MICROBIAL MULTI-DRUG RESISTANCE (MDR) AND OLIGODYNAMIC SILVER

Newsweek reported in 1992 that 13,000 hospital patients died from drug resistant infections.[1] The startling news was that this mortality rate climbed to 70,000 for the very next year. As a result, the CDC in 1994 declared this health crises as America's number one health issue.[2] Today, over 2 million Americans suffer with nosocomial super germ infections.[3] In fact, other the industrial countries such as Great Britain are reporting an infection rate for super germs that exceeds 3.5 per 1,000 hospital admissions.[4] This translates into a stunning 350 patients per 100,000 patients admitted. Simply stated, those numbers are approaching epidemic levels within many hospitals throughout the industrialized world.

As early as 1940 Goetz remarked that, "The minimum lethal concentration of oligodynamically active silver definitely depends upon the nature of the substrate in which the test is made as well as upon the nature and concentration of the test microorganisms."[5]

Right up to the present time, microbial resistance to medicinal silver has not been scientifically established. This point has been made by Lansdown (2002).

J Wound Care 2002 Apr 11:125-30

Silver. I: Its antibacterial properties and mechanism of action.
Lansdown AB

Abstract: Silver products have two key advantages: they are broad-spectrum antibiotics and are not yet associated with drug resistance. This article, the first in a two-part series, describes the main mechanism of action of this metallic element.

MeSH: Anti-Infective Agents, Local; History of Medicine, 18th Cent.; History of Medicine, 19th Cent.; History of Medicine, 20th Cent.; Human; Silver Compounds; Skin Diseases, Bacterial; Support, Non-U.S. Gov't; Wounds and Injuries

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So-Called Resistant Strains

Over the past two decades, multiple studies with differing designs and speciations of silver-based drugs have indicated that certain bacterial species and strains have physiological mechanisms that circumnavigate silver's toxicity.[6, 7, 8, 9] These mechanisms are essentially either plasmid based or chromosomal based;[10] the latter expressing as ATPase translocating mechanisms.[11] In neither case did investigators employ nanoscalar oligodynamic silver. Instead, the experimental designs typically utilized silver salt compounds, which deliver poor amounts of bioactive silver. Another most common problem of these experimental designs was the inadvertent culture contamination with various salts, something which will reduce silver efficacy. The colloidal state and dynamics of living tissues is at odds with typical culture techniques and mediums, and brings about the unfortunately situation of requiring readers to compare apples to oranges. Notwithstanding, within these parameters investigators have determined the following select strains of bacteria exhibit various degrees of resistance to the bactericidal effects of silver-based drugs:

1. Acinetobacter baumani BL88[12]
2. Citrobacter freundii[13, 14]
3. Entamoeba histolytica cysts[15]

4. Enterobacter cloacae[16, 17, 18, 19]
5. Enterobacteriaceae (some strains)[20, 21, 22]
6. Enterococcus hirae[a, 23]
7. Escherichia coli (J62, C600, R1 & S1)
8. E. coli (K-12 & 0157:H7)[24]
9. Helicobacter pylori[25]
10. Klebsiella pneumoniae[26, 27, 28 ,29]
11. Mycobacteria[30]
12. Pseudomonas aeruginosa 10, E. cloacae[31,32]
13. Ps. stutzeri (AG256, AG259, JM303) [33,34]
14. Ps. putida CYM318[35]
15. Proteus mirabilis[36, 37]
16. Salmonella typhimurium[38, 39]
17. Staphylococcus aureus[40]
18. Thiobacillus ferro-oxidans[41]
19. Thiobacillus thio-oxidans[42]
20. Vegetative B. Cereus Spores[43]

Zhao and Stevens stated that, "With the rise of antibiotic-resistant bacteria, silver is re-emerging as a modern medicine because all pathogenic organisms have failed to develop an immunity to it (silver ion)."[44] It is more probable than not that microbes lack sufficient defense mechanisms to circumvent the toxic effects of silver ions if sufficient Ag^+ reaches the foci over an appropriate time frame. That's the critical "if" and "must."

More specifically stated, the "apparent" resistance of microbes to silver-based drugs is typically due to (1) an inadequate protocol or procedure, or (2) neglect of the necessary parameters so carefully reviewed by Goetz, Zhao and a NASA commissioned study. Hamilton-Miller et al., have reported that bacterial strains completely resistant to the salt speciations of silver have proved erroneous when proper study designs were employed.[45]

J Antimicrob Chemother 1992 Jun 29:661-8

Comparison of the in-vitro activities of the topical antimicrobials azelaic acid, nitrofurazone, silver sulphadiazine and mupirocin against methicillin-resistant Staphylococcus aureus.
Maple PA, Hamilton-Miller JM, Brumfitt W

