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Is There A Correlation Between Antibiotic Resistance and Decreased Susceptibility to Biocides in Different Genus of Bacterial Genera?

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Abstract

Objective: Our aim was to assess a possible association between antibiotic resistance and decreased susceptibility to antiseptics or disinfectants, because published papers are contradictory. We used a great number of microorganisms from different bacterial genera and some biocides in order to conclude if there was an association between antibiotic resistances and decreased disinfectant (or antiseptic) effects.

Material and Methods: Serial dilutions were performed with six disinfectants and two antiseptics to study the MIC-dilution (maximal dilution of disinfectant or antiseptic that inhibits each microorganism) and that dilution was contrasted with the antibiograms of each of the 159 bacteria recently isolated from ICU patients. These antibiograms were determinated by the Kirby-Bauer method, noting only whether they were susceptible or resistant. After, univariate and multivariate analysis were run on the data.

Results: With the antibiograms and MIC-dilutions for every bacteria and biocide, the bivariate analysis found that only 4.7% of the antibiotic-biocide pairs showed a significant correlation ($p < 0.05\%$) between antibiotic resistance and decreased susceptibility to the disinfectant or antiseptic, 8.3% showed a significant inverse correlation, and the rest no correlation. Multivariate analysis of the above variables (controlling the effects of the type of microorganism and disinfectant or antiseptic used), showed that overall fit of the equation was very poor, since $R^2 = 0.032$.

Conclusion: In a large sample of different bacteria genera there was no significant correlation between antibiotic resistance and decreased susceptibility to disinfectants and antiseptics, except in 4.7% of the antibiotic-biocide pairs.

Keywords: Antibiotic-resistance; Bacteriostatic-effect; Correlation; ICU-bacteria

List of abbreviations: OPA: Ortho-phthalaldehyde; NFGNB: Non Fermentative Gram Negative Bacteria; ROC: Receiver Operating Characteristics; COR: Correlations with $p < 0.05$; Cor: Correlations with p between 0.05 and 0.1; SXT: Sulfamethoxazole trimethoprim; CPH: Cephalothin; LEVO: Levofloxacin; IPM: Imipenem; TOB: Tobramycin; CAZ: Ceftazidime; GM: Gentamicin; AN: Amikacin; FO: Phosphomycin; TZP: Tazobactam; ATM: Aztreonam; TEC: Teicoplanin

Introduction

As WHO warned in 2014 [1], antimicrobial resistance is a global problem. It increases the death risk for patients infected with resistant strains, who consume more healthcare resources than patients infected with sensitive bacteria. For this reason, we explored the possible correlation between antibiotic resistance and decreased susceptibility to biocides, in order to find the best biocide in this environment of increased antibiotic resistance.

Wullt [2] and Russell [3] explain that when we talk of resistance to disinfectants, we are really talking about MIC (minimum inhibitory concentration), since resistance is actually a lack of susceptibility to a given concentration of the compound in 24 hours, whereas the quantities of disinfectant used to carry out a disinfection are large and the times short. Therefore, when we use the word "resistance" we are attempting to express a greater tolerance or a decrease in the susceptibility of a microorganism to the concentration of a disinfectant to which it is normally susceptible [3].

In 1998, Russell [3] pointed out, as did Sheldon Jr [4] in 2005, that the mechanism of bacterial resistance to biocides can be intrinsic (as is the case with spores, mycobacteria, and Gram-negative bacteria), or acquired by means of plasmids or transposons, or by genetic mutation [5]. Every family of bacteria has certain intrinsic characteristics and resistances that determine cellular imperm-

eability such as the cortex in spores, the arabinogalactan coating, the concentration of Mg++ ions in the membrane produced by lipopolysaccharides [6-8], and how these bind, and other components of the bacterial cell wall and Gram-negative bacterial membrane (given that they limit the entry and binding of the active compound within the cell).

Antibiotic resistance is a natural expression of bacterial evolution and genetics, though there are certain factors that also contribute to the increased expression and dissemination of this inherent characteristic: the increased use of antibiotics and the respective selective pressure that they exert [5].

