

Disinfectants Resistance: Is There a Relationship Between Use and Resistance

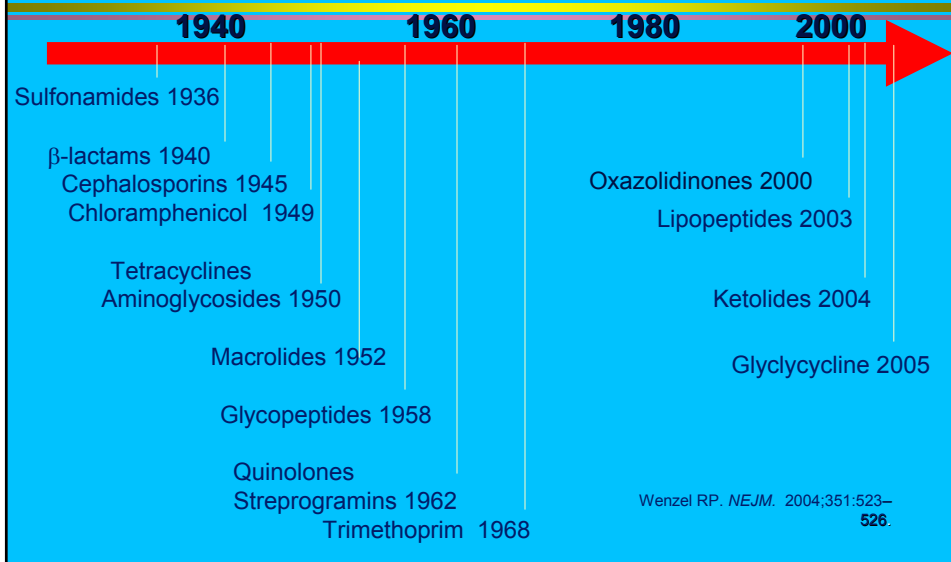
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Disinfectants Resistance: Is There a Relationship Between Use and Resistance

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

ANTIBIOTIC RESISTANCE

Introduction of New Classes of Antibiotics



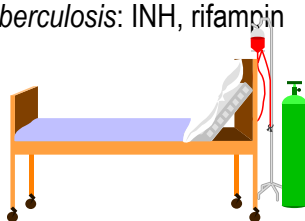
EMERGING RESISTANT PATHOGENS: COMMUNITY

- HIV: Multiple antivirals
- *Staphylococcus aureus*: Multiple drugs (including oxacillin)
- Group A streptococcus: Macrolides, tetracyclines
- *Neisseria gonorrhoeae*: Penicillin, tetracycline, quinolones
- *Salmonella typhimurium* (DT104): Multidrug (amp-, TMP-SMX, +/-quinolones)
- *Mycobacterium tuberculosis*: Multiple drugs (including INH, rifampin)
- *Plasmodium falciparum*: Multiple drugs (including chloroquine, mefloquine)

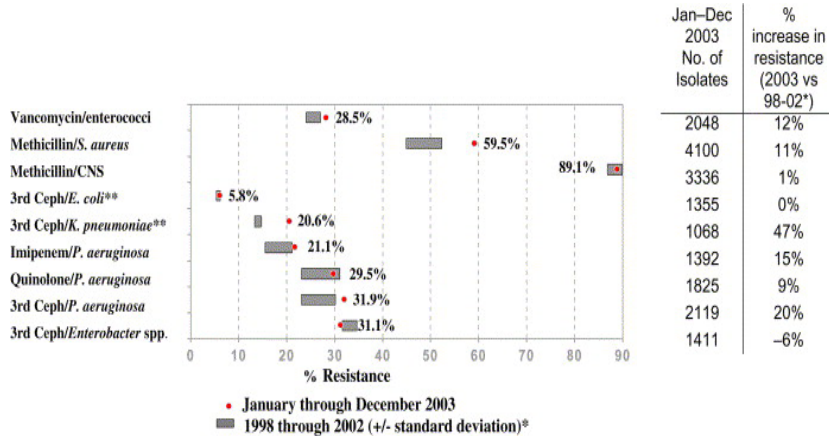


EMERGING RESISTANT PATHOGENS: HEALTH CARE FACILITIES

- *Staphylococcus aureus*: Oxacillin, vancomycin, linezolid
- *Enterococcus*: Penicillin, aminoglycosides, vancomycin, linezolid, dalfopristin-quinupristin
- *Enterobacteriaceae*: ESBL producers, carbapenems
- *Candida spp.*: Fluconazole
- *Mycobacterium tuberculosis*: INH, rifampin



