

"Antimicrobial Materials: - A Clinician's Perspective"

Dr. Jochen Salber

**Clinical Research Center, Ruhr University Bochum and University Hospital
Knappschaftskrankenhaus Bochum, Germany**



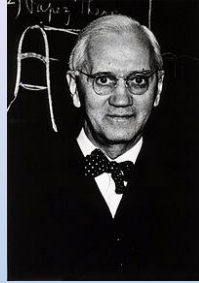
European
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Horizon 2020
European Union funding
for Research & Innovation

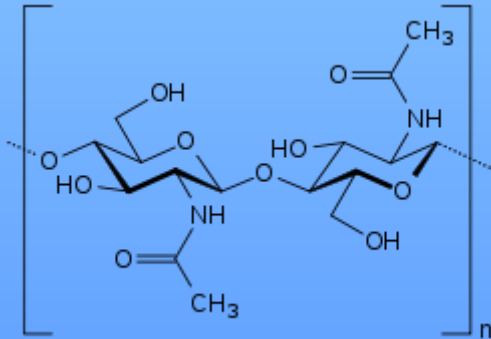
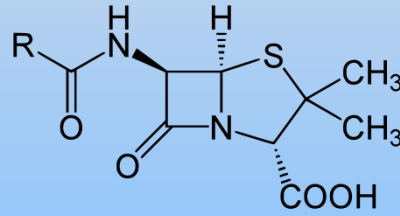
HyMedPoly received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie Grant Agreement No 643050

20th July 2016

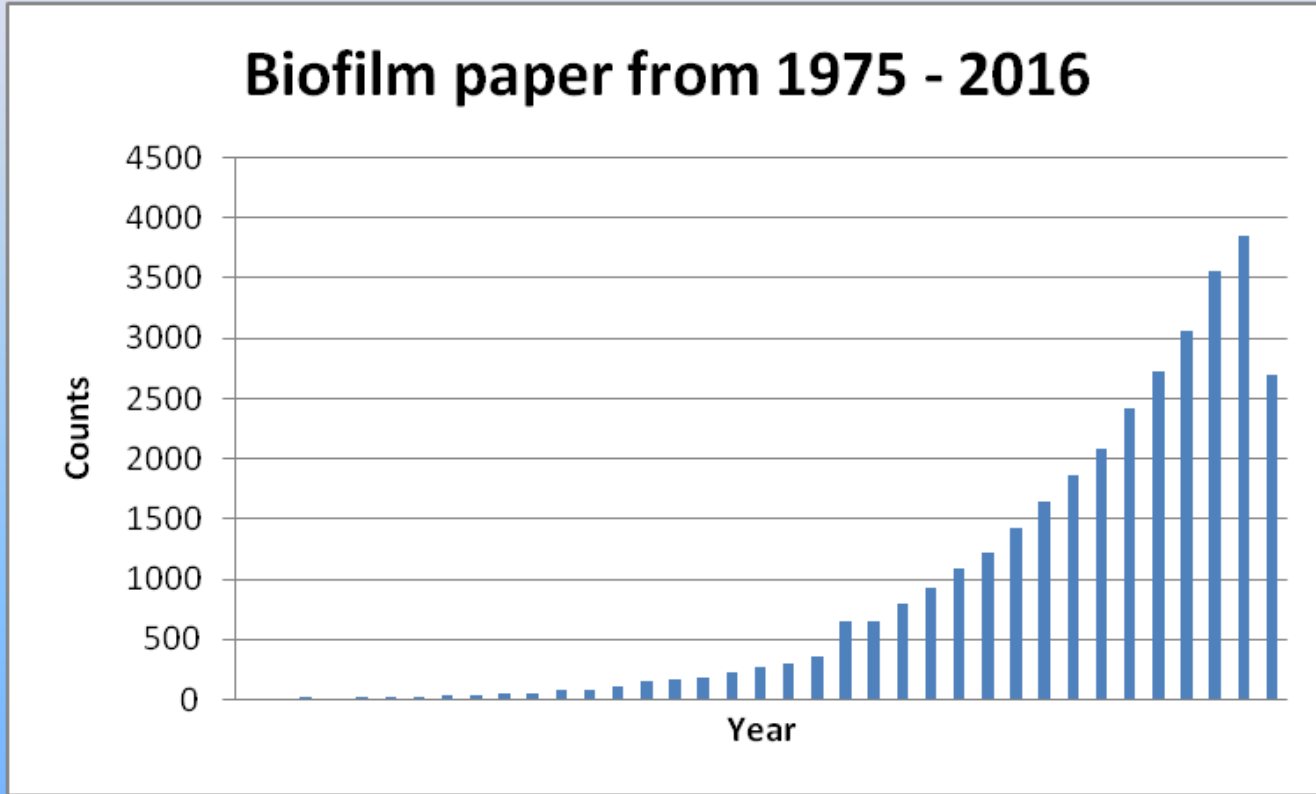
Introduction ??



1881 - 1955



PubMed search results



Biofilm: 32731 07/13/2016; + 30 07/16/2016
Clinical trials (CT): 390

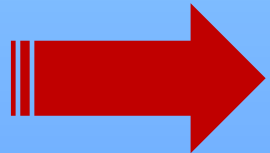
Biofilm formation: 20101; + 15 07/16/2016
CT: 133

