



BIOMATECH
NAMSA
Testing
Laboratory

Prevention of bacterial adhesion to medical polymers

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Infection = a public enemy

- 80% of adults are extremely/very worried about bacteria
- 75% consider food contamination by bacteria a serious health risk
- 11 times more articles about bacteria than 10 years ago
- In the past 6 years, 673 different antibacterial products were introduced

*Data from US market

Nosocomial infections

Source : *HermMed*, January 1996 ; *Clinician Reviews* 7:55-58, 61-62, 1997 ; *Compliance Control Center*, June 1998

2.4 Million nosocomial infections occur each year in the U.S.

30 000 related deaths occur each year in the U.S

5-10 per 100 hospital admissions suffer nosocomial infection



\$ 5-10 Billion is the estimated annual direct cost of nosocomial infection

\$ 2,300 is the average cost of nosocomial infection per incident



Prevention of infection

Medical device and infection

- Biomaterials = **essential components of health care** systems
- 5 to 20% of CVC catheters are potentially infected → 0.1 to 1 per 100 catheter-days
- 20% of patients with Foley catheters (> 25 days) will develop urinary infections

 Use of medical devices =  Infectious complications

Microorganisms involved

Part of the environmental flora

– Bacteria

- Gram positive Cocci (10%)
 - **Coagulase Negative Staphylococci** (CNS) → catheter (venous, peritoneal dialysis), cardiac valves, cardiac electrodes
 - ***Staphylococcus aureus*** (SA) → hemodialysis shunt, vascular prostheses
 - **CNS and SA** → hip and knee prostheses
- Gram positive Bacilli (sporulating or not)
- Gram negative Bacilli (50%) : ***E. coli*, *Pseudomonas*** → early and late urinary tubes infections

– Moulds and yeasts (10%)

