„Prevention of Biomaterial-associated Infections“

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Egyptian mummy
3000 years old

Biomaterials: Polymers

- Polyethylene
- Polypropylene
- Polyvinylchloride
- Polyethylene terephthalate (Dacron)
- Polytetrafluoroethylene (Teflon)
- Polydimethylsiloxane (Silikon)
- Polyurethanes
Biomaterials: Metals und Ceramic Compounds
Biomaterial-associated Infection

- Syn.: Foreign body, Polymer-associated, Implant-associated Infection, („Plastikinfektion“)

- Nosocomial, iatrogenous Infection

- Presence of a foreign body reduces the infectious dose (Elek und Konen 1957)

- Increasing rates through increasing use of biomaterials in modern medicine (catheters, implants)

- Predominant causative pathogens: *Staphylococci* (S.aureus, CNS= Coagulase negative staphylococci)
Etiology of Implant-associated Infections (here: ODRI = orthopedic device-related infection)

Early („Early postoperative“) Infection:

• Contamination with microorganisms during implantation; until 3 months (2-4 weeks) after surgery; acute symptoms (S. aureus)

Subacute („Delayed“) Infection:

• 3-24 months nach after surgery; Contamination during implantation and survival of microorganisms in a „dormant state“ (CNS)

Late Infection:

• >2 years after surgery; acute onset oder subacute picture; often hematogenous origin (streptococci)
Causative pathogens

- Staphylococcus epidermidis and other CNS
- Staphylococcus aureus
- Other grampositive organisms (eg enterococci)
- Enterobacteriaceae
- Pseudomonas aeruginosa
- Fungi (eg Candida sp.)
- Streptococci, Corynebacterium, Anaerobes
Frequency of Biomaterial-associated Infections

- Heart valves
  - Early: 0.8%
  - Late: <1 – 3%

- Vascular prostheses: 2%

- Artificial hip joint: <1%

- Artificial knee joint: <2%

- Intravascular catheters: 0.2 – 20%

- Cerebrospinal fluid shunts: 1 – 27%

- Artificial heart: 36 – 50%

- USA: 1 Million Implant-associated infections per year

- Estimated costs: ~3 Billion $ per year
Pathogenesis

Polymer surface → Adherence → Accumulation → Biofilm formation
Adherence

- electrostatic, van der Waals, hydrophobic interactions
- Polysaccharide adhesin, staphylococcal surface protein, 60 kDa Protein
Accumulation

- Polysaccharide intercellular adhesin (PIA)
- Accumulation associated protein (AAP)
- Slime-associated adhesin (SAA), Polysaccharide adhesin (PS/A)

SAA, PS/A = PIA?

- Regulation by icaABCD-Gene locus

- Microorganisms „react“ with polymer surface together with host factors
- Biofilm protects microorganisms against host defence mechanisms and antibiotic attack
- Detachment of microorganisms from the biofilm`s edge can lead to bacteremia und metastatic seeding (eg. abscess formation)
Implant-associated Infections: Examples

- Infection of an ocular lens (PMMA)
  - Frequency 0.1-0.3 %

Hypopyon

Colonisation of lens by S. epidermidis
Infections of orthopedic implants

- Hip - TEP: < 1%
- Knee - TEP: < 2%

Knee prosthesis loosening

Distal abscess

Study with Remigius-Hospital Opladen:

- in 42% of „aseptic prosthesis loosening“ detection of microorganisms (mainly CNS)
Diagnosis of Biomaterial-associated Infections

• Clinical signs
• Laboratory parameters
  – BSR, Leukocytes, C-reactive protein, Procalcitonin
• Imaging methods
  – X-ray, Echocardiography, CT, MRT, Scintigraphic methods
• Histology
• Microbiology
  – Blood culture, cerebrospinal fluid, tissue, implant (in case of explantation)
Therapy

• Removal of foreign body (implant)

• Antimicrobial therapy

• Removal + antimicrobial therapy
MIC/MBC_{Biofilm} \gg \text{MIC/MBC}_{Planktonic}

- Cidal antibiotics with activity on surface adherent, slow-growing microorganisms

- Selection of resistant sub-populations?

