SILVER vs ANTIBIOTIC

EMODIAL

Nosocomial infection

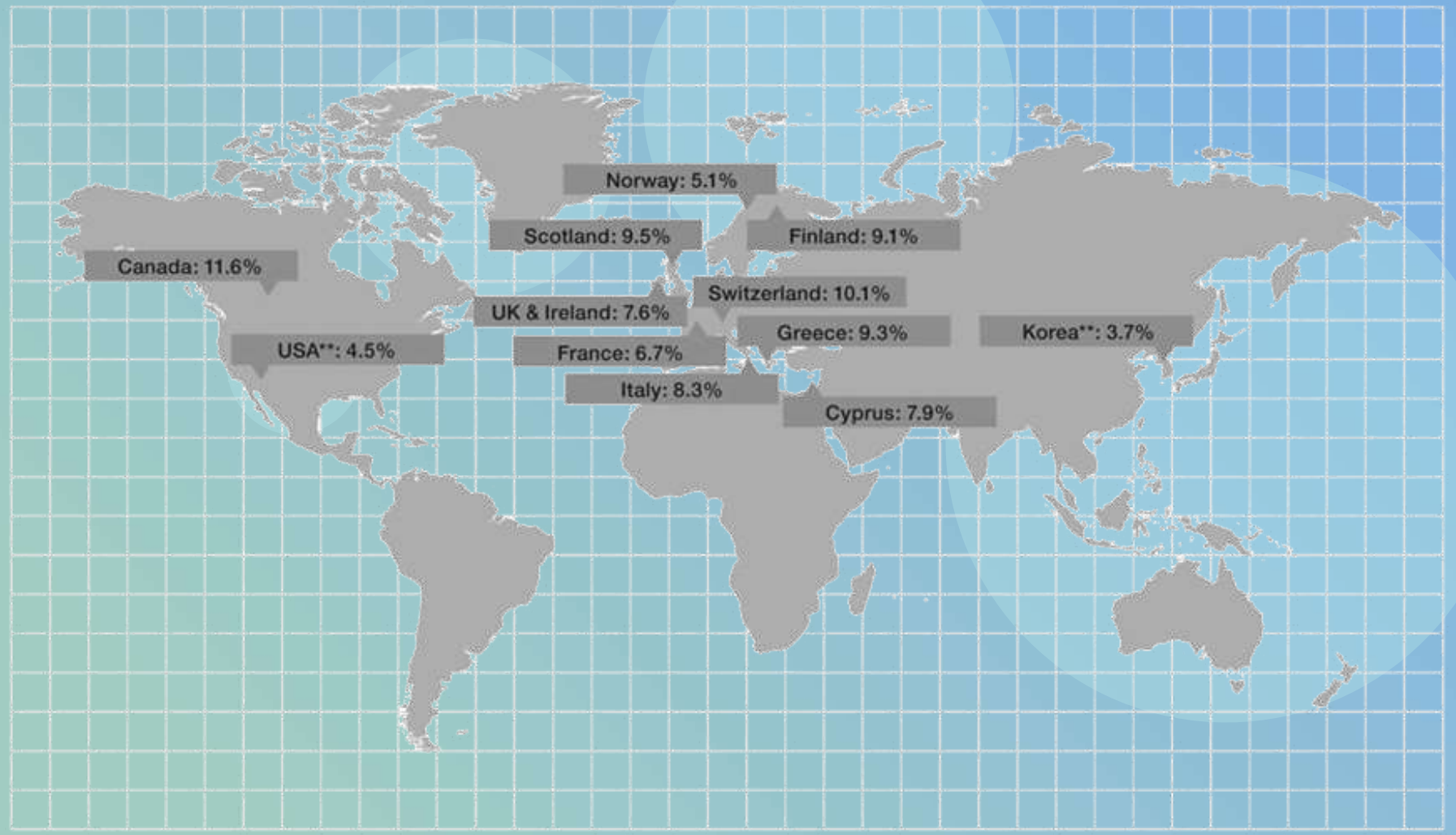
Nosocomial infection is a typical hospitalization infection, which was not manifested clinically or in incubation at the time of admission, but appears during or after admission and is determined by this.

(Circolare Ministero Sanità n. 52/1985)

Nosocomial infections occur with high rates of MORBIDITY and increase in MORTALITY, also contributing to increase hospitalization COSTS.

The frequency of these infections is generally not in decline.

Health Care-Associated Infection



Prevalence of HCAI in Developed Countries*

* Systematic review conducted by WHO, 1995-2008; HCAI: health care-associated infection.

Incidence of HCAI in Developed Countries**

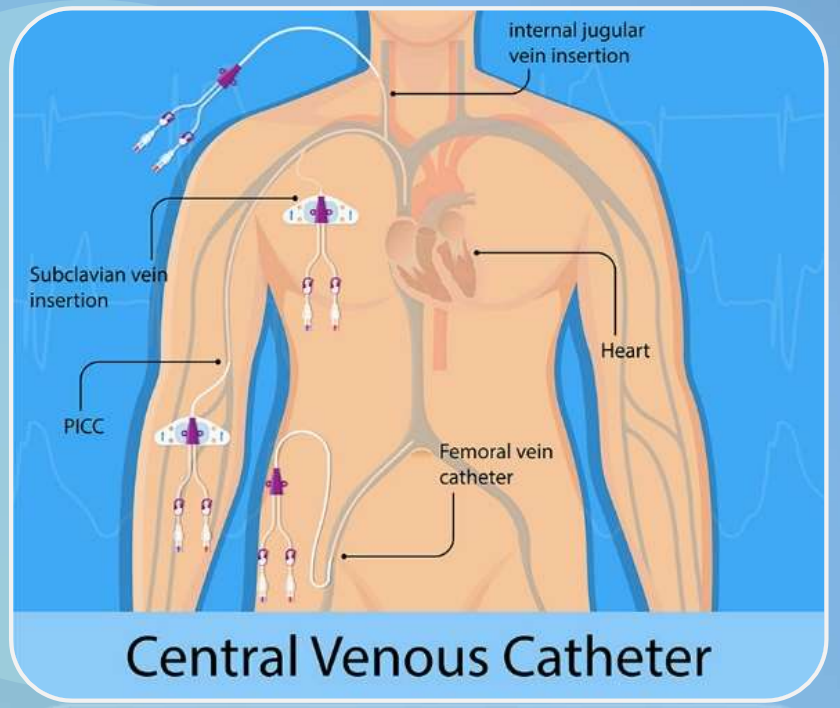
** World Health Organization. The Burden of Health Care-Associated Infection Worldwide: A Summary. 2010. Accessed Sep 3, 2013.

