Silver as a putative health concern

Lotte Jakobsen[1,2], Karen A. Krogfelt[1]

& Niels Frimodt-Møller[1,2]

Statens Serum Institut[1] & Hvidovre Hospital[2]

Hvidovre
Hospital

Use of silver: in and out of medicine

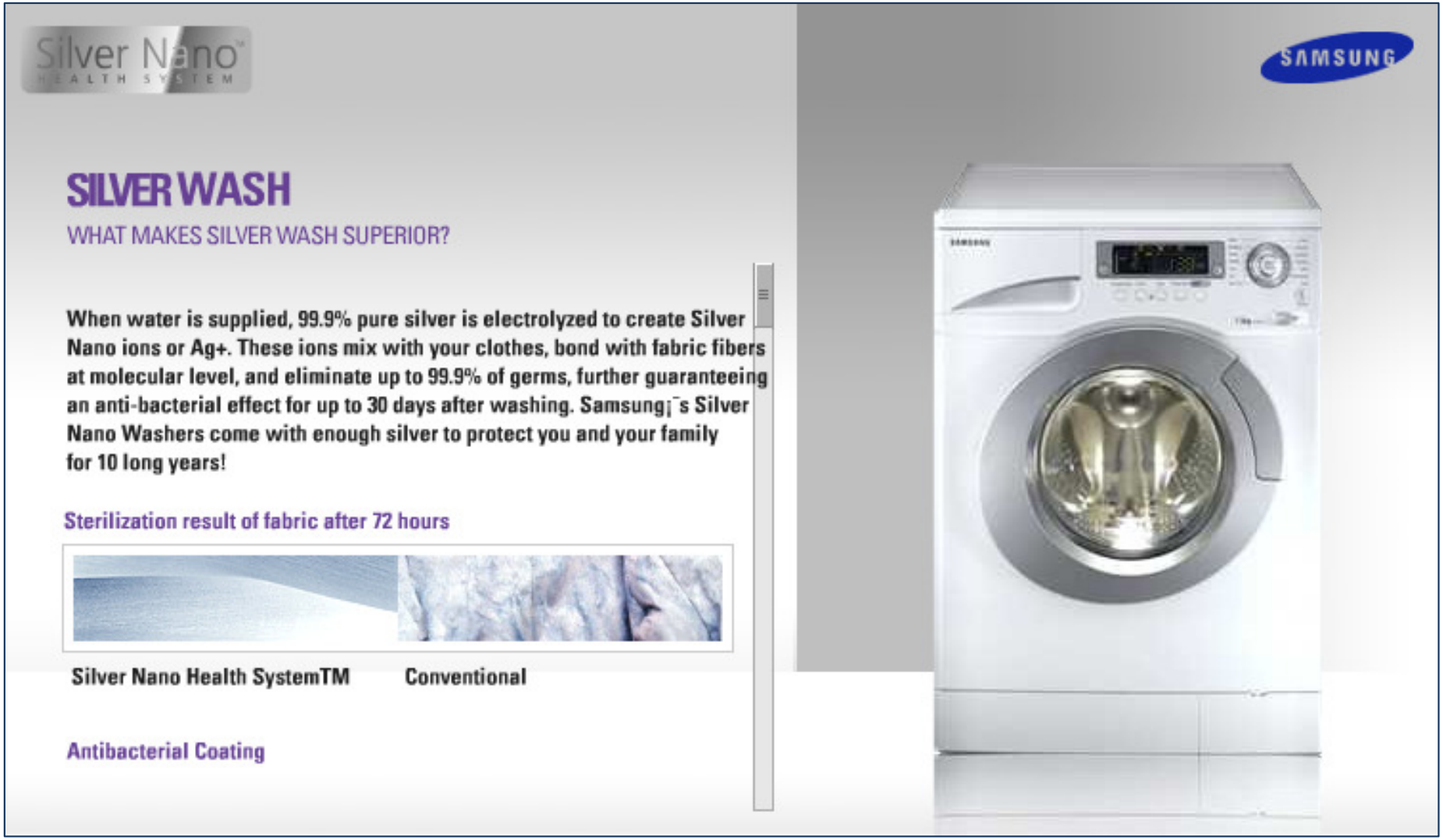
Medical:

- Topical antimicrobial agent in burns
- Topical use for tonsillitis
- Bandages for trauma and diabetic wounds
- Silver coated catheters and medical devices
- Dental silver amalgams
- Arsphenamine – iv treatment for syphilis

Non-medical:

- Desinfect water, e.g. Legionella, anthrax
- Sterilize drinking water, e.g. space shuttles
- Growth promoter i agriculture
- Additive in foods, traditional medicine
- Coating of clothing etc ,e.g. sports fabrics, sleeping bags, socks
- Coating supermarket surfaces for meat storage

Silver as antibacterial in household products



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Traditionally used in clinical settings -> today also outside the clinics!!

