ISSN print: 1224-5984
ISSN online: 2248-3942

Rom Biotechnol Lett. 2020; 25(4): 1823-1831
doi: 10.25083/rbl/25.4/1823.1831

Received for publication, October, 20, 2019
Accepted, January, 2, 2020

Review

Biocides role in the selection and dissemination of resistant *Acinetobacter baumannii* clones

CORNELIU OVIDIU VRANCIANU[1,2], CRISTINA FLORENTINA PELCARU[1,2], ALEXANDRU ALISTAR[1], IRINA GHEORGHE[1,2,*], LUMINITA MARUTESCU[1,2], MARCELA POPA[2], GRATIELA GRADISTEANU[2], MARIANA CARMEN CHIFIRIUC[1,2]

[1]University of Bucharest, Faculty of Biology, Microbiology-Immunology Department, Bucharest, Romania
[2]The Research Institute of the University of Bucharest, Romania

Abstract In recent years, the expansion of multidrug-resistant strains poses a severe threat to human health. The extensive and incorrect administration of antibiotics and other antimicrobial agents has led to their inefficiency in treating severe infections. Also, the selective pressure caused by the abusive use of biocides can co-select antibiotic resistance. Currently, one of the most common Gram-negative resistant pathogens is *Acinetobacter baumannii*. This bacterium has various resistance mechanisms, such as efflux pumps, alteration of membrane permeability, and production of antibiotic inactivating/modifying enzymes. In this review, we will present general aspects of *A. baumannii* biology and the mechanisms of resistance to antibiotics and biocides. We will subsequently discuss the biocides influence on antibiotic resistance and their involvement in co-selection and cross-resistance mechanisms. Due to the expansion of clinical isolates' resistance, the standardization of techniques for the rapid and specific detection of resistant strains must be considered. To this end, the transition from laboratory research to entrepreneurial solutions (new detection techniques and their patenting) represents an important desideratum to counteract the dramatic consequences of bacterial resistance.

Keywords Antibiotic resistance, Acinetobacter baumannii, biocides; co-selection; cross-resistance.

To cite this article: VRANCIANU CO, PELCARU CF, ALISTAR A, GHEORGHE I, MARUTESCU L, POPA M, GRADISTEANU G, CHIFIRIUC MC. Biocides role in the selection and dissemination of resistant *Acinetobacter baumannii* clones. *Rom Biotechnol Lett.* 2020; 25(4): 1823-1831. DOI: 10.25083/rbl/25.4/1823.1831

*Corresponding author: IRINA GHEORGHE, University of Bucharest, Faculty of Biology, Microbiology-Immunology Department, Bucharest, Romania
E-mail: IRYNA_84@yahoo.com

Introduction

Bacterial resistance is a critical concern both for the environment and the clinical sector. It is considered that the leading cause of the resistance expansion is the selection driven by incorrect administration of antibiotics, enhancing both the mobility of antibiotic resistance genes (ARGs) and the diversity of resistance mechanisms (HOLMES et al [1]). *Acinetobacter baumannii* is one of the main threats related to the emergence of resistant and pathogenic bacteria in hospital settings (PELEG et al [2]). Initially, bacteria belonging to the genus *Acinetobacter* were considered rather opportunistic, with a low degree of pathogenicity. In recent years, however, the emergence of multidrug-resistant (MDR) strains has significantly increased the scientific interest in this bacterium (HOWARD et al [3]).

A. baumannii has many adaptive mechanisms, among which numerous ARGs, efflux pumps and virulence factors that allow it to survive in extreme environmental conditions and to initiate infectious processes. In addition to the involvement of adaptive mechanisms in the antibiotic resistance (AR) of *A. baumannii* strains, biocides play an essential role in the growth and dissemination of AR. Biocides are used in various environments, such as the clinical environment, for disinfecting medical devices and controlling the transmission of infections caused by pathogens. The co-localization of biocide resistance and ARGs in the same genetic platforms as plasmids, integrons, or transposons has led to the hypothesis that biocides can co-select ARGs. Also, studies have shown that the use of suboptimal concentrations of biocides can lead to cross-resistance to both biocides and antibiotics (LANGSRUD et al [4]). Therefore, it is considered that the incorrect use of biocides can lead to the selection of MDR strains (RUSSELL et al [5]). In this review, we will initially present the main characteristics of the *Acinetobacter* genus and subsequently, we will present the main genetic mechanisms of resistance to antibiotics and biocides encountered in *A. baumannii*. We will discuss the role of biocides in increasing bacterial resistance and, implicitly, in the selection of MDR strains.

Acinetobacter spp.

1. General characterization

It was first isolated from soil in 1911, by the Dutch microbiologist Beijerinck, who used minimal media enriched with calcium-acetate. For the first time was described as *Micrococcus calcoaceticus*. After 43 years, Brisou and Prevot proposed the name *Acinetobacter* to differentiate it from motile organisms within the genus *Achromobacter* (BRISOU & PREVOT [6]). The name of the genus *Acinetobacter* comes from the greek "*akinetos*", meaning non-motile. The name was accepted in 1968, after Baumann et al, published complex research of *Micrococcus calcoaceticus*, *Mima polymorpha*, *Alcaligenes hemolysans*, *Moraxella lwoffi*, *Bacterium anitratum*, and *Herellea vaginicola*. The conclusion was that the above microorganisms belong to a single genus. Thereby, the subcommittee on the Taxonomy of *Moraxella* and Allied Bacteria, officially acknowledged the genus *Acinetobacter* in 1971 (LESSEL [7]).

Acinetobacter belongs to *Moraxellaceae* family and includes non-fastidious, strictly aerobic, and non-motile Gram-negative coccobacilli (Fig. 1), which are non-fermenting, catalase-positive and oxidase-negative and have a GC DNA content of 39% - 47% (PELEG et al [2]). Numerous species of this genus have been identified, the most clinically significant and common being *A. baumannii*, *A. pittii*, and *A. nosocomialis* (D'SOUZA et al [8]; CHEN et al [9]).

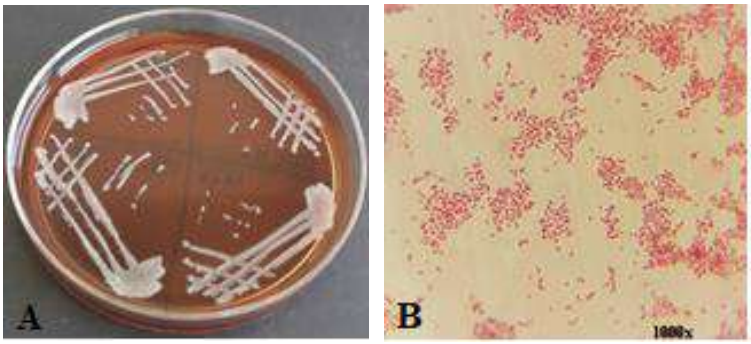

Figure 1. (**A**) *A. baumannii* – culture and colony aspects;
(**B**) Gram-staining aspect of log phase *A. baumannii* cells grown in Luria-Bertani Agar.

