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Sumario

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New materials and complications of prostheses in humans: situation in Spain

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ABSTRACT

Prostheses or implantable medical devices (IMDs) are parts made of natural or artificial materials intended to replace a body structure and therefore must be well tolerated by living tissues. The types of IMDs currently available and usable are very varied and capable of replacing almost any human organ. A high but imprecise percentage of Spaniards are carriers of one or more IMDs to which they often owe their quality of life or survival. IMDs are constructed with different types of materials that are often combined in the same prosthesis. These materials must combine harmlessness to human tissues with high wear resistance. Their durability depends on many factors both on the host and the type of prosthesis, but the vast majority last for more than 10-15 years or remain in function for the lifetime of the patient. The most frequently implanted IMDs are placed in the heart or great vessels, joints, dental arches or breast and their most frequent complications are classified as non-infectious, particularly loosening or intolerance, and infectious. Complications, when they occur, lead to a significant increase in morbidity, their repair or replacement multiplies the health care cost and, on occasions, can cause the death of the patient. The fight against IMD complications is currently focused on the design of new materials that are more resistant to wear and infection and the use of antimicrobial substances that are released from these materials. Their production requires multidisciplinary technical teams, but also a willingness on the part of industry and health authorities that is not often found in Spain or in most European nations. Scientific production on prostheses and IMD in Spain is estimated to be less than 2% of the world total, and probably below what corresponds to our level of socio-economic development. The future of IMDs involves, among other factors, examining the potential role of Artificial Intelligence in their design, knowledge of tissue regeneration, greater efficiency in preventing infections and taking alternative treatments beyond antimicrobials, such as phage therapy. For these and other reasons, the Ramón Areces Foundation convened a series of experts in different fields related to prostheses and IMDs who answered and discussed a series of questions previously formulated by the Scientific Council. The following lines are the written testimony of these questions and the answers to them.

Keywords: Prostheses, Implantable Medical Devices, arthroplasties, endovascular devices, infection, loosening, endocarditis, materials, biomaterials, cost, scientific production, design, health care expenditure.

Nuevos materiales y complicaciones de las prótesis en humanos: situación en España

RESUMEN

Las prótesis o dispositivos médicos implantables (DMIs) son piezas fabricadas con materiales naturales o artificiales destinadas a sustituir una estructura corporal y por tanto deben ser bien toleradas por los tejidos vivos. Los tipos de DMIs existentes y utilizables en el momento actual son muy variados y capaces de sustituir casi cualquier órgano humano. Un elevado pero impreciso porcentaje de españoles son portadores de uno o más DMIs a los que con frecuencia le deben su calidad de vida o su supervivencia. Los DMIs están construidos con tipos distintos de materiales que con frecuencia se combinan en una misma prótesis. Dichos materiales deben combinar su inocuidad para los tejidos humanos y una gran resistencia al desgaste. Su duración depende de muchos factores tanto del huésped como del tipo de prótesis, pero la gran mayoría duran más de 10-15 años o permanecen en funcionamiento incluso durante toda la vida del paciente. Los DMIs más frecuentemente implantados se ponen en el corazón o grandes vasos,

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en las articulaciones, en las arcadas dentales o en la mama y sus complicaciones más frecuentes se clasifican en no infecciosas, particularmente el aflojamiento o intolerancia, e infecciosas. Las complicaciones, cuando ocurren, suponen un significativo aumento de la morbilidad, su reparación o sustitución multiplica el coste sanitario y, en ocasiones, pueden causar la muerte del enfermo. La lucha frente a las complicaciones de los DMIs se centra en la actualidad en el diseño de los mismos con nuevos materiales, más resistentes al desgaste y a la infección y en la utilización de sustancias antimicrobianas que se liberan desde dichos materiales. Su producción requiere equipos multidisciplinares técnicos, pero también una disposición por parte de la industria y de las autoridades sanitarias que no se dan frecuentemente en nuestra nación ni en la mayoría de las naciones europeas. La producción científica sobre prótesis y DMIs en España se estima por debajo del 2% de la mundial y verosímilmente por debajo de lo que corresponde a nuestro nivel de desarrollo socioeconómico. El futuro de los DMIs pasa, entre otros factores, por examinar el potencial papel de la Inteligencia Artificial en su diseño, del conocimiento de la regeneración tisular, de una mayor eficiencia en prevenir mejor las infecciones y de llevar más allá de los antimicrobianos los tratamientos alternativos como es el caso de la fagoterapia. Por estas y otras razones, la Fundación Ramón Areces convocó a una serie de expertos en distintas materias relacionadas con las prótesis y DMIs que respondieron y discutieron una serie de preguntas formuladas previamente por el Consejo Científico. Las líneas que siguen son el testimonio escrito de esas preguntas y de las respuestas frente a las mismas.

Palabras clave: Prótesis, Dispositivos Médicos Implantables, artroplastias, dispositivos endovasculares, infección, aflojamiento, endocarditis, materiales, biomateriales, coste, producción científica, diseño, gasto sanitario

INTRODUCTION

Prostheses or implantable medical devices (IMDs) are made from a variety of materials and a high proportion of people over the age of 60 have one or more IMDs that improve their quality of life or enable them to continue living.

The biomaterials industry includes organisations and companies that design, manufacture, and fabricate materials that are used to make prostheses and there have been significant advances in the design of new biomaterials. At the same time, improvements have been made in the surgical techniques for implanting IMDs and in the management of their complications.

Despite all this, most of the scientific information available on IMDs is focused on very specific types of prostheses, such as joint or cardiac prostheses, and the orientation of the publications on them is very much oriented towards either the science of new materials or the field of medical practice.

As far as Spain is concerned, on the other hand, some aspects of the use of some prostheses, the workload they generate for the health system and the expenditure related to their implantation and maintenance are not well known.

For these reasons, the Scientific Council of the Ramón Areces Foundation asked itself a series of questions about the situation of prostheses in Spain, inviting a number of experts from different fields to answer them so that they could give the most global view possible of our situation.

At the meeting held at the Foundation Ramón Areces in Madrid in April 2024, aspects such as the most frequent types of prostheses currently in use in Spain, the materials of which they are composed, research into future new materials, infectious and non-infectious complications, the cost to the system and the evolution of our scientific production on this problem were discussed.

The following lines collect the questions and answers that were produced on the situation of prostheses in humans in Spain.

WHAT DO WE UNDERSTAND BY PROSTHESES AND BIOPROSTHESES? WHAT ARE THE MAIN DEFINITIONS IN THIS FIELD?

According to the Real Academia Española de la Lengua (RAE), prosthesis is: A part or device used to replace an organ or a limb of the body. A piece of animal tissue used to repair or replace a part of the human body, such as a heart valve, is called a bioprosthesis.

All prostheses are made of materials that can be implanted in a living organism, and it is now possible to replace almost all parts of the organism. Physical disability and age are closely linked to the need for prostheses. If during the first 10 years of life the need to replace damaged parts of the human body is very low, by the age of 60 the percentage can reach very high levels.

Prostheses must necessarily be biologically compatible with the human body. They are used to repair or replace damaged natural tissue, such as bones, heart valves, teeth or skin, and in the near future, organ tissues such as liver or kidneys. The goal of using biomaterials is to save people, improve their quality of life, reduce suffering and help them reach the end of life in a better condition. The science that deals with the design of prostheses and the study of the materials of which they are made is biomedical engineering.

Implanted prostheses can be temporary or definitive, but in any case, they must fulfil a specific function without causing any damage to the organism. Provisional prostheses, such as vascular catheters, have different construction requirements to those of definitive prostheses, such as hip prostheses, which must remain in perfect condition indefinitely.

In any case, prostheses must be biocompatible or biologically acceptable and must maintain their performance for the required periods of time, short in the case of provisional prostheses and very long in the case of definitive prostheses.

The greatest advances in the field of biomaterials have been made in developed countries as a result of the need to treat a large number of patients clinically. The increase in life

expectancy and the obligation to ensure a high quality of life for citizens have been key factors in the design and construction of prostheses.

The search for possible solutions to tissue problems has led to a high demand for materials to replace or repair them artificially. On the other hand, the improvement of surgical techniques has led to an accelerated growth in the demand for prostheses, implants and medical systems and devices that must work in contact with body tissues [1-6].

HOW MANY SPANIARDS LIVE WITH ONE OR MORE PROSTHESES? HOW MANY ARE IMPLANTED PER YEAR?. WHAT TYPE OF PROSTHESES ARE WE TALKING ABOUT? DO WE HAVE NATIONAL REGISTRIES IN SPAIN?

It is safe to say that millions of Spaniards today live with one or more implantable medical devices (IMDs) and that their health depends to a large extent on their proper functioning.

The distribution of the use of IMDs varies significantly between countries due to factors such as the availability of medical care, healthcare infrastructure and differences in rates of diseases and medical conditions. Countries with more advanced health systems tend to have a higher rate of IMDs [7].

To give just a few figures, according to the Spanish Society of Plastic, Reconstructive and Aesthetic Surgery (SECPRE), around 25,000 breast augmentation surgeries are performed in Spain every year. This number includes both cosmetic and reconstructive breast implants [8].

As for joint replacements, between 30-35,000 are implanted each year in our country and, at European level, it is estimated that the incidence rate is between 50 and 1,140 joint replacement procedures per 100,000 inhabitants/year [9].

In the cardiovascular field, we know that more than 17,000 valve prostheses are implanted annually by cardiac surgery or transfemoral surgery [10,11]. And if we look at cardiac electrostimulation devices, 8,000 permanent automatic defibrillators and more than 40,000 pacemakers are implanted in Spain every year, which means an implantation rate in this field of around 900 units/million inhabitants/year [12,13].

In Spain there are registers of implants in almost all the Autonomous Communities, but there is a lack of centralised registers as in other countries, which would make it possible to extract a multitude of useful data in a very short period of time, with little effort and at a low cost. By way of example, the Spanish registry of breast prostheses (SREIM) has been operating normally for several years now, and for cardiac prostheses, electrostimulation devices, circulatory and respiratory assistance devices we also have national registries [14].