Reports of silver resistance

Salmonella typhimurium resistant to silver nitrate, chloramphenicol and ampicillin
Lancet 1975

Silver-resistant Enterobacteriaceae from hospital patients
Can J Microbiol 1979

Instability and linkage of silver-resistance in E. cloacae
J Clin Pathol 1976

Gentamicin- and silver-resistant Pseudomonas
BMJ 1979

Plasmid-determined silver resistance in Ps. stutzeri
J Bacteriol 1984

Plasmid mediated silver resistance in A. baumannii
Biometals 1994

Plasmid mediated resistance to silver ions in E. coli
Indian J Med Res 1985

Modes of resistance

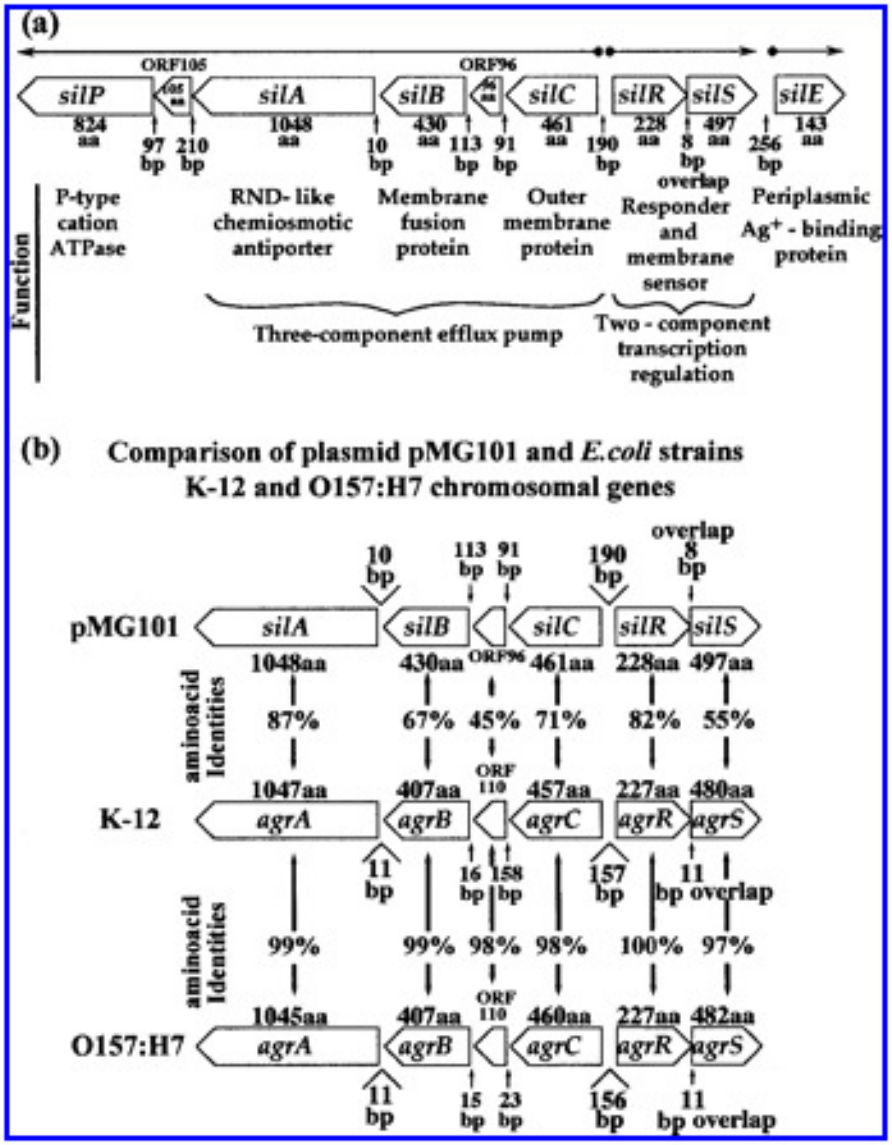
- Efflux mechanisms (encoded by sil genes)
- Silver binding peptides (silE)

Gupta et al, Microbiol 2001

- Peptide-mediated tolerance

Sedlak et al, Appl Environ Microbiol, Epub ahead of print

Diversity of silver resistance genes



Gupta et al. *Microbiology* (2001)

Comparison of the:

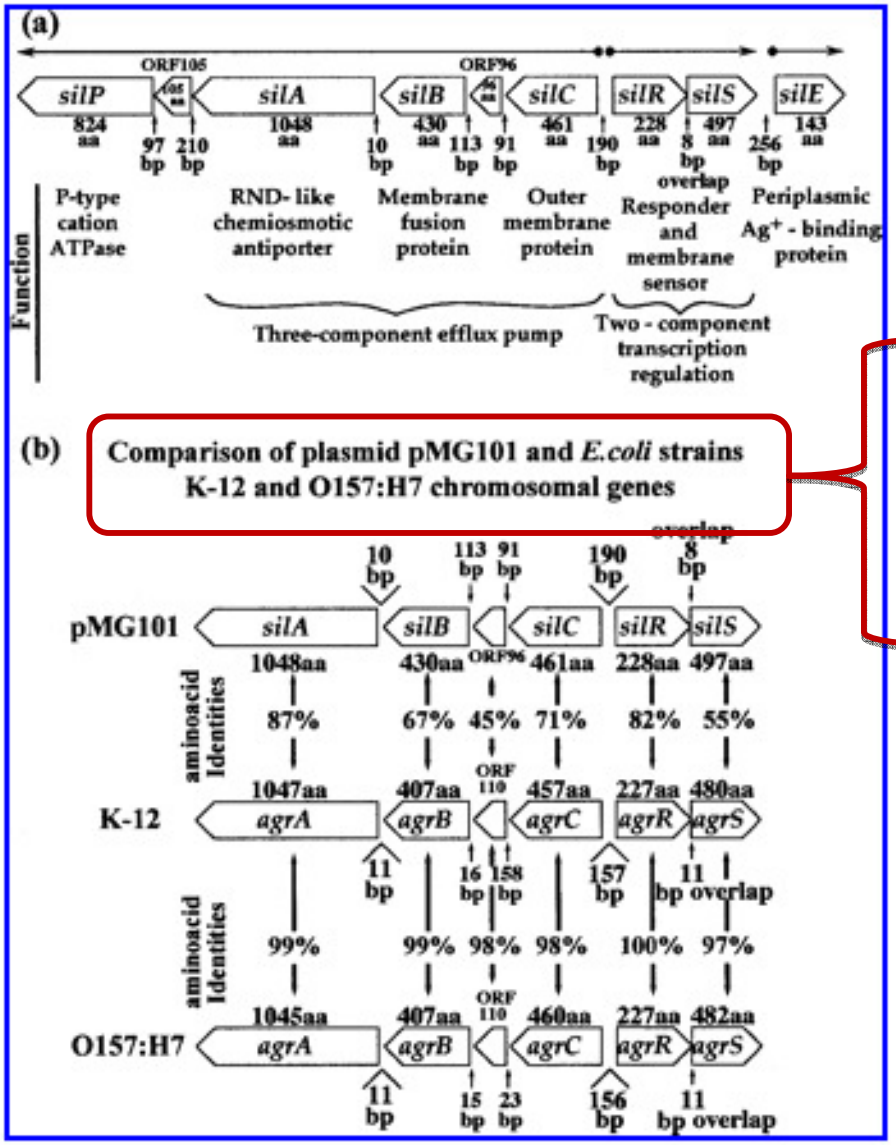
-pMG101 *sil* determinant

-*E. coli* K-12 and O157:H7 *agr* homologues.

-> up to 4% variation

-> wide distribution of homologues

Diversity of silver resistance genes



Located on plasmid->

horizontal gene transfer of silver resistance!

Gupta et al. *Microbiology* (2001)

Development of resistance *in vitro*

Table I. Antimicrobial susceptibility of *S. epidermidis*: MICs and MBCs before and after 20 passages through subinhibitory concentration of the drugs

	MIC (mg/L)		MBC (mg/L)	
Antimicrobial	pre-passage	post-passage	pre-passage	post-passage
MIN[a]	0.078	0.156	100	100
RIF[a,b]	0.02	>500	0.50	>500
RIF[b,c]	0.012	>500	0.05	>500
MIN+RIF[a] (1:1[d])	0.02	0.25	0.05	>100
MIN+RIF[c] (1:1[d])	0.015	0.25	0.05	>100
TC[a]	2.5	20	10	20
CHA[a]	0.5	1	2	4
PCMX[a]	125	125	250	250
PHMB[a]	0.31	0.31	1	1
CHA+TC[a] (3:1[d])	0.125	0.25	2	2
CHA+AgSD[a,c] (3:1[d])	0.5	1	1.25	2.5

MIN, minocycline; RIF, rifampicin; TC, triclosan; CHA, chlorhexidine acetate; PCMX, *p*-chloro-*m*-xylenol; PHMB, polyhexamethylene bis-biguanide; AgSD, silver sulphadiazine.