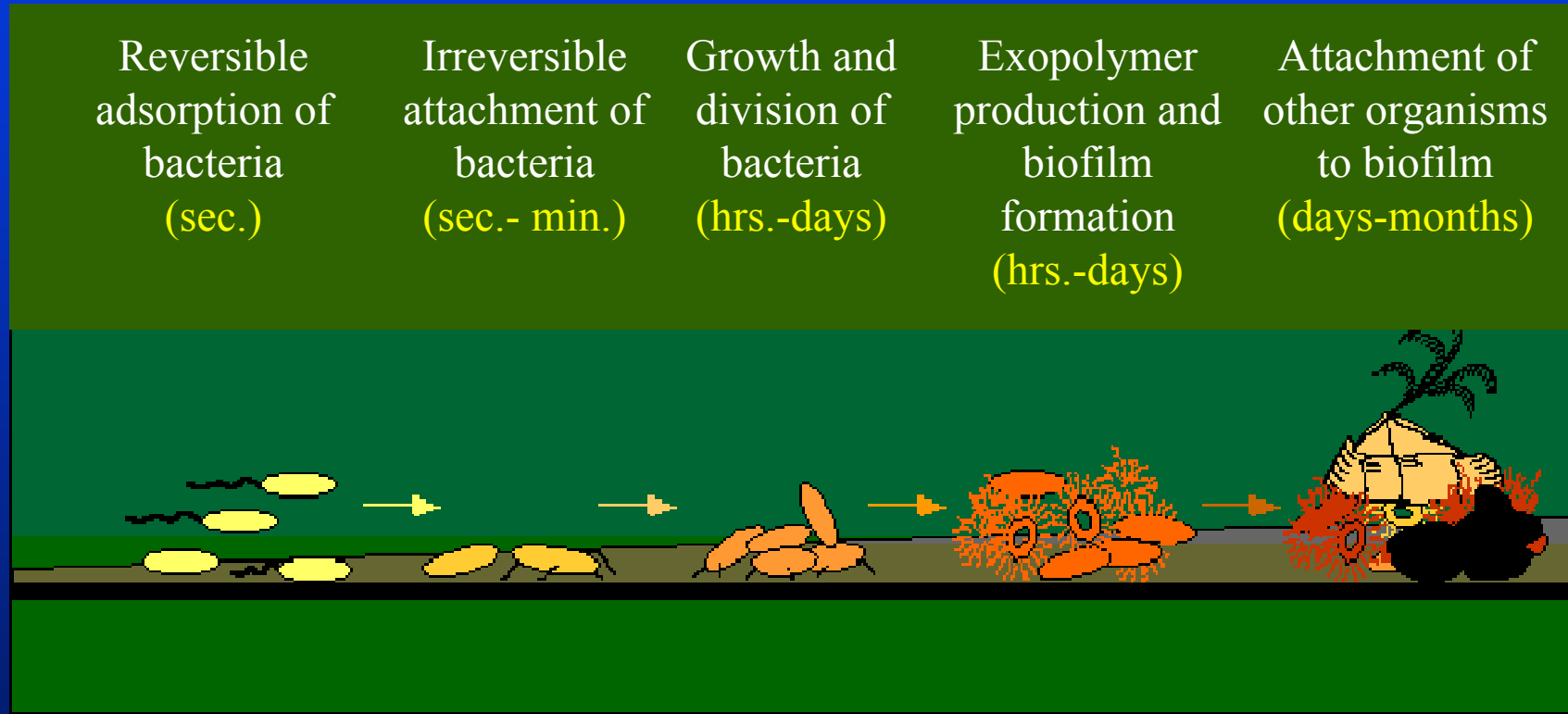
Bacterial infection of polymers

- Factors of adhesion
 - Bacterial factors :
Capacity of the microorganism to adhere to polymer surfaces
 - Polymer factors : type of polymer and surface
 - Adherence index = ➤ hydrophobic surface
 - Ex : PVC >>> teflon
 - Interfering factors from the host (blood, proteins...)
- Type of infection
 - Early infections : inoculation at the time of implantation
 - Long term infections :
 - inoculation during surgery
 - haematogenous spread from distant sites
 - without associated bacteriemia

Formation of a biofilm

Mark Wiencek

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Development of multicellular behaviour

The Biofilm : slime + bacteria

- Slime is produced by **some bacteria** : *S. epidermidis*, *S. aureus*, *P. aeruginosa*, *Legionella*
- Slime = **extracellular mucilaginous substance** : glyco-conjugate complex soluble in water = **glycocalix**
- Slime is responsible for
 - **Cohesion** between the germs
 - Creation of **cell layers**

Example of bacterial adhesion

Staphylococcus epidermidis

G. Pulverer et al.

15 min reversible non specific adhesion in irregular parts

Formation of microcolonies

12h

12-48h multiple layers of cells irreversible adhesion + secondary erosion areas?