The cells of *Acinetobacter* spp. are ~ 1.5 µm length, with a different shape, depending on the growth phase, from coccoid to coccobacillary. It can be quickly grown on simple microbiological media; clinically relevant species incubate at 37°C, while environmental strains at lower temperatures. For the recovery rate of *Acinetobacter* in culture or the enrichment of clinical or environmental specimens, slightly acidic mineral medium containing acetate and nitrate as carbon and nitrogen sources or Leeds selective medium can be used (VISCA et al [10]).

2. Adaptative mechanisms to different environments

A. baumannii is a successful pathogen due to its ability to acquire resistance determinants and adapt to harsh environments. The ability to acquire multiple virulence factors, as well as resistance determinants such as serum

resistance, motility, efflux pumps, and iron acquisition mechanisms, help this bacterium to survive in adverse environmental conditions, to persist for months in dry and harsh environments, leading to the emergence of nosocomial and community-acquired infections. These species can also survive exposure to common disinfectants – chlorhexidine, phenols, gluconate. Many strategies have been described to explain the survival on surfaces for long periods in changing environments or when basic requirements for growth are low: i) bust and boom – few surviving cells resume growth and replicate rapidly when the environmental conditions are suitable; ii) cellular quiescence – bacterial population persists in a viable nonreplicating state displaying metabolic capacity; iii) true dormancy – proper sporulation takes place (GALLEGO [12]); iv) biofilm formation ability (GALLEGO [12]). The ability to survive in hospital environments lead *A. baumannii* to become one of the most successful nosocomial pathogens, mainly in intensive care units (ICUs) (AL-KADMY et al [11]).

Molecular mechanisms of antibiotic resistance in *A. baumannii*

1. Enzymatic mechanisms

1.1. β-lactamases

In Gram-negative bacteria, β-lactamases are the primary mechanism of AR. The first enzyme with β-lactamase action was discovered by Abraham and Chain in 1940, being today's associated with the chromosomal cephalosporinase from *Escherichia coli* (ABRAHAM & CHAIN [68]; MATTHEW & HARRIS [69]). β-lactamases have been classified based on molecular (AMBLER [70]) and functional (BUSH et al [71]; BUSH & JACOBY [72]) analysis. Based on amino acid sequences, in the molecular structure classification, β-lactamases were grouped into four classes (A, B, C, and D). All four classes of β-lactamases have been identified in *A. baumannii* strains. In the functional classification, β-lactamases were included in 3 groups, depending on the degraded β-lactam substrate and the inhibitor's effects.

Class A β-lactamases are among the most important enzymes involved in the development of the bacterial resistance phenomenon (BUSH [73]). The enzymatic activity occurs in the presence of clavulanate. Regarding the hydrolysis capacity, class A β-lactamases can hydrolyze penicillins and cephalosporins (JEON et al [74]). In *A. baumannii*, studies reported several class A β-lactamases such as TEM, GES, CTX-M, SHV, SCO, PER, CARB, VEB, or KPC. Most are broad-spectrum β-lactamases (ESBL) (SHV-5, PER-1, PER-2, PER-7, TEM-92, CTX-M-15, VEB-1, GES-14, CARB-10, CTX-M-2), and some are narrow-spectrum (TEM-1, SCO-1).

Class B β-lactamases (MBL) can hydrolyze almost all β-lactam antibiotics, except monobactams, and have a heavy metal such as Zn at the catalytic site (JEON et al [74]). Due to the presence of metal at the catalytic site, MBLs are inhibited by a chelating agent such as ethylenediaminetetraacetic acid (EDTA) (AOKI et al [75]).

Class C β-lactamases are part of group 1 of the functional classification and are encoded by the *AmpC* gene, a non-inducible cephalosporinase (JACOBY [76]; THOMSON [77]). In *A. baumannii*, studies reported the presence of the *AmpC* gene in most strains analyzed (SUN et al [78]; LIN et al [79]). Class C β-lactamases are involved in resistance to penicillins, cefamycins, or cephalosporins (JEON et al [74]).

Class D β-lactamases (CHLD) or *oxacillinases* (OXA) can degrade oxacillin and contain serine in the active site and are included in group 2 of the classification made by Bush and Jacoby (BUSH & JACOBY [72]). In *A. baumannii*, OXA β-lactamases are the primary carbapenem resistance mechanism. In *A. baumannii* clinical isolates five groups of acquired, chromosomal or plasmid located CHDLs with variable geographic distribution have been identified, i.e., OXA-23, OXA-24/-40, OXA-58, OXA143 and OXA-235 (DA SILVA & DOMINGUES [80]). OXA-23 is the most worldwide spread enzyme in *A. baumannii*, having been implicated in outbreaks in multiple European (including Romania and other Eastern European countries), Asian and American countries, and Oceania (MUGNIER et al [58]).

1.2. Aminoglycoside-modifying enzymes

Modification of the aminoglycosides (AMG) molecule is an essential resistance mechanism generally determined by aminoglycoside-modifying enzymes (AMEs) (ZHOU et al [43]). Depending on the mechanism of action, AMEs are classified into acetyltransferases, phosphotransferases, and nucleotidyl transferases (RAMIREZ & TOLMASKY [44]). The main AMEs involved in resistance to AMGs in *A. baumannii* strains are aac(3')-I, aph(3')-I, aph(3')-VI, aac (6')-Ib, ant (2'')-Ia, ant (3')-I, aac (3)-Ia [aacC1], aac (3) -IIa [aacC2], aac (6')-Ib [aacA4], aac (6')-Ih, aac (6')-Im, aph (3')-Ia [aphA1], aph (3')-VIa [aphA6], ant (3'') Ia [aadA1], ant (2'')-Ia [aadB] , aac (6')-I ad and aac (6') - II (WEN et al [45]; HEIDARY et al [46]; NIGRO et al [47]; AGHAZADEH et al [48]; HASANI et al [49]; SHEIKHALIZADEH et al [50]; SALIMIZAND et al [51]; SHOOSHTARI et al [52]; AKERS et al [53]). Among the identified AMEs, aac (6')-I is cryptic and confers resistance to netilmicin, tobramycin, gentamicin, and amikacin (LUPO et al [54]). Recently, it has been observed another mechanism of AMG resistance represented by the action of 16S rRNA methylases (encoded by the armA gene) that confer resistance to tobramycin, amikacin, gentamicin, and netilmicin (LIOU et al [55]; DOI et al [56]).

1.3. Rifampin enzymatic resistance

One of the causes of rifampin resistance in *A. baumannii* strains is the acquisition of the enzyme ADP-ribosyltransferase encoded by the *arr-2* gene, generally localed in class 1 integrons, which modifies the antibiotic molecule (HOUANG et al [63]).

2. Non-enzymatic mechanisms

2.1. Efflux pumps

The efflux systems encountered in *A. baumannii* are involved in resistance to various antimicrobial agents when overexpressed (CHEN et al [13]). MDR efflux systems are encoded by chromosomal genes and are expressed either

constitutively, causing inherited resistance, or following mutations, are contributing to acquired resistance (BUTAYE et al [14]; POOLE [15]). In *A. baumannii*, four main categories of efflux systems were identified: superfamily RND (resistance-nodulation-division superfamily), MATE (multidrug and toxic compound extrusion family), MFS (major facilitator superfamily) and SMR (small multidrug resistance transporters) (LIN & LAN [16]).

