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Using Chlorhexidine Indiscriminately !! Can It Do More Harm Than Good ??

Simit Kumar[1], *Maitreyi Bandyopadhyay[2] , Subhadip Das[3], Manas Kumar Bandyopadhyay[4], Prabir Kumar Mukhopadhyay[5], Anindita Chatterjee[6], Mitali Chatterjee[7]

(Department of Microbiology, R.G.Kar Medical College, Kolkata / The West Bengal University of Health Sciences, India)
**Corresponding Author: Dr. Maitreyi Bandyopadhyay*

Abstract :
Introduction-*Chemical substances with antiseptic, disinfectant, and/or preservative activity have been defined as biocides. Chlorhexidine (CHX) is a biguanide compound, widely used in a clinical practice as a skin and mucous membrane antiseptic and disinfectant. However, bacterial resistance to CHX has been detected but there is a lack of simple method for routine testing of CHX susceptibility. Increasing frequency of hospital infection leads to overuse and pressure of biocides, similarly to antibiotics. The linkage between bacterial resistance and the use of biocides has been suggested.*
Objective- *Detection of decreased CHX susceptibility of clinical isolates from different wards in association with drug resistance pattern of these isolates.*
Materials And Methods: *The clinical isolates were isolated from various clinical samples obtained from wards and ICU. The MIC of chlorhexidine digluconate for all clinical isolates was determined as per CLSI guideline and antibiotic resistance pattern was noted.*
Results- *Among 235 isolates 47 showed MIC of >256 μg/ml and these isolates showed statistically significant (P value < 0.05) association between decreased susceptibility to CHX and resistance to sulfamethoxazole-trimethoprim, cephalosporin, carbapenem, aminoglycoside, penicillin with β lactamase inhibitors group of antibiotics. Thirty one isolates with MIC > 512 mg/L showed statistically significant (P value < 0.05) association between decreased susceptibility to CHX and resistance to Sulfamethoxazole-trimethoprim, carbapenems and aminoglycoside group of antibiotics*
Conclusion- *This study raises an important question whether the indiscriminate use of CHX in hospital settings might select the multi-drug resistant organisms to be the predominant flora in the hands of health care providers which in turn might be transmitted to the patient. Especially in view of the fact that biocides when used on the unclean and wet surfaces might itself promote the development of CHX resistance. Thus this study highlights the point that CHX resistance might itself trigger antibiotic resistance.*
Keywords : *chlorhexidine, resistance, decreased susceptibility, antibiotic resistance, biocides*

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I. Introduction

Disinfectants are chemical agents used to kill microorganisms on surfaces or in order to eliminate them from the environment. The chemical agents, which have been used to prevent or limit microbial infection on the skin, are called antiseptic or topical antimicrobial. There are chemical agents that have been used as preservatives against microbial contamination by adding them into pharmaceuticals, cosmetics, and other products. Chemical substances with antiseptic, disinfectant, and/or preservative activity have been defined as biocides. [1-3] CHX , a cationic bis-biguanide biocide with low mammalian toxicity and broad-spectrum antibacterial activity, was first described in 1954.[4,5] The primary mechanism of action of this biocide is membrane disruption, concentration-dependent growth inhibition and cell death.[6] Secondary interactions causing inhibition of proteolytic and glycosidic enzymes.[7]

CHX is widely used in clinical practice as a skin and mucous membrane antiseptic and disinfectant. The effectiveness of CHX in preventing growth of bacterial pathogens may vary with different organisms.[8,9] Concomitant antibiotic and biocide resistance have been previously reported in both Gram-negative and Gram-positive bacteria.[10,11] However, bacterial resistance to CHX has been detected but there is a lack of simple method for routine testing of CHX susceptibility.

Increasing frequency of hospital infection leads to overuse and pressure of biocides, similarly to antibiotics. The linkage between bacterial resistance and the use of biocides has been suggested. Resistance or insusceptibility to biocides can be either intrinsic, as a result of natural characteristics of microorganisms, or it can be acquired. Acquired resistance to biocides may arise from mutation and horizontal transfer of genetic material such as plasmids or transposons. [12–17] Efflux pumps are common mechanisms of acquired resistance to chlorhexidine digluconate. By this mechanism, other chemical substances are also excluded from the cell, which can therefore also lead to resistance to antibiotics [13,18,16].

