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Asociado:

Computadoras

PORTADA/ COVER

Nuestra portada combina imágenes de los temas abordados en los artículos de este ejemplar.

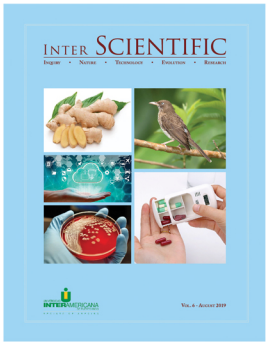

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Illustration of the diversity of topics covered in this issue.

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CONTENIDO
CONTENTS

MENSAJE DEL RECTOR
DR. RAFAEL RAMÍREZ RIVERA

Reiteramos nuestra felicitación a la facultad y a sus estudiantes por continuar desarrollando proyectos de investigación de envergadura y vanguardia. En este sexto volumen de *Inter Scientific* se presentan trabajos del campo de la farmacología, ecología, ciencias de computadoras, microbiología y enfermería. Extendemos nuestra felicitación al Decanato de Asuntos Académicos por promover la investigación y el apoyo incondicional a esta publicación.

MESSAGE FROM THE CHANCELLOR
DR. RAFAEL RAMÍREZ RIVERA

Congratulations to the faculty and students for continuing to develop research projects of scope, span and vanguard. In this sixth volume of *Inter Scientific* there are projects in the fields of pharmacology, ecology, computer sciences, microbiology and nursing. We extend our congratulations and thanks to the Dean of Academic Affairs for promoting research and the unconditional support for this publication.

MENSAJE DE LA
DECANA DE ASUNTOS ACADÉMICOS
DRA. ANNETTE VEGA

En esta edición nos complce presentar una diversidad de áreas temáticas en las investigaciones. Una vez más, la comunidad estudiantil y la facultad aportando nueva información a través de la investigación. Agradecemos a todos los que de una manera u otra aportan al desarrollo y publicación de la revista científica del Recinto de Arecibo.

MESSAGE FROM THE DEAN OF ACADEMIC AFFAIRS
DR. ANNETTE VEGA

In this edition we are pleased to present a diversity of thematic areas in the research projects. Once again, students and the faculty providing new information through research. We thank all those who in one way or another contribute to the development and publication of the scientific journal of the Arecibo Campus.

DESDE EL ESCRITORIO DE LA EDITORA
DRA. LIZBETH ROMERO-PÉREZ

Queremos presentarle nuestro sexto volumen de *Inter Scientific*. En este compartimos tres artículos de investigación y dos artículos de revisión de estudiantes en diversas universidades.

La primera investigación nos presenta compuestos naturales y sintéticos siendo evaluados por su efecto en adenocarcinoma pancreático. Este trabajo fue realizado por estudiantes del programa de bachillerato en Biotecnología de nuestro Recinto, dirigidos por la Dra. Karen Woolcock. El segundo trabajo tiene como objetivo evaluar las adaptaciones en vocalizaciones en el zorzal pardo y el zorzal patirrojo en ambientes urbanos. Este fue realizado por estudiantes de la Universidad de Puerto Rico en Mayaguez, bajo la mentoría del Dr. Alberto Puente. La tercera investigación es en el campo de las ciencias de computadoras y recoge la evaluación de la tecnología de la nube en los pasados cinco años. El primer artículo de revisión presenta el problema de infección por una bacteria resistente a antibióticos en hospitales. Este manuscrito fue desarrollado por estudiantes de Medicina de la Universidad Autónoma de Guadalajara, México. El segundo artículo de revisión nos plantea la adherencia a tratamiento en una población específica con el Virus de Inmunodeficiencia Humana (VIH). En la sección *Otras Investigaciones en el Campus*, encontrará resúmenes de otros trabajos que se han estado realizando en nuestro Recinto en los campos de farmacología y bioquímica, ecología y química.

FROM THE EDITOR'S DESK
DR. LIZBETH ROMERO-PÉREZ

With great pride, we present our sixth volume of *Inter Scientific*. In this occasion we are sharing five excellent manuscripts; three research articles and two review articles.

The first research presents the evaluation of natural and synthetic compounds and their effect on pancreatic adenocarcinoma. This project was developed by Biotechnology students in our Campus directed by Dr. Karen Woolcock. The objective of the second research is to evaluate the adaptations in the vocalizations of the brown thrush and the red-footed thrush in urban environments. This research was done by students at the University of Puerto Rico in Mayaguez mentored by Dr. Alberto Puente. The third research presented is in the computer sciences field and it evaluates the evolution of cloud technology in the past five years. The first review article states the problem of antibiotic-resistant bacteria in hospitals. This manuscript was developed by students at the Universidad Autónoma de Guadalajara in Mexico, School of Medicine. The second article raises the concern on treatment adherence in a particular population infected with the Human Immunodeficiency Virus (HIV). In the section *Other Research on Campus* you will find abstracts for other research projects worked in the fields of pharmacology and biochemistry, ecology and chemistry.

Evaluation of phenolic compounds from ginger, curcuminoids and EHop-16 to activate caspases and induce apoptosis in adenocarcinoma of the pancreas

Evaluación de compuestos fenólicos del jengibre, curcuminoides y EHop-16 para la activación de caspasas y la inducción de apoptosis en adenocarcinoma pancreático

Acevedo, N., Marrero, C., Ongay, K., Ortiz, J., Torres, J., and Woolcock, K.

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ABSTRACT

Pancreatic ductal adenocarcinoma is a highly aggressive type of cancer that is commonly treated with a wide range of chemotherapeutic drugs, but a major drawback is that is highly resistant to the pharmacological action of these drugs. Therefore, it is important to evaluate alternate approaches to improve patient prognosis. Since natural products derived from *Curcuma longa* and *Zingiber officinale* are known to induce apoptosis in several type of malignant cells, the effect of zingerone, 6-shogaol, curcumin and bisdemethoxycurcumin to induce a regulated dead process in PANC-1 cells was evaluated. Also, the effect of synthetic compounds such as gemcitabine, the currently approved pharmacological therapy, and Ehop-16 a novel compound were studied. Among the natural compounds, curcumin followed by 6-shogaol were the most effective for activating multiple caspases and for inducing apoptotic mechanisms. The activation of caspases was dose dependent and time dependent for both compounds. Although EHop-16 produced activation of caspase, after 48 hours only 25% of the caspase activity was implicated in cell death, therefore it is possible that activated caspases are not all related to a regulated cell death process.

RESUMEN

El adenocarcinoma ductal pancreático es un tipo de cáncer muy agresivo cuyo tratamiento envuelve quimioterapias con una amplia variedad de fármacos. Una desventaja que presenta, es su alta resistencia a la acción de dichas terapias. Por lo tanto, es importante evaluar distintos enfoques o alternativas para mejorar el pronóstico del paciente. Se conoce que productos naturales derivados de *Curcuma longa* y *Zingiber officinale* inducen apoptosis en varios tipos de células malignas. En este estudio evaluamos el efecto de zingerone, 6-shogaol, curcumina y bisdimethoxycurcumina en la inducción de un proceso de muerte regulada en células PANC-1. También estudiamos el efecto de compuestos sintéticos incluyendo gemcitabina, que es el fármaco aprobado como terapia y Ehop-16. Entre los compuestos naturales, curcumina seguido por 6-shogaol fueron los mas efectivos para activar múltiples caspasas e inducir apoptosis. La activación de caspasas fue dependiente de dosis y de tiempo para ambos compuestos. En cuanto a los compuestos sintéticos, Ehop-16 provocó activación de caspasas a las 48 horas, pero solamente 25% de dicha actividad fue implicada en muerte celular. Es posible que la activación de caspasas no este toda relacionada a un proceso de muerte celular.

KEYWORDS pancreatic adenocarcinoma, apoptosis, caspase activity, ginger, curcuminoids, EHop-16, gemcitabine, regulated cell death

PALABRAS CLAVE adenocarcinoma pancreático, apoptosis, actividad de caspasa, jengibre, curcuminoides, Ehop-16, gemcitabina, muerte celular regulada

INTRODUCTION

Pancreatic cancer is a type of disease in which the healthy cells of the pancreas stop working properly and grow out of control. As of today, there are two types of pancreatic cancers: the neuroendocrine tumor and pancreatic ductal adenocarcinoma, the latter being the most common. Pancreatic ductal adenocarcinoma is a highly aggressive epithelial cancer with a 5-year survival rate of less than 5% and a median survival of approximately 6-8 months from the time of diagnosis (Samulitis et al., 2015). Since a high proportion of patients with this type of cancer are diagnosed at late-stages, only 10–20% of pancreatic cancer patients are suitable for surgical resection of the cancer. Current chemotherapy and radiotherapies are largely ineffective in treating this type of cancer.

Advanced pancreatic cancer still has a poor prognosis, even with the approval of several new drugs, like gemcitabine (Zhou et al., 2014) which is one of the most frequently used drugs to treat this condition. After cellular uptake, gemcitabine is phosphorylated inside the cell by deoxycytidine kinase (dCK) and converted to gemcitabine di- and triphosphate by deoxycytidine kinase (dCK) producing termination of DNA elongation (Mini, Nobili, Caciagli, Landini, & Mazzei, 2006). Unfortunately, a downside of gemcitabine is its toxicity to normal tissues and the acquisition of resistance by tumor cells (Zhou et al., 2014). Studies has shown that natural compounds derived from ginger have a variety of pharmacological properties including antioxidant, anti-inflammatory, and anticancer activities being the most significant the inhibition of angiogenesis during tumor progression (Bae, Choi, Kim, Park, & Jeong, 2016). Other promising natural compounds are those derived from *Curcuma longa* commonly known as turmeric (Shah et al., 2018). The extract of turmeric contains 77% curcumin, 17% demethoxycurcumin, and 3% bisdemethoxycurcumin, collectively named curcuminoids (Chin, 2016). Curcumin has been shown to possess anticancer activity against pancreatic cancer through its effect on NFκβ (Huang et al., 2017). Another approach that can be considered for treating pancreatic cancer is the synthetic compound EHop-16, a GTPase Rac inhibitor that blocks Rac who has been shown to regulate breast cancer cell migration, survival, and proliferation (Montalvo-Ortiz et al., 2012).

A hallmark of malignant cells is their ability to evade the mechanisms of regulated cell death, producing dysregulated cellular proliferation. Apoptosis is a regulated cell death process that occurs in two different pathways; the extrinsic and intrinsic. This mechanism is highly organized and depends on cysteine rich aspartates known as caspases. Among these are the initiator caspases (8 and 9) that will eventually lead to the activation of the effector caspases (3 and 7) that play a key role in the final demise of the cell. Since both, synthetic and natural compounds have the ability to induce apoptosis, it is possible that either components can improve the apoptotic pathways in pancreatic cancer. Since malignant cells can be resistant to apoptosis, the objective of this study was to evaluate the efficacy of natural compounds derived from ginger (zingerone, 6-shogaol), curcuminoids and the synthetic compound EHop-16 for inducing apoptosis on the human pancreatic adenocarcinoma cell line PANC-1, in comparison with gemcitabine, the main current treatment for pancreatic cancer.

MATERIALS AND METHODS

Materials

Zingerone, 6-shogaol, gemcitabine, DMSO (HybriMax), curcumin, bisdemethoxycurcumin (BDMC), staurosporine and EHop-16 where purchased from Sigma/Millipore (MA, USA). Stock solutions of the treatments where prepared at a concentration of 100 mM and stored as small aliquots at -20°C. 6-shogaol was prepared at 74.4 mM. Further dilution of the treatments was done with cell culture media. The Multicaspase assay was purchased from Sigma/Millipore (MA, USA).

Cell line and maintenance

The human pancreatic adenocarcinoma cell line, PANC-1 was obtained from the American Type Culture Collection Manassas VA, USA (ATCC® CRL1469™). The cells were maintained in a humidified incubator (Galaxy 170R New Brunswick) at 37°C with 5% carbon dioxide. Cells were fed every other day with Dulbecco's Modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum and with streptomycin (0.1 mg/mL) and penicillin (100 U). Cell concentration and viability was determined manually counting cell with the hemocytometer, using trypan blue to exclude dead cells.

MultiCaspase Assay

The detection of caspase activation on PANC-1 cells was determined using the MultiCaspase kit, obtained from Sigma/Millipore (MA, USA), according to manufacturer's instructions (EMD Millipore Corporation, 2013). Cell confluence was observed previously to determine the preferable flask to perform the assay. The seeding of cells was done at a density of $5x10^5$ cells/well. Cells were exposed in duplicates to each treatment (6-shogaol, zingerone, gemcitabine, curcumin, BDMC and EHop-16) diluted previously in DMEM at concentrations of 10, 25, 50, and 100 µM. DMSO and staurosporine were used as controls for the assay. The exposure time of the treatments was 24 and 48 hours. Cells were analyzed using the Muse Cell Analyzer. The range of evaluated events (total cells) were between 5×10^4 cells/mL up to 2×10^5 cells/mL.

Data analysis

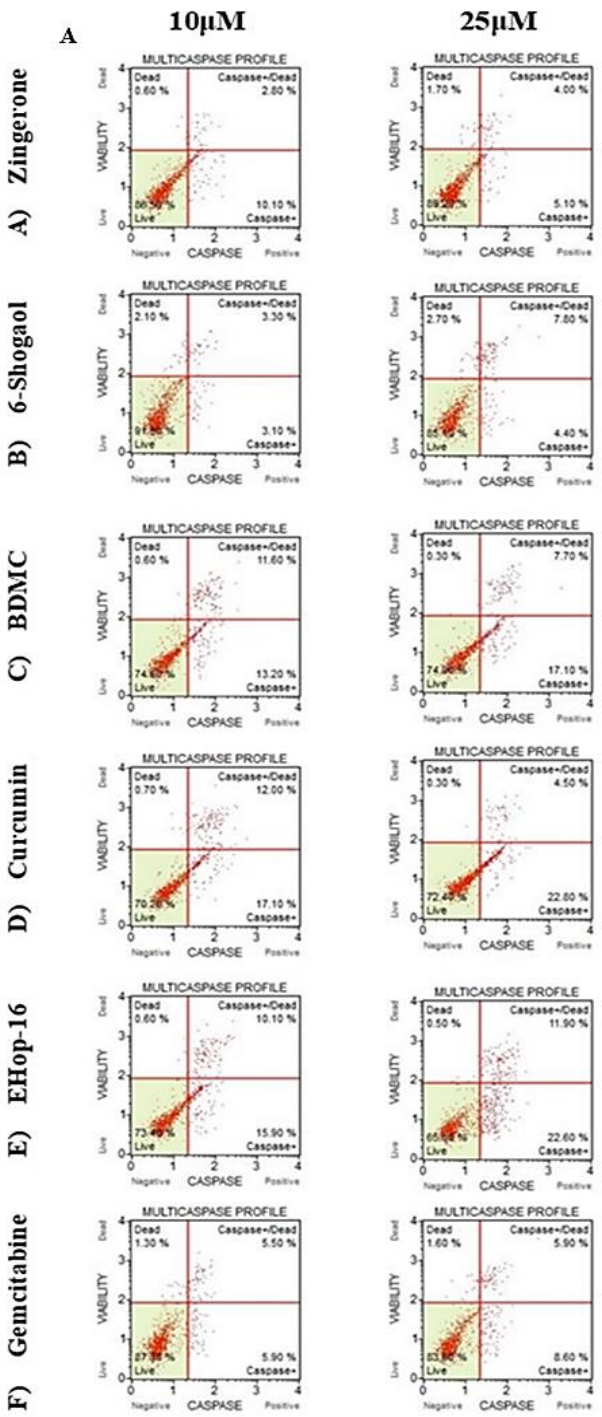
All graphs were constructed using Graph Pad Prism 8.1.2 software. Microsoft Excel was used to organize quantitative data.

RESULTS

Study of activation of multiple caspase and caspase mediated cell death

The activation of multiple caspases (1, 3, 4, 5, 6, 7, 8, and 9) was evaluated by flow cytometry after treating PANC-1 cells during 24 and 48 hours with ginger derivates (zingerone and 6-shogaol), curcuminoids (curcumin and bisdemethoxycurcumin), EHop-16 or gemcitabine, at 10, 25, 50 and 100 µM, using DMSO (0.0001, 0.01, 0.05, 0.025 and 0.1%) or cell culture media as a control. Also, staurosporine (1, 20, 100 and 1000 nM) was used as a positive control for apoptosis. Figure 1 shows representative dot plots obtained for the analysis of multicaspase activation, after treating cells during 24 hours. The obtained dot plot shows the

distribution of the evaluated cells at four different stages: live, dead, caspase/dead and caspases.



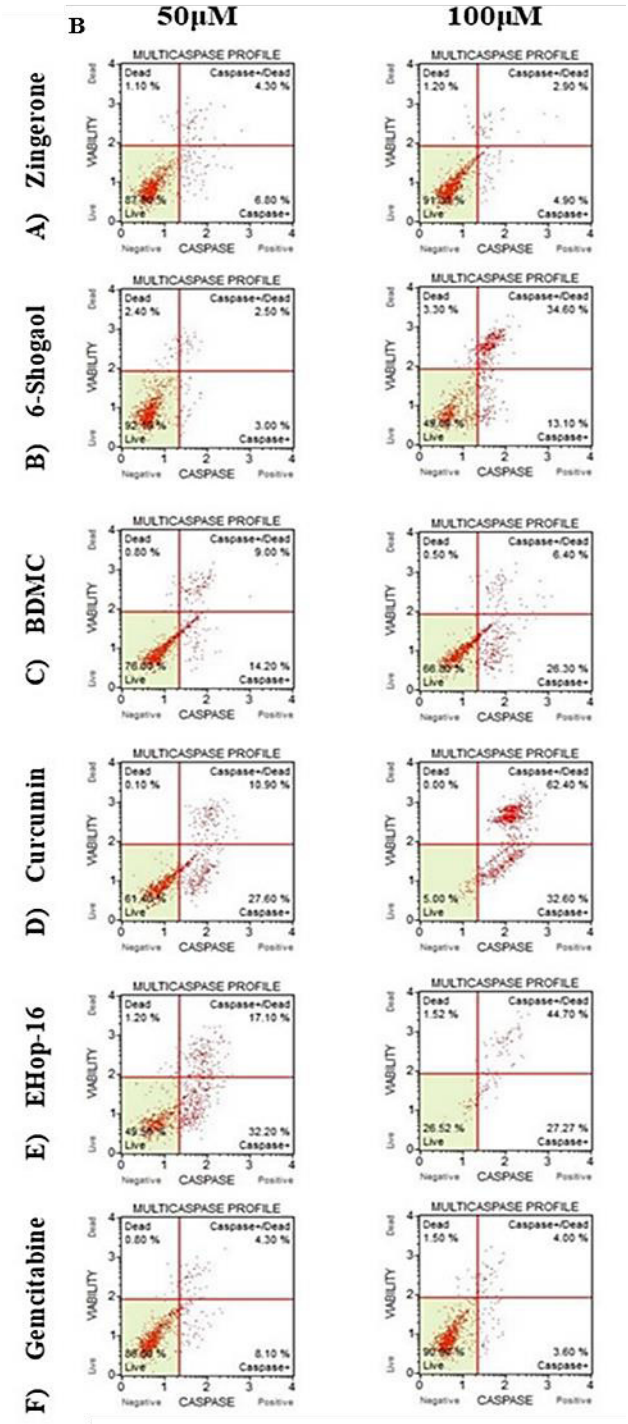


Figure 1. Effect of chemical compounds isolated from ginger and turmeric or synthetic compounds on the activation of multicaspase in PANC-1 cells (A, B). After 24 hours of treatments with A) zingerone B) 6-shogaol C) bisdemethoxycurcumin D) curcumin E) EHop-16 and F) gemcitabine at shown concentrations. The activation of caspases was determined by labelling the cells with VAD-FLICA. Dots plots show the cells sorting in four populations (live cells, cells

with activated caspase, caspase mediated dead cells, and dead cells), produced by the Muse™ Cell Analyzer. Fluorescence intensity for multi-caspase is indicated on the x-axis and that of 7-AAD incorporation, a death cell marker, is indicated on the y-axis. The range of evaluated events (total cells) were between 5 x 10^4 cells/mL up to 2x10^5 cells/mL.

