- *Corynebacterium* spp.
- *Listeria monocytogenes*
- *Actinomyces* spp.
- *Nocardia* spp.
- *Achromobacter* spp.
- *Pseudomonas* spp
- *Salmonella* spp.
- *Neisseria* spp.
- *Veilonella* spp.
- *Mycoplama hominis*
- *Tropheryma whipplei*

- *Brucella* spp
- *Franciscella tularensis*
- *Yersinia enterocilitica*
- *Pasteurella multocida*
- *Campylobacter* spp.

- *Aspergillus fumigatus*
- *Candida* spp.
- *Histoplasma capsulatum*
- *Sporotrix schenckii*

- *Mycobacterium tuberculosis*
- Rapidly growing mycobacteria

etc.

Virtually any microorganism can cause PJI

[Marculescu CE et al. Clin Orthop Rel Res 451:55-63,2006
Marculescu CE et al. Clin Orthop Rel Res 451:64-72, 2006]

DEFINITION OF PJI (modified IDSA criteria)

- Sinus tract communicating with device
- Elevated leukocyte count in synovial fluid (>2000/µl) and/or predominance of neutrophils (≥70%)
- Acute inflammation in histopathology of periprosthetic tissue
- Purulence around the prosthetic device without other explanation (e.g. wear particles, gout)
- **Detection of identical microorganism in 2 specimens (low-virulence) or 1 specimen (virulent microorganism)**

[Osmon DR et al., Clin Infect Dis56:e1-25, 2013: IDSA-guidelines
Zimmerli W, J Intern Med 276:111-9,2014]

CULTURE - NEGATIVE PJI

According to the definition of PJI, a positive culture is not a prerequisite for the diagnosis:

- 4-15% of the PJI are culture-negative
- Appropriate antimicrobial therapy and surgical strategy requires the knowledge of the infecting agent
- Negative culture has been shown to be a risk factor for failure (4.5times increased risk of relapse)

⇒ **There is a need for knowing the infecting agent**

[Parvizi J et al. J Bone Jt Surg 2006
Mortazavi SMJ et al. Clin Orthop Relat Res 2011
Berbari EF et al. Clin Infect Dis 2007]

TREATMENT CONCEPTS: SURGICAL STRATEGIES OF PJI

Different surgical options should be chosen according to a rational algorithm:

- **Debridement with antibiotics and implant retention (DAIR)**
- **1-stage exchange**
- **2-stage exchange**
- **Removal without reimplantation**

[Zimmerli W et al. N Engl J Med 351:1645-54, 2004
Osmon DR et al. Clin Infect Dis 56:e1-25,2013]

TREATMENT CONCEPTS: SURGICAL STRATEGIES OF PJI

For patients treated with DAIR or for those treated with 1-stage exchange, the microorganism and its susceptibility to antibiotics must be known, since a biofilm-active antibiotic must be used for an optimal outcome (80-95% success rate)

[Zimmerli W et al. N Engl J Med 351:1645-54, 2004
Osmon DR et al. Clin Infect Dis 56:e1-25,2013]

IMPACT OF SUSCEPTIBILITY ON TREATMENT STRATEGY: BIOFILM-ACTIVE ANTIBIOTICS

Microorganisms in a biofilm

- aggregate and produce an extracellular matrix
- have an anaerobic or microaerobic metabolism
- downregulate protein synthesis

Antibiotic efficacy against biofilm bacteria requires

- penetration into the biofilm
- bactericidal activity against stationary-phase bacteria