The RND system is well represented in *A. baumannii*, includes the AdeABC pump, with an essential role in resistance to antimicrobial and antibiotic agents, especially AMGs. AdeABC regulation is performed by the adeRS operon, whose expression occurs when the efflux pump is exposed to a high concentration of toxic agents or antibiotics, thus leading to resistance (YOON et al [17]). The appearance of point mutations in the adeRS operon causes the regulation of the AdeABC pump activity, leading to the increase of resistance level to different antibiotics such as AMG, β-lactams, fluoroquinolones, tetracyclines, macrolides, and chloramphenicol. The RND family also includes the AdeFGH and AdeIJK efflux pumps associated with tigecycline resistance (DAMIER-PIOLLE et al [18]).

MATE is another category of efflux pumps that includes the AbeM pump. The AbeM efflux pump is involved in resistance to different antibiotics such as norfloxacin, ofloxacin, ciprofloxacin, gentamicin, doxorubicin, triclosan, and imipenem (SU et al [19]; HOU et al [20]; RUMBO et al [21]).

The MFS superfamily is involved in resistance to antibiotics and various antimicrobial agents, contributing to both intrinsic and acquired resistance through overexpression caused by the acquisition of mutations. One such example is the CraA pump, involved in the IR to chloramphenicol in *A. baumannii* (ROCA et al [22]). This category also includes AmvA and AbaF pumps, which determine resistance to various antibiotics such as phosphomycin, disinfectants, and dyes (RAJAMOHAN et al [23]; SHARMA et al [24]). Recently, there have been reported AbaQ pump involved in the virulence and efflux of quinolone antibiotics (PEREZ-VARELA et al [25]).

Another category of efflux pumps found in *A. baumannii* is SMR, which includes the AbeS pump, with a role in AR and dyes (SRINIVASAN et al [26]).

The genes encoding the efflux mechanisms of specific antimicrobial agents are usually located in the structure of MGEs (plasmids, transposons, integrons), increasing the risk of their horizontal dissemination.

2.2. Outer membrane permeability

In *A. baumannii*, the pores of the outer membrane that mediate the transport of molecules play an essential role in the resistance and virulence of MDR strains (LEE et al [27]). It has been shown that the decrease in the density of some membrane pores such as Omp22-23, Omp43, Omp44, Omp47, Omp33-36, Omp37, and CarO) is associated with the increase of carbapenem resistance (BOU et al [28]; DUPONT et al [29]; QUALE et al [30]; DEL MAR TOMAS et al [31]; HOOD et al [32]; MUSSI et al [33]; MUSSI MA et al [34]; SIROY et al [35]; CATEL-FERREIRA et al [36]). Also, another membrane porin involved in the pathogenesis of *A. baumannii* is OmpA. Investigation of OmpA functions has demonstrated the association of this porin type with aztreonam, chloramphenicol, and nalidixic acid resistance (SMANI et al [37]). Recent studies have shown the role of OmpA in increasing virulence level (ESPINAL et al [38]), lung infections, sepsis, and increased mortality (SANCHEZ-ENCINALES et al [39]; SATO et al [40]). OmpA can bind to host epithelia and cause mitochondrial dysfunction, and after translocation to the nucleus, it leads to cell death (CHOI et al [41]; CHOI et al [42]).

2.3. Antibiotic target modification by point mutations

A well-known example of resistance caused by point mutations is resistance to fluoroquinolones (FQ), generally mediated by mutated gyrase and topoisomerase. In *A. baumannii*, the primary mechanism of resistance is based on the mutations in the *gyrA*, *gyrB*, and *parC* genes (PARK et al [57]; ARDEBILI et al [58]). Specific amino acid substitutions in the sequence of the following genes: gyrA Ser83Leu, parC Ser80Leu, and Glu84Lys play an essential role in increasing the FQ resistance level (VILA et al [59]). Another FQ mechanism is represented by mutations in genes encoding proteins from the outer membrane and efflux pumps. It has been observed that overexpression of the AdeABC efflux pump is associated with quinolone resistance. FQR can also be mediated by plasmid genes (PMQR), either by the *qnr* gene (quinolone resistance) (ALBORNOZ et al [60]) or by an aminoglycoside-modifying mutant enzyme, which can reduce the antibacterial action of the antibiotic molecule by adding an acetyl group (ROBICSEK et al [61]). It has been observed that rifampin resistance is associated with point mutations in the rpoB gene that produce changes in the amino acid sequence (FLOSS et al [62]).

Another example is the development of colistin resistance, used extensively in recent years due to the spread of the AR phenomenon. In *A. baumannii*, colistin resistance is mediated by two mechanisms: modification of lipid A from the structure of lipopolysaccharides (LPS) through mutations in the PmrAB component and loss of LPS production capacity due to mutations in the *lpxA*, l*pxC* and *lpxD* genes encoding enzymes involved in the synthesis stages of LPS. Mutational inactivation of the *lpxA*, *lpxC*, and *lpxD* genes, which are involved in the LPS synthesis stages, results in the loss of the antibacterial activity of colistin (ADAMS et al [64]; CHIN et al [65]).

Mechanisms of resistance to biocides

Biocides can be grouped into several categories, depending on the functional group they possess (e.g., derivatives of imidazole, phenols, aromatic diamidines, biguanides, chlorine compounds, etc.), the mode of action (oxidative, membrane-active, or thiol interactive) or their target (e.g., the cell wall, membranes, intracellular proteins, nucleic acids) (FRENZEL et al [66]). For example, oxygen-releasing chemicals act on enzymes in the membrane and cytoplasm, causing them to oxidize. Biocides such as

alcohol and chlorhexidine act on proteins and cause their denaturation. The quaternary ammonium compounds (QAC) and biguanides induce the physical denaturation and partial solubilization of the cell membrane and wall. Biguanides enter the cell following the destabilization of divalent cations associated with the cell membrane (D'ARCY & TAYLOR [67]). Bisphenol triclosan acts on the fabI protein reductase transporter of enoyl acyl compounds, involved in the synthesis of fatty acids (CAREY & MCNAMARA [68]).

Biocides, including antiseptics and disinfectants, have been used over time in various fields such as water treatment, wood or paint preservation, textiles, household products, plastics, cosmetics, and processed food industries. The use of biocides, especially in hospital environments for the disinfection of medical devices and infections control has led to the selection of resistant strains. Unlike antibiotics, the target sites of biocides are not very specific, which is why nonspecific resistance mechanisms might occur (GNANADHAS et al [69]) following the exposure to suboptimal or sublethal concentrations of biocides (POOLE [70]). The main mechanisms of biocidal resistance found in Gram-negative bacteria, including *A. baumannii*, are represented by the activation of efflux pumps and cell membrane permeability changes.