The literature on bacteria refers to relationships between decreased susceptibility to a disinfectant coupled with antibiotic resistance, or decreased susceptibility to several disinfectants. For example, resistance to gentamicin correlates with a reduction in susceptibility to propamidine, quaternary ammonium compounds, and ethidium bromide [7]. Methicillin-resistant *Staphylococcus aureus* is less susceptible to quaternary ammonium compounds than sensitive strains [8-13].

However the clinical relevance of these observations is debatable, since as there are studies in which antibiotic-resistant pathogens have been found that are sensitive to disinfectants [10-15], and vice-versa. Our aim was to assess the association between antibiotic resistance and decreased susceptibility to antiseptic or disinfectants in a large number of microorganisms of different bacterial Genera isolated from ICU-patients. In fact we have found a relation between decreased ortho-phthalaldehyde (OPA) efficacy and antibiotic resistance in our own hospital [16]. So, in light of the increasing frequency of colonization/infection by bacteria resistant to different antibiotics [17,18] and diluted quaternary ammonium, one of the disinfectants most associated to antibiotic resistance, the investigation was undertaken in order to decide if it is necessary to change the indications for antiseptics and disinfectants in ICU settings.

Bacteria commonly causing infections in hospitals and the community are: *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus*, etc [1]. We usually found the same resistant strains. These strains (and others) are commonly isolated in our hospital, so we used them for our study.

Materials and Method

Materials

Disinfectants: 2% glutaraldehyde (Panreac); 0.55% ortho-phthalaldehyde (OPA) (Johnson & Johnson), 5% chlorhexidine (Guinama), 70% Barquat (BQ) (alkyl dimethyl benzalkonium chloride) (Masterlabor), 0.5% hydrogen peroxide (Panreac), 10% povidone-iodine (Viatris), Sterillium® (alcohol solution with mecetronium) (Bode Chemie).

Antibiotics: Sulfamethoxazole trimethoprim; Cephalothin; Levofloxacin; Imipenem; Tobramycin; Ceftazidime; Gentamicin; Amikacin; Phosphomycin; Tazobactam; Aztreonam; Teicoplanin.

Microorganisms: Recently isolated from ICU patients at La Paz Hospital that had an antibiogram from the hospital's Laboratory of Preventive Medicine: *S. aureus; Staphylococcus epidermidis; Citrobacter freundi;, E. coli; K. pneumoniae; Enterobacter cloacae; Serratia marcescens; Proteus mirabilis; Proteus vulgaris; Pseudomonas aeruginosa; Acinetobacter baumannii; Stenotrophomonas maltophilia* and *Burkhordelia cepacia*. The last four species were grouped as "Non Fermentative Gram Negative Bacteria" (NFGNB).

Microtiter plate

Petri dishes with Müller-Hinton agar-Method: Agar-diffusion through microdilution technique.
The microorganism (standard strain or bacteria recently isolated from an ICU patient) was cultured for 24 h at 37 ºC. 0.1 ml of this culture medium was mixed with 9.9 ml of distilled water and poured into a Petri dish, seeding the entire Müller-Hinton agar surface. The dish was left to dry upside down for 30 min at 37 ºC.

Preparation of the 12 double dilutions of the disinfectant or antiseptic: In the microtiter plate, 100 µl of distilled water was placed in one of the 12 wells of one of the rows. 100 µl of the disinfectant or antiseptic was poured into the first of them; after thorough mixing we proceeded to place 100 µl of that dilution in the next well and added 100 µl of distilled water, mixing thoroughly to continue the process in the remaining ten wells.

Into each of the seeded and dry Petri dishes were placed (in 12 different points) the 12 dilutions of a disinfectant or antiseptic obtained in the microtiter plate, one 10 µl drop at each point. These plates were left for 24 h in the incubator at 37 ºC until they were read.