In contrast, the national registry of joint replacements (RENAPRO), which was launched in 2019, was not as successful. It should be clarified that these registers are voluntary, usually supplemented by the doctors who perform the implants, so they may differ slightly from the data provided by each manufacturer or even the data provided by the various supply departments of each hospital belonging to a health system in a given Autonomous Community.

Internationally, it is estimated that 8-10% of the American population and 5-6% of the inhabitants of industrialised countries have one or more IMDs to improve body function or for aesthetic reasons. In the case of cardiac implants, it is estimated that at least 400,000 Americans receive a cardiac electrostimulation implant (CIED) each year [15-17].

The most commonly used prostheses in our environment are valvular heart and vascular prostheses, cardiac electrostimulation devices, osteo-articular, mammary, genito-urinary, dental, ocular, auditory, nasal prostheses and also prostheses for the airways and digestive tract (mainly oesophagus) (Table 1).

An example of a very commonly used prosthesis is dental implants which have become an increasingly popular treatment option to replace missing teeth. Between 1999 to 2016 in the US there has been a large increase in the prevalence of dental implants, from 0.7% in 1999 to 2000 to 5.7% in 2015 to 2016. The largest absolute increase in prevalence (12.9%) was among those aged 65-74 years, while the largest relative increase was ~1,000% among those aged 55-64 years. There was a covariate-adjusted mean increase in dental implant prevalence of 14% per year.

The projected prevalence of dental implants until 2026 ranged from 5.7% in the most conservative scenario to 23% in the least conservative scenario [19].

The Italian Society of Otorhinolaryngology, for example, has recently reviewed the discussed situation of cochlear implants, their indications and limitations [20-22].

In addition, implantable biosensors to detect the presence of specific substances, or to monitor brain activity and systems to deliver drugs to specific points in the body, drug-coated vascular stents or nanoparticles for the treatment of different diseases, in particular cancer, should be considered as prosthetic material [23-25].

WHAT KINDS OF BIOMATERIALS ARE USED TO BUILD PROSTHESES?

Major advances in medicine and surgery since the second half of the last century have led to the development of increasingly complex clinical devices, and in particular to the development of prostheses that can be implanted inside the human body.

The main applications of biomaterials are manifold and have already been mentioned [26] (Table 1) and research in the field of biomaterials has grown enormously over the last fifty years. However, in the field of implantable prostheses, the range of biomaterials used remains very similar to those that were first used in the last century. Two reasons for this have to do with the need for clinical implants to meet all the safety and efficiency requirements demanded by regulatory and

Table 1 **Summary of surgically implanted prostheses covered by the national health system. Adapted from Ministerio de Sanidad [18].**

CARDIAC IMPLANTS
CA 0 IMPLANTS FOR CARDIAC STIMULATION
Include: Single-chamber pacemakers with/without remote monitoring, Single-chamber SSIR pacemakers (rate responsive), dual-chamber pacemakers with or without remote monitoring, pacemakers with cardiac resynchronisation therapy (rate responsive), implantable automatic defibrillators (ICDs) (single or dual-chamber), subcutaneous defibrillator and electrodes for cardiostimulation.
CA 1 CARDIOLOGICAL IMPLANTS
Include: Directly implanted or self-expandable mechanical or biological valves, transcatheter aortic valves (TAVI), valvuloplasty rings, valved or non-valved conduits, synthetic or biological pericardial substitutes (xenologues), cardiac and vascular occluder devices, VSD closure systems, ventricular assist devices, ...
GASTROENTEROLOGICAL IMPLANTS
They include: Oesophageal stents (valved or not), duodenal, colorectal, bilio-pancreatic, rectal anal, artificial anal sphincters and percutaneous portosystemic shunts (TIPS), adjustable gastric bands,...
GENITOURINARY IMDs
They include: Ureteral endoprostheses (mono or double J), prostatic endoprostheses, anti-incontinence prostheses, penile prostheses for erectile dysfunction, testicular, pelvic organ prolapse implants, tubal obstruction implants via hysteroscopy, ...
NERVOUS SYSTEM IMPLANTS
They include: Shunt systems and reservoirs, single or multi-channel neurostimulators for both brain and spinal or peripheral nerve channels, electrodes
OPHTHALMOLOGIC IMPLANTS
Including: anterior and posterior chamber intraocular lenses, capsular tension rings, glaucoma surgery devices, enucleation and evisceration prostheses, paepebral implants, tear duct implants, ...
ENT IMPLANTS
They include: middle ear prostheses, transtympanic drainage tubes, hearing implants, phonatory prostheses, laryngeal prostheses, ...
IMPLANTABLE DRUG DELIVERY DEVICES
These include: implantable infusion pumps, subcutaneous reservoirs, implantable catheters, ...
RESPIRATORY SYSTEM IMPLANTS
They include: Tracheal and bronchial prostheses, endobronchial valves, lung volume reduction devices, ...
RESTORATIVE IMPLANTS
They include: Breast prostheses, custom-made silicone prostheses, for thoracic defects secondary to congenital malformations, trauma or disease, which cannot be repaired with autologous tissue, prostheses with polyurethane surface, skin expanders, implants for cranio-facial surgery, dental implants, nasal implants, auricular pinna, temporomandibular joint prostheses, prostheses for reconstruction of mastoid cavities, cranial plasties, meshes for containment of eventrations and hernias, ...
OSTEOARTICULAR IMPLANTS
They include: Hip, knee, shoulder, elbow, wrist, wrist, hand, other joint prostheses, spacers, vertebral body prostheses, intervertebral prostheses, fixators, intramedullary nails, ...
VASCULAR IMPLANTS
They include: Vascular substitutes, coronary stents, vena cava filters,....
DIAGNOSTIC CARDIAC IMPLANTS
They include: Implantable Holters with/without remote monitoring, for the evaluation of patients with cardiac rhythm disorders, ...

accreditation agencies and on the other hand that from an economic and production point of view, the new biomaterial, after passing all the tests required by the regulators, will end up being more competitive than the current material on the market [27,28]. Generally speaking, these first-generation biomaterials that are well described by regulatory agencies meet characteristics such as having passed biocompatibility tests, being sterilisable, being stable in the long term (resistance to corrosion, degradation, wear, etc.), and also that they can be manufactured with common techniques (machining, extrusion, moulding, injection, etc.).

The types of biomaterials used in the manufacture of prostheses include the four major groups of materials: metals, polymers, ceramics and composites [24,26,29,30].

Metals are mainly used in joint prostheses, plates and screws for fixations in traumatology, staples, dental implants, etc. The types of metals most commonly used in prostheses are: stainless steels, always austenitic, as they allow cold working

and/or forging, are used in plates and screws for traumatology, vertebral fixations and joint prostheses; cobalt-chromium alloys (Co-Cr) which can be used cast (melted and annealed) or forged, have high rigidity and mechanical strength and are mainly used in joint prostheses and dental prostheses; pure titanium (Ti) grade 4 which is used in dental implants and its alloys (especially Ti-6Al-4V containing 6% aluminium and 4% vanadium) which is used in joint prostheses.

Polymers have a wide range of applications due to their diversity and properties. A distinction is made between synthetic polymers and natural polymers. Among the most commonly used synthetic polymers are: high-density polyethylene (PE) with good wear resistance and biostability used in joint replacements; polymethylmethacrylate (PMMA), a rigid, hard, hydrophobic, bioinert and transparent material used as bone cement, also in contact and intraocular lenses and dentures; polypropylene (PP) with high rigidity, mechanical strength and biostability used in non-biodegradable sutures and structures for heart valves; polyetheletheretherketone (PEEK) which has good mechanical properties, is bioinert and is used in orthopaedic implants and spinal implants; polyethyleneterephthalate (PET) (Dacron) which has good mechanical properties and is used in vascular implants, hernia repair and ligament reconstruction; polyurethane (PU) with elastomeric properties is used in tubing and catheters as well as in blood contact applications; polytetrafluoroethylene (PTFE) is hydrophobic and low strength, used in vascular implants, catheter coatings and heart valves; high mechanical strength polyamides (nylons) are used in haemodialysis membranes and non-resorbable sutures; polyglycolic acid (PGA) is biodegradable and used in drug delivery systems and resorbable sutures; and finally, polylactic acid (PLA) is biodegradable and used in drug delivery systems.

Natural polymers are mainly proteins, polysaccharides and polynucleotides and have the advantage of resembling biological substances in the body and can be degraded in the body. At the same time, they have major disadvantages in that they can produce immunological, toxic and inflammatory reactions. In addition, there can be variability from batch to batch. Among the most commonly used, often in combination with other materials, are collagen, elastin, alginate, chitosan, hyaluronic acid and silk. Mention should be made of the use of decellularised extracellularised matrices as scaffolds for tissue engineering.

Ceramics and glass are rigid and brittle materials that find different applications depending on whether they are inert or bioactive. In the case of inert ceramics, the most commonly used materials are aluminium oxides (alumina Al_2O_3) and zirconia (zirconia ZrO_2), which are used in joint prostheses, mainly hip prostheses (the sphere of the joint, although in the case of alumina the acetabulum can also be made of this material), and zirconia is also used in dental prosthesis crowns. Both alumina and zirconia have been used as coatings for metal substrates. Bioactive ceramics correspond to different formulations of calcium phosphates, with tricalcium phosphate (TCP) and hydroxyapatite (HA) being the most commonly used. Calcium phosphates, chemically close to the mineral phase of bone, induce biological activity when implanted into a bone substrate and help regenerate bone tissue or become anchored to it. They are low-strength and brittle materials. They are used in the form of porous particles or granules for fillers and in coatings for metal substrates. Bioactive glasses consist of different formulations with silicon oxide contents of over 40% and different contents of phosphate, calcium and sodium ions, among others. These glasses exhibit a great capacity for chemical bonding to bone. Their fragility and low strength also makes it necessary to use these materials in granular or particulate form and they find application in traumatology, fracture repair, spinal fusion, craniofacial and maxillofacial applications. Both calcium phosphates and bioactive glasses are also used as reinforcement and bioactive phase in composite materials.