1. Efflux pumps

One of the main mechanisms of biocide resistance is the expression of efflux systems, especially qac genes (*qacE* and *qacEΔ1*). The *qac* genes (quaternary ammonium compounds) are highly prevalent in Gram-negative bacteria (CHANG et al [72]), including *A. baumannii*, mainly due to the plasmid-mediated dissemination of class 1 integrons, which typically contain the *qacE*Δ1 gene (the functionally active deletion derivative of qacE gene) (RIANO et al [73]). Many of the *qac* genes are derived from MGEs such as *qacA / B*, *qacC / D*, *qacE*, *qacED1*, *qacF*, *qacJ* and *qacG*, while other are chromosomal (*sugE (c)*, *emrE*, *ydgE / ydgF*, *mdfA*) (COSTA et al [74]; ZOU et al [75]). The *qacA / B* gene encodes for MFS, while the *qacC* to *qacH* for the SMR superfamily (PRAG et al [76]; WASSENAAR et al [77]). *Qac* genes have been associated with diverse carbapenems, AMGs, trimethoprim, and sulfonamides ARGs (SHIRMOHAMMADLOU et al [78]) on the same genetic platforms, such as class 1 integrons. Given this, the inappropriate use of biocides may select antibiotic-resistant bacteria among Gram-negative rods (HEGSTAD et al [79]). Also, reducing the intracellular accumulation of biocides and other antimicrobial agents can be achieved by overexpressing efflux pumps, given that biocides and antimicrobial agents are a substrate for most efflux pumps (POOLE [15]). Studies have shown that the RND efflux system is involved in the development of biocidal resistance, although it mainly causes AR. It has been observed that inactivation of the adeB and adeJ genes increases the susceptibility of *A. baumannii* to biocides action (RAJAMOHAN et al [80]).

2. Outer membrane porins

Another mechanism involved in biocide resistance is represented by the modified porins expressions inducing changes in membrane permeability. It has been shown that the exposure to biocides is associated with the decreased expression of the OmpA and CarO genes, leading to both reduced susceptibility to biocides and co-resistance to certain antibiotics (e.g., AMGs, carbapenems, quinolones). Following these findings, it remains to be determined whether the effect of biocides is a consequence of altered permeability or is also due to acquired mutations that affect the level of biocide resistance (FERNANDEZ-CUENCA et al [81]).

3. Co- and cross-selection mechanisms

It has been observed that specific biocides can induce cross-resistance to antibiotics, due to the use of common resistance mechanisms (e.g., efflux pumps) or the acquisition of resistance genes through MGE (DENVER [71]). The expansion of the AR phenomenon as a result of exposure to the action of biocides was explained through 5 principles: cross-resistance (selection of genes that encode both biocide resistance and resistance to one or several antimicrobial agents), changes in the physiological response of the bacterial population following exposure to biocides (resulting in increased resistance to both biocides and antibiotics), co-resistance (selection of clones or MGEs that harbor different resistance genes that can be transferred and expressed in a new host bacterium), indirect selection of resistant bacterial subpopulations following exposure to biocides, leading to increased resistance and activation of the SOS response (SCENIHR [82]).

Unlike the many studies focusing on the AR mechanisms, there are fewer studies that examine biocide resistance and the link between biocide use and co-selection for AR. It is known that if biocide/metal and AR genes are located on the same genetic platform (plasmids), exposure to biocides or metals can lead to the spread of AR through horizontal gene transfer (HGT) (PIDDOCK [83]). In both natural and polluted environments, various metals or biocides can co-select resistant bacteria and implicitly for plasmids involved in resistance (GULLBERG et al [84]). An analysis of the biocide/metal and antibiotic resistance gene cluster (ARGs-BMRG) revealed that QACs have a high co-selection potential for different antibiotic classes and also contribute to the maintenance of the carrying MGEs (PAI et al [85]). It has been also shown that the exposure to chlorhexidine digluconate increases resistance to several antibiotics (KAMPF [86]), and in case of streptococci, the reduced susceptibility to biocides was linked to resistance to AMG (MARTIN & MARIS [87]). In the hospital settings, exposure of aerobic bacteria to high concentrations of biocides has led to increased MIC values for current antibiotics (TANDUKAR et al [88]). Exposure of *E. coli* strains to benzalkonium chloride and ciprofloxacin has shown an increase in efflux pump activity and biofilm formation capacity. It has also been observed that there is a more significant potential of biocide / chromosomal metal resistance genes to promote HGT of ARGs

through co-selection, than plasmid ones (PAGEDAR et al [89]). Studies have shown that prolonged exposure to sublethal concentrations of biocides causes overexpression of efflux pumps and, consequently, increased resistance (GILBERT & MCBAIN [90]). In *P. aeruginosa*, following prolonged exposure to the action of 2-phenoxyethanol biocide, an increase in MIC and cross-resistance to other biocides and antibiotics has been observed (ABDEL et al [91]). Exposure to subinhibitory concentrations of QAC of some *E. coli* strains has led to increased resistance to antibiotics but also to phenol compounds, due to the increased expression of efflux systems (LANGSRUD et al [4]). In *A. baumannii*, investigation of MBL-positive *A. baumannii* strains revealed the presence of at least one *qac* gene in each isolate. The presence of multiple copies of the *qacE*Δ*1* gene is associated with both AR and biocide resistance (GOMAA et al [92]). The high distribution of biocide resistance genes in *A. baumannii* clinical strains suggests the selective pressure in the hospital environment. The application of low levels of biocides can cause the persistence of microorganisms in the environment and contribute to the maintenance of MDR strains (BOOST et al [93]).

Conclusions

Resistance to antimicrobial agents has increased in recent years among strains associated with severe nosocomial infections (MARINESCU et al [94], OANCEA & STOIA [95]. *A. baumannii* is one of the most problematic opportunistic agents due to the multitude of adaptation mechanisms, allowing it to survive in extreme environments (NAWFAL HAITHAM AS et al [96]). Improper administration of antibiotics and other biocides has led to an uncontrolled expansion of resistance among *A. baumannii* isolates, which exhibit both intrinsic resistance mechanisms (e.g., efflux pumps) and mechanisms acquired through HGT of ARGs and biocide resistance genes (SAVIUC et al [97]). Studies have shown that there is a link between biocide exposure and the co-selection of AR (PIDDOCK [83]; GULLBERG et al [84]). In *A. baumannii*, activation of efflux pumps and co-selection of ARGs due to their localization on the same MGE with biocide resistance genes is the main mechanism by which biocides can contribute to increased bacterial resistance. Also, prolonged exposure to biocide concentrations lower than MIC causes selective pressure that leads to cross-resistance to biocides or antibiotics (TANDUKAR et al [88]).

Given the widespread use of biocides in various fields, future studies are needed to analyze the selective pressure of biocides on clinical isolates as well as the risk of selection of MDR strains associated with severe infections. Due to the expansion of clinical isolates' resistance, the standardization of techniques for detecting the minimum inhibitory concentration must be considered. To this end, the transition from laboratory research to entrepreneurial solutions (new detection techniques and their patenting) can be a way to counteract the adverse effects of bacterial resistance.

Acknowledgements

This paper was co-financed from the Human Capital Operational Program 2014-2020, project number POCU / 380/6/13/125245 no. 36482 / 23.05.2019 "Excellence in interdisciplinary PhD and post-PhD research, career alternatives through entrepreneurial initiative (EXCIA)", coordinator The Bucharest University of Economic Studies.

All authors have equally contributed as main authors.

