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Overview Perspective of Bacterial Strategies of Resistance to Biocides and Antibiotics

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Abstract

Context: Considerable controversy surrounds the use of biocides in an ever-growing range of consumer products and the eventuality that their indiscriminate consumption might decrease biocide effectiveness and modify susceptibilities to antibiotics. Several line of evidence suggest that exposure to biocides may cause increased antibiotic resistance. Thus, we reviewed the common resistance strategies of bacteria against both biocides and antibiotics.
Methods: Several publications have explained the cell target of biocides and the various mechanisms used by bacterial cells to escape biocides' toxic activity. Here, we briefly reviewed the commonly used resistance mechanisms of bacteria against both biocides and antibiotics.
Results: Biocides could act on multiple sites in microorganisms and cause resistance by non-specific means. We mentioned several mechanisms such as efflux pumps, cell wall changes to the reduction of permeability, genetic linkage with both biocide resistance genes and antibiotic resistance genes, the penetration/uptake changes in envelope by passive diffusion, effect on the integrity and morphology of membrane, and effects on diverse key steps of bacterial metabolism. Along with this toxic effect and stress, bacterial cells express some similar defense strategies that can overlap the main functions conferring resistance versus structurally non-related molecules.
Conclusions: It can be stated that healthcare-associated, community-acquired, and nosocomial infections should be surveyed annually. Since biocide-antibiotic cross-resistance can be conferred by a number of distinct mechanisms, it is important to evaluate the propensity of a bacterium to express these mechanisms. Advances in modern genetic methods and the development of an assay using specific chemosensitizers or markers might allow the development of routine tests to identify resistance mechanisms. Further studies are needed to establish a correlation between biocide exposure (s) and development of antibiotic resistance, but the number of studies in the clinical or environmental settings is limited.

Keywords: Bacterial Strategies of Resistance, Biocides, Antibiotics

1. How Can Bacteria Become Resistant to Biocides?

Generally, bacterial resistance to biocides is not very common due to the lack of known detoxifying enzymes and target multiplicity inside the cell. In general, some mechanisms related to resistance are cellular changes on biocide accumulation, cell envelope changes, limited uptake, and efflux mechanisms expression. Still, target site mutations related to biocide resistance are not clearly understood. Also, there are several multidrug efflux systems that play an important role in biocides resistance. There is a large body of information regarding biocide resistance such as high- and low-levels of resistance to triclosan, resistance to chlorhexidine and quaternary ammonium compounds (QACs) in low-level of resistance in *Staphylococcus aureus*, low level of resistance to chlorhexidine and QACs in *Pseudomonas aeruginosa*, low-level resistance to QACs, and chlorhexidine in *Pseudomonas stutzeri*. Most of the time, resistance level is not stable and not likely to be of significance.

Minimum inhibitory concentration (MICs) of highly resistant strains maybe much higher thanthose in some biocides at residual biocide concentrations used in clinical setting. Biocide resistance can increase through mutation or elaboration of an endogenous chromosomal gene or by obtaining the resistance characteristics related to extrachromosomal genetic elements by means of transposons or plasmids. Resistance related to the inactivation of biocides has been identified, but it is comparatively rare and

specific to a few classes of biocides. Mostly it happens due to the multiplicity of cellular targets for biocides, changes in cell envelope permeability or enhanced biocide efflux as summarized in Box 1.

Box 1. Common Strategies to Achieve Biocide Resistance

Biocide Resistance Mechanisms
Multiplicity of cellular targets for biocide
Changes in cell envelope permeability
Efflux determinants enhance biocide efflux
Change in surface properties
Modification
By-pass metabolic blockage

Here, we explained in detail the common strategies for biocide resistance mechanisms.

