
USE OF GERMICIDES IN HOME AND HEALTHCARE SETTINGS: IS THERE A RELATIONSHIP BETWEEN GERMICIDE USE AND ANTIMICROBIAL RESISTANCE

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Disclosures: Consultant to Germitec, PDI, Merck, Pfizer

Thanks to Dr. William Rutala for slides

USES OF GERMICIDES: OVERWHELMING EVIDENCE OF EFFICACY

- Water purification (chlorine compounds)
- Sterilization of critical medical equipment
- High-level disinfection of semicritical medical equipment
- Hand hygiene
- Skin antisepsis

BACKGROUND

DISINFECTANT RESISTANCE: IS THERE A RELATONSHIP BETWEEN USE AND ANTIMICROBIAL RESISTANCE

- Antibiotic use and overuse is the main driving force of antibiotic resistance
- Does the use of disinfectants/antiseptics result in antiseptic and/or disinfectant resistance?
- Do antibiotic resistant bacteria exhibit altered susceptibility to disinfectants/antiseptics?
- Do disinfectants/antiseptics precipitate antibiotic resistance?

CLASSIFICATION OF GERMICIDES

- Antisepsis (antiseptics = germicides used on skin or mucous membranes)
 - Hand hygiene
 - Skin antisepsis (e.g., surgical site preparation, IV site)
 - Patient treatment (bathing) to reduce HAIs in ICU
 - Surgical scrub of HCP
- Disinfection and Sterilization (Spaulding) (disinfectants = germicides used on equipment or inanimate environment)
 - Critical items (sterile tissue): Sterilants
 - Semi-critical items (mucous membranes): High-level disinfectants
 - Non-critical items (intact skin): Low-level disinfectants

ANTISEPTIC AGENTS

- Alcohols

- Usual use concentrations: 70-90%

- Chlorhexidine gluconate

- Usual use concentrations: Oral rinse, 0.12% (1,200 mg/L), 2% (20,000 mg/L), 4% (40,000 mg/L)

- Iodine and iodophors

- Parachlorometaxlenol (PSMX)

- Hexachlorophene

- Benzalkonium chloride

- Triclosan

CHEMICAL STERILANTS & HIGH-LEVEL DISINFECTANTS

- Peracetic acid plus hydrogen peroxide
- Glutaraldehyde
- Hydrogen peroxide
- Ortho-phthalaldehyde
- Peracetic acid
- Improved hydrogen peroxide

DISINFECTANTS: LOW-LEVEL

- Quaternary ammonium compounds
- Hypochlorites
- Phenolics
- Alcohol: Ethyl or isopropyl (70-90%)
- Improved hydrogen peroxide
- Hydrogen peroxide plus peracetic acid

CHARACTERIZING "RESISTANCE"

● Assessment

- Phenotypic: Growth patterns when exposed to antimicrobial
- Genotypic: Presence and/or expression of genes