Composite materials seek to combine two or more materials with the aim that their interaction leads to resulting properties that enhance those of the individual constituents. The scope of applications is very broad, as the different combinations allow for optimisation of important parameters such as mechanical properties, biostability, biodegradation, bioactivity, hydrophobicity, etc. For trauma and spinal fixation applications, bioinert combinations of carbon fibres in matrices of different polymers can be considered, which may include epoxy resins, PMMA or PP among others, as well as biodegradable combinations based on HA granules or PGA or PLA fibres in PLA or even PGA matrices. In the case of bone cements, a PMMA matrix has been reinforced with HA or bioactive glass granules. PEEK has been combined with carbon fibres for the manufacture of hip prosthesis stems. For bone filling and regeneration PLA or PGA have been combined with HA granules. Mixtures of natural polymers with synthetic polymers and/or bioactive ceramics have also been used but can hardly be qualified as composite materials due to the lack of interaction between the constituent phases.

WHAT CARDIAC PROSTHESES ARE IMPLANTED IN SPAIN AT THE PRESENT TIME? WHAT MATERIALS ARE THEY MADE OF? WHAT IS THEIR AVERAGE LIFE SPAN?

The cardiac prostheses currently implanted in Spain are either mechanical or biological. There are two methods of implantation: by open surgery or by catheterisation, known as TAVI procedure, which stands for Transcatheter Aortic Valve Implantation.

According to data from the Spanish Society of Cardiovascular and Endovascular Surgery, 11,257 cardiac prostheses were surgically implanted in Spain in 2021, 70% of which consisted of biological material [10]. On the other hand, according to the registry of the Spanish Society of Cardiology in 2022, 6,672 TAVI procedures were performed in Spain [11].

In terms of materials, mechanical prostheses usually con-

sist of two parts: the suture ring, which is usually made of Dacron or Teflon, highly resistant polyester fabrics; and the structure of the prosthesis itself, which is usually made of graphite bombarded with carbon atoms at high temperatures. They are also impregnated with tungsten to make them radiopaque.

Biological prostheses are classified as follows:

1. Xenografts(made of porcine or bovine animal material): they are designed in two parts: a Dacron suture ring and the leaflets themselves, sewn to the ring and composed of bovine pericardium or porcine valves. TAVI and some surgical prostheses may have a cobalt-chromium alloy or nickel-titanium (Nitinol) metal framework in addition to the biological tissue.
2. Homografts: grafts from a cadaveric donor and cold preserved.
3. Autografts. Composed of the patient's own biological material.

The half-life of a prosthesis will depend on the type of prosthesis and other factors such as age, position (aortic, mitral, tricuspid, pulmonary), associated pathology and the statistical method used to evaluate its durability.

Biological prostheses have a limited durability, undergoing a degenerative process called primary structural failure. After 10-15 years, approximately 30% of patients have to be operated on again to replace them. This failure is more rapid in young people, in valves in mitral position and in patients with diseases in which calcium metabolism is altered, such as renal insufficiency or hyperparathyroidism. The statistical method used is important when estimating the durability of a prosthesis. The Kaplan-Meir method, the actuarial method and the current method are used for this estimation. The first two are based on a probabilistic calculation by time intervals and assume that patients would live indefinitely and are removed from the calculation when they suffer the event under study, in this case the structural failure of the prosthesis. The potential pitfall with these two methods is that many patients die during the study and are removed from the analysis without being able to accurately estimate the durability of the prosthesis. This is known as the competing risks of the structural failure event and the death event. To solve this problem, the actuarial method with competing risks is used, which takes into account the two aforementioned events and provides a more realistic estimate of the durability of a prosthesis.

In general terms and depending on the patient's age and other factors, it is estimated that a biological prosthesis in the aortic position has an average durability of 15-20 years and in the mitral position of 10-15 years.

Mechanical prostheses do not undergo the degenerative process and are designed to last a lifetime. However, they may require replacement due to infection (endocarditis) or thrombosis or perivalvular leaks. They have the disadvantage that patients need to take anticoagulants to prevent thrombus formation.

WHAT IS THE NUMBER AND TYPE OF PACEMAKERS USED IN SPAIN TODAY?

There are three types of pacemakers that are implanted: conventional pacemakers (a generator that is connected to wires placed in the heart), pacemakers without wires (implanted directly in the heart) and resynchronisers/defibrillators that improve the contraction of the heart and give an internal shock if there is an episode of severe arrhythmia.

According to data from the Registry of the Spanish Society of Cardiology in 2022, 41,082 conventional pacemakers (866/million inhabitants) were implanted in Spain. To this must be added 4,604 (34/million inhabitants) resynchronisation devices and 813 pacemakers without leads [13].

WHAT ARE THE MAIN NON-INFECTIOUS COMPLICATIONS OF PROSTHESES?

Complications of prostheses are generally classified as infectious and non-infectious (aseptic). In this section we will refer to non-infectious complications.

In the case of prostheses for use in the locomotor apparatus, the work to be carried out during the patient's lifetime is extremely intense. It has been estimated that the load supported by the main lower limb prostheses (hip, knee) is 1 million cycles per year in a 70-year-old patient, and up to 5 million cycles per year in an active and sporty 40-50-year-old patient. This can lead to the implant withstanding 10 to 50 million load cycles of between 500 and 1,000 Newtons for a patient weighing 70 kg, and this in 10 years of implant survival. The mechanical fatigue problems faced by loaded joint replacements are therefore enormous. Consider that an automotive wiper system is validated by industrial quality controls for 100,000 operating cycles, and here we are talking about millions of cycles. Together with the aggressiveness of the internal environment (highly oxidising, in an aqueous environment), and exposed to trauma and impact, to injuries and atrophy of periarticular soft parts (ligaments, capsule, musculature), to inflammation of the joint which also deteriorates the bone around the implant, joint prostheses fixed to the bony ends of the joint can be said to be in a hostile environment, which will progressively deteriorate their functioning.

There are different sources for defining the complications associated with joint replacements and, as a basis, we will refer to arthroplasty registries and patient series from large hospitals. Different causes of prosthesis replacement due to short- or long-term complications have been identified, and differences are also observed between the main joint replacements of the lower limb, such as the hip and the knee. Due to the current interest and frequency of the knee prosthesis, which is currently 3 times more frequently implanted than the hip prosthesis, we will focus on non-infectious complications of these prostheses.

Non-infectious causes account for 60-70% of reoperations for knee replacement complications in different regis-

tries (Swedish Arthroplasty Registry; National Joint Registry of England, Wales, and Northern Ireland; Australian Orthopaedic Association National Joint Replacement Registry) [31]. Aseptic loosening predominates, followed by instability, extensor apparatus and patellar problems. After infection and aseptic loosening, other causes may combine in mechanical complications [32]. Aseptic loosening is associated with particulate matter from material deterioration and the resulting inflammatory reaction. Therefore, the temporal evolution observed after improvements in materials and designs leads to a decrease in aseptic loosening as the main non-infectious complication, although it is still remarkable [33]. In contrast, other long-term complications such as instability and periprosthetic fracture, which occurs in older patients and carriers of certain implant types, are increasing. Joint stiffness is also increasing as an early complication in younger patients and in arthroplasty for post-traumatic osteoarthritis [34].

Monitoring long-term complications of joint implants is essential to correct them, to drive improvements and innovation, and to obtain the best results for, if possible, the patient's entire life.

WHAT DOES INFECTION AS A COMPLICATION OF PROSTHESES REPRESENT IN TERMS OF NUMBERS? DOES IT DEPEND ON THE MATERIALS OF WHICH THE PROSTHESIS IS MADE? WHAT ARE THE CONSEQUENCES?

Although biomaterial infections have a generally low incidence (2-7% overall), their importance is paramount. Infection of a device is always a major complication that compromises its subsequent functioning, and sometimes even the life of the person who has received the implant, which may be essential for the normal functioning of an organ, such as cardiac prostheses, in which infection (prosthetic infective endocarditis) can exceed 30% mortality rate. [35]. And if we look strictly at the costs, they literally skyrocket when there is an infection. The cost of acquiring a joint replacement, for example, is around €6-7,000 in European countries [36]. The infection of this implant will increase the total cost of the process by a factor of 10 (€50,000) [37], and the same is true for electrostimulation device infections, as not only does the infected device have to be replaced, but the resulting hospital stays will necessarily be lengthy [38-43].

In the pathogenesis of infection of a biomedical device, the first step is the adherence of the micro-organism to the device. For many decades, when talking about prosthesis-associated infections, the biomaterial was given a secondary and passive role, with greater importance being given to the micro-organism and the patient's defence mechanisms. Nowadays, however, there are many data available that highlight the importance of the nature of the biomaterial, since adhesion is also decisively influenced by the surface and characteristics of the biomaterial. In fact, initial adhesion will depend on physicochemical interactions such as electrostatic interactions, van der Waals forces or hydrophobic interactions [44,45]. These interactions will also affect the adhesion of proteins and other tissue or serum components and the resultant of this may lead to a second, no longer reversible step, which is the specific adhesion of microorganisms mediated by both host (fibronectin and other adhesins) and host proteins [44]. From here, the micro-organisms will initiate the large-scale production of a "biofilm" or slime that will protect them from the host's defence mechanisms, as well as from other harmful agents such as antimicrobials, which penetrate these structures poorly and are often inactivated by enzymatic mechanisms. Today we also know that the colonies involved in these biofilms coordinate with each other through a fascinating communication network to work together, which has come to be known as quorum sensing, to control certain functions that will facilitate their survival, including through the selection of more resistant mutants [46]. It is undeniable that the nature of the biomaterial will influence the development of these biofilms to a greater or lesser extent, depending also on the microorganisms attached.

HAS THE COST OF IMPLANTING PROSTHESES IN SPAIN BEEN ESTIMATED?

The cost of the prosthesis itself varies depending on the type and complexity of the device. For example, hip and knee replacements can have significant upfront costs, ranging from thousands to tens of thousands of dollars, depending on factors such as the material, brand and technology used.

In addition to the cost of the device, the expenses associated with the surgery must be considered, including staff fees, anaesthesia, hospitalisation and post-operative rehabilitation. These costs can be considerably high and must be taken into account when assessing the economic impact of prosthetic implantation.

On the other hand, the long-term costs associated with maintenance and possible complications of prostheses must be considered. This may include surgical revisions, component replacements and treatment of complications such as infections or loosening of the prosthesis.

