Rev. sci. tech. Off. int. Epiz., 2012, **31** (1), 89-104

Cross-resistance between biocides and antimicrobials: an emerging question

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Summary
The widespread use of biocides, and their resulting dissemination in the environment, can contribute to adaptations in bacteria leading to the development of low-level susceptibility to antibacterial agents. The mechanisms of resistance in bacteria are similar for both antimicrobials and biocides, and exposure to biocides can result in cross-resistance to antibacterial agents. Resistance mechanisms altering the activity of biocide and antibiotic molecules are discussed with regard to regulation and mode of action in the light of laboratory studies of induced resistance. It is clear that in order to preserve their activity and avoid the development of possible cross-resistance, prudent use of antibacterial agents is to be strongly recommended, not only in clinical settings but also in veterinary and agricultural and other applications.

Keywords
Antibiotic – Antimicrobial – Biocide – Drug transport – Efflux pump – Genetic regulation – Multidrug resistance.

Introduction

The worldwide dissemination of 'multidrug-resistant' pathogens has markedly reduced the efficacy of our antibiotic arsenal and increased the frequency of therapeutic failure (for details of the resistance of specific pathogens, see the websites of the Centers for Disease Control and Prevention [www.cdc.gov/drugresistance/index.html], the European Food Safety Authority [www.efsa.europa.eu/en/topics/topic/amr.htm], the European Centre for Disease Prevention and Control [www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/Pages/index.aspx] and the World Health Organization [www.who.int/drugresistance/en/]). Today, antibiotic resistance is a major concern in the anti-infective treatment of both humans and animals. Bacteria are able to respond efficiently to new environmental stimuli such as antimicrobial molecules, and, consequently, resistance emerges and is disseminated by antimicrobial use (13, 27, 37, 42, 65). Serious concerns about bacterial drug resistance among nosocomial, community-acquired and foodborne pathogens have been increasing for a number of years, and have been raised at both national and international level.

In contrast to antibiotics, which have precise targets and modes of action, biocides have no specific microbial targets and may have multifactorial modes of action (103): biocides may act as electrophilic or membrane-active agents, depending on the concentration used (93, 132, 134). Electrophilic agents react with critical enzymes and inhibit growth and metabolism, with cell death occurring after several hours' contact. For example, modification of the functional groups of proteins and nucleic acids by oxidation or precipitation is characteristic of the mechanism of action of carbamates and isothiazolones (93). Membranotropic active products directly affect bacteria either by disrupting their membranes (surfactants, phenols, biguanides alcohols, amines, quaternary ammonium compounds [QACs]) or by a protonophoric interaction with membrane components (weak acids,

parabens, pyrithiones). This is a simplified classification of mechanisms of action, as some biocides exhibit multiple effects, for example, QACs exert their effect on proteins and enzymes by denaturation (solubilisation and depolymerisation) (2, 3, 4, 75, 76, 93). Table I presents a brief classification of the biocide family (disinfectants, antiseptics, preservatives). Interestingly, metals exhibit antimicrobial activity against a wide range of microorganisms, and have long been used as broad-spectrum antimicrobial agents (169). For this reason, they have not been included in Table I as a specific group. Recently, nanoparticle technology has produced several new antibacterial agents, including not only the usual antimicrobial and biocide molecules but also nanometal particles (e.g. silver, copper and zinc) (24, 30, 48). This new generation of antibacterials is particularly attractive in that it allows the development of new tools to combat bacterial resistance associated with biofilm structures or bacterial isolates exhibiting a modified envelope associated with reduced susceptibility to standard antibacterial drugs (15).

