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Catheter-related infections and biofilms

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What I would like to show:

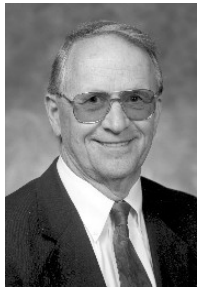
- **Bacteria in biofilms are different** in
  - Life style
  - Pathogenicity
  - Virulence
  - Pharmacodynamics
  - Pharmacokinetics
  - Immunology
- Device-related infections with biofilm formation
  - Prevalence
  - Diagnostics
  - Therapy
  - Prevention (antisepsis, adhesion/material coating, Antisepsis)

Biofilm

Mikroorganismen live "sessile" and "planctonic"

1683 **Leeuwenhoek:**

„an unbelievably great company of living animalcules ...“



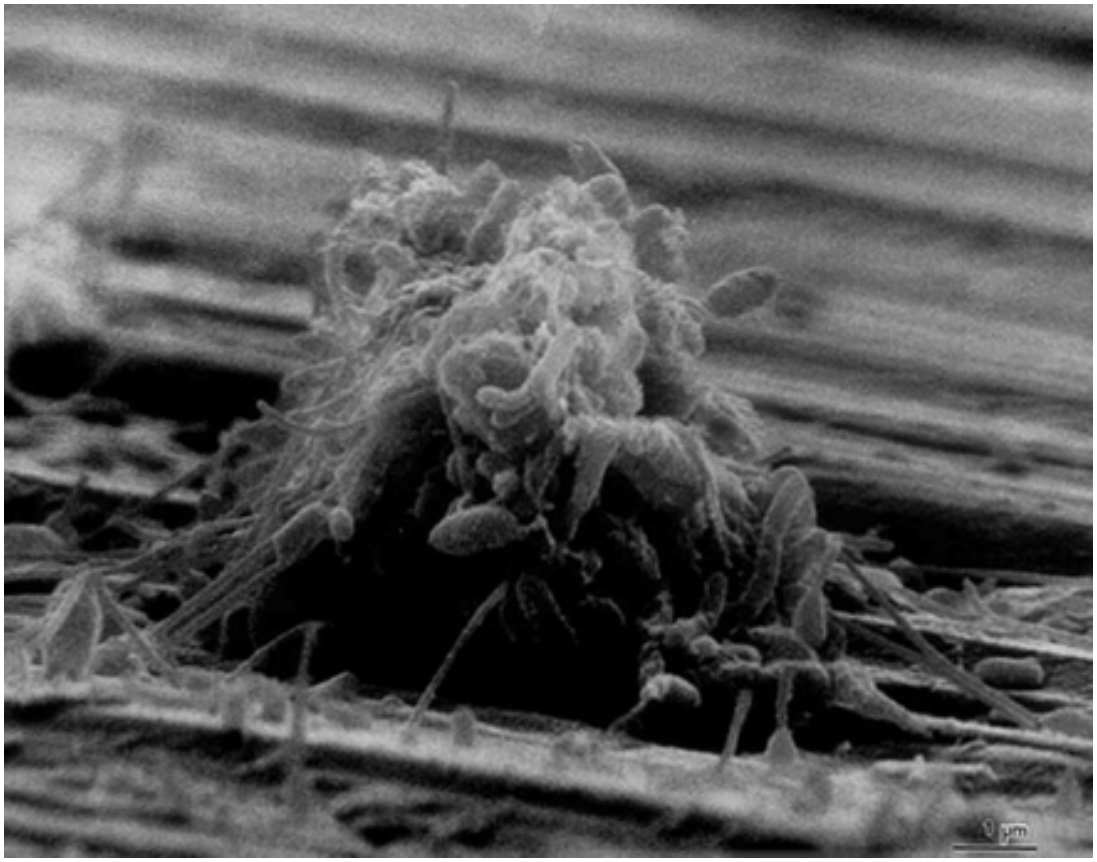
1978 **Costerton: Biofilm common in**

- **Technical systems**
- **Device-related infections**
- **Chronic infections**

Biofilm: Definition

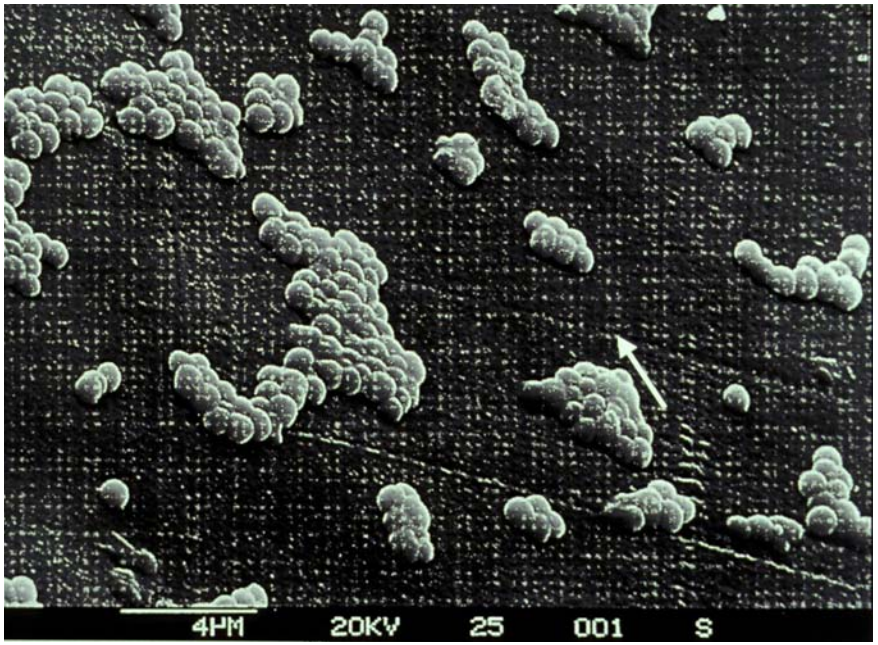
- A community of microorganisms irreversibly attached to a surface, producing extracellular polymeric substances, exhibiting an altered phenotye compared with corresonding planktonic cells, especially with regard to gene transcription, and interacting with each other.

