Efficacy of Antibiotic or Antiseptic Impregnated Medical Devices in Preventing Nosocomial Infections

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Goals of Lecture

• Provide brief overview of device facilitated healthcare-associated infections
• Discuss the pathogenesis of catheter related infections and the importance of biofilms
• Discuss the published data on efficacy of antiseptic or antibiotic impregnated medical devices
  – Efficacy of impregnated catheters in preventing infection (focus on central venous catheters, indwelling urinary tract catheters, endotracheal tubes)
  – Adverse events associated with impregnated catheters
DEVICE FACILITATED INFECTIONS

HAZARDS IN THE ICU

PREVALENCE: ICU (EUROPE)

- Study design: Point prevalence rate
  - 17 countries, 1447 ICUs, 10,038 patients
- Frequency of infections: 4,501 (44.8%)
  - Community-acquired: 1,876 (13.7%)
  - Hospital-acquired: 975 (9.7%)
  - ICU-acquired: 2,064 (20.6%)
    - Pneumonia: 967 (46.9%)
    - Other lower respiratory tract: 368 (17.8%)
    - Urinary tract: 363 (17.6%)
    - Bloodstream: 247 (12.0%)


RISK FACTORS FOR ICU-ACQUIRED INFECTIONS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA Catheterization</td>
<td>1.01-1.43</td>
</tr>
<tr>
<td>CVP Line</td>
<td>1.16-1.57</td>
</tr>
<tr>
<td>Stress Ulcer Prophylaxis</td>
<td>1.20-1.60</td>
</tr>
<tr>
<td>Urinary Catherization</td>
<td>1.19-1.69</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>1.51-2.03</td>
</tr>
<tr>
<td>Trauma on Admission</td>
<td>1.75-2.44</td>
</tr>
</tbody>
</table>
IMPACT OF CATHETER-RELATED INFECTIONS

• Central venous catheters
  – 15 million CVC days per year in ICU
  – ~80,000 CVC-associated bloodstream infections per year in ICU (~250,000 hospital wide)
• Urinary catheters
  – 4 million patients receive urinary catheterization per year
  – Catheterization ≥7 days = daily risk of bacteriuria 5%
• Endotracheal tubes
  – 10-40% of intubated patients develop pneumonia
  – Mortality of VAP ~30-40%

EVALUATION OF ANTISEPTIC IMPREGNATED DEVICES
PREVENTION OF CATHETER FACILITATED INFECTIONS

• Avoid insertion of catheter (if possible)
• Remove catheter as soon as feasible
• Aseptic insertion of catheter
  – Use sterile device
  – Maximum barrier precautions
  – Appropriate skin antisepsis
• Improved engineering to prevention catheter colonization
  – Inhibit microbial binding
  – Kill microbes: Impregnate catheter with antiseptic(s) or antibiotic(s)
• Use closed system (if system entered, use aseptic technique)
• If fluids instilled via catheter, use sterile fluids
• Do not routinely replace catheter

RATIONALE FOR DEVELOPING IMPREGNANTED INDWELLING MEDICAL DEVICES

• Indwelling medical devices (e.g., central venous catheters, foley catheters, endotracheal tubes) are one of the most important risk factors for development of a healthcare-associated infection
• Pathophysiology = colonization of the device by bacteria ⇒ development of biofilm ⇒ migration of bacteria via intraluminal or extraluminal surface into “sterile” tissue ⇒ infection
• Impregnation of catheter surface with antiseptic or antibiotic may decrease bacterial colonization and rate of nosocomial infections
PATHOGENESIS OF CR-BSIs


PATHOGENESIS OF CR-BSI, NONCUFFED SHORT-TERM CENTRAL VENOUS CATHETERS

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Extraluminal</th>
<th>Intraluminal</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase neg staph</td>
<td>12 (40%)</td>
<td>8 (30%)</td>
<td>7 (26%)</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>3 (75%)</td>
<td>1 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>E. cloacae</td>
<td>1 (33%)</td>
<td>0</td>
<td>2 (67%)</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>0</td>
<td>0</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>B. cepacia</td>
<td>1 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>0</td>
<td>0</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>16 (45%)</td>
<td>9 (26%)</td>
<td>10 (29%)</td>
</tr>
</tbody>
</table>