References

1. HOLMES AH, MOORE LSP, SUNDSFJORD A, STEINBAKK M, REGMI S, KARKEY A, GUERIN PJ, PIDDOCK LJ V. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet (London, England)*, 387 (10014):176-187 (2016).
2. PELEG AY, SEIFERT H, PATERSON DL. Acinetobacter baumannii: emergence of a successful pathogen. *Clin. Microbiol. Rev.*, 21(3):538-582 (2008).
3. HOWARD A, O'DONOGHUE M, FEENEY A, SLEATOR RD. Acinetobacter baumannii: an emerging opportunistic pathogen. *Virulence*, 3(3):243-250 (2012).
4. LANGSRUD S, SUNDHEIM G, HOLCK AL. Cross-resistance to antibiotics of Escherichia coli adapted to benzalkonium chloride or exposed to stress-inducers. *J. Appl. Microbiol.*, 96 (1): 201-208 (2004).
5. RUSSELL AD, TATTAWASART U, MAILLARD JY, FURR JR. Possible link between bacterial resistance and use of antibiotics and biocides. *Antimicrob agents and chemother.*, 2151 (1998).
6. BRISOU J, PREVOT AR. [Studies on bacterial taxonomy. X. The revision of species under Acromobacter group]. *Ann. Inst. Pasteur (Paris)*, 86(6):722-728 (1954).
7. LESSEL EF. International Committee on Nomenclature of Bacteria Subcommittee on the Taxonomy of Moraxella and Allied Bacteria: Minutes of the Meeting, 11 August 1970. Room Constitution C, Maria-Isabel Hotel, Mexico City, Mexico. *Int. J. Syst. Evol. Microbiol.*, 21(2): 213-214 (1971).
8. D'SOUZA R, PINTO NA, PHUONG N LE, HIGGINS PG, VU TN, BYUN J-H, CHO YL, CHOI JR, YONG D. Phenotypic and genotypic characterization of Acinetobacter spp. panel strains: a cornerstone to facilitate antimicrobial development. *Front. Microbiol.*, 10:559 (2019).
9. CHEN T-L, LEE Y-T, KUO S-C, YANG S-P, FUNG C-P, LEE S-D. Rapid identification of Acinetobacter baumannii, Acinetobacter nosocomialis and Acinetobacter pittii with a multiplex PCR assay. *J. Med. Microbiol.*, 63(Pt 9):1154-1159 (2014).
10. VISCA P, SEIFERT H, TOWNER KJ. Acinetobacter infection – an emerging threat to human health. *IUBMB Life*, 63(12):1048-1054 (2011).
11. AL-KADMY IMS, ALI ANM, SALMAN IMA, KHAZAAL SS. Molecular characterization of Acinetobacter baumannii isolated from Iraqi hospital environment. *New microbes new Infect.*, 21:51-57 (2018).
12. GALLEGO L. Acinetobacter Baumannii: Factors involved in its high adaptability to adverse environmental conditions. *Microb. Exp.*, 3(2):00085 (2016).
13. CHEN H, CAO J, ZHOU C, LIU H, ZHANG X, ZHOU T. Biofilm formation restrained by subinhibitory concentrations of tigecyclin in Acinetobacter baumannii is associated with downregulation of efflux pumps. *Chemotherapy*, 62(2):128-133 (2017).