RESISTANCE IN ICUs: NNIS DATA, 2003 vs 1998-2002



CDC. AJIC 2004;32:470-485

ANTIBIOTIC USE AND OVERUSE IS THE MAIN DRIVING FORCE OF ANTIBIOTIC RESISTANCE

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GERMICIDES

- Antiseptics
 - Germicides used on the skin or mucous membranes
- Disinfectants
 - Germicides used on equipment and inanimate environment

CLASSIFICATION OF GERMICIDES

- Disinfection and Sterilization (Spaulding)
 - Critical items (sterile tissue): sterilants
 - Semi-critical items (mucous membranes): high-level disinfectants
 - Non-critical items (intact skin): intermediate or low-level disinfectant
- Antisepsis
 - Hand hygiene
 - Skin antisepsis (e.g., surgical site preparation)
 - Therapy (e.g., burn therapy)

ANTISEPTIC AGENTS

- Alcohols
- Chlorhexidine gluconate
- Parachlorometaxylenol
- Hexachlorophene
- Iodine and iodophors
- Benzalkonium chloride
- Triclosan

DISINFECTANTS

- High level disinfectants
 - Glutaraldehyde
 - Ortho-phthalaldehyde
 - Hydrogen peroxide
 - Hydrogen peroxide and peracetic acid
 - Hypochlorite (>650-675 ppm)
- Intermediate or low-level disinfectants
 - Alcohol (ethyl and isopropyl)
 - Hypochlorite
 - Phenolic
 - Quaternary ammonium compounds

QUESTION

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

DEFINITIONS: RESISTANCE

Antimicrobial/Antibiotic resistance

- 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: 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 (NCCLS 2002).

DEFINITIONS: RESISTANCE

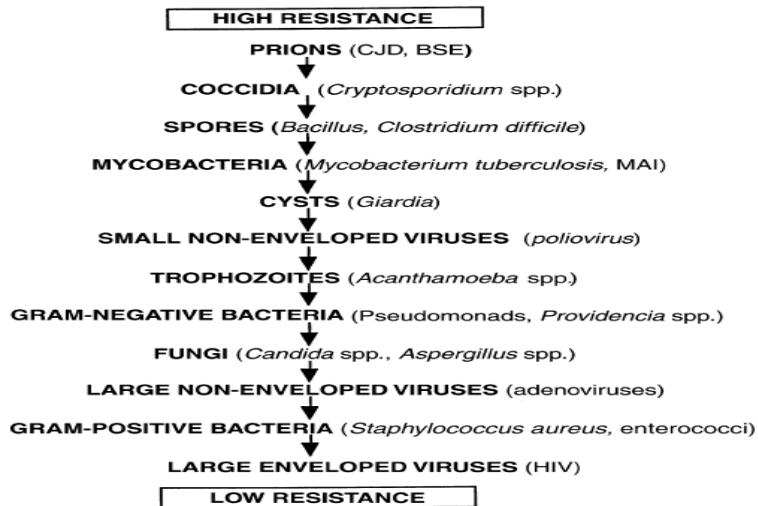
Germicide resistance

- Often used in the literature to refer to a strain of bacteria with an elevated MIC to the germicide (e.g., 1-25ug/ml); even if the MIC is easily exceeded by the use-concentration of the germicide (2,000-20,000ug/ml)
- “Resistant” strains should not be inactivated at the use dilution of the germicide
- Strains with an elevated MIC but still inactivated at the use dilution should be referred to as “tolerant” or “decreased susceptibility”