1.1. Multiplicity of Cellular Targets for Biocides

Compared with antibiotics, mutations related to target site are rare in biocide-resistant organisms, and biocides have effects on multiple cellular components. Interestingly, *Escherichia coli* appears to be triclosan resistant due to mutations in the *fab*I gene related to the enoyl-acyl carrier protein reductase synthesis that plays an important role in fatty acid biosynthesis. Based on crystallographic studies, triclosan interacts with FabI. FabI active site mutations inhibit complex formation. With mutations in triclosan targets such as *fab*I and *inh*A in a number of bacteria, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Mycobacterium smegmatis*, *Mycobacterium tuberculosis*, *E. coli* and *Bacillus subtilis*, resistance to triclosan happens. Remarkably, for less susceptibility to triclosan, bacteria can produce an enzyme, named enoyl-acyl carrier protein reductases (e.g., FabK), which naturally cannot be affected by this biocide (1).

1.2. Changes in Cell Envelope Permeability

Each permeability change causes reduction in biocide concentration in the target sites. In spore-forming bacteria, different parts of spore such as layers, cortex, and envelope can affect the level of resistance. In Gram-negative bacteria, changes in outer membrane protein composition, surface hydrophobicity, outer membrane ultrastructure, and some changes in outer membrane fatty acid composition, lipopolysaccharides, proteins (porins), fatty acids, and phospholipids phospholipids cause resistance that effect the accumulation of biocides. In mycobacteria, mycoylarabinagalactan plays an important role in resistance. Thus, Gram-negative organisms are more resistant to biocides compared to their Gram-positive ones. In addition, disruption of the outer membrane barrier function increases biocide susceptibility. Biofilm impermeability might play an important role in the lack of biocide susceptibility in biofilm-producing bacteria. Pathogens resist by forming biofilms to protect against the effects of biocides, inactivating biocides' targeting ability by means of produced enzymes and increasing alternatives to the target sites of the biocide (1, 2).

In response to cetylpyridinium chloride, triclosan, chlorhexidine diacetate, benzalkonium chloride, and trisodium phosphate, a kind of adaptive resistance was observed in *Campylobacter jejuni* and *Campylobacter coli*. Also, cross-resistance to erythromycin, ciprofloxacin and sodium dodecyl sulfate was identified The acquired resistance was limited and stable and was related to various types of active efflux, suggesting several mechanisms of resistance that are unique to every experimental strain due to differences in the outer membrane protein (OMP) profile in each bacterial strain (3-8).

1.3. Efflux Determinants Enhance Biocide Efflux

Biocide resistance related to efflux determinants shows wide substrate specificity and a diversity of structurally non-related agents that can also include antibiotics. Multidrug efflux systems are divided into one of the five classes, including MFS superfamily (the major facilitator superfamily), ABC family (the ATP-binding cassette), MATE family (the multidrug and toxic compound extrusion), SMR (the small multidrug resistance family), DMT (drug/metabolite transporter), and RND family (the resistance-nodulation-division). Interestingly, efflux systems such as MFS, ABC, SMR and MATE are found widely in both Gram-positive and negative bacteria, while RND superfamily is only distributed in Gram-negative bacteria. Efflux pumps present not only an inner membrane transporter but also an outer membrane channel and a periplasmic adaptor protein, such as the RND type efflux pumps. It was proven that RND family pumps are related to significant antibiotic resistance in *Pseudomonas aeruginosa* (MexB) and Escherichia coli and *Salmonella typhimurium* (AcrB). In Gram-positive bacteria, MFS family was identified (such as NorA in *Staphylococcus aureus* and PmrA in *Streptococcus pneumoniae*) (9-13).

Today, emergence of multi-resistance in Gram-negative pathogens (particularly *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*, *Acinetobacter* spp. and the Enterobacteriaceae) is the main problem in medicine. In these organisms, three-component multidrug efflux systems play important roles in both intrinsic and acquired multiresistance. The similarity of these efflux systems is also readily identifiable in a wide range of Gram-negative organisms. Perhaps, they advance efflux-mediated resistance

to multiple antimicrobials. Sometimes, these systems enhance multiresistance in Gram-negative pathogens. However, some arguments exist as to the natural task of these efflux systems. Their contribution to resistance in a diversity of pathogens makes them suitable targets for medical purposes. Presumably, many novel or yet to be demonstrated antimicrobials are themselves efflux substrates and, efflux inhibitors may become an important subject of antimicrobial therapy for Gram-negative bacteria (14, 15).