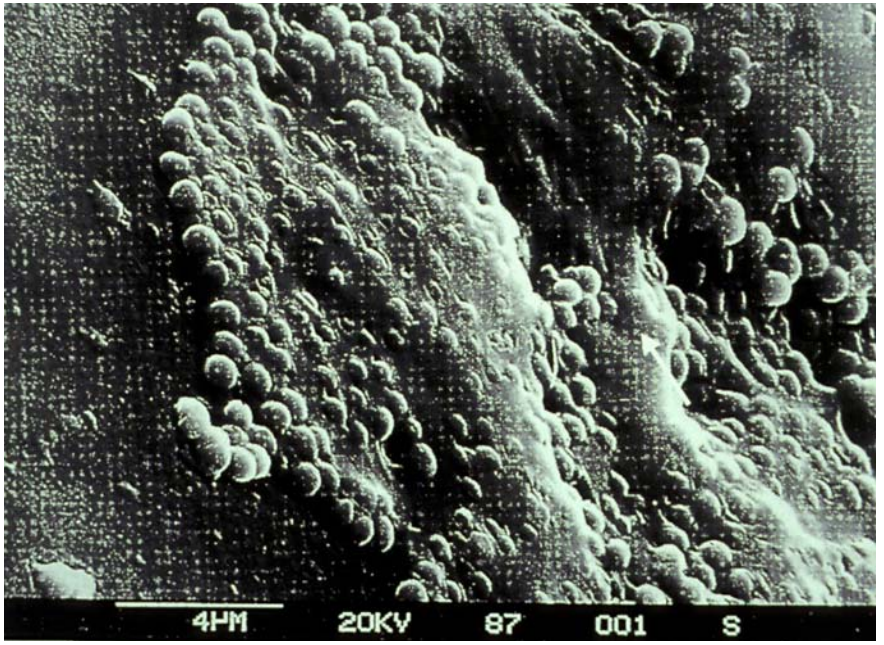
Lindsay, 2006

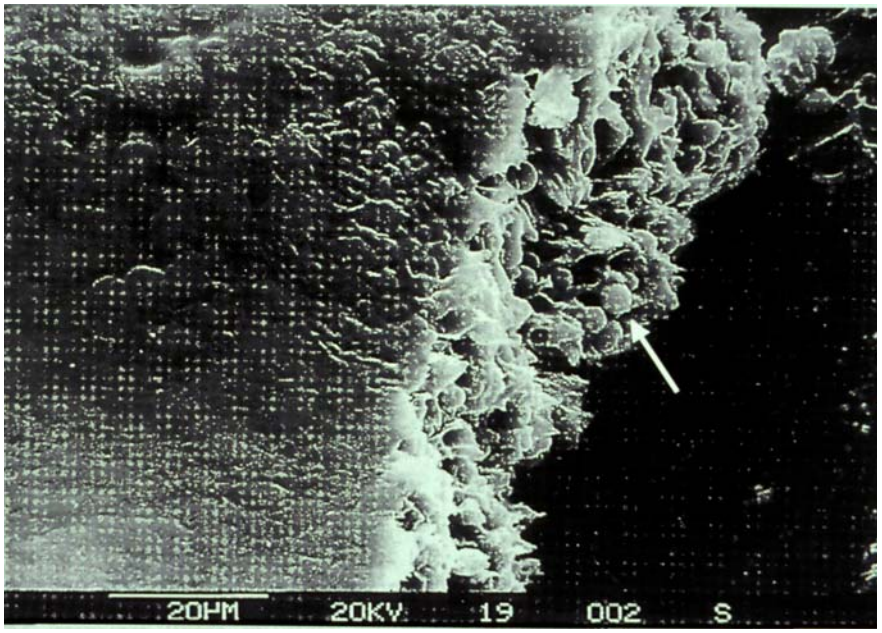


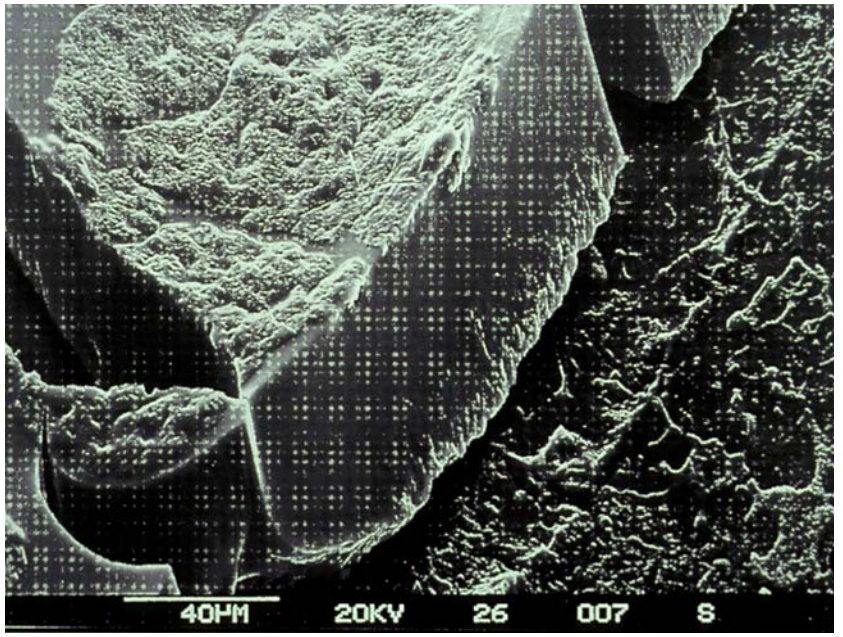
Biofilm on the metal surface of a water system