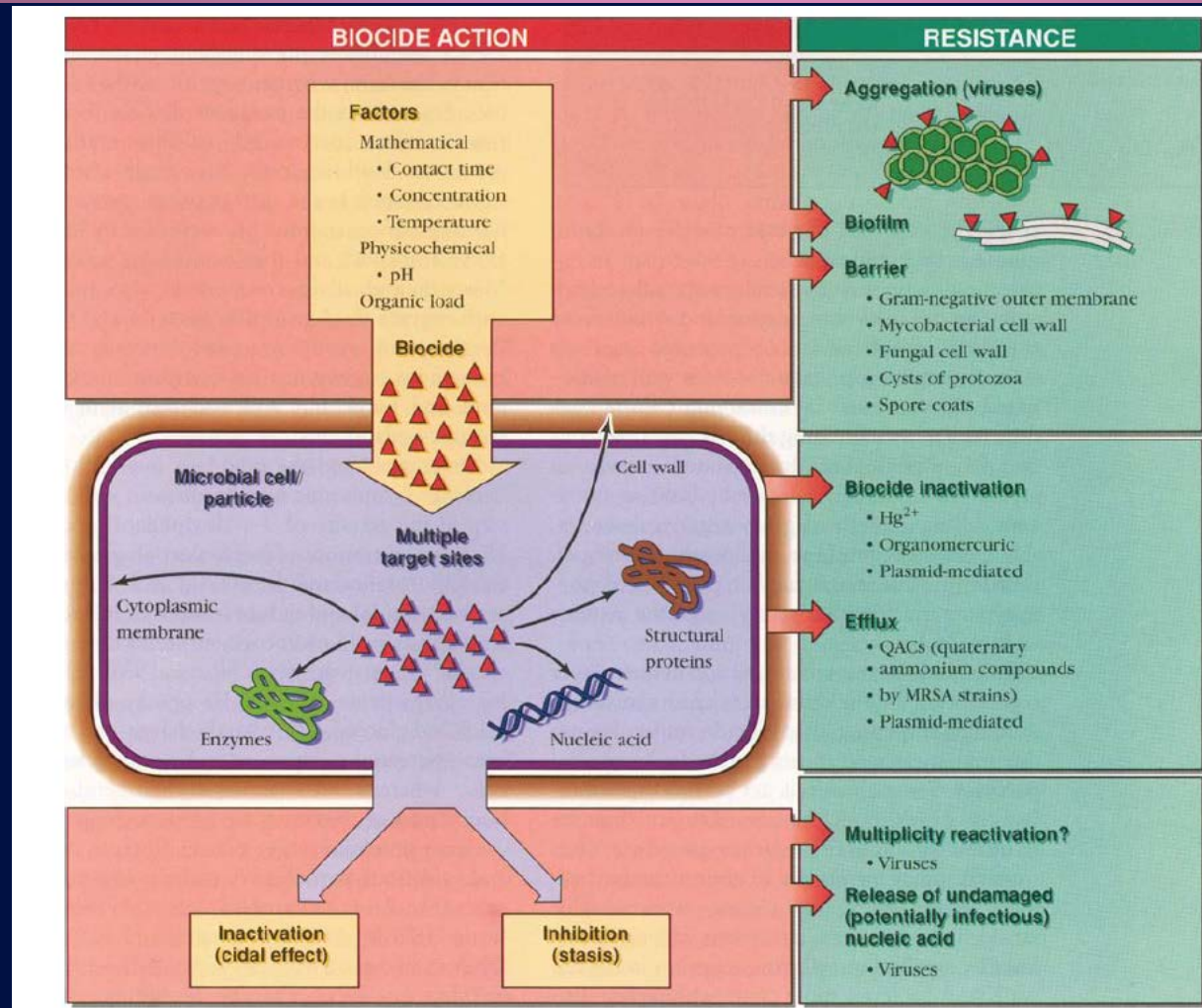
● Origin

- Intrinsic: Inherent in the pathogen (e.g., impermeability; spores, cell wall - efflux);
- Acquired: Acquisition of a genetic elements that results in "resistance" (e.g., altered target site, enzymatic inactivation, efflux, overproduction of target)

● Mechanism(s)

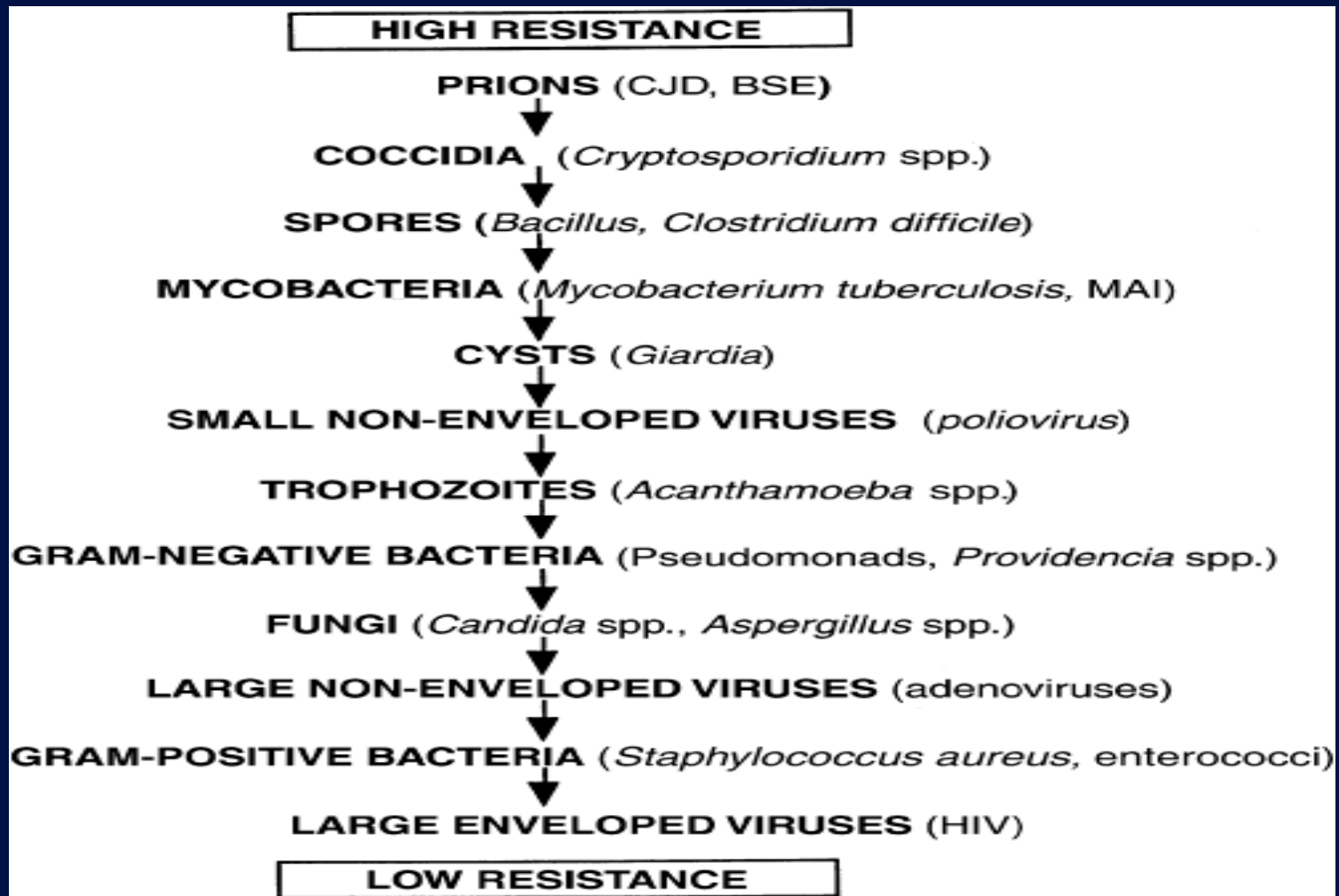
- Altered target site, enzymatic inactivation, efflux, overproduction of target, absence of enzyme/metabolic pathway)