[a]Tested against ATCC strain.

[b]After 10 passages.

[c]Tested against clinical isolate H.

[d]Ratios based on drug levels in catheters and concentrations are the total of the two drugs combined.

10 passages

Tambe et al. JAC 2001

Ingeniøren

NYHEDER BLOGS DEBAT AVISARKIV KURSUSGU

Forsiden / Nyheder / Biotek / Glansen er ved at gå af nanosølvet

Nyhedsbrev

Tilmeld dig og vind en Nintendo Wii.

E-mail-adresse:

Tilmeld

HVAD MENER DU?

Skal rejsekortet lægges i graven?

- Ja
- Nej
- Ved ikke

Deltag i debatten

Glansen er ved at gå af nanosølvet

Med nanoteknologien fremmarch anvendes sølv i stigende grad i hverdags som bakteriedræbende middel. Men nu slår svenske og amerikanske myn… resistente og skade…

Af Thomas Lemke, freda…

I februar 2006 udsend… Samsung en presseme… vaskemaskine, Silver …

I pressemeddelelsen a… helt nyt og revolutio…

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GUIDE: Find de skæve og fede film på Cph:Dox

MERE END RENT: Vaskepulver er fyldt med hemmelig kemi

Annonce

LAVPRISKALENDEREN:

Fra

København (CPH)

Til

- Vælg destination -

Søg

norwegian.com

Annonce

VIDENSKAB 15. DEC 2006 KL. 06.28

Ingen kender konsekvenserne af nanoteknologi

Der er postet 239 millioner forskningskroner i nanoteknologi i år. Men ingen ved, om den nye tids teknologi giver kræft, hjerte-kar-sygdomme eller ødelægger miljøet.

Ingeniøren

Nyheder Blogs Debat

Opposition kræver indgreb mod sølvpa…

Det offentlige skal købe så få produkter med sølvioner so…

Af Mette Holt, onsdag 28. mar 2007 kl. 00:00

En række partier vil sætte en stopper for at benytte sølvpartikler til at dræbe bakterier i plastre, vaskemaskiner og sportstøj til at dræbe bakterier..

De reagerer på, at Ingeniøren i sidste uge skrev om svenske forskningsresultater, der viser, at brugen af sølvpartikler gør bakterierne resistente over… lungebetændelse, halsbetændelse og gonoré, ikke kan nedkæmpes.

Susceptibility to silver nitrate in common human pathogens in Denmark

S. aureus (bacteremia):

MSSA, 1972-2007	N = 130
MRSA, 2001-06	N = 70
(Various mec-types)	
Total	N = 200
E. coli	
Human bacteraemia	N = 34
Human UTI	N = 34
Human volunteers	N = 34
Chicken	N = 34
Chicken meat	N = 34
Pigs	N = 34
Pork	N = 34
Total	N = 238

For each group, strains were chosen to vary in antibiotic susceptibility, from no - to multiple-resistant