96h multiple layers of cells embedded in mucilagenous substance

Single bacteria

Physicochemical forces

polymer

Growth and division

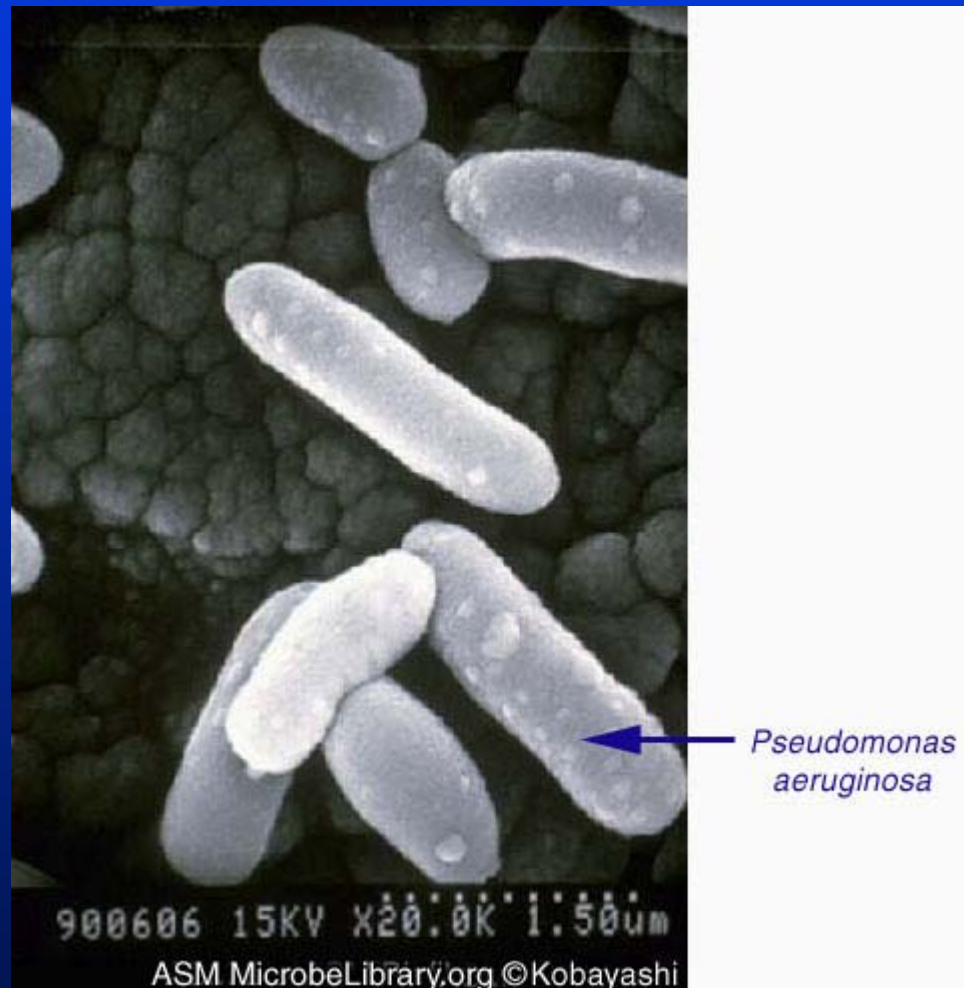
Production of SLIME

Exopolysaccharide matrix

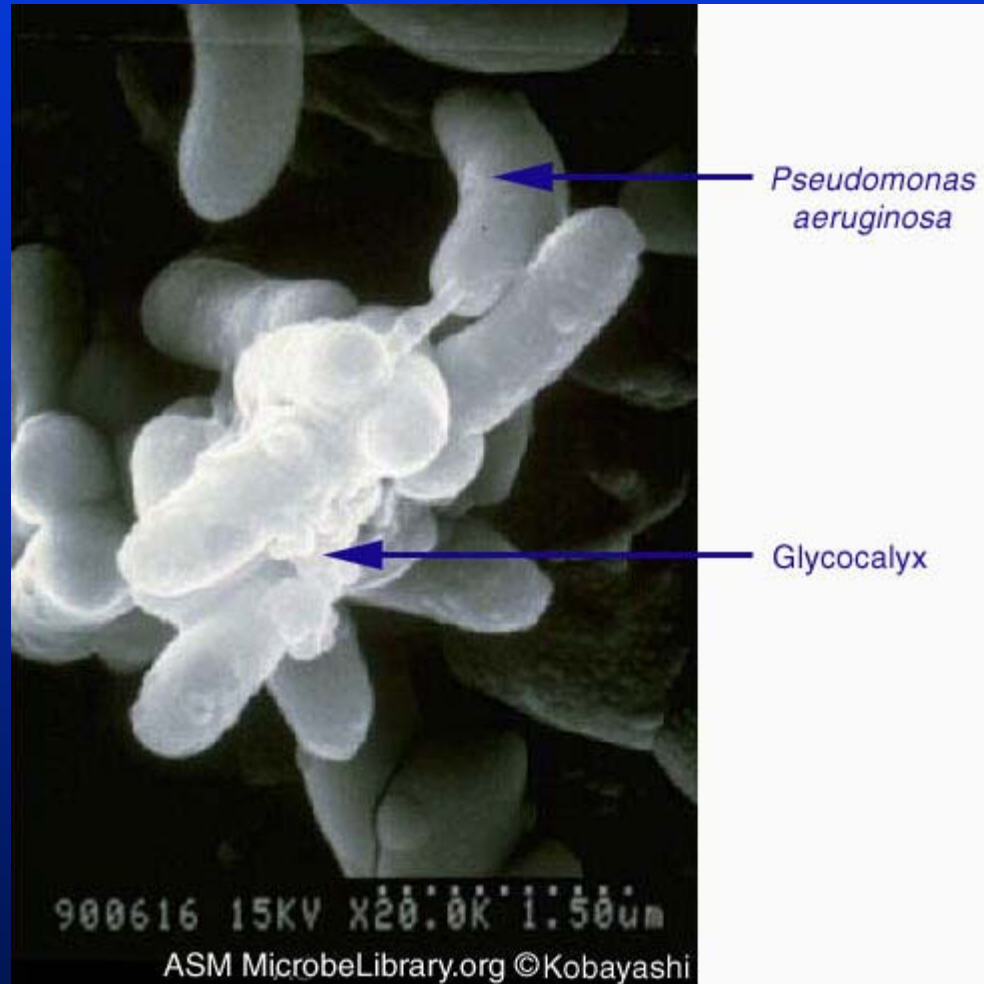
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Bacteria use N and C of the polymer?