Finally, there is a social cost resulting from prolonged periods of inability to work, which can have a significant impact on the patient's productivity and income, as well as costs associated with social care and disability insurance.

For many patients, the implantation of a prosthesis can mean a significant improvement in mobility and physical function, allowing them to lead a more active life and participate in daily activities that were previously difficult or impossible.

Well-designed and properly implanted prostheses can reduce or eliminate chronic pain associated with conditions such as osteoarthritis, improving the patient's overall well-being and quality of life.

Restoration of physical function and reduction of pain can have a positive impact on the patient's mental health and emotional well-being, improving their self-esteem and ability to cope with the challenges of everyday life.

The studies we have found on all these aspects are, however, scattered and partial [47-53]. As examples we can say that costs range from around $4000 to $6000 for expandable aorto-iliac prostheses [54] to figures of around £10,000 to £30,000 for uncomplicated knee prostheses [55] 18,000 to €20,000 for breast reconstruction after cancer resections in data from Spain [56]. Table 2 provides some guidance on prosthesis procurement costs.

In patients with heart valve replacements, the cost-effectiveness of having the valve replaced either by TAVI or implantation after open surgery in patients with severe aortic stenosis has been compared, with cost differences between the procedures ranging from $11,000 to $18,000[57]. In the case of mitral surgery, the episodes in which the natural mitral valve can be repaired versus those in which it has to be replaced represent a cost difference of between 34,000 and 55,000 € in favour of the conservative procedure in each episode [58].

WHAT IS THE CURRENT SITUATION OF PROSTHESES WITH NON-ADHESION MATERIALS AND WHAT IS THEIR FUTURE?

Antiadhesion biomaterials usually refer to materials whose surface has repellent properties that prevent adhesion or embedding of micro-organisms or cells. In general, this involves modifying the surface of biomaterials with coatings or treatments that impart these properties. One can speak in general terms of antifouling properties, but in many cases a specific antimicrobial action is also, or above all, sought.

The service life of implants depends in particular on the rejection reaction they receive inside the human body and the risk of infection. Surface modification processes for biomaterials aim to provide solutions to these problems by altering the physical, chemical and biological properties of their surfaces.

Although there are antiadhesion materials whose primary function is not antiinfective, which will be described below, most of them aim to prevent microbial adhesion and infection. There are two main strategies for this. The first involves surface coatings or treatments that kill microbes as soon as they approach the surface. The second is to prevent the accumulation of microbes through their repellent or antifouling properties.

Nosocomial (hospital-acquired) infections are caused by bacterial colonisation of different surfaces of biomedical devices and systems and can affect 4-10% of hospital admissions (and more than 15% in less developed countries), reaching sixth place among causes of death [77].

Biomaterials with antiinfection properties that have been approved by the FDA have increased in recent years, demonstrating their clinical need. Currently the group of biomaterials with antibacterial properties is far superior to those with antifungal properties.

The sequence of biological events that take place in the process of infection by microbial attack is complex and includes adsorption of proteins, adhesion of bacteria, proliferation, formation of biofilms with polysaccharide-based extracellular matrix, reaction with inflammatory cells and subsequent inflammation and infection. All this leads to complications, implant failure and, depending on the degree of infection, even death of the patient [77-79].

Antimicrobial coatings can be based either on the release of various antibacterial agents or on coatings that have antibacterial properties themselves. The former release agents such as antibiotics, silver ions, antiseptics, furanones or nitric oxide. They are applied to the biomaterial by techniques such as physical adsorption, impregnation in a biodegradable polymer matrix, complexation or conjugation. The latter are based either on polymers, which themselves have antibacterial properties, or on photoactive metal oxide nanoparticles. The first category includes cationic polymers with biocidal properties, either of natural origin such as chitosan, or of synthetic origin such as polyethyleneimine (highly cytotoxic), polyurethane or cationic silicones, while the second category includes metal oxides such as TiO_2, CuO or ZnO, which generate reactive oxy-

Table 2 **Some estimates of the cost of acquisition and implantation of various prostheses in different countries.**

Type of prosthesis	Acquisition cost	Implantation cost	References
Hip	2.500-7.000 $	15.000-40.000 $	[59, 60, 61]
Knee	3.000-9.000 $	20.000-50.000 $	[62, 63, 64]
Elbow	5.000-15.000 $	20.000-50.000 $	[65, 66]
Shoulder	5.000-20.000 $	20.000-50.000 $	[67, 68]
Implantable Cardiac Electronic Devices (ICED)	2.500 $-10.000 $	10.000-50.0000 $	[69, 70]
Heart valves	5.000-15.000 $	50.000-150.000$	[71, 72]
Mammary	1.000-3.000 $	5.000-20.000 $	[73]
Penis	5.000-20.000 $	5.000-20.000 $	[74]
Hernia meshes	50-500 $	2.000-10.000 $	[75, 76]

gen species capable of damaging organic biomolecules such as carbohydrates, lipids, proteins or DNA [78,79].

On the other hand, antifouling coatings that either show repellent properties towards micro-organisms or affect the biofilm architecture should be considered. In the first category are hydrophilic polymers, especially in polyethylene glycol (PEG), zwitterionic materials that also provide hydrophilic surfaces [80-82] and superhydrophobic surfaces with low surface energy and nanostructured surface topography. The availability of nanotechnology tools has enabled progress in the production of superhydrophobic surfaces with antibacterial activity [83,84]. Their clinical application does not seem immediate, although the successes achieved in paints and fabrics with superhydrophobic properties allow optimism for the future. In the second category are coatings based on enzymes that can degrade the polysaccharide-based extracellular matrix of the biofilm, or by inhibiting bacterial Quorum Sensing (QS), responsible for the regulation of gene expression and chemical signalling among the cell population, which should prevent biofilm formation [77-79].

As stated above, among the antiadhesion biomaterials, those whose function is not antiinfective but to prevent adhesions between tissues should also be considered. In abdominal surgery, almost 80-90% of patients suffer from post-surgical adhesions and this is a complication that can lead to bowel obstruction, chronic pelvic pain, infertility or the risk of having to operate again, and in the case of the intervertebral disc to paraplegia. The general strategy is to use barrier materials that block or prevent the connection between the surgical site and nearby organs or tissues. Gels, liquid solutions or films are used for this purpose. Anti-attachment strategies aim either to create physical barriers using hydrogels or films, or to create chemical barriers using anti-inflammatory agents, anti-coagulant agents or fibrinolytic agents. Natural polymers such as polysaccharides, gelatine, hyaluronic acid or alginate with short resorption times, or chitosan or carboxy methyl cellulose with longer resorption times, as well as biodegradable synthetic polymers such as polylactic acid, polyvinyl alcohol, polycaprolactone or polyethylene glycol with longer degradation times, modulable and non-toxic, can be used for this purpose [85,86].

The future of non-adherent materials will be strongly linked to the industrial scalability of some of the technologies proposed, as well as the demonstration of their effectiveness and cost-efficiency.

TO WHAT EXTENT CAN LOCAL ANTIBIOTICS ATTACHED TO THE STRUCTURAL MATERIALS OF THE PROSTHESIS BE USED TO PREVENT INFECTIONS?

Work is currently underway to develop biomaterials that prevent the initial adherence of the micro-organisms. One possibility is to coat the material with hydrophilic substances (which repel bacteria) such as polyethylene oxide, but once they undergo adsorption of serum proteins, this effect loses its value, so other strategies have been developed, such as the use of biomaterials coated with antimicrobial substances. One of the oldest and proven effective is polymethylmethacrylate (PMMA) bone cement, which can be added with antimicrobials to achieve high concentrations of these drugs after elution. Acrylic cements were developed a long time ago, in the 60s of the last century, and their function is to ensure the fixation of the implant (usually made of metal) to the bone. On the other hand, they also transmit the loads that the prosthesis has to bear, achieve a mechanical locking in the bone interstices and also compensate for imperfections associated with the surgical technique. These cements were subsequently added with antimicrobials to reduce the risk of infection. This can be done manually, but there are also commercial preparations containing gentamicin, vancomycin, ciprofloxacin, and combinations with other antimicrobials. These preparations have demonstrated efficacy over many years and are cost-effective when used in joint revision procedures (where the risk of infection is much higher) and in the eradication of active periprosthetic infection [87]. However, it should be noted that the addition of antimicrobials to these cements can interfere with the mechanical properties (mainly strength) of the material by almost 25%.

Interference with materials could be largely avoided by constructing natural polymers that are reabsorbed once their mission is accomplished. An example of this is tryptophan polymers containing antimicrobials, which have been used to wrap the generators of electrostimulation devices that are usually implanted under the subcutaneous cellular tissue of the pectoral region. These devices release high concentrations of antimicrobials in situ for several days, while degrading naturally, showing a reduction in the incidence of infection of almost 50%, which would make their use cost-effective in patients at high risk of infection [88]. Another strategy would be to inject antimicrobials in the target area (e.g. a joint with an infected prosthesis or in the ocular vitreous humour) with a controlled release, such as would be obtained with their vehicleisation by means of nanospheres.

However, from a microbiological point of view, the use of these antimicrobial-impregnated materials always involves the risk of resistance or even an increase in the generation of biofilms, so it is necessary to ensure adequate release in optimal quantities. It has been shown, for example, that sub-inhibitory concentrations of certain antimicrobials can activate the ica gene responsible for biofilm formation in *S. epidermidis* [89]. For this reason, polymer coating strategies are also being developed with substances that have a biocidal action other than antimicrobials. Thus, there are designs with anti-fibronectin antibodies, blocking agents of the messengers involved in the quorum sensing phenomenon or even components active against genes that regulate adhesion phenomena [90,91]. This opens up a hitherto unimaginable field of therapeutic possibilities that will change our old patterns. On the other hand, we should not be overconfident without first reflecting on the fact that bacteria have been on Earth for many millions of

years before us and that we will always be surprised by their ability to evolve in the face of threats, so that the fight has only just begun. However, small advances in both prevention and treatment will undoubtedly be cost-effective and will, above all, prevent much suffering.

TO WHAT EXTENT WILL TISSUE REGENERATION BE AN ALTERNATIVE TO CURRENT PROSTHESES?