MICROBIAL RESISTANCE TO BIOCIDES



Expert Report
 Comprehensive
 Rev Food Sci Food
 Safety
 2006;5:71

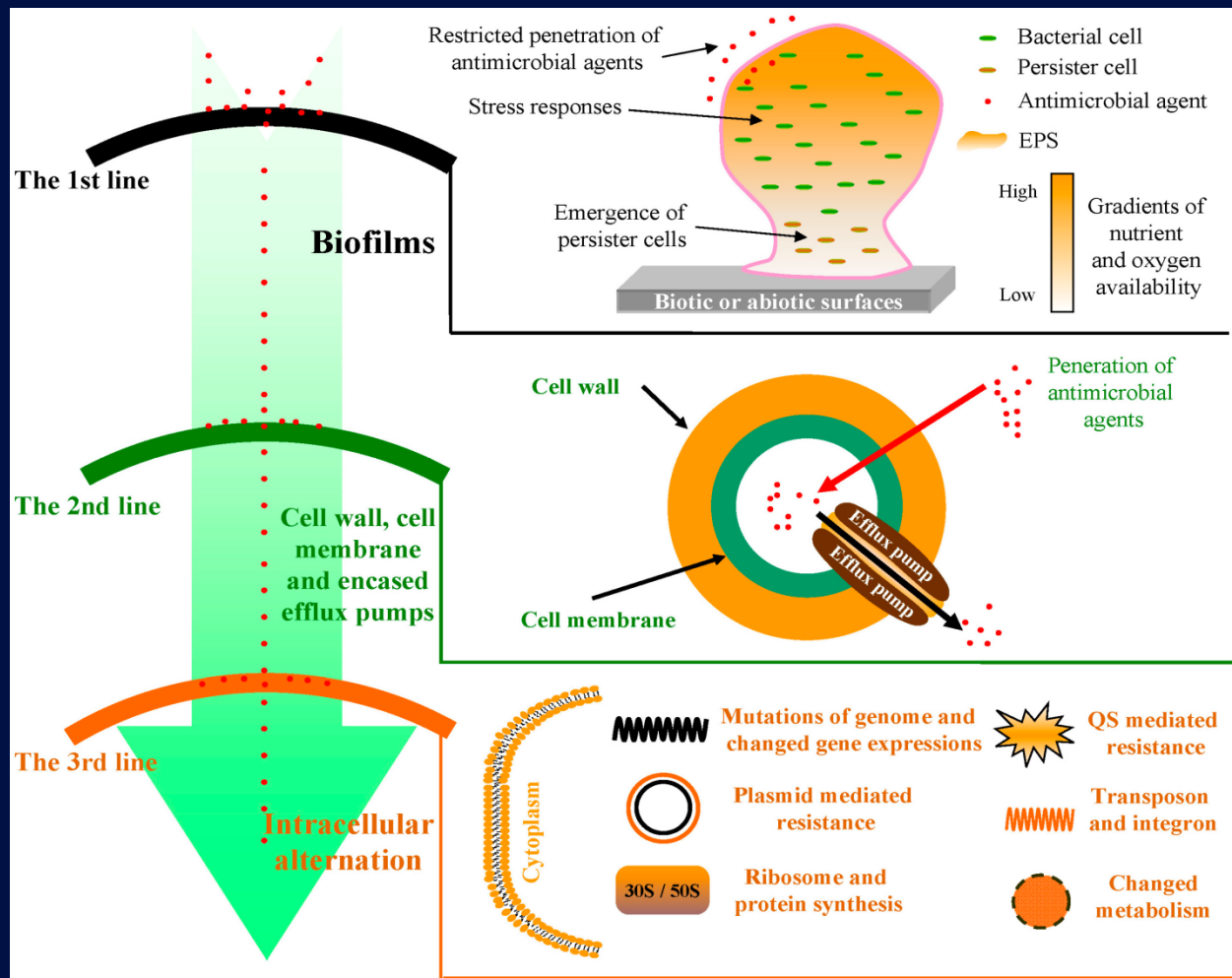
INTRINSIC RESISTANCE



COMMON REASONS FOR BIOCIDES FAILURE

- Use of an inappropriate product (i.e., pathogens if intrinsically resistant)
- Application of the product improperly (i.e., incorrect duration, concentration, pH, temperature)
- Failure to remove inorganic debris (i.e., improper cleaning) prior to disinfection
- Insufficient contact of the disinfectant with the surface to be treated
- Insufficient availability of active product

MICROBIAL RESISTANCE TO ANTIBIOTICS



Zhou G, et al
 Int J Mol Sci
 2015;16:21711-21733

SIMILARITIES AND DIFFERENCES BETWEEN ANTIBIOTIC AND BIOCIDES RESISTANCE

● Similarities

- Intrinsic (e.g., spores resistant to alcohols) and extrinsic resistance (e.g., efflux pumps for heavy metals) well described
- Similar mechanisms of resistance (e.g., impermeability, efflux pumps)
- Biofilms impair inactivation/killing
- Inactivation dependent of concentration and duration of contact

● Differences

- Most antibiotics inhibit a specific target in a biosynthetic process
- Most biocides have multiple concentration-dependent targets, with subtle effects occurring at low concentration and more damaging ones at higher concentrations

DEFINITIONS:

ANTIMICROBIAL RESISTANCE

- Antibiotic resistance
 - Objective is to predict clinical outcome (i.e., success or failure) of treatment
 - Measured *in vitro* by determining the MIC (minimum inhibitory concentration). Resistant strains are not inhibited by the usual achievable systemic concentrations of the agents.
 - NCCLS 2002 (now CLSI): The implication of the “susceptible” category implies that an infection due to the strain may be appropriately treated with the dosage of the antimicrobial agent recommended for the type of infection and infecting species.

