# Biofilm-Therapie bei TEP-Infektionen: PRO



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## Improved survival in breast cancer

- 10-year survival increased from 55% to 95%
- Interdisciplinary work: oncologists, gynecologists, plastic surgeons, radiologists, pathologists
  - Early diagnosis by routine screening
  - Improved combination treatment (surgery, hormonal, chemotherapy)
- Less mutilation & less toxicity
- Today still common, but curable disease

### Parallels for PJI?

# Implants: improve function or replace missing anatomic structure





















int Subpectoral Implant











## **Risk of implant-associated infection**

Device	No. inserted in the US per year	Rate of infection, %
Fracture fixation devices	2,000,000	5–10
Dental implants	1,000,000	5–10
Joint prostheses	600,000	1–3
Vascular grafts	450,000	1–5
Cardiac pacemakers	300,000	1–7
Mammary implants	130,000	1–2
Mechanical heart valves	85,000	1–3
Penile implants	15,000	1–3
Heart assist devices	700	25–50

Darouiche RO. Clin Infect Dis 2001;33:1567–1572

## Goal

### Functional implant

- Highly efficient concept (90% cure)
- Least invasive (retention, whenever possible)

Eradication of infection

- Combination of surgery + antibiotics (bundle)
- Not antibiotic suppression (whenever possible)

## Scientific evidence

- In vitro
- Animal models
- Clinical studies

What do we know?

## **Biofilms: life on surfaces**

# Most bacteria in nature live in biofilmsOne of the most resistant forms of life

Hot, acidic pools in Yellowstone National Park





#### **Glaciers in Antarctica**

## **Biofilm: characteristics**

1 min 3 h 12 h 1 day

3 days

Adherent to surface (min-h)

Embedded in matrix (70%)

Slowly replicating (stacionary-growth)



- Primary hip prosthesis 09/2013 (cemented)
- Since implantation pain, walking distance now 20 m
- CRP normal, no loosening on x-ray





validiert durch: Irene Grohsellus

## **Delayed (low-grade) infection**

- CRP normal, no prosthesis loosening
- Repeated joint aspiration 04/2014: Staphylococcus epidermidis (same susceptibility)
- Synovial fluid: WBC 59.000/µl, 90% PMN

- Prosthesis exchange: 1- or 2-stage exchange (short interval)
- Which antibiotic? Sugar pills or wonder drugs?

### The key to success...



# **Classification**

Time after	0–3 months	3–24 (36) months	Any time
Implantation			
Type of infection	Early postoperative	Delayed (low grade)	Late
Route	Perioperative		Haematogenous
Signs	Acute: fever, effusion, warmth, dehiscence	Chronic: Persistent pain, loosening, fistula	Acute or subacute
Pathogen	<i>S. aureus</i> Streptococci Enterococci	Coagulase-negative staphylococci <i>P. acnes</i>	S. aureus E. coli

# Definition

- Sinus tract (fistula)
- Visible purulence<sup>1</sup>
  - Wound discharge, abscess
  - Acute inflammation in tissue histology
    - ≥1 to ≥10 neutrophils/high-power field
- Leukocytes in synovial fluid<sup>2</sup>
  - Knee:  $\geq 1.7 \times 10^{9}$ /l leukocytes,  $\geq 65\%$  neutrophils
  - Hip:  $\geq 4.2 \times 10^{9}$ /l leukocytes,  $\geq 70\%$  neutrophils
- Microbial growth
  - Synovial fluid
  - ≥3 periprosthetic tissue (for low-virulent organisms >1 positive)
  - Sonication fluid (>50 CFU/ml)
- <sup>1</sup> Pseudopus: metal-on-metal prostheses
- <sup>2</sup> Excluded: Early postoperative (3 months) and inflammatory joint diseases

## **Route of implant infection**



# **Antibiotics today**



Rolinson GN. Int J Antimicrob Agents 2007;29:3-8

## Antibiotics with antibiofilm activity

- 1. Staphylococci: Rifampin (in combination)
- 2. Streptococci: Penicillin G
- **3.** Enterococci: Fosfomycin? (in combination)
- 4. Gram-negative bacilli: Ciprofloxacin (fosfomycin?)
- 5. Candida: echinocandins (caspofungin)?