Tissue regeneration aims to restore, replace and increase the ability of a tissue to reproduce. Different animal species differ markedly in their ability to recover injured tissues. Regeneration requires significant plasticity in terms of changes in cell cycle, proliferation, dedifferentiation and transdifferentiation.

Regeneration occurs by transformation of pre-existing body parts or tissues into new structures, which involves dedifferentiation followed by proliferation, and requires a subsequent stage of differentiation into specialised cells to complete tissue reconstruction.

Regeneration mechanisms occur in the complete recovery of amputated limbs in salamanders, starfish, and other animal species, but do not occur spontaneously in humans.

However, in mammals, therefore, in humans, repair of some tissues such as liver regeneration, and self-regeneration of hair, nails, skin, mucous membranes, endometrium, blood, muscles, and bones does occur, achieving the reproduction of the original structure.

In the absence of injury, human tissues regenerate naturally, replacing aged cells with new cells. The regeneration time is different for each tissue; for example, uninjured skin tissue regenerates in two weeks while a bone takes 10 years to fully regenerate.

When a tissue is injured, the body responds with an emergency reaction that leads to scar tissue formation rather than a regenerative response. The possibility of self-regeneration depends on the size of the injury. In the skin, wounds smaller than 2 mm can regenerate naturally before healing occurs. In contrast, if wounds larger than 3 mm are to be prevented from healing, a bridging material must be inserted to induce regeneration.

In the case of bone, when the injury exceeds a certain dimension, a critical defect, tissue repair becomes more difficult or even fails to occur. In addition, with age, the regenerative response becomes less and less effective.

Regeneration generally describes the process by which lost tissue is restored through the proliferation of specialised cells. The aim of regenerative medicine is to regenerate primarily by supplying cells, in particular stem cells that can stimulate regeneration.

Some major goals in regenerative medicine are:

Reversing and preventing paralysis, blindness or hearing loss by regenerating bone marrow, optic nerve, retina, auditory nerve, cardiac regeneration after a heart attack, curing Parkinson's and Alzheimer's diseases, minimising the after-effects of a thrombus by neuronal repair, cell therapy for diabetes (only 3,000 pancreas transplants are available for every 35,000 potential patients), access to new cartilage, muscle, tendons, ligaments, intervertebral discs in adulthood, reversing disc degeneration in the spine, kidney regeneration (living without dialysis), universal repair of all bone fractures, spinal fusion through bone regeneration, new teeth.....

If all this is achieved, the panorama will undoubtedly change and the alternative to current prostheses will be spectacular [26,92-94] (Figure 1).

WHAT IS THE FUTURE OF PHAGE THERAPY IN THE TREATMENT OF INFECTIONS ON PROSTHESES THAT CANNOT BE REMOVED AND DO NOT RESPOND TO ANTIBIOTICS?

When removal of biofilm and prosthetic material is not technically possible, antibiotics alone often fail to treat prosthetic infections. Bacteriophages are a possible alternative and complement to the use of antibiotics in these circumstances.

Bacteriophages (phages) are viruses, both DNA and RNA, abundant in nature, that have the ability to infect bacteria and can sometimes lyse them. They are harmless to humans and can be administered systemically or locally [95].

For a phage to be able to lyse a bacterium, it must be incorporated into the bacterium after binding to a surface receptor, be replicated by the bacterial machinery and its progeny must have lytic capacity against the bacterium. When the bacterium has been lysed by the phage, the cycle and propagation of the phage ceases. In contrast to lytic phages, temperate phages can remain quiescent as prophages and integrate into the genome.

Phage therapy has some important limitations such as the specificity of phages for certain bacterial species with a very narrow spectrum of action, the need to obtain and maintain phages, and the development of resistance. Fortunately, phage therapy has not been associated with major adverse effects.

Phage therapy was first used in 1917 and has been a therapeutic weapon applied safely and effectively to thousands of patients ever since [96-102], mainly in Eastern European countries where access to antibiotics was not easy. Phage therapy has even been used as monotherapy in urinary tract infections, but it is usually used in association with antibiotics [103].

The current status of phage therapy in the Western world is that of an experimental treatment in need of systematisation and prospective, randomised clinical trials. This treatment has not yet been approved by the FDA.

Phages could be particularly useful in infections on prosthetic material that cannot be removed, but the available studies very often publish only isolated cases or series with very small sample sizes.

The causative microorganisms most frequently treated

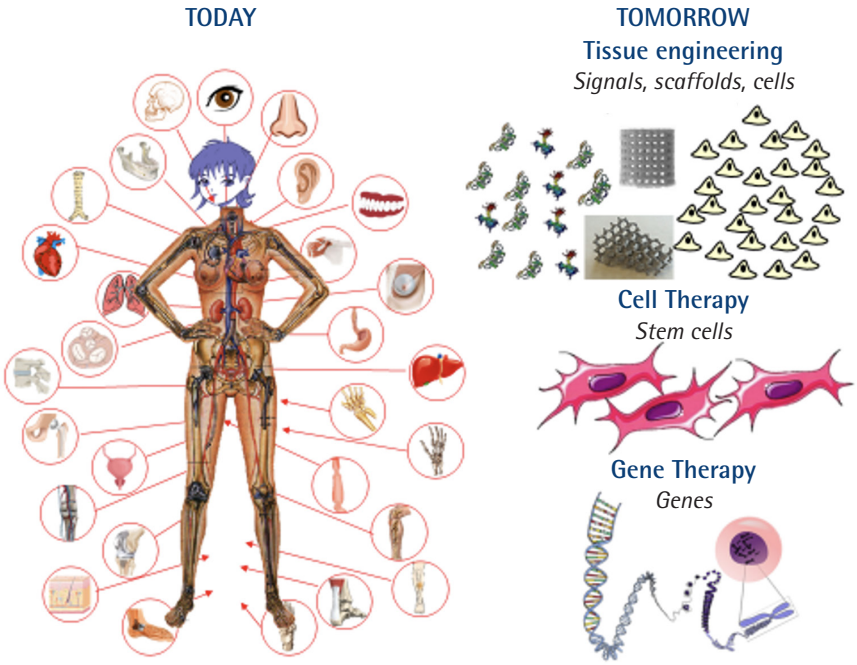

Figure 1 | **Diagram showing how tissue engineering and cell and gene therapies will change the world of prosthetics today. Figure taken from Vallet-Regí [93]. Copyright © 2022 Vallet-Regí.**

with phages have been *S. aureus, P. aeruginosa, S. epidermidis* and others. These were almost always patients who had failed conventional treatments and were not candidates for radical surgery.

Suh et al. [104], in a prospective, open-label, non-randomised study in patients with osteoarticular prosthesis infections who received combined therapy with phage and antibiotics, collected 23 cases that were compared to 22 historical controls who received antibiotics alone. The relapse rate in those treated with antibiotics alone was 8 times higher than in those receiving phages [104].

In another recent paper, Fedorov et al. from Russia publish a non-randomised, prospective, open-label, historically controlled study on the use of combined phage and antibiotic treatment of periprosthetic joint infection (PJI) in 45 adult patients with deep PJI of the hip joint, with a 12-month follow-up after one-stage revision surgery. All 23 patients in the study group were treated with a specific phage preparation and etiotropic antibiotics, while 22 patients in a retrospective comparison group received antibiotics only. The relapse rate of PJI in the phage group was 4.5% and in the control group 36.4% [105].

Experience with phage therapy in patients with infections of prosthetic material other than osteoarthritic material is even more limited and contradictory and does not allow for clear conclusions [106,107]. Phages can reduce bacterial colonisation of surfaces such as catheter tips, endotracheal tubes or urinary catheters [108,109] and could potentially have a prophylactic application but information in this regard is still very limited and partial.

In most cases a local strategy is used with administration of the phages at the surgical site either during surgery or via a catheter left in situ. Intravenous therapy has been used either alone or in combination with local treatment but experience is limited.

Neither ideal dosages nor ideal duration of phage therapy have been established. In published cases the amounts ranged from $1x10^7$ to $1x10^{11}$ plaque-forming units and the frequencies of administration varied from daily every 8 hours to once a week. The duration of the process of searching for, selecting and preparing the phages for administration lasted in the work of Suh et al. between 28 and 386 days, which implies that it is a treatment applicable only to patients with chronic diseases, who do not respond to conventional treatment [104].

Before phage therapy can become a tool for common therapeutic use, standardisation of phage preparation processes, systematisation of the study of their spectrum of antibacterial action and the creation of specific banks for therapeutic use are needed [110,111]. At the same time, standard monitoring of phage therapy in both tissues and blood is necessary to optimise doses and duration of treatment [112].

HOW CAN ARTIFICIAL INTELLIGENCE HELP IN THE DESIGN OF PROSTHESES?

Artificial intelligence (AI) is a branch of computer science that aims to create intelligent machines capable of performing tasks that require human intelligence. It is through the use of computer algorithms that AI enables the analysis, understanding and interpretation of complex data sets and from this to learn from experience and make predictions or decisions. AI is completely transforming economic, industrial and cultural sectors. Machine learning (ML) is an AI discipline that uses algorithms to train a machine to identify common patterns in large amounts of data in order to make predictions and decisions. Although from a definitional point of view the differences seem clear, when looking at how AI and ML are applied in the literature related to Biomaterials and Bioengineering in general, the differences are not so clear-cut in terms of the algorithms and computational models used.

As in other sectors, AI and ML are penetrating all areas of the life sciences. In fields such as diagnostic imaging, pharmacology or medicine/healthcare, experience is already well advanced and with tangible successes. In the field of prosthetics, apart from exo-implants, there is an abundance of literature on dental implants and orthopaedic implants [113]. The possibility of carrying out these predictive and design studies is due to the existence of both reliable databases and published works in which both the stress distribution in prostheses and their micro-movements have been calculated by means of finite element models. Therefore, it seems plausible to state that the application of AI can be of great help in finding virtual models of prostheses that can then be transformed into real, clinically usable implants.

In the cardiovascular field, AI also plays an important role in the field of imaging or in the planning of different interventions [114,115]. There are also studies for the development and manufacture of prostheses [116-118], although to a lesser extent than in the dental and orthopaedic fields. Without attempting an exhaustive review, it is also possible to find contributions in other clinical fields such as the design of a bionic eye [119].