As shown in the summary of results in Table 1, it was observed that the tested compounds have unique ways to induce caspase activation alone or induce both caspase activation and cell death. Among the ginger derivates 6-shogaol induced caspase mediated cell death after 24 hours and the effect was increased two-fold after 48 hours, and zingerone produced a slight activation of multiple caspases. Among the compound derived from turmeric, it was observed that curcumin produced multiple caspases activation and caspase mediated cell death, but the effect was not time dependent. However, treatment with BDMC only increased multiple caspase activity but did not induce caspase mediated cell death during the tested periods. It was observed that EHop-16 had a dramatic increase in multiple caspase when the exposure time was increased from 24 to 48 hours, but the caspase mediated cell death was reduced almost by half when the exposure time was doubled. Finally, gemcitabine treatment increased both multiple caspase activity and caspase mediated cell death, but only after 48 hours of treatment.

Table 1. Summary of caspase activation and caspase induced cell death in PANC-1 cells produced after exposure during 24 and 48 hours to natural and chemical compounds.

Treatment (100 µM)	24 hours		48 hours	
	A	B	A	B
Zingerone	4.9	2.9	12.3	4.6
6-shogaol	13.1	34.6	19.6	63.9
BDMC	26.3	6.4	6.0	6.8
Curcumin	32.6	62.4	32.6	64.8
EHop-16	27.3	44.7	56.8	27.1
Gemcitabine	3.6	4.7	20.7	24.3

BDMC: Bisdemethoxycurcumin
A: % of cell with multiple caspase activation
B: % of cell death mediated by caspase

Figure 2 shows the response of PANC-1 cells to staurosporine, a positive control for apoptosis. The highest activation (up to 42%) of total caspase activity was observed after exposing PANC-1 cells to 1 µM staurosporine for 48 hours. However, the highest caspase mediated cell death (31%) was observed after 24 hours of treatment. These results show that there are adequate intracellular pathways that elicit activation of caspase that will eventually cause apoptosis, and therefore further evaluation of other compounds, as an apoptotic inductor can be used.

After establishing the apoptotic induction capacity of staurosporine in PANC-1 cells, it was evaluated the ability of chemicals derived from ginger, turmeric or synthetic compounds to activate multiple caspases and produce caspase mediated cell death. Among the tested compounds it was found that, as shown in Figure 3, curcumin increased total caspase activity up to 85.2%, after treating the cells for 24 hours, and was further increased to 96.3% at 48 hours. Gemcitabine and 6-shogaol required an exposure of 48 hours to increase PANC-1 cell caspase activity while EHop-16, reduced its ability to increase total caspase activity when the exposure period was increased from 24 hours to 48 hours. These results suggest that each tested compound have unique ways to activate and sustain caspase activity and is time dependent.

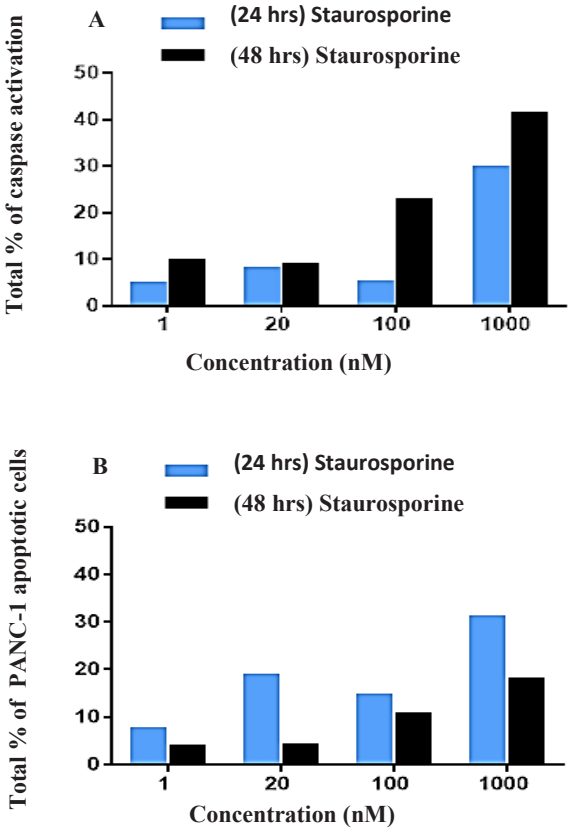


Figure 2. Staurosporine apoptotic profile. Total caspase activation (A) and caspase mediated cell death (apoptosis) activation (B) induced by staurosporine after 24 and 48 hours of treatment.

The total percent of PANC-1 cells undergoing apoptosis was determined after 24 and 48 hours of treatment. It was observed (see Figure 4) that among the tested compounds curcumin and EHop-16 were the most potent for inducing apoptosis followed by 6-shogaol. When the incubation period was increased to 48 hours 6-shogaol and curcumin apoptotic effect was slightly increased while the apoptotic effect of EHop-16 was reduced.

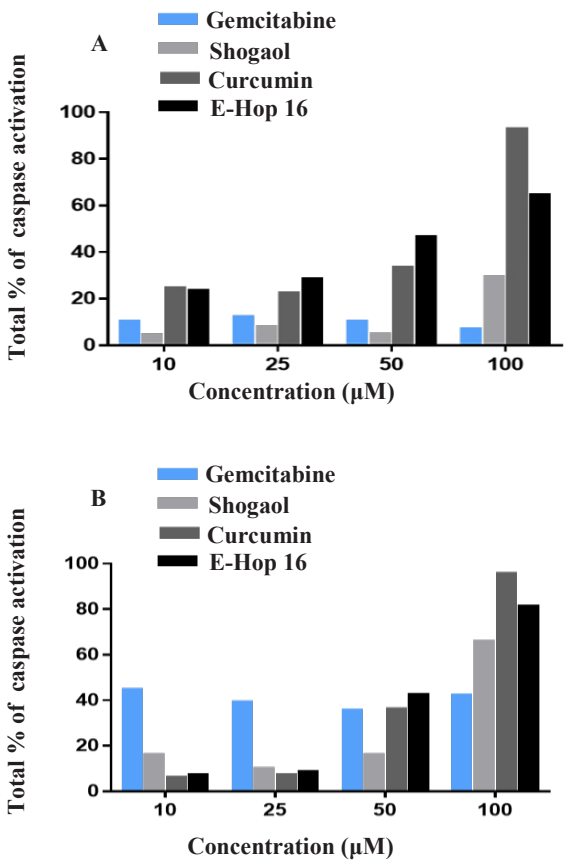


Figure 3. Total caspase activation induced by natural and synthetic chemical compounds. Caspase activation was evaluated after treatment with gemcitabine, 6-shogaol, curcumin, EHop-16 during A) 24 hours and B) 48 hours.

In order to determine what proportion of activated caspases are mediating regulated cell death, a ratio of total apoptosis vs. total caspase activity was done for 24 and 48 hours and is presented in Table 2. From the analysis it seems that when cells are treated for 24 hours, almost 50% of activated caspase is devoted to regulated cell death for the most of the treatment, however for EHop-16 when the period of exposure was increased to 48 hours, it was observed that only 25% is devoted to regulated cell death. This suggests that this treatment may cause other effects mediated by the non-apoptotic functions of caspase.

To determine the net caspase activation, the effect caused by DMSO was subtracted from the apoptosis reflected by the treatments. Table 3 shows the net caspase activation produced in PANC-1 cells when they were exposed to zingerone, 6-shogaol, curcumin, BDMC, EHop-16, and gemcitabine during 24 and 48 hours. Data demonstrates that when cells were treated for 24 hours curcumin and EHop-16 were able to induce net apoptosis but neither ginger derived compounds nor gemcitabine produced such effect. When the incubation period was increased to 48 hours curcumin apoptotic effect was reduced, and ginger derived compounds and gemcitabine had a modest apoptotic effect. Table 4 summarizes the net apoptosis induced by the tested compounds.

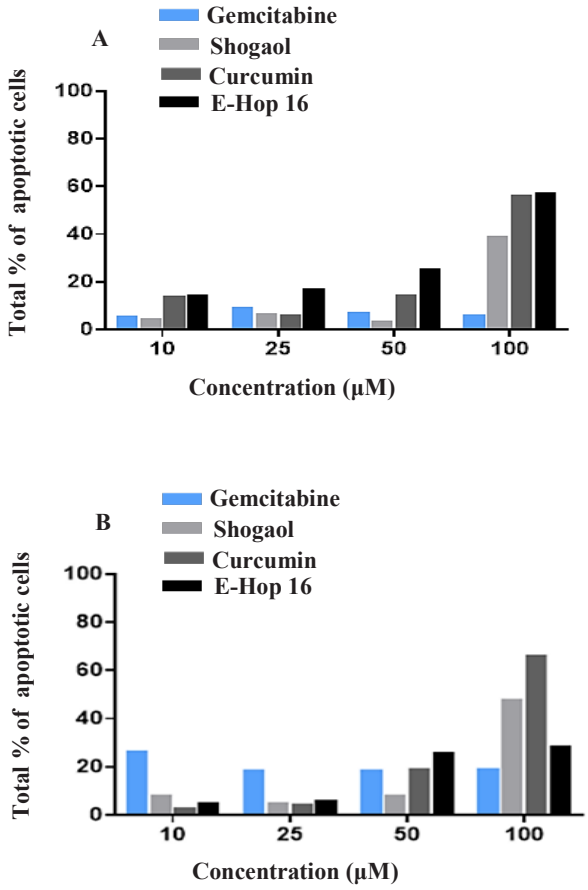


Figure 4. Total caspase mediated cell death (apoptosis) by natural and synthetic compounds. The total % of dead cells through caspase activation was determined after treatment with gemcitabine, shogaol, curcumin, E-hop 16 during A) 24 hours and B) 48 hours.

DISCUSSION AND CONCLUSION

The diverse analysis performed on the activation of multiple caspase in PANC-1 cells, shows that this model of pancreatic adenocarcinoma conserved the ability to both activate caspases and induce regulated cell death. PANC-1 cells response to staurosporine, was lower than the values reported in other publications for the same experimental model. For example, Molasy et al., (2019) reported that exposure to 1 µM staurosporine for 24 hours produced apoptosis in 65% of PANC-1 cells population using Annexin assay. When caspase mediated cell death was evaluated the highest amount of detected apoptotic cells was 42%, showing that have a functioning apoptotic pathway.

Curcumin (100 µM) was the natural compound that produced the highest activation of multiple caspases (-1, 3, 4, 5, 6, 7, 8, and 9), followed by EHop-16. Caspase mediated cell death (apoptosis) was induced more effectively with curcumin and EHop-16. Both effects were time-dependent for EHop-16 since it was observed that the activation of multiple caspases was increased but the apoptotic effect decreased when the exposure time was 48 hours. Also, it was observed that 6-shogaol increased lightly the activity of multiple caspase, but the population of apoptotic cells increased up to 63% when the incubation period was 48 hours. The activation of caspase and apoptosis induction was also dose-dependent for EHop-16, 6-shogaol and curcumin, but not for gemcitabine. The least effective compound was found to be ginger derivate zingerone.

Table 2. Total apoptosis and total caspase activity ratio in PANC-1 cells after a 24-hour exposure to chemical compounds isolated from ginger and turmeric or synthetic compounds.

Concentration (µM)	**Percent of activated caspase producing regulated cell death**			
	Gemcitabine		6-shogaol	
Incubation period (hrs)	24	48	24	48
10	56%	59%	43%	51%
25	80%	48%	69%	47%
	Curcumin		EHop-16	
10	55%	46%	76%	26%
25	26%	62%	71%	25%

Table 3. Analysis of net caspase activation in PANC-1 cells after a 24 and 48 hours exposure to chemical compounds isolated from ginger and turmeric or synthetic compounds.

Concentration (µM)	**Net caspase activation (%)**			
	Zingerone		6-shogaol	
Incubation period	24h	48h	24h	48h
100	ND	ND	22.1	40
50	ND	ND	ND	ND
25	ND	ND	ND	ND
10	ND	ND	ND	ND
	Curcumin		BDMC	
100	30.3	23.2	15.9	ND
50	14.3	12.7	2.2	ND
25	11.6	ND	7.4	ND
10	9.1	ND	6.0	ND
	EHop-16		Gemcitabine	
100	23.7	46.3	ND	10.9
50	19.4	11.6	ND	4.9
25	10.3	ND	ND	8.3
10	6.3	ND	ND	5.9

ND= Not detected

Net caspase activation= Total caspase activation induced by treatment-Total caspase activation induced by DMSO

When the proportion of activated caspase devoted to induce apoptosis was evaluated (see Table 2) it was found that the most drastic transition was observed for EHop-16 (10 and 25 µM), since during the first 24 hours approximately 75% of activated caspase are involved in apoptosis but when the exposure increased to 48 hours, only 25% of activated caspase were mediating cell death. This observation suggests that EHop-16 induces the activation of caspases that regulates other cellular process such as cell proliferation, cell migration or metastasis (Xu, Arthurton, & Baena-López, 2018). Regulation of caspase 8 activation has been related to a regulated cell death process called anoikis, produced by the detachment of epithelial cells from the extracellular matrix (Xu et al., 2018). Also, caspase 8 expression has been implicated in the suppression of metastasis in neuroblastoma cells (Stupack et al., 2006). Further evaluation of other cellular effect produced by EHop-16 in PANC-1 cells is needed.

Table 4. Analysis of net caspase mediated cell death (apoptosis) in PANC-1 cells after 24 and 48 -hour exposure to chemical compounds isolated from ginger and turmeric or synthetic compounds.

Concentration (µM)	**Net caspase mediated cell death (apoptosis)**			
	Zingerone		6-shogaol	
Incubation period	24h	48h	24h	48h
100	ND	ND	22.1	40
50	ND	ND	ND	ND
25	ND	ND	ND	ND
10	ND	ND	ND	ND
	Curcumin		BDMC	
100	40.0	57.1	ND	ND
50	ND	8.3	ND	ND
25	ND	ND	ND	ND
10	ND	ND	ND	ND
	EHop-16		Gemcitabine	
100	40.3	20.4	6.3	19.8
50	ND	16.0	7.2	19.0
25	ND	ND	9.2	19.0
10	ND	ND	5.8	26.0

ND= Not detected

Net apoptosis = Total apoptosis induced by treatment-Total apoptosis induced by DMSO

Since the solvent DMSO used for exposing the cells to treatments, produces a slight increase in caspase activity and caspase induced cell death, the net effect for each treatment was determined. It was found that 6-shogaol, curcumin, BDMC, EHop-16 and gemcitabine reflect net caspase activation when cells were treated for 24 hours. When the incubation period was increased to 48 hours BDMC lost the caspase activation effect, gemcitabine had dose independent apoptotic effect, and 6-shogaol and EHop-16 doubled the capacity for activating caspases. Also, it was observed that net apoptotic activity for EHop-16 was reduced when the incubation period was increased. In contrast the net apoptotic effect for 6-shogaol was doubled when the incubation period was increased from 24 hours to 48 hours. This

demonstrates that both caspase activation and the subsequent regulated death process is time dependent.

In conclusion, both natural and synthetic compounds induced apoptosis in PANC-1 cells. Among the natural compounds curcumin followed by 6-shogaol were the most effective for activating multiple caspase and for inducing apoptosis. The activation of caspases was dose dependent and time dependent for both compounds. It is noteworthy the effect of EHop-16 in producing activation of caspases. After 48 hours only 25% of the caspase activity is implicated in cell death, therefore it is proposed that not all activated caspases are related to regulated cell death and that this effect may regulate the capacity of invasion and aggressivity that is observed in pancreatic cancer cells.

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Adaptations in the vocalizations of *Margarops fuscatus* and *Turdus plumbeus* in urban environments

Adaptaciones en las vocalizaciones de *Margarops fuscatus* y *Turdus plumbeus* en ambientes urbanos

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ABSTRACT

With the continued expansion of urbanization, it has become necessary for wildlife to adapt to its new environment. Birds are just one of many animals who depends on sound for communication, reproduction, defense, etc. Our interest was to study how the pearly-eyed thrasher and the red-footed thrush were adapting to these challenges, if they had developed a different call. In order to study this we tested for significant differences across five variables: vocalizations per minute, duration, mean frequency, maximum frequency and minimum frequency. However, significant differences were only detected in the vocalizations per minute of the pearly-eyed thrasher in both the urban and rural environments, the vocalizations per minute in both species in rural environment and in the maximum frequency of the pearly-eyed thrasher in both environments. Future research in this area may use the same methodology but bigger sample sizes.

RESUMEN

Con la expansión continua de las zonas urbanas se ha vuelto necesario que la vida silvestre se adapte a su nuevo ambiente. Las aves son uno de muchos animales que dependen de sonido para comunicación, reproducción, defensa, etc. Nuestro enfoque fue estudiar como el zorzal pardo y el zorzal patirrojo se adaptaba a estos retos, si habrían desarrollado otro canto. Para estudiar esto hicimos pruebas estadísticas para determinar diferencias significativas a través de cinco variables: vocalizaciones por minuto, duración, frecuencia promedio, frecuencia máxima y frecuencia mínima. Sin embargo, solo se detectaron diferencias significativas en las vocalizaciones por minuto del zorzal pardo en áreas urbanas y rurales, las vocalizaciones por minuto de ambas especies en zonas rurales y en la frecuencia máxima del zorzal pardo en los dos ambientes. Estudios futuros en esta área pueden utilizar la misma metodología, pero una muestra más grande.

KEYWORDS Anthropogenic noise, bird song, vocalization frequency, acoustic adaptation

PALABRAS CLAVE Sonido antropogénico, canto de aves, frecuencia de vocalización, adaptación acústica

INTRODUCTION

Cities are growing at alarming rates and with this comes anthropogenic noise such as traffic and other day to day activities. This is not without consequence to local wildlife. A variety of animals have sound as a vital component for communication, reproduction, etc. A study on avian and anuran communities established that closeness to human activity affected bird community composition. When the background noise of traffic masked the bird's vocalizations they moved away to areas of lower noise (Herrera-Montes & Aide, 2011). This is common in birds with low frequencies who are only detected in quiet areas. Slabbekoorn in 2013, put forth the concern that this would lead to homogenization of avian communities where only those who had adapted to the new urban environment would flourish.

A study by Dooling and Popper (2016) summarized these new strategies for adapting to anthropogenic noise as long-term strategies or shor-t term strategies. While both long and short-term included a change in location, short-term strategies include modifying the duration of vocalization and changing the length, intensity and repetition. Long term changes include modifying the spectrum and singing time.

As a preliminary study, we decided to focus on the short-term strategies to answer how the vocalizations in these species vary in urban versus rural environment and, whether or not, there is a difference in the mechanisms for adaptations in these species. In order to answer these questions, we will be using *Margarops*

fuscatus, the pearly-eyed thrasher, and *Turdus plumbeus*, the red-legged thrush as our focal species.

MATERIALS AND METHODS

Recording sites and equipment

Focal species were recorded in five urban sites and two rural sites located in the municipalities of Mayagüez and Cabo Rojo. Of the urban sites, four were areas within the University of Puerto Rico (UPRM) campus and one was at the *Parque de los Próceres* located adjacent to the UPRM campus. Rural recordings took place at the *Adrian H. Acevedo Cruz* recreational park at Las Marías and at a residential area in Boquerón, Cabo Rojo (Table 1).

The audio was obtained during December 2017 up until mid-January 2018 at various hours within the 8:00 am to 5:00 pm range. To avoid recording the same bird, each one was selected from a different tree. When two birds of the same species were vocalizing at the same time, they were considered as one measure, as described by Hu and Cardoso (2010). Vocalizations were recorded spontaneously each time the focal species were heard and approximately 6 to 16 meters were kept to avoid any interference with normal bird activity. The duration of the audio ranged from 3 to10 minutes because the recording was stopped when the bird flew to an area that was too far to locate (Table 2). After the audio was obtained, the best quality samples were selected from the total of recordings. These audio samples were recorded using a smart phone and the applications Voice Recorder 2.0.22, Recorder and Voice Memo. The microphone was oriented towards the focal species during vocalization.

Frequency measurements

From the audio obtained, the samples with best quality were selected. The selected recordings were processed using the Audacity® Cross-Platform Sound Editor for noise reduction. After having filtered the recordings, total number of chirps were measured.

In order to obtain the duration, mean frequency, maximum frequency and minimum frequency, chirps were carefully chosen from each audio which had the best quality and the least interference with vocalizations from other species (Table 3). After these vocalizations were selected, Sound Analysis Pro 2011 was used for the mentioned measurements. An average of the vocalizations that corresponded to each recording was documented.

Intraspecific and Interspecific Statistical Analyses

By using t-test statistical analysis to determine significant differences among the studied species, five variables were compared (vocalizations per minute, duration, mean frequency, max frequency and minimum frequency). Intraspecific comparisons were made by calculating the t-values for these variables between urban and rural pearly-eyed thrashers as well as urban and rural red-legged thrush. In terms of interspecific comparisons and by using the same variables, t-values between urban pearly-eyed trashers and red-legged trush as well as between the rural pearly-eyed thrashers and red-legged thrush were calculated.