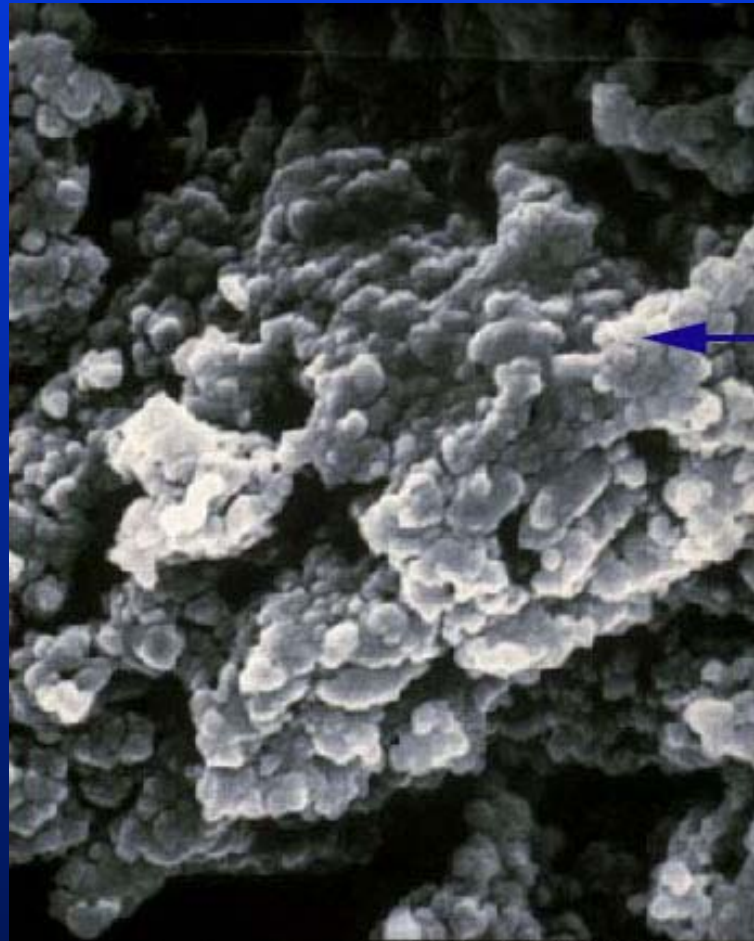
P. aeruginosa adsorption to the Teflon strip, one day after inoculation (1)



Three days after inoculation, reveals the beginnings of glycocalyx production (2)



Biofilm development six days after inoculation, with a well developed glycocalyx (3)



← Glycocalyx
obscuring
bacteria

900608 15KV X20.0K 1.50um

ASM MicrobeLibrary.org © Kobayashi

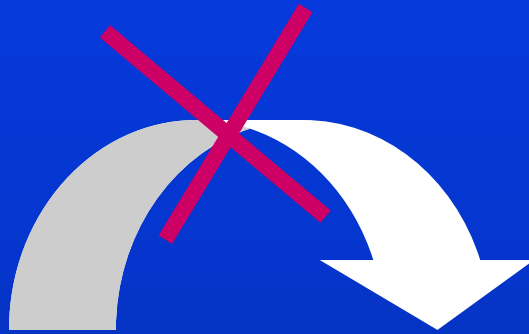
Resistance of bacteria in biofilms

- Formation of a « **bacterial abcess** »

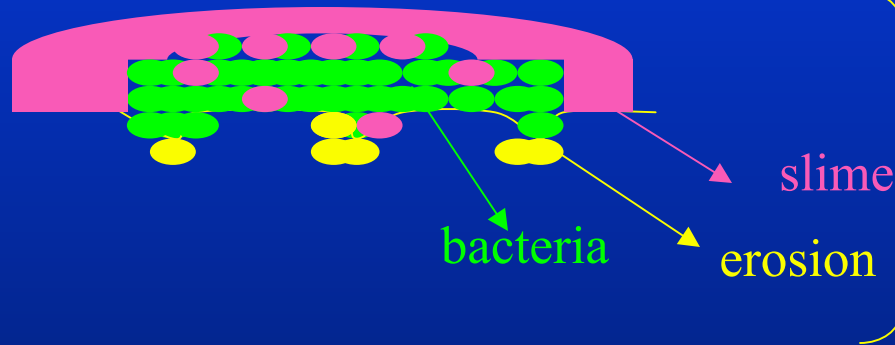
- Morphological changes : spore-like
- Reduced bacterial growth (↗ resistance to antibiotics)
- Genetic changes : under or over expression of some genes related to protein resistance to antibiotics
- Age of the biofilm : resistance increased with age and structuration of the biofilm