DONLAN & COSTERTON 2002 CMR 15:167-193

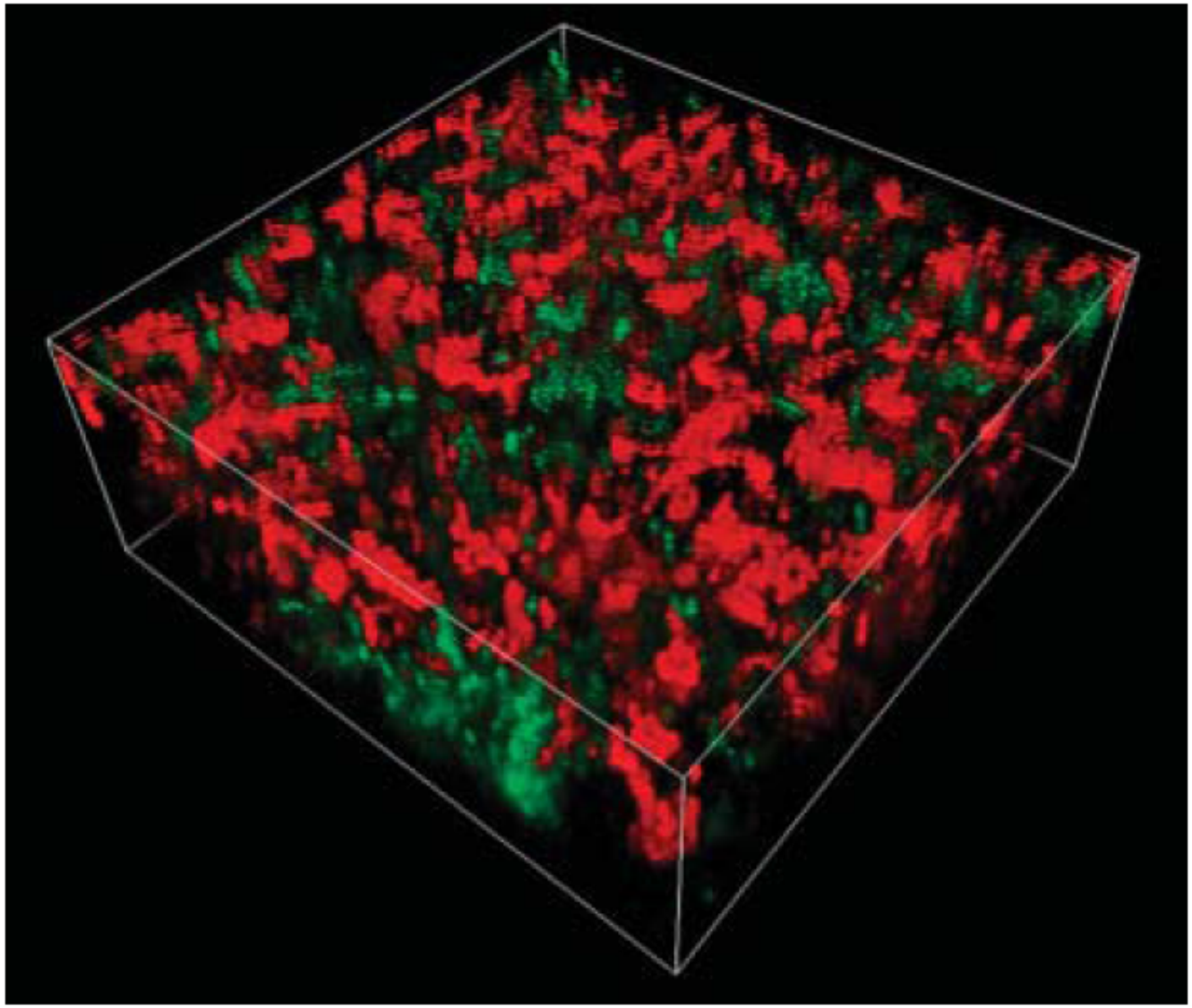