Catheter-associated infections

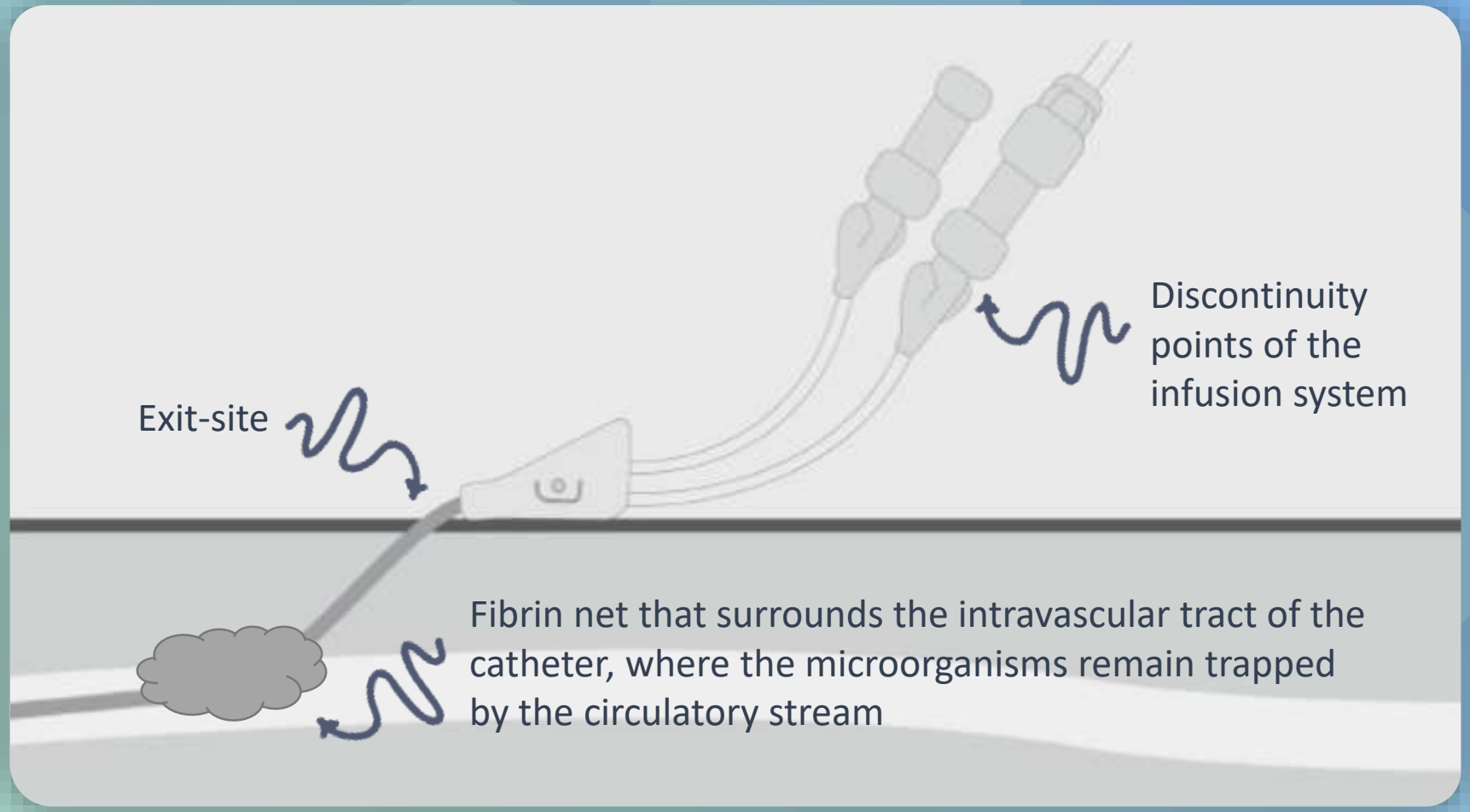
Catheter-associated infections are among the iatrogenic complications potentially more dangerous

Four **major risk factors** are associated with increased catheter-related infection rates:

- ✓ Cutaneous colonization of the insertion site
- ✓ Moisture under the dressing
- ✓ Prolonged catheter time
- ✓ Technique of care and placement of the central line