QUATERNARY AMMONIUM BIOCIDES

- Resistance mechanism = Qac A/B gene
 - May be plasmid or chromosomal mediated
 - Found in *S. aureus* (MSSA, MRSA); detection rate has varied from <2% (US) to >80% (Asia)
 - Also found in Gram negative bacilli
 - Level of resistance conferred is below use concentrations of CHG and Quats
- Cross-resistance between CHG and Quats, and antimicrobials not convincingly demonstrated (some studies have shown a correlation between qac A/B presence and increased frequency of antimicrobial resistance)
- Gerba: “Nonspecific action of Quats makes the development of resistance unlikely; multi-target nature of Quats means that mutation within a single target unlikely to result in treatment failure.

QUESTION 1

Does the use of disinfectants/antiseptics result in disinfectant/antiseptic resistance?

LAB DEVELOPED STRAINS WITH REDUCED SUSCEPTIBILITY TO GERMICIDE THAT DEMONSTRATED DECREASED SUSCEPTIBILITY TO ANTIBIOTICS

Bacteria (gene)	Germicide	Decreased Susceptibility	Reference
<i>E. coli</i> (Mar)	Pine oil	Amp, Tet, Chloro*	Moken 1997
<i>P. stutzeri</i>	Chlorhexidine	Triclosan, Polymyxin B [^] , Gent*, Erythro [^] , Amp [^]	Russell 1998
MRSA	Benzalkonium chloride	Ox, Amp, Cefazolin, Oflox, Tet, Kana, Chloro	Akimitsu 1999
<i>P. aeruginosa</i> (NfxB)	Triclosan	Tet*, Cipro, Trimeth [^] , Erythro [^] , Gent	Chaunchuen 2001

* Clinically significant based on NCCLS, [^] No standard

**Clinically relevant resistance was only occasionally demonstrated and involved antibiotics of limited current use (e.g., chloramphenicol resistance in *E. coli*).
Multidrug resistance was not demonstrated.**

LAB DEVELOPED STRAINS WITH REDUCED SUSCEPTIBILITY TO GERMICIDE THAT DEMONSTRATED DECREASED SUSCEPTIBILITY TO ANTIBIOTICS

Bacteria (gene)	Germicide	Ab Resistance	Reference
<i>P. stutzeri</i>	Chlorhexidine	Triclosan, Gent*, Rif^, Erythro^, Amp^	Tattawasart 1999
<i>P. aeruginosa</i>	Chlorhexidine	Triclosan, Gent, Rif, Erythro, Amp	Tattawasart 1999
<i>M. smegmatis</i> (InhA)	Triclosan	INH	McMurray 1999

* Clinically significant based on NCCLS, ^ No standard

**Clinically relevant resistance was only occasionally demonstrated and involved antibiotics of limited current use (e.g., gentamicin resistance to *P. stutzeri*).
Multidrug resistance not demonstrated.**

DOES HOME USE OF GERMICIDES LEAD TO ANTIBIOTIC RESISTANT PATHOGENS IN THE ENVIRONMENT

- Aim: To describe the relationship between antibiotic resistance in environmental isolates relative to the use of germicides
- Methods: Bacterial isolated collected from homes of 30 users and non-users of germicides (Quats, triclosan, PCMX, pine oil)
- Results: In general isolates from the homes of germicide users were not more antibiotic resistant

Table 4 Comparative antibiotic resistance in target bacterial isolates from clinical samples in user homes and nonuser homes according to standard susceptibility test panels

	Nonuser resistant/ total isolates	User resistant/ total isolates
Gram-positive cocci		
<i>Enterococcus</i> sp.*	3/4 (75.0%)	4/4 (100.0%)
<i>Staphylococcus aureus</i> †	3/3 (100.0%)	4/4 (100.0%)
<i>Staphylococcus</i> sp.‡	32/45 (71.1%)	40/52 (76.9%)
Viridans <i>Streptococcus</i> §	2/32 (6.3%)	7/36 (19.4%)
Gram-negative rods		
<i>Pseudomonas aeruginosa</i> *	3/3 (100.0%)	0/0 NA
Other <i>Enterobacteriaceae</i> ‡	11/13 (84.6%)	1/1 (100.0%)

*Resistance to 1–2 antibiotics.

†Resistance to 2 antibiotics.

‡Resistance to 1–5 antibiotics.

§Resistance to 1–3 antibiotics.