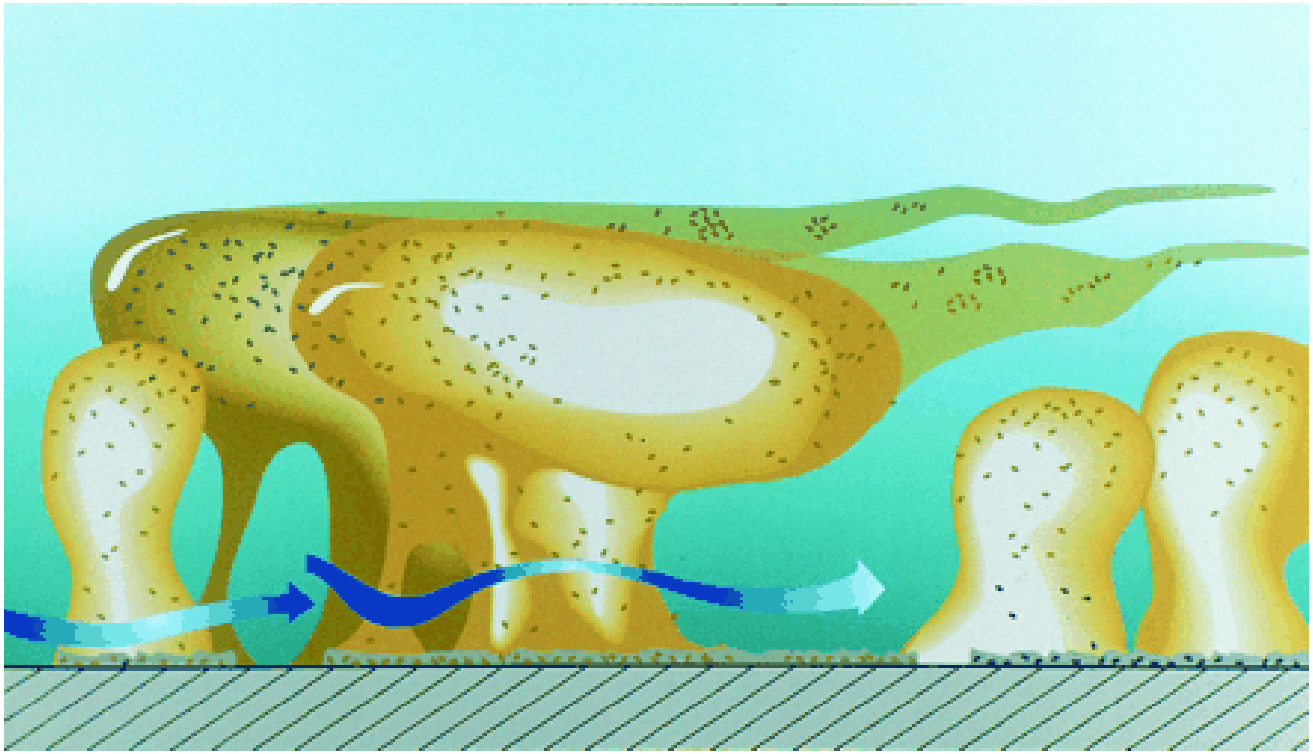
***Staphylococcus epidermidis* on plastic**