The importance of EfrAB in multidrug resistant enterococci was demonstrated by the role of EfrAB in the efflux of antibiotics and biocides. EfrAB could be an attractive target both in enterococci present in food matrix and those causing infections. Also EDTA is used as a therapeutic agent in combination with low doses of antibiotics (16).

1.4. Change in Surface Properties

Decreased binding and interaction between cell surface charge and biocides occur due to change in surface properties. The threshold value is different in the stationary and dividing states for a given bacterium. It was proven for the effect of cationic substrate charge density to the induction of bacterial death. Also, in Gram-positive and Gram-negative bacteria, the effect of cationic substrate charge density happens after adsorbing on the functionalized substrate and depends on the metabolic state. It can be stated that divalent counter ions removal from the bacteria pending adsorption on charged surfaces enforce non-viability following bacterial envelope disruption. In the case of Gram-positive bacteria, electrostatics is very important in the search for bacterial proliferation control by means of non-chemical methods. It can be stated that highly charged cationic surfaces by means of a substitute to antibiotics can emerge expanded resistant strains (17).

To create antimicrobial polymer brushes on inorganic surfaces, synthesis of poly (quaternary ammonium) compounds has been applied. For maximum kill efficiency, surface charge density is a critical element in designing a surface. The most biocidal surfaces had charge densities greater than 1 - 5 $\times$ 10^{15}. Antimicrobial species can be coupled covalently to material surfaces to obtain biocidal effect without biocide liberation into the environment. Also, such materials can decrease resistance to the active agent. In recent studies, the successful covalent attachment of polymeric antimicrobial materials onto glass, metal, paper, and polymer has been reported. Most of the time, the biocidal polymer included cationic groups, such as alkyl pyridinium or quaternary ammonium. Cationic antimicrobials are particularly well positioned to act as self-disinfecting surfaces. Newly, a cationic surfactant within polymer microspheres such as quaternized poly-2-(dimethylamino) ethyl methacrylate (poly DMAEMA) displays high levels of antibacterial activity. In the scope of surface-active compounds, the quaternary ammonium salts (QAS) as cationic antimicrobials display are highly promising (17-33).

1.5. Modification

Intracellular and extracellular concentration reduction of a biocide can cause resistance. Compared with their small molecule counterparts, biocides as dendrimer are more potent. It was proven that detriment to the cell membranes is a kind of primitive mechanism of the antimicrobial action for dendrimer biocides. The efficacy of the dendrimer biocides can be restricted by high concentrations of calcium ions. Also, studies based on differential scanning calorimetric demonstrated that at high concentrations, dendrimer biocides bring precipitates with phospholipid vesicles, and a severe interaction with this model of bacterial membrane occurs. In this respect, negatively-charged bacteria and high positive charge density in the dendrimer biocides brings them into contact with each other. The presence of dendrimer biocides in a bacterial suspension causes an initial wave of dendrimer biocides replace calcium and magnesium ions from bacteria and bind to the negatively charged phospholipid membranes. Thus, a slight conversion in the permeability of the membrane occurs. Also, it is thought that binding without delay frustrates and even reverses bacterial surface charge. At this stage, all changes pertaining to bacteria are reversible. Thus, more dendrimer biocides with relatively high concentrations may cause denaturation of membrane proteins and interpenetration of the phospholipid bilayer. Therefore, enhanced membrane permeability propels potassium ions leakage. This concentration of dendrimer biocides relates to a bacteriostatic level. If more dendrimer biocides exist, it can further unfix the membrane structure. Finally, high concentrations of dendrimer biocides propel a complete disintegration of the bacterial membrane related to a bactericidal effect (34).