Reading of the dilution that indicates MIC: After incubation the plate showed two types of circles obtained from the drop (10 µl) of the 12 dilutions of disinfectant or antiseptic. If we found a transparent circle (no bacteria present), the disinfectant had had a bacteriostatic effect. On the other hand, if we saw that the circle was opaque or porous, this showed that the disinfectant had not worked, meaning that the bacteria were still present and, therefore, at that given dilution, the microorganism was resistant to its action. This dilution is called the "MIC-dilution". A greater MIC-dilution (ex. 12) indicates a lower MIC (µl/ml) and greater susceptibility to the antiseptic or disinfectant used. We used Table 1 to convert these dilutions into MIC (minimum inhibitory concentrations) for each disinfectant or antiseptic used. But we noted both datum, the MIC and the MIC-dilution (1-12), because MIC varies greatly between the products (according to their initial concentration) but various antiseptics or disinfectants can have the same MIC-dilution for inhibiting one microorganism.

Disinfectant or Antiseptic	1	2	3	4	5	6	7	8	9	10	11	12
OPA® 5.55 g/100 ml	0.275	0.137	0.0687	0.0344	0.0172	0.0086	0.0043	0.0021	0.001	0.0005	0.0002	0.0001
Povidone-iodine 10 g/100 ml	5	2.25	1.25	0.625	0.312	0.156	0.078	0.039	0.0195	0.001	0.0005	0.00025
Barquat® 12.5 g/100 ml	6.25	3.1	1.6	0.8	0.4	0.2	0.1	0.05	0.025	0.012	0.006	0.003
Chlorhexidine 5 g/100 ml	2.5	1.25	0.62	0.31	0.15	0.075	0.032	0.016	0.008	0.004	0.002	0.001
Hydrogen peroxide 12.5 g/100 ml	6.2	3.1	1.65	0.83	0.41	0.205	0.102	0.051	0.025	0.0125	0.0062	0.0031
Sterillium®*	1/2	1/4	1/8	1/16	1/32	1/64	1/128	1/256	1/512	1/1024	1/2048	1/4096

*This being a mixture, the g/100 ml is not calculated, but instead the dilution performed in the original mixture.

Table 1: Conversion of MIC-dilutions (1 to 12) into MIC (μg/ml)

In parallel to the MIC-dilution (or MIC after transformation) for each microorganism, the antibiogram was constructed using the Kirby-Bauer method [the most common and reliable antimicrobial susceptibility testing, WHO [19]. This method is used by the Preventive Medicine Laboratory of La Paz Hospital, in weekly surveillance microbiota cultures from ICU patients, with all quality tests performed routinely. A sample of these isolated microorganisms is used in this paper. We only indicate whether they were susceptible or resistant to the studied antibiotics. The cut-off point was considered "resistant", according to CLSI [20].

Statistical method

All these data (bacterial strain, disinfectant or antiseptic, MIC-dilution, and antibiogram) were entered into an SPSS file for uni-, bi-, and multivariate analyses (linear and logistic regression).

a) The following descriptive statistics were used for the different variables: mean and standard deviation for the quantitative variables and percentage for the qualitative variables.

b) Analysis of variance of the MIC-dilution was run in respect to the bacteria and disinfectant or antiseptic.

c) Possible correlation between antibiotic resistance and MIC-dilution to different antiseptics or disinfectants was checked.

d) Logistic regression analyses with resistance to different antibiotics as the dependent variable, and MIC-dilution, disinfectant or antiseptic and bacterial strain as independent variables. Evaluation of the statistical significance at each step was performed by calculating the *2*log-likelihood*. A value of 0.05 was used by default as the entry point into the model for a variable, and 0.10 was used as the exit point. The overall goodness of fit of the models was assessed by ROC (Receiver Operating Characteristics) curves.

e) The multiple linear regression analysis employed the following independent variables: bacteria, disinfectant or antiseptic, and MIC-dilution. Evaluation of the statistical significance at each step was performed by calculating the maximum likelihood coefficient. A value of 0.05 was used by default as the entry point to the model for a variable, and 0.10 was used as the exit point. The overall fit of the equation was measured by its R^2.