- Transfer of resistance genes?
Antibiotics with activity on adherent microorganisms (ODRI)

• Ciprofloxacin, Ofloxacin (Levofloxacin, Moxifloxacin ?) + Rifampicin

• Fusidic acid, Cotrimoxazole, Minocyclin + Rifampicin

• Linezolide + Rifampicin ?
Vascular catheter-associated Infections

USA
- 5.3 CVC-associated bloodstream infections /1000 catheter days / ICU

D:
- 1.8 CVC-associated blood stream infections/1000 catheter days / ICU (KISS)

Overall:
- > 50% of ICU-patients are in need of a CVC
- infected CVC’s are responsible for 90% of primary bloodstream infections

Vascular catheter-associated Infections

USA:
- 50,000 infections/year/ICU
- 250,000 CVC associated bloodstream infections/year
- Mortality 14 - 40 %
- 7 days increased length of stay (LOS)
- 33,000 $ extra costs/infection
Diagnosis of catheter infections

• Clinical symptoms
  - redness, swelling, hyperthermia, purulent secretion from exit site, fever of unknown origin

• Positive culture of catheter tip with $> 15 \text{ cfu/segment}$ (MAKI)

• Positive blood culture from catheter und peripheral vein with identical isolates (quantitatively, time-consuming method)

• Differential time to positivity - Methode
Therapy of catheter infections

- Type of catheter? (peripheral, central, tunneled, totally implanted)
- Microorganisms? (CNS, S.aureus, Gramnegatives, Candida)
- Validity of diagnosis?
- Underlying disease, indication?
- Immunsuppressed patient?
- Implant patient?
- Vascular situation?
- Severity of infection, complicated course?
Therapy of catheter infections

• S. aureus, Gramnegatives, Candida
  – Catheter removal + antimicrobial therapy

• CNS, enterococci; long term-catheter
  – Timely limited administration of antibiotics,
    „Antibiotic lock“, „Flush-solutions“
Prevention (general)

• Strict aseptic measures during insertion of catheters and implantation procedures!
• Perioperative antimicrobial prophylaxis in implantation surgery (not: CVC)
• Antimicrobial prophylaxis during surgery in patients with permanent implants?
• Use of antimicrobial devices (eg antimicrobial catheters)?
Prevention of catheter-associated Infections

- Use of CVC only when indicated

- Strict aseptic procedure during insertion of CVC’s

- Adequate hygienic measures when handling with catheters /infusion systems/infusion solutions according to national/international guidelines

- Removal of catheters no longer needed
Actual Recommendations for the Prevention of Catheter Infections

- „Guidelines for preventing infections associated with the insertion and maintenance of central venous catheters“
  J Hosp Infect 47 Suppl (2001)

- „Guidelines for the Prevention of Intravascular Catheter-Related Infections“

- „Prävention Gefäßkatheter-assoziiierter Infektionen“
  Empfehlungen der RKI-Kommission
  Bundesgesundheitsbl 45 (2002)
RKI-Guideline

1. Peripheral catheters
2. CVC’s
3. Arterial a. PA catheters
4. Hemodialysis catheters
5. Umbilical vein catheters
6. Partially implanted catheters
7. Totally implanted catheters
8. Infusion therapy

Recommendations
- Personnel
- Catheter material
- Insertion site
- Catheterization
- Dressing
- Catheter exchange

Categories:
- IA, IB, II, III, IV
• Good recommendations for the prevention of CVC related infections do exist

...but are they implemented in real practice?
Reducing Central Line Associated Bacteremias: An Eight Year Performance Improvement Initiative in the Surgical ICU
L.L. Fauerbach*, M.A. Gross, C.W. Ruse, R. E. Kelly and L. K. Archibald
Shands Hospital at the University of Florida. Gainesville, FL.