Biofilm and implants: 1046 (1048)
CT: 19

Biofilm and endoprosthesis: 11
CT: 0

Biofilm and endoprostheses: 14
CT: 1

Biofilm formation + name of microbe



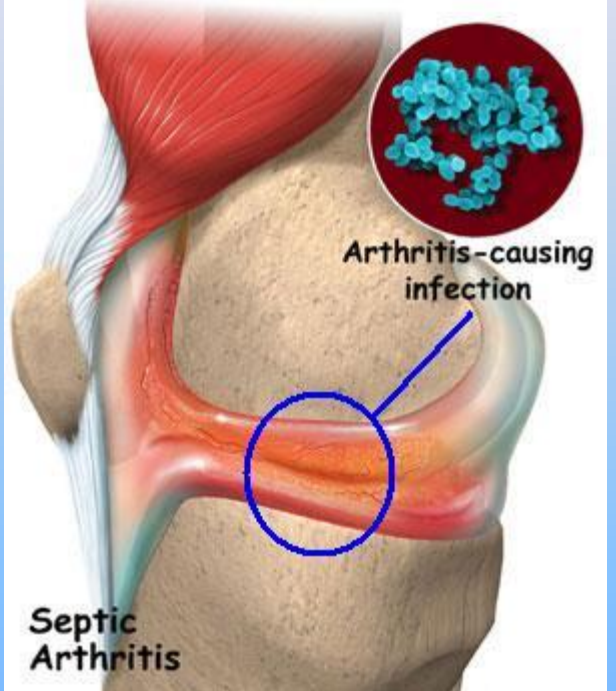
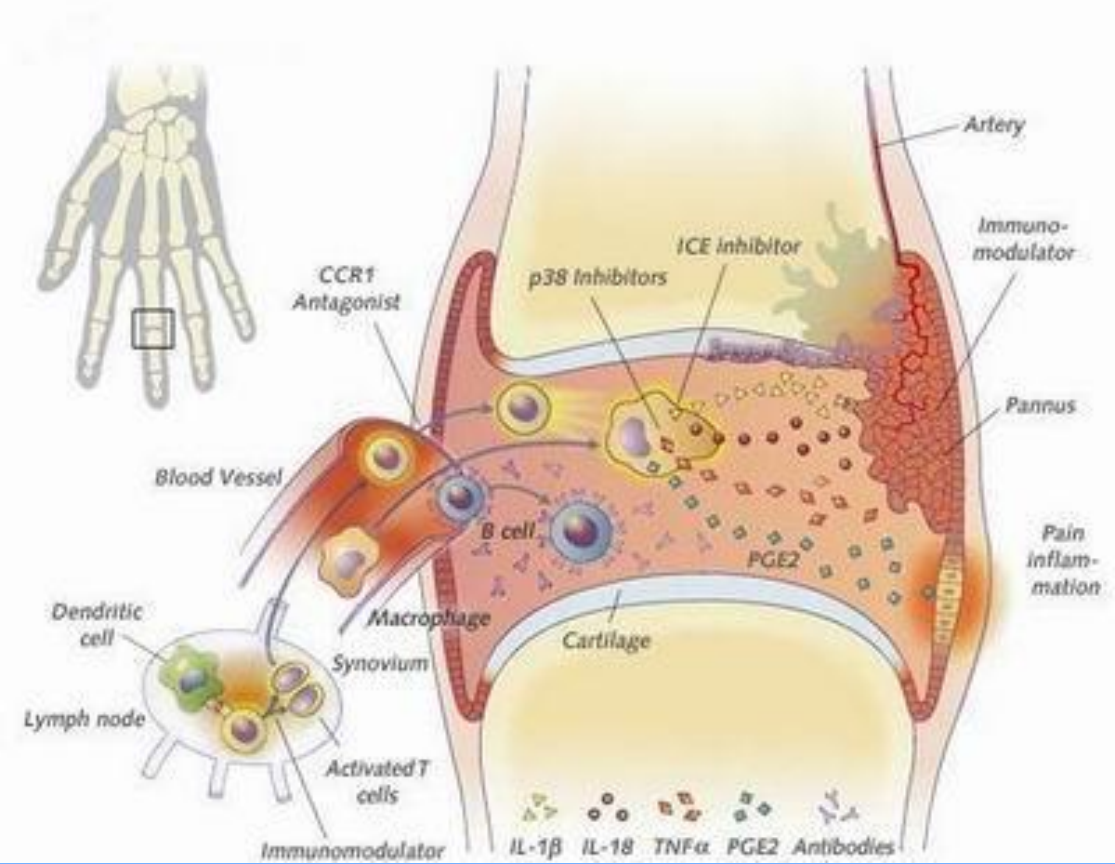
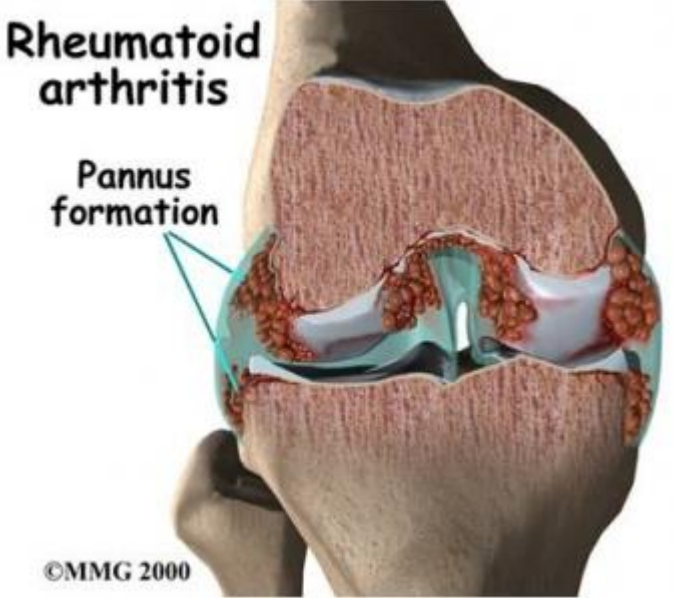
Search item: Biofilm formation + microbe // I

Domain	Phylum	Family	Genus	Species	Count	CT
Bacteria	Firmicutes	Staphylococcaceae	Staphylococcus	-	2640	10
				S. aureus	1854	7
				S. epidermidis	968	4
		Streptococcaceae	Streptococcus	-	1620	31
				S. mutans	942	24
				S. pneumoniae	167	2
	Proteobacteria	Enterobacteriaceae	Klebsiella	-	296	0
		Pseudomonadaceae	Pseudomonas	-	3257	6
				P. aeruginosa	2582	5
		Moraxellaceae	Acinetobacter	-	335	0
				A. baumannii	228	0

Microbes of clinical relevance ?

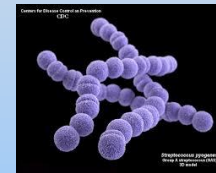
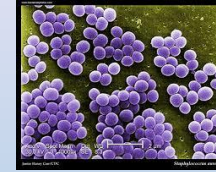
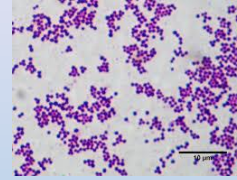
- 1.) Disease-related: - Cystic fibrosis (pneumonia), DM (chronic wounds), PVD (chronic wounds),
- 2.) Anatomic region-related: - Joints, , hollow organs i.e. heart, vessels, oesophagus, GIT, windpipe,..
- 3.) Foreign body-related:
 - 3.1) Natural external (mud), natural internal (non-viable tissue)
 - 3.2) Implant-associated (endoprostheses, catheters, others)

Acute suppurative synovitis



Microbes in acute suppurative synovitis

ORGANISM	NO. OF ISOLATES (% of Total)
Gram-positive	
<i>Staphylococcus aureus</i>	1066 (46)
<i>Staphylococci</i> , coagulase negative	84 (4)
<i>Streptococci</i>	512 (22)
<i>Streptococcus pyogenes</i>	183 (8)
<i>Streptococcus pneumoniae</i>	156 (7)
<i>Streptococcus agalactiae</i>	69 (3)
Other streptococci	104 (5)
Gram-negative	
<i>Escherichia coli</i>	91 (4)
<i>Haemophilus influenzae</i>	104 (5)
<i>Neisseria gonorrhoeae</i>	77 (3)
<i>Neisseria meningitidis</i>	28 (1)
<i>Pseudomonas aeruginosa</i>	36 (2)
<i>Salmonella</i> spp.	25 (1)
Other gram-negative rods	110 (5)
Miscellaneous (including anaerobes)	136 (6)
Polymicrobial	33 (1)