GERMICIDE RESISTANCE

- Mechanisms of germicide resistance in microorganisms similar to antimicrobial resistance
 - Intrinsic
 - Acquired
- However, germicides often have multiple targets and greater potency; thus resistance much less likely to develop

INTRINSIC RESISTANCE



INTRINSIC RESISTANCE

- Intrinsic resistance
 - Constitutive degradative enzymes
 - Cellular impermeability
- Acquired tolerance
 - Plasmid mediated resistance (CHG, triclosan, QUAT)
 - Acquired tolerance to germicides has rarely been described in microbes isolated from clinical specimens or the environment

EXAMPLES OF GERMICIDE TOLERANCE

<u>Mechanism</u>	<u>Example</u>
Impermeability	GNR
Efflux	Chlorhexidine (<i>S. aureus</i> , <i>qac</i> gene)
Modification of target site(s)	Triclosan (<i>E. coli</i> , <i>FabI</i> gene)
Drug inactivation	Organomecurials

Russell AD. J Appl Microbiol 2002;92:1S

DISINFECTANT RESISTANCE

- Acquired resistance to germicides has rarely been described in microbes isolated from clinical specimens or the environment
- Not aware of an example where acquired resistance to currently used germicides has been described in a microbe and with time the proportion of resistant microbes has increased rendering the germicide clinically ineffective
- This is in contrast to antibiotic resistance where resistance has occurred rendering the antibiotic no value
- Do not need to rotate germicides

QUESTION

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

NO

QUESTION

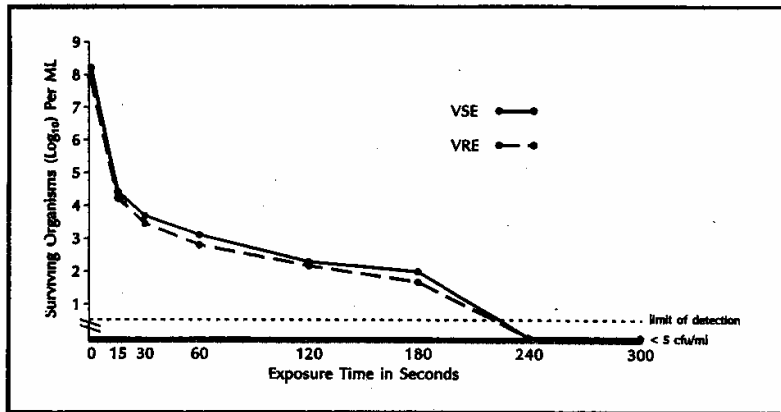
Do antibiotic resistant bacteria exhibit altered susceptibility to disinfectants/antiseptics?

SUSCEPTIBILITY OF ENTEROCOCCI TO DISINFECTANTS

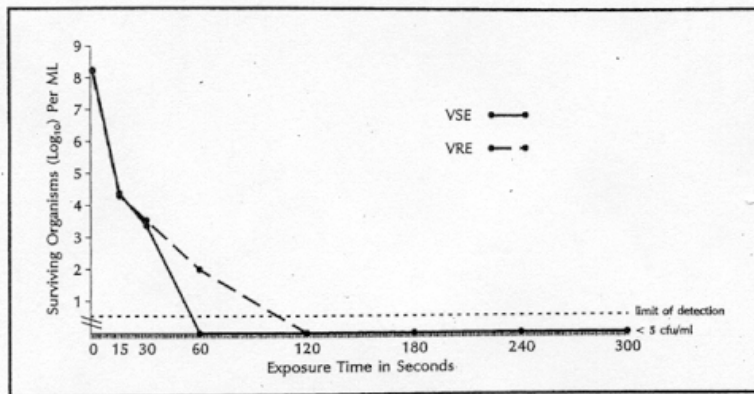
- Purpose of experiment
 - To determine susceptibility of VRE and VSE to various concentrations of commonly used hospital disinfectants (iodophor, quat, phenolic)
- Methods
 - Microbial suspension test to determine \log_{10} reduction
 - Exposure periods: 15 and 30 sec, then 1 min intervals for 5 minutes

Anderson R, et al. ICHE 1997;18:195-199.