The future of the use of AI in the design of prosthetics in general and biomaterials in particular is closely linked to the existence of reliable and accessible databases. There are an increasing number of materials or biological databases that comply with the FAIR (Findable, Accessible, Interoperable, and Reusable) principles of Open Science [120].

The development of new biomaterials that contribute to more effective and efficient implants has come about through trial and error. ML and AI are tools that can enable more holistic views of the material's working conditions, i.e. take into account the complexity of its environment, and eventually produce a "virtual twin" of the target material. This reduces the time-consuming and costly sequence of tests that could eventually lead to the specification of the desired material. In the field of materials, the US government announced in 2011 its "Materials Genome Initiative" (MGI) programme, which in May 2017 took the form of a workshop on "Advancing and Accelerating Materials Innovation Through the Synergistic Interaction among Computation, Experiment, and Theory: Opening New Frontiers". It is therefore an initiative that seeks to innovate in Materials Science and Engineering for the development of materials in all industrial fields using all the tools available: modelling and computation, experimental tests and theoretical foundations [121]. It is already at the beginning of the second decade of the present century that seminal works appear that bet on the development of data libraries obtained through the evaluation of cellular interactions with structured surfaces/materials by means of nanotechnological techniques [121-123]. The possibility then arises of asking what genetic responses the materials induce and hence the concept of "Materionomics" appears [124,125], i.e. how biomaterials are involved in the different omics of cellular responses. The application of AI to biomaterials science requires, as mentioned above, databases that comply with the FAIR principles, and in recent years these have become available in the fields of Materials, Biology and different fields of Health Sciences. The concept of "Biomaterialomics" has recently appeared [125] which aims to cover all the above aspects and lay the foundations for the design and development of new biomaterials using AI. In other words, it is about integrating computational tools such as AI or ML, large and different databases, and experimental techniques and tests with the aim of exploring and combining basic elements of materials to discover, design and develop new biomaterials aimed at obtaining clinical products or devices. We are still at the beginning of a new paradigm in innovation in the field of Biomaterials [126,127]. It seems that the more holistic vision generated by the "virtual twin" will allow the properties of the biomaterial to be adjusted, so that it can perform or induce the repair, replacement, integration or regeneration functions for which the biomaterial is used [128,129].

IS THERE A NATIONAL INDUSTRY PRODUCING COMPETITIVE PROSTHESES? IS THE DESIGN OF PROSTHESES ONLY WITHIN THE REACH OF LARGE MULTINATIONALS?

Although there are several national companies producing successful prostheses, the bulk of joint implants come from the USA and other EU countries. The combination of new ideas in joint replacement design, materials that make a difference, and systematic basic and clinical research are the ingredients that encourage innovation in joint replacement. Such a combination of factors, in the highly regulated and competitive environment that surrounds us, does not facilitate the emergence of new products that are commercially successful [130]. New ideas arise from collaboration between surgeons and engineers, scientists and manufacturers, which is not often the case in our country.

The demand for joint replacements continues to grow, due to the success of the technique and the ageing population, which is seeking to prolong its active life. The European market currently accounts for 20-25% of the world market,

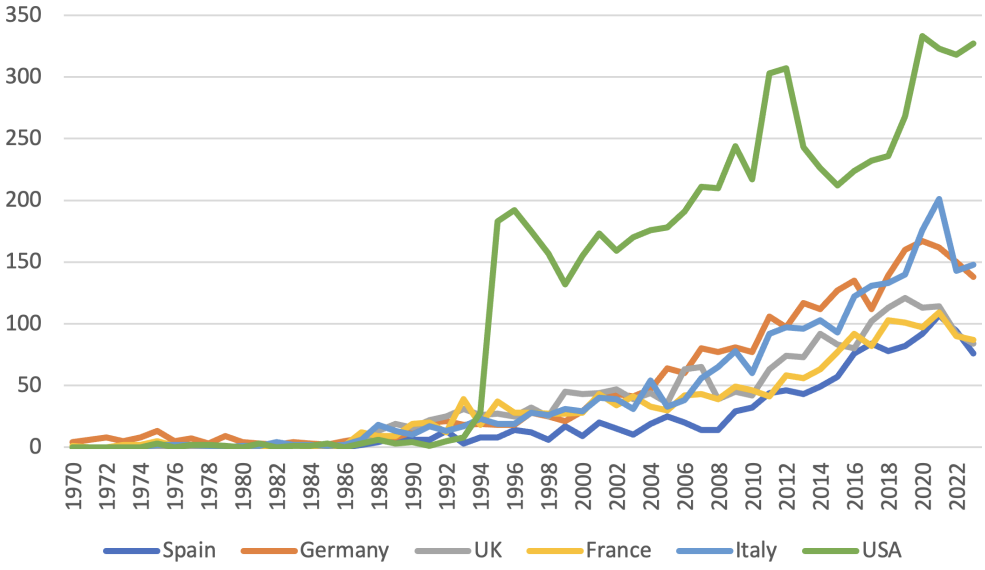

Figure 2 | **Evolution of scientific production on prosthetics in several developed countries.**

although its share is decreasing. The main countries in terms of population and deployment capacity are Germany, France, Great Britain, Italy and Spain. However, many of the national and even European companies in the sector are medium-sized, with few large, multinational companies, so competition, both in innovation and in marketing and distribution, may favour multinational companies from outside Europe.

The incentive to bring new solutions to market exists, due to growing demand, but it fades along the way. While most ideas arise from academic and clinical initiative, or from incremental improvements of already marketed products, their development and exploitation is very limited. The regulatory pathway is complex, both for new designs and new materials, and authorisation under the current Medical Device Regulation (MDR) Directive is a challenge [131] requires the demonstration of safety and efficacy of prosthetic implants for large joints (hip, knee, shoulder) through clinical trials, as they are considered Class III devices.

In this context, a solid strategy, based on collaboration between the different agents, is required for our country to position itself in the development of new solutions. Otherwise, the current wave of growing demand will be resolved by resorting to solutions defined in other countries and marketed by foreign multinational companies.

WHAT IS THE EVOLUTION OF SCIENTIFIC PRODUCTION ON PROSTHESIS IN SPAIN AND ABROAD?

A search in Pubmed since its beginnings, with the word "Prosthesis" as the main term MesH lists 416,235 documents published under this heading as of 8 March 2024. Scientific production on this subject has followed a growing trend. The introduction of the word Spain in any field reduces the figure to 7,368 documents, which represents 1.77% of this production.

If the search is done by the term Prosthe* in the title field, PubMed lists 58,514 total documents which when adding the term Spain in any field is reduced to 1,073 representing 1.83%.

In an attempt to compare our scientific production with that of other developed nations, both in the European Union and the United States of America, we have shown in Figure 2 the evolution of the scientific production of some countries of the European Union and the United States of America. It can be seen that the scientific output of the 5 largest nations of the European Union has evolved very much in parallel over the last half century.

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CONFLICTS OF INTEREST

The author declares no conflicts of interest

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Vascular catheter-related infections: an endemic disease in healthcare institutions. An opinion paper of the Spanish Society of Cardiovascular Infections (SEICAV)

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ABSTRACT

Catheter-related infections (CRI) are a serious healthcare problem due to their potential to cause serious complications, including bacteraemia or infective endocarditis, and to increase patient morbidity and mortality. In addition, these infections significantly prolong hospital stay and cost. Preventing CRI is crucial and is considered a criterion for quality and safety in healthcare.

For these reasons, the Spanish Society of Cardiovascular Infections (SEICAV) has considered it pertinent to review this topic, with experts in different areas including clinical microbiologists, infectious disease specialists, surgeons and nurses. The data were presented at a session held at the Ramón Areces Foundation, which was organised in the form of specific questions grouped into three round tables. The first panel analysed the scale of the problem including epidemiological, clinical and diagnostic aspects; the second panel addressed advances in the treatment of CRI; and the third panel reviewed developments in the prevention of CRI. The recorded session is available on the Areces Foundation website and we believe it may be of interest not only to health professionals, but also to any non-expert citizen interested in the subject.

Keywords: vascular catheter; infection; bacteremia; consequences; safety of healthcare.

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Infecciones relacionadas con catéteres vasculares: un mal endémico en las instituciones sanitarias. Un artículo de opinión de la Sociedad Española de Infecciones Cardiovasculares (SEICAV)

RESUMEN

Las infecciones asociadas a catéter (IRC) son un grave problema sanitario debido a su potencial para causar complicaciones graves, incluyendo bacteriemia o endocarditis infecciosa, y aumentar la morbilidad y mortalidad de los pacientes. Además, estas infecciones prolongan significativamente la estancia hospitalaria y el coste de la asistencia. Prevenir las IRC es crucial y se considera un criterio de calidad y seguridad de la atención sanitaria.

Por estos motivos, la Sociedad Española de Infecciones Cardiovasculares (SEICAV) ha considerado pertinente revisar este tema, contando con expertos en diferentes áreas que incluyen microbiólogos clínicos, infectólogos, cirujanos y enfermeras. Los datos se presentaron en una sesión celebrada en la Fundación Ramón Areces, que se organizó en forma de preguntas concretas agrupadas en tres mesas redondas. La primera mesa analizó la dimensión del problema incluyendo aspectos epidemiológicos, clínicos y diagnósticos; la segunda mesa abordó los avances en el tratamiento de las IRC; y en la tercera mesa se revisaron las novedades en la prevención de estas infecciones. La sesión grabada está disponible en la página de la Fundación Areces y creemos puede resultar de interés, no sólo para los profesionales de la salud, si no para cualquier ciudadano no experto interesado en el tema.

Palabras clave: catéter vascular; infección; bacteriemia; nosocomial; consecuencias; seguridad del paciente.

DIMENSION OF THE PROBLEM

Question 1: Which endovascular catheters are most frequently implanted in hospitals?