Results

Univariate analysis

Analysing MIC-dilution as a dependent variable in relation to the variables "disinfectants" and "microorganisms", without taking antibiotic resistance into account, gave us Table 2.

The disinfectants and antiseptics that could withstand the greatest dilutions were the surfactant and clorhexidine, whereas there was scarcely any variation among the others: povidone iodine, hydrogen peroxide, glutaraldehyde, OPA and the mixture alcohols + surfactants (see last row of Table 2).

In regard to the microorganisms, the Gram-positive microorganisms (*S. aureus* and *S. epidermidis*) were more sensitive to disinfectants and antiseptics than Gram-negative microorganisms (NFGNB and *Enterobacteriaceae*). And within the Gram-negative group, NFGNB were generally less susceptible (Table 2).

At the same time, the proportions that were resistant to antibiotics was smaller in comparison with the bacilli, although, in general, the microorganisms involved were resistant to one or more antibiotics. Accordingly, the percentage resistances to each of the antibiotics among all the microorganisms studied was as follows: 42% to sulfamethoxazole-trimethoprim, 60% to cefalotin, 21% to ceftazidime, 26% to levofloxacin, 28% to imipenem, 6% to gentamicin, 18% to tobramycin, 0% to amikacin, 15% to phosphomycin, 20% to tazobactam and 38% to aztreonam.

MICROORGANISM (n)	Glutaraldehyde	OPA®	Chlorhexidine	Hydrogen peroxide	Povidone-iodine	Barquat®	Sterillium®*
***S. aureus* (14)**	6.5	3.5	11.5	6.7	5.7	11.9	5.8
***S. epidermidis* (15)**	7.2	5.3	11.8	7.8	6.9	11.9	7.3
***E. coli* (17)**	6.7	3.7	11.4	4.9	5.1	11.0	1.3
***Klebsiella* (18)**	6.6	3.4	10.6	5.3	5.5	11.5	1.1
***Enterobacter* (17)**	6.5	3.0	10.0	5.9	5.3	11.1	1.6
***Serratia* (14)**	6.7	3.6	9.3	3.2	5.5	10.5	1.1
***Proteus* (16)**	4.2	2.4	8.3	2.7	3.6	9.5	1.2
***Pseudomonas* (15)**	6.0	1.2	8.2	5.6	4.7	9.2	1.1
***Acinetobacter* (17)**	6.4	2.9	9.8	5.3	6.0	11.7	1.3
Other NFGNB (15)	7.0	3.2	9.1	6.6	6.3	12.0	2.0
TOTAL (159)	**6.4**	**3.2**	**10.1**	**5.4**	**5.4**	**11.0**	**2.3**

Table 2: MIC-dilution (weighted mean) of the antiseptics and disinfectants against diverse bacteria

Analysing antibiotic resistance in relation to MIC-dilution, taking all 159 microorganisms together, gave us Table 3. In this table, correlations with a $p < 0.05$ are labeled by "COR", but, we also included comparisons in which p lies between 0.05 and 0.1, labeling them as "cor". A plus sign, (+), is added to the letter if there is "greater antibiotic resistance correlated with a lower susceptibility to the disinfectant or antiseptic" (designated hereafter as "in favor of the hypothesis") and with the minus sign (–) if the "antibiotic resistance was correlated with greater susceptibility" to the antiseptic or disinfectant (designated "against the hypothesis"). Blank squares indicate that there was no correlation between antibiotic resistance and disinfectant/antiseptic susceptibility.

