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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 advancements[1]. 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 present[2]. 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 2016[4]. 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 Spain[5]. 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 actions[6].

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 sediments[7]. In the modern era, the resistance has eventually been seen to nearly all antibiotics that have been developed[8-9], even Fleming noted resistance to penicillin and Abraham and Chain in 1940 describing first lactamasas[10-11]. 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 agents[4].

WHO has adopted annually during November the World Antibiotic Awareness Week aiming to increase awareness of global antibiotic resistance[12]. 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-lactamases and species of the genus Clostridioides causing diarrhea [13-15]. 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 Health[16].

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

JIACRA 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 2016[17]. 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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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

agricultura son bienvenidas y muy necesarias para un mayor conocimiento de las resistencias en nuestro medio que posibiliten tratamientos más eficientes.

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Brillante exposición de la Dra. Hernández y colaboradores que aborda el problema creciente de las bacterias multirresistentes analizando el nexo de unión entre salud humana y salud animal a través microbiota integrante de la cadena alimenticia.

Su trabajo está en completa sintonía con el Plan Nacional frente a la Resistencia a los Antibióticos (PRAN) también enfocado en esa doble vertiente humana y veterinaria y que desde su puesta en marcha ha impulsado numerosas iniciativas que, entre otras cosas, han conseguido que España pase de ser el tercer país de la Unión Europea en consumo de antibióticos en salud animal a establecer acuerdos para la reducción voluntaria del consumo de colistina en el sector del ganado porcino, favoreciendo la no aparición de resistencias en un antibiótico muchas veces empleado como única alternativa de tratamiento de los pacientes con bacterias multirresistentes.