14. BUTAYE P, CLOECKAERT A, SCHWARZ S. Mobile genes coding for efflux-mediated antimicrobial resistance in Gram-positive and Gram-negative bacteria. *Int. J. Antimicrob. Agents*, 22(3):205-210 (2003).
15. POOLE K. Efflux-mediated antimicrobial resistance. *J. Antimicrob. Chemother.*, 56(1):20-51 (2005).
16. LIN M-F, LAN C-Y. Antimicrobial resistance in Acinetobacter baumannii: From bench to bedside. *World J. Clin. cases*, 2(12):787-814 (2014).
17. YOON E-J, CHABANE YN, GOUSSARD S, SNESRUD E, COURVALIN P, DÉ E, GRILLOT-COURVALIN C. Contribution of resistance-nodulation-cell division efflux systems to antibiotic resistance and biofilm formation in Acinetobacter baumannii. *MBio*, 6(2):e00309-15 (2015).
18. DAMIER-PIOLLE L, MAGNET S, BRÉMONT S, LAMBERT T, COURVALIN P. AdeIJK, a resistance-nodulation-cell division pump effluxing multiple antibiotics in Acinetobacter baumannii. *Antimicrob. Agents Chemother.*, 52(2):557-562 (2008).
19. SU X-Z, CHEN J, MIZUSHIMA T, KURODA T, TSUCHIYA T. AbeM, an H+-coupled Acinetobacter baumannii multidrug efflux pump belonging to the MATE family of transporters. *Antimicrob. Agents Chemother.*, 49(10): 4362-4364 (2005).
20. HOU PF, CHEN XY, YAN GF, WANG YP, YING CM. Study of the correlation of imipenem resistance with efflux pumps AdeABC, AdeIJK, AdeDE and AbeM in clinical isolates of Acinetobacter baumannii. *Chemotherapy*, 58(2):152-158 (2012).
21. RUMBO C, GATO E, LÓPEZ M, RUIZ DE ALEGRÍA C, FERNÁNDEZ-CUENCA F, MARTÍNEZ-MARTÍNEZ L, VILA J, PACHÓN J, CISNEROS JM, RODRÍGUEZ-BAÑO J et al. Contribution of efflux pumps, porins, and β-lactamases to multidrug resistance in clinical isolates of Acinetobacter baumannii. *Antimicrob. Agents Chemother*., 57(11):5247-5257 (2013).
22. ROCA I, MARTI S, ESPINAL P, MARTÍNEZ P, GIBERT I, VILA J. CraA, a major facilitator superfamily efflux pump associated with chloramphenicol resistance in Acinetobacter baumannii. *Antimicrob. Agents Chemother.*, 53(9):4013-4014 (2009).
23. RAJAMOHAN G, SRINIVASAN VB, GEBREYES WA. Molecular and functional characterization of a novel efflux pump, AmvA, mediating antimicrobial and disinfectant resistance in Acinetobacter baumannii. *J. Antimicrob. Chemother.*, 65(9):1919-1925 (2010).
24. SHARMA A, SHARMA R, BHATTACHARYYA T, BHANDO T, PATHANIA R. Fosfomycin resistance in Acinetobacter baumannii is mediated by efflux through a major facilitator superfamily (MFS) transporter-AbaF. *J. Antimicrob. Chemother.*, 72(1):68-74 (2017).
25. PÉREZ-VARELA M, CORRAL J, ARANDA J, BARBÉ J. Functional characterization of AbaQ, a novel efflux pump mediating quinolone resistance in Acinetobacter baumannii. *Antimicrob. Agents Chemother.*, 62(9):e00906-18 (2018).
26. SRINIVASAN VB, RAJAMOHAN G, GEBREYES WA. Role of AbeS, a novel efflux pump of the SMR family of transporters, in resistance to antimicrobial agents in Acinetobacter baumannii. *Antimicrob. Agents Chemother.*, 53(12):5312-5316 (2009).
27. LEE C-R, LEE JH, PARK M, PARK KS, BAE IK, KIM YB, CHA C-J, JEONG BC, LEE SH. Biology of Acinetobacter baumannii: pathogenesis, antibiotic resistance mechanisms, and prospective treatment options. *Front. Cell. Infect. Microbiol.*, 7:55 (2017).
28. BOU G, CERVERÓ G, DOMÍNGUEZ MA, QUEREDA C, MARTÍNEZ-BELTRÁN J. Characterization of a nosocomial outbreak caused by a multiresistant Acinetobacter baumannii strain with a carbapenem-hydrolyzing enzyme: high-level carbapenem resistance in A. baumannii is not due solely to the presence of beta-lactamases. *J. Clin. Microbiol.*, 38(9):3299-3305 (2000).
29. DUPONT M, PAGÈS J-M, LAFITTE D, SIROY A, BOLLET C. Identification of an OprD homologue in Acinetobacter baumannii. *J. Proteome Res.*, 4(6):2386-2390 (2005)
30. QUALE J, BRATU S, LANDMAN D, HEDDURSHETTI R. Molecular epidemiology and mechanisms of carbapenem resistance in Acinetobacter baumannii endemic in New York City. *Clin. Infect. Dis.*, 37(2):214-220 (2003).
31. DEL MAR TOMÁS M, BECEIRO A, PÉREZ A, VELASCO D, MOURE R, VILLANUEVA R, MARTÍNEZ-BELTRÁN J, BOU G. Cloning and functional analysis of the gene encoding the 33- to 36-kilodalton outer membrane protein associated with carbapenem resistance in Acinetobacter baumannii. *Antimicrob. Agents Chemother.*, 49(12):5172-5175 (2005).
32. HOOD MI, JACOBS AC, SAYOOD K, DUNMAN PM, SKAAR EP. Acinetobacter baumannii increases tolerance to antibiotics in response to monovalent cations. *Antimicrob. Agents Chemother.*, 54(3):1029-1041 (2010).
33. MUSSI MA, LIMANSKY AS, VIALE AM. Acquisition of resistance to carbapenems in multidrug-resistant clinical strains of Acinetobacter baumannii: natural insertional inactivation of a gene encoding a member of a novel family of beta-barrel outer membrane proteins. *Antimicrob. Agents Chemother.*, 49(4):1432-1440 (2005)
34. MUSSI MA, RELLING VM, LIMANSKY AS, VIALE AM. CarO, an Acinetobacter baumannii outer membrane protein involved in carbapenem resistance, is essential for L-ornithine uptake. *FEBS Lett.*, 581(29):5573-5578 (2007).
35. SIROY A, MOLLE V, LEMAÎTRE-GUILLIER C, VALLENET D, PESTEL-CARON M, COZZONE AJ, JOUENNE T, DÉ E. Channel formation by CarO, the carbapenem resistance-associated outer membrane protein of Acinetobacter baumannii. *Antimicrob. Agents Chemother.*, 49(12):4876-4883 (2005).
36. CATEL-FERREIRA M, COADOU G, MOLLE V, MUGNIER P, NORDMANN P, SIROY A, JOUENNE T, DÉ E. Structure-function relationships of CarO, the carbapenem resistance-associated outer membrane protein of Acinetobacter baumannii. *J. Antimicrob. Chemother.*, 66(9):2053-2056 (2011).
37. SMANI Y, FÀBREGA A, ROCA I, SÁNCHEZ-ENCINALES V, VILA J, PACHÓN J. Role of OmpA in the multidrug resistance phenotype of Acinetobacter baumannii. *Antimicrob. Agents Chemother.*, 58(3):1806-1808 (2014)
38. ESPINAL P, PANTEL A, ROLO D, MARTI S, LÓPEZ-ROJAS R, SMANI Y, PACHÓN J, VILA J, LAVIGNE J-P. Relationship between different resistance mechanisms and virulence in Acinetobacter baumannii. *Microb. Drug Resist.*, 25(5):752-760 (2019).
39. SÁNCHEZ-ENCINALES V, ÁLVAREZ-MARÍN R, PACHÓN-IBÁÑEZ ME, FERNÁNDEZ-CUENCA F, PASCUAL A, GARNACHO-MONTERO J, MARTÍNEZ-MARTÍNEZ L, VILA J, TOMÁS MM, CISNEROS JM et al. Overproduction of outer membrane protein A by Acinetobacter baumannii as a risk factor for nosocomial pneumonia, bacteremia, and mortality rate increase. *J. Infect. Dis.*, 215(6):966-974 (2017).
40. SATO Y, UNNO Y, KAWAKAMI S, UBAGAI T, ONO Y. Virulence characteristics of Acinetobacter baumannii clinical isolates vary with the expression levels of omps. *J. Med. Microbiol.*, 66(2):203-212 (2017).