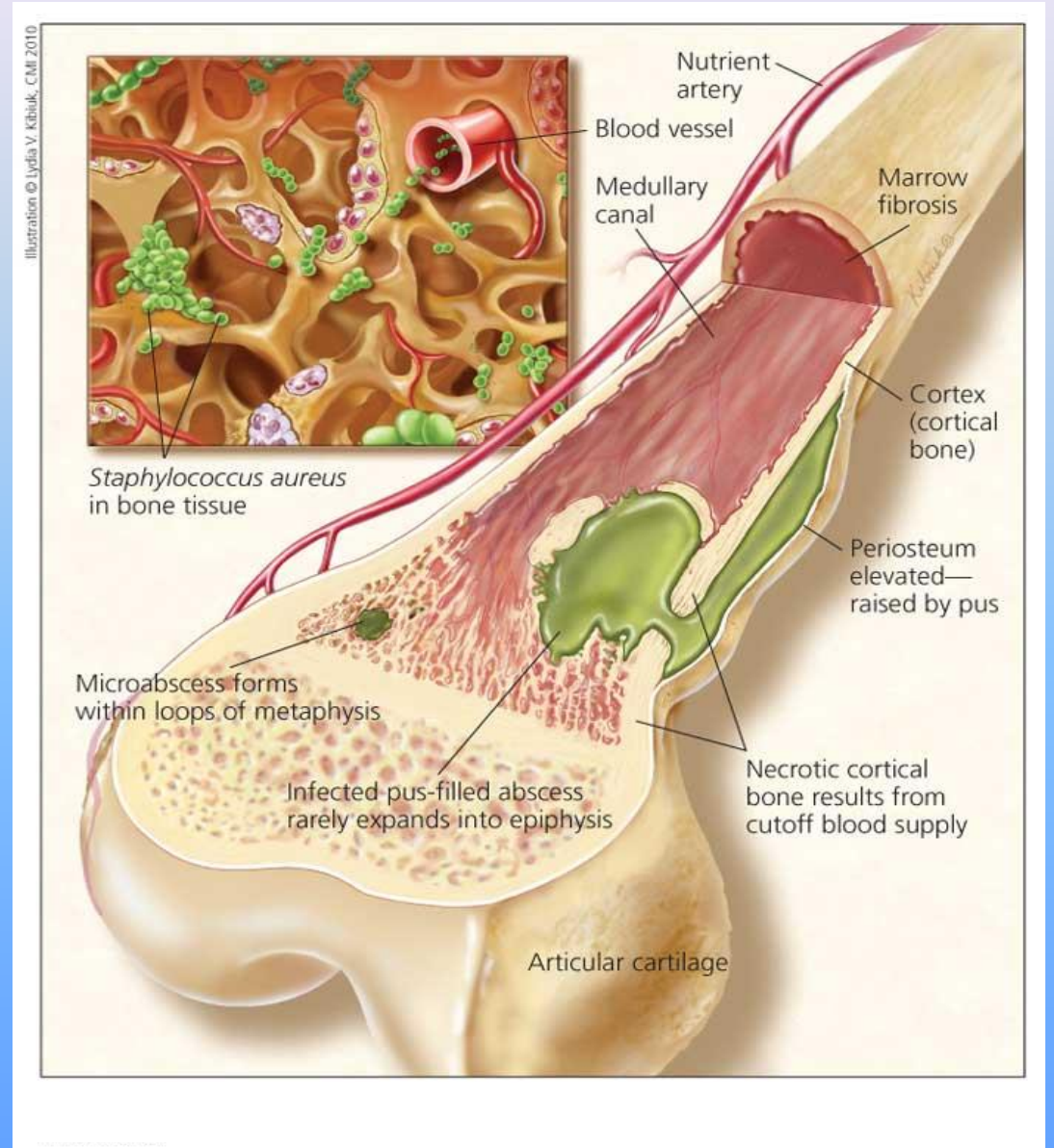
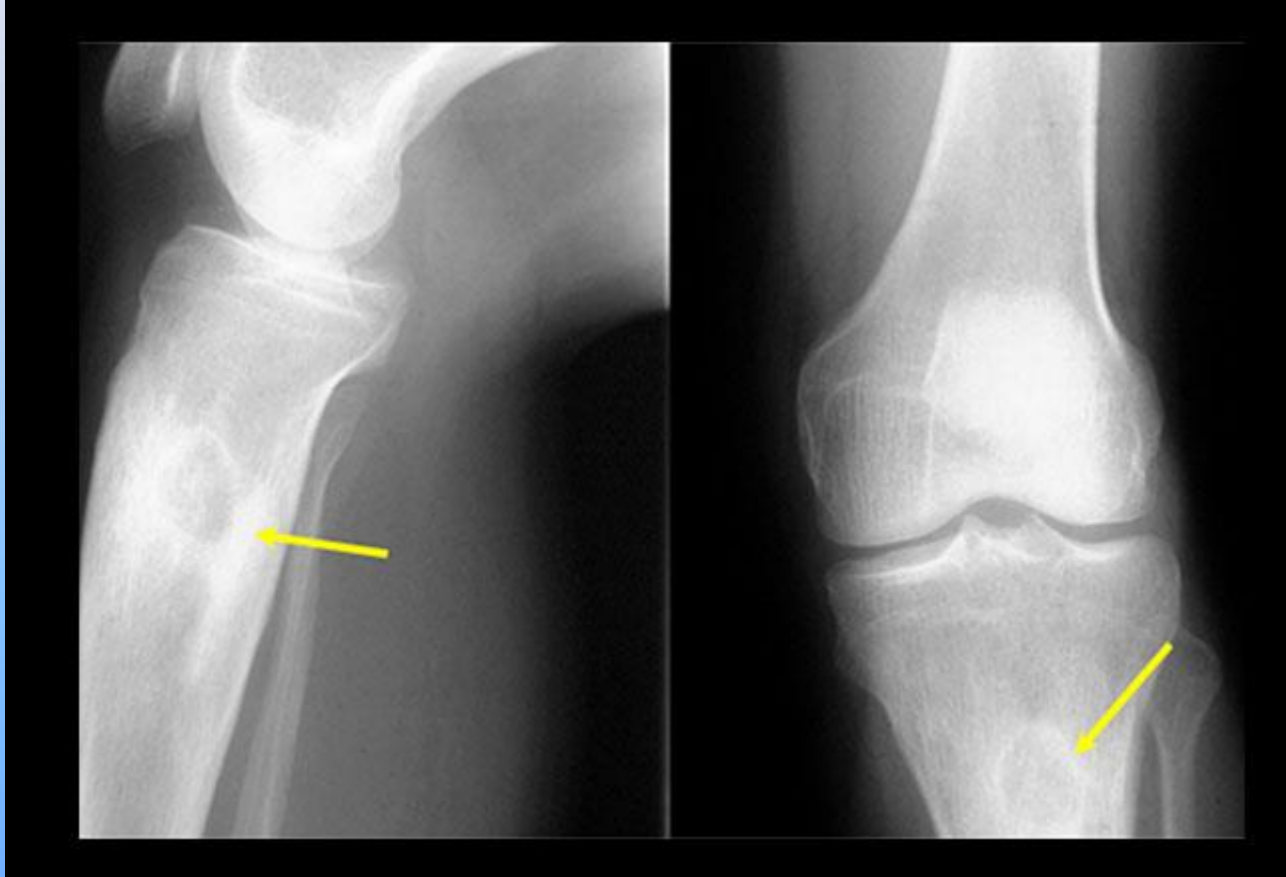
Approx. 75% Gram-positive bacteria