Biofilm of *Pseudomonas aeruginosa* (red) and *Klebsiella pneumoniae* (green)

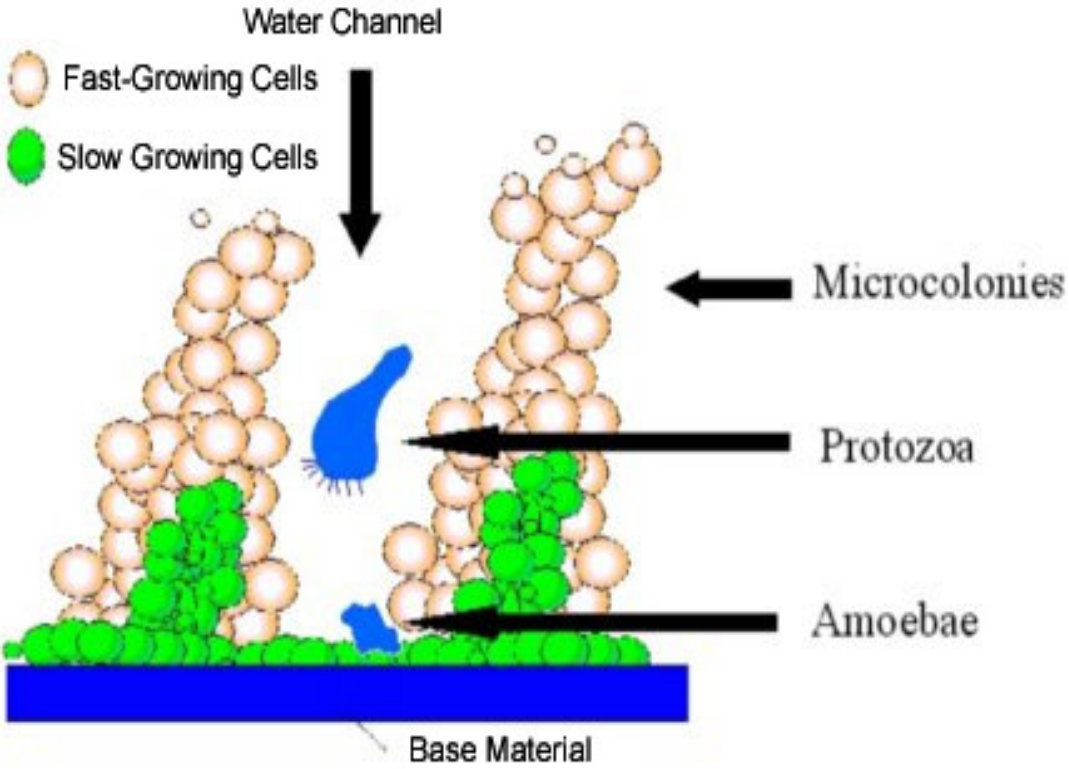
3D reconstruction of confocal laser scanning microscopy