Table 1. Identification for study subjects.

Bird number	Species	Environment
1	*Margarops f.*	Urban
2	*Margarops f.*	Urban
3	*Margarops f.*	Urban
4	*Margarops f.*	Urban
5	*Margarops f.*	Urban
6	*Margarops f.*	Urban
7	*Margarops f.*	Urban
8	*Margarops f.*	Urban
9	*Margarops f.*	Urban
10	*Margarops f.*	Urban
11	*Margarops f.*	Urban
12	*Margarops f.*	Urban
13	*Margarops f.*	Urban
14	*Margarops f.*	Urban
15	*Margarops f.*	Rural
16	*Margarops f.*	Rural
17	*Turdus p.*	Urban
18	*Turdus p.*	Urban
19	*Turdus p.*	Urban
20	*Turdus p.*	Rural
21	*Turdus p.*	Rural

RESULTS

Vocalizations per minute

The test between *Margarops fuscatus* in both environments gave us a t= -13.5676, df= 13.97, p-value= 1.954 x e(-9). Given the magnitude of t and the value of p we can see a significant difference in the number of vocalizations of the pearly-eyed thrasher in rural and urban environment. The test between *Turdus plumbeus* in both environments gave us a t= 1.424, df= 1.9, p-value= 0.2972. These values however are not enough to assume a significant difference in the number of vocalizations that a red-legged thrush may make in a rural and an urban environment. The test between both species in an urban environment gave us a t= 2.879, df= 14.67, p-value= 0.01168. These values show some difference in the number of vocalizations of both species in a rural environment but not to a significant amount. The test between both species in a rural environment gave us a t= -31.5, df= 1.6, p-value= 0.003. We can

detect a significant difference for vocalizations of both species in the same environment.

Table 2. Data for observation time, number of calls and calls per minute for sample group

Bird number	Observation time (mins)	Numer of calls	Calls per minute
1	6:00	0	0
2	10:00	15	1.5
3	10:00	0	0
4	2:44	40	14.6
5	10:51	49	4.5
6	10:00	2	0.2
7	10:00	82	8.2
8	6:10	33	5.4
9	7:00	12	1.7
10	8:05	29	3.6
11	9:00	155	17.2
12	6:58	140	20.1
13	8:13	14	1.7
14	10:13	39	3.8
15	1:09	36	31.3
16	1:13	37	30.4
17	20:00	0	0
18	10:00	0	0
19	3:11	5	1.6
20	4:33	5	1.1
21	12:00	32	2.7

Duration

The test between *Margarops fuscatus* in both environments gave us a t= -1.026, df= 2.81, p-value= 0.385. No significant difference was detected between the duration of calls for the pearly-eyed thrasher. The test between *Turdus plumbeus* in both environments gave us a t= -2.1105, df= 1.46, p-value= 0.2141. In urban environments both species behave similarly in terms of call duration (t= 1.839, df= 3.63, p-value= 0.147). The test between both species in a rural environment gave us a t= -0.8202, df= 1.2255, p-value= 0.5412. These values do not show a significant difference in the duration of vocalization for both species in a rural environment.

Mean frequency

The test between *Margarops fuscatus* in both environments gave us a t= -0.8177,df= 3.11734, p-value= 0.4714. These values do not show a significant difference in the mean frequency of pearly-eyed thrashers. The test between *Turdus plumbeus* in both environments gave us a t= -1.8512, df= 2.67, p-value= 0.1724. The values do not show a significant difference in the mean frequency of red-legged thrush. For both species in an urban environment mean frequency was not different (t= 0.6275, df= 2.3, p-value= 0.587). The test between both species in a rural environment gave us a t= -1.3416, df= 1.47, p-value= 0.3499. These tests do not show a significant difference between the mean frequencies of both species in a rural environment.

Maximum frequency

For *Margarops fuscatus* in both environments, comparison of maximum frequency was different (t= -3.1892, df= 13.37, p-value= 0.006895). However, for *Turdus plumbeus* in both environments there was not a difference (t= -1.8169, df= 0.1736, p-value= 0.1736). The comparison between both species in an urban environment gave us a t= 1.0922, df= 2.668, p-value= 0.3634. These tests do not show significant difference between the maximum frequencies in an urban environment for both species. On the other hand, comparison of both species in a rural environment gave us a t= -0.027, df= 1, p-value= 0.9828. These values do not show a significant difference for the maximum frequency of both birds.

Table 3. Data for duration, mean frequency, maximum frequency and minimum frequency for the sample group

Bird #	Duration (ms)	Mean Frequency (kHz)	Maximum Frequency (kHz)	Minimum Frequency (kHz)
1	0	0	0	0
2	130.7	2	2.9	1
3	0	0	0	0
4	155.79	4.8	7.1	1.4
5	74.86	2.2	2.8	2
6	59.9	4.4	9.8	1.3
7	192.73	3.8	5.5	1.8
8	256.4	3.3	6.2	2
9	0	0	0	0
10	96.775	3.4	6.1	0.9
11	97.03	2.7	3.4	2.4
12	167.9	4.2	6.8	2.2
13	210.8	3.8	5.2	1.1
14	185.16	3.9	5.1	2.1
15	178.06	3.8	6.8	2.4
16	125.29	2.8	7	2
17	0	0	0	0
18	0	0	0	0
19	110.915	5	6	3.4
20	141.2	4.3	5.1	3.4
21	297.32	3.8	8.8	2.4

Minimum frequency

The test between *Margarops fuscatus* in both environments gave us a t= -2.9855, df= 4.6, p-value= 0.03406. These values show some differences in the maximum frequencies but not that much. For *Turdus plumbeus* in both environments gave us a t= -1.4262,

df= 2.65, p-value= 0.2602. These values do not show significant differences. The comparison of both species in an urban environment showed not significant difference for the minimum frequency (t= 0.1442, df= 2.16, p-value= 0.8977).

DISCUSSION

For the variable of vocalizations per minute there was a significant difference in the vocalizations per minute in *Margarops fuscatus* with more vocalizations in a rural environment than in the urban environment. This could be due to one of two reasons. One is that in urban areas, there is more competition between the vocalizations versus the ambient noise making the species prefer to not invest energy in vocalizations that might be ineffective. The second possible explanation is that the recordings of the two variables were taken at different times throughout the day which means the obtained results might be affected by peak hours of activity. There was also a significant difference between both species in a rural environment with the pearly-eyed thrasher doing more vocalizations. But these differences could be a result of traits that are particular to the pearl-eyed thrasher in which it differs from the red-legged thrush.

The lack or the presence of significant differences may be owed to the irregular sample sizes. One demographic had an abundant sample while others had a few specimens and this proved to be a non-representative number of the population.

CONCLUSION

Margarops fuscatus shows preference for living in densely populated urban areas and was generally absent in more quiet areas. *Turdus plumbeus* was the opposite, being much more active in quiet rural areas and the specimens found in urban areas were flighty and difficult to find. As stated earlier, the sampled sizes were unrepresentative of the true population and so a future study must take into account the sample sizes. Another factor that might have affected our results is that our data was recollected at different points during the day which sometimes matched the active times of our focal species and sometimes did not. The calls per min may be affected by different high-activity times. The quality of our recordings and subsequent analysis was affected by the distance we had to keep from the birds and the relatively poor resolution of our recording instruments.

And the distribution of our focal species may have been affected by Hurricane Maria which brought about various challenges. The first being the destruction of habitat and the access to resources for these birds which may have been affected. Another consequence of the disaster was an increment of anthropogenic noise in the form of electric generators. This was especially noticeable in rural areas where the devastation remained much the same as the first week after the hurricane. The generators were heard for miles and this would affect the usually peaceful and quiet rural area for birds with low-frequency calls.

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Estudio sobre la evolución de la seguridad en la tecnología de la nube en los últimos cinco años

Study on the evolution of security in cloud technology in the past five years

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RESUMEN

Este estudio de investigación exploratoria y cuantitativa tiene como propósito informar y determinar cuánto ha evolucionado la seguridad en la tecnología de la nube en los últimos cinco años. Se explica detalladamente la arquitectura y las tres plataformas que son utilizadas para la creación de los servicios en la red: Infraestructura de Servicio (IaaS), *S*ervicio de *Software* (SaaS) y Plataforma de Servicio (PaaS). Se exploraron cuatro tipos de modelos que son utilizados para la creación de la arquitectura de la nube: privada, pública, híbrida y comunitaria. Con los datos de la estructura y los modelos, los usuarios analizaron si los proveedores de los servicios de la nube están brindando la seguridad necesaria para proteger la información. La población en esta investigación fueron sujetos que estaban brindando y recibiendo servicios en hospitales, universidades, bancos y comercios en la Zona Norte de Puerto Rico. La población fue seleccionada de forma aleatoria en los pueblos de Arecibo, Hatillo y Barceloneta. La población escogida tenía conocimientos básicos de cómo la tecnología de la nube ha evolucionado en los últimos años y la seguridad que proporciona la empresa para la cual brindan y reciben sus servicios. La muestra estuvo constituida por 113 sujetos a los que se administró un cuestionario diseñado por el investigador.

ABSTRACT

This exploratory and quantitative research study aims to inform and determine how security has evolved in the cloud technology in the last five years. It explains in detail the architecture of the cloud technology and the three platforms that are used for the creation of the services in the network: Infrastructure as a Service (IaaS), *Software* as a Service (SaaS) and Platform as a Service (PaaS). We explored four types of models that are used for the creation of cloud architecture: private, public, hybrid and community. With the data of the structure and the models, the users analyzed whether the providers of the cloud services are providing the necessary security to protect the information. The population in this research were subjects that are providing and receiving services in hospitals, universities, banks and businesses in the Northern Zone of Puerto Rico. The population was randomly selected in the towns of Arecibo, Hatillo and Barceloneta. The chosen population had basic knowledge of how cloud technology has evolved in recent years and the security provided by the company for which they provide and receive their services. The sample was obtained personally from the employees and clients who are providing and / or receiving services in banks in the Northern Zone of Puerto Rico. The sample consisted of 113 subjects who were administered a questionnaire designed by the researcher.

PALABRAS CLAVE tecnología de la nube, evolución, seguridad, y protocolos

KEYWORDS cloud technology, evolution, security, and protocols

INTRODUCCIÓN

Andrew (2014) expone que en los últimos años la tecnología haevolucionado en forma eficiente como un recurso que la población utiliza y cada vez depende más para lograr alcanzar las metas. Uno de esos recursos es la tecnología de la nube y es un factor determinante en la vida de los usuarios. Para Furht y Escalante (2010), con la tecnología de la nube se puede acceder, editar u obtener cualquier documento, buscar, solicitar y/o comprar cualquier servicio profesional. Un beneficio de la tecnología de la nube es facilitar el desempeño de las personas en sus labores diarias, personales y profesionales. Además, es utilizada en la descripción de productos y compañías en diferentes partes del mundo.

La evolución en la tecnología de la nube ha cambiado la manera en que se comunican las personas, empresas, organizaciones y negocios (Andrew, 2014). La tecnología de la nube provee todas las herramientas necesarias para la búsqueda de cualquier tipo de servicio y es parte del diario vivir de la población mundial (Nepal

y Pathan, 2014).

Fearne (2015) explicó que la tecnología de la nube es un modelo de la informática que ha evolucionado y se ha expandido sin control. Con dicha tecnología se aprovechan las ventajas de la Internet al acceder información y datos personales en otros dispositivos electrónicos. Según Paczkowski (2009), en el pasado los dispositivos electrónicos se dañaban y eran reemplazados, por lo que la información se perdía. La tecnología de la nube ha cambiado drásticamente la forma en que los datos se guardan en los servidores. Debido a estos cambios Paczkowski (2009) presenta varias preguntas a considerar: ¿Cuándo se acceden y guardan los datos en la tecnología de la nube?; ¿Qué seguridad tienen?; ¿Quién tiene acceso a la información?, ¿Cómo alguien puede tener acceso a datos personales y documentos que se encuentran en la red? A este respecto, para Flantrmskv (2012), los nuevos modelos de la tecnología de la nube son peligrosos, porque al utilizar estos servicios para almacenar los datos personales de clientes se pueden perder los derechos legales. Esto implica que los proveedores de los servicios pueden utilizar toda la data que tienen de sus clientes para otros fines.

Walton (2012) realizó una encuesta acerca de la definición de la nube. Participaron 1,000 estadounidenses y la mayoría relacionó la nube con el clima, no como una nueva tecnología. Específicamente, se encontró que el 51% de los encuestados contestó que los cambios de clima interfieren con la tecnología de la nube; 29% que la nube es una real y 16% sabía realmente lo que era la tecnología de la nube.

Mather, Kumaraswamy y Latif (2009) presentaron que la tecnología de la nube es utilizada por el 40% (aproximadamente) de las personas a nivel mundial con un incremento anual de usuarios de 10%, lo que significa que al menos tres billones de personas en el mundo tienen y/o han tenido acceso a esta tecnología. También establecen que los usuarios carecen del conocimiento sobre cómo funciona y cómo ha evolucionado en los últimos años. Esa carencia de conocer cómo las empresas proveedoras en servicios protegen las fotos, los programas, los datos y/o información personal puede conllevar problemas personales y legales.

En los últimos años, la seguridad en la red de la tecnología de la nube ha tenido que evolucionar significativamente, desde implementar nuevos algoritmos, programas y aplicaciones para proveer seguridad a los datos de sus usuarios, entre otros. En la última década compañías como Sony, Apple y Facebook, han sido atacadas cibernéticamente y los servidores han comprometido la data de los clientes. La tecnología de la nube es una forma de aumentar la capacidad en forma dinámica sin invertir en nuevas infraestructuras y licenciar nuevos programas. La tecnología de la nube ha pasado de ser un concepto de negocio prometedor, a uno de los segmentos de rápido crecimiento de la industria de TI (Tecnología de la información). Sin embargo, a medida que más y más información sobre los individuos y las empresas se colocan en la nube, las preocupaciones están empezando a crecer sobre cuán seguro es su entorno. A pesar de toda la euforia, los clientes empresariales siguen siendo reacios a desplegar su negocio en la tecnología de la nube (Mather, Kumaraswamy y Latif, 2009).

De acuerdo con Gierbolini-Bonilla (2009), la seguridad es uno de los principales problemas que reduce el crecimiento de la tecnología de la nube. Por lo que, las complicaciones con la privacidad de los datos y la protección de datos afectan al mercado. La tecnología de la nube plantea una amenaza a la seguridad de las tecnologías existentes cuando se usa en un entorno de nube. Los usuarios de servicios deben estar atentos a la comprensión de los riesgos de las violaciones en este nuevo entorno. Jin, Dai y Zou (2016) exponen que esta es un modelo para permitir el acceso conveniente a un grupo compartido de recursos informáticos configurables. Por lo que, durante mucho tiempo ha estado a la cabeza de una lista de las diez principales tecnologías estratégicas.

El mayor obstáculo para su desarrollo son los problemas de seguridad y privacidad. Para asegurarla, se deben superar tres desafíos principales: La necesidad de un entorno de ejecución seguro para máquinas virtuales (VM, por sus siglas en inglés) en la tecnología de la nube; el problema de incoherencia de tiempo y estado de las VM; y la necesidad de la alta confiabilidad (Jin, Dai y Zou, 2016).

La tecnología de la nube promovió un cambio de paradigma de la informática. Las aplicaciones científicas y de ingeniería, la minería de datos, la financiación computacional, los juegos y las redes sociales, y muchas otras actividades computacionales y de uso intensivo de datos se beneficiaron de misma. Por ejemplo, en 2011, Apple anunció iCloud, como una alternativa centrada en la red para integrar música, videos, películas e información personal. El contenido que previamente estaba confinado a dispositivos personales, como estaciones de trabajo, computadoras portátiles, tabletas y teléfonos inteligentes, ya no se almacenaría localmente, sino que se compartiría y accedería siempre con el Internet (Marinescu, 2017).

La tecnología de la nube se convirtió en una realidad técnica y social. Solamente se podía especular la evolución de la infraestructura y de las aplicaciones. Por otro lado, las implicaciones económicas, sociales, éticas y legales serían significativas. Los usuarios confiarían en los servicios proporcionados por los grandes centros, almacenarían datos privados y utilizarían software en sistemas que no controlarían. Esto representó un cambio dramático en el diseño de sistemas con grandes cantidades de ciclos de computación y espacio de almacenamiento (Ahmadian, Paya y Marinescu, 2014).

El movimiento de la tecnología de la nube no estuvo exento de escépticos y críticos. Los críticos argumentaban que era solo una

táctica de marketing, en donde los usuarios serían dependientes de sistemas propietarios. Para ellos, el fallo de un sistema tan grande tendría consecuencias significativas para los que dependían de la nube para sus necesidades de computación y almacenamiento. La seguridad y la privacidad eran las principales preocupaciones de los usuarios. Los escépticos cuestionaron lo qué era realmente, cómo difería de otros tipos de sistemas distribuidos a gran escala, y por qué podría ser exitosa (Marinescu, Paya y Morrison, 2014).

Los tres modelos de entrega en la tecnología de la nube, Software as a Service (SaaS), Platform as a Service (PaaS) e Infraestructure as a Service (laaS) continuarían coexistiendo en el futuro previsible. Los servicios basados en SaaS probablemente serían cada vez más populares porque eran más accesibles. Mientras que, los servicios basados en laaS serían del dominio de las personas con experiencia en informática. Si el esfuerzo de estandarización fuera exitoso, se podría ver que las PaaS estaban diseñadas para migrar de una infraestructura a otra y superar las preocupaciones relacionadas con el bloqueo de proveedores (Marinescu, 2017).

Por lo tanto, lograr una seguridad efectiva de la información en la nube no fue un proceso trivial. Durante mucho tiempo, esta responsabilidad de la administración fue un principio fundamental de la buena gestión corporativa durante mucho tiempo. A menudo, las empresas trataban de demostrar que habían logrado la seguridad a través de la garantía. Esta garantía, generalmente se logra mediante el cumplimiento de las normas o mediante las auditorías. Sin embargo, una de las dificultades con la tecnología de la nube fueron los más de 30 organismos que trabajaron en los estándares de seguridad. Aún se está por ver el desarrollo de un estándar de seguridad completamente integral. Ante estos datos, las preguntas de investigación fueron las siguientes:

1. ¿Cómo la tecnología de la nube ha evolucionado en los últimos cinco años?
2. ¿Qué protocolos, configuraciones y encriptación están disponibles en el mercado para asegurar los datos, las informaciones, los programas y las aplicaciones guardadas en la tecnología de la nube de las empresas?
3. ¿Cómo las compañías que proveen el servicio de la tecnología de la nube protegen la confidencialidad de los usuarios?
4. ¿Cuántas capas de seguridad aplican los proveedores de la tecnología de la nube en sus servidores?
5. ¿Cómo los usuarios identifican la seguridad que proveen las compañías de servicios de la tecnología de la nube y sus aplicaciones?
6. ¿Cómo se manejan las fotos, datos e información personal de las bases de datos en las empresas?
7. ¿Qué personas en las empresas acceden a la información de las bases de datos?
8. ¿Qué hacen las empresas con la información obtenida en las bases de datos?
9. ¿Cuáles son los beneficios que trae utilizar la tecnología de la nube?

El Equipo de Investigación de ESET Latinoamérica (2015) redactó un informe para comunicar el estado actual de las amenazas informáticas y proyectar la posible evolución en los próximos años. En los datos, se especifica que para el 2011 hubo una consolidación en cuanto a las redes de computadoras que quedaron a merced de un grupo de ciberdelincuentes. En el 2012, la principal tendencia se relacionó directamente con las amenazas diseñadas para las plataformas móviles. En el 2013 se encontró un crecimiento de códigos maliciosos para dispositivos como el mobile3, los cuales son el principal tema de la privacidad en Internet. Otra tendencia fue la complejidad de estos códigos maliciosos diseñados para los dispositivos Android. Este aumento de códigos al igual que el almacenamiento en la nube ha experimentado una preocupación por la seguridad de los usuarios. Actualmente la tendencia es el uso masivo de la nube en comparación con otros medios tradicionales. La Tabla 1 presenta este crecimiento de la nube en algunas regiones del mundo y la cantidad de datos almacenados (Equipo de Investigación de ESET Latinoamérica, 2015).