VRE AND VSE SUSCEPTIBILITY TO A QAC



VRE AND VSE SUSCEPTIBILITY TO AN IODOPHOR



SUSCEPTIBILITY OF ENTEROCOCCI TO DISINFECTANTS

- Results
 - Survival curves demonstrated no difference between the VRE and VSE strains
- Conclusion
 - VRE and VSE are sensitive to a spectrum of commonly used hospital disinfectants and have parallel inactivation rates
 - No relationship between antibiotic-susceptible and antibiotic-resistant strains

SUSCEPTIBILITY OF ANTIBIOTIC-RESISTANT AND SUSCEPTIBLE BACTERIA TO GERMICIDES

Effect of Antibiotic Resistance on Germicide
Susceptibility

<u>Bacteria</u>	<u>None</u>	<u>Reduced</u>	<u>Resistant</u>	<u>Reference</u>
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

HOW GERMICIDES DIFFER FROM ANTIBIOTICS

- Multiple cellular targets
- Not natural substances (i.e., not derived from microbial organisms)
- Very potent (i.e., enormous gap between use dilution and MIC)
- Usually cidal

QUESTION

Does the use of disinfectants/antiseptics precipitate antibiotic resistance?

DISINFECTANT TOLERANCE LABORATORY

- Develop mutants with reduced susceptibility to disinfectants and antiseptics
- As the concentration of disinfectants used in practice greatly exceed the MICs observed, the clinical relevance is questionable

LINK BETWEEN GERMICIDE AND ANTIBIOTIC RESISTANCE LABORATORY

- 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

LAB DEVELOPED STRAINS WITH GERMICIDE LINKED ANTIBIOTIC RESISTANCE

<u>Bacteria (gene)</u>	<u>Germicide</u>	<u>Ab Resistance</u>	<u>Reference</u>
<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

LAB DEVELOPED STRAINS WITH GERMICIDE LINKED ANTIBIOTIC RESISTANCE

<u>Bacteria (gene)</u>	<u>Germicide</u>	<u>Ab Resistance</u>	<u>Reference</u>
<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

CONCLUSIONS

- Antimicrobial resistance a growing public health problem in the community and healthcare facilities
- Major driving force of antimicrobial resistance is the use and overuse of antibiotics in humans
- Does the use of disinfectants/antiseptics result in disinfectant/antiseptic resistance? NO
- Do antibiotic resistant bacteria exhibit altered susceptibility to disinfectants/antiseptics? NO
- Do disinfectants/antiseptics precipitate antibiotic resistance? NO evidence in nature

FUNDAMENTAL QUESTION

Does the use of germicides decrease human disease?

USES OF GERMICIDES: OVERWHELMING EVIDENCE OF EFFICACY

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

ENDOSCOPY: TRANSMISSION OF INFECTION

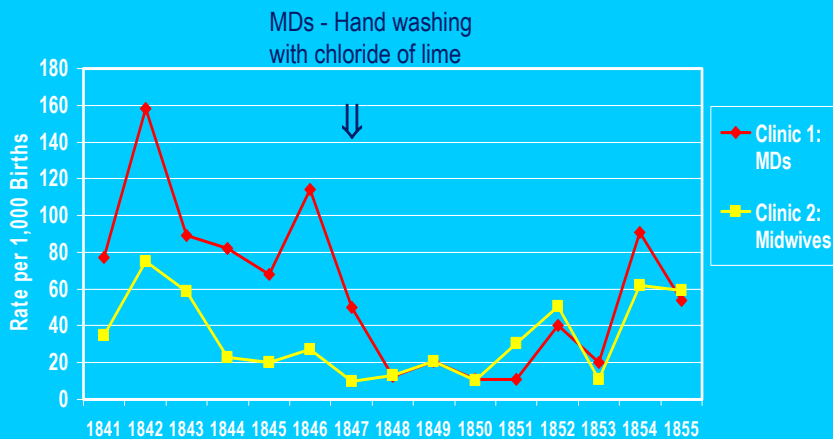
- Gastrointestinal endoscopy
 - >300 infections transmitted
 - 70% agents *Salmonella sp.* and *P. aeruginosa*
 - Clinical spectrum ranged from colonization to death (~4%)
- Bronchoscopy
 - 90 infections transmitted
 - *M. tuberculosis*, atypical *Mycobacteria*, *P. aeruginosa*
- *All outbreaks resulted from use of ineffective disinfectants or failure to adhere to current guidelines*

