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UNCOMPLICATED CYSTITIS TREATED WITH HIGH PROANTHOCYANIDINS CRANBERRY CONCENTRATION IN PATIENTS AGED 70 YEARS OLD AND BELOW WITH RECURRENT URINARY TRACT INFECTIONS

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RESUMEN: CISTITIS NO COMPLICADA TRATADA CON ALTA CONCENTRACIÓN DE PROANTOCIANIDINAS DE ARÁNDANO EN PACIENTES DE 70 AÑOS O MENOS CON INFECCIONES RECURRENTE DEL TRACTO URINARIO

El objetivo de nuestro estudio fue evaluar originalmente la eficacia y seguridad de Cysticlean® (CYS), un extracto de cramberry que contiene 240 mg de proantocianidinas (PAC) por píldora, para tratar y prevenir la infección urinaria recurrente (rUTI) en pacientes adultos menores de 70 años y evaluar si: un año de tratamiento con CYS podría modificar o no varios parámetros de la función renal, así como la evaluación funcional geriátrica en aquellos pacientes entre 60 y 70 años.

Material y métodos: Se estudiaron 27 pacientes, con edades entre 53-70 años. En todos ellos se evaluó el antecedente rUTI confirmando al menos 3 episodios de infección urinaria / año. Todos los pacientes incluidos recibieron instrucciones de suspender los antibióticos durante un período de lavado de dos semanas antes de introducir CYS en un régimen de 1 cápsula de CYS por la mañana y 1 cápsula por la noche hasta que se controlaron los signos y síntomas de la cistitis. Los pacientes que sufrieron un nuevo episodio de infección urinaria durante el período de tratamiento con CYS lo detuvieron y fueron tratados de acuerdo con el mejor antibiótico necesario. Estos pacientes fueron considerados como un fracaso del tratamiento con CYS.

Resultados: Veintiún pacientes no sufrieron infección urinaria durante el período de estudio. Entre ellos, 17 eran mujeres y 4 hombres (p <0,044). Solo 6 pacientes (2 mujeres y 4 hombres) sufrieron una infección urinaria en el período de estudio. Todos estos tratamientos fallidos de CYS fueron tratados con antibióticos apropiados. CYS no modificó la función renal de los pacientes ni el estado funcional de los pacientes en este estudio.

Conclusión: Cysticlean® es un extracto de arándano americano que ha podido controlar la rITU en el 78% de los pacientes tratados en este estudio gracias a su alta actividad antiadhesiva proporcionada por su muy alta concentración de PAC. No se informaron efectos secundarios ni reacciones adversas.

PALABRAS CLAVE: Arándano, vaccinium macrocarpon, Cysticlean®, proantocianidinas, cistitis, infecciones del tracto urinario.

ABSTRACT:

The objective of our study was to originally evaluate the efficacy and safety of Cysticlean® (CYS), a cranberry extract which contains 240 mg of proanthocyanidins per pill, to treat and prevent recurrent urinary tract infection (rUTI) in adult patients younger than 70 years old and to evaluate if one year of treatment with CYS could modify or not several parameters of the renal function, as well as the geriatric functional evaluation in those patients between 60 and 70 years old.

Material and methods: 27 patients were studied, aged 53-70 years. In all of them was evaluated rUTI antecedent confirming at least 3 episodes of UTI/year. All included patients were instructed to stop antibiotics for a washing out period of two weeks before introduce CYS in a regime of 1 capsule of CYS in the morning and 1 capsule in the evening up to the signs and symptoms of cystitis were controlled. Patients who suffered from a new episode of UC during the CYS treatment period stopped it and were treated accordingly to the best antibiotic needed. These patients were considered as a fail of the CYS treatment.

Results: Twenty-one patients did not suffer any UC during the study period. Among them 17 were women and 4 men ($p < 0,044$). Only 6 patients (2 women and 4 men) suffered a UC in the study period (Table II). All this failed CYS treatments were treated with appropriate antibiotics. CYS modified neither patients' renal function nor patient's functional status in this study.

Conclusion: Cysticlean® is an American cranberry extract who has been able to control the UTI in 78% of patients treated in this study thanks to its high anti-adhesion activity provided by its very high PAC concentration. Neither side effects nor adverse reactions were reported.