TREATMENT CONCEPTS: BIOFILM-ACTIVE ANTIBIOTICS

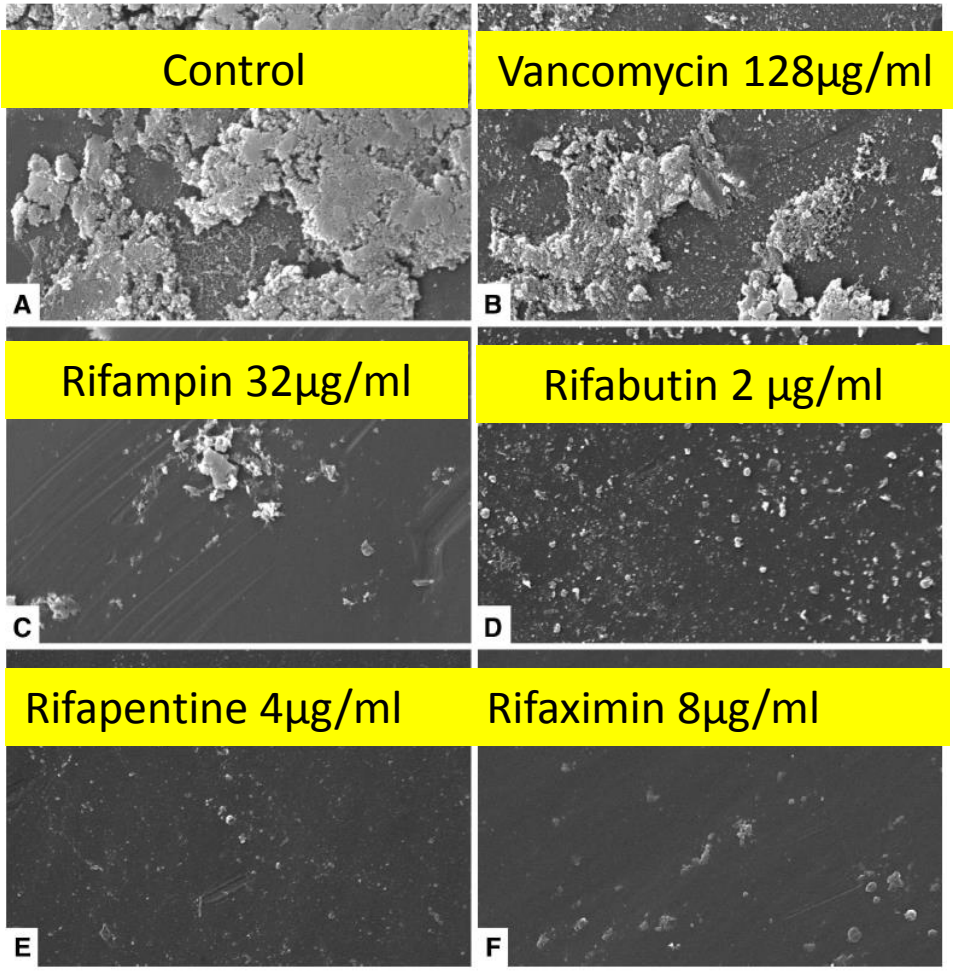
Most antibiotics are not able to eliminate biofilm microorganisms from the implant. There are only two exceptions:

- **Rifamycins against staphylococci**
- **Fluoroquinolones against Gram-negative bacilli**

Implant retention has only a good outcome, if the PJI is caused by a microorganism susceptible to a biofilm-active antimicrobial agent

[Zimmerli & Sendi chapter 2015, in: Mandell, Douglas, Bennett's PPID 9th ed. 2020]

ACTIVITY OF RIFAMYCIN DERIVATIVES ON BIOFILMS



SEM images of *S. aureus* (ATCC 29213) 24h-biofilms.

All rifamycin derivatives, but not vancomycin eradicate biofilm bacteria during a 24-h incubation in vitro.

[Sanchez CJ et al. CORR 473:2874-84, 2015]

ROLE OF RIFAMPIN IN STAPHYLOCOCCAL PJI TREATED WITH IMPLANT RETENTION

Author	Reference	Success No Rifa	Success Rifa
Deirmengian et al	*J Arthroplasty, 2003*	35%	NA
Zimmerli et al	*JAMA, 1998*	58%	**100%**
Giulieri et al	*Infection, 2004*	50%	**87%**
Barberán et al*	*Am J Med, 2006*	ND	**83%**
El Helou et al*	*EJCID, 2010*	63%	**93%**
Ascione et al**	*J Infection, 2015*	57%	**91%**

Rifampin combination therapy is now standard in orthopedic device-associated staphylococcal infection treated with implant retention

** Qualifying for retention (algorithm) **Not all treated with implant retention*

ACTIVITY OF FLUOROQUINOLONES ON BIOFILMS

In vitro:

Fluoroquinolones are bactericidal against non-growing and adherent Gram-negative bacilli.