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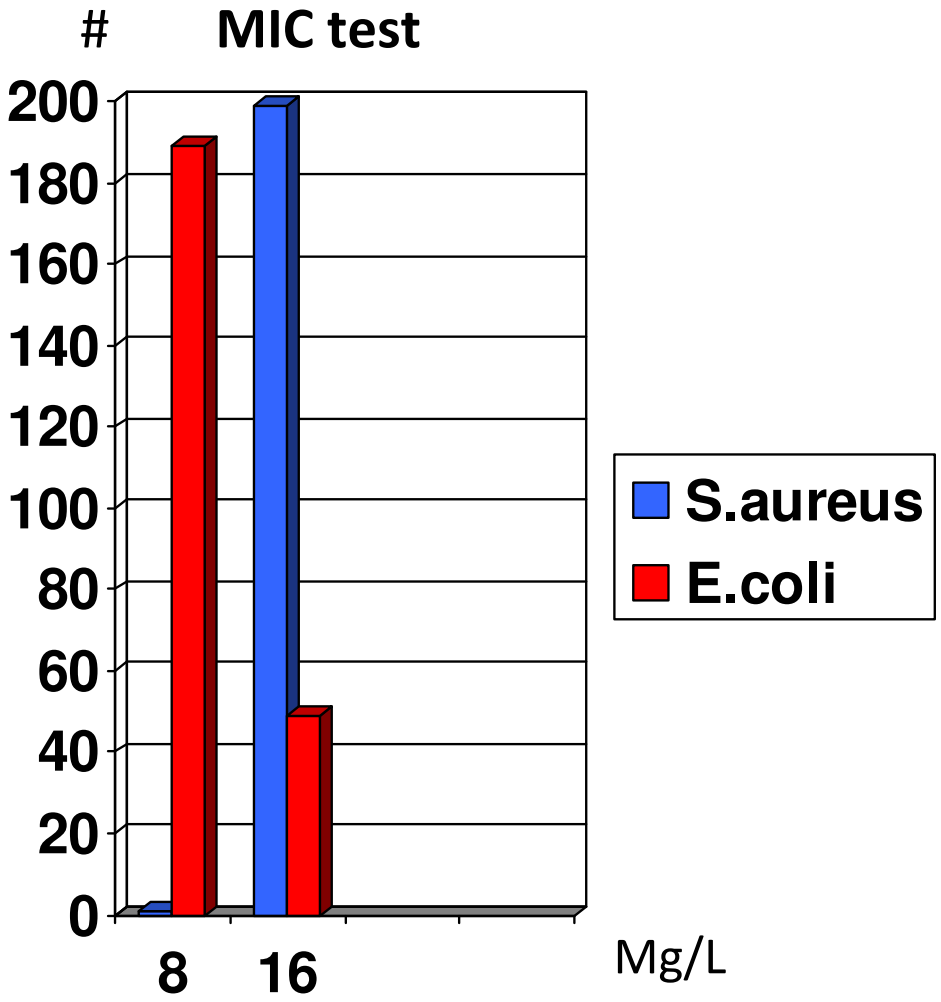
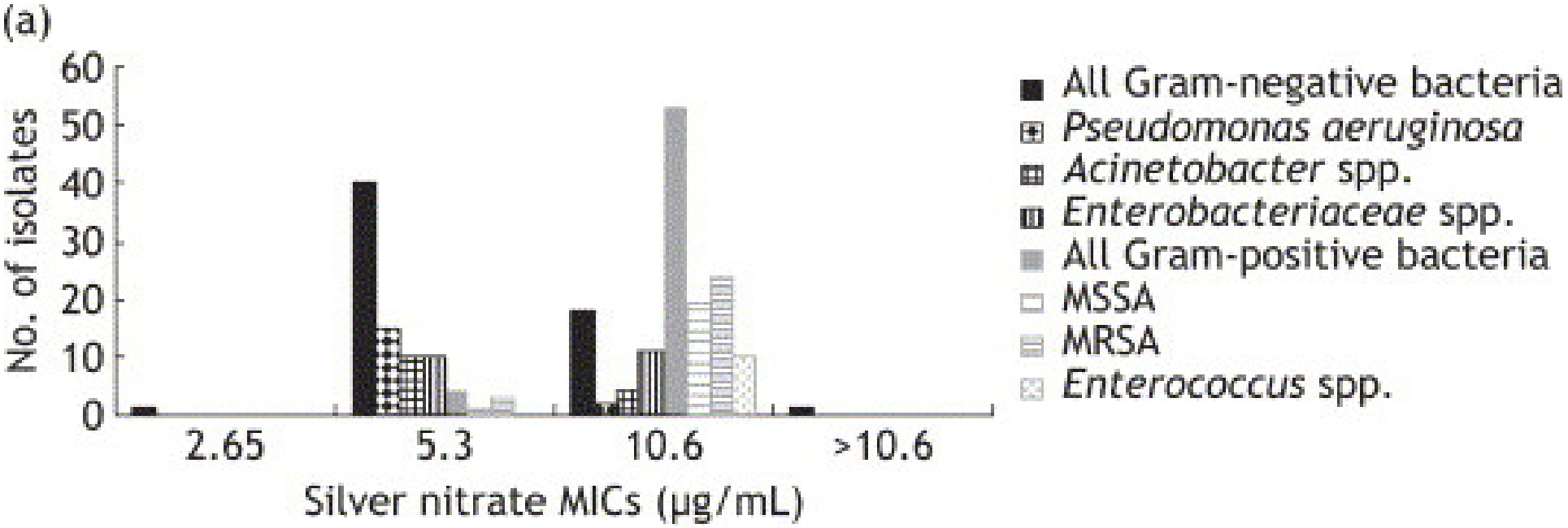


Control silver-nitrate resistant isolates from Åsa Melhus, MIC ≥ 128 mg/L

Prevalence of resistance to silver in a Burns unit



117 bacterial non-duplicate clinical isolates from 71 patients :