Safdar N, Maki DG. Intensive Care Med 2004;30:62-68
BIOFILMS

• Definition*: A microbial derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, are embedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription
• Rapidly develop on percutaneous catheters; function of:
  – Duration of catheterization
  – Location of catheter
  – Catheter material


BIOFILMS

• Enhanced microbial survival (impairs host defenses)
• Impairs antimicrobial activity
• Common microbes
  – *Staphylococcus aureus*, coagulase negative staphylococci, *Enterococcus* spp., *Streptococcus viridans*
  – *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*
  – *Candida albicans*
FORMATION OF BIOFILMS

- Deposition of a conditioning film produced by the host to the foreign body
- Attachment of microorganisms
- Microbial adhesion and anchorage to the surface by exopolymer production
- Growth, multiplication and dissemination of microbes


BIOFILM ON A CENTRAL VENOUS CATHETER
## ANTISEPTIC AND ANTIBIOTIC IMPREGNATED MEDICAL DEVICES

<table>
<thead>
<tr>
<th>Multiple studies evaluating efficacy</th>
<th>Limited studies evaluating efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Central venous catheters</td>
<td>• Endotracheal tubes (animal only)</td>
</tr>
<tr>
<td>• Urinary tract catheters</td>
<td>• Hemodialysis catheters</td>
</tr>
<tr>
<td></td>
<td>• Peritoneal dialysis catheters</td>
</tr>
<tr>
<td></td>
<td>• Central nervous system shunts</td>
</tr>
<tr>
<td></td>
<td>• Bone screws (external fixation)</td>
</tr>
<tr>
<td></td>
<td>• Sutures</td>
</tr>
<tr>
<td></td>
<td>• Bone cement (antibiotics only)</td>
</tr>
<tr>
<td></td>
<td>• Catheter cuffs</td>
</tr>
</tbody>
</table>

## FACTORS POTENTIALLY AFFECTING EFFICACY OF IMPREGNATED CATHETERS

- Antiseptic versus antibiotics
- Agent(s)
  - Spectrum of activity
  - Likelihood of resistance developing
- Coating
  - 1st generation = external surface only
  - 2nd generation = external and internal surfaces
- Duration of protection (related to concentration and leaching)
ANTIMICROBIALS USED TO IMPREGNATE CATHETERS

**Multiple clinical studies**
- Chlorhexidine/silver-sulfadiazine (CVC)
- Minocycline/rifampin (CVC, UC, HD, VD)
- Silver oxide (UC)
- Silver hydrogel (UC)

**Limited clinical studies**
- Silver (CVC, OS, PD)
- Silver/platinum/carbon (CVC)
- Benzalkonium chloride (CVC)
- Cefazolin (CVC)
- Cefoxitin (PD)
- Nitrofurazone (UC)
- Clindamycin/rifampin (VS)
- Miconazole/rifampin (CVC)
- Triclosan (S)

CVC, central venous catheter; HD, hemodialysis catheter; OS, orthopedic screws; PD, peritoneal dialysis catheter; S, sutures; UC, urinary catheter; VD, ventricular drain; VS, ventricular shunt

MECHANISMS OF ACTION OF ANTIMICROBIALS COMMONLY USED TO IMPREGNATE CATHETERS

- **Chlorhexidine**
  - Bactericidal; precipitates cytoplasmic contents of the cell
- **Silver-sulfadiazine**
  - Bactericidal; disrupts cell wall
- **Minocycline**
  - Bacteriostatic; blocks the binding aminoacyl-tRNA mRNA-ribosome complex
- **Rifampin**
  - Bacteriostatic; inhibits DNA-dependent, RNA-polymerase
### EFFICACY OF CVCs IMPREGNATED WITH CHLORHEXIDINE/SILVER SULFADIAZINE