Table I
Biocide classification

Agents	Examples	Bacterial target	Bacterial spectrum	Applications		
				Antisepsis	Disinfection	Preservation
Alcohols	Ethylic alcohols Ethanol Phenoxyethanol Propanol Propyleneglycol Isopropanol	Membrane uncoupler Protein denaturation	Gram positive Gram negative Mycobacteria	•	•	•
Aldehyde	Formaldehyde Glutaraldehyde	Cell wall	Gram positive Gram negative Mycobacteria		•	
Anionic surfactants	Diethylamine	Cell wall	Gram positive Gram negative Mycobacteria		•	
Biguanides	Chlorhexidine digluconate	Cytoplasmic membrane	Gram positive Gram negative	•	•	•
Diamidines	Hexamidine	Cytoplasmic membrane	Gram positive	•		
Dyes (acridines, triphenylmethane)	Acridine Eosin	Nucleic acids	Gram positive	•		
Halogens – Chlorine compounds – Iodine	Sodium hypochlorite Chloramine Iodine Povidone–iodine	Nucleic acids	Gram positive Gram negative Mycobacteria	•	•	•
Hydrogen peroxide		Nucleic acids	Gram positive Gram negative Mycobacteria		•	
Metals	Silver nitrate	Enzymes	Gram positive		•	
Metal chelates complexes	Copper Mercuric chloride Phenyl mercury Thiomersal	Nucleotides	Gram negative		•	
Organic acids and esters	Parabens Propionic acid Potassium sorbate Sodium benzoate	Cytoplasmic membrane Transport inhibition	Gram positive Gram negative		•	•
Phenolics	Chlorophenols triclosan	Cytoplasmic membrane	Gram positive Gram negative		•	•
Quaternary ammonium compounds	Benzalkonium chloride Cetrimide Cetylpyridinium Dequalinium chloride	Cytoplasmic membrane	Gram positive	•	•	•

Unfortunately, some intrinsic or genetically acquired bacterial resistance processes, such as efflux pumps, are effective against both antimicrobials and metals (9, 151). Resistance to both metals and antimicrobials has been reported in isolates collected from the environment (9, 47, 151).

The mechanisms of resistance to antibiotics have been widely studied and reported in the scientific literature; in contrast, mechanisms of resistance to biocides have been studied and characterised only recently. However, there are similarities in the antibacterial properties and resistance mechanisms employed by bacteria against these two groups of drugs (131, 132, 133, 134, 135, 144). Consequently, it is important to understand the molecular and genetic basis for the selection of resistant bacteria by antimicrobial agents (even when they are used correctly) and to evaluate the corresponding health risks. It is also essential to decipher the genetic, biochemical and physiological basis of the mechanisms which underlie the resistance of pathogens to biocides so that we can combat the emergence and dissemination of resistant pathogens, which limit the efficacy of our antibacterial arsenal. This is especially important in view of a recent report that triclosan can trigger the expression of a drug efflux pump in the opportunistic pathogen *Stenotrophomonas maltophilia*: the biocide removes the repressor from the operator region and promotes the synthesis of the multidrug efflux pump SmeDEF (62). There is also serious concern over the definition and interpretation of the terms 'resistance' and 'susceptibility' with regard to the activity of antimicrobials and biocides against bacteria (23).

Biocides may be used for a variety of applications, including water treatment, wastewater treatment or industrial use. The expansion in the use of biocides is predicted to continue; consequently, the hazard or risk of biocide use leading to the selection of drug-resistant bacteria, followed by the selection and dissemination of resistant pathogens, is of increasing concern (95, 97). Therefore, the aim of this paper is to describe the main mechanisms involved in biocide resistance and the capacity of resistant bacteria to disseminate, and to evaluate the possible interactions between the use of biocides and the emergence of antimicrobial resistance in pathogenic bacteria.

Biocides and bacterial resistance

The activity of biocides against bacteria has been reported to be in decline since the 1950s (94, 96, 131, 132, 133, 134, 135). In most cases, a low bacterial susceptibility to biocides is correlated with a decrease in the effective biocide concentration (131). Furthermore, bacterial resistance to all known preservatives has been reported (26, 97).

Most reports of bacterial resistance to biocides are based on laboratory-based investigations describing a decrease in susceptibility to a variety of agents such as cationic biocides, isothiazolones, phenolics and other compounds (36, 89, 91, 157, 159, 166, 172). In addition, clinical resistance of bacteria to numerous biocidal compounds such as chlorhexidine, QACs, bisphenol, triclosan, parabens and other substances, including glutaraldehyde and peroxygens, has been reported (10, 36, 38, 41, 44, 49, 50, 52, 57, 64, 100, 111, 112, 128, 138, 164, 166).