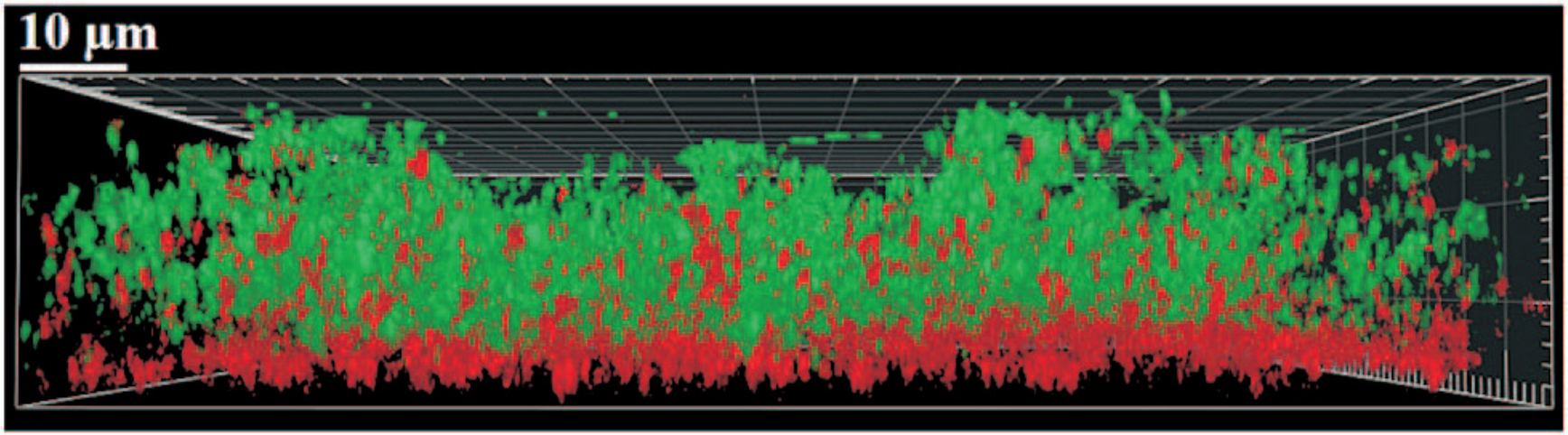
Only one isolate, an *Enterobacter cloacae*, was resistant with an MIC of silver of >5440 µg/mL.

Ip et al, J Hosp Infect 2006

Silver-palladium surfaces inhibit biofilm formation

Or do they?

In the case of a high load of a silver resistant E. coli J53 pMG101 biofilm occured upon a layer of surface-associated dead bacteria



Chiang et al, Appl Environ Microbiol 2009

Live bacterial cells

Dead bacterial cells

Cross-resistance

Silver resistant mutant of E. coli selected after stepwise exposure to silver nitrate or silver sulfadiazine
-> low-level cross-resistance to cephalosporins and HgCl2

TABLE 1. MICs of heavy metal compounds and antibiotics for Ag-susceptible and Ag-resistant strains[a]

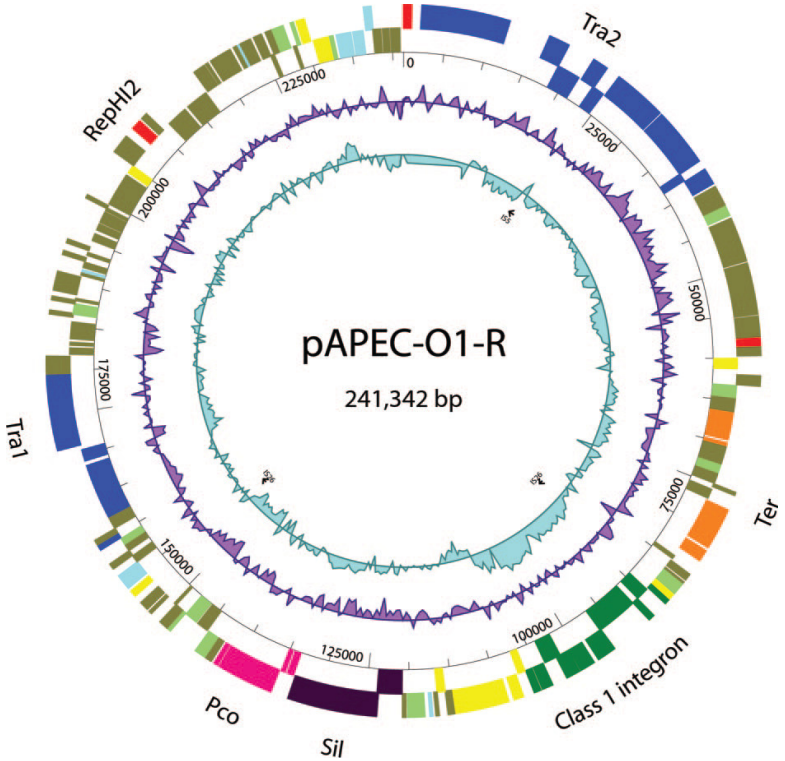
Strain	MIC (μg/ml)								
	$AgNO_3$[b]	AgSD[c]	$HgCl_2$	Cephaloridine	Cephalothin	Cefepime	Cefpirom	Tetracycline	Chloramphenicol
116	8 (16)	16	1.4	4	8	0.03	0.06	0.8	5
116$AgNO_3$R	>1,024 (64)	>1,024	6.4	16	32	0.13	0.25	0.8	6
496	8 (16)	16	1.4	4	8	0.06	0.06	1.0	4
496$AgNO_3$R	>1,024 (64)	1,024	6.4	8	32	0.13	0.13	1.3	5
496AgSDR	>1,024 (64)	>1,024	12.8	16	32	0.13	0.13	1.0	5
B1	8 (16)	16	1.4	16	32	0.13	0.13	0.6	3
B1$AgNO_3$R	>1,024 (64)	>1,024	2.8	128	64	1.00	1.00	1.0	5
B1AgSD	>1,024 (64)	>1,024	1.4	256	64	0.50	1.00	1.0	2