Low-level plasmid-mediated resistance to cationic biocides such as CHX has been observed in antibiotic-resistant strains [19, 20, 21], and it has been postulated that strains in which qac genes are present might have enhanced survival in the clinical environment. Extensive use of cationic biocides could lead to the selection of clinical isolates showing resistance to both antibiotics and biocides [22, 23], but the clinical relevance of this possibility remains contentious [24].

It has been proposed that intrinsic resistance in gram-negative bacteria is of greater significance than plasmid-mediated resistance. [24] Resistance to both antibiotics and biocides in gram negative organisms is more likely where less specific mechanisms are involved, e.g., the outer membrane may act as a nonspecific exclusion blanket thereby preventing the uptake of chemically unrelated molecules. [23,25,26] There have, however, been some instances where biocides have been claimed to select for resistant gram-negative bacteria. It was proposed that the widespread use of CHX was responsible for selecting antibiotic-resistant strains. [27]

II. Aims & Objectives

Detection of decreased chlorhexidine susceptibility of clinical isolates from different wards in association with drug resistance pattern of these isolates.

III. Materials And Methods

The clinical isolates were isolated from various clinical samples obtained from wards and ICU. The MIC of chlorhexidine digluconate for all clinical isolates was determined as per CLSI guideline and antibiotic resistance pattern was noted.

IV. Result

Among 235 isolates 47(20 %) showed MIC of >256 μg/ml of which 33(70%) showed resistance to levofloxacin, 42 (89%) showed resistance to cotrimoxazole, 33 (70%) showed resistance to imipenem, 44 (94%) showed resistance to ceftriaxone, 34 (72%) showed resistance to amikacin, 38 (81%) showed resistance to cefoperazone, 34 (72%) showed resistance to piperacilin-tazobactum, 26 (55%) showed resistance to aztreonum, 27 (57%) showed resistance to azithromycin, 28 (60%) showed resistance to meropenem, 28 (60%) showed resistance to cefoperazone-sulbactum, 28 (60%) showed resistance to lomefloxacin, 29 (62%) showed resistance to ticarcilin-clavulunic acid, 2 (4%) showed resistance to polymyxin B. Among 235 isolates 47 showed MIC of >256 μg/ml, which included Acinetobacter spp- 16(34%), Pseudomonas spp- 11(23%), Klebsiella spp- 17(36%), Sphingomonas paucimobilis- 2(4%), Proteus mirabilis- 1(2%) depicted in **Figure 1**. These 47 isolates showed statistically significant (P value < 0.05) association between decreased susceptibility to CHX and resistance to sulfamethoxazole-trimethoprim, cephalosporin, carbapenem, aminoglycoside, penicillin with β lactamase inhibitors group of antibiotics **(Table 1)**.

Thirty one isolates showed MIC of >512 μg/ml which included Acinetobacter spp- 11(35.5%), Pseudomonas spp- 7(23%), Klebsiella spp- 11(35.5%), Sphingomonas paucimobilis - 1(3%), Proteus mirabilis- 1(3%), which has been depicted in **Figure 2.** These 31 isolates showed statistically significant (P value < 0.05) association between decreased susceptibility to CHX and resistance to Sulfamethoxazole-trimethoprim, carbapenems and aminoglycoside group of antibiotics **(Table 2).**