Bacteria isolated in 2302 compiled cases of bacterial septic arthritis in adults.

Modified from Ross JJ, Saltzman CL, Carling P, et al. Pneumococcal septic arthritis: review of 190 cases. Clin Infect Dis.2003;36:319-327.

Acute osteomyelitis



Microbes in osteomyelitis

Common (>50% of Cases)

Staphylococcus aureus
Coagulase-negative staphylococci

Occasionally Encountered (>25% of Cases)

Streptococci
Enterococci
Pseudomonas spp.
Enterobacter spp.
Proteus spp.
Escherichia coli
Serratia spp.
Anaerobes (*Finnegoldia* [*Peptostreptococcus*] spp., *Clostridium* spp., *Bacteroides fragilis* group)
Mycobacterium tuberculosis

Rarely Encountered (<5% of Cases)

Mycobacterium avium-intracellulare complex
Rapidly growing mycobacteria
Dimorphic fungi (blastomycosis, coccidioidomycosis, sporotrichosis)
Candida spp.
Cryptococcus
Aspergillus spp.
Mycoplasma spp.
Tropheryma whipplei
Brucella spp.
Salmonella spp.
Actinomyces



Staphylococcus epidermidis

Staphylococcus aureus

Mannitol - Agar

Staph. aureus: strains i.e. MSSA, MRSA (ORSA); ??

Staph. epidermidis: Coag.-neg.: strains i.e. MSSE, MRSE; ??

Implant-associated infections

The five signs of inflammation based on Celsus', Galens', Sydenhams' and Virchows' observations:



- 1.) T
- 2.) R
- 3.) C
- 4.) D
- 5.) F I

Microbes in implant-associated infections

Classification	Moment of clinical manifestation	Source of infection & typical microbes
Acute postoperative	Up to 4 - 6 weeks	Intra-operative contamination: Staph. aureus, Gram-negative bacilli, Coagulase-negative Staphylococci
Late	4 - 6 weeks to 2 years	Skin flora: Coagulase-negative Staphylococci, Propionibacterium acnes, Streptococcus spp., Corynebacterium spp.
Hematogenous late	after 2 years	Transient bacteraemia: Streptococcus spp. (oral cavity), Streptococcus pneumoniae (pneumonia), Staph. aureus (Skin), Streptococcus pyogenes (soft tissue infection), Enterococcus & enterobacteriaceae (urine tract infection)

- *S. aureus*, 21% to 43%
- Coagulase-negative staphylococci, 17% to 39%
- Streptococci, 7% to 12%
- Gram-negative aerobic bacilli, 5% to 12%
- Enterococci, 1% to 8%
- Anaerobic bacteria, 2% to 6%

Mandell et al., Princ and Pract of Infect Dis 2015

Holzmann et al., Der Orthopäde 2015

Microbes of clinical relevance ?

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Hospital-acquired infections

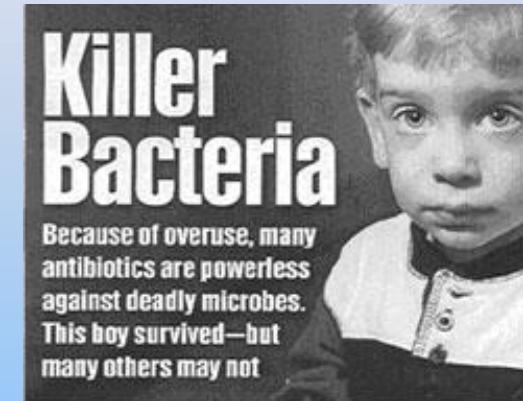
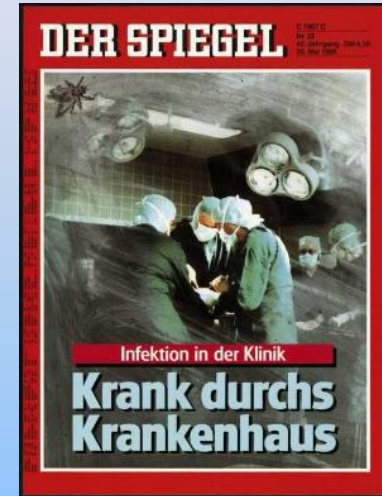
Hospital-acquired infection (HAI); Synonym: Nosocomial infection

"Black death (??) was defeated, but sepsis (??) not"

Each year 500.000 patients are infected by persevering bacteria - probably resulting in:

- ▶ suppurated wounds
- ▶ urinary tract inflammation
- ▶ and pneumonia

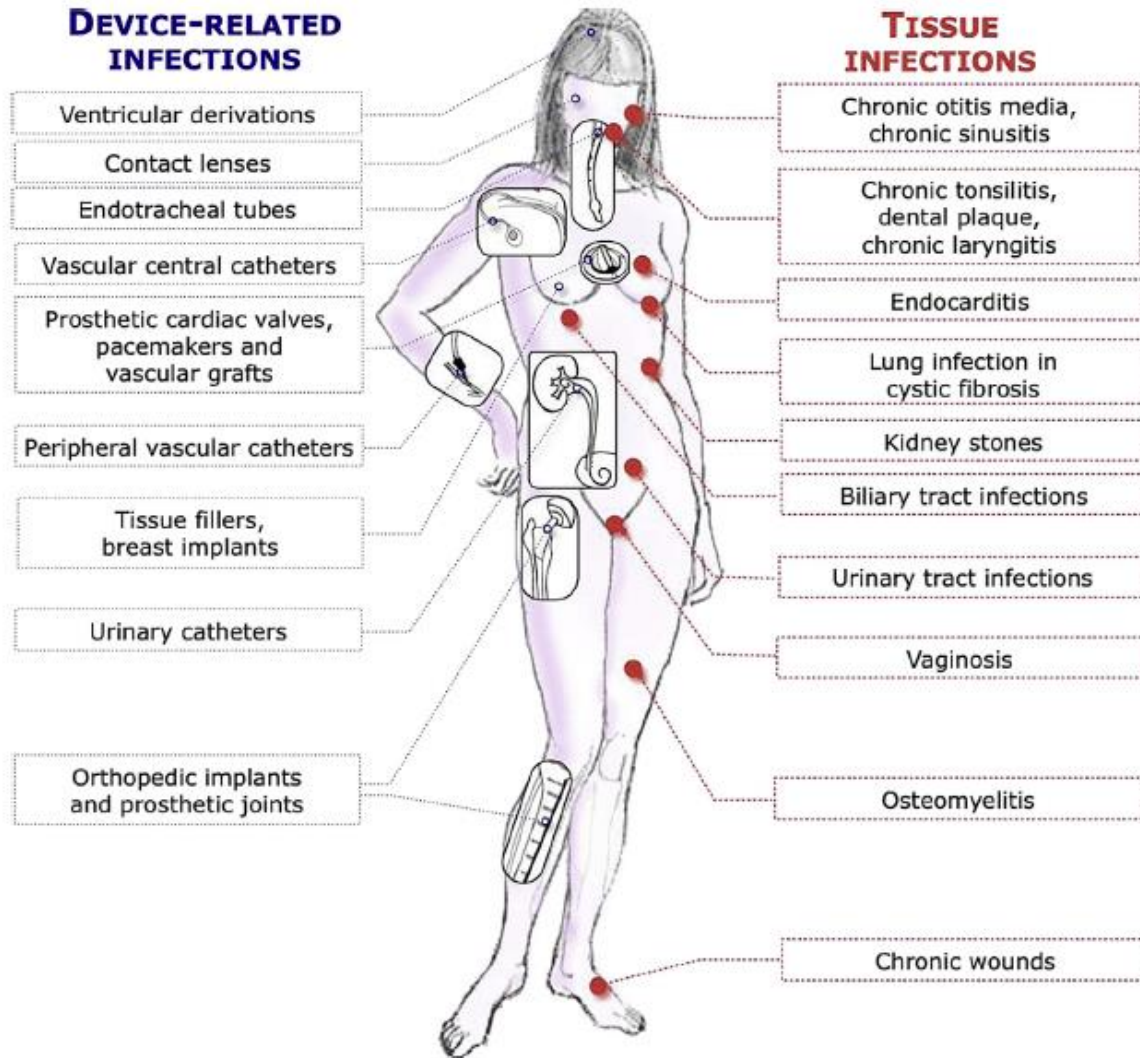
Often it is caused by iatrogenic sloppiness, because physicians lack knowledge about **hygiene** and they don't wash hands enough!!



Antibiotic overuse ??

- ▶ Approx. 4 to 8 % of all patients staying inpatient at a hospital or clinic are affected by HAI (600.000 - 1.2 million);
- ▶ 30 % were ICU patients → **Why??**
- ▶ Approx. 4 % of the ICU patients died and infection was the primary cause;
- ▶ 20 - 30 % would be avoidable

Biofilm-related infections



Primary diseases:

- Obesity (BMI); **Classification??**
- Metabolic syndrome; **Clustering at least 3 (5) ??**
- Cardiovascular diseases (CVDs); **??**
- Peripheral vascular diseases; **??**
- Diabetes; I, NIDDM II, IDDM II

Acute versus chronic infection ??

FIG. 1. Typical biofilm infections (3) (reproduced with permission).

Life-forms of microbes

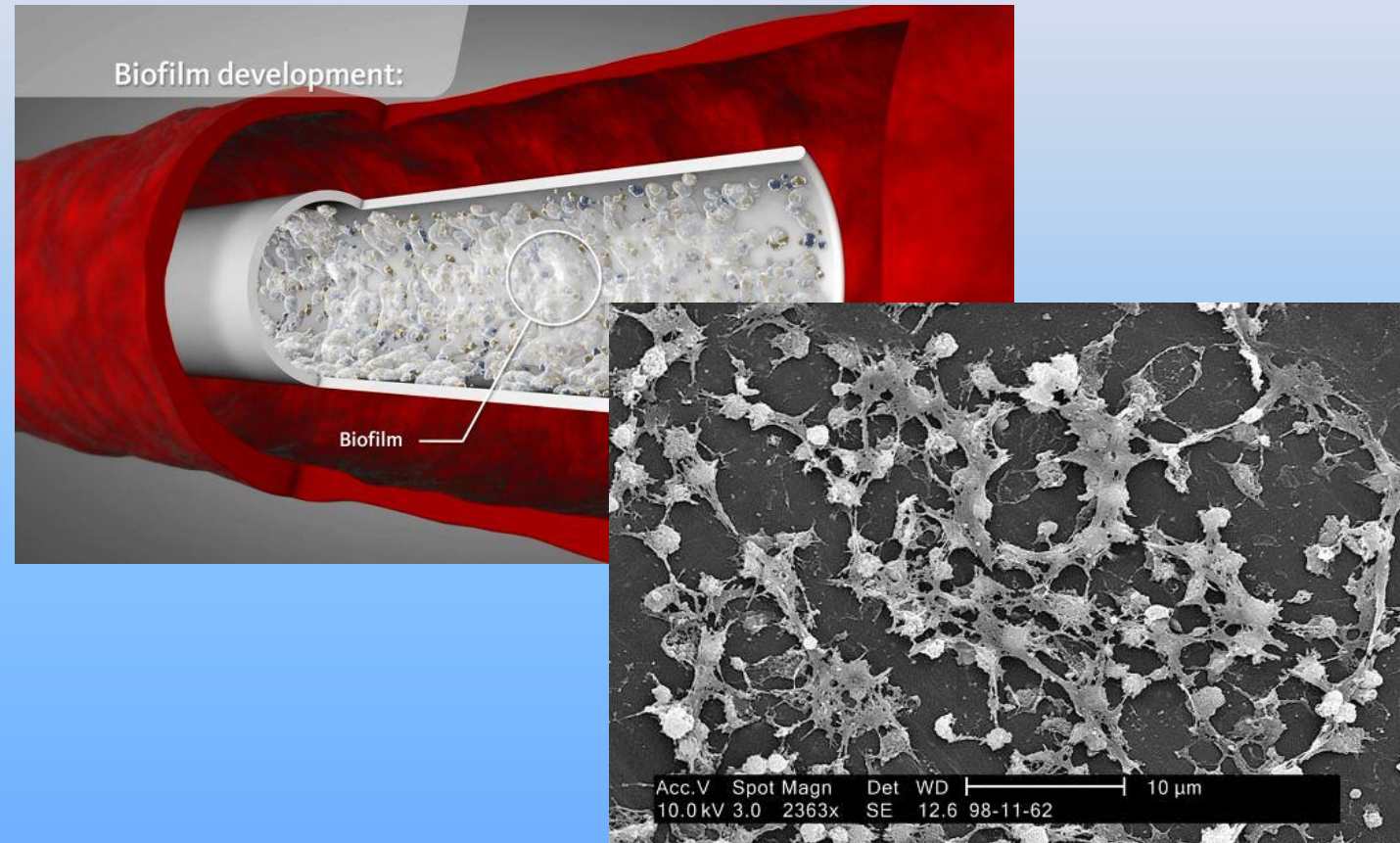
Bacteria have two life-forms during growth and proliferation:

Planctonic

- Metabolic active
- Fast replication

Sessile (Biofilm)

- Reduced metabolism
- Stationäre growth phase



Properties of biofilms

❖ Universalised form of living together of microbes:

- Bacteria and fungi (to share a flat)
- In many cases polymicrobial

❖ Synthesis of a matrix (EPS; polymerised exopolysaccharide):

- Attached (anchored) to viable oder non-viable surfaces
- Integration of components of the host
- Affecting the hosts' immune system
- Tolerance against biocides and environmental stress

❖ Cooperative behaviour of different species/ genus to protect each other:

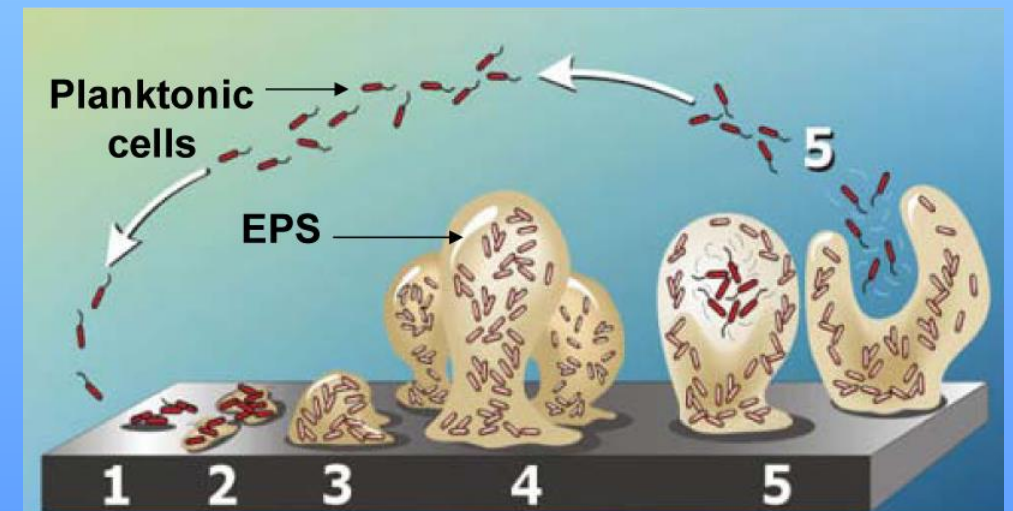
- Secretion of enzymes and biofilm matrix-associated proteins
- Gene transfer/ shift (antibiotic resistance, adhesion....)
- Quorum sensing (cell density regulation)

❖ Partially metabolic inactive resting state:

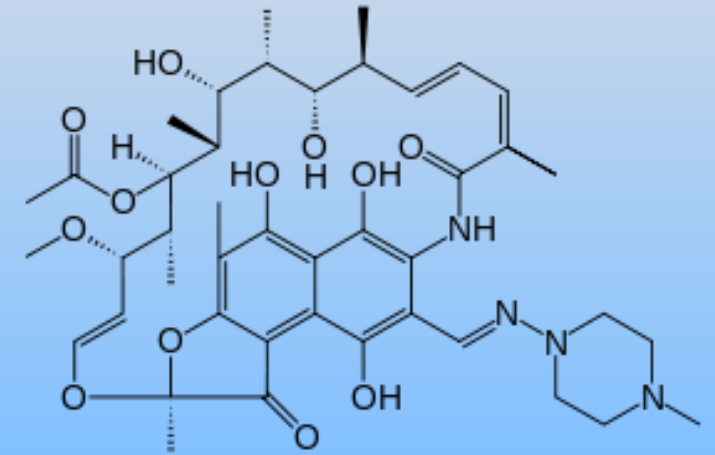
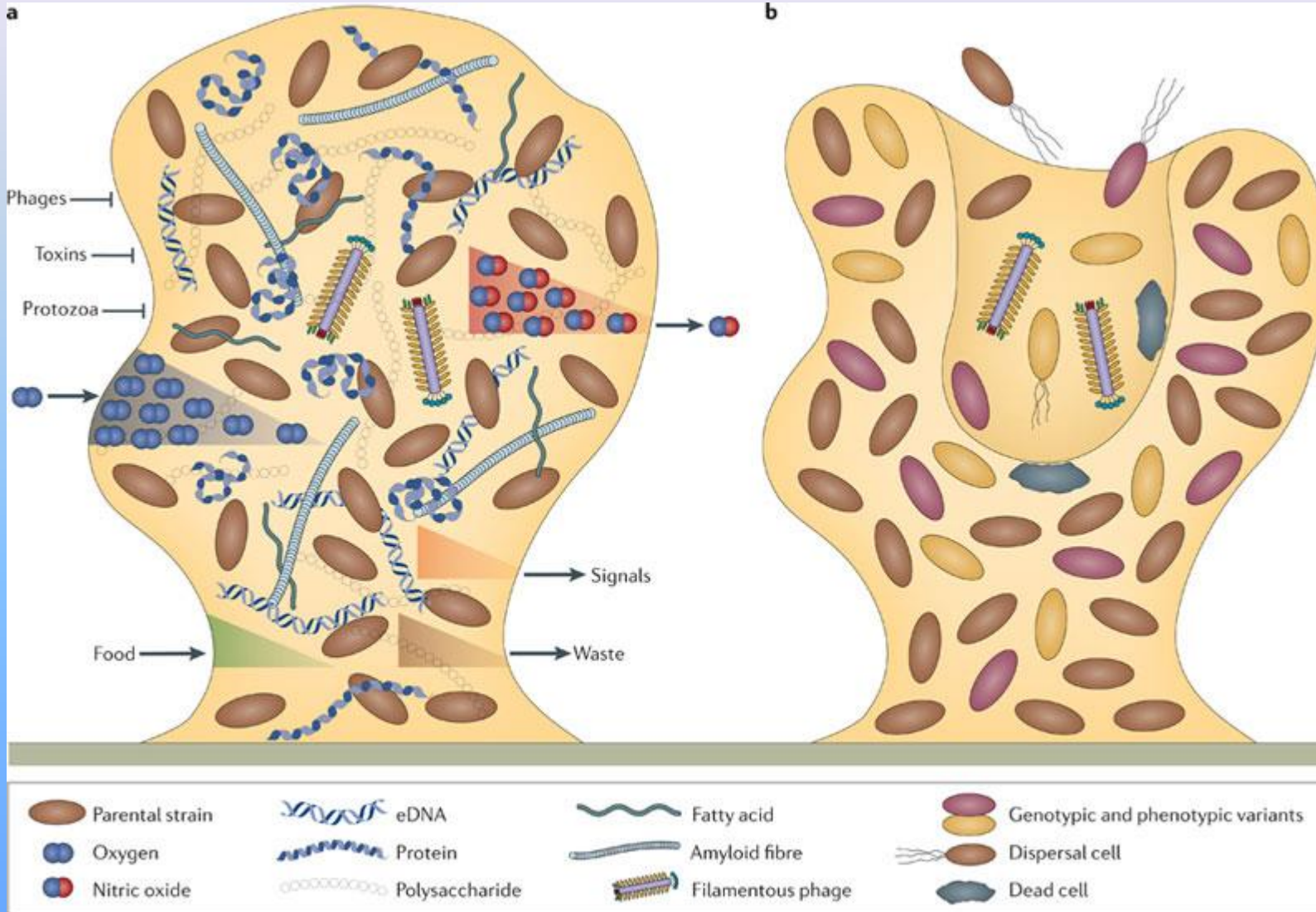
- "Small colony variants"
- VBNC status (viable but not culturable)