- Consequences

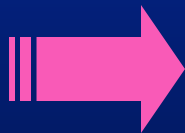
- Reduced sensitivities to antimicrobial agents
 - ➔ No activity of antibiotic on bacteria covered by 100 µm of slime
- Increased resistances to various stresses = protective environment



Antibiotics
Antimicrobials
Physiological defenses



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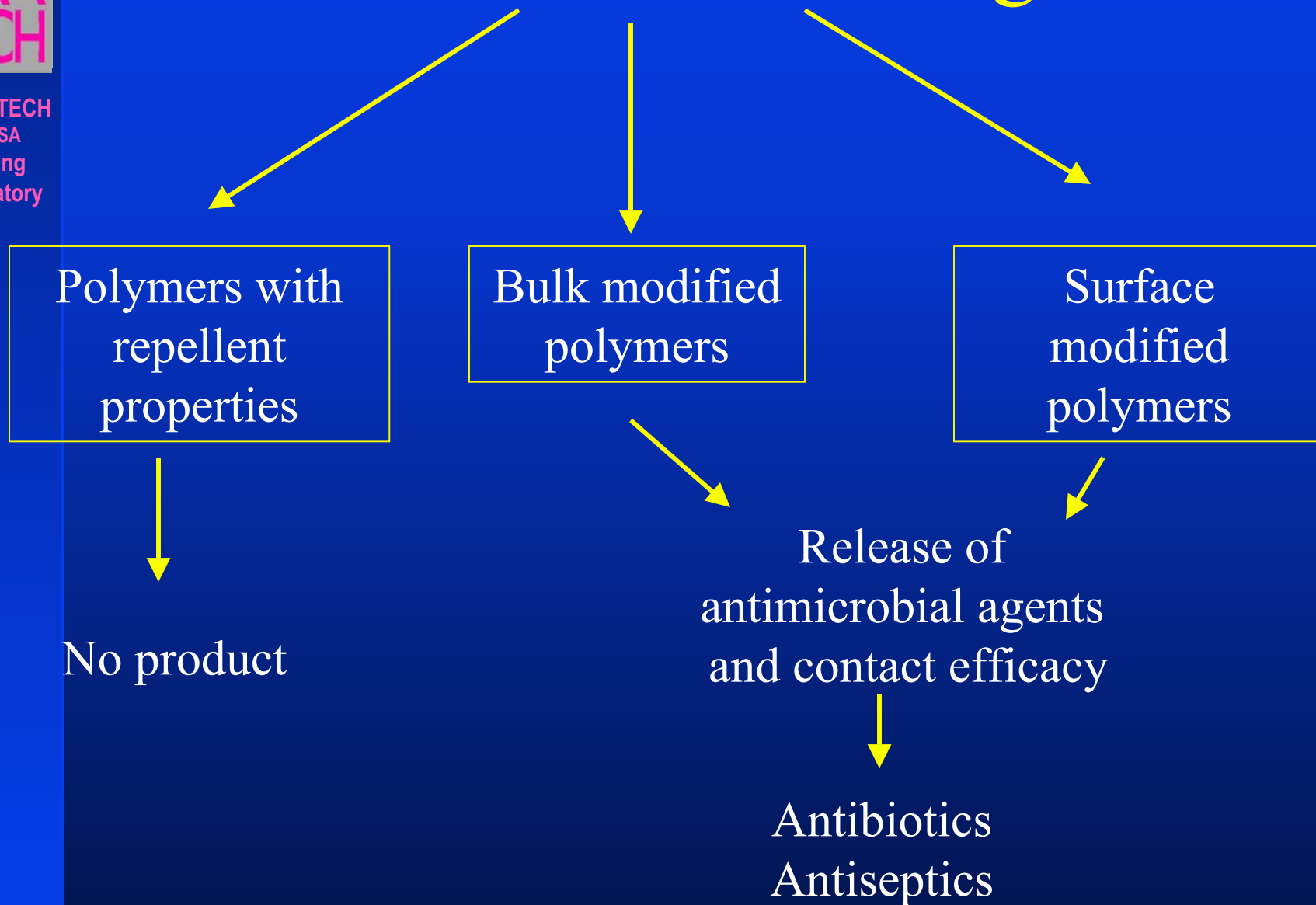