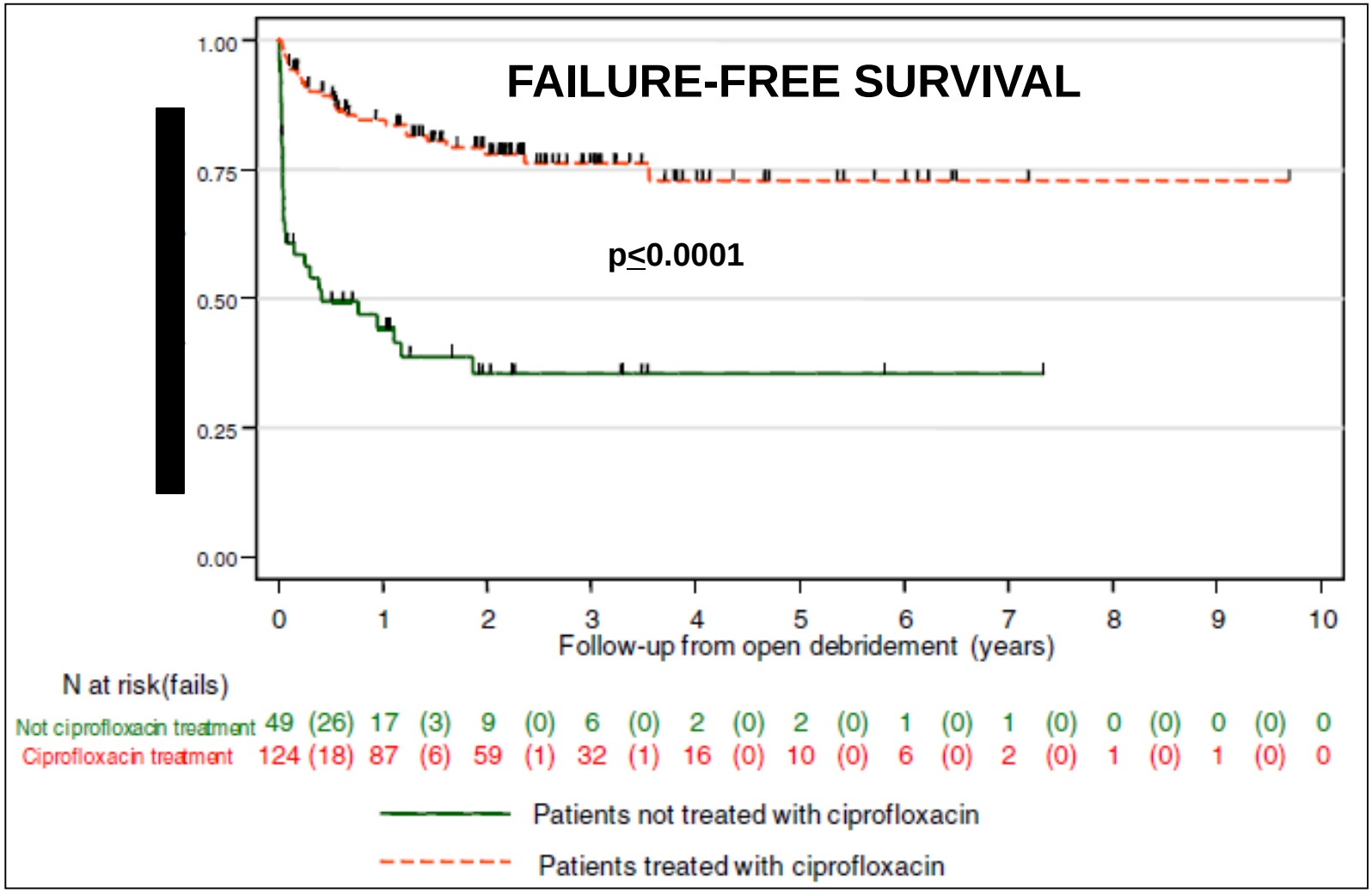
[Widmer et al. AAC 35:741-6,1991]

In animal model:

Fluoroquinolones are more efficacious against implant-associated infections than cotrimoxazole.