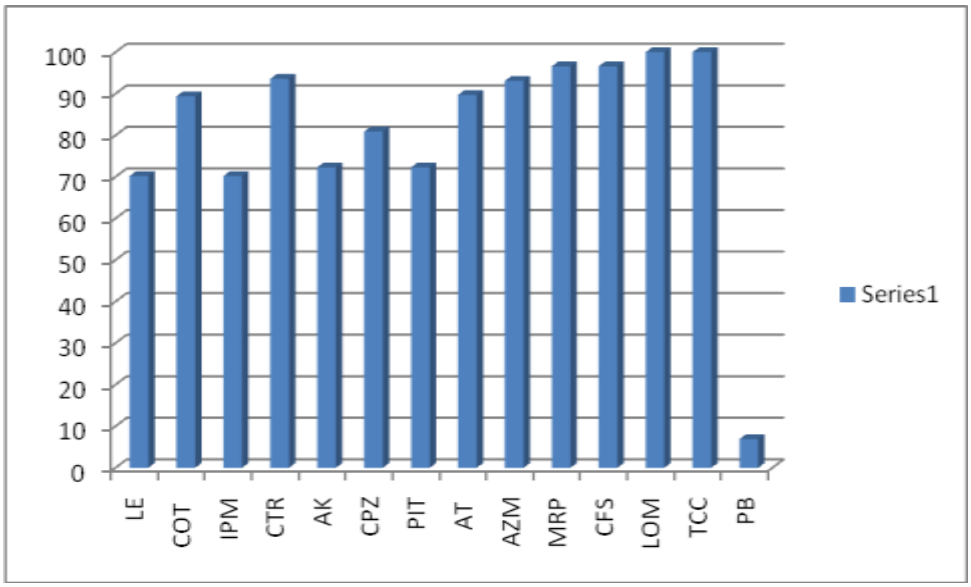

Figure 1: Bar diagram showing correlation between CHX resistance (>256mg/L) and resistance to different antibiotics.

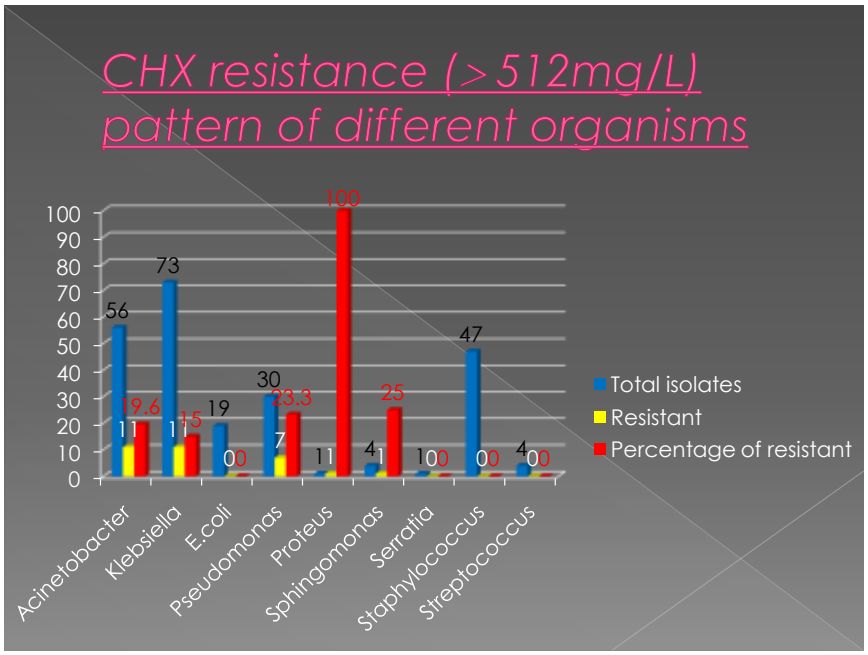

Figure 2: Bar Diagram distribution of the isolates showing decreased susceptibility to CHX (> 512 mg/L)

Table 1: Statistically significant association between different antibiotics and CHX resistance (>256mg/L)

ANTIBIOTICS	P VALUE	ASSOCIATION
Levofloxacin	0.087	NO
Cotrimoxazole	**0.017**	**SIGNIFICANT**
Imipenem	**0.000**	**SIGNIFICANT**
Ceftriaxone	**0.006**	**SIGNIFICANT**
Amikacin	**0.000**	**SIGNIFICANT**
Cefoperazone	0.332	NO
Piperacillin-tazobactum	**0.001**	**SIGNIFICANT**
Aztreonum	0.300	NO
Azithromycin	1.000	NO
Meropenem	**0.021**	**SIGNIFICANT**
Cefoperazone-sulbactum	0.389	NO
Lomefloxacin	0.075	NO
Ticarcilin clavulinic acid	1.000	NO
Polymyxin-b	0.566	NO

Table 2: *Statistically significant association between different antibiotics and CHX resistance(>512mg/L)*