RESULTS

SICU CVL Associated Bacteremia Rate*
1997-2005 (1st qtr)

Constant improvement in patient outcome has been noted over the past 8 years. The CVL associated BSI/1000CVL days was 15.5 in 1997 and decreased with the introduction of the multiple new strategies to 4.16 in 2004 even with the utilization rate for CVLs nearly doubling.

*C = CVL rate/1000 catheter days.
Sustained reduction of Central-Line Associated Bloodstream Infections in a large Healthcare System
C. Muto et al., SHEA Meeting 2006, Chicago, 18.-21. März

• 33 participating hospitals (60 –1100 beds) in Pennsylvania
• Interventions
  – Standard protocol
  – Continuing education
  – CHX-gluconate for antisepsis, routine use of antimicrobiellal catheters (short-term), „maximal barrier precautions“
• Campaign for the reduktion of CR-BSI
• Surveillance by a multi-disciplinary team

• Result:
  – > 70 % reduction of CR-BSI
An intervention to decrease catheter-related bloodstream infections in the ICU

P. Pronovost et al., NEJM 2006

• Catheter infection rates before and after intervention (Hand disinfection, maximum sterile barriers, skin-antisepsis with CHX-G, no CVC insertion via V. femoralis, prompt catheter removal) in 103 ICU’s in Michigan

• Decrease from 2,7 CR-BSI/1000 Catheter days to ~0 already 3 months after implementation of intervention measures

• No use of antimicrobial catheters!
Prevention of Biomaterial-associated Infections by new technologies

- Antiadhesive materials
- Antimicrobial materials
- „Intelligent“ polymers
# Modification of biomedical materials using antibiotics

Table 1: Preventing catheter-related infection by bonding antibiotics to polymers.\(^2\)

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Antibiotic used</th>
<th>Method used to determine antimicrobial activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyurethane catheter</td>
<td>Clindamycin, Fusidic acid, Ciproglaxacin, Cefuroxime, Cefotaxime, Dicloxacillin</td>
<td>In vivo model</td>
</tr>
<tr>
<td>Polyurethane catheter</td>
<td>Clindamycin, Flucloxacillin, Vancomycin, Ciprofloxacin</td>
<td>In vitro model</td>
</tr>
<tr>
<td>Polyurethane catheter</td>
<td>Teicoplanin</td>
<td>In vitro and in vivo models</td>
</tr>
<tr>
<td>Silicone catheter</td>
<td>Vancomycin, Teicoplanin</td>
<td>In vitro model</td>
</tr>
</tbody>
</table>

\(^2\) aus: Duran LW, Med Dev Technol 2000
Modification of materials with antimicrobials other than antibiotics