# Animal data: Guinea pig foreign-body infection model

Inoculum per cage: Duration of infection: Duration of treatment: 10<sup>5</sup> cfu 24 hours 4 days

# **Foreign-body infection (FBI) model**

- 4 Teflon cages implanted subcutaneously in guinea pigs
- Aspiration of cage fluid (planktonic bacteria)
- Cages removed 5 days after treatment (eradication)





Zimmerli W et al. J Clin Invest 1984;73:1191–1200

# Efficacy in the guinea pig infection model (MRSA)

#### **Rifampin resistance rate**



John AK et al. Antimicrob Agents Chemother 2009 & unpublished data

# Activity of fosfomycin and rifampin against MRSA in the guinea pig model



Highest cure rate with FOS+RIF (83%), which was superior to other RIF-combinations.

No *in vivo* emergence of FOS resistance was observed in mono- or combination therapy.

Mihailescu R et al. Antimicrob Agents Chemother 2014

# Activity of fosfomycin and gentamicin against *E. faecalis* biofilm



Oliva A et al. Antimicrob Agents Chemother 2014

# Treatment against adherent *P. acnes* in the guinea pig model



- No spontaneus cure
- Rifampin necessary for eradication of *P. acnes* biofilm

Furustrand Tafin U et al. Antimicrob Agents Chemother 2012

# Activity of lipoglycopeptide dalbavancin against MRSA (telavancin, oritavancin)



Baldoni D & Furustrand Tafin U. IJAA 2013

# **Clinical evidence**

### **ROLE OF RIFAMPIN IN IMPLANT-RELATED INFECTIONS:** Randomized controlled trial: acute staph. infections

Treatment: Initial débridement and antibiotics:

2 weeks i.v.

(Flucloxacillin or Vancomycin) + (Rifampin or Placebo)

followed by:

3-6 months p.o.

Ciprofloxacin + (Rifampin or Placebo)

Zimmerli W et al. JAMA 1998

	Ciproflox- placebo (n=15)	Ciproflox- rifampicin (n=18)
Microbiology: - S. aureus (0/26 methicillin-resistant)	11	15
- S. epidermidis (2/7 methicillin-resistant)	4	3
Initial iv-treatment:		
- Flucloxacillin	13	13
- Vancomycin	2	5
Follow-up (months) (median,range)	33 (15-41)	35 (24-46)

Zimmerli W et al. JAMA 1998

#### Results CIP + RIF CIP + placebo Cure (ITT) 9/15 (60%) 16/18 (89%) 12/12 (100%)\* Cure (as treated) 7/12 (58%) 3/156/18 Drop-out Follow-up 33 (15-41) 35 (24-46) (months)

\*p=0.019 (Fisher's exact test)

Zimmerli W et al. JAMA 1998

The NEW ENGLAND JOURNAL of MEDICINE

**REVIEW ARTICLE** 

### CURRENT CONCEPTS Prosthetic-Joint Infections

Werner Zimmerli, M.D., Andrej Trampuz, M.D., and Peter E. Ochsner, M.D.