Abstract: The in-vitro activities of the topical agents azelaic acid, nitrofurazone, silver sulphadiazine and mupirocin have been determined against 80 strains of MRSA collected from worldwide sources. MICs were determined by agar dilution (with an inoculum of approximately 5.0 x 10(5) cfu) in Iso-Sensitest agar, and MBCs were measured by replica-plating from MIC plates using velvet pads. The agents tested were uniformly active against MRSA, mupirocin being the most active (MIC50 0.15 mg/L) followed by nitrofurazone (MIC50 19 mg/L), silver sulphadiazine (MIC50 85 mg/L) and azelaic acid (MIC50 850 mg/L). Concentrations of azelaic acid, nitrofurazone and silver sulphadiazine close to the MIC were bactericidal, but mupirocin was only bactericidal at concentrations substantially greater than the MIC. In time-kill experiments, azelaic acid and nitrofurazone were gradually bactericidal, silver sulphadiazine was rapidly bactericidal and mupirocin was not bactericidal. Silver sulphadiazine killed sulphonamide-sensitive and sulphonamide-resistant strains equally rapidly. No resistant mutants were found to azelaic acid, nitrofurazone or silver sulphadiazine in an inoculum of 10(9) cfu, but two strains yielded (frequency: 1.0 x 10(-9)) mutants resistant to mupirocin. Our in-vitro results suggest azelaic acid, nitrofurazone and silver sulphadiazine could be of use for clearing staphylococcal carriage.

[a] By way of Cu(I)/Ag(I)-translocating ATPases.

MeSH: Anti-Infective Agents; Comparative Study; Dermatologic Agents; Dicarboxylic Acids; Drug Resistance, Microbial; Human; Methicillin Resistance; Microbial Sensitivity Tests; Mupirocin; Nitrofurazone; Silver Sulfadiazine; Staphylococcus aureus

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Grier stated that, "Some so-called Ag^+ resistant microorganisms may result from an apparent neutralization of the metal's inhibitory action or other assay artifacts. These include the presence of chelators such as serial amino acids, constituents of hard water, different buffers, light, incubation temperature, and particularly, soluble components of trypticase soy agar (TSA) and tryptose glucose extract agar (TGE)."[46] Schierholz in 1998 reviewed the majority of the salient issues governing inactivation of oligodynamic Ag^+ in the varieties of media now in common use.

Zentralbl Bakteriol 1998 May 287:411-20

Activity of silver ions in different media.

Schierholz JM, Wachol-Drewek Z, Lucas LJ, Pulverer G

Abstract: A major problem in medicine is the large number of infections associated with implanted and indwelling devices. Silver coating of medical devices is believed to preserve infection resistance. Several in vitro and animal studies as well as clinical observations on silver-nylon, silver-intramedullary pins, silver-oxide-Foley catheters and silver-coated vascular protheses have been interpreted as successful for the prophylaxis of foreign-body infections. Nevertheless, these products have not been established in clinical use. In this study we have been able to present physico-chemical and pharmacological data as well as simple microbiological experiments explaining the reduced anti-microbial activity of silver-ions in some biological fluids.

MeSH: Bacterial Adhesion; Culture Media; Escherichia coli; Ions; Microbial Sensitivity Tests; Silver Nitrate; Staphylococcus aureus; Staphylococcus epidermidis

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J Hyg Epidemiol Microbiol Immunol 1988 32:299-306

Effect of certain chelating agents on the antibacterial action of silver nitrate.

Kaur P, Vadehra DV

Abstract: EDTA and EGTA when used in conjunction with AgNO3 enhanced the antibacterial action of the latter significantly, so that strains of Klebsiella pneumoniae and Staphylococcus aureus resistant to 70 micrograms/ml of AgNO3 were observed to become sensitive to 10 micrograms/ml of this compound. The synergistic effect of EDTA appears to be due to a mechanism other than the removal of lipopolysaccharide from outer membrane, as its effect could be observed in even non-LPS containing gram positive S. aureus cells. Penicillamine, another potent chelator had an opposite effect so that it decreased the toxicity of silver ions.

MeSH: Antibiotics; Chelating Agents; Drug Resistance, Microbial; Drug Synergism; Edetic Acid; Egtazic Acid; Klebsiella pneumoniae; Penicillamine; Silver Nitrate; Staphylococcus aureus

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Conclusion

The physician's skill is challenged when using oligodynamic silver hydrosol because of four key factors: (1) where is the foci and what form of administration will best deliver oligodynamic silver;

(2) what is the total pathogen load; (3) what specific pathogen strain is involved; and (4) what frequency and concentration of oligodynamic silver is required to bring about a sero-negative conversion (typically from 1 ppm to 10 ppm of bioactive silver is required within a specific therapeutic window). These factors applying to the physician's skill set mean the difference between therapeutic failure or success. Success against the so-called resistant strains of infection may only be a matter of follow-through when the proper speciation of bioactive silver is employed along with competent and skillful medical management.[47]

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