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Review

Is reduced susceptibility to disinfectants and antiseptics a risk in healthcare settings? A point/counterpoint review

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SUMMARY

Background: Given the breadth and depth of antiseptic use, it is surprising how few large-scale studies have been undertaken into the consequences of their use, particularly in clinical practice. Depending on your point of view, this may either reflect an assurance that reduced susceptibility to antiseptics, and notably whether this confers cross-resistance to systemically administered antimicrobial agents, is not an issue of concern, or relative ignorance about the potential threat.

Aim: This point/counterpoint review offers a differentiated perspective and possible answers to the question, 'Should we be worried about reduced susceptibility to disinfectants and antiseptics in healthcare settings?'.

Methods: This topic was the subject of a debate by MHW (point) and SH (counterpoint) during the SHEA Spring Conference 2013: Advancing healthcare epidemiology and the role of the environment, held in Atlanta, GA, USA on 4th May 2013. This review is a general representation of the main themes presented during the debate, rather than a systematic review of the literature.

Findings: There are examples of reduced susceptibility to antiseptics in clinical practice; however, to date, there is no strong evidence that reduced susceptibility to antiseptics is a major clinical problem. Given the growing number of potential indications for use of biocidal active ingredients, the potential for emergence of reduced susceptibility remains a concern.

Conclusions: Changes in the clinical use of antiseptics should be matched with surveillance studies to understand whether there are unintended microbiological or clinical consequences, including the selection of bacterial strains that can survive exposure to antiseptics.

Statement for debate

Reduced susceptibility to antiseptics and disinfectants is a risk to patients in healthcare settings.

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Introduction

Antimicrobial agents comprise antibiotics and biocidal products. Antibiotics may be used for systemic or topical treatment of infections, pre-emptive therapy of contaminated sterile sites, and as prophylactics in patients undergoing surgery.[1] Biocidal products are commonly used for everyday purposes and are not restricted to use in the healthcare setting. The EU Biocidal Products Regulation (EUBPR) 528/2102 includes 22 product types that are divided into four categories: disinfectants, preservatives, pest control and other biocidal products.[2] The 22 product types encompass a range of uses, including products used for the preservation of manufactured products (e.g. cosmetics and personal hygiene products) and products that are used by the veterinary and farming industries.

It is the products categorized by the EUBPR as disinfectants that are central to this review. Disinfectants can be divided into five groups, and this review will concentrate on those agents that are used topically for the purposes of hand hygiene and skin decolonization (commonly known as antiseptics) and those agents that are used to remove viable microorganisms from inanimate objects and surfaces (disinfectants).[2]

Bacterial survival following exposure to antiseptics has been recognized for many decades, and multiple mechanisms conferring decreased susceptibility to antiseptics have been identified and described. Reduced susceptibility to antiseptics and disinfectants in health care has received little attention, in contrast to the threat of antibiotic resistance.[3] Is this lack of attention justified or could reduced susceptibility to antiseptics and disinfectants be a reason for major concern?

When discussing the potential clinical implications of reduced susceptibility to antiseptics, the prime concern is when bacterial survival can occur following challenge with in-use concentrations of an antiseptic. Multiple terms have been used in the context of susceptibility to antiseptics (e.g. insusceptible, phenotypically tolerant, tolerant or resistant), and 'resistance' may be acquired, intrinsic or functional. Intrinsic resistance, or insusceptibility, to antiseptics is well described; for example, *Mycobacterium chelonae* recovered from endoscope washer-disinfector rinse water samples despite exposure to 2% glutaraldehyde.[4] Intrinsic properties of the outer cell membrane of Gram-negative bacteria also confer resistance to antiseptics at in-use concentrations.[5] Phenotypic tolerance or functional resistance refers to the survival of a micro-organism in the presence of an antiseptic during specific growth conditions, such as *Pseudomonas* spp. growing in a biofilm or clostridial spores. The most concerning form of insusceptibility to antiseptics, however, is acquired resistance, which has the potential for intra- and interspecies transfer. Acquired resistance to antiseptics and disinfectants will form the main subject of this review, rather than intrinsic or functional resistance. Table I summarizes a selection of published examples of the emergence of reduced susceptibility to antiseptics. While there are multiple examples, such as alterations to porins,[6] efflux mechanisms (quaternary ammonium compounds)[7] and oxidative stress regulators (OxyR, PerR),[8] mechanisms of acquired resistance to antiseptics are often poorly understood.

Point: reduced susceptibility to antiseptics and disinfectants is a risk in healthcare settings

Information concerning the amount of antiseptics used in the healthcare setting is lacking, and the use of biocidal active ingredients is often unregulated and unrestricted

The use of antiseptics in general and the variety of products containing biocidal active ingredients have increased substantially over the last 10 years.[3] For instance, biocidal active ingredients, such as chlorhexidine and triclosan, are often used in domestic and cosmetic products;[9] however, the evidence to support the inclusion of biocidal active ingredients in such products is often limited.[10,11] Indeed, the use of some biocidal active ingredients for some indications has limited or no clinical benefit when equivalent alternatives are available.[12] When biocidal agents are used without indication, their presence may add to the overall selective pressure of nosocomial pathogens without a clear benefit.

A European expert committee report[13] in 2009 noted that it was not possible to obtain any valid tonnage information on the quantities of biocides, including antiseptics, used in health care, but noted that production volumes of many compounds are several orders of magnitude higher than those of antibiotics. This absence of data is telling in itself, possibly reflecting a lack of concern about unintended consequences of antiseptic use, and needs to be addressed. Better stewardship, regulation and restriction of biocidal active ingredients in non-healthcare settings would limit bacterial exposure to antiseptics and biocidal active ingredients, and may decrease the selection of bacteria with reduced susceptibility to these agents.

Lack of a standardized method for measuring reduced susceptibility to antiseptics hinders understanding of the clinical impact of this phenomenon

Defining and detecting bacterial resistance to antiseptics is not straightforward.[14] Using standardized methods of susceptibility testing and parameters such as minimum inhibitory concentrations (MICs), bacterial resistance to antibiotics is generally well defined; however, for various reasons, resistance measured in terms of MICs and minimum bactericidal concentrations (MBCs) is of less relevance to antiseptics. Firstly, MICs and MBCs relate to specific concentrations attainable in body fluids (e.g. serum, urine), which is not relevant to antiseptics.[15] Secondly, lethal rather than inhibitory effects are important when using antiseptics.[5] Thirdly, bacteria are tested *in vitro* against much lower concentrations of antiseptics, and bacterial survival at an MIC such as 4–32 mg/L does not necessarily guarantee bacterial survival at the much higher concentrations that are achieved in practice.[16] The lack of a standard definition of resistance to antiseptics, and absence of standardized methods of detection mean that, to date, there is no systematic method for measuring the clinical impact of reduced susceptibility to antiseptics.

Cross-resistance and co-resistance occurs between antiseptics and antibiotics

A European expert committee concluded that biocides disseminated in the environment may pose a biological hazard