KEY WORDS: Cranberry, Vaccinium macrocarpon, Cysticlean®, Proanthocyanidins, cystitis, Urinary tract infections, UTIs.

INTRODUCTION

Recurrent urinary tract infection (rUTI) is a very frequent disease in children with congenital urological diseases, fertile ladies and old women and men worldwide¹.

These infections are usually defined as uncomplicated cystitis (UC) when fever and general discomfort are not present. Up to 75% of all UC are caused by *Escherichia coli* (Ec), and no differences have been found among countries regarding its prevalence. Ec is a saprophyte bacterium in the human gut, which becomes a pathological one in the human urinary tract^{1,2}.

Symptoms and signs of UC included local ones like abdominal pain, dysuria, pollakiuria, emergency to urination and itching among others. Leucocyturia and hematuria (macro and micro) are also frequent and the urine culture is usually positive, mainly to Ec. There are patients, mostly old patients that show positive urine culture without symptoms and signs of UC. In fact, it is difficult to consider this positive urine culture as a sign of UTI/UC unless the total number of colonies of bacteria is higher than

100.000/field².

UC is usually successfully treated with antibiotics. However, the bacterial antibiotic resistance is an important current problem which leads to look for alternative therapeutic strategies. Bacteria antibiotic resistance is not an exclusive problem of UC treatment, but it has been described as a global problem, and being currently considered one of the most important health issue world-wide^{3,4}.

Since late sixties in the XX century, non-antibiotic products have been used as an alternative to mainly prevent rUTI. Among them the most common ones have been vitamin C, D-mannose and cranberry extracts. It was considered that vitamin C could reduce the urinary pH to reduce the infectious capacity of several bacteria. However, the doses of vitamin C needed to reduce the urinary pH were very high (4 g/day), therefore its use was discontinued. In this sense, the D-mannose was also used with controversial results. However, now a day these products start to be used due to the documented currently bacteria antibiotic resistance^{5,6}.

Regarding the American cranberry fruits, they were used with medical purpose by Canadian First Nations during the XIX century, then its use was abandoned when the antibiotics era started, but they have come back late in the XX century. Cranberry extracts have proven to be quite effective to treat and prevent rUTI due to its anti-adhesion effect against Ec thanks to the proanthocyanidins (PAC) concentration (7-13). More recently, several studies have proven a strong relationship between PAC concentration and anti-adhesion activity. Unfortunately, the lack of a standard analysis method to evaluate PAC concentration of cranberry extracts, as well the lack of information about the anti-adhesion property of many of the cranberry extracts available, are not facilitating its standards use as the first step to treat and prevent UC and rUTI caused by Ec. Cranberry extracts were originally suggested to be used to prevent Ec urinary re-infections by Cochrane Institute in 2008 and the European Urologist Association, however these recommendations were not maintained due to lack of clinical studies, lack of a standard PAC analysis method, and lack of information of its anti-adhesion property¹⁴⁻²¹.

Cysticlean®(CYS) is a very high PAC (240 mg capsule/sachet) concentrated cranberry extract that shows a high anti-adhesion activity against Ec (up to 80%) which is related to PAC concentration²². Several published studies have documented its safety and efficacy profile to for treating and preventing rUTI and UC. More than 600 patients in different studies have been treated with CYS showing an effective prevention of rUTI in different populations: children with congenital urological disease, fertile and postmenopausal women, post-coital infections and elderly people, successfully treated up to 1 year or more. No side effects /adverse reactions have been reported associated to this product²²⁻²³.

The objective of our study was to originally evaluate the efficacy and safety of CYS to treat and prevent rUTI in adult patients younger than 70 years old and to evaluate if one year of treatment with CYS could modify or not several parameters of the renal function, as well as the geriatric functional evaluation in those patients between 60 and 70 years old.

MATERIAL AND METHODS

In this study 27 patients were included: 8 men aged 53-70 years (x: 61.5 ± 6.5) and 19 women aged 18-68 years old (x: 49.2 ± 15.2). In all of them was evaluated rUTI antecedent confirming at least 3 episodes of UTI/year (Table I).

Exclusion criteria were: patients younger than 18 years or older than 70 years, presence of pregnancy, or active oncologic disease.