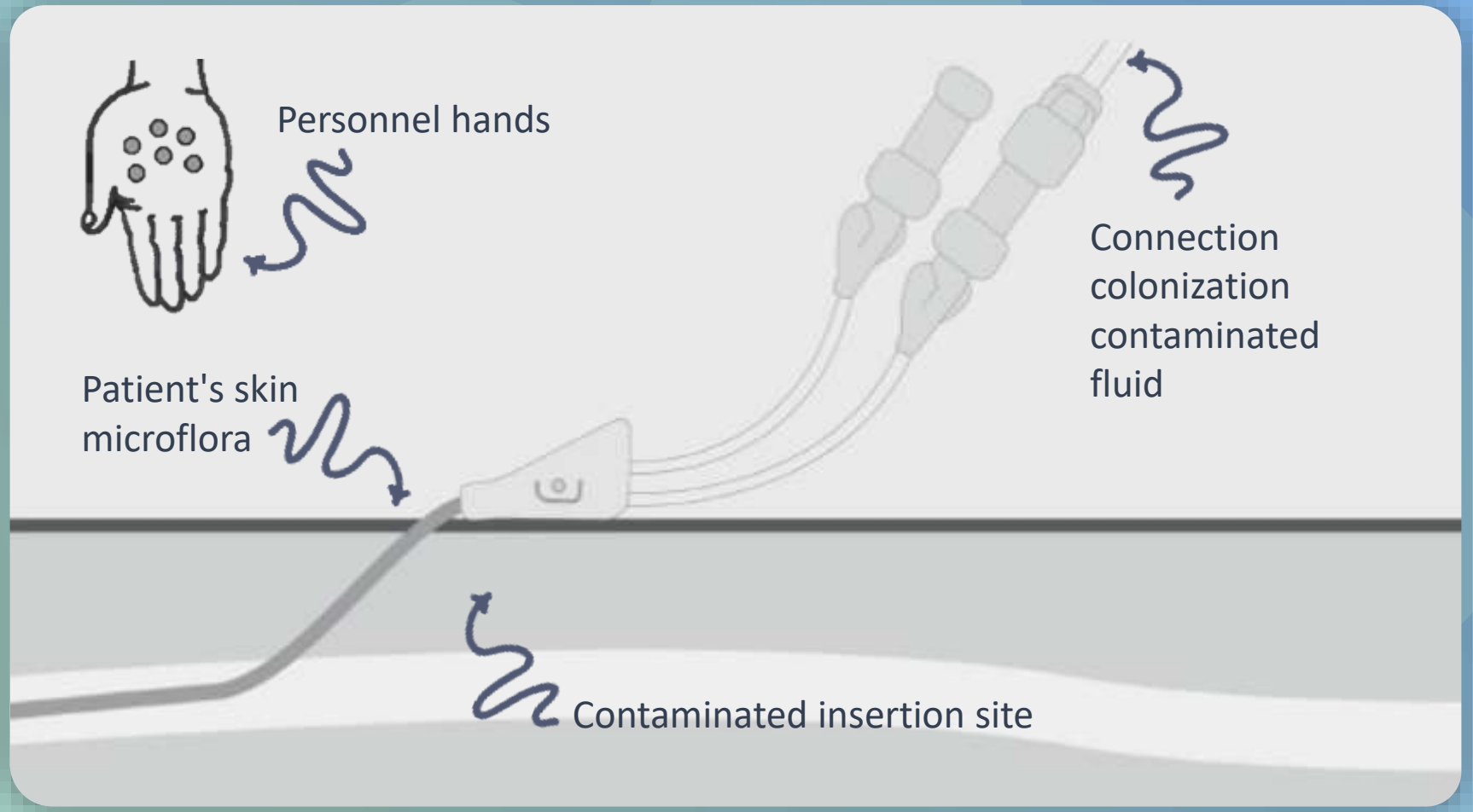
Catheter infection



- ✓ CRBSI
- ✓ Exit site infection
- ✓ Catheter tract infection

Catheter infection

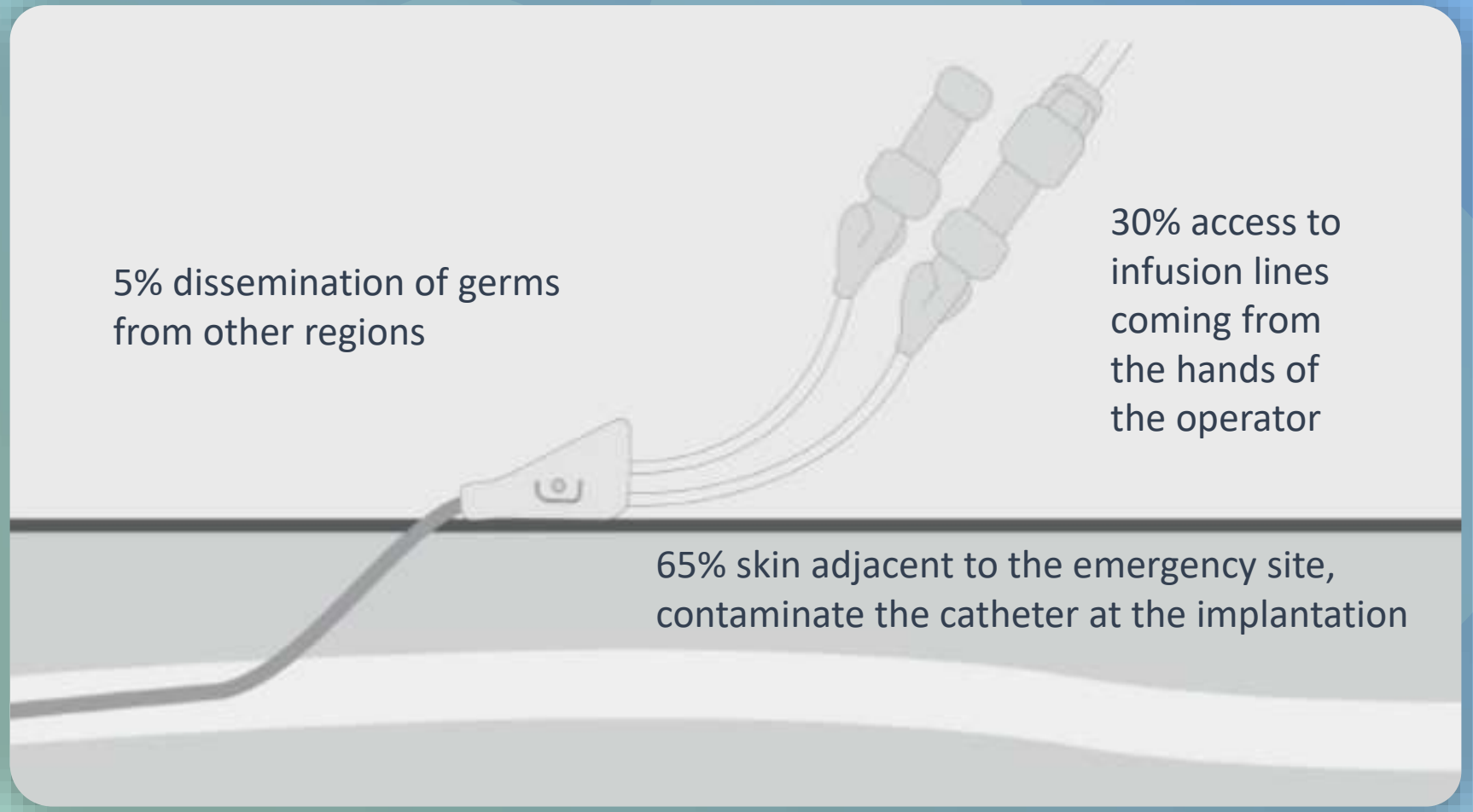
Factors promoting related catheter infection



