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Resistance to disinfectants in food industry associated bacteria – a review*

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Introduction

Disinfectants and antiseptics have for decades been used in the human and veterinary medicine as well as in the food industry. A recent trend is the use of such compounds in other areas including various household products (1). In vitro studies suggest that bacterial exposure to disinfectants may contribute to antimicrobial resistance development (2, 3). It is therefore a potential risk that broad-scale use and possibly mis-use of antiseptics and disinfectants will contribute to the emergence and/or selection of pathogens that are less susceptible to both disinfectants and antibiotics (4, 1). Failure in cleaning and disinfection increases the ability of bacteria to survive, adapt and establish in food processing equipment or environments with potential unintended transfer of bacteria to food products. This could have serious economical and health consequences. As connections between disinfectant and antibiotic resistance have become obvious, mechanisms of disinfectant action and resistance have gained renewed attention. To design safe and effective disinfection strategies that prevent bacterial tolerance/resistance development, knowledge on how bacteria and disinfectants interact under various conditions is essential.

The antimicrobial effects of disinfectants depend on several factors. In this review, we give a brief overview of the biological basis for bacterial tolerance/resistance to disinfectants in the food industry and discuss potential consequences of bacterial disinfectant resistance. Here, we apply the term resistance to describe bacteria growing or surviving in higher concentrations of disinfectants than other bacteria within a species. A special emphasis is on bacterial resistance to disinfectants based on quaternary ammonium compounds (QACs) which have been a focus in our laboratory.

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Occurrence of bacterial disinfectant resistance in the food industry

It has been suggested that the use of disinfectants has selected for resistant bacteria in the clinical area (5, 6). Less attention has been paid to resistance in the food processing environments. The limited data available on this area is also often difficult to compare because different definitions of resistance and resistance determining methods have been used.

In most screening studies, MIC-value determination has been used to assess resistance. Using this method it is possible to compare level of resistance between different strains or species. In Norway, 13 % of *Staphylococcus* spp., mostly from meat processing industry, were resistant to the QAC benzalkonium choride (BC) based on MIC-values (7, 8). For *Listeria monocytogenes,* between 13 and 19 % of the isolates were reported resistant to BC (9, 10). Strains being persistent in food processing environments had higher MIC-values against disinfectants than non-persistent strains (11). Another study found no significant differences in disinfectant resistance between persistent and non-persistent *L. monocytogenes* and *Escherichica coli* strains (12). Resistance to QAC was reported more frequent in isolates from the meat industry compared to human infectious strains (13). Although lactic acid bacteria (LAB) are generally considered non-pathogenic, LAB are important food spoilage bacteria. In a survey of 320 LAB isolated from food processing industry only 1.5 % were considered resistant to QAC (MIC>45 ug/ml) (14). *Pseudomonas* spp. are important food spoilage organisms and have high biofilm producing abilities. In an investigation of *Pseudomonas* spp. from chicken carcasses approximately 30 % of the strains could grow in the lowest recommended in-use concentration of BC (200 ug/ml) while the sensitive population had MIC-values of 40–60 ug/ml (15). *Pseudomonas* spp isolated from food or food processing equipment were in general equal or less tolerant to QAC than *Ps. aeruginosa* which is associated with infection (16). For enterobacteria between 1 and 3 % were reported resistant to amphoteric and QAC-based disinfectants, respectively (17). Interestingly, *Langsrud et al.* (18) described growth of *Serratia marcescens* strains in disinfectant footbaths containing in-use concentrations of an amphotheric disinfectant.

Resistance to oxidative disinfectants, such as hypochlorite and peroxide is rarely reported. Bacteria isolated from disinfecting footbaths with hypochlorite were not resistant to user-concentration of hypochlorite and had similar tolerance level as laboratory strains (16).