Inclusion criteria were: patients who were complaining from a new episode of symptomatic cystitis.

Table I: Characteristics of the studied population

	All			Women			Men		
n	27			19			8		
Age	52.19	±	14.13	49.21	±	15.18	60.29	±	5.94
W	69.50	±	12.66	63.38	±	10.36	7.82	±	7.82
H	162.45	±	8.51	159.85	±	9.14	167.29	±	4.54
BMI	26.31	±	4.19	24.92	±	4.32	28.90	±	2.52
Hto	39.85	±	4.50	41.76	±	3.06	35.23	±	2.63

Age=years,y W=weight, Kg H=height, cm
 BMI= Body Mass Index, kg/m², Hto = hematocrit %

Basic demographic data and renal functional parameters were obtained from all patients. Furthermore, patients aged between 60 and 70 years were completely assessed for physical, psychological, functional and social status (quadruple geriatric evaluation) before and after proanthocyanidins cranberry extract treatment.

All included patients were instructed to stop antibiotics for a washing out period of two weeks before introduce CYS in a regime of 1 capsule of CYS (240 mg of proanthocyanidins cranberry extract) in the morning and 1 capsule in the evening up to the signs and symptoms of cystitis were controlled. Patients who suffered from a new episode of UC during the CYS treatment period stopped it and were treated accordingly to the best antibiotic needed. These patients were considered as a fail of the CYS treatment.

Written informed consent was obtained from all patients involved in the study. This study was carried out in accordance with the Helsinki Declaration (2000) of the World Medical Association and was performed in accordance with the principles of Good Clinical Practice.

Statistical analyses were performed using PASW Statistic 18 (SPSS) (2009, IBM Company, Chicago, Illinois). Standard descriptive statistics were used (mean ± standard deviation, max, min, and n) for continuous measurements. univariate correlations (Pearson coefficient) between patient's characteristics (ages, sex and weight), number of signs and were calculated using a two-sided p-value. Comparative evaluation (t test) were performed for comparison; p-value of <0.05 was considered statistically significant.

RESULTS

In this study female patients were less weighted, smaller, younger and had a lower body mass index and slightly lower hematocrit compared to male patients. The glomerular filtration rate (GFR) according to the age ranged 65,6 -105,6 ml/min (women: 65.6 -105.6 ml/min, men: 74.0 - 87.6 ml/min), estimated GFR (by Gregori-Macías equation) ranged 38.0 - 142,98 ml/min (women: 47.56 - 142.9 ml/min, men: 38 - 78.9), serum creatinine (Cr) ranged 0.47 - 2.54 mg/dl (women: 0.47 - 1.98, men: 0.83 -2.54), serum urea (U) ranged 15.0 -75 mg/dl (women: 15.0 - 72 mg/dl, men: 29 -75 mg/dl), chronic kidney disease screening equation (HUGE equation) ranged +5.08 to -7.38 (women: -7.38 to -0.07, men: -3.69 to +5.08). Geriatric assessment remained unchanged along the CYS treatment.

Twenty-one patients did not suffer any UC during the study period. Among them 17 were women and 4 men (p<0,044). Only 6 patients (2 women and 4 men) suffered a UC in the study period (Table II). All this failed CYS treatments were treated with appropriate antibiotics.

Table II: Patients with UC during treatment period

	Not infected	Infected
Total patients	21	6
Women*	19	2
Men	4	4

*p=0,044

No side effects/adverse reactions were reported during the study. The elapsed time between the start of

the treatment and clear up of clinical and bacteriological episode ranged between 3.3-14.8 months (x: 5.3±2.4 months).

At the end of the study, evaluated renal functional parameters showed that women had a significantly lower serum creatinine, serum urea and HUGE values, as well as higher GFR values than men (Table III).

Table III: Renal functional evaluating parameters

	All			Women			Men		
n	27			19			8		
Serum Urea (mg/dl) **	40.00	±	19.1	33.88	±	16.78	54.86	±	16.9
HUGE ***	-2.91	±	3.5	-4.53	±	2.43	1.05	±	2.6
Serum Creatinine*	1.01	±	0.6	0.84	±	0.46	1.42	±	0.6
eGFR ***	85.26	±	35.5	101.2	±	34.73	57.95	±	14.0

Urea=mg/dl; Hto=hematocrit, %; Crea=creatinine, mg/dl; HUGE;
GFR=glomerular filtration rate, ml/min.