Haematic spread of pathogens from a distant infectious process

Catheter infection

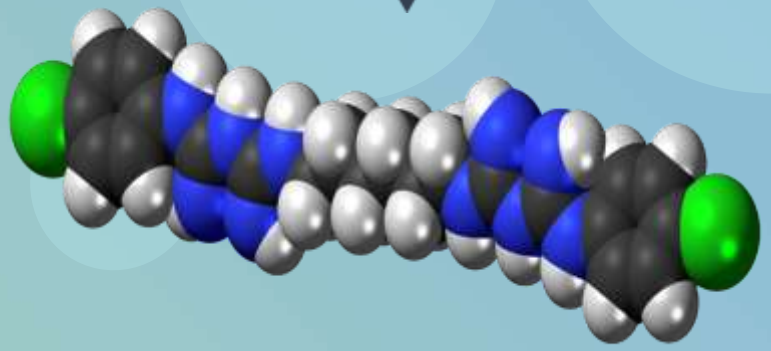
Micro-organisms most frequently implicated in CI



- ✓ Staphylococcus epidermidis
- ✓ S. aureus
- ✓ Candida
- ✓ Enterococchi

Prevention?

2 ALTERNATIVES



Guidelines for the Prevention of Intravascular Catheter-Related Infections, 2011

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

2017 Updated Recommendations on the Use of Chlorhexidine-Impregnated Dressings for Prevention of Intravascular Catheter-Related Infections

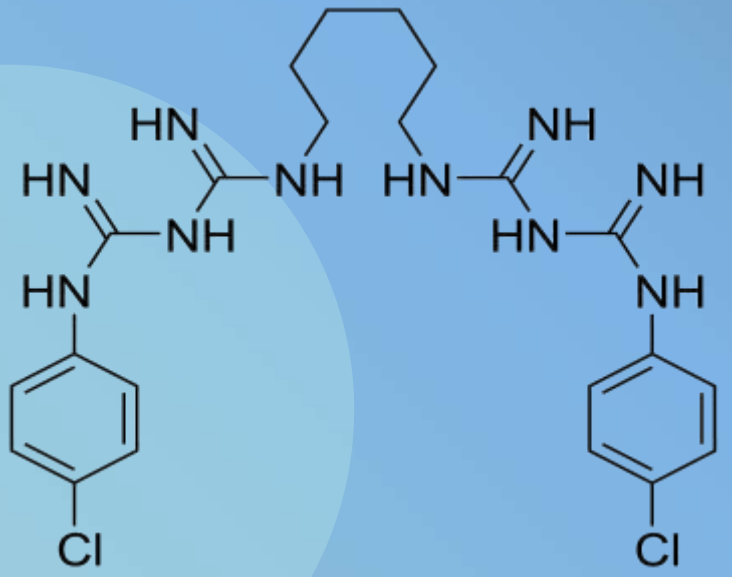
Centers for Disease Control and Prevention
National Center for Zoonotic and Emerging Infectious Diseases
Division of Healthcare Quality Promotion

Chlorhexidine
DISINFECTANT AGENT

The most effective disinfectant agent for cleansing the skin around the insertion site and for dressing changes seems to be **Chlorhexidine**.

Broad-spectrum biocide active against Gram-positive bacteria weakly against Gram negative bacteria, some enveloped viruses, and fungi.

It shows poor activity against non enveloped viruses, and is inactive against bacterial spores.