❖ Cause of chronic infections:

🔥 Juvenile ??
🔥 Matured ??



Matured biofilms



Challenges

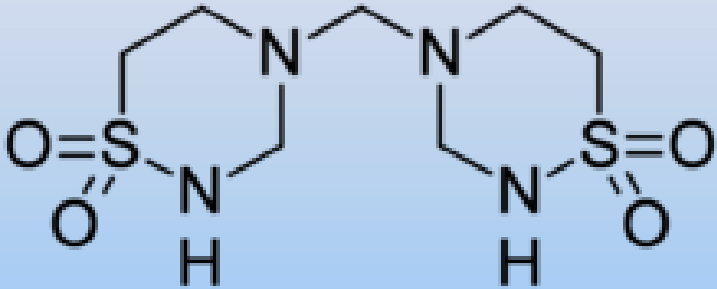
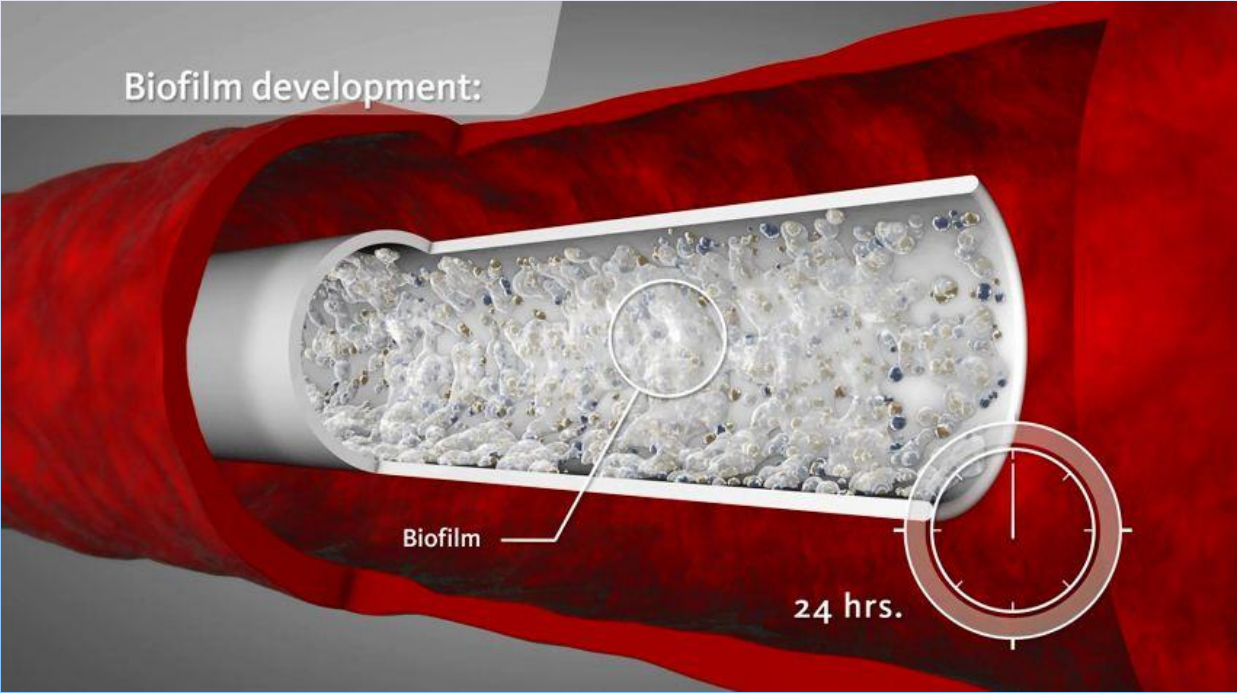
1. Intensive and responsible patient - MD - relationship **????**
2. Hit Hard, Hit Fast, Hit Often
3. Hit Early & Hit Hard and Diversified (using the whole repertoire)
4. Be First ⇒ Prevention



Bull Halsey Jr.

Intention ?????

Prevention



4,4'-Methylenebis (1,2,4-thiadiazinane)-1,1,1',1'-tetraoxide)