<table>
<thead>
<tr>
<th>Device</th>
<th>Modification</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyurethane, silicone</td>
<td>Silver</td>
<td>Boswald et al (76)</td>
</tr>
<tr>
<td>Central venous catheter (Hydrocath®)</td>
<td>Silver</td>
<td>Gatter et al (77)</td>
</tr>
<tr>
<td>Polyurethane</td>
<td>Parabens</td>
<td>Golomb and Shpigelman (78)</td>
</tr>
<tr>
<td>Modified polyurethane</td>
<td>Silver</td>
<td>Jansen and Kohnen (28)</td>
</tr>
<tr>
<td>Central venous catheter (Hydrocath®)</td>
<td>Iodine</td>
<td>Jansen et al (79)</td>
</tr>
<tr>
<td>Silicone urinary catheter</td>
<td>Silver oxide</td>
<td>Johnson et al (80)</td>
</tr>
<tr>
<td>Ethylvinyl acetate, polyethylene, polypropylene, poly (4-methyl-1-pentene)</td>
<td>IRGASAN®</td>
<td>Kingston et al (81)</td>
</tr>
<tr>
<td>Modified poly (vinyl fluoride)</td>
<td>Iodine</td>
<td>Kristinsson et al (82)</td>
</tr>
<tr>
<td>Latex urinary catheter</td>
<td>Silver</td>
<td>Liedberg et al (83)</td>
</tr>
<tr>
<td>Collagen cuff</td>
<td>Silver</td>
<td>Maki et al (84)</td>
</tr>
<tr>
<td>Polyurethane catheter</td>
<td>Chlorhexidine and silver sulfadiazine</td>
<td>Maki et al (51)</td>
</tr>
<tr>
<td>Silicone, poly (vinyl/chloride), teflon, butyl rubber</td>
<td>Sputter coating</td>
<td>McLean et al (85)</td>
</tr>
<tr>
<td>Swan-Ganz pulmonary artery catheter</td>
<td>Benzalkonium chloride, oligodynamic iontophoresis-enhanced material</td>
<td>Merrel et al (86), Milder (87)</td>
</tr>
<tr>
<td>Silicone catheter</td>
<td>Electrically generated silver</td>
<td>Raad et al (88)</td>
</tr>
<tr>
<td>Silicone catheter</td>
<td>Ion implantation</td>
<td>Sioshanai (89)</td>
</tr>
<tr>
<td>Megaendoprosthesis</td>
<td>Silver</td>
<td>Gosheger et al (90)</td>
</tr>
</tbody>
</table>
Commercially available antimicrobial catheters

- Chlorhexidine-Silbersulfadiazine (Arrowgard Plus®)
- Minocyclin-Rifampicin (Cook Spectrum®)
- Benzalkoniumchloride-Catheter (Hydrocath Assure®)
- Silver-Zeolithe Catheter (Expert®)
- Bi-Catheter (Dolphin protect®)
Desirable properties of antimicrobial catheters

- Longlasting antimicrobial activity
- No inactivation of antimicrobial by host factors
- Coating internally and externally
- Use of antimicrobial substances not primarily used in therapy of infectious diseases
- No or low toxicity and allergy potential
- No negative effects of the antimicrobial compound on physico-chemical properties of basic polymer
Clinical studies

- Maki et al., Ann Int Med 127, 1997:
  
  **Arrowgard**
  158 Patienten, 403 Katheter
  Kolonisation: 13.5 vs. 24.1/100 Katheter
  BSI: 1.6 vs. 7.6 /1000 Kathetertage (p=0.03)

- Darouiche et al.: NEJM 140, 1999
  
  **Cook vs. Arrowgard**
  738 Katheter in 12 centers investigated
  Kolonisation: 7.9% (Cook) vs. 22.8% (Arrow)
  BSI: 0.3% vs. 3.4% (p<0.002)
Comparison: Arrowgard plus vs. Cook-Katheter

**In vitro:**
15-fold increase in MIC for Minocyclin und Rifampicin (S. epidermidis) and 4-fold increase in E. coli
Guideline-Recommendations

• HICPAC- Guidelines
  - „The decision to use Chlorhexidine/Silversulfadiazine or Minocyclin/Rifampicin catheters should be based on the need to enhance prevention of CR-BSI balanced against the concern for emergence of resistant pathogens and the cost of implementing this strategy“

• RKI-Empfehlung
  – No current recommendation for the use of antimicrobial catheters (Category III)
Open questions concerning the use of antimicrobial catheters

- Resistance ? (Minocyclin/Rifampicin catheter)
- Allergy ? (CHX/SS catheter)
- Cost effectiveness ?
- Impact on mortality ??
"Intelligent" Polymers

Antibiotic

Microorganism

Chemical Bonding to active agent

Polymer
„Delivery-on-demand“: PET- Fe- Ciprofloxacin

M. Streck: MD thesis 2007

Synthesis of system

Adherence of *Pseudomonas aeruginosa*
“Bacteria stick, tenaciously and often with exquisite specificity, to surfaces ranging from the human tooth or lung and the intestine of a cow to a rock submerged in a fast-moving stream...“