Though a precise estimate is not possible, indirect data suggest that approximately 20-22 million peripheral venous access devices (VAD) are inserted in Italian hospitals each year [1-3]. According to the World Congress on Vascular Access (WoCoVA) classification, peripheral venous access devices are classified as short peripheral cannulas, long peripheral cannulas, and midline catheters (see the ERPIUP consensus). The vast majority of peripheral VADs used in Italian hospitals are short peripheral cannulas. The rate of infections related to peripheral VADs is currently unknown, though it is considered not as negligible as once assumed, probably around 0.2-0.5 episodes per 1,000 VAD days.

In recent years, the use of midline catheters has increased progressively. The main advantage over peripheral venous accesses is their greater durability, which avoids having to perform multiple cannulations of peripheral accesses during the patient's admission, and they can also have more than one lumen for simultaneous perfusions.

The number of central VADs inserted each year in Italian hospitals is almost one million, which includes 900,000 external central venous catheters (CVCs) (of which, about 200,000 are peripherally inserted central catheters [PICCs]), either tunneled or non-tunneled, plus approximately 50 thousand ports (of which, about 10 thousand are PICC-ports). The incidence of catheter-related bloodstream infection (C-RBSI) is extremely variable, depending on the device and on the clinical setting, and ranges between 0.1-0.2 episodes per 1,000 catheter days for chest-ports and PICC-ports, vs. 0.5-3.0 episodes for 1,000 catheter days for non-tunneled CVCs. The incidence of C-RBSI is higher for CVCs used for parenteral nutrition; also, CVCs with exit site at the neck or at the groin have higher risk of C-RBSI than CVCs with the exit site in the infra-clavicular area or at mid-arm.

The use of some new types of VADs is increasing very rapidly in Italy, which include (a) long peripheral catheters (also called mini-midline, 6-15 cm in length), (b) PICC-ports (brachial ports inserted with PICC technology), and femorally Inserted Central Catheters (FICCs) introduced into the superficial femoral vein, with exit site at mid-thigh. Current clinical studies suggest that mini-midlines may have the same risk of infection than other peripheral VADs, and that PICC-ports have the same infection risk of chest-ports. On the contrary, FICCs inserted by ultrasound guided cannulation of the superficial femoral vein, with exit site at mid-thigh, appear to have lower infection risk than FICCs inserted into the common femoral vein, with exit site at the groin.

Question 2. What are the most frequent microorganisms causing C-RBSI and what is their pathogenesis?

In general, the most frequent microorganisms causing C-RBSI are Gram-positive cocci, in particular coagulase-negative staphylococci (CoNS) (50%-80%), followed by Gram-negative bacilli (15%-30%) and yeasts (5-20%) [4, 5]. However, in specific populations or catheter types, this distribution may change.

According to data from studies of the evolution of the etiology of CR-BSI, the distribution of microorganisms has fluctuated over the years, with variations according to country or type of catheter [5, 6]. Specifically, in a recent study carried out in 100 ICUs in 9 Latin American countries, it has been reported that the rates of Gram-positive and Gram-negative bacteria have been equalized with a rate of 48.5% [7]. However, these trends can be affected by different events, as was the case in the COVID-19 pandemic, where the rates of C-RBSI/1,000 admissions increased significantly compared to previous years, with CoNS being the major causative agent [8]. Likewise, there are peculiarities in the etiology of C-RBSI depending on the population, as is the case of patients with renal disease, in whom an increase in Gram-negative bacilli has been detected [9-12], as well as in the neonatal ICU, in solid organ transplant recipients or neutropenic patients [11, 13]. *Staphylococcus aureus* is frequently associated to bacteremias related to peripheral venous catheters (PVCs) conferring increased risk of morbidity [14].

In terms of specific microorganisms, it is also important to highlight the role of *Enterococcus* spp., which is the fourth leading cause of C-RBSI and whose incidence, mainly due to *E. faecalis*, has increased in recent years [15]. *Candida* spp. represents a smaller percentage of C-RBSI, but its incidence can be very variable depending on the centre, both in adults and children [16]. Finally, although C-RBSI caused by fast-growing non-tuberculous mycobacteria are rare and often occur in immunocompromised patients [17-19], a series of 19 cases in PICCs of immunocompetent injecting drug users has recently been described [20].

Regarding the pathogenesis of C-RBSI, it is important to remember that it is mainly by microorganisms that migrate through the catheter into the bloodstream from two main sources: the *extraluminal route,* from patient's skin microbiota, which is one of the most frequent, and typically appears 5-7 days after insertion; and *the intraluminal route,* from the manipulation of hub connectors during catheter maintenance, which appears normally >7 days after catheter insertion. There are, however, other less frequent routes of C-RBSI acquisition such as: infusion of a contaminated fluid or hematogenous dissemination from another source [21-23].

Question 3. What do we know about biofilm and bacterial quorum sensing in this situation?

Bacteria and fungi are able to adhere to both natural tissues and artificial devices forming a biofilm, which is a complex structure in which microorganisms are in a latent state surrounded by an extracellular matrix composed of proteins and extracellular DNA [24, 25]. One of the most important nosocomial infections mediated by biofilm formation is C-RBSI, in which microorganisms migrate to the catheter and begin to adhere to its surface developing biofilm [24, 25]. Biofilm

formation occurs through a 5-step cycle: reversible adhesion, irreversible adhesion, aggregation, maturation, and dispersion [25]. This phenomenon is primarily responsible for the lack of therapeutic success with systemic antibiotics, since biofilm confers antimicrobial tolerance, reduces antibiotic diffusion and penetration, and evades the host immune response. Recently, it has been described that the extracellular matrix is one of the main factors responsible for resistance, in addition to other intrinsic factors specific to each strain that directly affect biofilm formation and cell dispersion [26-31].

Quorum sensing (QS) is the ability of bacteria to communicate with each other through coordinated behavior by releasing molecules, called autoinducers, to regulate their physiological activities, such as: virulence, conjugation, motility, sporulation or biofilm production. This mechanism occurs when a threshold concentration of autoinducers is reached, indicating that the cell population has reached quorum and gene expression begins [32-35]. However, host factors can also interfere with QS, as can autoinducers in other bacterial species [36]. Therefore, the complexity of this phenomenon calls for the search for new QS inhibitors to combat biofilm-related infections [37].

Question 4. What are the diagnostic methods for catheter infection?

Catheter related infection (CRI) should be suspected if the patient presents with fever, chills or hypotension, with or without signs of infection of the catheter insertion site or in the skin overlying the subcutaneous tract of a tunneled catheter. The different strategies to achieve a diagnosis have deserved excellent reviews [38-43].

1. Diagnosis of C-RBSI without device removal (conservative diagnosis)

Differential time to positivity of blood cultures. In patients with suspected central-line associated bloodstream infection (CLABSI), at least, two pairs of blood cultures should be taken, one from a peripheral vein and the others from all catheter lumens. Blood cultures should be obtained prior to the initiation of antimicrobial therapy and using a strict aseptic technique. This is especially important since pathogens involved in C-RBSI are also the most frequent contaminants of blood culture bottles.

Several studies have confirmed that measuring the time difference to positivity (TDP) of conventional blood cultures obtained from a central venous catheter and a peripheral vein is very sensitive in diagnosing C-RBSI, although it does not exclude it. A TDP ≥ 120 min is associated with a sensitivity of 81% and specificity of 92% for short-duration catheters (<30 days) and a sensitivity of 93% and specificity of 75% for long-duration catheters (>30 days). An optimal cut-off point for the diagnosis of catheter-related candidemia has not been established [41].

Quantitative blood cultures have also been used, and a differential colony count (3-5 times) higher in the blood culture obtained through the catheter than in that obtained through the peripheral vein is suggestive of C-RBSI. Quantitative blood cultures are laborious and expensive, making them less viable for routine use [40].

Semiquantitative **cultures of the skin around the catheter insertion site and catheter connections** with counts ≥15 colony forming units (CFU) may be indicative of C-RBSI [9, 41, 42]. These procedures should be combined with the drawing of peripheral blood cultures if bacteremia is suspected. Gram stain of the connections and the peri-catheter skin may also be useful [44].

2. Diagnosis of C-RBSI with catheter removal

As a general recommendation, a catheter tip should only be sent for culture when an associated infection is suspected, thus avoiding unnecessary cultures and overtreatment. Several factors should be considered in determining whether a catheter should be removed: the type of catheter, the ease of insertion of a new catheter, the immune status, the severity of the patient's underlying disease, and the presence and severity of associated sepsis [45].

The most used laboratory technique for processing the catheter tip is the semi-quantitative method described by Maki, in which the catheter segment is rotated on a blood agar plate using sterile forceps. After 24 hours of incubation, the number of CFU on the plate is counted. The catheter is considered to be the focus of infection if the growth of a catheter tip culture is ≥15 CFU, while <15 CFU without associated clinical signs is considered catheter colonization. A limitation of this method is that it detects mainly colonization on the external surface of the catheter. Moreover, there is no established cut-off point for mycobacteria and fungi [46]. In the case of long-duration catheters, where the endoluminal route is the main pathogenic route, endoluminal surface culture techniques (Cleri, Brun-Bruisson or Liñares) can be performed [47]. For quantitative cultures (internal surface wash and vortex), the cut-off point has been set at 103 CFU/segment, again based on their association with bacteremia [48, 49]. In the case of CVCs with subcutaneous reservoir, cultures should be taken from the catheter tip, from the inside of the reservoir, and from the sonication broth of the silicone septum [50]. The latter procedure has shown the highest sensitivity and specificity (78% and 93%, respectively) for diagnosing device colonization with a cut-off point of 110 CFU/ml [39].

Question 5. What are the consequences of CRI in terms of morbidity, mortality, and cost for the National Health Systems?

Intravascular devices have become an essential component of modern medicine for the administration of intravenous fluids, medication, blood products and parenteral nutrition, as well as for monitoring hemodynamic status and performing hemodialysis. According to national data provided by the study on the prevalence of nosocomial infections in Spain (EPINE), it is estimated that around 70% of patients admitted to Spanish hospitals will carry one of these devices

at some time during their stay [51, 52]. Local or systemic infections represent one of the main associated complications. The incidence of CRI varies considerably depending on the type and intended use, the insertion site, the experience, and training of the person placing the catheter, the frequency with which the catheter is accessed, the duration of catheter placement, patient characteristics, and the use of proven prevention strategies.