41. CHOI CH, HYUN SH, LEE JY, LEE JS, LEE YS, KIM SA, CHAE J-P, YOO SM, LEE JC. Acinetobacter baumannii outer membrane protein A targets the nucleus and induces cytotoxicity. *Cell. Microbiol.*, 10(2):309-319 (2008).
42. CHOI CH, LEE EY, LEE YC, PARK TI, KIM HJ, HYUN SH, KIM SA, LEE S-K, LEE JC. Outer membrane protein 38 of Acinetobacter baumannii localizes to the mitochondria and induces apoptosis of epithelial cells. *Cell. Microbiol.*, 7(8):1127-1138 (2005).
43. ZHOU Y, YU H, GUO Q, XU X, YE X, WU S, GUO Y, WANG M. Distribution of 16S rRNA methylases among different species of Gram-negative bacilli with high-level resistance to aminoglycosides. *Eur. J. Clin. Microbiol. Infect. Dis.*, 29(11):1349-1353 (2010).
44. RAMIREZ MS, TOLMASKY ME. Aminoglycoside modifying enzymes. *Drug Resist. Updat. Rev. Comment. Antimicrob. Anticancer Chemother.*, 13(6):151-71 (2010).
45. WEN J-T, ZHOU Y, YANG L, XU Y. Multidrug-resistant genes of aminoglycoside-modifying enzymes and 16S rRNA methylases in Acinetobacter baumannii strains. *Genet. Mol. Res.*, 13(2):3842-3849 (2014).
46. HEIDARY M, SALIMI CHIRANI A, KHOSHNOOD S, ESLAMI G, ATYABI SM, NAZEM H, FAZILATI M, HASHEMI A, SOLEIMANI S. Molecular detection of aminoglycoside-modifying enzyme genes in Acinetobacter baumannii clinical isolates. *Acta Microbiol. Immunol. Hung.*, 64(2):143-150 (2017).
47. NIGRO SJ, POST V, HALL RM. Aminoglycoside resistance in multiply antibiotic-resistant Acinetobacter baumannii belonging to global clone 2 from Australian hospitals. *J. Antimicrob. Chemother.*, 66 (7):1504-1509 (2011).
48. AGHAZADEH M, REZAEE MA, NAHAEI MR, MAHDIAN R, PAJAND O, SAFFARI F, HASSAN M, HOJABRI Z. Dissemination of aminoglycoside-modifying enzymes and 16S rRNA methylases among acinetobacter baumannii and Pseudomonas aeruginosa isolates. *Microb. Drug Resist.*, 19(4):282-288 (2013).
49. HASANI A, SHEIKHALIZADEH V, AHANGARZADEH REZAEE M, RAHMATI-YAMCHI M, HASANI A, GHOTASLOU R, GOLI HR. Frequency of aminoglycoside-modifying enzymes and ArmA among different sequence groups of Acinetobacter baumannii in Iran. *Microb. Drug Resist.*, 22(5): 347-353 (2016).
50. SHEIKHALIZADEH V, HASANI A, AHANGARZADEH REZAEE M, RAHMATI-YAMCHI M, HASANI A, GHOTASLOU R, GOLI HR. Comprehensive study to investigate the role of various aminoglycoside resistance mechanisms in clinical isolates of Acinetobacter baumannii. *J. Infect. Chemother.*, 23(2):74-79 (2017).
51. SALIMIZAND H, ZOMORODI AR, MANSURY D, KHAKSHOOR M, AZIZI O, KHODAPARAST S, BASERI Z, KARAMI P, ZAMANLOU S, FARSIANI H et al. Diversity of aminoglycoside modifying enzymes and 16S rRNA methylases in Acinetobacter baumannii and Acinetobacter nosocomialis species in Iran; wide distribution of aadA1 and armA. *Infect. Genet. Evol.*, 66:195-199 (2018).
52. SHOOSHTARI FS, NAVIDIFAR T, AMIN M, GOODARZI H. Coexistence of genes encoding aminoglycoside modifying enzymes among clinical Acinetobacter baumannii isolates in Ahvaz, Southwest Iran. *Acta Microbiol. Immunol. Hung.*, 67(1):1-9 (2019).
53. AKERS KS, CHANEY C, BARSOUMIAN A, BECKIUS M, ZERA W, YU X, GUYMON C, KEEN EF 3RD, ROBINSON BJ, MENDE K et al. Aminoglycoside resistance and susceptibility testing errors in Acinetobacter baumannii-calcoaceticus complex. *J. Clin. Microbiol.*, 48(4):1132-1138 (2010).
54. LUPO A, HAENNI M, MADEC J-Y. Antimicrobial resistance in Acinetobacter spp. and Pseudomonas spp. *Microbiol. Spectr.*, 6(3) (2018).
55. LIOU GF, YOSHIZAWA S, COURVALIN P, GALIMAND M. Aminoglycoside resistance by ArmA-mediated ribosomal 16S methylation in human bacterial pathogens. *J. Mol. Biol.*, 359(2):358-364 (2006).
56. DOI Y, ADAMS JM, YAMANE K, PATERSON DL. Identification of 16S rRNA methylase-producing Acinetobacter baumannii clinical strains in North America. *Antimicrob. Agents Chemother.*, 51(11):4209-4210 (2007).
57. PARK S, LEE KM, YOO YS, YOO JS, YOO J IL, KIM HS, LEE YS, CHUNG GT. Alterations of gyrA, gyrB, and parC and activity of efflux pump in fluoroquinolone-resistant Acinetobacter baumannii. *Osong public Heal. Res. Perspect.*, 2(3):164-170 (2011).
58. ARDEBILI A, LARI AR, BEHESHTI M, LARI ER. Association between mutations in gyrA and parC genes of Acinetobacter baumannii clinical isolates and ciprofloxacin resistance. *Iran. J. Basic Med. Sci.*, 18(6):623-626 (2015).
59. VILA J, RUIZ J, GOÑI P, JIMENEZ DE ANTA T. Quinolone-resistance mutations in the topoisomerase IV parC gene of Acinetobacter baumannii. *J. Antimicrob. Chemother.*, 39(6):757-762 (1997).
60. ALBORNOZ E, TIJET N, DE BELDER D, GOMEZ S, MARTINO F, CORSO A, MELANO RG, PETRONI A. QnrE1, a member of a new family of plasmid-located quinolone resistance genes, originated from the chromosome of Enterobacter species. *Antimicrob. Agents Chemother.*, 61(5):e02555-16 (2017).
61. ROBICSEK A, STRAHILEVITZ J, JACOBY GA, MACIELAG M, ABBANAT D, PARK CH, BUSH K, HOOPER DC. Fluoroquinolone-modifying enzyme: a new adaptation of a common aminoglycoside acetyltransferase. *Nat. Med.*, 12(1):83-88 (2006).
62. FLOSS HG, YU T-W. Rifamycin-mode of action, resistance, and biosynthesis. *Chem. Rev.* (2005); 105 (2): 621-632. doi:10.1021/cr030112j.
63. HOUANG ETS, CHU Y-W, LO W-S, CHU K-Y, CHENG AFB. Epidemiology of rifampin ADP-ribosyltransferase (arr-2) and metallo-beta-lactamase (blaIMP-4) gene cassettes in class 1 integrons in Acinetobacter strains isolated from blood cultures in 1997 to 2000. *Antimicrob. Agents Chemother.*, 47(4):1382-1390 (2003).
64. ADAMS MD, NICKEL GC, BAJAKSOUZIAN S, LAVENDER H, MURTHY AR, JACOBS MR, BONOMO RA. Resistance to colistin in Acinetobacter baumannii associated with mutations in the PmrAB two-component system. *Antimicrob. Agents Chemother.*, 53(9):3628-3634 (2009)
65. CHIN C-Y, GREGG KA, NAPIER BA, ERNST RK, WEISS DS. A PmrB-regulated deacetylase required for lipid A modification and polymyxin resistance in Acinetobacter baumannii. *Antimicrob. Agents Chemother.*, 59(12):7911-7914 (2015).
66. FRENZEL E, SCHMIDT S, NIEDERWEIS M, STEINHAUER K. Importance of porins for biocide efficacy against Mycobacterium smegmatis. *Appl. Environ. Microbiol.*, 77(9):3068-3073 (2011).
67. D'ARCY PF, TAYLOR EP. Quaternary ammonium compounds in medicinal chemistry. I. *J. Pharm. Pharmacol.*, 14:129-146 (1962).
68. CAREY DE, MCNAMARA PJ. The impact of triclosan on the spread of antibiotic resistance in the environment. *Front. Microbiol.*, 5:780 (2014).