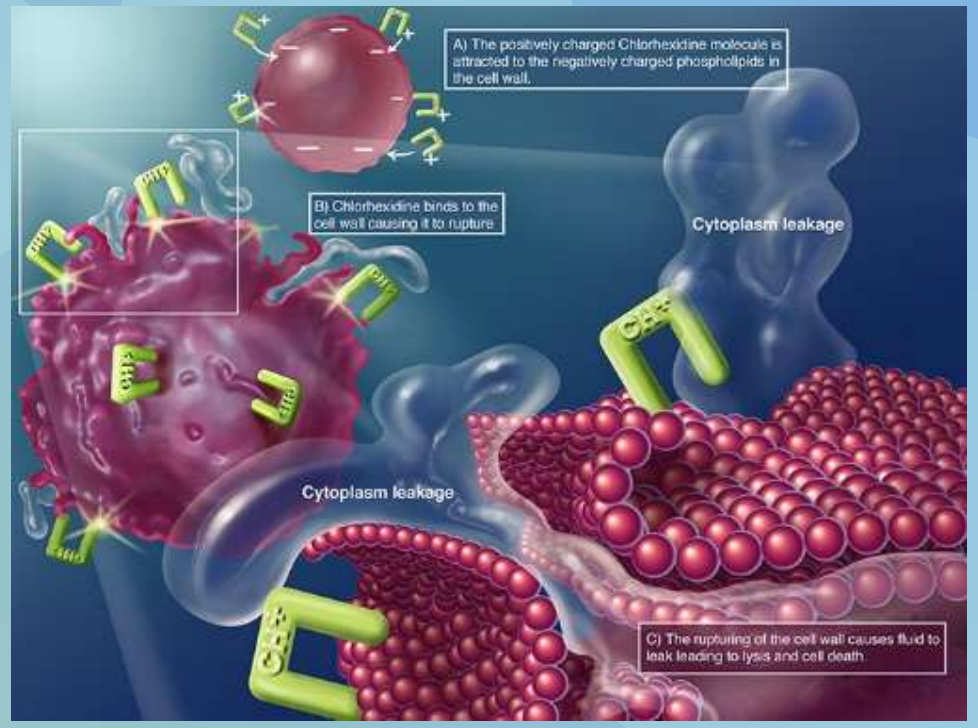


Chlorhexidine is a divalent cationic biguanide molecule that was first described in 1954.

Chlorhexidine

HOW DOES IT WORK?

- positively charged
- binds
- negatively charged bacterial surface



At low concentration

- ✓ loss of osmoregulatory and
- ✓ metabolic capacity
- ✓ loss of cytosolic potassium ions
- ✓ inhibition of cellular respiration

- ✓ bacteriostatic

At high concentration

- ✓ loss of membrane integrity
- ✓ leakage of cellular contents
- ✓ cell lysis and death

- ✓ bactericidal

WARNING

Organic substances limit the disinfectant action. Inactivated by anionic and non-ionic surfactants by inorganic anions present in high concentrations in tap water.

Chlorhexidine
ADVERSE REACTIONS

Mild adverse effects include skin irritation and, more rarely, allergic reactions that include severe anaphylaxis, ototoxicity, neurotoxicity.

FDA REPORT

In the USA the number adverse events was 85 between 2007 and 2014, reached 183 in 2015 and 226 in 2016. Anaphylaxis or shock would have been reported 120 times, skin irritation, erythema and burns, 325. The overall balance includes 48 potentially lethal events, and 7 deads.

ENGLISH MEDICINES & HEALTHCARE PRODUCTS REGULATORY AGENCY REPORT

First events of anaphylactic reactions to the product were recorded as early as 2012, and the number of adverse events related to chlorhexidine increased from 14 in 2007, to 117 in 2016.

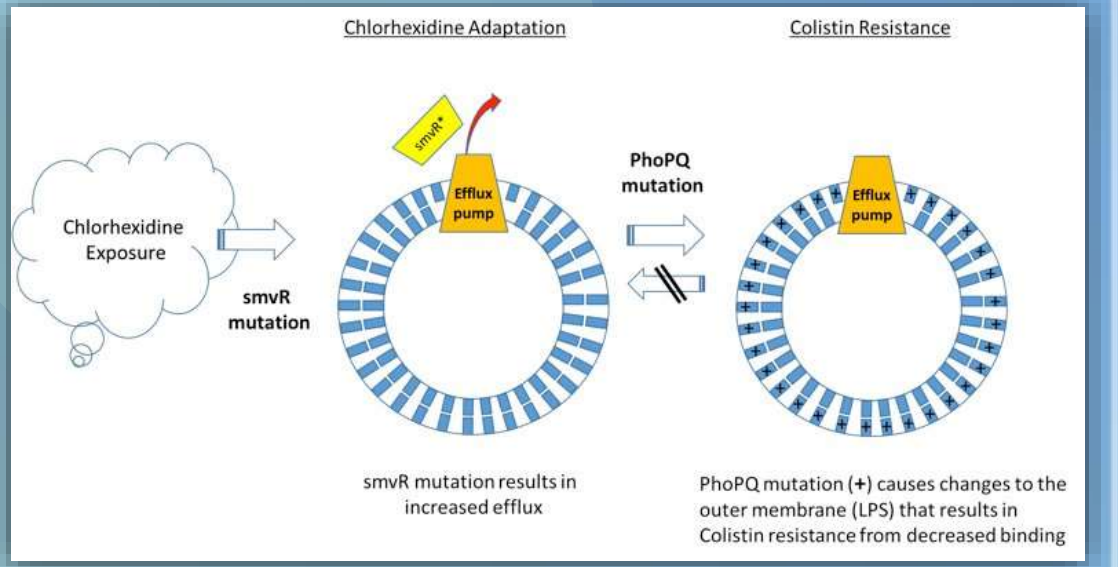
Chlorhexidine

The indiscriminate use could lead to CHLORHEXIDINE RESISTANCE

AMERICAN SOCIETY FOR MICROBIOLOGY

Mechanisms of Increased Resistance to Chlorhexidine and Cross-Resistance to Colistin following Exposure of Klebsiella pneumoniae Clinical Isolates to Chlorhexidine.