DISINFECTANT/ ANTIBIOTIC	SXT	CPH	LEVO	IPM	TOB	CAZ	GM	AN	FO	TZP	ATM	TEC
Glutaraldehyde	COR+											
Ortho-phthalaldehyde		cor+							cor+		cor-	
Chlorhexidine		COR+			COR-							
Barquat®					COR-	COR-					COR-	
H_2O_2					COR-						COR-	
Povidone iodine					COR-	cor-				cor-	cor-	
Sterilium®	COR+		cor+						COR+			

COR: $p < 0.05$; cor: p between 0.05 and 0.1; "+": resistance to antibiotics correlates with lower susceptibility to antiseptics and disinfectants (according to initial hypothesis). "–": resistance to antibiotics correlates with greater susceptibility to antiseptics and disinfectants.
SXT: Sulfamethoxazole trimethoprim; CPH: Cephalothin; LEVO: Levofloxacin; IPM: Imipenem;
TOB: Tobramycin; CAZ: Ceftazidime; GM: Gentamicin; AN: Amikacin; FO: Phosphomycin; TZP: Tazobactam; ATM: Aztreonam; TEC: Teicoplanin

Table 3: Correlations between antibiotic resistance and susceptibility to antiseptics and disinfectants

As can be seen, some antibiotics did not show any correlation ($p > 0.1$) with the disinfectants: imipenem, gentamicin, amikacin, and teicoplanin.

Among antibiotics showing a correlation, sulfamethoxazole trimethoprim, cephalothin, levofloxacin, and phosphomycin, only presented cases in favor of our hypothesis, while ceftazidime, aztreonam, tobramycin, and tazobactam only presented cases against. In conclusion, with $p < 0.1$ there were 7 antibiotic-biocide pairs in favour of our hypothesis, 11 against, and 66 pairs with a $p > 0.1$, of the 84 possible pairs. But at $p < 0.05$, only 4 pairs (4.7%) demonstrated an association between antibiotic resistance and decreased susceptibility to an antiseptic or disinfectant.

Multivariate analysis

Multiple linear regression: We created a multiple linear regression equation to check all three variables (bacteria, disinfectants or antiseptics, and antibiotics) simultaneously. Aztreonam was the only antibiotic showing significant relation with decreased disinfectant/antiseptic susceptibility (Table 4). However, the overall fit of the equation was very poor, since its $R^2 = 0.032$.

Accordingly, after controlling for the effect of other variables (such as the type of disinfectant and bacterial strain), we saw that the MIC-dilution for the antiseptics and disinfectants increased when the microorganism was resistant to aztreonam. As a bacteria went from being sensitive to being resistant to aztreonam, the MIC-dilution increased by one unit (the concentration was half of what it had been previously). Sensitivity or resistance to the other antibiotics did not affect the increase or decrease in the MIC-dilution.

Model, t and significance					
Model	Non-standardised coefficient		Standardised coefficient	t	Significance
	B	Typical error	Beta		
Constant	6.410	0.432		14.829	< 0.001
Disinfectant or antiseptic	-0.193	0.049	-0.132	-3.975	< 0.001
Aztreonam-resistance	1.012	0.275	0.147	3.680	< 0.001
Bacterial Genera	-0.11	0.058	-0.077	-1.918	0.05

overall fit of the equation was very poor: $R^2 = 0.032$.

Table 4: Multivariate analysis by multiple linear regression of the "MIC-dilution" and "antibiotic resistance", controlling the biocide (antiseptic or disinfectant) and bacterial Genera

Logistic regression

We ran a logistic regression in order predict resistance to the various antibiotics according to the bacteria involved and the MIC-dilution of the antiseptics or disinfectants, and got a very poor fit for the results. Accordingly, these data will not be considered further as they would not be particularly practical in daily clinical practice.

Discussion

The Kirby-Bauer method for studying antibiotic resistance is a very easy and reliable test, with few errors in determining resistance, including NFGNB and carbapenems [21,22]. Moreover, the test is run in a solid medium, as occurred with our MIC-dilution method used in disinfectants and antiseptics, permitting a better correlation.

Some authors [23,24] have studied the role of plasmids in coding for resistance (or increased tolerance) to antiseptics and disinfectants and concluded that apart from certain specific examples, plasmids were not responsible for the high levels of resistance to antiseptics and disinfectants of certain species or strains. However, Cookson [9] discovered a plasmid that could confer resistance to gentamicin and a decreased susceptibility to chlorhexidine.