*p<0,01, **p<0,005, ***p<0.001 (between sex)

Due to the size of the sample of this study it is difficult to get any conclusion from these data, but it could suggest that UTI may be more frequent in men with slightly reduction of their renal function (Table III).

Further studies on this area should be performed to better know if impaired renal function could be a risk factor of recurrent UTI.

No patient reported any side effect/adverse reaction related to CYS treatment during the study, and cystitis was well controlled in all patients with CYS or antibiotics depending on UC responded to CYS or fail to respond to it, respectively.

DISCUSSION

UTI treatment is on focus of all infections due to their high incidence (2nd infection in the world), being up to 80% caused by *E. coli*, and the non-stop increasing bacteria antibiotic resistance^{1,2}.

According to the UTI characteristics, it seems that alternative non-antibiotic treatments are crucial to be evaluated due to the increasing frequency of antibiotic. From XIX century American cranberry extracts have been used to treat UTI. Unfortunately, lack of cranberry extracts standardization, the influence of the antibiotic era and a non-scientific approach on the use of vitamin C to treat UTI, has made difficult the recognition of its utility³⁻⁵.

Since late XX and further, antibiotic resistance has increased again the interest on American cranberry extracts to prevent and treat UTI⁷.

It is worth pointing out that 2008 Cochrane review recommended the use of such extracts to prevent UTI. Unfortunately, almost all American cranberry products in Europe are commercialized as food supplements. Until August 2017, there were very little sold as a medical product due to its anti-adhesion effect was not considered a pharmacologic action. However, the European Community commission decides that such effect was not a pharmacologic action and then these products were not allowed to continue to be commercialized as medical product. Many studies published since 2004 and beyond have proven that *E. Coli* adhesion to the inner wall of urinary bladder was directly related to the PAC concentration and such effect was directly related to its efficacy to prevent and treat UTI¹⁵⁻²⁰.

In addition, there is currently a real problem to use these extracts as an alternative to antibiotics to treat and prevent UTI because, as food supplements, is not possible to write any medical claim on their labels. Furthermore, there are not clinical trials performed with American cranberry extracts as food supplements and there are not any standard criteria to fix the PAC concentration and the anti-adhesivity of these products to be used as an alternative to antibiotics. This one of the biggest health problem facing by the

world and not too many alternatives are available to antibiotics to treat Ec UTI apart from the documented American cranberry extract products.

CYS with a very high anti-adhesion activity, secondary to its very high PAC concentration, has proven its safety and efficacy to treat and prevent UTI in children, elderly, post coital, fertile and postmenopausal women with no side effects/adverse reactions reported since first commercialization in 2007 ²²⁻²³.

In this study, it was confirmed the high proportion of patients who did not need any antibiotic to treat and prevent their UTI. Furthermore, it was documented that CYS modified neither the renal functional parameters nor the functional status in the studied patients aged 60-70 years.

CONCLUSION

Cysticlean® is an American cranberry extract who has been able to control the UTI in 78% of patients treated in this study thanks to its high anti-adhesion activity provided by its very high PAC concentration. Neither side effects nor adverse reactions were reported. Furthermore, Cysticlean® modified neither patients' renal function nor patient's functional status in this study.

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Comment of the reviewer José R Jauregui MD, PhD. Geriatrician. Hogar Ledor Vador. Buenos Aires, Argentina.

The objective of the study was to originally evaluate the efficacy and safety of CYS to treat and prevent rUTI in adult patients younger than 70 years old and to evaluate if one year of treatment with CYS could modify or not several parameters of the renal function, as well as the geriatric functional evaluation in those patients between 60 and 70 years old, and this objective was obtained.

Comment of the reviewer Laura C Pezzano Pegorer, MD. Internal Medicine physician. Hospital Italiano de Buenos Aires, Argentina.

This study tries to prove an alternative treatment to antibiotics for urinary infection (UI), and the extract of cranberry for its effect of avoiding the adhesiveness of E. Coli can be a valid alternative. Anyway, the number of patients in the study does not allow us to draw valid conclusions and more research is necessary to determine it.