Zimmerli W et al. N Engl J Med 2004:351:1645–1654

Table 1. Treatment of Infection Associated with a Prosthetic Joint Caused by Common Microorganisms.*			
Microorganism	Antimicrobial Agent	Dose	Route
<i>Staphylococcus aureus</i> or coagulase-negative staphylococci			
Methicillin-susceptible	Nafcillin or floxacillin† <i>plus</i> Rifampin for 2 wk, <i>followed by</i> Rifampin <i>plus</i> Ciprofloxacin <i>or</i> Levofloxacin	2 g every 6 hr 450 mg every 12 hr 450 mg every 12 hr 750 mg every 12 hr 750 mg every 24 hr to 500 mg every 12 hr	IV PO or IV PO PO PO
Methicillin-resistant	Vancomycin <i>plus</i> Rifampin for 2 wk, <i>followed by</i> Rifampin <i>plus</i> Ciprofloxacin‡ <i>or</i> Levofloxacin‡ <i>or</i> Teicoplanin§ <i>or</i>	l g every 12 hr 450 mg every 12 hr 450 mg every 12 hr 750 mg every 12 hr 750 mg every 24 hr to 500 mg every 12 hr 400 mg every 24 hr	IV PO or IV PO PO PO
	Fusidic acid∬ <i>or</i> Trimethoprim– sulfamethoxazole <i>or</i> Minocycline	500 mg every 8 hr 1 DS tablet every 8 hr 100 mg every 12 hr	PO PO PO
Streptococcus species (except <i>Streptococcus agalactiae</i> )	Penicillin G <i>or</i> Ceftriaxone for 4 wk, <i>followed by</i> Amoxicillin	5 million U every 6 hr 2 g every 24 hr 750–1000 mg every 8 hr	IV IV PO
Enterococcus species (penicillin-susceptible) and <i>Streptococcus agalactiae</i>	Penicillin G <i>or</i> Ampicillin or amoxicillin <i>plus</i> Aminoglycoside¶ for 2–4 wk, <i>followed by</i>	5 million U every 6 hr 2 g every 4–6 hr	IV IV IV
	Amoxicillin	750–1000 mg every 8 hr	PO

# Surgical and antibiotic treatment concepts



## **Controversies in management of PJI between North America and Europe**

### North America

- Standard: 2-stage exchange with long interval (6–8 weeks)
- No rifampin dogma that infection is not possible to eradicate without implant removal
- Retention: life-long suppression of infection

### Europe

- 4 surgical approaches according to situation (algorithm)
- Early and aggressive revision to make salvage of the implant possible
- Highest success with lowest invasiveness

### Low cure of debridement & retention

- Marculescu CE et al. Clin Infect Dis 2006;42:471–478
  - 60% cure rate at 2 years<sup>1</sup>
- Berbari EF et al. Clin Infect Dis 2006;42:216–223
  - 32% cure rate at 2 years<sup>2</sup>
- Chiu FY, Chen CM. Clin Orthop Relat Res 2007;461: 130–135
  - 30% cure rate, minimum 3-years follow up<sup>3</sup>
- 1. Improper patient selection
- 2. Insufficient surgical debridement
- 3. No rifampin use for biofilms

# **PJI (n = 118)**

#### Treatment outcome in 118 PJIs (1994–2006)\*



\*Infections included hip (n=78), knee (n=22), ankle (n=10) and shoulder (n=8)

# Hip and knee PJI (n = 68)

Estimate of survival without treatment failure in 68 infections (1995–2004)



# **Elbow PJI (n = 27)**



# Hip PJI (n = 63), 1985-2001



Giulieri S. Infection 2004

## **Staphylococcal PJI**



# **Prosthetic join infection: Outcome**

#### (Charité Berlin)

Variable	Long	Long	Short
	interval w/o	interval with	interval with
	optimal AB	optimal AB	optimal AB
	(n =83)	(n =79)	(n = 80)
Patient age (years)	$68,5 \pm 7,7$	$68,6 \pm 14,4$	$65,4 \pm 9,6$
Duration from implantation to infection (years)	3,2 ± 3,0	5,7 ± 5,1	4,2 ± 3,9
Interval from explantation to reimplantation	66,7 ± 12,8	66,7 ± 38	15,9 ± 5,8
Length of hospital stay (days)	$25,7 \pm 8,6$	30 ± 10	30 ± 7
Follow-up (months)	25,2	18,3	17,8
	(7-68)	(6–29)	(8-19)
Aufenthalt in Geriatrie im Intervall (d)	204	210	0
Relapse of the infection	6 (32%)	1 (5%)	0 (0%)
No. revisionens in interval (median)	2	2	0

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## Long-term treatment toxicity

- Quinolones: tendinopathy, long QT syndrome
- **Rifampin:** hepatotoxicity, GI-intolerance, rash, polyarthralgia
- Betalactams: myelosuppression, interstial nephritis
- Cotrimoxazole: rash → Steven Johnson, renal insufficiency, hyperkaliemia
- Doxycycline: phototoxicity
- Daptomycin: eosiophilic pneumonia, rhabdomyolisis
- Linezolid: myelosuppression, neuropathy
- All: rash, drug fever, *C. difficile* colitis (except rifampin)