ANTIBIOTICS	P VALUE	ASSOCIATION
Levofloxacin	0.843	NO
Cotrimoxazole	**0.040**	**SIGNIFICANT**
Imipenem	**0.000**	**SIGNIFICANT**
Ceftriaxone	0.096	NO
Amikacin	**0.012**	**SIGNIFICANT**
Cefoperazone	0.663	NO
Piperacillin-tazobactum	0.119	NO
Aztreonum	0.572	NO
Azithromycin	1.000	NO
Meropenem	0.160	NO
Cefoperazone-sulbactum	0.666	NO
Lomefloxacin	0.312	NO
Ticarcilin clavulinic acid	1.000	NO
Polymyxin-b	0.552	NO

V. Discussion & Conclusion

The varying effect of CHX upon clinical isolates is of importance as it may mean that certain isolates will have an ability to survive CHX treatment and that the use of biocides could act as a selective pressure to allow these isolates to predominate. The alarming finding in this study is that there is a significant correlation between the decreased susceptibility to Chlorhexidine (Table 1 &2) and resistance to various class of antibiotics. The study shows that decreased susceptibility of >256 mg/L was associated with resistance to sulfamethoxazole-trimethoprim, cephalosporin, carbapenem, aminoglycoside, penicillin with β lactamase inhibitors group of antibiotics. In hospitals, the contact of bacteria with biocides at low concentrations can create selective pressure for some isolates, similar to the sub inhibitory concentration effects of antibiotics. [12, 13,28, 29]

Thus, it appears that biocide concentration is a major factor in the development of bacterial resistance. If the surface to be disinfected was not clean and yet to be dried after disinfection, if the disinfectant was prepared at lower concentrations than in-use concentrations, and if the diluted disinfectant was kept longer than suggested by the manufacturer, then a low concentration of biocide is in contact with the bacteria. [28] It has been documented that sub inhibitory concentrations of chlorhexidine digluconate can cause a permanent increase in MIC values of clinical isolates. [30]These findings emphasize the importance to clean surfaces first before biocides are applied. It is thereby important to pay attention to possible biofilm formation in wet surfaces.

This study raises an important question whether the indiscriminate use of CHX in hospital settings might select the multi-drug resistant organisms to be the predominant flora in the hands of health care providers which in turn might be transmitted to the patient. Especially in view of the fact that biocides when used on the unclean and wet surfaces might itself promote the development of CHX resistance. Thus this study highlights the point that CHX resistance might itself trigger antibiotic resistance.

References

[1]. European Union Biocidal Products Regulation. EU Biocides Regulation 528/2012.Health and Safety Executive.Biocides. Brussels, Belgium: EU; 2012.
[2]. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. Clin Microbiol Rev 1999;12:147–179.
[3]. Russell AD. Biocide usage and antibiotic resistance: the relevance of laboratory findings to clinical and environmental situations. Lancet Infect Dis 2003; 3:794–803.
[4]. Denton, G. W. 1991. Chlorhexidine, p. 274–289. In S. S. Block (ed.), Disinfection, sterilization and preservation, 4thed. Leaand Febiger,Philadelphia, Pa.
[5]. Davies, G. E., J. Francis, A. R. Martin, F. L. Rose, and G. Swain. 1954. 1:6-Di 4-chlorophenyldiguanidohexane ("Hibitane"). Laboratory investigation of a new antibacterial agent of high potency. Br. J. Pharmacol. 9:192-196.
[6]. Hugo, W. B., and A. R. Longworth.. The effect of chlorhexidine on the electrophoretic mobility, cytoplasmic constituents, dehydrogenase activity and cell walls of Escherichia coli and Staphylococcus aureus. J. Pharm. Pharmacol. 1966;18:569–578.
[7]. Hastings, D. C. 2000. Non-antibiotic plaque chemotherapy, p. 523–548. In H.N.Newman and M.Wilson(ed.).Dental plaque revisited: oral biofilms in health and disease. Bioline Press, Cardiff, United Kingdom.
[8]. Thomas L, Russell AD, Millard JY. Antimicrobial activity of chlorhexidine diacetate and benzalkonium chloride against Pseudomonas aeruginosa and its response to biocide residues. J Appl Microbiol 2005; 98: 533–43.