Tabla 1. Crecimiento del tráfico en la nube por regiones

Región	2012	2013	2014	2015	2016	2017	Crecimiento
AL	77	117	159	203	249	298	31%
AP	319	505	736	1042	1415	1876	43%
ECO	69	101	140	191	253	325	36%
OMA	17	31	51	77	112	157	57%
NA	469	691	933	1211	1526	1826	32%
EO	225	311	400	501	623	770	28%

(AL: América Latina; AP: Asia Pacífico; ECO: Europa Central y Oriental; OMA: Oriente Medio y Africa; NA: Norteamérica; EO: Europa Occidental) (Equipo de Investigación de ESET Latinoamérica, 2015)

MÉTODOS

El estudio se enmarcó en una investigación con un enfoque cuantitativo. La población (N= 500) fueron las organizaciones que utilizan la nube tecnológica en los pueblos de Arecibo, Hatillo y Barceloneta. El muestreo fue no probabilístico, ya que no se basa en el uso de técnicas de aleatorización para seleccionar los miembros (Creswell y Creswell, 2017). Para esto, se entregó la carta para autorizar la administración del instrumento. Al recibir la autorización, se obtuvo una muestra (n=113) de sujetos con puestos en universidades y comercios. Los participantes en la investigación fueron seleccionados sobre el criterio de que tendrían algo que decir sobre el tema, están dentro del rango de edad y residen en los pueblos de Arecibo, Hatillo y Barceloneta. Los criterios de inclusión son ser mayor de 21 años, tener como mínimo un grado asociado, y al menos un año de experiencia en la tecnología de la nube.

Los participantes fueron informados del propósito del estudio considerando la confidencialidad y el anonimato expuesto en la Hoja de Consentimiento Informado. En esta hoja se requirió la

firma del participante. Al aceptar de manera libre y voluntaria su participación en el estudio, se hizo entrega del cuestionario. La participación en este estudio solo conllevó riesgos mínimos, cansancio, dejadez o aburrimiento. La investigación cuantitativa incorporó el respeto a la diversidad cultural en el estudio del fenómeno. Se instó a la eliminación de los riesgos en el estudio con actitudes respetuosas y democráticas sin juzgar moralmente las vivencias y experiencias de los participantes. El investigador eliminó los riesgos con interacciones que reflejaron los buenos modales, el tacto y la sensibilidad a las narraciones de los participantes. El respeto por la dignidad humana se integró cuando el investigador tuvo una moralidad alta, posee valores y conoce todos los aspectos legales de la investigación con seres humanos. Las variables en una investigación deben ser medibles u observables. Es necesario definir las variables conceptualmente para poder compararlas y llegar a conclusiones. Las definiciones conceptuales provienen de los diccionarios, enciclopedias y libros especializados. Las definiciones de algunas de las variables son las siguientes:

1. Tecnología de la nube- Modelo de la informática que accede información y datos personales por medio del Internet (Fearne, 2015).
2. Seguridad en la tecnología de la nube- subraya restricciones y establece la no violación de la integridad de las leyes de confidencialidad (Chang y Ramachandran, 2015).
3. Protocolos- reglas que permiten a las entidades tener un sistema de comunicación para transmitir información (Raya y Raya, 2008).
4. Configuraciones- elementos considerados como externos e internos que forman parte de un ordenador con características específicas (Raya y Raya, 2008).
5. Encriptación- medida de seguridad basada que codifica la información de forma indescifrable a simple vista (Carbonell, 2015).

En resumen, la variable dependiente es la evolución y seguridad de la tecnología de la nube. Las variables independientes incluyen los protocolos, configuraciones, encriptación, confidencialidad, capas de seguridad, adiestramientos y beneficios en el uso de la tecnología de la nube para las empresas. El instrumento fue un cuestionario estilo Escala Likert creado por el investigador. El cuestionario fue revisado por 7 expertos con grado doctoral, de acuerdo con sus recomendaciones fue distribuido en empresas de la zona norte de Puerto Rico donde se haya verificado que utilizan la tecnología de la nube para brindar servicios. Antes de la administración del cuestionario, se obtuvo la autorización de la organización, y los participantes firmaron el documento de consentimiento informado, el cual se discutió en forma breve de cómo ha evolucionado la tecnología de la nube. La primera parte de cuestionario incluyó los datos demográficos como género, preparación académica, años en la compañía, puesto que ocupa en la compañía y tiempo que lleva usando la tecnología de la nube. La segunda parte presentó 48 premisas relacionadas al uso y la seguridad de la tecnología de la nube. Cada premisa tuvo opciones de contestarse de acuerdo con la escala Likert: Totalmente en Desacuerdo, En Desacuerdo, Ni en desacuerdo ni en Acuerdo, De Acuerdo, Totalmente en Acuerdo. Para obtener la puntuación promedio general, deberán sumarse las puntuaciones de los criterios específicos y dividirse entre el número de ítems en total (Hernández, Fernández y Baptista, 2010).

La investigación contó con la participación de 39 profesionales del género femenino (65.5%) y 39 varones (34.5%). Concerniente a la escolaridad, 59 (52.2%) de los 113 participantes tenían un grado universitario de bachillerato. El restante se distribuyó en: 23.9% maestría, 10.6% un doctorado, 8.8% grado asociado, 3.5% poseen créditos doctorales, y un .9% no contestó la premisa. Respecto a sus años en la compañía, un 49% lleva de 1 a 5 años, otro 16.8% contestó de 6 a 10 años y un 15.9% lleva más de 21 años. Otro 13.3% contestó 11 a 15 años y el restante 4.4% de 16 a 20 años. En el puesto de los participantes se destaca que un 32.7% no contestó; un 15.9% son educadores; 13.3% trabajan en ventas y la misma cantidad se desempeñan como Net Developer.

RESULTADOS

De acuerdo con el análisis estadístico, la mayoría de los participantes contestaron estar de acuerdo en que la tecnología ha evolucionado con los años en expansión, flexibilidad, y reduciendo los gastos operacionales. Contestaron estar de acuerdo en que provee menos costos en la seguridad, y herramientas adecuadas para la empresa. Se reflejó un rango de 4 y medias entre 3.32 hasta 4.32. La desviación fluctuó entre .975 hasta 1.23 (Ver Tabla 2).

Tabla 2. Evolución de la nube tecnológica

	n	Rango	Media	Desv.Est.
Ha evolucionado en los últimos años	113	4	4.30	1.025
Se ha expandido sin control	112	4	3.32	1.133
Ha aumentado su flexibilidad	113	4	3.98	1.052
Ha reducido los gastos	112	4	3.84	.945
Provee menos costos	112	4	3.45	1.161
Provee herramientas	112	4	4.15	1.015

n es la muestra

Para la segunda pregunta: ¿Qué protocolos, configuraciones y encriptación están disponibles en el mercado para asegurar la data, la información, programas y aplicaciones guardadas en la nube de las empresas?; se utilizaron las 6 premisas. De acuerdo a las estadísticas, la moda fue 5 (Totalmente de acuerdo) en todas las premisas. La mediana fluctuó entre 3.96 hasta 4.32 (Ver Tabla 3).

Para contestar la pregunta: ¿Cómo las compañías que proveen el

servicio de la tecnología de la nube protegen la confidencialidad de los usuarios?, se integraron 5 premisas en el apartado nombrado confidencialidad.

Tabla 3. Protocolos de la tecnología de la nube

	n		A	B	C	D	E
	v	m					
La empresa en la que laboro tiene reglas	111	2	4.32	.105	5.00	5	1.105
El protocolo de la empresa instruye	112	1	3.96	.117	4.00	5	1.237
El protocolo exige	113	0	4.22	.099	5.00	5	1.050
La empresa tiene un conjunto	113	0	4.25	.099	5.00	5	1.057
La empresa usa la encriptación	111	2	4.20	.101	5.00	5	1.060
La empresa se rige por un protocolo	113	0	4.32	.092	5.00	5	.975

v: valid, m: missing, A: media; B: error estándar de la media; C: mediana; D: moda; E: desviación estándar

De acuerdo con las estadísticas, las personas están de acuerdo en que la organización protege la confidencialidad, la información personal de las bases de datos es protegida por la empresa en la que laboran y las personas que acceden a la información de las bases de datos firman acuerdos de confidencialidad. Por el contrario, están en desacuerdo en que en el trabajo se pueden acceder los datos sin ninguna seguridad tecnológica y que pudiera perjudicar la confidencialidad (Ver Tabla 4).

Tabla 4. Confidencialidad

	n	Media	Desv.Est.	B
La organización protege la confidencialidad	111	4.24	1.011	.096
En el trabajo se pueden acceder	113	2.20	1.383	.130
El trabajo…pudiera perjudicar la confidencialidad	113	2.65	1.420	.134
La información personal…es protegida	112	4.26	1.046	.099
Las personas que acceden…	111	4.05	1.056	.100

B: error estándar de la media

En la próxima pregunta: ¿Cuántas capas de seguridad aplican los proveedores de la tecnología de la nube en sus servidores?, se obtuvo que los participantes no están de acuerdo ni en desacuerdo (Ver Tabla 5).

En relación con la pregunta: ¿Cómo los usuarios identifican la seguridad que proveen las compañías de servicios de la tecnología de la nube y sus aplicaciones?; los participantes contestaron estar de acuerdo. Los participantes aseguraron que la organización tiene protocolos para asegurar la data, la información, programas y aplicaciones guardadas en la nube; corrige rápidamente cualquier peligro de seguridad tecnológica, aunque resulte costoso; considera los protocolos de seguridad; realiza inspecciones de seguridad tecnológica; investiga los problemas de seguridad tecnológica; provee el equipo de seguridad tecnológica para realizar las tareas y los mantiene informado de los riesgos a los que están expuestos al realizar su trabajo. Por otro lado, no están de acuerdo ni en desacuerdo en que los/las especialistas de seguridad tecnológica siempre están disponibles cuando se necesitan (Ver Tabla 6).

Tabla 5. Capas de Seguridad

	La empresa cuenta con mas de tres	Las capas de seguridad…
Valid	112	111
Missing	1	2
Media	3.76	3.85
B	0.099	0.096
Mediana	4.00	4.00
Moda	3	3[a]
Desv. Est.	1.050	1.011

a. Múltiples modas existen. Se muestra el valor menor.
B: error estándar de la media

Tabla 6. Identificación de la seguridad

	n	Media	Desv. Est.	B
La organización tiene protocolos	111	4.13	1.001	.095
La organización corrige	110	4.09	1.045	.100
La organización considera	112	4.17	0.939	.089
Los especialistas de seguridad…	112	3.86	0.994	.094
La organización realiza	111	3.90	1.035	.098
La organización investiga	112	4.02	1.004	.095
La organización provee	112	4.07	0.975	.092
La organización nos mantiene	111	4.04	1.044	.099

B: error estándar de la media

En la pregunta: ¿Cómo se manejan las fotos, datos e información personal de las bases de datos en las empresas?; se obtuvo que los participantes no están de acuerdo ni en desacuerdo en cuanto a

poder acceder a fotos, datos y/o información personal en las bases de datos. Los participantes están de acuerdo en que se utilizan protocolos en las bases de datos y que las fotos son protegidas por las empresas. Por último, están completamente de acuerdo en que los datos son protegidos por las empresas (Ver Tabla 7).

Tabla 7. Manejo de Datos

	n		A	B	C	D	E	R
	v	m						
Puedo acceder fotos	112	1	3.06	.131	3.00	2	1.390	4
Se utilizan protocolos	112	1	4.13	.092	4.00	4[a]	0.978	4
Las fotos son protegidas	112	1	3.91	.099	4.00	4	1.045	4
Los datos son protegidos	112	1	4.15	.093	4.00	5	0.988	4

a. Múltiples modas existen. Se muestra el valor menor.
v: valid, m: missing, A: media; B: error estándar de la media; C: mediana; D: moda; E: desviación estándar; R: rango

Tabla 8. Acceso a la información

	n	Media	Desv.Est.	B
Las personas acceden	113	2.27	1.376	.129
La información obtenida	112	4.10	1.048	.099
El acceso a la información esta regulado	112	4.13	1.009	.095
El acceso a la información esta en continua revision	112	4.08	0.978	.092
El acceso a la infromacion incluye claves segurdas	112	4.18	0.922	.087
Las claves	113	4.04	1.077	.101

B: error estándar de la media

El análisis de datos para la pregunta: ¿Qué personas en las empresas acceden a la información de las bases de datos?; reveló que los participantes están en desacuerdo en que las personas acceden sin ninguna seguridad a la información en las bases de datos. Por otro lado, están de acuerdo en que la información obtenida es para uso de la organización; el acceso a la información en las bases de datos está regulado; está en continua revisión; y que incluye claves seguras. La misma tendencia se expresó en cuanto a que las claves para la información en las bases de datos son reemplazadas constantemente (Ver Tabla 8).

En la próxima pregunta: ¿Qué hacen las empresas con la información obtenida en las bases de datos?; los participantes contestaron estar de acuerdo en que la información es para uso exclusivo de la empresa. Por lo que, están en desacuerdo en que la información es compartida con otras empresas, que esté accesible para todas las personas de la empresa y que provenga de otras empresas. No están en desacuerdo ni de acuerdo en que está prohibido compartir la información con otras empresas (Ver Tabla 9).

En el último apartado utilizado para contestar: ¿Cuáles son los beneficios que trae el utilizar la tecnología de la nube?; los participantes indicaron estar de acuerdo en que la empresa se ha beneficiado con la tecnología de la nube. La misma tendencia se observó en cuanto a que la tecnología de la nube agiliza las operaciones. No están en acuerdo ni desacuerdo acerca de la tecnología de la nube sea costosa, imprescindible, fácil y se utilice diariamente (Ver Tabla 10).

Tabla 9. Uso de la información

	n	Media	Desv.Est.	B
La información es para uso	112	4.02	1.107	.105
La información es compartida	113	2.70	1.401	.132
La información está accesible	112	2.70	1.381	.130
Está prohibido	113	3.41	1.406	.132
La información proviene	112	2.76	1.364	.129

B: error estándar de la media

Tabla 10. Beneficios

	n	Media	Desv.Est.	B
La empresa se ha beneficiado	110	4.00	1.040	.099
La tecnología agiliza	112	4.17	0.958	.090
La tecnología no es costosa	110	3.47	1.106	.105
La tecnología es imprescindible	111	3.79	1.019	.097
La tecnología es utilizada diariamente	111	3.95	1.021	.097
La tecnología es fácil	112	3.83	1.073	.101

B: error estándar de la media

DISCUSIÓN

El análisis estadístico estableció que los participantes reconocen que la tecnología de la nube ha evolucionado en los últimos años, provee herramientas adecuadas para la empresa y que se tienen reglas en sus sistemas de información. El protocolo de la empresa instruye a qué hacer cuando termina la sesión de conexión y exige estrategias para asegurar la seguridad. La empresa tiene un conjunto de los elementos internos y externos para asegurar la data; usa la encriptación para asegurar la data y se rige por un protocolo para el acceso a la información.

Se pudo establecer que los participantes están de acuerdo en que la tecnología de la nube se ha expandido sin control. Esta ha evolucionado con los años en expansión, flexibilidad, y reduciendo los gastos operacionales. La tecnología de la nube provee menos costos en la seguridad, y herramientas adecuadas para la empresa. Por lo que las organizaciones y/o empresas protegen la confidencialidad, la información personal de las bases de datos es protegida por la empresa en la que laboran y las personas que acceden a la información de las bases de datos firman acuerdos de confidencialidad. Estas empresas tienen protocolos para asegurar la data, la información, programas y aplicaciones guardadas en la nube. Además, corrigen rápidamente cualquier peligro de seguridad tecnológica, aunque resulte costoso; consideran los protocolos de seguridad; realizan inspecciones de seguridad tecnológica; investigan los problemas de seguridad tecnológica; y proveen el equipo de seguridad tecnológica para realizar las tareas. Las empresas mantienen informados a sus empleados acerca de los riesgos a los que están expuestos al realizar su trabajo; utilizan protocolos en las bases de datos y protegen las fotos. En cuanto a la información, se corroboró que es para uso de la organización. El acceso está regulado, en continua revisión e incluye claves seguras. Las claves para la información en las bases de datos son reemplazadas constantemente y son para uso exclusivo de la empresa.

El estudio se limitó a obtener información de 113 profesionales del área norte de Puerto Rico en el tema de la evolución de la seguridad en la nube tecnológica. Estos profesionales residen en el área norte de Puerto Rico en pueblos como Arecibo, Barceloneta y Hatillo. No obstante, los hallazgos en esta investigación deben ser tomados en consideración por las empresas para establecer políticas y prácticas institucionales que aporten a la seguridad en la tecnología de la nube. Además, se recomienda aplicar este estudio en otros escenarios para confirmar los hallazgos aquí presentados, ampliar la muestra que sea más significativa, y contribuir a la identificación de las necesidades específicas que puedan afectar a las empresas. Finalmente, se recomienda en futuros estudios similares se considere lo siguiente: realizar estudio con una muestra más alta y en diferentes tipos de empresas; capacitar a las empresas sobre la seguridad en la tecnología de la nube y ofrecer charlas o conferencias a las empresas acerca de la seguridad en la tecnología de la nube.

Aunque las nubes son cada vez más populares, se ha podido observar que algunas cosas pueden "salir mal" cuando se confía en un proveedor de nube con sus datos. Proporcionar defensas para estos es un área activa de investigación. Se presentaron los datos de una encuesta de las situaciones que pueden ocurrir en las empresas. Sin embargo, estas soluciones son, en este momento, académicas. Todavía hay preguntas sobre qué tan bien estas protecciones pueden funcionar en la práctica y, además, qué tan fáciles de usar pueden ser. Por último, todavía hay que ver qué tan popular será el almacenamiento de datos en las nubes, y qué protecciones los usuarios elegirán usar.

En muchos escenarios de aplicaciones, como los de empresas u organizaciones, el acceso de los usuarios a los datos suele ser selectivo y altamente diferenciado. Diferentes usuarios disfrutan de diferentes privilegios de acceso con respecto a los datos. Cuando los datos se subcontratan a la nube, es fundamental la aplicación de un acceso a datos seguro, eficiente y confiable entre una gran cantidad de usuarios. Tradicionalmente, para controlar la diseminación de datos sensibles a la privacidad, los usuarios establecen un servidor confiable para almacenar datos localmente en forma clara, y luego controlan ese servidor para verificar si los usuarios solicitan a los usuarios una certificación adecuada antes de permitirles acceder a los datos. Desde el punto de vista de la seguridad, esta arquitectura de control de acceso ya no es aplicable cuando se subcontratan datos a la nube. Debido a que los usuarios de datos y los servidores en la nube no se encuentran en el mismo dominio de confianza, es posible que ya no se confíe plenamente en el servidor como un monitor de referencia omnisciente para definir y aplicar políticas de control de acceso y administración de detalles del usuario. En caso de compromiso del servidor o posibles ataques internos, los datos privados de los usuarios podrían incluso estar expuestos.

Una implicación del estudio es desarrollar un enfoque para imponer el acceso a los datos sin depender de los servidores de la nube y cifrar los datos de una manera diferenciada y divulgar las claves de descifrado correspondientes solo a los usuarios autorizados. Sin embargo, este enfoque generalmente adolece de graves problemas de rendimiento y, especialmente cuando un gran número de usuarios bajo demanda desean un control de acceso a datos detallado. Se insta a las empresas a trabajar en cómo realizar un diseño de control de acceso detallado que aproveche al máximo la riqueza de recursos de la tecnología en la nube. De esta forma, los usuarios de datos podrían delegar de forma segura a la nube las cargas de trabajo de administración de datos, el manejo frecuentes actualizaciones de privilegios de acceso de usuarios en grandes sistemas dinámicos, al tiempo que se preserva la confidencialidad de los datos subyacentes.

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Methicillin-resistant *Staphylococcus aureus* and the effectiveness of vancomycin in hospitals and nursing homes

Staphylococcus aureus resistente a la meticilina y la efectividad de la vancomicina en hospitales y hogares de ancianos

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ABSTRACT

***Staphylococcus aureus* is an opportunistic pathogen, frequently found in the human body asymptomatically. Methicillin-resistant *Staphylococcus aureus* (MRSA) are resistant to methicillin and essentially all other beta-lactam antibiotics. The objective of this manuscript is to present the effectiveness of vancomycin in the treatment of MRSA as well as the prevalence in hospitals and nursing homes in the United States (US) and Mexico. The present study shows high incidence of MRSA in different hospital areas and nursing homes as well as by population and nationality. It is important that medical researchers and scientists can create awareness of this problem and promote more research on the creation of new antimicrobials.**

RESUMEN

Staphylococcus aureus es un agente patógeno oportunista que con frecuencia se encuentra en el cuerpo humano de forma asintomática. *Staphylococcus aureus* resistente a meticilina (MRSA, por sus siglas en inglés) es resistente a meticilina y esencialmente a todos los antibióticos betalactámicos. El objetivo de este manuscrito es dejar de manifiesto la efectividad de la vancomicina en el tratamiento de MRSA, así como su prevalencia en hospitales y hogares de ancianos en los Estados Unidos (E.U.) y México. El presente estudio muestra una alta incidencia de MRSA en las diversas zonas hospitalarias y hogares de ancianos al igual que por poblacionales y nacionalidad. Es importante que los investigadores médicos y los científicos creen conciencia de este problema y promuevan más investigaciones para la creación de nuevos antimicrobianos.