Bacterial strategies to survive disinfection

It has been claimed that resistance to disinfectants is not a problem in practical use since bacteria are often killed by user-concentrations in laboratory tests. However, bacterial tolerance to disinfectants and antiseptics varies and is dependent on a range of factors including properties of both the environment and the bacteria subjected to the disinfectants. Environmental factors affect the genotypic and phenotypic properties of bacteria and hence their susceptibility to disinfectants. The pres-

ence of resistant bacteria may also protect more sensitive bacteria against disinfectants (19). Therefore, the level of resistance found in laboratory tests (often using exponentially grown single cultures of laboratory strains in suspension) will not reflect the level in practical conditions.

In real world situations, bacteria attached to surfaces or within complex microbial communities (e.g. biofilms) exert a number of resistance mechanisms that provides protection to antimicrobial agents bacteria (4). The variations in disinfectant tolerance are due to differences in innate and acquired properties of the organisms (20). These include membrane structure, efflux pumps, the ability to inactivate disinfectants, and mutations conferring altered targets sites and differences in expression of protective mechanisms. The ability of bacteria to combine various resistance mechanisms is a powerful strategy to obtain resistance. A schematic illustration of bacterial disinfectant resistance mechanisms is presented in Figure 1. An overview of bacterial resistance mechanisms towards disinfectants commonly used in the food industry is presented in Table 1. A further description of these bacterial strategies/mechanisms to tolerate disinfectants is presented below.

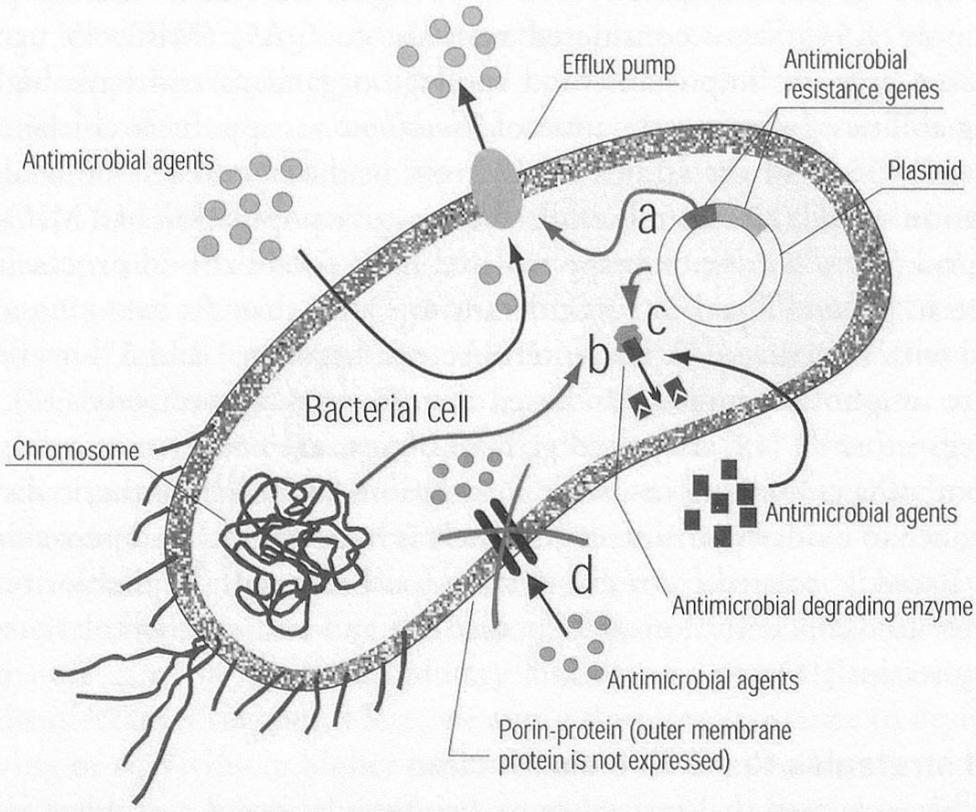

Figure 1 **Illustration of resistance mechanisms of the bacterial cell. (a) efflux of antimicrobials across the cell membrane (b) enzymatic degradation of antimicrobials (d) changes in the outer membrane illustrated by reduced influx of antimicrobials through membrane proteins. Resistance mechanisms may be encoded by genes present on the chromosome as well as on plasmids (c)**