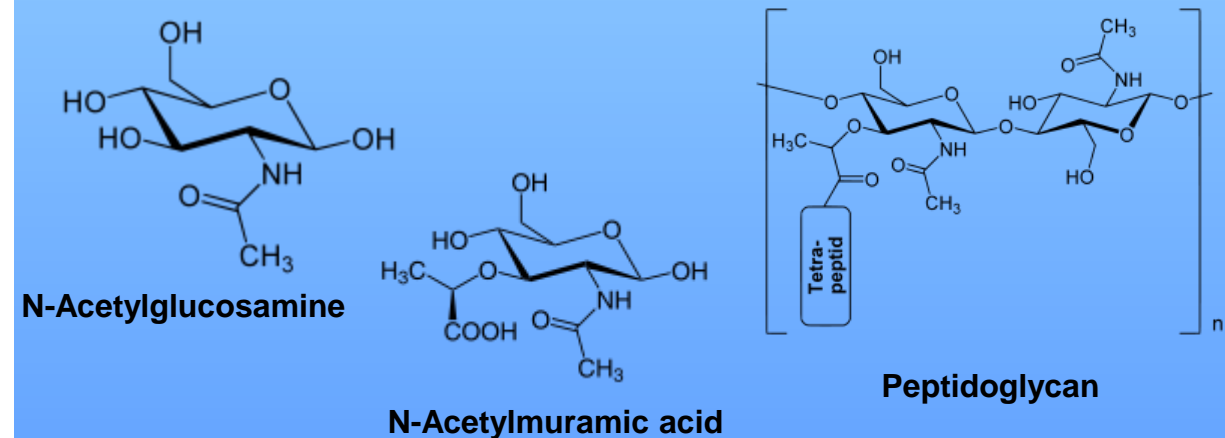
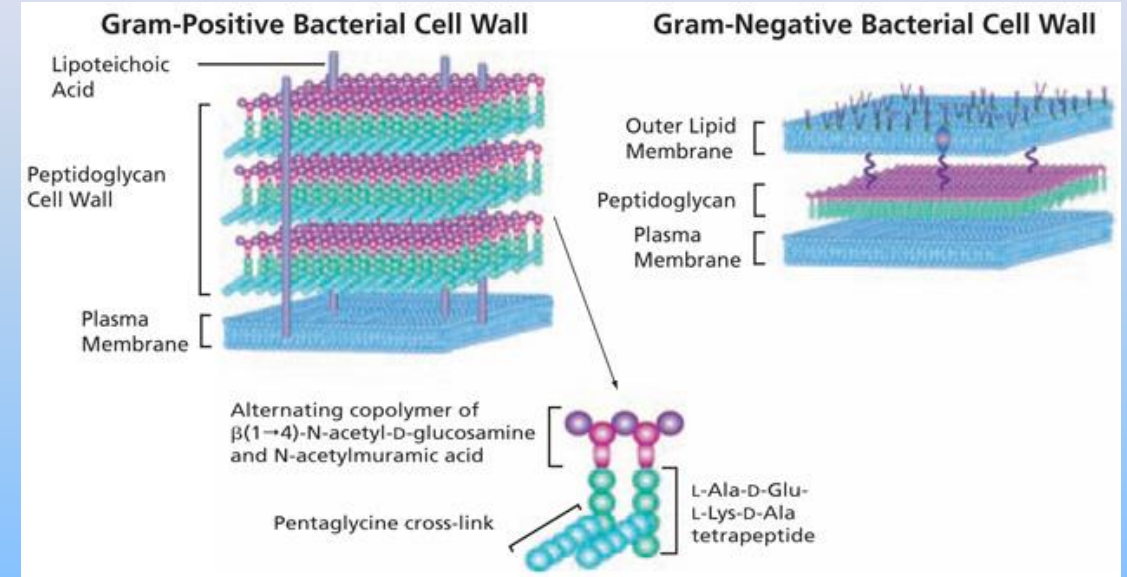
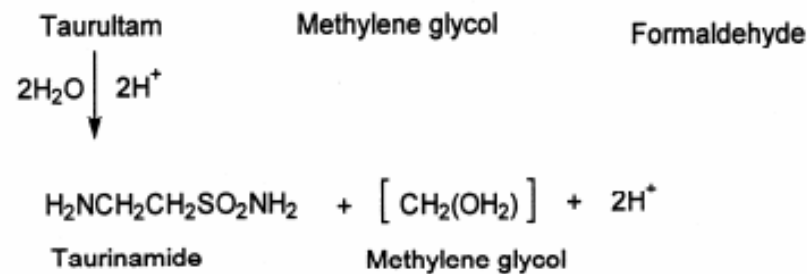
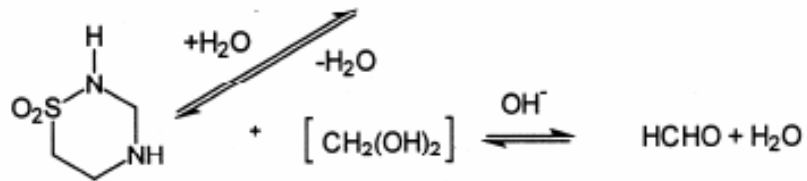
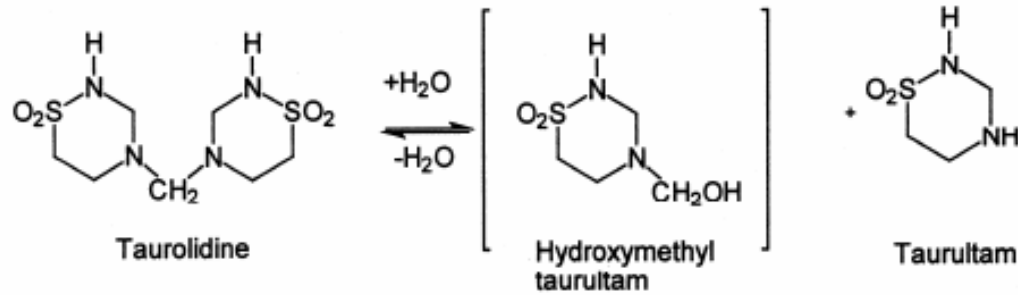


TauroLock™

JPEN J Parenter Enteral Nutr. **1998**;22(4):242-4. Taurolidine 2% as an antimicrobial lock solution for prevention of recurrent catheter-related bloodstream infections. Jurewitsch B, Lee T, Park J, Jeejeebhoy K.

How does it work ?

During the metabolism of taurolidine to taurinamide and ultimately taurine and water, methylol groups are liberated that chemically react with the mureins in the bacterial cell wall and with the amino and hydroxyl groups of endotoxins and exotoxins. This results in denaturing of the complex polysaccharide and lipopolysaccharide components of the bacterial cell wall and of the endotoxin and in the inactivation of susceptible exotoxins.^[3]



What can we do - Strategien ?

1. Einsatz von Defensinen oder Defensin-Analoga (Löcher schlagen!)¹
2. Quorum Sensing Inhibitoren: Bromierte Furanone (Delisea Pulchra)²
3. Biofilm-Inhibition mittels Ellagsäure (Oligophenole) o. Proanthocyanidine (z. B. Corilagin)³
4. Polyvinyl-sulphonat-stabilisierte Ag⁺-Nanopartikel⁴
5. Lineare antimikrobielle Arg-Trp-Peptide (RW)_n-NH₂, n = 2, 3, 4⁵
6. D-Aminosäuren (Biofilm-Disassembly)⁶
7. Antifouling-Beschichtungen⁷

1 Wehkamp J. et al. Dtsch Med Wochenschr. 2006;131:1960.

2 Lönn-Stensrud J. et al. J Antimicrobial Chemoth. 2009;63:309.

3 Hancock V. et al. J Med Microbiol. 2010;59:496.

4 Vasilev K. et al. Nanotechnology. 2010;21:1.

5 Hon S. et al. Appl Environ Microbiol. 2010;76(6):1967.

6 Kolodkin-Gal I. et al. Science. 2010;328(5978).

7 Gasteier, P. et al. Macromol Biosci. 2007;7:1010.