DEVELOPMENT OF DISINFECTANT TOLERANCE IN THE LABORATORY

- Possible to develop mutants with reduced susceptibility to disinfectants and antiseptics that demonstrate decreased susceptibility or resistance to antibiotics.
- As the concentration of disinfectants used in practice greatly exceed the MICs observed, the clinical relevance is questionable
- Clinically relevant resistance was only occasionally demonstrated and involved antibiotics of limited current use (e.g., chloramphenicol resistance in *E. coli*)

LINK BETWEEN GERMICIDE AND ANTIBIOTIC RESISTANCE IN LABORATORY STRAINS

- Some strains show decreased susceptibility to both germicides (CHG, QUAT) and antibiotics (tetracycline).
- To date no evidence that using antiseptics or disinfectants selects for antibiotic-resistant organisms or that mutants survive in nature
- Germicides should only be used where there are scientific studies demonstrating benefit

QUESTION 1

Does the use of disinfectants/antiseptics result in disinfectant/antiseptic resistance?

No clinically significant resistance!

QUESTION 2

Do antibiotic resistant bacteria exhibit altered susceptibility to disinfectants/antiseptics?

Summary of published studies illustrating similar effectiveness of routine disinfectants against antibiotic-susceptible and antibiotic-resistant hospital micro-organisms

Authors	Year	Study	Finding
Rutala <i>et al.</i> ⁷¹	1997	Susceptibility of antibiotic-susceptible and antibiotic-resistant hospital bacteria to disinfectants	Examples of antibiotic-susceptible and antibiotic-resistant <i>Staphylococcus aureus</i> , enterococci and <i>Pseudomonas aeruginosa</i> had similar susceptibilities to phenolic and quaternary ammonium compounds
Sakagami and Kajimura ³⁵	2002	Bactericidal activities of disinfectants against vancomycin-resistant enterococci	No differences in bactericidal time for activity against VRE vs vancomycin-susceptible enterococci. VRE strains demonstrating slightly reduced susceptibility to germicides were readily inactivated at concentrations of germicides used in hospitals
Rutala <i>et al.</i> ⁷²	2006	Bacterial contamination of keyboards: efficacy and functional impact of disinfectants	Disinfectants containing alcohol, chlorine, phenol or quaternary ammonium were effective at removing MRSA, <i>P. aeruginosa</i> and VRE on contaminated computer keyboards. Excellent sustained activity of quaternary ammonium-containing products against VRE and <i>P. aeruginosa</i> for up to 48 h
Wisplinghoff <i>et al.</i> ⁷³	2007	Resistance to disinfectants in epidemiologically defined clinical isolates of <i>Acinetobacter baumannii</i>	Susceptibility of different strains of <i>A. baumannii</i> to disinfectants; 10 outbreak-related strains highly resistant to multiple antibiotics vs 10 sporadic multi-susceptible isolates. No significant differences between different disinfectants for both outbreak-related and sporadic <i>A. baumannii</i>
Koo <i>et al.</i> ⁴⁹	2012	Multidrug-resistant NDM-1 <i>Klebsiella</i> outbreak and infection control in endoscopic urology	Routine disinfection methods were effective to control outbreaks of highly resistant organisms such as NDM-1 <i>Klebsiella</i> spp.
Robustillo Rodela <i>et al.</i> ⁷⁴	2012	Emergence and outbreak of carbapenamase-producing KPC-3 <i>Klebsiella pneumoniae</i> in Spain, September 2009 to February 2012: control measures	Routine disinfectants were effective against highly resistant carbapenamase-producing <i>K. pneumoniae</i> isolates
Campos <i>et al.</i> ⁷⁵	2012	Isolation, molecular characteristics and disinfection of methicillin-resistant <i>Staphylococcus aureus</i> from ICU units in Brazil	Study of <i>S. aureus</i> isolates in two Brazilian ICUs: 36% were resistant to oxacillin; all tested disinfectants were effective against <i>S. aureus</i> isolates; no difference in resistance to disinfectants was found between MRSA and methicillin-susceptible <i>S. aureus</i>

VRE, vancomycin-resistant enterococci; MRSA, methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit.

ASSESSMENT OF GERMICIDE SUSCEPTIBILITY FOR VRE VS VSE

- Aim: To assess the susceptibility of VRE and VSE to hospital disinfectants
- Design: Microbial suspension tests with Quat, phenolic or iodophor
- Results: No difference in germicide susceptibility noted for VRE and VSE

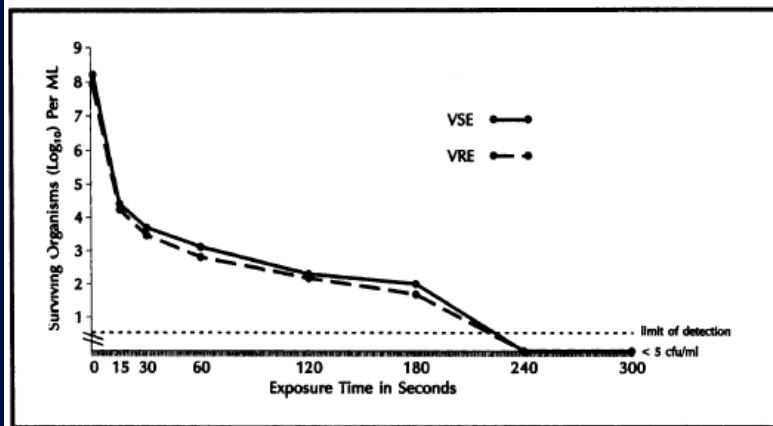


FIGURE 1. Survival of vancomycin-resistant enterococci and vancomycin-sensitive enterococci in a 1:35 further dilution of the Hi-Tor use-dilution over 5 minutes of sampling.