1.6. Bypass Metabolic Blockage

The common use of biocidal compounds is free of risks. FabI, a unique cellular target for triclosan, is an enoyl-acyl carrier protein (ACP) involved in the biosynthesis of fatty acids. Also, it is thought to act non-specifically on bacterial cell membranes. By-pass metabolic blockage increases synthesis of pyruvate and the production of fatty acids by means of an altered metabolic pathway (expression of 'triclosan resistance network'). There is concern as to the biocides misusage in industries related to animal husbandry

and food production. The appearance of cross-resistance to antibiotics occurs by selective pressures due to biocide usage and tolerance enhancement to one or more of these compounds. Biocide tolerance has been reported for most classes of agents. It has been documented for several pathogens related to zoonotic infections involving *Campylobacter* spp., *Escherichia coli*, *Staphylococcus*, *Pseudomonas* spp. and *Listeria* spp., about tolerance to biocide and related to reduced susceptibility to clinically main antimicrobial compounds is argumentative (34-45).

2. How Can Bacteria Become Resistant to Antibiotics?

Antibiotics have greatly influenced life on earth since 1930s. Antimicrobial resistance is one of the most important health concerns. In the last decade, the occurrence multidrug-resistant bacteria in community and hospitals along with the problem of nosocomial infections has spiked. Emerging of threats to the end of the "antibiotic period" during four decades of extravagant antibiotic utilization has caused practicable selective pressure on high-level antimicrobial resistance and multiple-drug resistance (MDR) antibiotics (46, 47).

Bacteria have some resistance strategies against antibiotics as follows: the clinical broad-spectrum application may be restricted by resistance single-step acquisitions. Thus, specific antibiotics against a pathogen will have potential to dominate this liability if suitably designed. The "multi-target hypothesis" discusses that antibiotics designed to for single protein targets will lose out. Because in human infections, high load of bacteria is sufficient to choose mutants strains due to missense changes that will cause the antibiotic useless. This information lead to expanding the utilization of single-target inhibitors as monotherapy, but to slow down the rapid improvement of clinical resistance in single-target inhibitors, emerging resistance profiles of FabI inhibitors propose key drug properties that should be optimized. It is very important that drugs have very high potency or low MIC. Drugs with high potency and a low toxicity profile permit to use for clinical setting. For single-step resistance to shifting the antibiotic dose, this suppressed potency enhances the potential required to medicate concentrations resistant strains that cannot be sustained. To increase drug binding, each side-chain interaction causes a chance for a missense mutation. By a rate-controlling step in the missense mutations, catalytic residues confer a fitness cost to the cells. Thus, experimental evaluation of drug resistance must be an early and integral part of the antibiotic expansion procedures rather than something figured out at the end (48).

Slow-binding inhibitors improves potency and target selectivity. For drug efficacy, slow-binding conformational change is critical but for maintaining the desired conformational change, resistance mutations should occur at residue positions. Two slow-binding FabI inhibitors triclosan and isoniazid cause vulnerability. There are several isoniazid-resistant InhA mutations located in positions that do not directly encounter the drug. These mutations are related to protein sequences that play important roles in the conformational change responsible for the slow-binding characteristics. Increased bacterial infections are now problematic or impossible to cure because of the misuse of antimicrobial drugs and the epidemic spread of bacterial resistance to these drugs (49-51).

Diarrhea is one of the gastrointestinal diseases related to inappropriate antibiotic treatment, and enhanced antibiotic resistance causes problems in the health systems which can vary in different societies (52). According to studies on human gut microbiome, adopting a pathogen-selective approach can be beneficial. Treatment with broad-spectrum antibiotics lead to severe disturbances in the human microbiome, reduced infection resistance, and allergic and metabolic diseases development (53, 54). It has been proven that treatment with broad-spectrum antibiotics in early life is significantly related to the development of type 2 diabetes, obesity, and celiac disease (55, 56).