[a] MICs of $CoSO_4$ (440 μg/ml), $CrCl_3$ (1,335 μg/ml), and $CuSO_4$ (1,250 μg/ml) were identical for all strains, except for B1$AgNO_3$R, which showed a twofold higher value. MICs of $MnSO_4$ (1,690 μg/ml) and $ZnCl_2$ (170 μg/ml) were also identical for all strains, except that of $MnSO_4$ for B1AgSDR (211 μg/ml) and that of $ZnCl_2$ for 496 (340 μg/ml). The MIC of Na_2HAsO_4 was identical (500 μg/ml) for the two strains tested, 116 and 116$AgNO_3$R.
[b] The values in parentheses are the MICs determined in LB broth without NaCl.
[c] MICs of this compound were unchanged, in every case, in LB broth without NaCl.

Li et al, J Bacteriol 1997

IncHI2 plasmid from extraintestinal pathogenic *E. coli*

Genes	Phenotype
terY3Y2XY1W, terZABCDEF	Potassium tellurite
silESRCBAP	Silver nitrate
pcoEABCDRSE	Copper sulfate
aadA	Streptomycin
aac3-VI	Gentamicin
tetAR	Tetracycline
qacE 1	Benzylkonium chloride
SulI	Sulfisoxazole



Co-resistance

Johnson et al, Antimicrobial Chemother 2006

Characteristics of silver resistance isolates

Table III. *Characteristic of strains with phenotypic and/or genetic resistance to silver in the study*

Strain	Silver-resistance genes *Sil*E	*Sil*P	*Sil*S	No. of passages[a]	Other properties
E. cloacae SM0700965 II	+	+	+	NA Stable	Cefotaxime I
E. cloacae S4279/06	+	+	+	2 Stable	D mutant Carbapenems R[b]
E. cloacae S0707396	+	–	+	3 Stable	D mutant Colistin R
E. coli B0709322	–	–	–	5 Unstable	
E. coli S0506373	–	–	–	8 Stable	ESBL positive
K. pneumoniae B0716185	+	+	+	NI	
K. pneumoniae CCUG 54718	+	+	+	2 Stable	ESBL positive, outbreak strain
P. aeruginosa AI2884	+	–	+	NI	

[a]For induction of silver-resistance and its stability.
[b]After silver exposure.
NA: not applicable; NI: no induction; D: derepressed, ESBL: extended spectrum beta-lactamase; I: indeterminate; R: resistant.