[9]. Pacheco-Fowler V, Gaonkar T, Wyer PC, Modak S. Antiseptic impregnated endotracheal tubes for the prevention of bacterial colonization. J Hosp Infect 2004; 57: 170–4.
[10]. Ko ˇljalg S, Naaber P, Mikelsaar M. Antibiotic resistance as an indicator of bacterial chlorhexidine susceptibility. J Hosp Infect 2002; 51: 106–13.
[11]. Russell AD, Tattawasart U, Millard J-Y. Possible link between bacterial resistance and use of antibiotics and biocides. Antimicrob Agents Chemother 1998; 42: 2151.
[12]. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. Clin Microbiol Rev 1999; 12: 147–179.
[13]. Russell AD. Biocide usage and antibiotic resistance: the relevance of laboratory findings to clinical and environmental situations. Lancet Infect Dis 2003; 3:794–803.
[14]. Maillard JY. Bacterial resistance to biocides in the healthcare environment: should it be of genuine concern? J Hosp Infect 2007; 65: 60–72.
[15]. Russell AD. Bacterial resistance to disinfectants: present knowledge and future problems. J Hosp Infect 1998; 43 (Suppl.): S57–S68.
[16]. Harbarth S, Soh Tuan S, Horner C, Wilcox MH. Is reduced susceptibility to disinfectants and antiseptics a risk in healthcare settings? A point/counterpoint review. J Hosp Infect 2014; 87: 194–202.
[17]. McBain AJ, Gilbert P. Biocide tolerance and harbingers of doom. Int Biodeter Biodegr 2001; 47: 55–61.
[18]. Horner C, Mawer D, Wilcox M. Reduced susceptibility to chlorhexidine in staphylococci: is it increasing and does it matter? J AntimicrobChemother 2012; 67: 2547–2559.
[19]. Behr, H., M. E. Reverdy, C. Mabilat, J. Freney, and J. Fleurette. 1994. Relation entre le niveau des concentrations minimalesinhibitrices de cinqantiseptiqueset la pr´esence du ge`neqac A chez Staphylococcus aureus. Pathol. Biol. 42:438–444
[20]. Leelaporn, A., I. T. Paulsen, J. M. Tennent, T. G. Littlejohn, and R. A. Skurray. 1994. Multidrug resistance to antiseptics and disinfectants in coagulase-negative staphylococci. J. Med. Microbiol. 40:214–220.
[21]. Lyon, B. R., and R. A. Skurray. 1987. Antimicrobial resistance of Staphyloccusaureus: genetic basis. Microbiol.Rev. 51: 88–134.
[22]. Russell, A. D., and I. Chopra. 1996. Understanding antibacterial action and resistance, p. 226–237, 266–269. Ellis Horwood, Chichester, United Kingdom.
[23]. Russell, A. D., and N. J. Russell. 1995. Biocides: activity, action and resistance,p.327–365.InP.A.Hunter,G.K.Darby,andN.J.Russell(ed.),Fifty years of antimicrobials: past perspectives and future trends. 53rd. Symposium of the Society for General Microbiology. Cambridge University Press, Cambridge, United Kingdom.
[24]. Russell, A. D. 1997. Plasmids and bacterial resistance to biocides. J. Appl. Microbiol. 82:155–165.
[25]. Russell, A. D., J. R. Furr, and J.-Y. Maillard. 1997. Microbial susceptibility and resistance to biocides. ASM News 63:481–487.
[26]. Stickler, D. J., B. Thomas, J. C. Clayton, and J. A. Chawla. 1983. Studies on the genetic basis of chlorhexidine resistance. Brit. J. Clin. Prac.Symp. 25 (Suppl.):23–28
[27]. Russell AD. Tattawasart U, Maillard J-Y et al. Possible link between bacterial resistance and use of antibiotics and biocides. Antimicrob Agents Chemotherapy 1998; 42: 2151
[28]. Meyer B, Cookson B. Does microbial resistance or adaptation to biocides create a hazard in infection prevention and control? J Hosp Infect 2010; 76: 200–205
[29]. Rutala WA, Weber DJ. Bacterial resistance to disinfectants: present and future problems. J Hosp Infect 1999; 43: 57S–68S.
[30]. Thomas L, Maillard JY, Lambert RJW, Russell AD. Development of resistance to chlorhexidine diacetate in Pseudomonas aeruginosa and the effect of a 'residual' concentration. J Hosp Infect 2000; 46: 297–303.

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