Many studies have reported that, in contrast to their efficacy against planktonic cultures, there has been a noticeable decrease in the activity of a number of biocides, including chlorine, QACs and aldehydes, against bacterial biofilms (83, 146). The precise mechanisms that contribute to this resistance remain unclear but may involve a multifactorial process associated with the physiological and structural characteristics of the biofilm. Smith and Hunter (146) reported that, although biocides may be effective against planktonic populations of bacteria such as meticillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, some biocides currently used in hospitals are ineffective against bacterial pathogens growing as biofilms attached to surfaces, and fail to control this source of hospital-acquired infections (146). The tolerance to triclosan of *Salmonella* spp. in a biofilm has been attributed to limited diffusion of the biocide through the extracellular matrix, while changes in gene expression might provide further resistance both to triclosan and to other antimicrobials (153).

It is now well accepted that biofilms are heterogeneous structures of which there are various subtypes with distinct physiological states and resistance phenotypes (148). A recent study reported the dynamics of peracetic acid and benzalkonium chloride activity against *Pseudomonas aeruginosa* biofilms and concluded that diffusion through the biofilm structure could be the main factor contributing to the resistance to these biocides (19).

Biocide concentration and bacterial susceptibility

Biocide concentration has been recognised as the key factor that controls their antibacterial efficacy (97, 136). Biocide concentration, and consequently bacterial susceptibility, is markedly reduced as a result of a reduction in the number of active molecules passing through the bacterial biofilm (6, 78, 95, 154). Normative

tests have established specific recommendations (guidelines for use) for all biocides regarding the dilution of product, how the diluted solution should be stored and the contact time required for each specific application. The misuse (dose, dilution, contact time, etc.) of biocides in medical practice has sometimes resulted in bacterial adaptation to low concentrations of product (26, 94, 95).

Numerous reports on bacterial resistance to biocides have referred to the determination of minimum inhibitory concentrations (MICs), which are largely used to determine susceptibility to antibiotics and used in many studies to measure alterations in bacterial susceptibility to a biocide (136, 166). Using low concentrations of a biocide might select bacteria with decreased susceptibility or those with some resistance to or tolerance of the biocide. The level of resistance can increase as a result of repeated exposure to a low concentration or to increasing concentrations (a gradient) of a biocide (1, 73, 95, 157, 160, 166). The evaluation of bacterial growth kinetics in the presence of a low concentration of a biocide can also give an indication of a change in bacterial phenotype (45, 95, 160).

Mechanisms of resistance to biocides

As for antibiotics, there are many different target sites for biocides in bacterial cells. Consequently, different resistance mechanisms have been selected by bacteria to combat biocide activity, as previously described for antimicrobials (5, 31). The main mechanisms of biocide resistance are summarised in Table II.

Intrinsic bacterial resistance to biocides

Modification of the bacterial envelope

Among the intrinsic mechanisms of resistance, some are associated with the bacterial cell itself, others with the organisation of biofilms. The most common mechanism arises from an alteration in the structure of the bacterial envelope that results in a reduction in the membrane permeability. Consequently, the penetration of microbicide molecules is reduced, leading to a reduction in the effectiveness of biocides against bacterial cells (25, 34, 72). Lipopolysaccharides play a key role as a protective barrier in Gram-negative bacteria (34, 40, 86, 149, 150). There are also reports of reduced biocide activity associated with the modification of the outer membrane components, including proteins and phospholipids (14, 17, 53, 54, 102, 155, 156). According to these reports, exposure to low concentrations (less than the MIC) of biocides promoted significant changes in membrane organisation, resulting in reduced susceptibility to biocides.

The charges on the exposed cell surface contribute to bacterial mechanisms of resistance to positively charged biocides such as QACs (21). It is likely that bacterial resistance arises from a combination of different mechanisms (17, 156, 157).

In mycobacteria, the mycolyl-arabinogalactan layer increases the impermeability of the envelope to many antimicrobials (72, 92, 131). Similarly, the effective amount of biocide molecules that can penetrate mycobacteria is affected by the sugar composition of the cell wall (20, 55, 100, 165). Consequently, mycobacteria exhibit a low intrinsic susceptibility to most antiseptics, except QACs and povidone used as oxidants.