KEYWORDS MRSA, antimicrobial, vancomycin

PALABRAS CLAVE MRSA, antimicrobiano, vancomicina

INTRODUCTION

Resistance to antibiotics is the new challenge of medical researchers, and consequently the search for new antibiotics as a result of the resistance presented by microorganisms specifically *Staphylococcus aureus* resistant to penicillin. In this manuscript we evaluate it in the north american and mexican state populations. There are several problems with antibiotics; diseases in the present are often not diagnosed in time and it is becoming more difficult to treat them because some antibiotics are losing effectiveness due to their excessive or improper use (Agencia EFE, 2017).

In search of new antibiotics, the *World Health Organization* (WHO) tries to promote research around dangerous bacteria. The critical priority groups include multi-resistant bacteria, which are especially dangerous in hospitals, nursing homes and among patients who need to be treated with devices such as ventilators and intravenous catheters. These include the (ESKAPE) group, *Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species, which can cause serious and often lethal infections (Agencia EFE, 2017).

Since the discovery of penicillin in 1928, techniques have been developed to study the effectiveness of antibiotics in different species of bacteria. One of these tests is the disk diffusion test that has been used for more than 70 years in microbiology laboratories (Soto, Gonzalez, & Ortiz, 2015). By 1959, methicillin, the first semisynthetic penicillin was obtained by altering the chemical structure of natural penicillin, which was rapidly reaching 90% resistance levels. Methicillin became the agent of choice for the treatment of infection by this beta-lactamase producing bacteria due to its ability to evade the actions of beta-lactamases (Murillo-

Llanes, González-Ibarra, Velarde-Felix, & Alejo-Armenta, 2016).

MRSA are prevalent bacterial pathogens that cause both health care and community-associated infections. Increased resistance to the prescribed antibiotics has made MRSA a serious threat to public health worldwide (Murillo et al., 2016). This review article is focused in the emergence resistance of MRSA and the use of Vancomycin as a treatment. The presence of MRSA is demarcated in hospitals and nursing homes in two countries with a large population in the E.U. and Mexico. This study shows a high incidence of MRSA in the different hospital areas, nursing homes as well as by population and nationality.

Antibiotic treatment for MRSA

MRSA is a common cause of infection in community and health care settings (Batina, Crnich, Anderson, & Dofter, 2016). In the past, before the origin of the antibiotics, infections from common opportunistic pathogens such *S. aureus* had a higher risk of mortality rates. Although, new antibiotic can provide a temporary solution, they are prone to the development of resistance profiles. The pattern of antibiotic resistance with respect to age of patients depended on the antibiotic mode of action. This resistance mutation rates can be significantly altered for a given antibiotic in their concentration, use or misuse (Garcia, Delorme & Nasr, 2017).

The use of methicillin in medicine has been replaced by newer antibiotics. In clinical practice, MRSA indicates resistance to oxacillin and analogue of methicillin and cefoxitin a second generation cephamycin. A few antibiotics that also present resistance besides vancomycin are: fluoroquinolone, rifampin, tetracycline and sulfamethoxazole-trimethoprim. Being fluoroquinolone resistance the one that displayed a gradual and steady increase among age patients. Sulfamethoxazole-trimethoprim maintain a low resistance percentage across all age classes (Batina et al., 2016).

There are various alternatives to vancomycin in MRSA treatment. A glycopeptide with a similar mode of action is teicoplanin. It is a bactericidal antibiotic, it inhibits bacterial cell wall synthesis by the blockage of glycopeptide polymerization (Lee & Howden, 2015). With higher and appropriate dosing, it can be compared with Vancomycin, this was shown by recent data and meta-analysis. Teicoplanin is associated with lower rate of adverse events. On the contrary, in patients with MRSA pneumonia and bacteremia treated with higher teicoplanin MICs have been associated with increased mortality and poor clinical outcomes (Holmes, Tong, Davis, & Van, 2015).

Another good alternative is memisynthetic lipopoly peptide analogues of vancomycin, which are dalbavancin, oritavancin and telavancin. They have a heptapeptide core, which enables the inhibition of cell wall synthesis. They are also bactericidal and destabilize cell membrane (Lee & Howden, 2015). These semisynthetic lipopolypeptide have a prolonged half-life and increased activity against gram-positive cocci due to its lipophilic side chain. *S. aureus* membrane barrier function is affected by telavancin and oritavancin. These three drugs also present activity against vancomycin -resistant *S. aureus* (VRSA) (Holmes et al., 2015).

Telavancin compared with vancomycin has a 10-fold more potency. This antibiotic shows *in vitro* activity against vancomycin intermediate *Staphylococcus aureus* (VISA), MRSA, linezolid nonsusceptible and daptomycin non-susceptible S. *aureus*. Compared with linezolid and vancomycin, telavancin demonstrated superior bactericidal activity shown in *in vitro* studies of hVISA clinical strains. Various concerns were raised because there was no additional benefit over vancomycin, increased QT prolongation, potential increased nephrotoxicity compared with vancomycin and possible impurities in the manufacturing of the drug (Holmes et al., 2015).

In the United States telavancin is used for hospital acquired pneumonia due to gram-positive bacteria in which alternate treatments (Holmes et al., 2015). This medication has a black box warning due to the its negative effects to the kidneys. Other adverse side effects were thrombocytopenia and an elevated serum creatinine.

Another antibiotic that is a lipoglycopeptide derived from teicoplanin is dalbavancin. This medication can be administered once a week due to its increased terminal half-life up to 250 hours. Dalbavancin compared with daptomycin and vancomycin has an 8 to 16-fold more activity against VISA and MRSA (Holmes et al., 2015). In a study dalbavancin was equal and there were few adverse effects mainly gastrointestinal complications and pruritus (Holmes et al., 2015).

Oritavancin is a bactericidal antibiotic with extensive tissue distribution with an increased half-life up to 393. Studies to compare its potency are not clear since the drug sticks to to plastic tubes and microdilution wells. It affects VISA, VRSA and MRSA. For the treatment of bacteremia, endocarditis and invasive infection there are no clinical trials. Oritavancin showed non-inferiority compared with vancomycin for the primary composite endpoint of early clinical evaluation at 48 to 72 hours (Holmes et al., 2015).

Anti-MRSA cephalosporins, ceftaroline and ceftobiprole, show *in vitro* activity against MRSA. This antibiotic is bactericidal and inhibit bacterial wall synthesis and activation of autolysis due to inactivation of penicillin-binding proteins (Lee & Howden, 2015). Compared with Vancomycin or glycopeptides, ß-lactams are associated with improved clinical outcomes.

Ceftaroline, an anti-MRSA and VISA cephalosporin, is approved

in the U.S. for the treatment community-acquired pneumonia (CAP) and acute bacterial skin and skin structure infections (ABSSSI). In patients with incessant MRSA bacteremia, salvage therapy and ceftaroline was effective. Several adverse side effects were reported: rash, headaches and infusion-related symptoms. Also, formation of urinary crystals, elevation in liver transaminases and creatinine kinase. Ceftaroline resistance has been reported in MRSA, and other (VISA, hVISA, daptomycin nonsusceptible and linezolid nonsusceptible *S. aureus)* laboratory isolates. These strains of *S. aureus* have mutations in PBP2a, this leads to reduced efficacy, lower binding affinity and higher ceftaroline MICs (Holmes et al., 2015).

Another anti-MRSA cephalosporin is ceftobiprole. It has larger spectrum of activity than ceftaroline. It retains activity against more resistant *S. aureus* strains. In a study, patients with MRSA pneumonia treated with ceftobiprole saw microbiological eradication and favorable rates of clinical cure. (Holmes et al., 2015). Adverse side effects are similar to does showed by other cephalosporins.

Daptomycin is a bactericidal cyclic lipopeptide antibiotic. It has a rapid membrane depolarization and efflux of potassium, due to its calcium-dependent binding to the cytoplasmic membrane (Holmes et al., 2015). This antibiotic shows concentration-dependent bactericidal activity (Lee & Howden, 2015). Daptomycin leads to rapid cell death because it arrests protein synthesis, RNA and DNA. One of the disadvantages is that daptomycin is inactivated by pulmonary surfactant and cannot be used in used in pneumonia. In cerebrospinal fluid, this antibiotic has poor penetration which can improve the setting of inflamed meninges (Holmes et al., 2015). It shows activity against MRSA and VRSA. If vancomycin therapy fails daptomycin is used as a primary choice, especially in infections with high Vancomycin MICs. Daptomycin resistance has been linked with previous use of vancomycin and retained prosthetic devices. The Infectious Diseases Society of America guidelines for MRSA infections recommends that if the patient suffering from complicated bacteremia has been treated with Vancomycin and failed, if daptomycin is to be used it has to be combined with another agent (Holmes et al., 2015).

Linezolid is another antibiotic used against MRSA, it is bacteriostatic. It is an oxazolidinone that prevents the formation of the 70s-initiation complex and shows activity against MRSA. (Holmes et al., 2015). Tedizolid is an oxazolidinone engineered to improve efficacy and bioavailability and to decrease its toxicity compared with linezolid. In contrast to linezolid it needs to be administered once daily and it 4 to 16 times greater potency. This antibiotic shows activity against linezolid nonsusceptible *S. aureus*. Tedizolid shows less gastrointestinal problems and myelotoxicity than linezolid. One problem that can arise is that at clinical relevant doses, the risk of serotonergic syndrome is negligible due to lack of monoxidase inhibition (Holmes et al., 2015).

Quinupristin/dalfopristin (QD) is an antibiotic that combines two semisynthetic streptogramin. This antibiotic inhibits bacterial protein synthesis by binding to the 50s-bacterial ribosome in two sequential steps. The combination of quinupristin /dalfopristin is synergistic and bactericidal, each drug alone is bacteriostatic against susceptible gram-positive organisms including MRSA. In animal trials QD showed mixed results, rapid bactericidal activity in a *S. aureus* mouse endocarditis but showed decreased results to Vancomycin in MRSA rabbit endocarditis model and both rabbit arthritis model (Holmes et al., 2015).

Tigecycline is an antibiotic derived from minocycline, a parenteral glycylcycline. In 30 to 40% of treated patients with tigecycline showed vomiting and nausea. Tigecycline is highly active against MRSA isolates in *in vitro*. In a MRSA rat thigh infection model, tigecycline has activity similar to Vancomycin against MRSA. This antibiotic is similar to teicoplanin in rabbit osteomyelitis model. In 2010, the FDA issued a safety warning and in a 2013 a black box warning, due to an increased risk of mortality in patients in treatment with tigecycline compared with other antibiotics (Holmes et al., 2015).

As a summary, we list some of the most importants antibiotics mentioned above with their characteristics (Table 1). All the antibiotics mentioned were acquired from (Holmes et al., 2015).

Vancomycin treatment for MRSA

In the early 1950's recognition of emerging antibiotic-resistant strains of *S. aureus* began (Lee & Howden, 2015). As a response, pharmaceutical companies began screening programs for antibiotics with high specificity and activity against staphylococci. The most common antibiotics used against MRSA are vancomycin and daptomycin (Hassoun, Linden and Friedman, 2017). Vancomycin is produced by *Streptococcus orientalis* and is a tricyclic glycopeptide antibiotic. It is used in hospital, to combat infections by Gram-positive bacteria including MRSA, penicillin- resistant pneumococci and in patients that are allergic to cephalosporins and penicillin (Bruniera et al., 2015). Its administration is intravenously since little is absorbed in the gastrointestinal tract.

Vancomycin became the standard treatment for MRSA infections for decades after its development. In 1958 due to studies reporting adverse effects of vancomycin including infusion reaction, ototoxicity and nephrotoxicity, its clinical use was limited due to these effects (Lee & Howden, 2015). Vancomycin 's utility is restricted by its low tissue penetration, decreased bactericidal activity and escalating reports of treatment failure and resistance (Hassoun, Linden & Friedman, 2017). In the 1970s it was determined that some of the adverse effects were due to impurities that were eliminated. Vancomycin became a regular treatment for

S. aureus in 1980s.

Table 1. List of antibiotic treatments for MRSA

Antibiotic	Characteristics
Vancomycin	Is produced by *Streptococcus orientalis* and is a tricyclic glycopeptide antibiotic. It's used in hospital, to combat infections by Gram positive bacteria including MRSA
Teicoplanin	Is a bactericidal antibiotic, it inhibits bacterial cell wall synthesis by the blockage of glycopeptide polymerization.
Dalbavancin Oritavancin Telavancin	Analogues of Vancomycin, they have a heptapeptide core, which enables the inhibition of cell wall synthesis
Ceftaroline	Is an Anti-MRSA cephalosporin? Has high activity against daptomycin nonsusceptible *S. aureus*, MRSA, MSSA, hVISA and VISA.
Ceftobiprole	Anti-MRSA cephalosporin. Retains activity against more resistant S. aureus strain including ones with increased Vancomycin.
Daptomycin	Is a bactericidal cyclic lipopeptide antibiotic.
Linezolid	Is a bacteriostatic, prevents the formation of the 70s-initiation complex and show activity against MRSA.
Tedizolid	Is an oxazolidinone engineered to improve efficacy and bioavailability and to decrease its toxicity compared with linezolid.
Quinupristin/ Dalfopristin (QD)	Inhibits bacterial protein synthesis by binding to the 50s- bacterial ribosome in two sequential steps. Each drug alone os a bacteriostatic against susceptible gram-positive organism including MRSA.
Tigecycline	Is derived from minocycline, a parenteral glycylcycline.

Due to *mecA*, a gene that encodes modified penicillin-binding protein (PBP) 2a, MRSA exhibits β-lactam resistance. It allows ongoing cell wall synthesis with PBP 2a as a surrogate transpeptidase, due to its significant reduced binding affinity to β-lactam antibiotics. The worldwide spread of MRSA is due to the carriage of *mecA* on a mobile genetic element, staphylococcal chromosomal cassette *mec* (SCC*mec*) (Lee & Howden, 2015).

In the 1990s an epidemiological discriminator between the location of MRSA acquisition (community or hospital) was a distinct molecular group. In the 2000's, relationship between the molecular characteristics and location of disease onset diminished. Different isolates disseminated in the community and were implicated in nosocomial outbreak (Lee & Howden, 2015).

The first clinical strain of *S. aureus* that showed reduced susceptibility to vancomycin (MIC 8 μg/ml) was identified in 1997. It was named Mu50 and classified as Vancomycin - intermediate *S. aureus* (VISA). Later another strain of *S. aureus*, Mu3, was isolated that was identical to Mu50 on pulse field gel electrophoresis. Mu3 showed subpopulations that grew within the intermediate range with a vancomycin MIC of only 3 μg/ml, susceptible at that time. The isolates that demonstrate this became known as heteroresistant VISA (hVISA). In 2006 the Clinical Laboratory Standards Institute (CLSI) in US decreased the vancomycin MIC breakpoints for *S. aureus* due to the evidence that failure of vancomycin therapy was associated with strains of hVISA and VISA (Lee & Howden, 2015).

In 2002 was reported the first clinical report of VRSA of high level, MIC 1024 μg/ml. This high level VRSA was isolated from a dialysis catheter tip. The patient was treated with rifampicin and vancomycin for chronic diabetic foot ulcers and a prosthetic, arteriovenous graft-associated MRSA bacteremia. From both sites were isolated VRSA and Vancomycin -resistant *Enterococcus*. The enterococcal vancomycin resistance element *vanA* mediated the resistance in both organisms. DNA sequencing was performed in both organisms and it was identical; this suggested that there was a transfer of locus from *Enterococcus* to *S. aureus*. Studies later on determined that the transfer was transposon mediated (Lee and Howden, 2015).

Due to the uncertainties and adverse side effects of vancomycin more studies were performed. In which nephrotoxicity was correlated when the common doses of vancomycin were used for MICs ranging from 0.5 to 2 μg/ml. *S. aureus* strains with an MIC of 2 μg/ml treated twice a day with vancomycin 2 g had a probability of target accomplishment of 57% and ≥ 35% probability of nephrotoxicity. To attain a likelihood of target attainment of at least 80%, with a predictable 10% minimum risk of nephrotoxicity in a MIC of 1 μg/ml a daily dose of ≥ 3 g was imperative when a creatinine clearance was in the lesser range of normal. (Lee and Howden, 2015).

Research from 1996 to 2011 showed that independent from the MIC methodology or the source of infection treatment failure was greatly associated with vancomycin MIC. Increased mortality risk is associated with a MIC of ≥ 2 μg/ml for MRSA. An independent predictor of mortality was found to be a vancomycin MIC of > 1.5

µg/ml in a study of 532 patients with *S. aureus* bacteremia. There are various indirect predictors of mortality: hospital onset bacteremia and age (Lee and Howden, 2015).

Vancomycin with combined therapy has been in use since the 1970s. Accelerated development of rifampicin resistance is the result of monotherapy against *S. aureus*, this is one of the various reasons for recommending combination therapy. Rifampicin is recommended as an adjunctive in device-associated infection for its biofilm activity and tissue penetration. The treatment for MRSA prosthetic valve endocarditis is vancomycin and gentamicin, according to Clinical *Practice Guidelines by the Infectious Disease Society of America for the Treatment of MRSA Infections in Adults and Children*. Rifampicin dosage should also have added to the treatment. This guideline also suggests the addition of rifampicin to vancomycin for central nervous system infections and to vancomycin or daptomycin in osteomyelitis (Lee and Howden, 2015).

Nonetheless, recent studies suggest that these combination therapies predispose a reduction of glycopeptide susceptibility and treatment failure (Lee and Howden, 2015). In a recent study in which vancomycin was compared to vancomycin plus rifampicin for MRSA treatment in Intensive Care Unit, the failure of vancomycin against emerging rifampin resistance was clearly showed (Lee and Howden, 2015). This study had issues: the trough level of vancomycin was not the recommended and design issues, which questions the study (Lee and Howden, 2015). A 34% of the patients who received vancomycin plus rifampicin developed rifampicin resistance. Fourteen days into the study, both subgroups developed poor clinical cure rate.

Telavancin is a new lipoglycopeptide antibiotic that has good activity against MRSA. It has shown activity against vancomycin resistance, VISA, hVISA and its dosage is a once a day administration (Keynan & Rubinstein, 2013).

MRSA prevalence in hospitals

In the present, MRSA is a major global cause of morbidity and mortality, increasingly a cause of nosocomial and community onset infection with unknown national scope and magnitude. To mid-1990s, MRSA was largely a healthcare associated pathogen, causing infection predominantly in people with frequent or recent contact with healthcare facilities (healthcare associated MRSA [HA-MRSA]). In general hospital in US, MRSA carriage with both asymptomatic and symptomatic is estimated at 6-12% patient populations by other side estimated 9-24% (Hudson et al., 2013) in intensive care units (ICUs).

Furthermore, community associated MRSA (CA-MRSA), which often causes infections among healthy children and young adults with no exposure to the healthcare setting, has become increasingly prevalent across the globe, particularly in the US. CA-MRSA has caused outbreaks in the hospital setting since 2003 (Hudson et al., 2013), often in pediatrics and obstetrics where (HA-MRSA) prevalence is low and community influx of patients without prior healthcare exposure is common.

The *National Hospital Discharge Survey* used data to calculate the number of US hospital discharges listing *S. aureus* specific diagnoses. From 1999 to 2000, an estimated 125,969 hospitalizations with a diagnosis of MRSA infection occurred annually, including 31,440 for septicemia, 29,823 for pneumonia, and 64,706 for other infections, accounting for 3.95 per 1,000 hospital discharges (Hudson et al., 2013).

S. aureus is a major cause of infection in both healthcare and community settings. *S. aureus* is also a frequent cause of community associated infections, particularly skin and soft tissue infections. Although most community onset infections are treated in the outpatient setting, some invasive infections, including bacteremia, septic arthritis, toxic shock syndrome, osteomyelitis, and endocarditis, have devastating complications and may require hospitalization specifically in United States (Kuehnert et al., 2005).