Several factors including stress, metabolism, genetics, age, diet, geographical region, and antibiotic treatment are dynamic entities which influence on microbiome. The microbiota profile of children is affected by the consumption of antibiotics. Yet, the impact of early life antibiotics treatment on development of CNS has not yet been realized (57). Also, some changes occurred in the brain development and behavior of mice after treatment with antibiotics and gut microbiota depletion from early adolescence, and some changes emerged with a restructuring of gut microbiota populations (58). For example, the treatment of colitis infections due to *Clostridium difficile* with broad-spectrum antibiotics leads to the elimination of the gut microbiome. Broad-spectrum antibiotics make several thousand-fold reductions in gut microbial load (54, 59).

Firmicutes include bacteria belonging to the gut microbiome. It is assumed that firmicutes are immune against FabI inhibitors by means of encoding an FabK (different enoyl-ACP reductase isoform). Some pathogens encoding FabI include *Neisseria*, *Shigella*, *Acinetobacter*, *Campylobacter*, *Staphylococcus aureus*, Enterobacteriaceae, *Pseudomonas, Salmonella*, and *Mycobacterium* spp. (60).

Lack a proper combination of antibiotics, would have various consequences on public health (61-68). The specific strategies for antibiotic resistance have been summarized in Box 2.

Each of these specific strategies to achieve common antibiotic resistance are explained below.

Box 2. Specific Strategies for Common Antibiotic Resistance Mechanisms

Antibiotic Resistance Mechanisms
Beta-lactams
Enzymatic destruction
Altered target
Decreased uptake
Glycopeptides
Altered target
Aminoglycosides
Enzymatic modification
Decreased uptake
Altered target
Quinolones
Decreased uptake
Altered target

2.1. Beta-Lactams (Such as Penicillin, Mezlocillin, Ampicillin, Ceftazidime, Aztreonam, Imipenem, Cefazolin, Piperacillin, and Cefotaxime)

2.1.1. Enzymatic Destruction

Beta-lactamase enzymes can destruct beta-lactam rings and lead to achieving resistance. When the beta-lactam ring is destroyed, the antibiotic cannot bind to penicillin-binding protein (PBP) and interfere with cell wall synthesis. Resistance of Enterobacteriaceae against cephalosporins, penicillins, and aztreonam and resistance of staphylococci to penicillin are related to enzymatic destruction of beta-lactam drugs.

Extended-spectrum β-lactamase (ESBL) is an enzyme that can cause resistance to monobactams and extended-spectrum third generation cephalosporins but does not affect cephamycins or carbapenems. If the infectious agent is an ESBL-producing organism, it can result in the failure of treatment using third-generation cephalosporins and monobactams. Because ESBL-producing strains are resistant to penicillin, cephalosporin, and aztreonam. Additionally, ESBL has been identified in a range of Enterobacteriaceae and Pseudomonadaceae worldwide. Thus, the A, B, C, and D molecular classes of β-lactamase enzymes are identified according to conserved amino acid motifs. B β-lactamases that use at least one active-site zinc ion for β-lactam hydrolysis are metalloenzymes, while classes A, C, and D contain enzymes that can hydrolyze substrates by forming an acyl enzyme by means of an active site serine (64).

2.1.2 Altered Target

Inhibition of cell wall synthesis occurs when mutational changes in original PBPs or acquisition of different PBPs change the ability of the antibiotic to bind to PBPs. Altered target occurs in staphylococci resistance to methicillin and oxacillin. The presence of *mec*A causes the resistance of *S. aureus* to methicillin. For all beta-lactam antibiotics, PBP2a has a low affinity compared to other PBPs. It is proposed that the origin of *mec* operon in *S. aureus* is *S. sciuri* and the *mec*A-positive coagulase negative staphylococci (CoNS), particularly *S. epidermidis*. Also, the acquirement of the *mec*A region from *S. fleurettii*, a commensal bacterium of animals, has been reported (61-63, 69).

Unfortunately, methicillin-resistant *Staphylococcus aureus* (MRSA) is resistant to all beta-lactam antimicrobial drugs such as penicillin, cefoxitin and oxacillin, except for newer cephalosporins with anti-MRSA activity (63).