Expression of efflux systems

The involvement of efflux pumps in biocide and antimicrobial resistance is well described (for documented reviews see references 5, 75, 76, 79, 109, 118, 121). Efflux pumps actively expel many antibacterial compounds, including biocides, and decrease their intracellular concentration (16, 76, 88, 108, 116, 118, 120, 122, 123, 124, 125). Several main classes of efflux system have been identified: the drug/metabolite transporter (DMT) superfamily, including the small multidrug resistance (SMR) family; the major facilitator superfamily (MFS); the

Table II
Biocide susceptibility and mechanisms of resistance
Adapted from reference 141

Biocide susceptibility	Resistance mechanism	Origin/Nature	Cross-resistance between biocides and	
			Biocides*	Antibiotics
Decreased susceptibility to resistance	Change in envelope properties (structure, permeability)	Intrinsic/acquired	+	+
Decreased susceptibility	Expression of efflux pumps	Intrinsic/acquired	+	+
Decreased susceptibility to resistance	Compound modification	Intrinsic/acquired	+/–	–
Decreased susceptibility	Target modification (mutation)	Acquired	+/–	–
Decreased susceptibility	Phenotypic change (by metabolic step)	Intrinsic/acquired	?	?

*to other biocides – level of susceptibility defined according to the concentration of biocides

ATP-binding cassette (ABC) family; the resistance nodulation division (RND) family; and the multidrug and toxic compound extrusion (MATE) family (16, 79, 88, 122, 123). Efflux pumps are involved in reducing the efficacy of a number of biocides, including QACs, triclosan, phenolic parabens and intercalating agents (8, 29, 32, 59, 60, 61, 74, 80, 81, 101, 152, 158). In *Staphylococcus aureus* several efflux pumps have been identified, for example QacA-D (80, 129, 168), Smr (84), QacG (59, 61) and QacH (60), and in Gram-negative bacteria several others have been characterised, for example MexAB-OprM, MexCD-OprJ, MexEF-OprN and MexJK (28, 106, 123, 142) in *Pseudomonas aeruginosa* and AcrAB-TolC, AcrEF-TolC and EmrE (90, 105, 110, 123, 124) in *Escherichia coli*.

The increasing reliance on biocides for pathogen control in food production and processing heightens the risk of selection of biocide-resistant strains of pathogens. Of particular concern is the potential for sublethal exposure to biocides to select bacteria with enhanced multidrug efflux pump activity capable of providing both resistance to biocides and cross-resistance to various other drugs (167). This indicates that the increased expression of efflux pump production contributes to decreasing the intracellular antibiotic concentration, in addition to increasing the selectivity of the efflux transporter. Moreover, in some isolates, efflux pumps are able to handle not only antimicrobials but also biocides, including disinfectants, antiseptics, sterilants and preservatives, that are frequently used in medical practice (58, 76, 79, 118, 124, 162). Importantly, it has recently been demonstrated that triclosan can release the repressor SmeT from its binding site on the operator region of the *SmeDEF* region, promoting the expression of the efflux pump that is involved in the expulsion of quinolones (62).

Modification of biocides and target mutations

The enzymatic modification of biocides has also been reported as a mechanism of bacterial resistance to heavy metals, parabens, aldehydes and peroxygens (29, 33, 71, 163). The biodegradation of various compounds has been well described, notably among pseudomonas and complex microbial communities. The alteration of target sites is not often characterised in biocide resistance and does not seem to be a general mechanism among bacteria. At low concentration, triclosan has been shown to interact specifically with an enoyl-acyl carrier protein reductase (56, 57, 77, 130, 147). The modification of this enzyme has been associated with low susceptibility to triclosan (56, 98, 115). Triclosan can interact with other bacterial targets when it is used at high concentrations (e.g. the bacterial membrane). The resulting alteration contributes to the lethal effect of the molecule (45, 46). In *E. coli*, FabI, which is involved in each step of the fatty acid elongation cycle, has been reported to be blocked by triclosan (90). Two enoyl-acyl carrier protein reductase isozymes, the previously characterised FabI enzyme plus a homologue of FabV, a triclosan-resistant enoyl-acyl carrier protein reductase identified in *Vibrio cholerae*, have been detected in *P. aeruginosa* (173). Consequently, a deletion of the *fabV* gene induces triclosan susceptibility, whereas the *fabI* mutant remains completely resistant (173).