## **Bone penetration**



# **Common reasons for failure**

#### Surgical

- No (late) surgery
- Arthroscopic instead open surgery (change of mobile parts)
- Retention attempt of <u>loose</u> prosthesis
- Prosthesis removal in <u>early and hematogenous</u> infection

#### Antimicrobial

- No highly-active bactericidal antibiotic (initial i.v.)
- Short duration (total 3 months)
- No rifampin for staphylococcal biofilms
- Rifampin with open wound, fistula or VAC

## 4 most common mistakes

- Use of oral drugs with low bioavailability: beta-lactams (penicillins, cefalosporins)
- 2. Use of bacteriostatic antibiotics: linezolid, clindamycin
- Wrong interpretation of in vitro susceptibility:
  quinolones against staphylococci or enterococci
- 4. Rifampin: use in draining wounds, without implant (in prosthesis-free interval)

# Error: use of oral drugs with poor bioavailability

Drug	Oral bioavailability	Bone penetration
Amoxicillin/clavulanic acid or ampicillin/sulbactam	15% (AUC 6x lower with PO dose)	7%
Cefuroxim, cefadroxil	10% (AUC 10x lower with PO dose)	12%
Ciprofloxacin	70%	48%
Levofloxacin	100%	77%
Rifampin	80%	51%
Co-trimoxazole	85%	55%
Clindamycin	90%	45%

Sanford Guide to Antimicrobial Therapy 2013. 43<sup>nd</sup> ed. Lorian. Antibiotics in Laboratory Medicine. 5<sup>th</sup> ed.



## **Risik factors for rifampin resistance**

Characteristics	Cases $(n = 48)$	Controls $(n = 48)$	P value <sup>a</sup>
Treatment			
Treated with any antibiotics	44 (91.7 %)	30 (62.5 %)	$0.001^{f}$
Treated with rifampin	41 (85.4 %)	20 (41.7 %)	<0.001 <sup>f</sup>
Rifampin always adequate <sup>b</sup>	25	15	
Rifampin inadequate	16	5	
Monotherapy and/or	4	3	
Empiric therapy <sup>c</sup> and/or	6	1	
Other reasons <sup>d</sup>	7	1	
Treatment with high bacterial load	34 (70.8 %)	13 (27.1 %)	<0.001 <sup>f</sup>
<2 weeks iv antimicrobial treatment	12	4	
No surgical debridement	7	1	
No iv and no surgical debridement	15	8	

#### Achermann Y et al. Infection. 2013;41:431-437

# High-dose daptomycin for PJI: ongoing phase II study



\*Daptomycin is not licensed for the treatment of PJI

# **Results (n = 72)**

### Microbiology:

- Staphylococcus aureus 30 cases (31 MRSA, 5 MSSA and 1 VISA)
- Coagulase-negative staphylococci 33 cases (26 MR-CNS, 7 MS-CNS)
- [Enterococci 9 cases (no VRE)].

## Efficacy:

 Clinical and microbiological cure was observed in 64 patients (89%) with a median follow-up of 21.5 months. All failed cases were enterococci.



European Prosthetic Joint Infection Cohort (EPJIC)

www.pro-implant-foundation.org

Enton de Canton de Vaud

### www.PRO-IMPLANT-foundation.org





# March 5-6, 2015 June 1-2, 2015 September 24-25, 2015





## **Educational material**



# Infektionen des Bewegungsapparates

Grundlagen, Prophylaxe, Diagnostik und Therapie





eLearning tool (for iPad and tablets)

Essentials in diagnosing PJI

Available free for download (iTunes) Palacademy

By the Expert Group of Swiss Societies of Orthopedic & Trauma surgeons and Infectious Diseases & Microbiology (Fall 2014)

CMSC Centrum für Muskuloskeletale Chirurgie





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Focus on implant, bone and joint-associated infections:

- Surgery: New concepts (retention, 1-stage, short interval)
- Diagnosis: Fast innovative methods
- Antibiotics: Active against biofilms

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