2.1.3. Decreased Uptake

Reduced uptake occurs because of porin channel formation. Porin channel is where beta-lactams pass the outer membrane of Gram-negative bacteria to obtain the PBP. Thus, every change in these channels can decrease uptake of beta-lactams. Resistance of *Enterobacter aerogenes*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* to imipenem occurs due to decreased uptake (61).

Recently, porin channels have been demonstrated in relation to bacterial resistance to antimicrobial agents and, particularly, to efflux phenomenon. In *Escherichia coli*, several porin proteins have been identified, such as OmpC, OmpF, PhoE, OmpC and OmpF. In *Pseudomonas aeruginosa*, outer membrane proteins such as OprB, OprC, OprD, OprE, OprF, and OprP have been identified to act as porins (70).

2.2. Glycopeptides (Such as Vancomycin)

Vancomycin is a glycopeptide antibiotic. There are nine vancomycin resistance genes including *van A, B, C, D, E, G, L, M*, and *van N* in Enterococci. *Van A* is the most common type worldwide, which is mainly related to vancomycin-resistant *Enterococcus faecium*, allowing a great rate of vancomycin and teicoplanin resistance. *Van B* causes a high degree of vancomycin resistance, yet it is susceptible to other glycopeptides such as teicoplanin. MRSA isolates which are susceptible only to glycopeptides, such as vancomycin, are becoming multidrug-resistant. Now, low level resistance to vancomycin is emerging and increasing (48, 70).

2.2.1. Altered Target

Enterococci resistance to vancomycin is due to altered target. Alterations in cell wall precursor components emerge and can decrease vancomycin binding so

that cell wall synthesis can be continued. Increasing antibiotic resistance in common bacterial pathogens, in both hospitals and communities, causes a growing threat to human health worldwide. Vancomycin-resistant enterococci (VRE) are a major concern in medical practice. Their increased prevalence and their ability to transfer vancomycin-resistance genes to other bacteria (including MRSA) have made them a subject of close scrutiny and intense investigation (61, 62).

2.3. Aminoglycosides (Such as Amikacin, Netilmicin, Streptomycin, Kanamycin, Gentamicin, and Tobramycin)

VRE can acquire resistance to erythromycin, glycopeptides, tetracycline, and vancomycin. *Enterococcus* is capable of acquiring resistance genes, including high-level resistance (HLRA) to aminoglycoside antibiotics. High-level gentamicin resistant (HLGR) enterococci are resistance to gentamicin. HLSR are enterococci with high-level resistance streptomycin. It is so difficult to drug selection for treatment of infected patients with carbapenems resistant strains. Alternative therapeutic options include tigecycline, aminoglycosides, sulbactam, and polymixyns. For example, both tolerance to desiccation and bacterial resistance development by means of antibiotic selective pressure caused the spread of *A. baumannii* in a hospital setting. Resistance to several classes of antibiotics including aminoglycosides, fluoroquinolones, beta-lactams, and third generation of cephalosporins was reported in MDR *A. baumannii*. Also, pandrug resistant (PDR) *A. baumannii* was resistant to all tested antibiotics except tigecycline and colistin.

Limitation of polymyxins and aminoglycosides consumption was reported to be due to wide range of antimicrobial resistances in MDR *P. aeruginosa*. Thus, these drugs may or may not be as efficient as first-line drugs of choice, and detrimental effects such as ototoxicity, neurotoxicity and nephrotoxicity occur after their consumption. In serious infections such as burn wound infections caused by *Pseudomonas aeruginosa*, treatment is by means of combination of beta-lactam drugs and an aminoglycoside. Emerging resistance of *Pseudomonas aeruginosa* to β-lactams, aminoglycosides, and fluoroquinolones can cause serious problems in the treatment of burns patients (59).