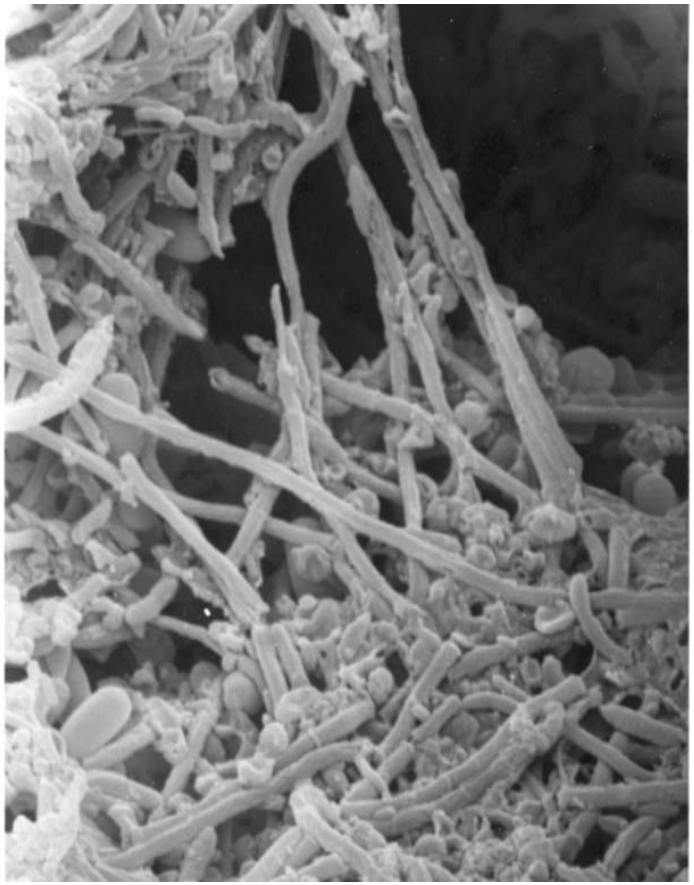
Bryers, Biotechnology and Bioengineering, 2008



Biofilm -
„the coral reefs of microorganisms“

DONLAN & COSTERTON 2002 CMR 15:167-193





Biofilm:

- **Complex composition:**
  - **Different microorganisms**
  - **Organic substances: Glykocalix, host**
  - **Anorganic substances**
  - **High water content**
- **Organisation in space and time**

Costerton, 2004

Biofilm – Natural function

Protection from

- Antimicrobial Substances
- Phage
- Amoeba
- Dessication

Exchange of

- Nutrients
- Signals
- Genetic information

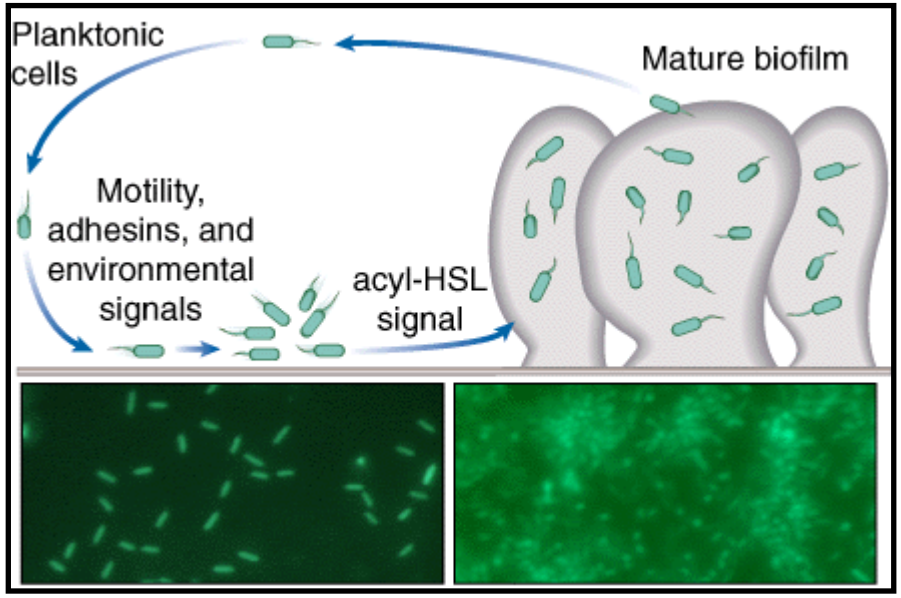
Quorum Sensing

Cell-density dependent bacterial signalling mechanism

acetylated

homoserinlactone

- efflux-mediated transport -



Autoinducer ⟶

Expression of

QS-controlled Genes, „cross talk“

Quorum Sensing-controlled genes in *Pseudomonas aeruginosa*

Elastase A, B **Alkalic Protease**	**Proteasen**
Phospholipase C **Rhamnolipid**	**Hemolysin,** **Biosurfactant**
Exotoxin A	**EL2-Blockade**
Pyocyanin, Pyoverdin	**Fe-binding**
Alginate	**Slime capsule**
Katalase, Superoxid-Dismutase	**H_2O_2, O_2**

Van Delden, Emerging Infectious Diseases, 1998

Mortality of mice at 48 h post-burn/infection with *P. aeruginosa*

	% Mortality
PAO1, wild type	94.3
*las*R$^-$	28.3
*rhl*I$^-$	46.7
*las*I/*rhl*I$^-$	6.7
*las*I/*rhl*I$^-$ + *las*I plasmid	73.3
*las*I/*rhl*I$^-$ + *rhl*I plasmid	46.7
*las*I/*rhl*I$^-$ + *las*I/*rhl*I plasmid	93.3

Rumbaugh, Microbes and Infection, 2000

"From whence I conclude, that the Vinegar with which I washt my Teeth, kill'd only those Animals which were on the outside of the scurf, but did not pass thro the whole substance of it."