Adapted strains had mutations in two components of phoPQ and this leads to LPS modification. Exposing these mutated strains to colistin, it was observed that as many as five of the six adapted strains exhibited antibiotic resistance.
This is because the changing decreased the negative charge of the membrane of bacteria and reduced the affinity for substances with net positive charge such as chlorhexidine and colistin.



AAC
Journals.ASM.org

Prevalence of Chlorhexidine-Resistant Methicillin-Resistant *Staphylococcus aureus* following Prolonged Exposure

Carey D. Schlett,[a] Eugene V. Millar,[a] Katrina B. Crawford,[a] Tianyuan Cui,[a] Jeffrey B. Lanier,[b] David R. Tribble,[a] Michael W. Ellis[c]

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Chlorhexidine has been increasingly utilized in outpatient settings to control methicillin-resistant *Staphylococcus aureus* (MRSA) outbreaks and as a component of programs for MRSA decolonization and prevention of skin and soft-tissue infections (SSTIs). The objective of this study was to determine the prevalence of chlorhexidine resistance in clinical and colonizing MRSA isolates obtained in the context of a community-based cluster-randomized controlled trial for SSTI prevention, during which 10,030 soldiers were issued chlorhexidine for body washing. We obtained epidemiological data on study participants and performed molecular analysis of MRSA isolates, including PCR assays for determinants of chlorhexidine resistance and high-level mupirocin resistance and pulsed-field gel electrophoresis (PFGE). During the study period, May 2010 to January 2012, we identified 720 MRSA isolates, of which 615 (85.4%) were available for molecular analysis, i.e., 341 clinical and 274 colonizing isolates. Overall, only 10 (1.6%) of 615 isolates were chlorhexidine resistant, including three from the chlorhexidine group and seven from nonchlorhexidine groups ($P > 0.99$). Five (1.5%) of the 341 clinical isolates and five (1.8%) of the 274 colonizing isolates harbored chlorhexidine resistance genes, and four (40%) of the 10 possessed genetic determinants for mupirocin resistance. All chlorhexidine-resistant isolates were USA300. The overall prevalence of chlorhexidine resistance in MRSA isolates obtained from our study participants was low. We found no association between extended chlorhexidine use and the prevalence of chlorhexidine-resistant MRSA isolates; however, continued surveillance is warranted, as this agent continues to be utilized for infection control and prevention efforts.

Journal of Antimicrobial Chemotherapy (2008) **62**, 514–517
doi:10.1093/jac/dkn208
Advance Access publication 13 May 2008

JAC

Longitudinal analysis of chlorhexidine susceptibilities of nosocomial methicillin-resistant *Staphylococcus aureus* isolates at a teaching hospital in Taiwan

Jann-Tay Wang[1], Wang-Huei Sheng[1], Jiun-Ling Wang[1], Duckling Chen[1], Mei-Ling Chen[2], Yee-Chun Chen[1] and Shan-Chwen Chang[1,3]*

[1]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [2]Department of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan; [3]Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan

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APMIS
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ET IMMUNOLOGICA SCANDINAVICA

APMIS 122: 961–967

DOI 10.1111/apm.12239

Decreased susceptibility to chlorhexidine and prevalence of disinfectant resistance genes among clinical isolates of *Staphylococcus epidermidis*

GUSTAF PRAG,[1] KARIN FALK-BRYNHILDSEN,[2] SUSANNE JACOBSSON,[1] BENGT HELLMARK,[1] MAGNUS UNEMO[1] and BO SÖDERQUIST[1,3,4]

Departments of [1]Laboratory Medicine, Clinical Microbiology; [2]Cardiothoracic and Vascular Surgery; [3]Infectious Diseases, Örebro University Hospital, Örebro; [4]Faculty of Medicine and Health, Örebro University, Örebro, Sweden

International Journal of Antimicrobial Agents ■■ (2016) ■■–■■

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International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Susceptibility to chlorhexidine amongst multidrug-resistant clinical isolates of *Staphylococcus epidermidis* from bloodstream infections

Karolin Hijazi [a,*], Indrani Mukhopadhya [a], Felicity Abbott [b], Kathleen Milne [b], Zaaima J. Al-Jabri [c], Marco R. Oggioni [c], Ian M. Gould [b]

[a] *School of Medicine and Dentistry, University of Aberdeen, Aberdeen, UK*
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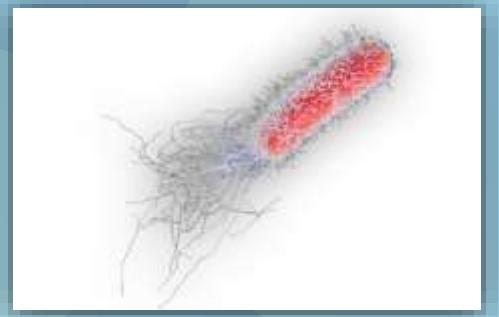
[c] *Department of Genetics, University of Leicester, Leicester, UK*

Antibiotic prophylaxis



Antibiotic prophylaxis refers to the administration of antibiotics according to well-defined modalities, without infection in act, with the aim to prevent infection.