2.3.1. Enzymatic Modification

This alters various sites on the aminoglycoside molecule, such that this drug's ability to bind to ribosomes and inhibit protein synthesis is greatly reduced or lost entirely. Aminoglycosides resistances due to enzymatic modification occur in many Gram-positive and Gram negative bacteria (71). Most plasmid-mediated AmpC β-lactamases belong to the DHA, FOX, and CMY families, and Qnr, aac(6')-Ib-cr and QepA are three plasmid-mediated quinolone resistance (PMQR) mechanisms. Seriously, reduced effectiveness of amikacin and other amino-glycosides in MDR bacteria increase due to existing of *aac*(6')-*Ib* gene. These mechanisms are widely prevalent among common clinical isolates (68).

2.3.2. Decreased Uptake

Any change in the number or characteristic of porin channels for the passing of aminoglycosides during the outer membrane can cause reduced uptake of aminoglycosides. Resistance of a variety of Gram-negative bacteria to aminoglycosides occurs in this situation (71).

2.3.3. Altered Target

Ribosomal proteins modification of 16s rRNA is very important in emerging resistance. It decreases aminoglycosides' ability to successfully bind and halt protein synthesis. Resistance of *Mycobacterium* spp. to streptomycin happened through this mechanism (71).

Commonly, serious infections due to *Pseudomonas aeruginosa* are treated with a combination of aminoglycosides and beta-lactams. Thus, an extremely important antibacterial resistance profile may emerge due to the production of a 16S rRNA methylase. The mechanism of aminoglycosides resistance by means of 16S rRNA methylase production has been detected since 2003. Methylation of 16S rRNA has occurred as a high-level aminoglycoside resistance mechanism among bacteria in recent yearsAminoglycosides, often in combination with broad-spectrum beta-lactams, play an important role in the management of serious bacterial infections. So far, seven types of methylases have been identified including *RmtB*, *RmtE*, *RmtD*, *ArmA*, *RmtA*, *RmtC*, and *NpmA*. These genes are encoded by bacterium-specific recombination systems, such as transposons, and are easily translocated to other DNA target sites (68).

2.4. Quinolones (Such as Ciprofloxacin, Norfloxacin, Levofloxacin, and Lomefloxacin)

DNA gyrase and topoisomerase IV are two enzymes essential for bacteria viability which are inhibited by quinolones. Frequently, quinolone resistance is related to chromosomal mutations such as *gyrA*, *gyrB*, *parC* and pare. Sometimes, a decreased uptake or an increased efflux due to mutations causes reduced drug accumulation. Also, quinolone resistance genes related to plasmids have been identified, such as the *qnr* gene that blocks the action of quinolones on the DNA gyrase and topoisomerase. Another one is the *aac*(6')-*Ib-cr* gene that modifies piperazine ring amino group of the fluoroquinolones. Efflux

pump encoded by the *qepA* gene can decrease intracellular drug levels. It can be stated that all plasmid-mediated resistances cause a low-level resistance (72).

2.4.1. Decreased Uptake

Resistance to various quinolones in Gram-negative bacteria and staphylococci (efflux mechanism only) is due to decreased uptake. Several alterations in the outer membrane reduces drug uptake and/or an "efflux" pump activation. This situation causes the removal quinolones just before the intracellular concentration of quinolones is sufficient for inhibiting DNA metabolism (71).

2.4.2. Altered Target

Resistance to various quinolones in Gram-negative and Gram-positive bacteria is due to altered target. Decreased ability of quinolones to bind to DNA gyrase subunits and interfere with DNA processes causes this resistance (71).

The incidence of antimicrobial resistance, including quinolone resistance in *Klebsiella pneumonia* and *Escherichia coli*, is increasing both in developed and developing countries. Successful treatment occurred in 83% of patients with quinolone monotherapy, and who had no infection-related mortality was reported in these cases, but the success rate in treatment was lower in intravenous treatment (73).