Sütterlin et al, Acta Derm Venereol 2012

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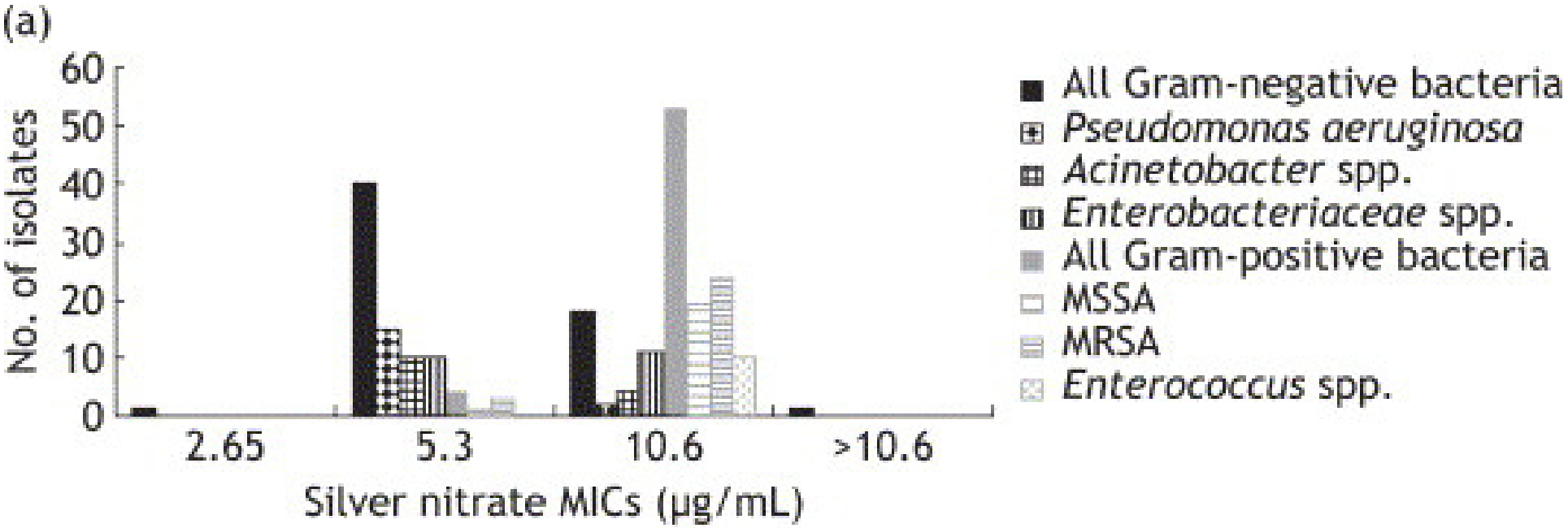
← Cross-resistance

← Silver R after 2 x exposure

Sütterlin et al, Acta Derm Venereol 2012

The prevalence of resistance to silver in a Burns unit



117 bacterial non-duplicate clinical isolates from 71 patients

Only one isolate, an *Enterobacter cloacae*, was resistant (MIC >5440 µg/mL)

-> extended-spectrum beta-lactamase (ESBL) producer, and was multi-drug resistant (only susceptible to imipenem)

Ip et al, J Hosp Infect 2006

Silver resistance linked to E. coli ST131

ST131: associated with the CTX-M-15 extended-spectrum beta-lactamase, has emerged internationally as a multidrug-resistant pathogen causing serious infections

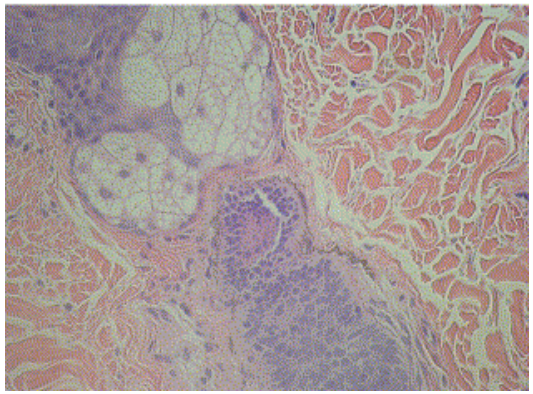
Plasmid: a hybrid between a ST131 plasmid and a Klebsiella pneumonia plasmid

Plasmid was associated with a major nosocomial outbreak

Resistance to b-lactams, aminoglycosides, tetracyclines, trimethoprim, sulphonamides, macrolides, silver, copper and arsenic.

Sandegren et al, J Antimicrobial Chemother 2012

Argyria induced by silver



Argyria – deposit of silver in tissues e.g. skin

53-year old man in good general health

8-month progressive gray hyperpigmentation

Denied using any prescription medications

Induced by silver-containing dietary supplement

Bowden et al, J Cutan Pathol 2011

Tonsillitis - silver nitrate is used topically: Cumulative dosage needed to produce argyria ~ 6 g

Syphilis – silver arsphenamine is used IV: Argyria becomes clinically apparent after the exposure to 8 doses ~ a total dose of silver of 1.84 g

Silver: conclusions

- Resistance occur in human pathogenic bacteria
- Cross- and co-resistance have been shown:
  - > selection by other antimicrobials likely
- At the moment, prevalence of silver resistance is low
- Silver – a health concern??
  - Increase awareness -> i.e. monitoring of resistance (and consumption) needed to avoid future spread

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- Bo Jørgensen, Bispebjerg Hospital

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