In the last 20 years, MRSA has spread throughout the world in healthcare settings, leading to an increased reliance on vancomycin for empiric treatment (Kuehnert et al., 2005). Recently, *S. aureus* resistance to vancomycin, the last commonly used antimicrobial drug to which this organism was considered uniformly susceptible, has emerged (Chang et al., 2003).

MRSA strains are prevalent bacterial pathogens that cause both health care and community associated infections. Increased resistance to the prescribed antibiotics has made MRSA a serious threat to public health worldwide (Murillo et al., 2016).

To mention some findings that are already exposed in our review article we can say that in general hospitals or specialties such as the intensive care unit both in Mexico and the United States exhibit show *S. aureus* strains resistant to antibiotics. In Mexico, a study of more than 1,500 samples collected from July 30, 2004 to July 4, 2007 including different areas of the hospital, such as: general surgery, internal medicine, neurosurgery and in the intensive care unit has been done. (Murillo et al., 2016). Of a total of 1,511 samples 206 (13.63%) were positive for *S. aureus*; 27 (13.10%) of central venous catheter, 36 (17.47%) of wound and ulcers, 70 (33.98%) of sputum, 32 (15.53%) of blood cultures, 13 (6.31%) of third space fluid (cerebrospinal fluid, ascitis, pleural fluid, pericardial or peritoneal fluid), foley catheter 24 (11.65%) and other sites 4 (1.94%) (Murillo et al., 2016). The proportion of positive cultures for *S. aureus* according to the service was 52 of 374 (13.9%) samples from the intensive care unit (ICU), 58 of 415 (13.79%) from general surgery, 75 of 550 (13.63%) from internal medicine and 21 of 172 (12.20%) of neurosurgery. Of the sites of infection with positive cultures for *S. aureus* in the ICU, 4 (7.69%)

were central venous catheter, 2 (3.85%) for sores and wounds, 33 (63.46%) sputum, 10 (19.23%) for blood cultures, 2 for the third space fluid and 1 for foley tip (Murillo et al., 2016).

S. aureus was identified in sputum samples in 63.43% of cases, and of these, 73.52% were methicillin resistant. In their study, they tried to find antimicrobial resistance patterns in tracheal aspirates of patients with ventilator-associated pneumonia in an intensive care unit of a hospital in Mexico. They found a frequency of *S. aureus* of 24% and in turn reported a frequency of 70% methicillin resistance. (Murillo et al., 2016).

Recently, community and hospital acquired infections with *S. aureus* have increased and raised antibiotic resistant isolates. A total of 1,116 *S. aureus* isolates were produced and MRSA to 21% of all *S. aureus* isolates between 2009 and 2014. According to the results of susceptibility tests of all isolates of *S. aureus*, they have been identified as sensitive to vancomycin, daptomycin, linezolid, and levofloxacin. The highest percentage of methicillin resistance was determined as 30% in 2009, and the resistance was determined to have decreased in subsequent years (20%, 16%, 13%, 19%, and 21%) compared to the rates during 2010-2013 ($p < 0.01$); no statistically significant difference was found in MRSA isolates between 2009 and 2014 ($p > 0.05$). (Ragbetli, Parlak, Bayram, Guducuoglu, & Ceylan, 2016).

S. aureus presents a historical sequence as one of the most successful and adaptable human pathogens. Its advantageous ability to acquire resistance to antibiotics has contributed to its appearance as an important pathogen in a variety of environments. In the pre-antibiotic era, *S. aureus* infections were associated with a very high mortality rate throughout history (Table 2) (Sampathkumar., 2007).

By the 1980s, MRSA had been firmly established in US hospitals and rates of infection with MRSA have continued to increase. In the big US hospitals MRSA rates (the proportion of all isolates of *S. aureus* that are MRSA) increased from 4% in the 1980s to 50% in the late 1990s. According to the Surveillance Data National Nosocomial Infections, the increase in MRSA rates in the intensive care units was even higher, reaching 60% in 2003. Currently, the 5 main MRSA clones represent approximately 70% of the MRSA isolates in hospitals in the United States, South America and Europe (Sampathkumar., 2007).

Traditional risk factors for MRSA acquisition include prior hospitalization, use of antibiotics, residence in long-term care facilities, and long-term hemodialysis. The increased use of Vancomycin to treat MRSA led to the emergence of *S. aureus* with intermediate resistance to vancomycin (VISA) and then to *S. Aureus* vancomycin -resistant (VRSA) in the 1990s. Fortunately, infections VISA and VRSA have been sporadic, and intensive infection control measures have ensured that they do not circulate widely in healthcare settings (Sampathkumar., 2007).

Table 2. Timeline of *S. aureus* infections.

Year	Event
1940	Penicillin introduced
1942	Penicillin-resistant *S. aureus* appears
1959	Methicillin introduced; most *S. aureus* strains in both hospital and community settings are penicillin resistant
1961	MRSA appears
1963	First hospital outbreak of MRSA
1968	First MRSA strain in US hospitals
1970s	Clonal spread of MRSA globally, very high MRSA rates in Europe
1982	4% MRSA rate in the United States
1980s, early	Dramatic decreases in MRSA rates due to search-and- destroy programs in Northern Europe
1990s	By 1999, <1% MRSA rate in the Netherlands; that rate has been sustained to date despite increasing MRSA rates in other parts of the world
1996	Vancomycin -resistant *S. aureus* (VRSA) reported in Japan
1997	Approximately 25% MRSA rate in US hospitals; Vancomycin use increases; Vancomycin-intermediate *S. aureus* (VISA) appears; serious community-acquired MRSA (CA-MRSA) infections reported; pediatric deaths reported
2002	First clinical infection with VRSA in the United States
2003	MRSA rates continue to increase; approximately 60% MRSA rate in intensive care units; outbreaks of CA- MRSA (predominantly EE.UU. 300 clone) reported in numerous community settings and also implicated in hospital outbreaks
2006	>50% of staphylococcal skin infections seen in emergency departments caused by CA-MRSA HA MRSA rate continues to increase Distinction between HA-MRSA and CA-MRSA on epidemiological basis becomes increasingly difficult
2007	The Year of MRSA? Report of active, population- based surveillance for invasive MRSA done in 2004-2005 estimates 95,000 invasive MRSA infections and 19,000 deaths from MRSA per year Continued reports in the medical literature and the lay press about severe CA-MRSA infections Several states pass or are considering

	legislation regarding control of MRSA and public reporting of MRSA rates Strategies to control MRSA, including public reporting of MRSA infections, are hotly debated; "staph" and MRSA become household words

There is a difference between HA-MRSA and CA-MRSA in the editorial article of (Sampathkumar., 2007). The strains HA-MRSA and CA-MRSA carry different types of genetic complexes known as *staphylococcal chromosome cassette* (SCC*mec*), which contain the *mecA* gene that confers resistance to methicillin. MRSA strains acquired in healthcare have SCC*mec* types I, II and III and tend to be multiresistant. Thus, causing infections in the blood and postoperative wounds along with nosocomial pneumonia in hospitalized patients.

On the other hand, strains of CA-MRSA that have SCC*mec* type IV and V and generally cause skin and soft tissue infections in children and adults living in communities. The most common clinical presentations are boils, superficial abscesses and boils that are often mistakenly attributed to spider bites. In some metropolitan areas, CA-MRSA accounts for 80% of all *S. aureus* infections observed in emergency services (Sampathkumar., 2007).

Other researchers conducted a study of MRSA and SCC*mec* in bacteria along the mexican border in southern Texas. Between September and December 2008, 375 samples from previous nares were collected by students attending the *University of Texas-Pan American* (UTPA) and cultivated for MRSA. The easy access of the Texas border community to antibiotics in Mexico without a prescription, and the strong partition in SCC*mec* types between MRSA and non-*S. aureus* bacteria suggests that this border region of Texas may be especially suitable for the study of emerging SCC*mec* types, their horizontal transfer and perhaps other aspects of antibiotic resistance in bacteria. It has been shown that an increase in antibiotic resistance occurs in the presence of SCC*mec*. Fifty-seven bacterial isolates from 375 nasal swabs were maintained for further analysis that included the suspicion of MRSA and other bacteria containing SCC*mec* (Ammons et al., 2009).

Prevalence of S. aureus in skin and nose was evaluated in a population study during 2001-2002 in the United States. (Sampathkumar., 2007) It showed nasal colonization with *S. aureus* and MRSA in 31.6% and 0.84%, respectively, that is, approximately 2.3 million people colonized by MRSA in the United States. United. On the other hand, it is shown that women, people over 65 years, people with diabetes mellitus or those who have been in long-term care in the last year are more likely to be colonized with MRSA. Insulin-dependent diabetes mellitus, long-term dialysis, intravenous drug abuse, repeated allergy injections, liver cirrhosis, liver transplantation, human immunodeficiency virus infection and people undergoing hospitalization are the most exposed to MRSA (Sampathkumar., 2007).

Regarding prevention and epidemiology in hospitals, a study of 50 hospitals in the United States found no significant differences in the rates of *S. aureus* bacteremia between the medium size hospitals (58% of *S. aureus* susceptible to methicillin [MSSA]; 42% of MRSA) and large hospitals. However, the proportion of *S. aureus* bacteremia caused by MSSA was higher in medium sized hospitals and did not correlate with MRSA bacteremia. (Fakih et al., 2018). Also, they sought to determine whether bacteremia by *Hospital-Onset MRSA or Hospital-Onset S. aureus* (HO-MRSA) or (HO- *S. aureus*) would better reflect the presence of invasive *S. aureus* in a large health system, specifically depending on the size of the hospital. Hospital initiated MRSA bacteremia has been used as a substitute for invasive MRSA acquired at the hospital.

Historically, MRSA bacteremia has been the focus of research and has been associated with poorer outcomes and higher mortality; However, MSSA bacteremia may be more frequent in hospitals. By measuring only bacteraemia by HO-MRSA, a significant portion of patients at risk of damage by *S. aureus* can be overlooked (Fakih et al., 2018).*S. aureus* bacteremia initiated in the hospital may provide a better measure to assess the risk of invasive *S. aureus* in the hospital setting and could mitigate the prevalence factor of MRSA. These findings are important for policy decisions related to the definition of a condition acquired in the hospital (Fakih et al., 2018).

The impact of MRSA in colonized patients is more likely to develop colonized infections with methicillin-sensitive *S. aureus* (MSSA). MRSA infections prolong hospital stays (by an average of 10 days) and are associated with a 2.5 times higher mortality rate and an increase in medical care costs. A diagnosis of *S. aureus* infection represents an estimated 292,000 hospitalizations per year in the United States. In 2005, approximately 94,000 people were diagnosed with invasive (ie, serious) MRSA infections, and an estimated 19,000 died. Of these MRSA infections, 86% were acquired health services and 14% were acquired in the community.1 The annual cost of treating MRSA in hospitalized patients in the United States is estimated at between $ 3.2 and $ 4.2 billion (Sampathkumar., 2007).

MRSA represents a serious threat to the health of hospitalized patients. Attempts to reduce the spread of MRSA have largely depended on hospital hygiene and patient isolation. Although *S. aureus* is asymptomatic in 30% of healthy adults (the vast majority is MSSA), it is an important cause of invasive disease among hospitalized patients. In this situation, MRSA is limited to *"epidemic"* behavior; long periods without MRSA are marked by short outbreaks of infection, often traceable to imported cases. In other places, similar approaches have failed and an endemic state is reached (ie, MRSA is continuously present) (Cooper et al., 2004).

A study by Gerber and colleagues, 2009 considered hospitalized children. It was a 6-year study from January 1, 2002 to December 31, 2007 (Gerber, Coffin, Smather, and Zaoutis, 2009), 5,794 children with *S. aureus* infection were identified; 29,309 (51%) of whom had MRSA infection. The mean age of patients with *S. aureus* infection was 3.1 years, and less than one third of these patients had chronic and complex medical conditions. Over time, there was a significant increase in cases of MRSA infection (from 6.7 cases per 1000 admissions in 2002 to 21.1 cases per 1000 admissions in 2007; P p .02, per trend test). The incidences of skin and soft tissue infection, pneumonia, osteomyelitis and bacteremia caused by *S. aureus i*ncreased with time, and were exclusively MRSA. The mortality rate of hospitalized children with MRSA infection was 1% (360 of 29,309 children). There has been a recent increase in the number of hospitalized children with MRSA infection (Gerber et al., 2009).

They established that for many years, cases of MRSA were limited to hospitalized patients, but the recent emergence of MRSA (CA-MRSA) infections associated with the community has widened the scope of MRSA infections to include *S. aureus* infections with an epidemiology fundamentally different from that of MRSA infections (HA- MRSA) associated with the hospital. CA-MRSA infections often occur in people with no history of exposure to medical care and, most often, they manifest as skin and soft tissue infections. *S. aureus* infections in the skin and soft tissues are treated in the US emergency services. In the same way, skin and soft tissue infections that start in the community are the cause of most MRSA infections in children. The rate of MRSA infection in the community should generate an increase in the frequency of hospitalization due to MRSA infection (Gerber et al., 2009).

Like any disease there is a mode of transmission and control. for MRSA is not the exception, to the contrary, medical attention is prevailing since it is transmitted from patient to patient mainly through the hands of health professionals (Sampathkumar., 2007). Good hand hygiene practices will limit the transmission from person to person and decrease the number of people who are colonized. In health care settings, active surveillance cultures have been proposed to identify patients with MRSA, contact precautions (use of gowns and gloves while caring for these patients) and good environmental cleansing as additional strategies to limit the transmission of MRSA.

Studies have implicated *S. aureus* as the main cause of septicemia in the metropolis of Tamale in Ghana. The high multidrug resistance of MRSA in hospital environments in Ghana reinforces the need for efficient and routine cleaning of hospital door handles. Additional research is needed to understand if *S. aureus* from the door handles could be the possible cause of nosocomial diseases in hospitals. There is a need for regular monitoring and monitoring of *S. aureus* and MRSA in the hospital environment, as well as regular and effective cleaning of door rails and contact surfaces in Ghanaian hospitals (Saba, Amenyona, and Kpordzih, 2017).

Physicians can help control the spread of CA-MRSA in communities by promoting hand hygiene, maintaining a high degree of suspicion of MRSA as an etiologic agent when treating skin and soft tissue infections, knowing local rates of CA-MRSA (public health departments may be able to provide this data), emphasizing the importance of patients with MRSA and discouraging the exchange of personal items such as towels and razors. Flu vaccines (especially in children) may be useful in reducing the risk of post influenza bacterial pneumonia with MRSA (Sampathkumar., 2007).

MRSA has traditionally been regarded as a nosocomial pathogen, but more recently, MRSA infections have appeared in community settings. The clones typically responsible for hospital- and community-acquired MRSA infections have been classified as healthcare associated MRSA (HA-MRSA) and community-associated MRSA (CA-MR- SA), respectively. These clones can be distinguished based on specific microbiologic and genetic characteristics, and often have different epidemiologic, clinical and therapeutic characteristics (Table 3) (Rodríguez and Seas, 2010). Occasionally, hospital-acquired infections may be derived from CA-MRSA strains, and infections acquired in the community may carry healthcare associated risk factors. Definitive HA-MRSA and CA-MRSA designations for individual clones, therefore, rely on microbiologic and genetic characterization, and the terms 'health- care-acquired' and 'community-acquired' refer to the location at which the infection was acquired (Rodríguez and Seas, 2010).

MRSA clones are genetically diverse, but they often share common genes encoding multidrug resistance to lactams, erythromycin, chloramphenicol and clindamycin, and variable resistance to rifampin, the fluoroquinolones and *trimethoprim-sulfamethoxazole* (TMP-SMX). Three classes of antimicrobials, including glycopeptides, oxazolidinones and the new tigecycline derived from tetracycline, are uniformly active against these clonal variants in the region (Rodríguez and Seas, 2010).

In Latin America, pandemic clones are common in hospitals in the region, and infections associated with the community are growing in number. Clones circulating in the region show genetic diversity, although common genes encoding resistance to multiple drugs to antimicrobials. Improved pathogenic properties, including the production of biographies and the production of enterotoxins, have been described for certain clones, and the ability of nosocomial and community clones to exchange genetic material has also been identified (Rodríguez and Seas, 2010).

Rodríguez and Seas conclude that regional surveillance protocols are required, using central reference laboratories and information from health centers with different complexities, if we want to understand more about the development of MRSA infections in

Latin America and design better treatment and prevention strategies (Rodríguez and Seas, 2010).

Table 3. *S aureus* clone characteristics including microbiologic and genetic characteristics, as well as epidemiologic, clinical and therapeutic characteristics

Characteristic	CA-MRSA	HA-MRSA
Year of discovery	1961	1980s
Population at risk	Patients having previous hospitalization, surgery, residence in long-term care facilities, dialysis, permanent indwelling catheters, intensive care unit	Children, homeless, men who have sex with men, athletes, military recruits, jail inmates, native Americans, Pacific Islanders, adult emergency department patients
Main clinical syndromes	Bacteremia, HAP, VAP, catheter- and prosthetic-related infections	SSTI, necrotizing CAP, bacteremia, osteomyelitis
Antibiotic resistance profile	Multidrug resistant; including b-lactams, macrolides, TMP-SMX, lincosamides, tetracyclines, rifampin, quinolones Growing resistance to glycopeptides also	Resistant to b-lactams. Variable susceptibility to macrolides, TMP-SMX, tetracyclines, lincosamydes
SCC*mec* type associated with strains causing infection	I, II and III	IV and V
Expression of PVL	Rare	Common

HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia; SSTI: skin and soft tissue infection; CAP: community-acquired pneumonia; TMP-SMX: trimethoprim-sulfamethoxazole; SCCmec: staphylococcal chromosomal cassette mec; PVL: Panton-Valentine leukocidin; PFGE: pulsed-field gel electrophoresis.

MRSA prevalence in nursing homes

Even though S. *aureus* is known to cause severe infection in the elderly, colonization and infection are increased among nursing home residents; most facilities have been concerned primarily with antibacterial-resistant strains of staphylococci, specifically MRSA. This interest developed because of MRSA outbreaks in acute care facilities in the late 1970s and early 1980s. Several epidemic strains of MRSA were widely disseminated to patients in large tertiary acute care facilities, particularly those in intensive care units. Delays in the initiation of appropriate treatment occurred because of the lack of clinical awareness and unavailability of accurate antimicrobial testing. As a result, many patients died of their MRSA infection. In this way, nursing homes became identified as a potential source of MRSA that could be introduced into acute care hospitals. Once introduced, the subsequent spread of MRSA between patients would create a reservoir of MRSA within a nursing home, providing the potential for an outbreak and further hospital outbreaks when affected nursing home residents require hospital treatments (Hughes, Tunney, and Bradley, 2013).

MRSA causes an estimate of 80,461 invasive infections and 11, 285 deaths per year in the United States and leading Healthcare associated infections. 80% of the MRSA infections occur outside hospitals, within more than 60% of cases occurring within 12 weeks after hospital discharge. Approximately 4 million individuals receive care in 15,600 nursing homes each year in United States. While, number of mathematical models have been used to describe the dynamic of MRSA in acute care settings and to predict the role of nursing homes in the regional spread of MRSA, their use in describing the dynamic of MRSA within the nursing homes remain limited (Grigg et al., 2018).

Above all, a number of factors could influence the dynamic of MRSA within nursing homes. Some of the risk factors known to increase the risk of MRSA colonization and common among older people include:

- Chronic illness and debilitation
- Multiple exposure to antibiotics
- Presence of pressure ulcers
- Indwelling devices

Although some of these risk factors may apply to younger residents (less than 65 yrs.) most residents in nursing homes are older than this. Furthermore, epidemiological work has indicated that there is and increased relative risk of dying within six months in nursing homes residents who carry MRSA compare to non-carriers (Hughes, Tunney, and Bradley, 2013).

Furthermore, a study based on how MRSA could be eliminated or reduced on the nursing home settings affirm that the elimination of MRSA from nursing homes in the U.S. is highly rare. This intuitive finding is similar to the finding of the other modeling study, which conclude that MRSA would persist in the nursing homes for as long as colonized residents continue to enter the facilities (Batina, Crnich, Anderson, and Dopfer, 2016).

On the other hand, another matter in this article is the relationship between MRSA with treatments such as vancomycin in the nursing home settings. The antibiotic treatment of choice for

MRSA is vancomycin. However, this antibiotic treatment in the recents years has increasingly resulted in treatment failure and poor for clinicals outcomes (Heinze et al., 2018).