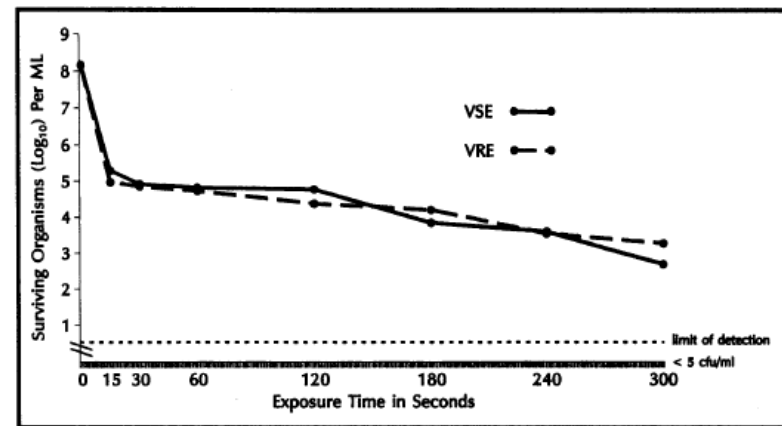


FIGURE 2. Survival of vancomycin-resistant enterococci and vancomycin-sensitive enterococci in a 1:64 further dilution of the Hi-Tor use-dilution over 5 minutes of sampling.

SUSCEPTIBILITY OF ANTIBIOTIC RESISTANT PATHOGENS OF GERMICIDES

No relationship between antibiotic resistance and disinfectant resistance

SUSCEPTIBILITY OF ANTIBIOTIC-RESISTANT AND ANTIBIOTIC-SUSCEPTIBLE BACTERIA TO A PHENOLIC AND QUATERNARY AMMONIUM DISINFECTANT

Bacteria		Number of Positive Penicylinders per 60 Replicates at Manufacturers' Use-Dilution and 2× Use-Dilution			
		Phenolic		Quaternary Ammonium	
		1:256	1:128	1:64	1:32
<i>Staphylococcus aureus</i>	Susceptible	2	0	5	1
	Resistant	0	0	4	1
<i>Staphylococcus epidermidis</i>	Susceptible	10*	3	3	1
	Resistant	2	1	5	0
<i>Escherichia coli</i>	Susceptible	3 [†]	3 [†]	23 [‡]	14 [‡]
	Resistant	4	3	4	1
<i>Klebsiella pneumoniae</i>	Susceptible	1 [†]	2 [†]	0*	2
	Resistant	3	1	6	2
<i>Pseudomonas aeruginosa</i>	Susceptible	2	0	10	6
	Resistant	4	5	7 [†]	4 [†]
<i>Enterococcus</i> species	Resistant	4	1	2	3
<i>Salmonella choleraesuis</i>	Susceptible	0	0	0	1

* $P < .05$, comparing susceptible versus resistant strains for each disinfectant at same concentration.

[†]Number of positive penicylinders per 90 replicates.

[‡] $P < .001$, comparing susceptible versus resistant strain for each disinfectant at same concentration.

SUSCEPTIBILITY OF ANTIBIOTIC RESISTANT PATHOGENS OF GERMICIDES

Antibiotic resistance does not correlate to increased resistance to disinfectants

TABLE 2
DISINFECTANT ACTIVITY AGAINST ANTIBIOTIC-SUSCEPTIBLE AND ANTIBIOTIC-RESISTANT BACTERIA

Product	Log ₁₀ Reductions							
	VSE		VRE		MSSA		MRSA	
	0.5 min	5 min	0.5 min	5 min	0.5 min	5 min	0.5 min	5 min
Vesphene IIse	>4.3	>4.3	>4.8	>4.8	>5.1	>5.1	>4.6	>4.6
Clorox	>5.4	>5.4	>4.9	>4.9	>5.0	>5.0	>4.6	>4.6
Lysol Disinfectant	>4.3	>4.3	>4.8	>4.8	>5.1	>5.1	>4.6	>4.6
Lysol Antibacterial	>5.5	>5.5	>5.5	>5.5	>5.1	>5.1	>4.6	>4.6
Vinegar	0.1	5.3	1.0	3.7	+1.1	+0.9	+0.6	2.3

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S aureus*; VRE, vancomycin-resistant *Enterococcus*; VSE, vancomycin-susceptible *Enterococcus*. Data represent mean of two trials (n=2). Values preceded by ">" represent the limit of detection of the assay. Assays were conducted at a temperature of 20°C and a relative humidity of 45%. Results were calculated as the log of Nd/No, where Nd is the titer of bacteria surviving after exposure and No is the titer of the control.

QUESTION 2

Do antibiotic resistant bacteria exhibit altered susceptibility to disinfectants/antiseptics?

No clinically significant resistance (reduced susceptibility)!

QUESTION 3

What about the susceptibility of antibiotic-resistant organisms to disinfectants at very low concentrations?