Do not routinely apply prophylactic topical antimicrobial or antiseptic ointment or cream to the insertion site of peripheral venous catheters (107,213). **Category IA****

NEVER USE TO PREVENT

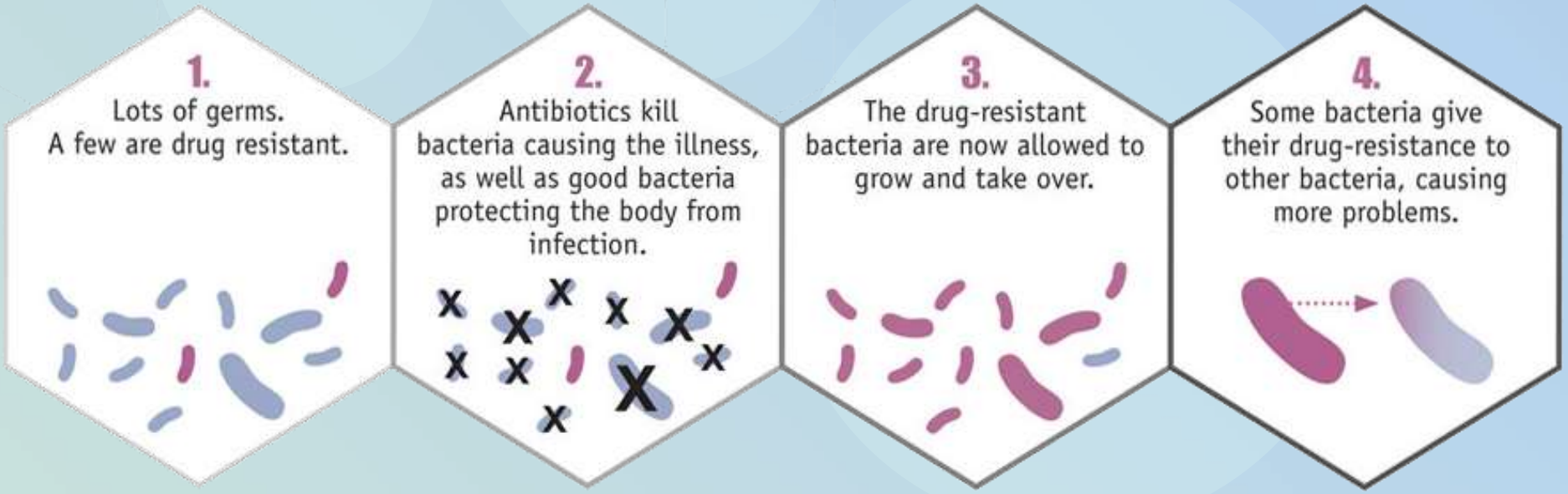
Do not administer routine systemic antibiotic prophylaxis, either before implantation or during use of an intravascular catheter, in order to **prevent** catheter colonization or CRBSI (114). **Category IB****

Do not routinely use antibiotic lock solutions to prevent CRBSI. Use prophylactic antibiotic lock solution only in special circumstances (eg, in treating a patient with a long-term cuffed or tunneled catheter or port who has a history of multiple CRBSIs despite optimal maximal adherence to aseptic technique) (150-153) **Category II ****

**Guidelines for the Prevention of Intravascular Catheter–Related Infections

A.M.R.
AntiMicrobial Resistance

Antibiotic-resistant microorganism: microorganism that cannot be inhibited in growth or killed at the pharmacological concentrations of the molecule following the administration of a «usual» therapeutic dose.



Antibiotic resistance indicates a partial or total loss of activity by an antibiotic vs previously sensitive microorganism. Predicts the possible failure of antibiotic therapy.

Antibiotical Resistance

ANTIBIOTIC RESISTANCE
KILLS

214,000 newborns are estimated to die every year from blood infections caused by resistant bacteria – representing at least 30% of all sepsis deaths in newborns.

ANTIBIOTIC RESISTANCE
SPREADS SILENTLY ACROSS THE WORLD

More than 60% of the populations in some areas carry multidrug-resistant bacteria in their normal bacterial flora.

ANTIBIOTIC RESISTANCE
IS COSTLY

It is estimated that the median overall increased cost to treat a resistant bacterial infection is around 700 USD. Novel treatments for multidrug-resistant infections can cost up to tens of thousands of dollars, making them unaffordable for many.

ANTIBIOTIC RESISTANCE
IS HERE NOW

Resistance has already developed to the last-line antibiotics for gonorrhea, which in some cases is nearly untreatable.

With 106 million new cases/year, the consequences of total resistance would be devastating

No studies have demonstrated that oral or parenteral antibacterial or antifungal drugs might reduce the incidence of CRBSI among adults. However, among low birth weight infants, two studies have assessed vancomycin prophylaxis; both demonstrated a reduction in CRBSI but no reduction in mortality. Because the prophylactic use of vancomycin is an independent risk factor for the acquisition of vancomycin-resistant enterococcus (VRE), the risk for acquiring VRE likely outweighs the benefit of using prophylactic vancomycin.

Guidelines for the Prevention of Intravascular Catheter-Related Infections

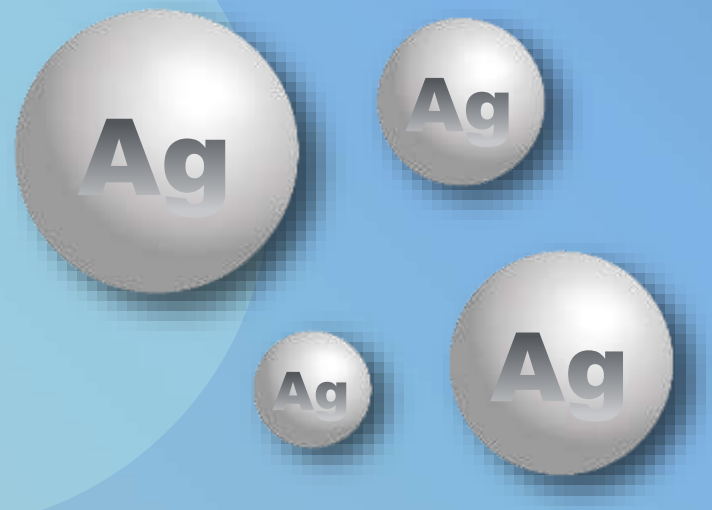
Antibiotical Resistance

Silver Dressings

One of the most urgent threats to the public's health the major need for antimicrobial dressing is NO toxicity and NO bacterial-resistance

Silver dressings are broad spectrum against gram-positive and gram-negative bacteria.