Removal of the device

Prevention of infection : Ideal antimicrobial surfaces

- **Broad spectrum or very specific biocidal activity**
- **High differential toxicity between mammalian cells and bacteria**
- **Biocompatible**
- **Infinite life time**

Different technologies



Actual products and technologies

(1) non silver agents

Products	Antimicrobial	Application
AMC™ Thromboshield	Benzalkonium Chloride + heparin	PUR CVC
Hydrocath Assure	Benzalkonium Chloride + hydrophilic matrix	PUR CVC
Cook Spectrum	Minocycline/rifampicin	PUR CVC
Spectramed hydrocath	PVP with an isocyanate prepolymer	PUR CVC

Rationale for selecting silver (2)

- Old antiseptic → new technologies
- Different active forms : ions, salts ...
- Broad spectrum :
 - Bacteria Gram + and Gram –
 - Yeasts
 - Active on biofilms
- Very low toxicity
- No actual case of resistance described

Surface treatments by silver ions (3)

Product	Antimicrobial	Application
Arglaes	Silver in alginate polymer	Wound dressing (burns) + urology devices
SPI-Ag	Silver ion (PVD + IBAD)	Medical devices
Acticoat	Silver (PVD)	Burn dressing
Infectguard	Silver ion implantation	PUR CVC

Surface treatments by silver in hydrogel (4)

Product	Antimicrobial	Application
Bard-X I.C.	Silver/hydrogel	Foley catheter
LubriLAST-K	Ag ₂ O ₃ AgCl/hydrogel	Medical devices

Other surface technologies using silver (5)

Product	Antimicrobial	Application
SLIP-COAT	AgX, Antibiotics in hydrophilic polymers	Coating for medical devices
SURFACINE	Photolink technology and UV radiation + silver	Medical devices
ARROW GARD I and II	Chlorhexidine and silver sulfadiazine	PUR CVC

SLIP-COAT[®] : STS biopolymer

Hybrid polymer system (polyvinylpyrrolidone and cellulose esters formulated in organic solvent solutions)

