

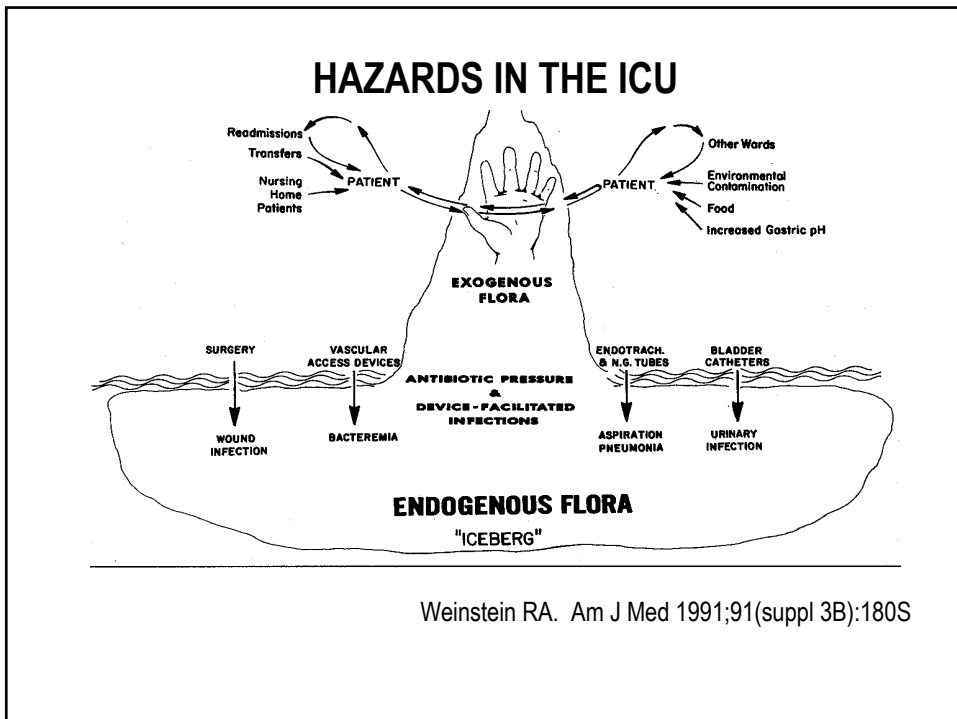
# EFFICACY OF ANTIBIOTIC OR ANTISEPTIC IMPREGNATED MEDICAL DEVICES IN PREVENTING NOSOCOMIAL INFECTIONS

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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

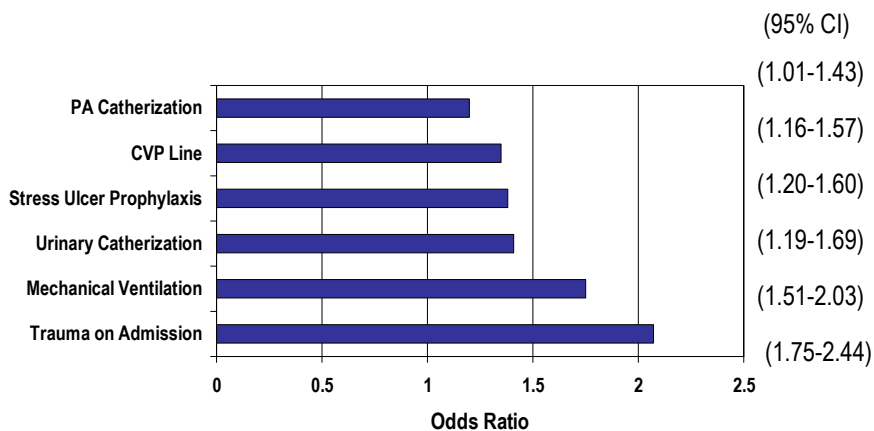


## PREVALENCE: ICU (EUROPE)

- 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%)

Vincent J-L, et al. JAMA 1995;274:639

## RISK FACTORS FOR ICU-ACQUIRED INFECTIONS



## 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  $\geq 7$  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

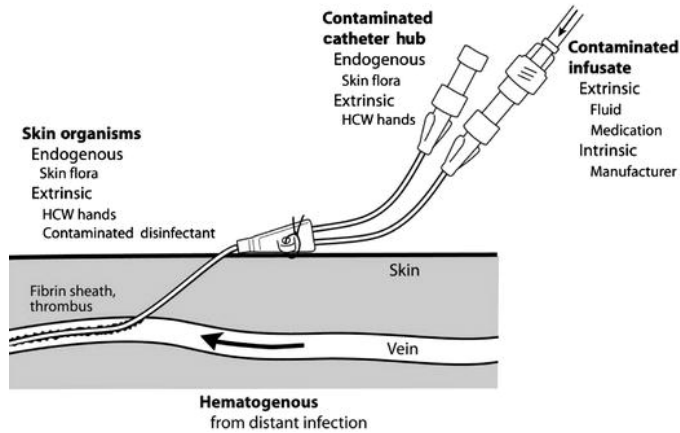
## PREVENTION OF CATHETER FACILITATED INFECTIONS

- 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 IMPREGNATED 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  $\Rightarrow$  development of biofilm  $\Rightarrow$  migration of bacteria via intraluminal or extraluminal surface into “sterile” tissue  $\Rightarrow$  infection
- Impregnation of catheter surface with antiseptic or antibiotic may decrease bacterial colonization and rate of nosocomial infections