<table>
<thead>
<tr>
<th>Author (coating)</th>
<th>CC*</th>
<th>CR-BSI*</th>
<th>CC®</th>
<th>CR-BSI®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osma 06 (E)</td>
<td>0.016 (NS)</td>
<td>0.049 (NS)</td>
<td>3.9 (NS)</td>
<td>3.7 (NS)</td>
</tr>
<tr>
<td>Jaeger 05 (E)</td>
<td>0.066</td>
<td>0.13 (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rupp 05 (E/I)</td>
<td></td>
<td></td>
<td>10.8</td>
<td>0.82 (NS)</td>
</tr>
<tr>
<td>Ostendorf 05 (E/I)</td>
<td>0.23</td>
<td>0.041 (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dunser 05 (E)</td>
<td>0.046 (NS)</td>
<td></td>
<td>3.6 (NS)</td>
<td></td>
</tr>
<tr>
<td>Brun-Buisson 04 (E/I)</td>
<td>0.094</td>
<td>0.02 (NS)</td>
<td>7.4</td>
<td>3.2 (NS)</td>
</tr>
<tr>
<td>Sheng 00 (E)</td>
<td>0.12 (NS)</td>
<td>0.040 (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hannan 99 (E)</td>
<td>0.13</td>
<td>0.030 (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heard 98 (E)</td>
<td>0.12</td>
<td>0.005 (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maki 97 (E)</td>
<td>0.11</td>
<td>0.037</td>
<td></td>
<td>6.0</td>
</tr>
</tbody>
</table>

Per 100 catheters, ® per 1000 line days; CC, catheter colonization; CR-BSI, catheter-related bloodstream infections; E, external coating; I, internal coating; NS, not significant

### EFFICACY OF CVCs IMPREGNATED WITH MINOCYCLINE/RIFAMPIN

<table>
<thead>
<tr>
<th>Author (coating)</th>
<th>CC*</th>
<th>CR-BSI*</th>
<th>CC®</th>
<th>CR-BSI®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raad 97 (E/I)</td>
<td>0.18</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leon 04 (E/I)</td>
<td></td>
<td></td>
<td>13.6</td>
<td>2.8 (NS)</td>
</tr>
<tr>
<td>Hanna 04 (E/I)</td>
<td>0.064</td>
<td></td>
<td></td>
<td>1.03</td>
</tr>
<tr>
<td>Darouiche 05 (E/I)</td>
<td>0.034 (NS)</td>
<td>0.052</td>
<td>1.6 (NS)</td>
<td>1.07 (NS)</td>
</tr>
</tbody>
</table>

Per 100 catheters, ® per 1000 line days; CC, catheter colonization; CR-BSI, catheter-related bloodstream infections; E, external coating; I, internal coating; NS, not significant
CVCs:
CONCLUSION AND LIMITATIONS

• Evidence demonstrates reduction of catheter colonization and suggests reduction in CR-BSIs
• No clear benefit to antiseptic vs antibiotic impregnated catheters
• Anaphylaxis to chlorhexidine impregnated catheters rarely reported
• No evidence that clinical use leads to development of bacterial resistance

EFFICACY OF SILVER HYDROGEL IMPREGNATED URINARY CATHETERS

<table>
<thead>
<tr>
<th>Author</th>
<th>Outcome</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lundeberg, 1986</td>
<td>&gt;100 CFU/mL d3</td>
<td>12% vs 34% (p&lt;0.001)</td>
</tr>
<tr>
<td>Liedberg, 1990</td>
<td>&gt;100,000 CFU/mL d6</td>
<td>10% vs 37% (p&lt;0.01)</td>
</tr>
<tr>
<td>Liedberg, 1990</td>
<td>&gt;100,000 CFU/mL d5 (vs hydrogel)</td>
<td>10% vs 33% (NS)</td>
</tr>
<tr>
<td></td>
<td>&gt;100,000 CFU/mL d5 (vs standard)</td>
<td>10% vs 50% (p&lt;0.002)</td>
</tr>
<tr>
<td>Liedberg, 1993</td>
<td>&gt;100,000 CFU/mL d7</td>
<td>10.8% vs 24.0% (p=0.03)</td>
</tr>
<tr>
<td></td>
<td>&gt;100,000 CFU/mL d14</td>
<td>34.3% vs 58.7% (p&lt;0.01)</td>
</tr>
<tr>
<td>Maki, 1998</td>
<td>Not stated</td>
<td>15.7% vs 21.2% (p=0.03)</td>
</tr>
<tr>
<td>Verleyen, 1999</td>
<td>&gt;100,000 CFU/mL d14</td>
<td>50% vs 53.3% (NS)</td>
</tr>
<tr>
<td></td>
<td>&gt;100,000 CFU/mL d5</td>
<td>6.3% vs 11.9% (NS)</td>
</tr>
<tr>
<td>Karchmer, 2000</td>
<td>CDC definition UC-UTI</td>
<td>2.1% vs 3.1% (p=0.001)</td>
</tr>
<tr>
<td>Thibon, 2000</td>
<td>&gt;100,000 CFU/mL &amp; &gt;10 WBC/mL</td>
<td>10% vs 11.9% (NS)</td>
</tr>
<tr>
<td>Srinivasan, 2006</td>
<td>CDC definition UC-UTI</td>
<td>14.3 vs 16.2 (NS)*</td>
</tr>
</tbody>
</table>