Acquired resistance to biocides

The acquisition of resistance genes and the development of resistance mechanisms have been described previously (26, 171), and are involved in conferring cross- or co-resistance in different strains or species (12, 26, 69, 123).

Several studies have reported the induction of reduced susceptibility by exposing bacteria to a low concentration of a biocide. The mechanisms identified include the overexpression of efflux pumps, the overexpression of multigenic systems such as *soxRS* and *oxyR*, and the production of guanosine 5´-diphosphate 3´-diphosphate (36, 43, 51, 98, 126, 127). It is important to note that biocides can affect the expression of some genes involved in drug resistance in bacteria. Huet *et al.* (63) described how the transcription of efflux pump genes is stimulated during the exposure of clinical isolates of *S. aureus* to low concentrations of a variety of biocides and dyes. Bailey *et al.* (8) recently reported that exposure to triclosan induces a species-specific response in *E. coli* and *S. enterica*, corresponding to an increased expression of efflux pump genes. Finally, Hernández *et al.* (62) have demonstrated that triclosan can induce the expression of the SmeDEF pump, which is involved in the efflux of quinolones in *S. maltophilia* (62).

Exposure to biocides has been reported to have a drastic effect on bacterial physiology, for example, the emergence of small colonies, modification of growth rates and altered gene expression (143). Isothiazolones have been found to induce changes in metabolic processes in *P. aeruginosa* (1). Recently, it has been shown that resistance to triclosan could involve several distinct resistance mechanisms, including the overexpression and mutation of *fab1* and the production of the active efflux pump in *Salmonella* spp. and in *S. maltophilia* (62, 170). Interestingly, triclosan can also up-regulate the transcription in bacterial biofilms of various key genes including *acrB*, the gene coding for the major efflux pump, *marA*, the activator of the genetic cascade controlling multidrug resistance, and the genes *bcsA* and *bcsE* (153). This alteration in the membrane permeability may induce a marked decline in susceptibility to antimicrobial molecules and biocides.

A number of studies have described bacterial resistance to biocides in specific contexts, for example health care, consumer products, food production, animal husbandry

and foods of animal origin, and also resistance occurring in the environment. Moreover, the European Union Directorate-General for Health and Consumers has recently published two opinions regarding the possible risks associated with cross-resistance between biocides and antimicrobials (see references 140 and 141).

Mechanisms of resistance to biocides and antibiotics

The modes of action of antibiotic and biocide molecules share many similarities despite some differences in their activity, for example target and killing rate, and their behaviour and clinical features (124).

To a bacterium, these chemicals are noxious compounds, and a battery of mechanisms can be used to protect the cell irrespective of the contact site and the mode of use, for example in hospitals, animals, the environment, etc. In addition, some of these molecules can stimulate bacterial regulators triggering the membrane barrier that is the first line of defence against external chemical attacks (31). Consequently, bacterial response or adaptation to a chemical belonging to these drug families may involve some non-specific mechanisms that can also confer resistance to structurally unrelated molecules (Fig. 1).

Gram-negative bacteria can control the intracellular concentration of antibacterial agents by regulating membrane permeability. Two methods are currently described:

– a decrease in influx (uptake) by reducing the expression of active porins in the outer membrane or by altering the lipopolysaccharide structure

– the expression or overexpression of the efflux pumps (31, 79, 107, 114, 118, 122).

These strategies are associated with reduced susceptibility and resistance to antimicrobials and biocides (95, 161, 162). In addition, mechanisms of resistance, including mutations and acquisition of mobile genetic elements (transposons, plasmids) coding for resistance factors (enzymes, membrane transporters), can be acquired independently or favoured by activation of the membrane barrier. These different processes may provide complementary protection against antibiotics and biocides (95, 145). During the selection of biocide-resistant bacteria, the production of efflux pumps is often reported. The stable, resistant *Salmonella* spp. variants, selected with a quaternary ammonium disinfectant containing formaldehyde and glutaraldehyde, or with a tar acid-based disinfectant, conjointly exhibit a deficiency in outer membrane porins and an expression of efflux pump (mainly AcrAB-TolC) and all are less susceptible to