# PATHOGENESIS OF CR-BSIs



Safdar N, Maki DG. Intensive Care Med 2004;30:62-67

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

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

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

Donlan RM, Costerton JW. Clin Microbiol Rev 2002;15:167-193

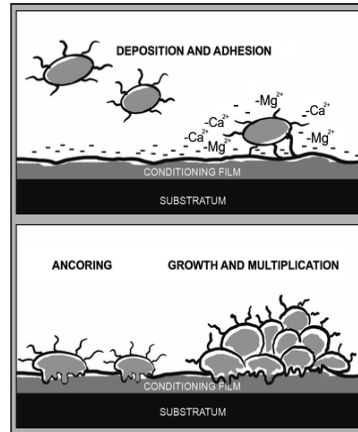
# BIOFILMS

- 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*

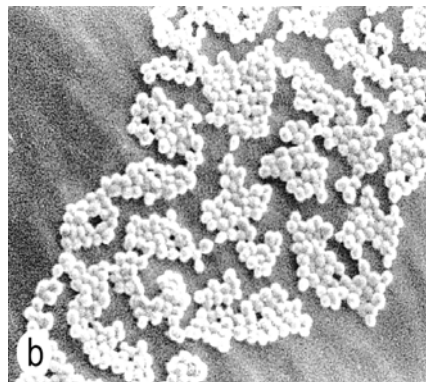
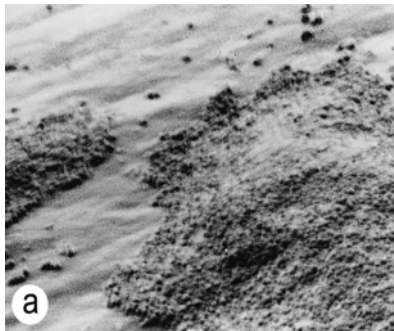
# FORMATION OF BIOFILMS

- 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

Tenke P, et al. World J Urol 2006;24:13-20



## BIOFILM ON A CENTRAL VENOUS CATHETER





## ANTISEPTIC AND ANTIBIOTIC IMPREGNATED MEDICAL DEVICES

Multiple studies  
evaluating efficacy

- Central venous catheters
- Urinary tract catheters

Limited studies evaluating  
efficacy

- Endotracheal tubes (animal only)
- Hemodialysis catheters
- Peritoneal dialysis catheters
- Central nervous system shunts
- Bone screws (external fixation)
- Sutures
- Bone cement (antibiotics only)
- Catheter cuffs

## FACTORS POTENTIALLY AFFECTING EFFICACY OF IMPREGNATED CATHETERS

- Antiseptic versus antibiotics
- Agent(s)
  - Spectrum of activity
  - Likelihood of resistance developing
- Coating
  - 1<sup>st</sup> generation = external surface only
  - 2<sup>nd</sup> 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
  - Bacteristatic; blocks the binding aminoacyl-tRNA mRNA-ribosome complex
- Rifampin
  - Bacteriostatic; inhibits DNA-dependent, RNA-polymerase

## EFFICACY OF CVCs IMPREGNATED WITH CHLORHEXIDINE/SILVER SULFADIAZINE

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

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

Author (coating)	CC*	CR-BSI*	CC@	CR-BSI@
Raad 97 (E/I)	0.18	0.05		
Leon 04 (E/I)			13.6	2.8 (NS)
Hanna 04 (E/I)		0.064		1.03
Darouiche 05 (E/I)	0.034 (NS)	0.052	1.6 (NS)	1.07 (NS)

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

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

\* per 1000 catheter days

## EFFICACY OF IMPREGNATED URINARY CATHETERS FOR BACTERIURIA

Agent	Risk Reduction	Efficacy Demonstrated
Silver oxide	0.10-0.12	1/4
Silver hydrogel	0.12-0.76	7/11
Nitrofurazone	0.32-0.92	2/3
Minocycline/rifampin	0.24	1/1

## 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

\* Olson ME, et al. Chest 2002;121:863-70; \*\* Berra L, et al. Anesthesiol 2004;100:1446-56

## 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
  - 2<sup>nd</sup> generation catheters superior to 1<sup>st</sup> 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