Furthermore, it was documented that CYS modified neither the renal functional parameters nor the functional status in the studied patients aged 60-70 years.

Further studies on this area should be performed to better know if impaired renal function could be a risk factor of recurrent UI.



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ANTIMICROBIAL USE AND CONTROL OF RESISTANCE: AN INTEGRATING VISION

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RESUMEN: Los antimicrobianos y en particular los antibióticos representan uno de los descubrimientos médicos más importantes. Sin embargo, casi simultáneamente al descubrimiento del primer antibiótico, la penicilina en 1928 por Fleming, surgió la aparición de las resistencias a los mismos.

Hoy en día el uso indiscriminado de los antibióticos, sobre todo en el ganado (79% del consumo total), y también en la agricultura y en el ámbito clínico, ha propiciado que nos encontremos ante una situación de alarma mundial ante la falta de antibioterapias efectivas, agravado por el hecho de la falta de descubrimientos de nuevos agentes. Por tanto, se recomienda un uso prudente de los mismos y su administración correcta para controlar las resistencias. Si bien en muchos casos estas resistencias están mediadas por genes, muchos de ellos plasmídicos y por tanto transferibles, otras son mutaciones cromosómicas puntuales reversibles.

La monitorización conjunta de estas resistencias por médicos, farmacéuticos y veterinarios siguiendo una aproximación "One Health" mediante el uso de técnicas de secuenciación masiva, suma potencialidades entre diferentes perfiles profesionales, permitiendo la

caracterización de las resistencias, el conocimiento de la transmisión ambiental y el estudio epidemiológico de las mismas para mejorar el estado de alarma mundial ante la inefectividad antibiótica.

PALABRAS CLAVE: antibióticos, resistencia, secuenciación masiva, colaboración, "One Health"

ABSTRACT:

Antimicrobials, particularly antibiotics, represent one of the most important medical advancements that started in 1928 with the discovery of penicillin by Fleming, simultaneously to the appearance of the antimicrobial resistance (AMR).

Several decades of antibiotic overuse and misuse in humans, animals (79%), and agricultural practices has led to a global critical situation in the absence of effective antibiotics, aggravated by the lack of discoveries of new agents. The policy on antibiotic stewardship promotes the prudent use of antibiotics to avoid the further emergence and spread of antibiotic (multi-)resistance. Some of the resistances are mediated by genes, some of them plasmidic and so transferable, but other are reversible chromosomal point mutations.

The monitoring and identification of common multiresistance patterns circulating in the environment by joint efforts of clinicians, pharmacists and veterinarians, following an "One Health" approach, and using next generation sequencing will share a common goal to characterize the environmental transmission routes and to decide on the best control strategies that ultimately will improve the state of global alarm to face antibiotic ineffectiveness.

KEY WORDS: antibiotics, resistance, next generation sequencing, collaboration, "One Health"

INTRODUCTION

Antimicrobials, particularly antibiotics, represent one of the most important medical advancements¹. Over a half of all deaths in the first quarter of the 20th century were caused by infectious diseases; much higher than the 3% registered at present². Nowadays, thanks to these drugs used in medical or surgical prophylactic schemes and in therapeutic protocols, a large number of clinical procedures can be solved decreasing the impact of an infectious complication.

The antibiotic era began in 1928 with the discovery of penicillin by Fleming, and today more than 100 antibiotics are commercially available, mainly produced by species of the bacterial genus *Streptomyces*. However, only 8 new antibiotics have been approved by the US FDA for sale in the United States from 2011 to 2016⁴. The Spanish Society of

Infectious Diseases and Clinical Microbiology (SEIMC) reported in May 2018 hospital data on multidrug-resistant bacterial infections and estimated that more than 35,000 people die each year with infections caused by these microorganisms, 30 times higher than traffic accident death rate. In 2018, SEIMC has also predicted that the number of infections attributable to multidrug-resistant bacteria will be 180,600 in Spain⁵. The WHO estimates that over ten million people will die from drug-resistant infections each year by 2050, with an economic cost in terms of lost global production between now and 2050 of 100 trillion USD if we do not take actions⁶.