Not coated

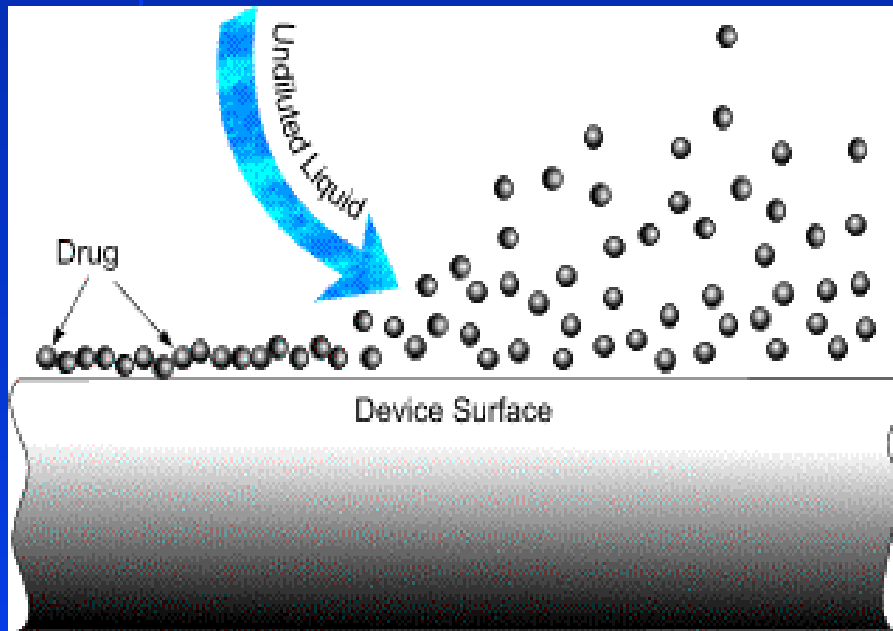


Figure 1

Coated with the polymer system

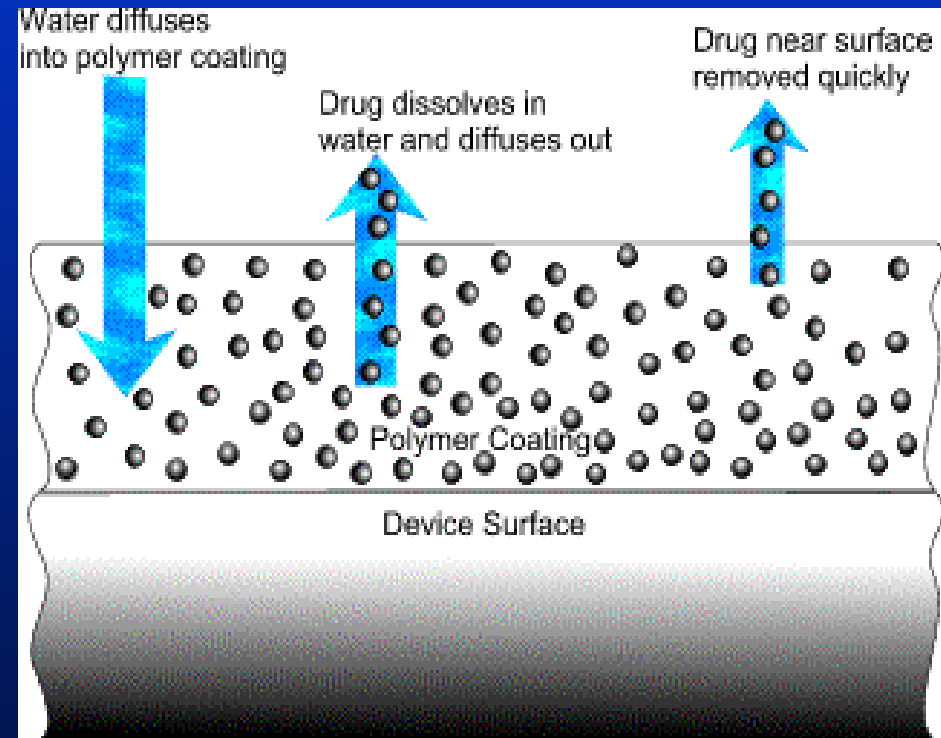


Figure 2

Surfacin[®] inert antimicrobial surface

- Kill microorganisms upon **contact** with the surface
- **Does not elute or leach** into solution → Insignificant elutables (80° C, 5 days \simeq 1 year ambient temperature)
- **Long-term and broad spectrum** of antimicrobial efficacy
- Treatment of **external surfaces** only
- **Non toxic** for cells : biologically inert
- **Durability** : blood, urine, autoclaving, EtO, E-beam, Gamma radiation
- **Compatibility** : almost all materials

Incorporation of silver into the material (6)

Product	Antimicrobial	Application
OLIGON (IMPLEMED)	Silver-platinum iontophoresis	Polyurethane CVC catheter
Erlanger silver catheter	Silver particules	PUR CVC
AgION	Silver zeolites	Medical devices

OLIGON Technology – IMPEMED

- Composite polymers containing silver and platinum particles that generate silver ions via iontophoresis to provide antimicrobial action
- Microscopic electrical fields within that drive Ag^+ into the surrounding environment (Ag, Pt act as electrodes)
- **Substrate compatibility** : plastics, rubbers, fibers through the entire material
- Bacteria killing on the device surface and surrounding environment
- *In vitro* and *in vivo* tests indicate a ten-fold reduction of bacterial colonization for 2 months (to years)
- **Inside and outside surfaces** (catheter, tubings) can be treated

AgION technology

- Completely inorganic antimicrobial treatment
- Medium = bio-inert ceramic = **zeolite**
- Active ingredient = **silver** ionically bounded to the zeolite
- **Long term** antimicrobial protection
- **Broad range of microbes**, no antibiotic resistance
- Surface coating or compounded into the material

Conclusion

- At least, 7-10 new antimicrobial products and technologies are under development.
- At least 10 companies, worldwide are active in antimicrobial coatings area.
- BUT
 - Cost
 - Development of bacterial resistances to antibiotics/antiseptics
 - Biological secondary risks (hypersensitivities to antiseptic agents)

Strategies for infection prevention

Large scale prevention for everybody
 OR
 Specific prevention only for
 particular risk patients

Selection of the appropriate product