Even though, the hospitals are the main environments for the MRSA and VRSA co-colonization in infected individuals, studies suggest that other health care's such nursing facilities present a unique pattern for the dissemination of resistance. Patients are admitted to these facilities for rehabilitation following discharge from acute care hospitals, and they have high rates of bacterial colonization based on several factors, including impaired functional status, widespread antibiotic use, and frequent long-term use of indwelling devices such as urinary catheters and feeding tubes (Heinze et al., 2018).

Lastly, further studies are needed to investigate the benefits of identifying the high risk of the individuals and implementing specific infection prevention measures, such as collecting surveillance cultures, utilizing proper contact and isolation precautions also, hand hygiene is very important on patient's co-colonization rates (Heinze et al., 2018). Little attention has been given to infection prevention and control in nursing homes with respect to MRSA, unlike the situation in the hospital setting an institutional setting. Visitors, staff and residents constantly come and go, thereby increasing the risk of transmission (Hughes, Tunney, and Bradley, 2013).

The nursing home environment is highly conductive to the acquisition and spread of infection, with susceptible residents sharing sources of air, food, water and health care within an institutional setting. Visitors, staff and residents constantly come and go, thereby increasing the risk of transmission (Hughes, Tunney, and Bradley, 2013). The quality of care provided to older people in nursing homes has been of concern for many years and in this context, infection prevention and control is related issue that has not been adequately addressed (Hughes, Tunney, and Bradley, 2013). There may be many factors that contribute to this situation, such as the ownership status of nursing homes, lack of formal infection prevention, control advice to nursing homes and staffing levels.

The US has adopted an adversarial approach to nursing home regulation through the Omnibus, which exerts its effects through regulation, inspection and sanctions. Constant reminders to staff will be required to ensure adherence to an infection prevention and control protocol, and this may be difficult to achieve in setting where there are staff shortages and rapid staff turnover (Hughes, Tunney, and Bradley, 2013). Most staff had no previously thought about protecting themselves from MRSA. Nonetheless, staff and administrators suggested several strategies to reduce MRSA transmission including staff education and changing practice (Albrecht et al., 2018).

DISCUSSION

In our review article, we compare the prevalence of MRSA in both hospitals and nursing homes in the US and Mexico. Since late 1980s, there has been a gap in the discovery of new antimicrobial drugs and their introduction to combat staphylococcal infections, the latter being the lipopeptide daptomycin in 1987 (Sampathkumar., 2007). It is clear that *S. aureus* has an extraordinary ability to develop resistance to any antibiotic to which they have been exposed (Foster, 2017). There have been pronouncements that the end of the antibiotic era is near and that it has been widely published in the media. In certain infections, treatment options are running low (Aminov, 2010; Segung, Keshavjee, and Rich, 2015). It is still possible to treat most of *S. aureus* infections caused by changing medications or employing different combinations, considering that the persistent bacteremia and endocarditis are very difficult to treat because underlying diseases can lead to an immunocompromised state; and the ability of bacteria to avoid antibiotics. Since the development of new drugs is feasible, better administration should prolong their activity and, together with a more informed use of the combinations, should guarantee the continuous ability to treat many MRSA infections (Foster, 2017).

The burden of MRSA in nursing homes is less well studied compared to hospital settings. In addition, nursing homes may have unique risk factors (Murphy et al., 2012). Social interaction between residents distinguishes nursing homes from acute care settings, and has an unknown impact upon MRSA acquisition (Murphy et al., 2012). However, a recent study states that in nursing homes in comparison to hospitals, the burden and predictors of MRSA are not well understood (Murphy et al., 2012).

The quality of care provided to older people in nursing homes has been of concern for many years and in this context, infection prevention and control is a related issue that has not been adequately addressed. Person to person transmission plays a central role in the spread of MRSA in healthcare settings. MRSA is a common cause of colonization and infection for patients in hospitals and nursing homes, causing significant excess morbidity, mortality and cost (Albrecht, Croft, Morgan and Morgan, 2018).

Even though *S. aureus* is commonly seen in the hospital onset it has been proved that the prevalence and impact in the nursing homes has been relatively increasing in the past years. Nursing home residents have a 10% risk of MRSA infection within the first month of arrival, with risks as high as 40% within one year (Lee et al., 2014). These infections are costly and often result in hospital readmission of patients (with MRSA infection, 20–40% were recently in nursing homes) (Lee et al., 2014). It is likely that the prevalence of MRSA within nursing homes is increasing as a result of the increased prevalence of MRSA within hospitals, which may have been compounded by the considerable movement

of patients from long-stay hospitals to community-based nursing homes.

On the other hand, nursing homes can influence hospital infection control by several means. First, nursing homes can multiply/magnify the effects of a hospital outbreak on other hospitals. A nursing home can link two hospitals that were not otherwise strongly linked, acting as a bridge for infectious pathogens to spread from facility to facility. Secondly, outbreaks originating a nursing home can affect multiple hospitals in a region, even those geographically distant. Even if a hospital keeps its own MRSA levels low, it is at risk for an outbreak if nursing homes in the same region do not maintain effective infection control (Lee et al., 2014).

As already discussed there has been much debate about how to prevent and control the transmission of MRSA. Since many hospitals report high MRSA colonization rates among elderly patients, and because it has been shown that *S. aureus* colonization increases with advancing age, there are concerns about the introduction of MRSA into nursing homes by MRSA positive patients discharged from hospital. Nursing homes provide an ideal environment for the acquisition and spread of MRSA, since residents have an increased risk of colonization due to chronic illness and debilitation, multiple exposures to antimicrobial agents, and the presence of pressure ulcers and indwelling devices. Furthermore, epidemiological work has indicated that there is an increased relative risk of dying within six months in nursing home residents who carry MRSA compared to non-carriers (Hughes, Tunney and Bradley, 2013).

The selection of initial antibiotic regimens should be guided by the local prevalence of MRSA, the presence of risk factors associated with medical care, and the severity and type of clinical presentation. For severe infections, intravenous Vancomycin should be included in the initial empirical therapy. Microbiological data and antibiotic sensitivity tests should be used to guide subsequent therapy. Approved for the first time in 1958, Vancomycin became a standard therapy for MRSA in the 1960s. Its advantages include its good safety profile, long experience with its use and its relatively infrequent dosing regimen. Disadvantages include the need for intravenous administration and monitoring of levels in critically ill patients and in those with changing renal function. Recently, there have been reports of Vancomycin insufficiency due to relative resistance to Vancomycin or MRSA infections at sites that have little Vancomycin penetration (Sampathkumar., 2007). The clones of *S. aureus* have a history of resistance to antibiotics that began 4 years after the introduction of penicillin in clinical practice, and by 1944, penicillin resistant *S. aureus* clones had been isolated. In later years, *S. aureus* become resistant to all natural penicillins. The first clones of MRSA had genetic properties similar to those of *S. aureus* (MSSA) susceptible to methicillin that were epidemic in Europe (Rodríguez and Seas, 2010).

The spread of MRSA and other drug-resistant organisms may be limited by infection control measures. It is time for us, as health professionals, to incorporate proven infection control measures, such as hand hygiene and the use of appropriate personal protective equipment (gowns and gloves) in our daily patient care routines. The next influenza pandemic may or may not occur in our lives. The MRSA pandemic is constantly present. Patient orientation to this we refer to the patient medical relationship and the worldwide orientation a unification of efforts of both medical researchers and scientific researchers to inform in a conclusive way the problem that addresses us in this 21st century with the resistance and the exams of antibiotics. Raise awareness and promote more informative investigations that encourage and invite more scientists to investigate the creation of new antimicrobials.

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Adherencia terapéutica en el adulto mayor que vive con VIH: barreras y facilitadores

Therapeutic adherence in the elderly that lives with HIV: barriers and facilitators

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RESUMEN

Las personas que tienen el Virus de Inmunodeficiencia Humana (VIH) requieren un régimen terapéutico complejo a través de su vida. El seguimiento o adherencia a dicho régimen ha sido motivo de estudio en múltiples ocasiones. Debido a la complejidad de los tratamientos muchos estudios se han enfocado en la adherencia y no en otros factores que puedan afectar positiva o negativamente dicha adherencia. En este manuscrito consideramos las deficiniones sobre adherencia terapéutica, factores identificados como barreras o facilitadores de adherencia y enfocamos los hallazgos en la población adulto mayor. Encontramos estudios que consideran poblaciones jóvenes y de adultos, pero hay carencia de información en relación al adulto mayor.

ABSTRACT

People with the Human Immunodeficiency Virus (HIV) require a complex therapeutic regime throughout their lives. Adherence to that regime has been studied on multiple occasions. Because of the complexity of the treatments, many studies have been focused on the adherence to the treatment and have not considered factors that can affect positively or negatively that adherence. This manuscript presents the definitions of therapeutic adherence, factors identified as barriers or facilitators of adherence and the findings are focused on the elderly population. Studies described consider young and adult populations, but information on the elderly is limited.

PALABRAS CLAVE VIH, adulto mayor, adherencia terapéutica

KEYWORDS HIV, elderly, terapeuthic adherence

INTRODUCCIÓN

El Virus de Inmunodeficiencia Humana (VIH) es considerado una enfermedad crónica que requiere un régimen terapéutico complejo a lo largo de la vida (Ball, 2014). Dicho régimen, se refiere al programa de tratamientos para una enfermedad y sus secuelas. Abarca la terapia farmacológica, los procedimientos médicos, los cambios en los hábitos de vida y la adherencia terapéutica, entre otros. Para Varela Arévalo y sus colegas (2008), la adherencia terapéutica en los pacientes con VIH incluye: tomar los medicamentos antirretrovirales, seguir las prescripciones médicas, asistir a las citas médicas periódicas y con otros profesionales de la salud. Además, incluye realizarse los exámenes de control (CD4, carga viral, citología, etc.), hacer ejercicio con regularidad, alimentarse según las recomendaciones de los médicos y nutricionistas y controlar su estado emocional para evitar emociones que afecten su sistema inmunológico.

La adherencia al régimen terapéutico ha llegado a ser una de las líneas de investigación más importantes para los profesionales de la salud en especial a los que brindan servicios a personas que padecen VIH (Cahill y Valadéz, 2013; Rodríguez Quesada, 2016; Ortiz, Ortega, Viveros y Herrera, 2011; Sepúlveda Carrillo et al., 2016). Según Abara, Adekeye, Xu, Heiman, y Rust, (2016), este tema es esencial en el adulto mayor que vive con VIH, sin embargo existe una escasez de estudios dirigidos a la adherencia al régimen terapéutico en dicha población.

La investigación realizada con el adulto mayor que vive con VIH, presenta por un lado a un adulto mayor con alto riesgo de no adherencia terapéutica (Abara, Adekeye, Xu, Heiman, y Rust, 2016) por factores relacionados con la complejidad de los medicamentos, los efectos secundarios, los altos costos del tratamiento y la falta de conocimiento o información de los mismos; además de la pérdida cognitiva, entre otros (Hinkin et al., 2002; Pinheiro et al., 2016). Por otra parte, presenta a un adulto mayor con índices altos de adherencia terapéutica cuando se compara con sus contrapartes jóvenes (Brañas et al., 2008; Negin y Cumming , 2010; Newman et al., 2012; Silverberg et al., 2007). Esta contradicción de evidencia aporta a que sea altamente

recomendada la realización de estudios sobre la adherencia en la población adulto mayor según Nachega, Hsu, Uthman, Spinewine, y Pham, (2012). Esta incongruencia, en la manera de visualizar y evaluar al adulto mayor con VIH, en relación con la adherencia al régimen terapéutico es motivo de interés para evaluar otros elementos relacionados con la misma. Por ejemplo, existen varios elementos que contribuyen a que el paciente desarrolle o no la adherencia terapéutica. En la literatura se presentan diversas clasificaciones de estos elementos asociados con la adherencia al tratamiento. Autores como Knobel y Guelar (2004) y la OMS (2003) indicaron la existencia de factores que facilitan y otros que son barreras en el mencionado proceso.

Régimen Terapéutico

El régimen terapéutico es un plan de tratamiento individualizado, estructurado para mejorar y mantener la salud. Una de las áreas que incluye es, los medicamentos antirretrovirales. Para los adultos mayores al igual que para los demás pacientes con VIH, independientemente de la cifra de linfocitos CD4, está plenamente justificada la instauración temprana del tratamiento antirretroviral (TAR). Los regímenes recomendados para el tratamiento inicial de la infección por el VIH incluyen una combinación de tres o más medicamentos antirretrovirales (ARV) pertenecientes por lo menos a dos clases diferentes. Un tratamiento de elección debe ser una combinación que incluya dos inhibidores de la transcriptasa inversa de análogos de nucleósidos (ITIAN) asociados a un inhibidor de la transcriptasa inversa de análogos no nucleósidos (ITINN), un inhibidor de la proteasa potenciado con ritonavir (IP/r) o un inhibidor de la integrasa (infoSIDA, 2017; Huldrych, et al, 2014; Sociedad Española de Geriatría y Gerontología (SEGG), 2015).

En la selección de tratamiento se debe tener en cuenta las comorbilidades, la interacción entre medicamentos, efectos adversos secundarios y la resistencia a los medicamentos (infoSIDA, 2017; Huldrych et al, 2014) ya que el adulto mayor toma como mínimo cuatro medicamentos diarios además del TAR. Según las guías de manejo para los pacientes adultos mayores con VIH (Aitchesen et al, 2014; ACRIA del 2012: HIV Clinical Resourse, 2015) se deben incluir el manejo de las comorbilidades, y dos o más enfermedades crónicas como las enfermedades cardiovasculares, diabetes mellitus, enfermedad psiquiátrica, hepatitis viral, fallo renal crónico, neuropatía peri feral, enfermedad respiratoria y malignidades asociadas y no asociadas al VIH.

En las visitas iniciales se debe analizar el historial completo de salud (enfermedades pasadas, enfermedades en la familia), antecedentes de viajes y vacunas. También se debe realizar un examen físico completo, incluyendo medidas antropométricas (peso, estatura y circunferencia abdominal), temperatura, presión arterial, respiraciones por minuto, pulso y dolor (si está presente), confirmar el estatus de VIH con un segundo ELISA (o similar) y una prueba confirmatoria (Western Blot), solicitar carga viral plasmática de VIH, solicitar recuento absoluto y relativo de CD4 (opcional: CD8 absoluto y relativo), y verificar con laboratorios de referencia para buscar condiciones de salud o funcionamiento de órganos internos (conteo total de células sanguíneas con diferencial, enzimas hepáticas, glucemia, urea, creatinina, colesterol total, HDL, LDL, triglicéridos, solicitar VDRL, HAV IgG, HbS Ag, anticore total, Ac HCV, toxoplasma IgG y análisis de orina completo).

En las visitas de seguimiento, los pacientes deben ser evaluados para detectar otras enfermedades de transmisión sexual. Deben ser controlados los factores de riesgo a enfermedad cardiovascular incluyendo tabaquismo, dieta habitual y peso, determinar riesgo cardiovascular con escore de Framingham, solicitar PAP cervical (mujeres), el cual debe realizarse cada 6-12 meses, evaluar condición social y psicológica, administrar vacunas correspondientes y solicitar PPD. El proceso es uno largo y abarcador, es por ello que cuando nos referirnos a la adherencia terapéutica en el adulto mayor debemos evaluar todas estas dimensiones y no solo la adherencia a la terapia antirretroviral (GeSIDA, 2017).

Adherencia al régimen terapéutico

En la literatura encontramos diferentes términos para referirnos a el concepto adherencia. Los más utilizados son cumplimiento y adherencia, sin embargo, han sugerido otros como alianza terapéutica, seguimiento, observancia, adhesión, concordancia, colaboración y cooperación. Una definición muy utilizada en la literatura es de Hentinen y Kingäs (1992) quienes definen el término como un proceso activo, intencional y responsable de cuidado, donde el paciente trabaja mano a mano con el equipo de salud.

La adherencia terapéutica o comportamiento de adherencia puede ser definido también, como la coincidencia entre el comportamiento de una persona y los consejos sobre salud o prescripciones que ha recibido (Martos Méndez, Pozo Muñoz, Alonso Morillejo, y Universidad de Almería, 2010). Como es un fenómeno multifacético, cambia con el tiempo: los pacientes pasan por fases de mayor o menor adherencia, por tal motivo el seguimiento debe ser constante. Según Tashiro et al.,(2013) para que se dé la adherencia se debe promover un nuevo modelo de cuidado de la salud donde las personas participen en la creación de su plan de cuidados y desarrollen una relación de colaboración con el equipo de profesionales de la salud de manera que las responsabilidades sean compartidas. Si logramos explorar y describir los factores que afectan ya sea positiva o negativamente las conductas de adherencia, entonces podríamos elaborar intervenciones más asertivas que llevarán a una conducta de adherencia terapéutica satisfactoria.

La investigación sobre adherencia al régimen terapéutico en

el VIH

La adherencia al régimen terapéutico ha sido investigada por más de tres décadas, según explican Bosworth, Oddone y Weinbeger (2008) la adherencia terapéutica ha sido examinada desde varias perspectivas científicas y en diferentes culturas, naciones y poblaciones. Se han realizado estudios con adultos y el VIH, pero no se han encontrado específicos para la población adulto mayor.

García Cedillo y Rodríguez Delgado (2014) realizaron un estudio en la provincia de San Luis Potosí, México, con el objetivo de comparar la situación en que viven y el nivel de adherencia al régimen terapéutico en una muestra de 29 mujeres y 47 hombres que viven con VIH. Realizaron una entrevista semi estructurada y los resultaron mostraron que los hombres tienen mayor adherencia. Justificaron que para las mujeres es más difícil por todas sus responsabilidades y el poco apoyo familiar. Otro estudio realizado en Tamaulipas, México fue el de Peñarrieta et al., (2009), el propósito del mismo era conocer la magnitud de la no adherencia al tratamiento antirretroviral e identificar los factores que intervienen en personas adscritas al programa de VIH de la Secretaría de Salud de Tamaulipas entre junio de 2006 hasta octubre del 2008. Se desarrolló un estudio de corte transversal, incluyendo a las 117 personas del programa de tratamiento, identificando no adherencia en los cuatro días y cuatro semanas últimas previas de aplicada la encuesta. Los factores identificados en la no adherencia son no guardar el medicamento en un lugar específico, percepción insatisfecha de su salud actual y considerar difícil el manejo de su tratamiento. Las condiciones reconocidas son factibles para ser modificado por el sistema de salud, sobre todo, antes del inicio del tratamiento.

En el continente africano encontramos los estudios por Musumari et al., (2013), en el Congo. En el mismo se utilizó el método cualitativo de entrevista profundo para explorar los determinantes que facilitaban y cuales servían de obstáculos para la adherencia en un grupo de adultos. Se entrevistaron 28 participantes de los cuales 24 fueron féminas con una media de edad en 41 años. Se encontró que la inseguridad de no tener alimentos para ingerir fue la mayor barrera para la adherencia, además de falta de recursos económicos, olvido, miedo al estigma y creencias religiosas. Curiosamente las creencias religiosas también figuraron como facilitador.

Kumarasamy y colegas (2003) realizzaron un estudio cualitativo fenológico etnográfico en Chennai, India. Participaron 49 hombres y 11 mujeres. Se realizaron entrevistas profundas y observaciones de campo. Los resultados presentaron como barreras el costo de los servicios, el estigma, aislamiento social y la inhabilidad de tomar pastillas. Como facilitadores se encontraron los beneficios del tratamiento y sentir las consecuencias de no adherirse al mismo.

Otro estudio fue realizado en Kiev, Ucrania, por Mimiaga y colegas (2010). Estos realizaron un estudio cualitativo utilizando grupos focales. Participaron 16 personas con una media de edad de 31 años y todos estaban en terapia de sustitución para opioides. El objetivo era utilizar esta información para adaptar y ajustar, a la cultura ucraniana, una intervención basada en la evidencia para mejorar la adherencia al TARGA. Las barreras identificadas fueron acoso y discriminación por parte de la policía, dependencia al opio, complejidad del régimen de medicamento, efectos secundarios, olvido, problemas de salud mental y estigma por VIH. Los facilitadores para la adherencia fueron las indicaciones para tomar las píldoras, apoyo y recordatorios de familiares, y amigos, terapia de sustitución de opioides y querer mejorar la salud. Otros factores explorados fueron conocimiento sobre la terapia antirretroviral, almacenamiento de los medicamentos y enfermedades de transmisión sexual.