69. GNANADHAS DP, MARATHE SA, CHAKRAVORTTY D. Biocides--resistance, cross-resistance mechanisms and assessment. *Expert Opin. Investig. Drugs*, 22(2):191-206 (2013).
70. POOLE K. Mechanisms of bacterial biocide and antibiotic resistance. *Symp. Ser. Soc. Appl. Microbiol.*, 92, Suppl: 55S-64S (2002).
71. DENYER SP. Mechanisms of action of antibacterial biocides. *Int. Biodeterior. Biodegradation*, 36(3):227-245 (1995).
72. CHANG Y-C, SHIH DY-C, WANG J-Y, YANG S-S. Molecular characterization of class 1 integrons and antimicrobial resistance in Aeromonas strains from foodborne outbreak-suspect samples and environmental sources in Taiwan. *Diagn. Microbiol. Infect. Dis.*, 59(2): 191-197 (2007).
73. RIAÑO I, MORENO MA, TESHAGER T, SÁENZ Y, DOMÍNGUEZ L, TORRES C. Detection and characterization of extended-spectrum beta-lactamases in Salmonella enterica strains of healthy food animals in Spain. *J. Antimicrob. Chemother.*, 58(4):844-847 (2006).
74. COSTA SS, NTOKOU E, MARTINS A, VIVEIROS M, POURNARAS S, COUTO I, AMARAL L. Identification of the plasmid-encoded qacA efflux pump gene in meticillin-resistant Staphylococcus aureus (MRSA) strain HPV107, a representative of the MRSA Iberian clone. *Int. J. Antimicrob. Agents*, 36(6):557-561 (2010).
75. ZOU L, MENG J, MCDERMOTT PF, WANG F, YANG Q, CAO G, HOFFMANN M, ZHAO S. Presence of disinfectant resistance genes in Escherichia coli isolated from retail meats in the USA. *J. Antimicrob. Chemother*, 69(10): 2644-2649 (2014).
76. PRAG G, FALK-BRYNHILDSEN K, JACOBSSON S, HELLMARK B, UNEMO M, SÖDERQUIST B. Decreased susceptibility to chlorhexidine and prevalence of disinfectant resistance genes among clinical isolates of Staphylococcus epidermidis. *APMIS*, 122(10):961-967 (2014).
77. WASSENAAR TM, USSERY D, NIELSEN LN, INGMER H. Review and phylogenetic analysis of qac genes that reduce susceptibility to quaternary ammonium compounds in Staphylococcus species. *Eur. J. Microbiol. Immunol. (Bp)*, 5(1):44-61 (2015).
78. SHIRMOHAMMADLOU N, ZEIGHAMI H, HAGHI F, KASHEFIEH M. Resistance pattern and distribution of carbapenemase and antiseptic resistance genes among multidrug-resistant Acinetobacter baumannii isolated from intensive care unit patients. *J. Med. Microbiol.*, 67(10):1467-1473 (2018).
79. HEGSTAD K, LANGSRUD S, LUNESTAD BT, SCHEIE AA, SUNDE M, YAZDANKHAH SP. Does the wide use of quaternary ammonium compounds enhance the selection and spread of antimicrobial resistance and thus threaten our health? *Microb. Drug Resist.*, 16(2):91-104 (2010).
80. RAJAMOHAN G, SRINIVASAN VB, GEBREYES WA. Novel role of Acinetobacter baumannii RND efflux transporters in mediating decreased susceptibility to biocides. *J. Antimicrob. Chemother.*, 65(2):228-232 (2010).
81. FERNÁNDEZ-CUENCA F, TOMÁS M, CABALLERO-MOYANO F-J, BOU G, MARTÍNEZ-MARTÍNEZ L, VILA J, PACHÓN J, CISNEROS J-M, RODRÍGUEZ-BAÑO J, PASCUAL Á. Reduced susceptibility to biocides in Acinetobacter baumannii: association with resistance to antimicrobials, epidemiological behaviour, biological cost and effect on the expression of genes encoding porins and efflux pumps. *J. Antimicrob. Chemother.*, 70(12):3222-3229 (2015).
82. SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks), Assessment of the antibiotic resistance effects of biocides. 19 January (2009).
83. PIDDOCK LJV. The crisis of no new antibiotics – what is the way forward? *Lancet. Infect. Dis.*, 12(3):249-253 (2012).
84. GULLBERG E, ALBRECHT LM, KARLSSON C, SANDEGREN L, ANDERSSON DI. Selection of a multidrug resistance plasmid by sublethal levels of antibiotics and heavy metals. *MBio*, 5(5):e01918-14 (2014).
85. PAL C, BENGTSSON-PALME J, KRISTIANSSON E, LARSSON DGJ. Co-occurrence of resistance genes to antibiotics, biocides and metals reveals novel insights into their co-selection potential. *BMC Genomics*, 16:964 (2015).
86. KAMPF G. Acquired resistance to chlorhexidine – is it time to establish an "antiseptic stewardship" initiative? *J. Hosp. Infect.*, 94(3):213-227 (2016).
87. MARTIN H, MARIS P. [Antiseptic and antibiotic resistance of 310 gram-positive strains isolated from udders after use of post-milking teat germicides]. *Vet. Res.*, 26(1):43-56 (1995).
88. TANDUKAR M, OH S, TEZEL U, KONSTANTINIDIS KT, PAVLOSTATHIS SG. Long-term exposure to benzalkonium chloride disinfectants results in change of microbial community structure and increased antimicrobial resistance. *Environ. Sci. Technol.*, 47(17):9730-9738 (2013).
89. PAGEDAR A, SINGH J, BATISH VK. Adaptation to benzalkonium chloride and ciprofloxacin affects biofilm formation potential, efflux pump and haemolysin activity of Escherichia coli of dairy origin. *J. Dairy Res.*, 79(4):383-389 (2012).
90. GILBERT P, MCBAIN AJ. Potential impact of increased use of biocides in consumer products on prevalence of antibiotic resistance. *Clin. Microbiol. Rev.*, 16(2):189-208 (2003).
91. ABDEL MALEK SMA, BADRAN YR. Pseudomonas aeruginosa PAO1 adapted to 2-phenoxyethanol shows cross-resistance to dissimilar biocides and increased susceptibility to antibiotics. *Folia Microbiol. (Praha)*, 55(6):588-592 (2010).
92. GOMAA FAM, HELAL ZH, KHAN MI. High prevalence of bla(NDM-1), bla(VIM), qacE, and qacEΔ1 genes and their association with decreased susceptibility to antibiotics and common hospital biocides in clinical isolates of Acinetobacter baumannii. *Microorganisms*, 5(2):18 (2017).
93. BOOST M V, CHAN J, SHI G, CHO P. Effect of multipurpose solutions against Acinetobacter carrying QAC genes. *Optom. Vis. Sci.*, 91(3):272-277 (2014).
94. MARINESCU F, MARUTESCU L, SAVIN I, LAZAR V. Antibiotic resistance markers among Gram-negative isolates from wastewater and receiving rivers in South Romania. Rom Biotechnol Lett. 2015.20(1): 10055-69.
95. OANCEA S, STOIA M. Antibiotic resistance of bacterial pathogens: the magnitude of the problem from two perspectives – Romanian and worldwide. *Rom Biotechnol*. 2010. 15(5); 5519-29.
96. NAWFAL HAITHAM AS, I ALI AO, CHIFIRIUC MC, MIHAESCU G, ALSHWAIKH RMA, MOHSIN S, MOHAMMED HB, PIRCALABIORU GG, GHEORGHE I. Antibiotic resistance determinants of Acinetobacter baumannii strains isolated from nosocomial infections. *Rom Biotechnol Lett*. 2020; 25(3): 1658-1665.
97. SAVIUC C, GHEORGHE I, COBAN S, DRUMEA V, CHIFIRIUC MC, BANU O, BEZIRTZOGLOU E, LAZAR V. Rosmarinus Officinalis Essential Oil and Eucalyptol Act as Efflux Pumps Inhibitors and Increase Ciprofloxacin Efficiency against Pseudomonas Aeruginosa and Acinetobacter Baumannii MDR Strains. *Rom Biotechnol Lett.* 2016. 21(4); 11782-90.