Antimicrobial resistance (AMR) is one of the biggest public health concerns of our time, but genes encoding antibiotic resistance have been authenticated in ancient DNA from 30,000-year-old Beringian permafrost sediments⁷. In the modern era, the resistance has eventually been seen to nearly all antibiotics that have been developed⁸⁻⁹, even Fleming noted resistance to penicillin and Abraham and Chain in 1940 describing first lactamasas¹⁰⁻¹¹. Even these facts, several decades of antibiotic overuse and misuse in humans, animals (79% of all antimicrobials used in the US), and agricultural practices has led to that we are facing a world alarm situation in the absence of effective antibiotics, aggravated by the lack of discoveries of new agents⁴.

WHO has adopted annually during November the World Antibiotic Awareness Week aiming to increase awareness of global antibiotic resistance¹². It is recommended from all institutions the prudent use of antibiotics regard to agent selection, dosing, administration and duration of treatment, in order to avoid the further emergence and spread of antibiotic resistance. Furthermore, to address this alarming global threat, it is important to monitor and identify common multiresistance pattern circulating in the environment, in order to decide on the best strategies to avoid the development and propagation of resistances and to be able to define better treatment guidelines. Antibiotics resistance not only concerns clinical isolates, but there is a resistome (the collection of all genes that contribute to resistance) in pathogenic, commensal and environmental bacteria, either integrated in the chromosome, but also in mobile genetic elements and bacteriophages, which they form a reservoir that can be acquired by horizontal transmission (Horizontal Gene Transfer, HGT).

In the Area of Microbiology of the University of Burgos, the Laboratory of Molecular Biology and Microbiology of the Agricultural Technological Institute of Castilla y León, and the Microbiology Service of the "Río Hortega" University Hospital (HURH), medical practitioners, pharmacists and veterinarians joint efforts to monitor antibiotic resistance in hospitals, animals, and environments, with particular interest in the food microbiota, from farm to food, and the human microbiota, focusing on the study of enterobacteria resistant to carbapenems due to the production of beta-lactamasas and species of the genus *Clostridioides* causing diarrhea¹³⁻¹⁵. The bacterial genomic studies involve the use of High-Throughput Sequencing Technologies (HTS) or Next Generation Sequencing (NGS) that allow to identify and genotype bacteria species applying "One Health" holistic approach, and how and why those bacteria have develop resistance. The generated knowledge serves as a basis for efficient treatment of the patients and minimize the risk of infection during admission into a hospital to improve Public and Animal Health¹⁶.

In order to combat the lack of new antibiotics and reduce their consumption, the use of natural antimicrobials is being tested in cattle and at the same time recommendations for a better management in livestock farms can contribute to reduce the use of antibiotics. In the

JACRA report (Joint Inter-agency Antimicrobial Consumption and Resistance Analysis) published in Spain in May 2018 that integrates data on consumption and resistance to antibiotics with a joint analysis of the possible associations between consumption and the occurrence of antibiotic resistance in human and animal health, a reduction of 14% in the total consumption of antibiotics was observed from 2014 to 2016¹⁷. In addition, and thanks to the Agreement for the Voluntary Reduction of Colistin Consumption in the Porcine Sector of Spain, the consumption of colistin (last resort antibiotic) has decreased by 85.9% from 2015 (51.09 mg / PCU) until mid 2018 (7.2 mg / PCU).

As in other areas of knowledge, to join potentialities between different professional profiles at the same time that represents a challenge of human and labor understanding, constitutes a system of synergies that, in our modest experience, should not be underestimated.

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Comment of the reviewer Maria Angeles Mantecón, PhD. Servicio de Microbiología del Hospital Universitario de Burgos. España.

El aumento y diseminación de bacterias multirresistentes así que como la falta de desarrolla de nuevas moléculas antibacterianas es una de las amenazas más importantes, hoy en día, para la Salud Pública tal y como han puesto ya de manifiesto desde hace algunos años organismos tanto nacionales como internacionales.

Este problema al que nos enfrentamos no se quede reducido solo al ámbito de la salud humana, sino que también alcanza a la salud animal y al medio ambiente. Este hecho justifica que el abordaje de este problema se tenga que hacer desde una perspectiva "One Health". Por ello, iniciativas como la de la Dra. Hernández con un equipo de trabajo formado por profesionales de diferentes ámbitos de la salud humana, veterinaria y de la