En el 2015, Pacifico y Gutiérrez realizaron un estudio cuantitativo en Lima, Perú. El propósito de este fue determinar la asociación entre la información sobre la medicación y adherencia al tratamiento antirretroviral de gran actividad (TARGA) en pacientes con VIH/SIDA de un hospital de Lima, Perú. Se realizó un estudio de corte transversal analítico. Por medio de entrevistas se aplicó el cuestionario SIMS (*Satisfaction with Information about Medicines Scale*) para medir la satisfacción con la información recibida sobre los medicamentos y el cuestionario SMAQ (*Simplified Medication Adherence Questionnaire*) para determinar la adherencia al TARGA. Mediante la revisión de historias clínicas se recogieron datos sociodemográficos y clínicos. Los resultaron reflejaron que la satisfacción con la información recibida sobre los medicamentos no estuvo asociada a la adherencia a TARGA. La satisfacción con la información recibida sobre el TARGA se incrementa con la edad y es menor en mujeres y el grado de instrucción superior. Hay deseos de mayor información sobre las potenciales reacciones adversas al TARGA.

Youngran Yang (2014), realizó un análisis sistemático sobre el tema de la adherencia. El estudio presentó una revisión sistemática de una intervención multicomponente para abordar la adherencia al TAR y exploró si la intervención, comparada con la atención estándar, resultó en una mejor adherencia al TAR. Se revisaron once estudios de ensayos controlados aleatorios publicados entre 1999 y 2008. Siete de éstos demostraron un efecto beneficioso de la intervención multicomponente, que incorporó principalmente la educación individual y de una a tres intervenciones adicionales. Las intervenciones dirigidas a la mejora de las habilidades de manejo de medicamentos del paciente fueron particularmente exitosas. Sin embargo, debido a los resultados incongruentes entre los estudios, no se pudo determinar si la mejora de la adherencia se extendió a la mejora virológica o resultados inmunológicos. Existe una necesidad de estandarización y un mayor rigor metodológico en la ejecución de los ensayos de adherencia.

Factores relacionados con la adherencia terapéutica

La literatura revisada se ha concentrado en el estudio de la adherencia terapéutica relacionada con la terapia de los medicamentos antirretrovirales, dejando a un lado la observación de los otros factores relacionados con la adherencia terapéutica sin evaluar. Por ejemplo, Haynes (1976,1979, citado en Martos Méndez et al., 2010) mencionó la existencia de más de 200 factores que podrían relacionarse con la adherencia a las prescripciones terapéuticas.

Estudios como el de Tavares Pinheiro, et al (2016), donde se investigaba la relación entre la adherencia terapéutica en adultos mayores con VIH y la perdida de destrezas cognitivas revelaron una alta prevalencia en la pérdida de destrezas cognitivas en el adulto mayor con VIH, no obstante, independientemente de estos resultados su índice de adherencia terapéutica se mantenía más elevado que el de sus contrapartes jóvenes. En la investigación de Bello, et al (2016), el propósito era presentar como múltiples sindémicos (syndemic en inglés) factores sicosociales están asociados con la no adherencia terapéutica en adultos latinos con VIH. Estas variables sicosociales sindémicas fueron nombradas como: depresión, silencio, estigma, abuso de sustancias, alcoholismo y discriminación. Los resultados encontrados fueron comparados con otros estudios realizados en los Estados Unidos de América, los mismos fueron consistentes en presentar una relación directamente proporcional entre altos "odds" de no adherencia terapéutica a medida que aumentaban los factores sicosociales sindémicos.

Facilitadores para la adherencia terapéutica en el adulto mayor con VIH

Como mencionamos anteriormente, son escasos los estudios realizados en adultos mayores, sí se encontraron varios estudios en la población adulta en general. De los encontrados con adultos mayores tenemos por ejemplo, el estudio de Burgess, Zeuli, y Kasten, (2015) quienes mencionan como facilitadores para la adherencia, el tener amigos o conocidos que fallecieron por VIH, el uso de recordatorios (llamadas telefónicas, textos) educación e instrucción sobre el uso de los medicamentos, a través de herramientas que facilitan su dosificación (pastillas o unidades de una sola dosis) la utilización medicamentos combinados y la inclusión de familiares o cuidadores.

Por otra parte, en el estudio de Abara, Adekeye, Xu, Heiman y Rust (2016) estos mencionan que el darles seguimiento continuo a los adultos mayores mantiene unos niveles altos de adherencia especialmente en las féminas. Otros autores como Croome, Ahluwalia, Hughes y Abas (2017), clasificaron estos factores como los que son relacionados a: proveedores de salud, trabajar, fe en Dios, tener control de su salud, creer en el tratamiento y tener buenos proveedores de salud, creer en la medicación, en las relaciones interpersonales, la salud mental y el bienestar general, las creencias de salud, creencias sobre el VIH y su tratamiento, creencias sobre los antirretrovirales, sobre el recogido del medicamento y los factores relacionados al tratamiento. Mientras que Bezabhe y sus colaboradores (2014) clasificaron estos factores como: factores personales, factores relacionados con los profesionales de la salud, con los medicamentos y con los centros de servicios de salud. Otros autores como Davis, Thornton, Oslin, & Zanjani, (2014) y Williams, Amico, & Konkle-Parker (2011) clasificaron los facilitadores en: los de apoyo de la familia, de amigos de pares y personal de salud, la actividad alrededor del cuidado, aspectos positivos de las visitas al servicio de cuidados y percepción de vulnerabilidad a consecuencias negativas como el no abandono del tratamiento. De otra parte, Rasmussenaeh et al., (2013) presenta los factores que benefician la adherencia como: la experiencia de los beneficios del tratamiento y el uso de las redes sociales por internet.

Los autores, Vedhanayagan, et al. (2016), encontraron como factores facilitadores: el apoyo familiar, excelentes relaciones entre el paciente y el equipo de salud, el entendimiento por parte del paciente de la relación entre la adherencia y los niveles de CD4, disminución de infecciones y enfermedades oportunistas, disminución de la frecuencia de dosis, menos pastillas por día, menos restricciones en la dieta, ajustar los medicamentos a los estilos de vida de cada individuo, creencias sobre la efectividad de los medicamentos y creencias positivas sobre los beneficios del tratamiento. Así como los factores facilitadores son varios y clasificados de distintas maneras así también las barreras para la adherencia terapéutica.

Barreras para la adherencia terapéutica en el adulto mayor con VIH

Las barreras en la adherencia terapéutica han sido uno de los temas con mayor discusión en la literatura, pero aparentemente no han sido superadas según Horne, Weinman, Barber, & Elliott, (2005), ellos se refieren a las causas para la no adherencia terapéutica como multifactoriales y que las mismas pueden ser intencionales como no intencionales.

Dentro de las no intencionales podemos mencionar: las limitaciones de capacidad y recursos, como por ejemplo no entender las instrucciones o no poder pagar los medicamentos; Por el contrario, entre las intencionadas, donde media la decisión del paciente, pueden estar influenciadas por sus creencias y preferencias. Basett, et al (2017) en un estudio realizado con adultos mayores de 18 años en Durban, África del Sur, presentó como barreras: esperar mucho tiempo para poder ver a un proveedor servicios, no ser tratado con respeto por los profesionales de la salud, no ser elegible para la medicación gratuita o la transportación, no sentirse tan enfermo, tener otras responsabilidades, servicios inaccesibles entre otros. Croome, Ahluwalia, Hughes y Abas (2017), clasificaron las barreras como las relacionadas con: proveedores de salud, trabajar, fe en Dios, tener control de su salud, creer en el tratamiento y tener buenos proveedores de salud, creencias sobre la medicación, las

relaciones interpersonales, la salud mental y el bienestar general, creencias de salud, creencias sobre el VIH y el tratamiento, creencias sobre los antirretrovirales, creencias sobre el recogido del medicamento y los relacionados al tratamiento. Otros han identificado como barreras para la adherencia terapéutica; el estrés financiero (SMcallister et al., 2013); el estigma (Heckman et al., 2001) problemas sociales y de comunicación médico-paciente (Nelsen et al., 2013)l comorbilidades y el proceso de vejez,(Ball, 2014; Cahill et al., 2013); el sistema inmunológico disminuido, disminución de la habilidad de metabolizar los retrovirales aumentando la toxicidad (Cahill et al., 2013; Ford, et al, 2013); desconfianza en los servicios de salud, desinformación sobre la condición (Ford et al, 2013); depresión y aislamiento (Brennan, Emlet, y Eady, 2011). Otros autores como Williams, Rivet-Amico & Konkle-Parker, (2011) presentan las barreras como: competencia entre prioridades de familia, el trabajo y los hijos, aspectos del sistema de cuidado, como la calidad acceso y fragmentación de los servicios. El estigma, las experiencias negativas como el miedo al abandono, la negación, la desesperanza y sus creencias sobre el VIH. Otro punto de vista (Rasmussennaeh, et al, 2013) presenta las barreras como la diferencia entre los costos del tratamiento vs los costos de las necesidades diarias, la pobre infraestructura de las clínicas de servicio, el estigma, y prácticas culturales.

Vedhanayagan, et al. (2016), describieron como barreras: el estrés del cuidado de los niños, asuntos femeninos, ausencia de soporte familiar y social, enfermedades asintomáticas, alteraciones severas a los estilos de vida, eventos familiares difíciles, efectos adversos del tratamiento, olvido, una vida estresada, abuso de alcohol y drogas ilegales, depresión, desesperanza y angustia, creencias que el alcohol y las drogas interfiere con el tratamiento, dejar de tomar los antiretrovirales para tomar otros medicamentos, sentir que los medicamentos los envenenan, problemas de transportación, olvidar llevarse los medicamentos cuando sale del hogar, problemas de suplido y servicios.

DISCUSIÓN

El propósito de esta revisión de literatura integrada era describir los factores que intervienen en la adherencia terapéutica de los adultos mayores con VIH. Este pretende aportar a un mejor entendimiento de la necesidad de realizar estudios sobre el tema en esta población. Y añadir un recurso a la literatura que está disponible. Aunque hemos encontrado gran cantidad de literatura relacionada con el tema de adherencia terapéutica, queremos resaltar varios puntos (lagunas) donde se necesita profundizar e investigar.

La adherencia al régimen terapéutico es un concepto multifactorial y hasta el momento su estudio se ha centrado en la adherencia al uso de los antirretrovirales dejando a un lado componentes importantes para que el proceso de adherencia terapéutica se dé y sea efectivo. Los factores que intervienen con la adherencia terapéutica pueden ser a favor, facilitando la misma o puede ser obstaculizadores o barreras de la adherencia.

Por otro lado, la población adulto mayor con VIH puede ser clasificada en tres grupos diferentes (Services and Advocacy for GLBT Seniors, 2016): sobrevivientes de largo tiempo, los de diagnóstico reciente y los recién infectados cada uno de ellos con necesidades diferentes y reacciones diferentes. Por lo que deben realizarse investigaciones por los diferentes grupos y culturas. Las intervenciones publicadas destinadas a mejorar la adherencia en pacientes con el VIH de mayor edad son muy escasas y no permiten determinar unas recomendaciones de apoyo específicas. Aunque podría considerarse la idea de extrapolar las llevadas a cabo en otras patologías como la diabetes o HTA, es necesario evaluar su utilidad en poblaciones específicas como aquellos pacientes con el VIH con deterioro cognitivo o con una mayor fragilidad física o emocional.

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OTRAS INVESTIGACIONES EN EL CAMPUS/ OTHER RESEARCH ON CAMPUS

Resumen de otras investigaciones realizadas por nuestros estudiantes en el Recinto durante el año académico 2018-2019 en los campos de farmacología y bioquímica, ecología y química.

Summary of other research conducted on campus by our students during the academic year 2018-2019 in the fields of pharmacology and biochemistry, ecology and chemistry.

FARMACOLOGÍA-BIOQUÍMICA/ PHARMACOLOGY-BIOCHEMISTRY

1-A Time-course analysis of PANC-1 cells viability after exposure to phytochemicals and evaluation of the pharmacological interactions with synthetic compounds

Linette Cruz Romero, José Raúl Rivera Cordero, Melanie Cubano Santiago, Michael Soto Cintrón and Karen Woolcock Rodríguez

Pancreatic Cancer is the 3rd leading cause of cancer-related death in the United States and has the lowest five-year survival rate of any major cancer. Gemcitabine is the most common treatment for pancreatic cancer, but the efficacy is not fully satisfactory. Possible intracellular circuits that can be targeted with alternate treatments are those that regulates proliferation, induces apoptosis, and reduce the capacity of invasion and metastasis. Rac is a monomeric G-protein, member of the Rho family that regulates the mentioned circuits and can be inhibited by EHop-16. In the present study a time-course analysis of the effect of 6-shogaol, EHop-16 and Bortezomib on PANC-1 cells viability was done. Also, the pharmacological interaction among natural compounds and chemical compounds was characterized. Results show that 6-shogaol and EHop-16 reduced the percentage of PANC-1 cells viability in a dose-dependent manner. Bortezomib produced a time and dose dependent reduction of cell viability. The treatments with highest potency were Ehop-16 + 6-shogaol (GI_{50} = 3.8 nM) and Bortezomib (GI_{50} = 52.8 nM). It was observed that Ehop-16 + 6-shogaol and Bortezomib + 6-shogaol caused 80% of cell mortality. The combination of EHop-16 with 6-shogaol resulted in a potentiation among them. In conclusion, PANC-1 cells are sensitive to Rac inhibition, and Unfolded Protein Response (UPR) since administration of EHop-16 and Bortezomib produced a reduction (30%) of cell viability. All tested compounds and combinations were more efficient than gemcitabine in reducing PANC-1 cells viability. Combinations of natural and synthetic compounds can be a logical approach to be established in clinical practice.

1-B Apoptosis induction and detection of E-cadherin expression on PANC-1 cells after treatment with EHop-16 and 6-shogaol

Natalia Acevedo, Isabeliz Seijo, Cristopher Marrero, Kevin Ongay and Karen Woolcock

Pancreatic ductal adenocarcinoma is an aggressive type of cancer and the fourth leading cause of cancer-related deaths in the United States. Common treatments for pancreatic cancer include a broad range of chemotherapeutic drugs, with the major disadvantage being the development of chemoresistance to the pharmacological action of these drugs. Therefore, the evaluation of alternative treatments including synthetic and natural compounds, that decrease the metastasis and invasion activity of pancreatic cancer cells and reduces their ability to avoid apoptosis are important to improve patient prognosis and life expectancy in the future. Since it has been shown that synthetic (Bortezomib, E-Hop016) and natural (6-shogaol) compounds could possess anticancer activity, the objectives of this project were to: 1) Evaluate the efficacy of natural compounds (6-shogaol) and chemical compounds (Ehop-16) to induce apoptosis on pancreatic cancer cells in vitro, and 2) To evaluate cellular morphological changes and E-cadherin expression of PANC-1 cells after exposure to gemcitabine, EHop-16 and 6-shogaol. Results demonstrate

that Bortezomib (100 μM) and 6-shogaol (100 μM) induced Caspase 3/7 mediated apoptosis in 46 % and 26% of cells respectively, when were exposed for 48 hours. The activity was reduced at 72 hours. Morphological studies revealed that EHop-16 seems to induce Mesenchymal-Epithelia Transition, as demonstrated with the increased expression of E-cadherin in the cell membrane. Moreover, improved cell-cell adhesion was observed. 6-shogaol improved cytoskeletal structure which may reduce the invasion capability of the cell. These effects suggest that the combination of EHop-16 with 6-shogaol could be considered as treatment protocol for pancreatic cancer.

ECOLOGÍA/ ECOLOGY

2-A Bacterial (16S) and Symbiodiniaceae (ITS2) metagenomic analyses in the endangered coral *Dendrogyra cylindrus* (Scleractinia: Meandrinidae) from north central and southwestern Puerto Rico

Génesis Pérez Cartagena, Edwin De León Perez, Norberto Rodriguez, Maria Pagan, Arlyn Perez, Lizbeth Romero, Alex Veglia, Daniel Toledo, Ernesto F. Weil, Nikolaos V. Schizas, and Mathew Lucas

Scleractinian corals associate with a diverse microbiome (bacteria, archaea, viruses, fungi, algae), deemed the “coral-holobiont”. Symbiosis with the photosynthetic dinoflagellates (family Symbiodiniaceae) has been fundamental to their evolutionary success. Thermal stress increases susceptibility to pathogens and destabilizes the coral microbiome, often leading to disease and mortality. The gap in our understanding of the mechanisms by which the coral microbiome supports coral health and increases resistance needs attention. Listed as endangered, Dendrogyra cylindrus is a widespread, but low abundance species due to low juvenile survivorship, and recent mortalities by bleaching, disease, hurricanes and local environmental degradation. This species is a good candidate to examine the diversity, symbiotic associations and potential manipulations that could enhance survivorship. This study aims to understand the effect of local environment, thermal history, and coral host (mitochondrial lineages) on the bacterial and Symbiodiniaceae associations in *D. cylindrus* from two contrasting environments, the north central, oceanic and rough coast (Arecibo), and the calm, southwestern (Parguera) coast of Puerto Rico. We are currently using PCR and sequencing in D. cylindrus colonies in two mitochondrial DNA regions. Bacterial (16S rRNA) and Symbiodiniaceae (ITS2) diversity will be characterized using high-throughput sequencing (Illumina platform). Multivariate statistics will be used to explain sequence data in colonies sampled from different environments. Collectively, microbial communities play important roles in ecological resilience. These data will serve as an important baseline on the microbial contributions, both bacterial and Symbiodiniaceae, for future studies in *D. cylindrus*. Further understanding the role of the coral holobiont, their environmentally-related differences, and their influence on future coral resistance and adaptation are important for species conservation and coral reef management.

Química/ Chemistry

3-A Síntesis de nanopartículas de plata, caracterización y efectos bactericidas

Johan Salvá-Martí y Gloria Herrera Sandoval

Las nanopartículas de plata son reconocidas por un amplio rango de aplicaciones. Se ha encontrado que tienen una vasta aplicación en la industria biomédica, médico-farmaceútica, electrónica, industria textil, pinturas, cosméticos, bactericidas, biofungicidas, y alimentaria. Sus aplicaciones antimicrobianas y fungicidas han sido reconocidas y estudiadas desde la época antigua. Actualmente en el mercado hay disponibles para la venta generadores de plata coloidal (nanopartículas de plata) para su uso como antibiótico natural, para la curación del cuerpo, especialmente de quemaduras, infecciones y daños en los

tejidos blandos (músculo y cartílago). Uno de los objetivos de esta investigación fue llevar a cabo la síntesis de nanopartículas de plata por métodos electroquímicos y por reducción química. El método electroquímico consistió en el uso de un equipo comercial disponible en el mercado, para la síntesis del coloide de plata que las personas consumen. El método de reducción fue un método de química verde o ecoamigable, donde se hizo uso del extracto de hojas de guanábana para convertir iones plata a nanopartículas de plata a través de la reducción. Se llevó a cabo la caracterización de las nanopartículas a través del uso de técnicas como espectroscopia ultravioleta - visible y espectroscopia infrarroja. Las nanopartículas fueron analizadas por el método Kyrbi-Bauer para evaluar los efectos bactericidas de las nanopartículas de plata en las bacterias Gram-positivo y Gram-negativo, como lo son la *Escherichia Coli*, *Pseudomonas Aeruginosa* y *Staphylococcus Aureus*.

3-B Obtención de biodiesel por medio de aceite de cocina usado
Dannytza B. Reyes-Hermina y Gloria Herrera Sandoval

Uno de los problemas ambientales más grandes en los cuerpos de agua y en el suelo es producido por la mala disposición de aceites de cocina usados. En este trabajo, se investigó la obtención de Biodiesel a partir de aceite de cocina usado. Se convirtió el aceite a biodiésel haciendo uso de química orgánica, por medio de una reacción de trans-esterificación. Esta reacción se realizó con dos tipos de aceite: un aceite con poco uso y uno que había sido utilizado en varias ocasiones. La reacción de trans-esterificación consiste en la reacción del aceite con metanol y empleando un catalizador básico, en este caso, hidróxido de sodio. El proceso de producción de este biocombustible requiere de varias etapas y técnicas químicas tales como: filtración, titulación, reacción de trans-esterificación, decantación; posteriormente, el biodiesel es lavado y finalmente secado. Para caracterizar el producto final obtenido se llevó a cabo la determinación de propiedades importantes en el biodiesel tales como la densidad, viscosidad, punto de neblina y un análisis espectroscópico infrarrojo. La comparación de los datos obtenidos con el Diesel comercial reflejó que, si se llevó a cabo la conversión de aceite a biodiesel, teniendo los resultados de sus propiedades en los parámetros esperados según la literatura.

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