SUSCEPTIBILITY OF ANTIBIOTIC-RESISTANT AND SUSCEPTIBLE BACTERIA TO GERMICIDES

	Effect of Antibiotic Resistance on Germicide Susceptibility			
Bacteria	None	Reduced Suscep	Resistant	Reference
MRSA	Phenol, chlorhexidine	QACs	None	Al-Masaudi 1988
MRSA	---	QACs	None	Al-Masaudi 1991
VRE	Chlorine, alcohol, glutaraldehyde	None	None	Bradley 1996
VRE	Phenol, QAC, iodophor	None	None	Anderson 1997
MRSA, VRE	Phenol, QAC	None	None	Rutala 1997
GNR	---	CHG	None	Koljalg 2002
VRE	Aldehydes, alcohols, iodines, biguanide group	None	None	Sakagami 2002

CHG, chlorhexidine; QAC, quaternary ammonium compound; MRSA, methicillin-resistant *S. aureus*; VRE, vancomycin resistant enterococcus

PLASMA-MEDIATED RESISTANCE TO GERMICIDES IN STAPHYLOCOCCI

Biocide	MSSA (ppm)	MRSA (ppm)	Reference
BAK	<1	6	Townsend 1983
Cetrimide	1.5	2.5-5	Al-Masaudi 1991
CHG	0.9	4.2	Brumfit 1985
Cresol	750	1250	Al-Masaudi 1991

CLINICAL IMPACT OF MUPIROCIN AND CHG "RESISTANCE"

- Aim: To assess whether failure of decolonization related to low-level mupirocin resistance plus genotypic CHG resistance (qacA/B gene detection by PCR)
- Design: Nested case-control study
- Results: Presence of combined mupirocin and CHG resistance a predictive factor for failure of decolonization therapy (intranasal mupirocin plus CHG baths)
- Limitation: CHG susceptibility not determined

Table 4. Independent Risk Factors Associated With Failure of Decolonization-Multivariate Analysis

Risk factor	Adjusted OR (95% CI)	<i>P</i>
Combined mupirocin and chlorhexidine resistance	3.4 (1.5–7.8)	.004
Age (per 1-year increment)	1.04 (1.02–1.1)	.001
Prior hospitalization (previous 2 years)	2.4 (1.1–5.7)	.04
Wound or pressure sore	5.7 (1.8–17.6)	.003
Exposure to MRSA-inactive antibiotic	3.1 (1.3–7.2)	.01
Central venous catheterization	5.7 (1.4–23.9)	.02

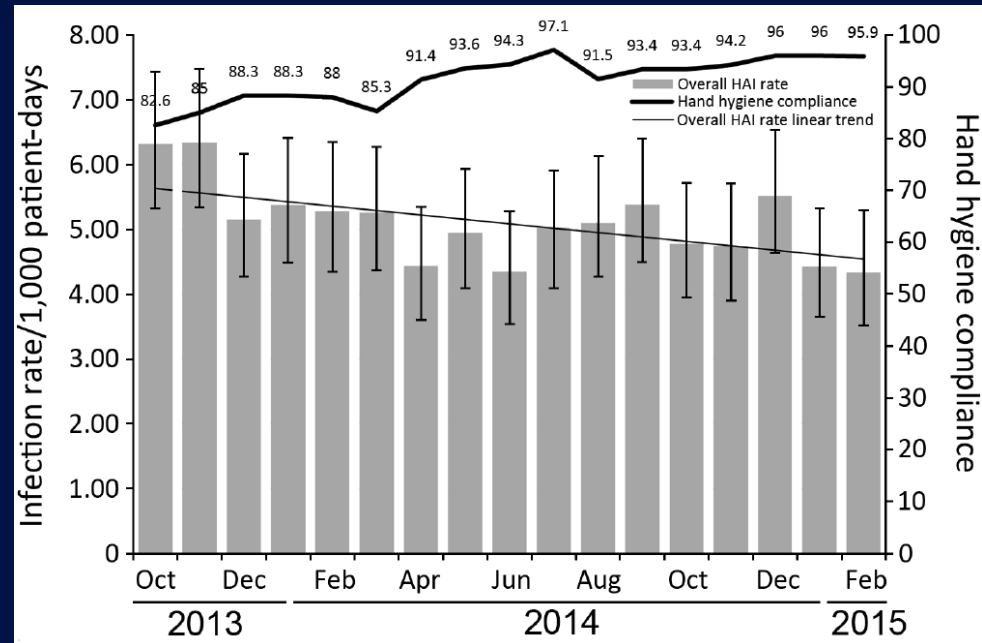
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No clinically significant resistance (reduced susceptibility)!