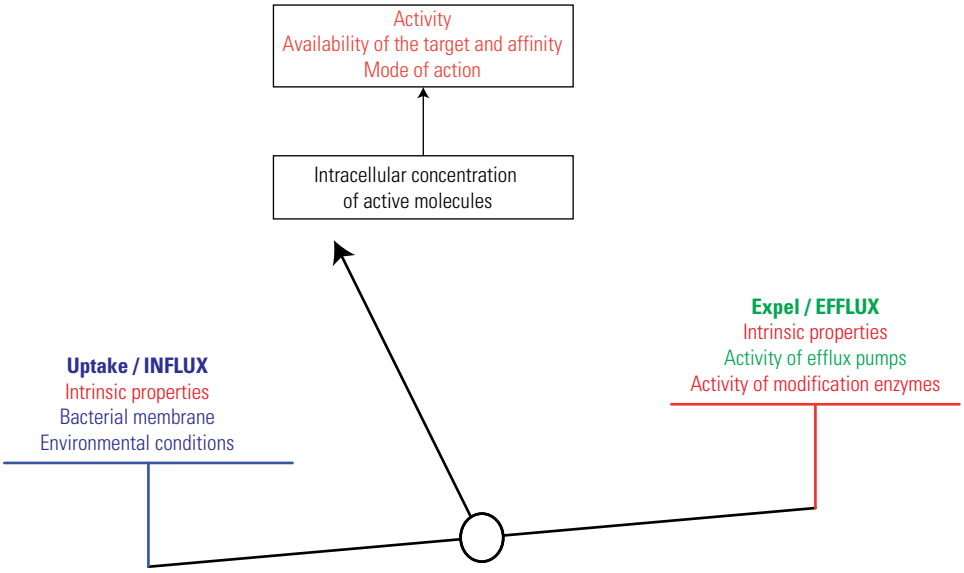

Fig. 1

Antibiotics and biocides, diffusion to the target and concentration

The figure summarises the various steps involved in the action of antibacterial agents in the case of an isolated bacterium. It is clear that in the case of antibiotics and biocides, in addition to the intrinsic molecular properties (in red), some common characteristics associated with bacterial physiology may favour the intracellular concentration of active molecules; for example, the organisation of the bacterial membrane, including the lipopolysaccharide structure, and the expression of functional porins provide efficient ways to penetrate the membrane barrier (in blue). Alternatively, different bacterial parameters can alter the concentration, for example activation of efflux pumps and expression of various transporters, and can contribute to the decrease in antibacterial activity (in green). Interestingly, the affinity of the molecule for its target also plays a role by fixing and protecting the drug towards the efflux mechanism

antimicrobials, including ciprofloxacin, chloramphenicol, tetracycline and ampicillin, than the wild-type original strain (66). A similar result was reported when *S. enterica* serovar Typhimurium was exposed to triclosan (67). A change in the susceptibility to antibiotics of *S. enterica* strains following exposure to various disinfectants at low concentrations has been also described (126, 127).

In *Stenotrophomonas* clones selected on triclosan, overexpression of the SmeDEF efflux pump, involved in antimicrobial resistance, has been detected (137). Recently, the same team demonstrated that exposure to triclosan can remove the SmeT repressor that controls the expression of this efflux pump (62). In *P. aeruginosa*, exposure to chlorhexidine triggers the overexpression of multidrug efflux systems (39). It is interesting to note that the exposure of *P. aeruginosa* to benzalkonium chloride induces the selection of a variant that is resistant to ciprofloxacin and novobiocin and exhibits an increase in MexB and MexD efflux pumps concomitant with a decrease in expression of the repressor MexR (85). A study performed in the community highlighted a significant relationship between high MICs for QACs and triclosan and resistance to one or more antibiotics (22). Interestingly, it has been reported in a study of *P. aeruginosa* adaptation to benzalkonium chloride that, among the two selected variants examined for cross-resistance, one strain exhibited resistance to chloramphenicol and polymyxin B, associated with an alteration in outer membrane proteins, cell surface change and hydrophobicity, whereas the other was resistant to tobramycin. This indicates that such adaptation is unique to each strain of *P. aeruginosa* (82).

Conclusion

The emergence of resistance mechanisms that alter the activity of antibacterial molecules is of international concern with regard to human health. The increased worldwide use, and misuse, of antibacterial agents and continuing widespread exposure to this drug family has resulted in the selection of less susceptible or resistant pathogenic strains. The principal driving force underlying the selection of resistant bacterial populations is the high concentration of antibacterial agents in the environment.