On the other hand, we found that there was an increase in susceptibility to quaternary ammonium compounds that correlated with antibiotic resistance in drugs with very different action mechanisms (tobramycin, ceftazidime, and aztreonam).

Moreover, the method used for surface disinfection in our hospital was a diluted (0.5%) quaternary ammonium, and an association with antibiotic resistance could be possible. But this relation was only an exception (4.7%).

Sutton and Jacoby [25] noted that the conversion of plasmid RP1, which codes resistance to carbenicillin, tetracycline, neomycin, and kanamycin in *E. coli* or *P. aeruginosa,* did not increase the sensitivity of these bacteria to antiseptics and disinfectants. This response was similar to results found in our experiment.

Recently (as we found), Morrissey [26], examining strains from around the world, detected greater susceptibility to benzalconium chloride and chlorhexidine in *S. aureus* strains than in *K. pneumoniae, E.coli* or *Enterobacter* spp.

In addition, we found that bacteria behaved in a similar manner in the presence of aldehydes, irrespective of their antibiotic resistances, since their bacteriostatic effects were very stable, independently of the bacterial Genus and its antibiotic resistance or sensitivity.

P. mirabilis strains resistant to chlorhexidine were also resistant to sulfamethoxazole trimethoprim, ampicillin, azlocillin, carbapenem, gentamicin, and tobramycin [5]. In our study, we did not find a single chlorhexidine-resistant strain and the only strain with a lower MIC was not sensitive to sulfamethoxazole, trimethoprim, gentamicin, or tobramycin.

In some studies *P. aeruginosa* was more resistant to most of these agents, including chlorhexidine [5,15,27] and quaternary ammonium compounds. In our study, in contrast, our strains of *Pseudomonas* were more susceptible to chlorhexidine than to all the other disinfectants, except for the quaternary ammonium compound used, to which they also exhibited high susceptibility (0.08 mg/ml).

Before 2000, Russell [28] considered that there was no correlation between resistance to antibiotics and resistance to disinfectants, but in 2002 [29,30], he drew attention to the possibility of an increase in cross-resistance between antibiotics and disinfectants [18]. Following our bacteriostatic study, using a large number of bacteria with high resistance to the various antibiotics, we can state that this relationship is not common in the population of these microorganisms, as we found only 4 instances in the 84 possible comparisons (MIC - dilutions versus resistance to the various antibiotics) for each of 159 bacteria investigated here. On several occasions, moreover, we observed an inverse correlation (antibiotic-resistant bacteria that were more susceptible to disinfectants). The four significant comparisons in favor of the initial hypothesis could be explained by the type of bacteria (e.g. resistance to sulfamethoxazole trimethoprim was associated with *Pseudomonas* and resistance to cephalothin with *Pseudomonas* and *Enterobacteriacae*), but in terms of the bacterial genus it was apparently irrelevant, which is why it was not confirmed in the multivariate analysis. Finally, the correlations found depended on a lower intrinsic - rather than acquired - susceptibility of the bacteria, so that antibiotic resistance ceased to be significant when viewed in terms of the type of microorganism.

Conclusion

In spite of some papers reporting an association between antibiotic resistance and decreased efficacy of antiseptics or disinfectants, this association was only seen in 4.7% of antibiotic-biocide pairs in a large sample of ICU-bacteria while no correlation or even a negative correlation was found in the rest.

Controlling (by multivariate analysis) the effect of other variables, like bacterial Genus (intrinsic resistance) and type of antibiotic or biocide studied, on the susceptibility of antiseptic or disinfectant, only one antibiotic – aztreonam – remained significant. However, the overall fit of the equation was very poor, since its $R^2 = 0.032$.

For the above reasons, there is no need for any change in the established disinfection and antisepsis criteria in a hospital department, even though antibiotic-resistant bacterial strains are being isolated all the time.

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