USES OF GERMICIDES: OVERWHELMING EVIDENCE OF EFFICACY

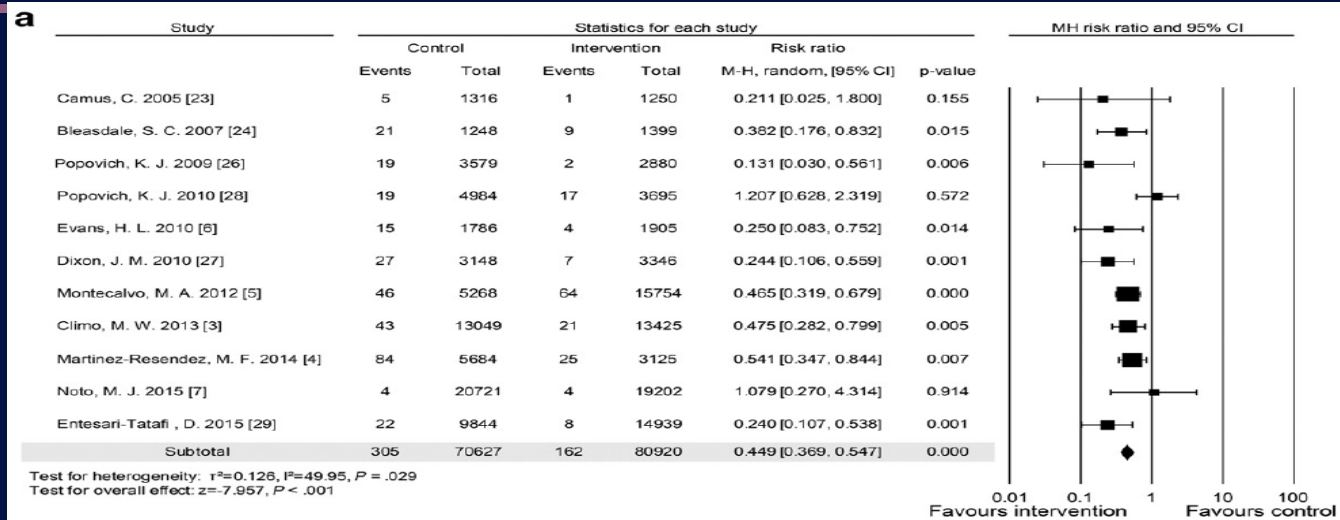
- Water purification (chlorine compounds)
- Hand hygiene
- Sterilization of critical medical equipment
- High-level disinfection of semicritical medical equipment
- Low-level disinfection of environmental surfaces
- Skin antisepsis: CHG treatment {bathing} of ICU patients, prior to surgery or insertion of indwelling medical devices



Sickbert-Bennett EE, et al.

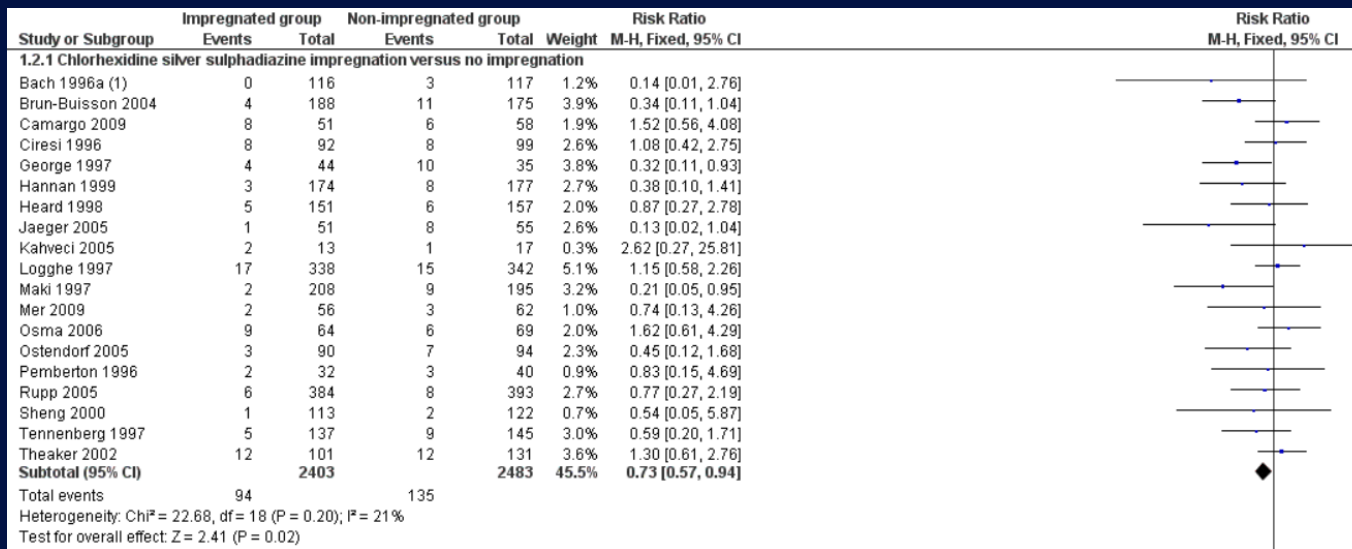
Emerging Infect Dis 2016;22:1628-1630

BENEFITS OF GERMICIDES: REDUCTION IN HAIs (meta-analyses)



55% reduction in CLABSI with CHG treatment

Kim HY, et al.
J Crit Care
2016;32:126-137



37% reduction in CLABSI with impregnated central lines, silver-sulfadiazine

Lai NM, et al. Cochrane Database Syst Rev. 2016 Mar 16;3:CD007878.

Disinfectants Resistance: Is There a Relationship Between Use and Resistance

Antibiotic use and overuse is the main driving force of antibiotic resistance

- Does the use of disinfectants/antiseptics result in disinfectant and/or antiseptic resistance? **No**
- Do antibiotic resistant bacteria exhibit altered susceptibility to disinfectants/antiseptics? **No**
- Do disinfectants and/or antiseptics precipitate antibiotic resistance? **No**
- Does the use of germicides decrease human disease? **Yes**

Conclusion

- Benefit of continued use of antiseptics and disinfectants, benefits overwhelming superior to risks

THANK YOU!!