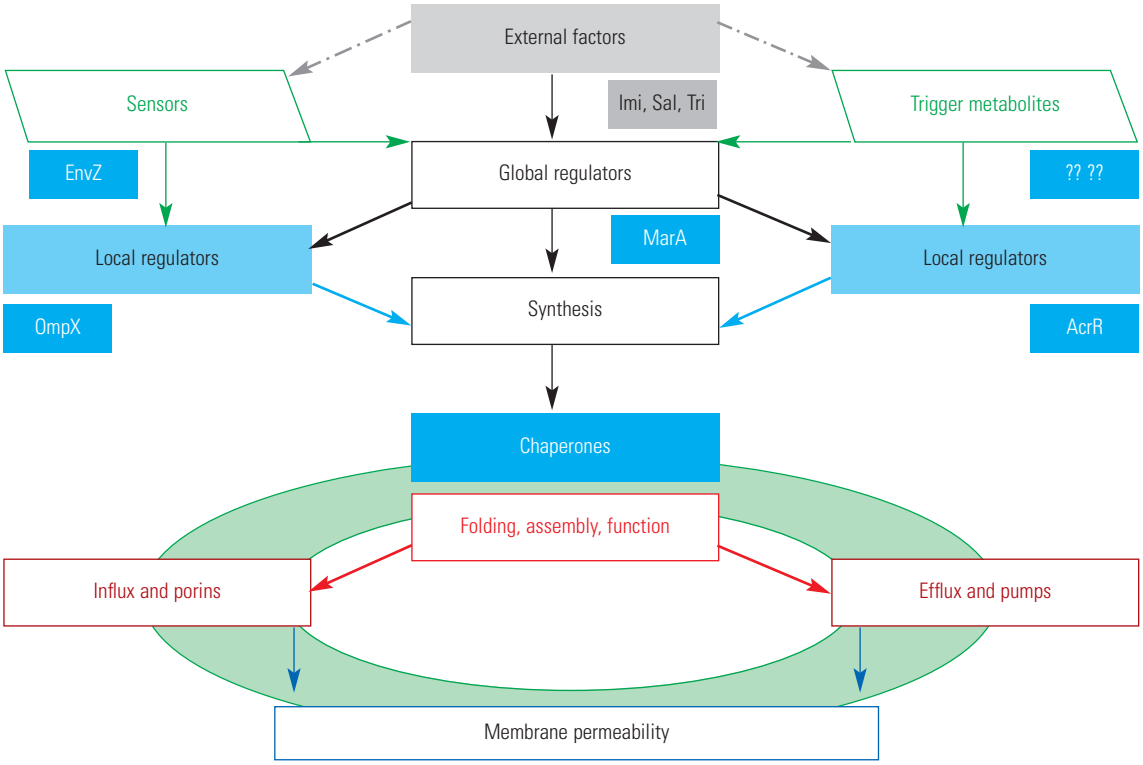

Fig. 2

Illustration of the sophisticated cascade of regulation controlling membrane permeability (adapted from reference 31)

Different levels are presented: (*i*) transcriptional and translational levels controlled by various sensors (EnvZ for porins), global regulators (RamA, SoxS are not indicated here) and local regulators (AcrR for efflux pumps and OmpX for porins), the accumulation of trigger metabolites can also modulate expression via local or global regulators, (*ii*) final membrane assembly in a functional conformation (via chaperones)

Imi: imipenem; Sal: salicylate; Tri: triclosan. These chemicals have been found to trigger the expression of resistance mechanisms during exposure of susceptible bacteria

EnvZ, MarA, OmpX and AcrA are various regulators or sensors involved in the control of drug transport

Notable concentrations of some biocide molecules have been detected in the environment and in wastewater treatment plants and effluent (18, 70, 87). This last point is highly significant as the presence of biocide concentrations in wastewater, aquatic wildlife, and animal and human samples may favour the exposure of previously susceptible bacteria to external selection pressures and lead to the emergence of less susceptible strains expressing resistance mechanisms.