* per 1000 catheter days
EFFICACY OF IMPREGNATED URINARY CATHETERS FOR BACTERIURIA

<table>
<thead>
<tr>
<th>Agent</th>
<th>Risk Reduction</th>
<th>Efficacy Demonstrated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver oxide</td>
<td>0.10-0.12</td>
<td>1/4</td>
</tr>
<tr>
<td>Silver hydrogel</td>
<td>0.12-0.76</td>
<td>7/11</td>
</tr>
<tr>
<td>Nitrofurazone</td>
<td>0.32-0.92</td>
<td>2/3</td>
</tr>
<tr>
<td>Minocycline/rifampin</td>
<td>0.24</td>
<td>1/1</td>
</tr>
</tbody>
</table>

URINARY CATHETERS: CONCLUSION AND LIMITATIONS

• Impregnated catheters associated with reduced risk of asymptomatic bacteriuria
  – No demonstration of reduction in incidence of symptomatic UTIs, secondary bloodstream infections, length of stay, or mortality
• Limitations of studies
  – Quasi-randomized design often used
  – Lack of masking
  – Outcome generally bacteriuria
  – No assessment for development of resistant microbes
IMPREGNATED ENDOTRACHEAL TUBES: ANIMAL STUDIES

• Randomized study of 8 dogs challenged with *P. aeruginosa*
  – Agent = Silver coated
  – Control = Standard
  – Results = Decreased colonization ET tube & lung parenchyma
• Randomized trial of 16 intubated sheep**
  – Agent = Silver-sulfadiazine and chlorhexidine
  – Control = Standard
  – Results = Decreased colonization ET tube & lung parenchyma


ENDOTRACHEAL TUBES: CONCLUSION AND LIMITATIONS

• No human studies available
• Small animal studies suggest possible benefit
POTENTIAL ADVERSE EVENTS ASSOCIATED WITH IMPREGNATED CATHETERS

• Allergic reaction
  – Anaphylaxis to chlorhexidine impregnated central venous catheters rarely reported (also to topical chlorhexidine)

• Systemic toxicity
  – Increases in serum silver levels described (silver coated orthopedic screws)

• Inducement of resistance
  – Not reported (but limited studies)

CONCLUSIONS

• Multiple studies have evaluated the efficacy of impregnated catheters for the prevention of CR-BSIs
  – 2nd generation catheters superior to 1st generation catheters
  – Adverse events rare
  – Induction of resistance not reported
  – Impregnated CVCs have reduced rates of colonization and likely lead to a reduction in CR-BSIs

• Consider use of impregnated central venous catheters as part of a multi-faceted approach to reducing CR-BSI
CONCLUSIONS

• Multiple studies have evaluated the efficacy of impregnated urinary catheters for the reduction of bacteriuria
  – No demonstrated reduction of symptomatic UTIs, secondary bacteremia, or mortality
  – Not recommended for use
• No recommendation for use of other impregnated devices (or devices impregnated with other antimicrobials)
  – Endotracheal tubes, hemodialysis catheters, peritoneal dialysis catheter, catheter cuffs, ventricular catheters/shunts, orthopedic screws for external fixation