A. van Leeuwenhoek, 1684

MIC-values (µg/ml) of sessile and planktonic bacteria

	AB	Plankt.	Sessile
S. aureus[1]	VAN	2	20
P. aeruginosa[2]	IMI	1	> 1,024
E. coli[2]	AMP	2	512
P. pseudomallei[3]	CEF	8	800
S. sanguis[4]	DOX	0.063	3.15

[1]Williams, 1997; [2]Ceri 1999; [3]Vorachit 2002; [4]Larsen 1996

Reduced activity of antibiotics in biofilms

- **Reduced penetration?**

  Psae and CIP, TOB; koag.-neg. Staph and TOB,

- **Slow growth?**

  Esco and CET, koag.-neg. Staph and CIP; Psae and TOB

- **Modified importance of target?**

  Esco and *rpoS*

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Medical devices associated with biofilm infetions

- Endocardial Pacemakers
- Hickman Catheters
- Urinary Catheters
- Mechanical Heart Valves
- Acetubular Cup Failure
- Vascular Graft Infections
- Esophegal Mechanical Valves

Nos. Sepsis – estimated data for Germany 1998

6 Mio. ICU patient days (Stat. Bundesamt)

76% CVC application rate*	4.6 Mio. CVC days
1.9 cases of sepsis/1,000 days*	9,000 CVC-ass. sepsis
25% mortality**	2,200 deaths
+ 8 days additional**	70,000 additional ICU days

Gastmeier, 1998

* KISS, **Meta analysis

Education of physicians-in-training can decrease the risk for vascular catheter infection

1-day course on infection control practices and procedures

	Before course	6 m after	*P*
Need of full-size drapes	22 %	73 %	<0.001
Use of full-size drapes	44 %	65 %	<0.001
Cath. rel. inf. (/1,000 cath. days)	4.51	2.92	<0.01

Estimated cost savings: $ 63,000 - 800,000

Sherertz et al., Ann Intern Med. 2000

Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter

403 chlorhexidine-silver-sulfadiazine-catheters vs. control

- **Colonization** **13.5 vs. 24.1/100 catheters (p = 0.005)**
- **Bbloodstream infection** **1.0 vs. 4.7/100 catheters (p = 0.03)**

  1.6 vs. 7.6/1,000 catheter-days
- **No adverse effects**

Maki et al., Annals of Internal Medicine, 127, 257-266

Rifampin for treatment of orthopedic implant-related staph infections

Stable orthopedic devices; debridement,

2 wks OXA/VAN + RIF; 3 - 6 months:

	CIP	CIP + RIF
Dosing	**2 x 750 mg**	**2 x 750/450 mg**
n	**12**	**12**
Cured	**58%**	**100%**
CIP^R after failure	**4/5**	**-**

Zimmerli et al., JAMA, 1998

Intravascular catheter exchange and duration of candidemia

Amphotericin B 93 patients; fluconazole 94 patients:

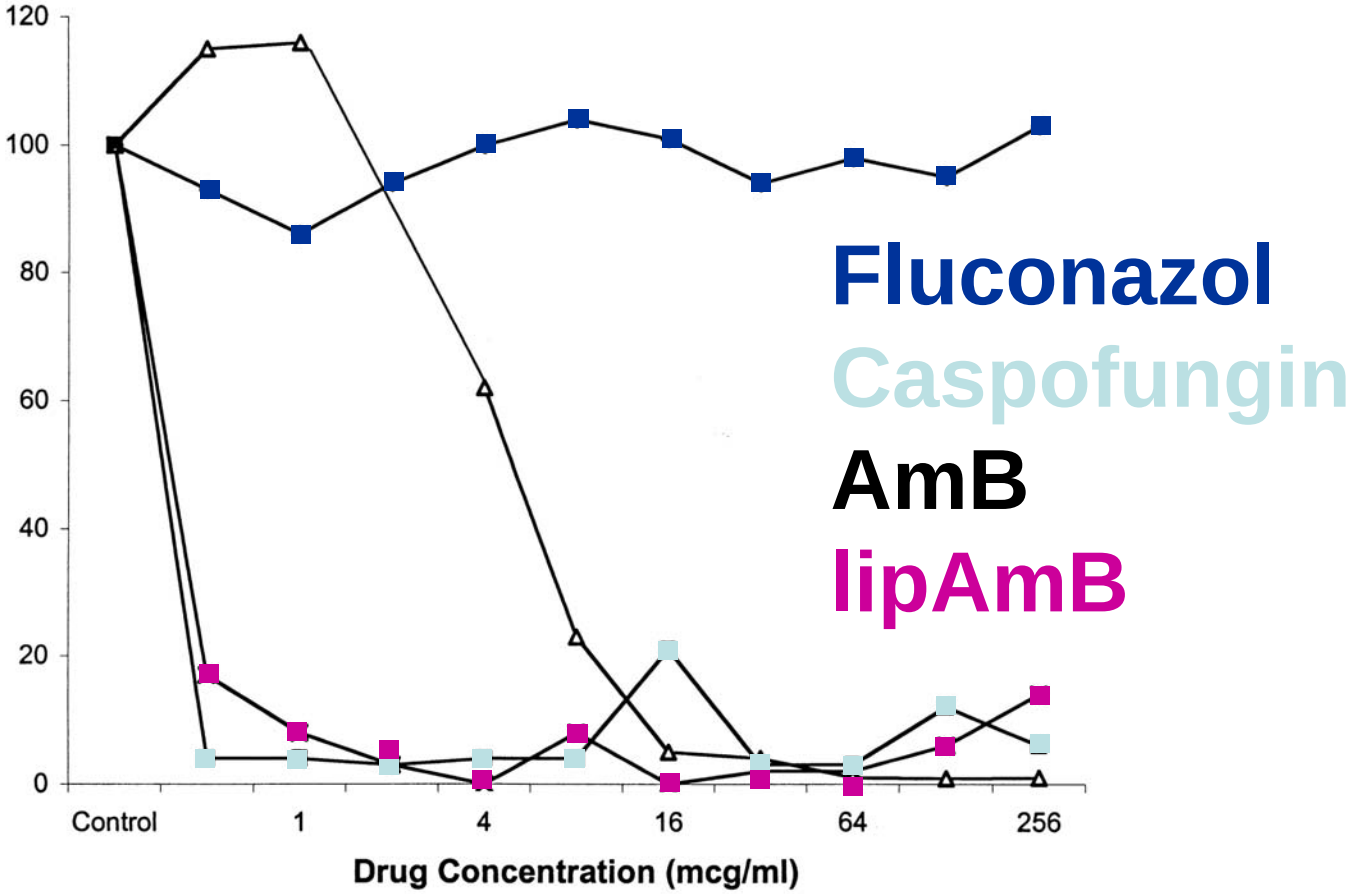
	Catheter removal	no removal	*p*
Days to clearance	2.6 ± 0.5	5.6 ± 0.8	< .001
APACHE II	14.5 ± 0.6	16.9 ± 0.8	.03

- change all lines
- do not change over guide wire

Rex et al., Clin Inf Dis 1995;21:994-6

Candida biofilms: unique efficacy of lipAMB and echinocandins

Bioprosthetic model, *C. albicans/parapsilosis*



Kuhn, AAC, 2002

Approach	Mode of action	Key reference
pilicides	inhibits bacterial pilus biogenesis and surface attachment	71
RNA III inhibiting peptide (RIP)	disrupts quorum-sensing pathways in staphylococci	72
acyl-homoserine lactone mimetics	disrupts quorum-sensing pathways	73
furanones	disrupts quorum-sensing pathways	74
omigard (omiganan cationic peptide)	topical gel for prophylaxis settings including CRBSIs	http://www.cadencepharm.com
aganocides	hypochlorous acid–based compounds	http://www.novacal.com
ceragenins	depolarizes membrane potential; device coatings	http://www.ceragenix.com
lysostaphin	prevents or disrupts staphylococcal biofilms	http://www.biosynexus.com
device coatings	controlled release of antimicrobials from device surfaces	http://www.surmodics.com
		http://www.bacterin.com
hydrogel coatings	controlled release of silver compounds	http://www.bardmedical.com
surface acoustic waves	disrupts device adhesion and colonization	62
pulsed ultrasound	enhances local release of antibiotic from cements	64
electric direct current	prevents or disrupts biofilm colonization	63
intelligent implants	MEMS-based release of antimicrobial(s) from reservoir	61
gallium compounds	antimicrobial potentiator via disruption of iron metabolism	75

Abbreviations: CRBSI, catheter-related bloodstream infection; MEMS, microelectromechanical systems.

Lynch, 2008

Authors are employees of Cumbre Pharmaceuticals Inc., which has a rifamycin-quinolone hybrid antibiotic agent (CBR-2092) in clinical development that is intended for the treatment of biofilm infections