The persistence of genetic mobile elements containing resistance genes involved in biocide and antimicrobial resistance is an additional risk factor. The presence of conjugative plasmids has been associated with co-resistance among a number of biocides such as cationic compounds, metallic salts (e.g. organomercurials) and antimicrobials (11, 73, 104, 117). Moreover, some chemicals are now described as 'efficient factors', able to trigger the expression of resistance mechanisms when bacteria are exposed to sublethal concentrations of the drug.

Various transcriptional regulators, for example SoxS, MarA and RamA, and several other genetic or biochemical factors (Fig. 2) play a strategic role in the genetic cascade controlling the expression of mechanisms involved in the modulation of bacterial susceptibility to biocides and antibiotics (31, 79, 113, 118, 124). The authors of a transcriptional study have reported that paraquat can induce the expression of several genes that are directly involved in antibiotic resistance (119). Similarly, exposure to triclosan can stimulate the expression of the SmeDEF efflux pump (62), and exposing *E. coli* and *S. enterica* cells to triclosan generates a modification in the expression of regulator genes (*soxS*) involved in the genetic control of antibiotic resistance (8). Moreover, paraquat activates the expression of the *soxRS* regulon, involved in the induction of resistance to ampicillin, nalidixic acid, chloramphenicol and tetracycline in laboratory strains of *E. coli* and *S. enterica*, and the *soxRS* regulon has also been associated with antibiotic resistance in clinical strains (68).

Currently, the involvement of biocides as selectors and/or inducers of mechanisms involved in the emergence of strains with reduced susceptibility to biocides and antimicrobials has been elicited from several genetic and bacteriological studies. Conjointly to the national and international recommendations regarding the use of antibiotics, these data clearly indicate the need for prudent use of this valuable family of antibacterial compounds in order to preserve their efficacy (103, 139). With an increasing number of products containing low concentrations of biocides, it is important to limit their release to the environment to reduce the selective pressure on bacteria likely to develop resistance (7, 35, 99).

■

La résistance croisée entre biocides et agents antimicrobiens : une question émergente

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Résumé

L'utilisation généralisée des biocides et leur subséquente dissémination dans l'environnement ont pour effet de renforcer les capacités d'adaptation des bactéries, induisant une diminution de leur sensibilité aux agents antibactériens. Les mécanismes de la résistance bactérienne étant similaires pour les antimicrobiens et pour les biocides, l'exposition aux biocides risque d'entraîner l'apparition d'une résistance croisée aux agents antibactériens. Les auteurs examinent les mécanismes de la résistance qui modifient l'activité moléculaire des biocides et des antibiotiques au niveau de leur capacité de régulation et de leurs modes d'action, à la lumière des études conduites en laboratoire à partir de résistances induites. Il convient de préconiser clairement l'utilisation prudente des agents antibactériens afin de préserver leur efficacité et d'éviter l'apparition

d'éventuelles résistances croisées, et ce non seulement dans les lieux de soins mais également dans le cadre d'autres applications, notamment vétérinaires et agricoles.

Mots-clés
Antibiotique – Antimicrobien – Biocide – Multirésistance – Pompes à efflux – Régulation génétique – Transport de médicaments.

El incipiente problema de la resistencia cruzada entre biocidas y agentes antimicrobianos

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Resumen
La extendida utilización de biocidas, y su consiguiente dispersión en el medio, pueden participar en un proceso de adaptación de las bacterias por el que estas resulten menos sensibles a los agentes antibacterianos. Los antimicrobianos y los biocidas inducen mecanismos parecidos de resistencia en las bacterias, y la exposición a biocidas puede engendrar resistencia cruzada a agentes antibacterianos. A partir de estudios de laboratorio sobre resistencia inducida, los autores examinan mecanismos de resistencia que alteran la actividad de moléculas biocidas y antibióticas desde el doble punto de vista de su regulación y su modo de acción. Es obvio que para preservar la eficacia de los agentes antibacterianos y evitar la aparición de posibles resistencias cruzadas conviene favorecer enérgicamente un uso prudente de esos productos, no sólo en los centros de atención médica, sino también en sus aplicaciones veterinarias y agrícolas, entre otras.

Palabras clave
Antibiótico – Antimicrobiano – Biocida – Bomba de achique (*efflux*) – Multirresistencia – Regulación genética – Transporte de fármacos.

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