[Widmer et al. Scand J Infect Dis 22:611-8,1990 and AAC 35:741-6,1991]

ROLE OF CIPROFLOXACIN IN GRAM-NEGATIVE PJI TREATED WITH DAIR



[D Rodriguez-Pardo et al. Clin Microbiol Infect, 2014]

IMPACT OF MICROORGANISM ON SURGICAL STRATEGIES OF PJI

Age of the biofilm is crucial:

In vitro: killing of biofilms rapidly drops with the age of the biofilm *[Antimicrobial tolerance in biofilms. In: Microbiol Spectr 3: June 2015]*

In vivo: success rate of staphylococcal PJI treated with implant-retention:

- <1 month duration: 83%

2-6 months duration: 65%

>6 months duration: 31%

[Barberan J et al. Am J Med 993.e7-993.e10, 2006]

KILLING DEPENDS ON THE AGE OF THE BIOFILM in vitro

Slide by courtesy of:
Paul S. Stewart

Source:
Antimicrobial tolerance in biofilms. In: Microbiol Spectr 3: June 2015.

Time for development of biofilm tolerance:
$t_{½}$ = 2.7 ± 2.0 d

Data from the literature: different bacterial species, different antibiotics.

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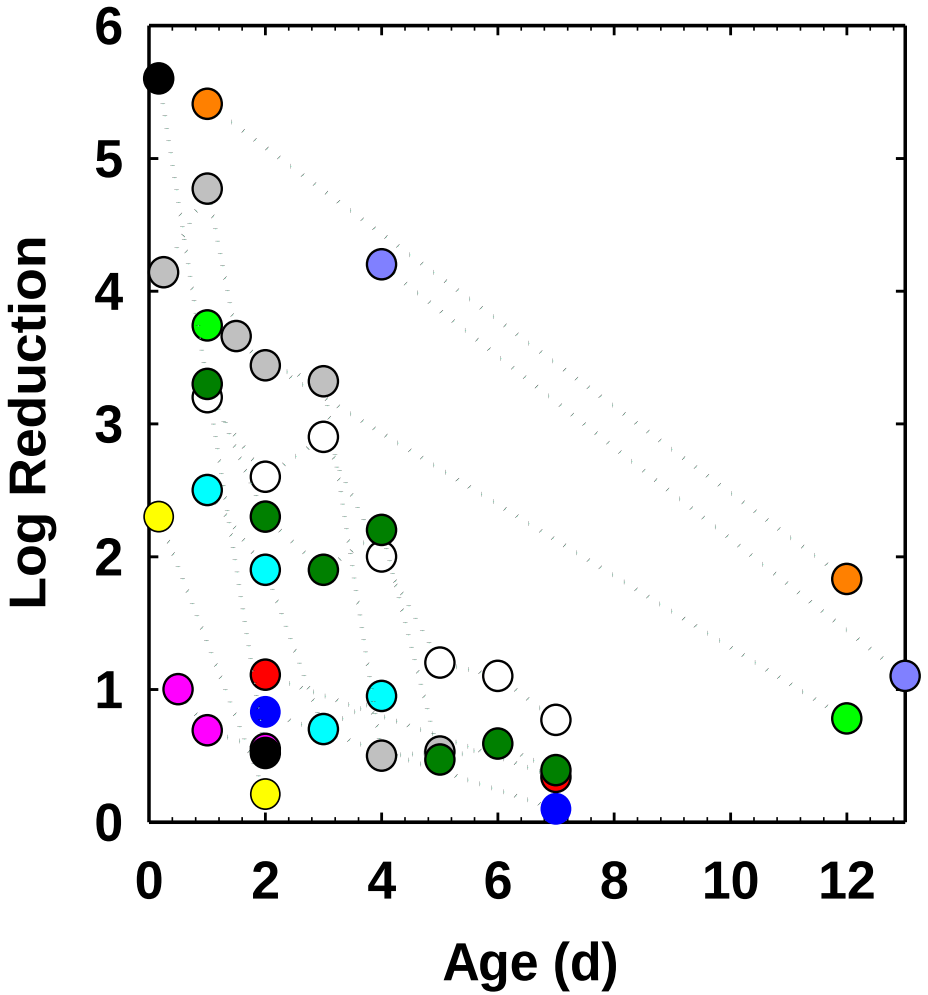


The older the biofilm, the lower the bacterial killing

ASEPTIC LOOSENING VERSUS LOW-GRADE INFECTION

Aseptic loosening may be due to undetected low-grade infection:

In 7/195 (3.6%) of cases with aseptic loosening, a microorganism has been detected with metagenomic shotgun sequencing