Table 1
Classes, applications and bacterial resistance mechanisms of disinfectants commonly used in the food industry

Class	*Applications*	*Bacterial resistance mechanisms**				
		Inactivation	*Membrane impermeability*	*Efflux*	*Slime production*	*Other mechanism*
Alcohols (ethanol, isopropanol)	Skin Equipment Surfaces					Change in phospholipids
Alkyl amino acetate	Footbath Surfaces		(X)			
Amphoteric tensides	Equipment Surfaces Footbath		X			
Bisphenols (Triclosan)	Skin Equipment Surfaces Domestic	X	X	x		Change in lipid synthesis
Halogens/ Chlorine releasing agents (Hypochlorite, iodophores)	Equipment Surfaces Footbath				X	
Peroxygens (Hydrogen peroxide, peracetic acid)	Equipment Footbaths	X			X	
Quaternary ammonium compounds	Equipment Surfaces Footbath	(x)	X	x	X	

* Parentheses indicate that significance of this mechanism is unknown.

Membrane properties

The antimicrobial effect of disinfectants is dependent, at least in part, on the ability of the compound to interact and permeate the cell membrane. Bacterial membranes vary considerably in their permeability. Gram-negative bacteria are generally more tolerant to disinfectants than gram-positives, mainly caused by the relatively impermeable outer membrane of the former (21). Bacterial membrane properties are not static, but vary significantly according to environmental factors. Some bacteria form aggregates and slime (exopolysaccharides) when exposed to stressful conditions. This increases their disinfectant tolerance (22, 23). In natural environments, most bacteria are either attached to surfaces or present in biofilms.

This makes them much more tolerant to disinfectants than bacteria in solution (20). The tolerance of biofilm-embedded bacteria to disinfectants is dependent on the biofilm structure and the physiological state of bacteria. Anoxic conditions and nutrient depletion is typical at least in parts of biofilms.

A common strategy for gram-negative bacteria to achieve non-susceptibility is to reduce passage of biocides over the cell membrane by regulation of membrane structure and porin proteins under stressful conditions (24). Earlier studies indicated that resistance to QAC in *E. coli* and *Pseudomonas* was linked to decreased membrane permeability (25, 26). More recent studies have demonstrated that efflux also plays a significant role in resistance to QAC (and low-level cross-resistance to some antibiotics) in gram-negative bacteria (27, 28, 29). Bacteria adapted to grow in higher concentrations of disinfectants also often show increased efflux activity (30, 28, 10).

Efflux of antimicrobials

Bacteria contain cell membrane proteins that transport compounds across the membrane. Of special note is the broad substrate specificity of many of these proteins, termed efflux pumps, meaning that they can transport divergent compounds across the membrane. Gram-negative efflux systems have often the ability to pump out a broader range of substrates than gram-positive efflux proteins (29). Efflux can provide protection of the bacteria against antibiotics, and in combination with other mechanisms or bacterial phenotypic properties, it is a highly effective and flexible resistance mechanism towards many disinfectants. Bacteria within the genera *Pseudomonas* for instance are highly tolerant to many antimicrobials. This property is obtained through a combination of impermeable outer membrane and activity of broad-substrate efflux pumps (31, 32). Many efflux systems are active when the bacteria are exposed to certain stresses while they are inactive when their function is unnecessary. It has been demonstrated that sub-lethal exposure of certain bacteria to disinfectants or other stresses relevant in food and food production can activate efflux mechanisms (30, 10).