A positive correlation was reported between emergence of MRSA and β-lactam combinations consumption. Also, a positive correlation was reported between resistance to carbapenems and aminoglycosides and use of β-lactams combinations and quinolones and β-lactam combinations. Interestingly, the consumption of β-lactamase-sensitive antibiotics was negatively related to resistance to methicillin, quinolones, and aminoglycosides. Consumption of the different antimicrobial therapeutical subgroups was also correlated. Consumption of β-lactamase-sensitive antibiotics (penicillin) was positively correlated to consumption of β-lactamase resistant penicillins and negatively correlated to consumption of quinolones, carbapenems, and glycopeptides, whereas cephalosporins consumption was positively correlated to consumption of aminoglycosides, glycopeptides and, quinolones. The annual increase in the incidence of coagulase-negative staphylococci (CoNS) isolates is global concern. Also, the presence of antibiotic resistance among CoNS species, which cause nosocomial infections, has increased. Resistance to antibiotics, including aminoglycosides, develops quickly in CoNS species, where these antimicrobial agents are widely used. Annual surveillance for monitoring integrons and the associated gene cassettes among nosocomial pathogens of MRSA to determine clones distribution and detect emergence of new MRSA clones is needed. Multi-drug resistant MRSA is an increasingly common hospital pathogen in burns patients, which is associated with integrons. It is known to cause over 50% of burn-related mortalities (74, 75).

3. Biocide-Antibiotic Cross-Resistance

Bacteria face a myriad of stresses in natural environments. A variety of specific and highly regulated adaptive responses were elicited by these stresses. These stresses elicit a variety of specific and highly regulated adaptive responses that not only protect bacteria from the offending stress, but also manifest cellular changes that impact innate antimicrobial susceptibility. Thus, exposure to envelope stress, reactive oxygen, oxidative/nitrosative stress, heat stress, nutrient stress, and ribosomal stress can positively impact resistance determinants or promote physiological changes that compromise antimicrobial activity. This review summarized the main advancements in determining the mechanisms of bacterial resistance to both biocides and antibiotics (1, 76).

There are several protocols suggested for measuring antibiotic susceptibility in bacterial strains, showing resistance, tolerance or increasing insusceptibility to biocides or vice versa. The different protocols cause the variability of the results reported on antibiotic "resistance". More meaningfully studies used standardized antibiotic susceptibility methodologies such as those given by the British Society for Antimicrobial Chemotherapy (BSAC) or Clinical and Laboratory Standards Institute (CLSI) to measure a change in antibiotic susceptibility profile. Currently, there are no well-referenced criteria for the evaluation of biocide capability to induce or select for resistance to antibiotics. Hence, it is necessary to develop methods to describe the minimal concentration of a biocide which is able to select or trigger the emergence/expression of a resistance mechanism that will cause clinical resistance against an antibiotic class in a defined bacterium.

4. Conclusions

Health authorities, such as the World Health Organization (WHO), the European Centre for Disease Prevention and Control (ECDC), and the Infectious Diseases Society of America (IDSA), have enhanced industrial incentives in an attempt to arouse research into novel antimicrobial combination, ameliorate antibiotic surveillance force to cover the remaining therapeutic options to physicians and encourage a focused, concerted endeavor against life-threatening infections due to multidrug-resistant (MDR), and pandrug-resistant Gram-negative bacteria. Patients

with infections due to these microorganisms can be treated with empiric antibiotic therapy. However, it has been proven that improper antimicrobial therapy can be decreased through using an empiric combination therapy. However, combination therapy is a useful method for obtaining a synergistic consequences and preventing the emergence of resistance (49, 68, 70-76).

It was demonstrated that a patient's clinical response after receiving antibiotic does not always correlate with the laboratory results. Because of emergence of biocide-antibiotic cross-resistance, it is important to evaluate the propensity of a bacterium to express these cross-resistance mechanisms. Advances in modern genetic methods (e.g. PCR, -omics) and the development of an assay using specific chemosensitizers or markers (e.g. efflux pumps inhibitors) might allow the development of routine tests to identify resistance mechanisms. To establish a correlation between biocide exposure(s) and development of antibiotic resistance, further studies are needed.

Footnotes

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