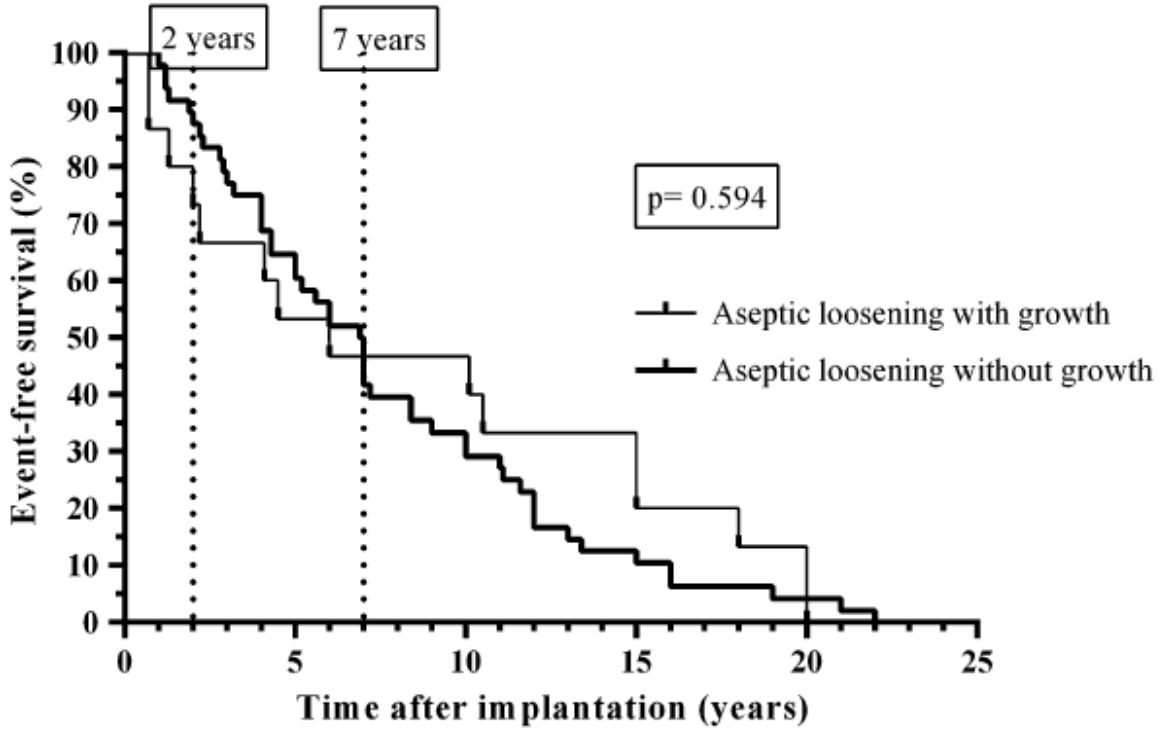
[Thoendel MJ, Clin Infect Dis 67:1333-8,2018]

In 8/63 (13%) of cases with aseptic loosening, periprosthetic tissue/sonication fluid culture was positive (prospective cohort study)

[Portillo ME et al CORR 471:3672-8,2013]

Does this indicate that these cases have low-grade PJI despite not fulfilling diagnostic criteria?

ASEPTIC LOOSENING VERSUS LOW-GRADE INFECTION



[Portillo ME et al CORR 471:3672-8,2013]

Identical event-free device survival in patients with aseptic loosening with and without growth

REMAINING PROBLEMS

- Detection of an unusual or low-virulence pathogen in one single specimen has to be considered as contaminant.
- If new diagnostic techniques are tested, an established gold standard for the diagnosis is needed.
- Not only conventional bacteria, but also mycobacteria or fungi can cause PJI. Thus, performing 16S rRNA gene cloning is not comprehensive.
- Since long-term antibiotic therapy is required, the antibiotic susceptibility of the microorganism must be known.

CONCLUSIONS

Modern genomic techniques are indicated

- **in patients treated with antibiotics before diagnostic work-up, because this is a major risk for culture-negative PJI, which has an increased risk for recurrence.**
- **in patients with suspicion for polymicrobial PJI (sinus tract), because the correct management requires knowledge of all microorganisms.**

Genomic techniques are not indicated

- **in patients with aseptic loosening, because the role of microorganisms in aseptic loosening remains unclear.**

Thank you for your attention