A higher frequency of resistance to a range of antibiotics among clinical staphylococci resistant to the QAC BC was demonstrated by Sidhu et al. (33). This indicates that the presence of one resistance determinant selects for the other during antimicrobial therapy in hospitals. In gram-positive bacteria (e.g. staphylococci), genes *(qacA–qacJ)* encoding pumps for efflux of QACs are often located on plasmids that can be transferred between bacteria (34, 35, 30, 7, 36, 5). Some antibiotic resistance genes are frequently co-located on these plasmids. This contributes not only to effective spread of disinfectant resistance genes but also to concurrent spread of antibiotic resistance. Coagulase negative staphylococci are suspected to be a reservoar of resistance genes with gene transfer to pathogens like *S. aureus* (37). Efflux pumps thus effectively contribute to increased resistance to a wide spectre of compounds in many bacteria. In a recent study, QAC resistance in staphylococci

was positively correlated with biofilm formation on steel and polystyrene (38). For *L. monocytogenes,* efflux seems to be important for QAC resistance (39, 10). This could indicate a synergistic effect between biofilm formation and efflux. *Heir et al.* (2004) also reported an overall higher occurrence of QAC-resistant *L. monocytogenes* isolates from the meat industry compared to human isolates (13).

Although the contribution of efflux mechanisms in providing resistance to QACs at recommended user concentrations seems limited in laboratory in-vitro experiments, synergistic effects by the combination of reduced uptake and efflux may provide a selective advantage in real world QAC containing environments. An important consideration is the practical real-life concentrations of disinfectants that often will be far below recommended user-concentrations. In practical use there will be concentration gradients and sub-effective concentrations will occur in the environment (4). At low concentrations, biocides may be much more selective in their action than when used at higher concentrations. This emphasis the need for studying the effects of low-level disinfectant concentrations to understand bacterial adaptation and resistance to disinfectants and antibiotics (see below).

Additional bacterial resistance mechanisms

Some bacteria have enzymes that degrade certain disinfectants (e.g. QACs and triclosan). Others have the ability to use disinfectant compounds as a carbon source, thus potentially stimulating growth rather than inhibiting or killing the bacteria (40). Although of unknown significance, bacteria with the ability to degrade disinfectants could lower the concentrations of active bactericidal compounds. This may also stimulate survival, adaptation and/or selection of more susceptible bacteria in a community. This mechanism of resistance is expected to be more effective with sessile cells (e.g. biofilms) where bacterial clusters capable of enzymatic disinfectant degradation will confer resistance to adjacent susceptible bacteria (4, 20).

Exposure to antimicrobials may provoke genetic mutations. The effect of triclosan exposure to various bacteria has been extensively studied since the first reports of the antibacterial mechanisms of triclosan (41, 42, 6, 43). This indicated triclosan, at least at sub-lethal concentrations, to exert its antibacterial action on a single bacterial enzyme (enoyl reductase; involved in bacterial lipid synthesis). Triclosan thus acted more as an antibiotic than as a multi-target disinfectant. Notably, sub-lethal concentrations of triclosan can select for mutations in the gene encoding this enzyme, making triclosan inactive and thus increase the resistance to triclosan among bacteria. Of significant concern was the observation that this enzyme also is the target for the antitubercular agent isoniazide. Recent data suggests that selection of high-level bacterial resistance by triclosan exposure is not widespread but linked to certain enteric bacteria (44). However, the considerable increases in use and environmental exposure to triclosan, the often limited antibacterial effects of triclosan reported and still unresolved issues regarding resistance development, question the widespread use of triclosan (45, 43). In general, strategies to avoid repeated sub-

lethal exposures to disinfectants should be emphasised to reduce the risk for development and selection of bacterial mutants with increased resistance to antimicrobials.

Perspectives on disinfectant resistance

Recent studies using both gene expression and proteomic analyses on *E. coli* has revealed an increased understanding of the resistance mechanisms and cellular stress responses involved when bacteria are exposed to sub-inhibitory QAC concentrations and during bacterial adaptation to QAC (46, 47). These studies showed activation of several resistance mechanisms, including general stress regulators (SoxS and MarA), efflux proteins (e.g. AcrB) and porins (reduced expression of OmpF). QAC exposure induced stress responses normally related to protection against oxidative stress. Exposure to sub-MIC levels also indicated activation of genes having direct functions in protecting the outer membrane against cell damaging agents (47). The mechanisms involved in the maintenance of resistance and potential effects this could have on the development of cross-resistance to other antimicrobials (including antibiotics) needs still to be investigated.