Bill Costerton 1978

Vielen Dank für Ihre Aufmerksamkeit

from: Schaudinn C et al., Microbe 2007; Vol.2(5)
General principles
Prevention of microbial adherence to surfaces by **material modification**

**Antiadhesive materials**  **Antimicrobial materials**

from: Tiller J, Nachr Chem 2007;55
Antiadhesive materials

Self-polishing surfaces („Antifouling“)

Superhydrophilic surfaces

from: Tiller J, Nachr Chem 2007;55
Hydrocath-Katheter:
PUR + Poly-N-Vinylpyrrolidon

in vitro-Adherence of
*S. epidermidis* to various polymers
„Minimum adherence“ - Hypothesis

Thermodynamische Typple
Der Bakterielle Adhäsion

\[ \Delta F_{adh} = \gamma_{SB} - \gamma_{SL} \]

\[ \text{Freie Adhäsionsenthalpie} \quad \text{(mJ/m}^2\text{)} \]
Rifampicin-coated ventricular shunts

Ventricular shunt-Infections: 2-31%

In vitro-Adherence

In vivo-Model

S. aureus $10^5$; S. epidermidis $10^6$

<table>
<thead>
<tr>
<th></th>
<th>Katheter-segment</th>
<th>Hirngewebe</th>
<th>Liquor</th>
<th>Blut</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silikon</td>
<td>12</td>
<td>14</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Silikon-Rifampicin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Ventricular catheter with a combination of Rifampicin + Trimethoprim

Patientin Isabell H. *30.05.1987:

11.03.96 Revision wegen Fehlfunktion des Ventils
16.03.96 Externe Drainage wegen Infektion
04.04.96 Wechsel der Drainage wegen Infektion
15.04.96 Ventrikel-Shunt
20.04.96 Revision wegen Katheterverschluss
13.06.96 Revision wegen Katheterverschluss
17.06.96 Appendicitis, externe Drainage
05.08.96 Antibiotika-beladener Shunt
CODMAN®
BACTISEAL®
Antimicrobial Impregnated Catheter System

0.15% Clindamycin
0.054% Rifampicin
A Novel Microbial Infection-Responsive Drug Release System

Synthese des PVA-Gentamicin-Systems

Gentamicin-Freisetzung vs. Thrombin Konz.

Gentamicin-Freisetzung bei *S.aureus*
Immobilisierung von antimikrobiellen Substanzen an Oberflächen

- Zytoplasma
- Gram-positive Bakterienzelle
  *z.B. Staphylococcus aureus*

- Phospholipidmembran
- Peptidoglycanzellwand

- Materialoberfläche

- Biozid
  - nicht wirksam
  - wirksam
Designing surfaces that kill bacteria on contact
Joerg C. Tiller, Chun-Jen Liao, Kim Lewis, and Alexander M. Klibanov

Poly (4-vinylpyridin) alkyliert
Wachstum von *S.aureus* auf Glas (li) und Hexyl-PVP (re)
Kontaktaktive antimikrobielle Beschichtungen aus wässrigen Suspensionen
Fuchs AD, Tiller JC: Angew Chem 2006, 118, 6911-14
Polymere Systeme mit Freisetzungs von NO


Synthese von Diazeniumdiolat-NO-Donoren und NO-Freisetzungs

Adhäsion von *P. aeruginosa* auf beschichteten PVC-Oberflächen in Abhängigkeit von der NO-Konzentration

Fig. 7 The influence of NO flux on *P. aeruginosa* adhesion to PVC-coated surfaces. Reprinted with permission from Nablo et al. **Biomacromolecules**, 2004, 5, 2034. Copyright (2004) American Chemical Society.
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