Silver ions (Ag+) are released in the presence of exudate, binding to bacteria cells. The amount of silver ions released are proportionate to the amount of exudate.



Silver Dressings

LOW TOXICITY

- ✓ Only a small amount of the silver applied to the wound by dressing is involved in the antimicrobial action
- ✓ Most remain within the dressing or bind to proteins or necrotic wound cells
- ✓ Systemic absorption is minimal
- ✓ Although absorbed at the systemic level, silver is mostly excreted via the bile through the faeces, while a small part is excreted through the urine
- ✓ Silver is not absorbed either by the central or peripheral nervous system

Silver Dressings

Have not yet shown any bacterial resistance

Silver

Active against multiple targets

Reduced possibility to develope a resistance mechanism

Antibiotic

Active against a single target

Increased possibility to develope a resistance mechanism

Particularly against MDROs (MultiDrug Resistant Organisms)

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journal homepage: www.elsevier.com/locate/ijantimicag

Targeting biofilms of multidrug-resistant bacteria with silver oxynitrate

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ABSTRACT

A topical antimicrobial, silver oxynitrate (Ag_7NO_{11}), has recently become available that exploits the antimicrobial activity of ionic silver but has enhanced activity because highly oxidised silver atoms are stabilised with oxygen in a unique chemical formulation. The objective of this study was to use a multifaceted approach to characterise the spectrum of antimicrobial and antibiofilm activity of a wound dressing coated with Ag_7NO_{11} at a concentration of 0.4 mg Ag/cm^2. Physiochemical properties that influence efficacy were also evaluated, and Ag_7NO_{11} was found to release a high level of Ag ions, including Ag^{2+} and Ag^{3+}, without influencing the pH of the medium. Time–kill analysis demonstrated that a panel of multidrug-resistant pathogens isolated from wound specimens remained susceptible to Ag_7NO_{11} over a period of 7 days, even with repeated inoculations of 1×10^6 CFU/mL to the dressing. Furthermore, established 72-h-old biofilms of *Pseudomonas aeruginosa*, *Staphylococcus aureus* and two carbapenem-resistant Gram-negative bacteria (bla_{NDM-1}-positive *Klebsiella pneumoniae* and bla_{VIM-2}-positive *P. aeruginosa*) were disrupted and eradicated by Ag_7NO_{11} in vitro. Ag_7NO_{11} is a proprietary compound that exploits novel Ag chemistry and can be considered a new class of topical antimicrobial agent. Biocompatibility testing has concluded Ag_7NO_{11} to be non-toxic for cytotoxicity, acute systemic toxicity, irritation and sensitisation.

Inorganic Chemistry

Article

Cite This: Inorg. Chem. XXXX, XXX, XXX−XXX

pubs.acs.org/IC

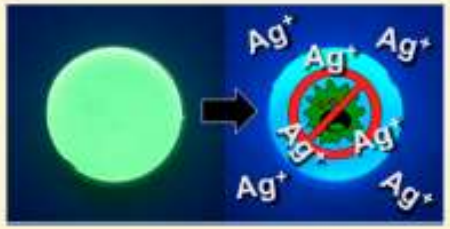
Incorporation of a Theranostic "Two-Tone" Luminescent Silver Complex into Biocompatible Agar Hydrogel Composite for the Eradication of ESKAPE Pathogens in a Skin and Soft Tissue Infection Model

Miguel N. Pinto, Jorge Martinez-Gonzalez, Indranil Chakraborty, and Pradip K. Mascharak*

Contribution from Department of Chemistry and Biochemistry, University of California, Santa Cruz, California 95064, United States

Supporting Information

ABSTRACT: Microbial invasion and colonization of the skin and underlying soft tissues are among the most common types of infections, becoming increasingly prevalent in hospital settings. Systemic antibiotic chemotherapies are now extremely limited due to emergence of drug-resistant Gram-positive and multidrug-resistant Gram-negative bacterial strains. Topical administration of antimicrobials provides an effective route for the treatment of skin and soft tissue infections (SSTIs). Therefore, the development of new and effective materials for the delivery of these agents is of paramount importance. Silver is a broad-spectrum antibiotic used for the treatment and prevention of infections since ancient times. However, the high reactivity of silver cation (Ag^+) makes its incorporation into delivery materials quite challenging. Herein we report a novel soft agar hydrogel composite for the delivery of Ag^+ into infected wound sites. This material incorporates a Ag(I) complex $[Ag_2(DSX)_2(NO_3)_2]$ (**1**; DSX = 5-(dimethylamino)-*N*,*N*-bis(pyridin-2-ylmethyl) naphthalene-1-sulfonamide) that exhibits a change in fluorescence upon Ag^+ release and qualitatively indicates the end point of silver delivery. The antibacterial efficacy of the material was tested against several bacterial strains in an SSTI model. The complex **1**−agar composite proved effective at eradicating the pathogens responsible for the majority of SSTIs. The theranostic (therapeutic/diagnostic) properties coupled with its stability, softness, ease of application, and removal make this material an attractive silver-delivery vehicle for the treatment and prevention of SSTIs.



Silver Line Dressings

EMODIAL

EXIT-PAD® AG

EXIT-PRO® AG

NOVA SOVAN® AG

EXIT-POCKET® AG

NOVA BETAFIX® AG

Thank you

For Your Attention