It has been suggested that the widespread use of disinfectants in clinical environments has selected for strains being resistant to both disinfectants and antibiotics (5, 6). Adaptation and exposure to sub-lethal concentrations of disinfectants can also confer increased resistance to clinically relevant antibiotics. It is also clear that certain disinfectants (e.g. triclosan) and antibiotics have similar effects on bacteria. Use of certain disinfectants may also co-select for antibiotic resistance since disinfectant resistance genes may be located adjacent to antibiotic resistance genes in both gram-positive and gram-negative bacteria (48, 33). However, the capacity of bacteria to adapt to disinfectants is not general, but dependent on a number of factors where the antibacterial mechanisms of the disinfectant as well as the properties of the microorganism or microflora are the most obvious.

More information is needed on the long-term effects of widespread use of disinfectants with regard to bacterial ecology, resistance development and environmental effects. Until more knowledge is obtained, use of disinfectants should be restricted to areas and products where they have a documented and needed antimicrobial effect.

How to avoid resistance in practice?

From scientific studies and our experience, it is possible to make some recommendations regarding measures to avoid resistance:

1) Choose an effective disinfectant: Classes of disinfectants differ in their properties regarding e.g. targets and modes of action and in their ability to inhibit and kill bacteria under various conditions.
2) Disinfect at optimal conditions: Never disinfect a dirty surface, use the recommended concentration, temperature and exposure time.

3) Rinse thoroughly after disinfection: Exposure to sub-lethal concentrations of disinfectants may allow bacteria to adapt, survive and grow in higher concentrations of disinfectants and to develop cross-resistance to antibiotics.
4) Rotate between different disinfectants: Using another disinfectant e.g. every second week will probably kill resistant bacteria. It is important to choose disinfectants with completely different mechanisms of action.

Summary

In vitro studies suggest that bacterial exposure to disinfectants may contribute to antimicrobial resistance development. It is therefore a potential risk that broad-scale use of antiseptics and disinfectants will contribute to the emergence and/or selection of pathogens that are less susceptible to both disinfectants and antibiotics. Failure in cleaning and disinfection increases the ability of bacteria to survive, adapt and establish in food processing equipment or environments with potential unintended transfer of bacteria to food products. Here, we apply the term resistance to describe bacteria growing or surviving in higher concentrations of disinfectants than other bacteria within a species. A special emphasis is on bacterial resistance to disinfectants based on quaternary ammonium compounds (QACs) which have been a focus in our lab.

Zusammenfassung

In vitro Studien zeigen, dass der häufige Kontakt von Mikroorganismen mit Desinfektionsmitteln zur Entwicklung von Resistenzen beitragen kann. Dabei wird der Ausdruck «Resistenz» gebraucht, um die Tatsache zu beschreiben, dass gewisse Bakterien in höheren Konzentrationen von Wirksubstanzen wachsen oder überleben können als andere, der gleichen Spezies. In diesen Ausführungen wird der Focus auf die Resistenz gegenüber quarternären Ammoniumverbindungen (QAV) gelegt, da dies einer unserer Forschungsschwerpunkte ist.

Résumé

Les études in vitro suggèrent que l'exposition bactérienne aux désinfectants puisse contribuer au développement antimicrobien de résistance. Ici, nous appliquons la terme «résistance» pour décrire des bactéries accroissant ou survivant dans des concentrations plus élevées des désinfectants que d'autres bactéries de la mème espèce. Une considération particulière est sur la résistance bactérienne aux désinfectants basés sur les composés d'ammonium quaternaire (QACs) qui a été un point principal de la recherche dans notre laboratoire.

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