Spach DH, et al. Ann Intern Med 1993;118:117-128;
Weber DJ, Rutala WA. Gastrointestinal Disease, 2002

USES OF GERMICIDES: STRONG EVIDENCE OF EFFICACY

- Hand hygiene
 - Food preparation
 - Day care center providers
 - Healthcare personnel
 - Laboratories handling microbiologic specimens
- Environmental
 - Food preparation
 - Close environment of hospitalized patients
 - Day care centers
 - Laboratories handling microbiologic specimens

MATERNAL MORTALITY, VIENNA MATERNITY HOSPITAL, 1841-1855



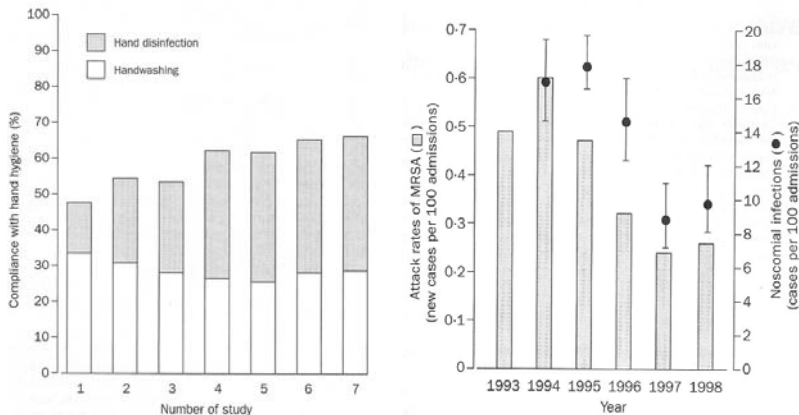
Loudin I. Death in Childbirth. Oxford Press, 1992

ASSOCIATION BETWEEN HAND HYGIENE COMPLIANCE AND HAI RATES

<u>Author, year</u>	<u>Setting</u>	<u>Results</u>
Casewell, 1977	Adult ICU	Reduction HAI due to <i>Klebsiella</i>
Maki, 1982	Adult ICU	Reduction HAI rates
Massanari, 1984	Adult ICU	Reduction HAI rates
Kohen, 1990	Adult ICU	Trend to improvement
Doebbeling, 1992	Adult ICU	Different rates of HAI between 2 agents
Webster, 1994	NICU	Elimination of MRSA*
Zafar, 1995	Newborn	Elimination of MRSA*
Larson, 2000	MICU/NICU	85% reduction VRE
Pittet, 2000	Hospital-wide	Reduction HAI and MRSA cross-transmission

HAI, hospital-associated infections *Other infection control measures also instituted
 Boyce JM, Pittet D. MMWR 2002;51(RR-16)

EFFECTIVENESS OF HAND HYGIENE IN THE HOSPITAL



Pittet D, et al. Lancet 2000;356:1307-12.

USES OF GERMICIDES: SUGGESTIVE EVIDENCE OF EFFICACY

- Handling animal wastes (e.g., “kitty litter”)
- Cleaning/disinfecting hospital environments not directly in contact with hands (e.g., curtains)

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- Do disinfectants/antiseptics precipitate antibiotic resistance? No
- Does the use of germicides decrease human disease?
Yes

Thank you

REFERENCES

- Weber DJ and WA Rutala. Use of germicides in the home and health care setting: Is there a relationship between germicide use and antibiotic resistance? Infect Control Hosp Epidemiol. In press
- Russell AD. Introduction of biocides into clinical practice and the impact of antibiotic-resistant bacteria. J Appl Microbiol 2002;92:121S-135S
- Gilbert P and AJ McBain. Potential impact of increased use of biocides in consumer products on prevalence of antibiotic resistance. Clin Microbiol Rev 2003;16:189-208