C-RBSI is one of the most frequent in-hospital infections. According to current estimates, between 15% and 30% of all nosocomial bacteremias are catheter related. These infections lead to significant associated morbidity, increased hospital costs, estimated at approximately 11,000-56,000 euros per episode, and increased average length of stay. Attributable mortality ranges from 12% to 25% [53-55]. The costs of intravenous antibiotic treatment include acquisition costs, costs associated with disposable materials and overhead. Other expenses include nursing and medical intervention costs, as well as indirect costs associated with the specialized personnel who supervise or administer the medication.

TREATMENT ADVANCES

Question 6. Which infected catheters should be removed immediately?

The clinical guidelines for the diagnosis and treatment of catheter-related bacteremias of the Spanish Society of Critical Intensive Care Medicine and Coronary Units (SEMICYUC) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) published in 2018 establish a series of recommendations in this regard [4]. Cases with suspicion of CRI and those in which there is microbiological confirmation should be differentiated.

Immediate and systematic removal of vascular catheters in patients with suspected related infection is not routinely recommended and would only be indicated in specific situations [56, 57].

CVCs should be withdrawn immediately upon suspicion of CRI in patients with suppuration at the site of infection, septic shock, organ dysfunction, intravascular devices or septic emboli. In patients in whom there is suspicion in other conditions, but it is not possible to perform quantitative or differential cultures, the device should also be withdrawn. In the case of documented CRI, it is mandatory to remove these devices in patients with difficult to treat infectious such as those caused by *S. aureus* and *Candida* spp. Catheter removal should be considered when there is isolation of Gram negative bacilli in the presence of septic shock, in patients with other implanted intravascular devices, or when there is an isolation of CoNS in the same circumstances [58,59].

In relation to infection of the insertion site: in PVCs, removal is mandatory if there is pain, induration, or erythema (A-I); non-tunneled CVCs should be removed in case of erythema or purulence (B-II) and in any case if clinical signs of infection persist 72 hours after the start of conservative treatment (B-II).

Question 7. What situations allow conservative treatment to be attempted?

In patients with suspicion of catheter related infection, immediate systematic removal of **non-tunneled** CVCs is **not** routinely recommended (conservative treatment) in hemodynamically stable patients, in patients without autoimmune disease or immunosuppressive therapy, in patient with no other intravascular devices or organ transplantation, suppuration at the insertion site or associated bacteremia/fungemia [21, 40, 56].

In the case of long-term **tunneled** CVCs in which the route of progression of microorganisms is the intraluminal, the use of antibiotic lock therapy, in addition to treatment with systemic antimicrobial agents, is recommended in stable patients with isolation of low virulence microorganisms, such as CoNS (except *Staphylococcus lugdunensis*). In stable patients without local or systemic complications, conservative treatment can also be attempted in bacteremia caused by enterococci, corynebacteria (except *Corynebacterium jeikeium*) and gram-negative bacilli (in these cases it is suggested to consult an infectious disease expert) [60-63].

The antibiotic lock solution should be prepared under sterile conditions. The recommended duration of the lock is around 10-14 days. The lock solution should remain in the catheter lumen for a minimum of 12 h per day and should be replaced every 24-72 h. Ethanol 70% and taurolidine solutions could also be used as lock solutions. However, there is no evidence to advocate their routine use [40].

Question 8. What is the empirical treatment of suspected CRI?

If CRI is suspected, antimicrobial therapy with an agent active against *S. aureus* and CoNS should be initiated as soon as possible, especially if associated with sepsis or septic shock [21, 40]. The initial choice of antimicrobial should be based on an assessment of the risk factors for infection, the severity of the clinical scenario, and the pathogens likely associated with the specific intravascular device. An effective empirical therapy is especially important in patients with *S. aureus* C-RBSI who are at high risk of hematogenous metastases, especially when the catheter cannot be removed and/or the antibiotic treatment is inadequate [64].

Since most CoNS are methicillin-resistant, the choice of empirical treatment should include antibiotics active against methicillin-resistant strains. In recent decades, vancomycin has been the most prescribed antimicrobial for methicillin-resistant *S. aureus* (MRSA) bacteremia. Studies comparing the efficacy and safety of glycopeptides (vancomycin vs. teicoplanin) for staphylococcal bacteremia (including MRSA) have not observed significant differences, although strains of *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* with reduced susceptibility to teicoplanin have been described [65].

Daptomycin is probably more advantageous in cases of septic shock, acute renal failure, to patients with recent van-

comycin exposure (>1 week in the last 3 months) or if the local prevalence of *S. aureus* isolates with vancomycin MIC ≥1.5 mg/L is high [66].

Although there is lack of clinical trial-based evidence, ceftaroline or its combination with daptomycin is probably an alternative empirical anti-staphylococcal therapy.

Patients with suspected C-RBSI should also receive empirical coverage against gram-negative bacilli in the following circumstances: hemodynamic instability, neutropenia or hematologic neoplasia, solid organ or bone marrow transplantation, femoral catheter in place, high rate of gram-negative bacilli colonization, or prolonged ICU admission [67]. Antimicrobial therapy should be adapted to the local epidemiology.

Empiric therapy for suspected catheter-related candidemia should be considered in hemodynamically unstable patients with one or more of the following conditions: total parenteral nutrition, prolonged use of broad-spectrum antibiotics, malignancy, femoral catheterization, colonization due to *Candida* spp. at multiple sites, or prior intense anaerobicidal therapy [41,68].

Question 9. What should be the duration of treatment?

The duration of antimicrobial treatment of catheter infection depends on whether there is associated bacteremia, on the causative microorganism and the presence of complications, such as endocarditis, suppurative thrombophlebitis, or metastatic infections, which will be treated independently in this review.

In Table 1 we summarize the treatment duration recommendations according to the characteristics previously discussed.

Positive culture of the catheter tip, but without associated bacteremia

Starting with the least serious situation, which would be the isolation of a microorganism in the catheter, but without proven bacteremia, we will also take into account the microorganism cultured and the clinical situation of the patient. When a CoNS, enterococcus or enterobacteria is recovered, treatment may not be administered in a stable patient. However, isolation of *S. aureus, Pseudomonas aeruginosa* or *Candida* spp. although not constitute per se an indication of treatment, should lead to a clinical evaluation of the patient and if fever or clinical deterioration, consideration of whether the patient requires blood cultures if these have not been drawn recently. If the patient is septic some authors considered prudent to initiate treatment until blood cultures are proven to be negative [69-73].

However, it is necessary to clarify that these recommendations are not based on clinical trials, so decisions should be individualized.

It is necessary to emphasize that the recommended durations refer to days of effective systemic treatment and that days of empirical treatment should not be included if this was not optimal for the microorganism involved.

Table 1 **Duration of antimicrobial treatment in intravascular catheter-associated infections.**

Microorganism	Characteristics	Length of treatment
S. aureus, Candida spp.	No blood cultures (BC) obtained or negative BC	No indication of treatment per se in patients without symptoms. 3-5 days may be prudent until BC come negative in high-risk patients.
	BC + without complications	14 days since first negative BC
	BC + with complications[a]	4-6 weeks
CoNS, *Enterococcus* spp., enterobacteria	Negative BC	No therapy in stable patients[b]
	BC + without complications	5-7 days if the catheter has been removed, including observation without antibiotics if the patient is stable, has no risk factors (prosthetic material) and has transient bacteremia that disappears only with catheter removal (B-III)
		10-14 days with lock therapy if the catheter has been retained (C-III)
	BC + with complications	4-6 weeks
P. aeruginosa	Negative BC	3-5 days
	BC + without complications	7 days
	BC + with complications	4-6 weeks

CoNS: coagulase negative *Staphylococcus*; [a]Complicated bacteremia: persistent fever, presence of prosthetic material or septic metastasis, positive control blood cultures, failure to remove the catheter; [b]These proposals are based on low quality epidemiological data and are presented only as a guide. They should be modulated according to the clinical presentation of the patient, the existence of intravascular devices or immunosuppression.

Uncomplicated C-RBSI (catheter segment and peripheral blood with the same microorganism)

In this case the duration will essentially depend on the microorganism and whether or not the patient is considered to have a complicated bacteremia.

To be considered uncomplicated, C-RBSI must meet the following criteria:

- Catheter removal within five days of diagnosis.
- Rapid resolution of bacteremia with sterile blood cultures within 72 hours of initial positive culture.
- Clinical response and absence of symptoms or signs of metastatic infection.

- Patients without endovascular or orthopedic implants.
- For infections due to *S. aureus*, an additional criterion for bacteremia to be considered uncomplicated is an echocardiogram without evidence of endocarditis.

When all criteria for uncomplicated bacteremia are met, a treatment duration of 5-7 days can be considered for CoNS, enterococci and enterobacteria, 7 days for *P. aeruginosa* and 14 days from the first negative blood culture for *S. aureus* [21,58].

In the presence of endovascular implant or orthopedic hardware (in the absence of evidence of IE or infection of the orthopedic hardware) and C-RBSI in patients in whom the catheter has been removed with rapid clearance of bacteremia, some authors recommend prolonging systemic antimicrobial therapy for 14 days taking into account the possibility of seeding of the prosthetic hardware.

In general, treatment is usually prolonged in patients with persistent bacteremia (>72 h after catheter removal), but the level of evidence is higher for *S. aureus* (A-II) than for other microorganisms (C-III) [21].

The duration of treatment of C-RBSI caused by Gram-negative bacilli has recently been shortened based on a recent meta-analysis of uncomplicated episodes and without the use of lock therapy and on a retrospective series comparing the evolution in patients with long or short treatment [74-76]. No significant differences were observed with respect to mortality or microbiological relapse between short- and long-duration systemic antibiotic treatment.

The duration of treatment of complicated bacteremia will be addressed in another question in this review.

Question 10. What is the role of new long half-life drugs?

In order to establish the role of these new antibiotics, it is important to consider three concepts: (1) not all catheter infections produce bacteremia, which has direct implications on the duration of antibiotic treatments; (2) the most frequent etiology of catheter infections are CoNS, which usually do not require more than 3 to 5 days of antibiotherapy even in the presence of bacteremia [77]; and (3) it is essential to determine which patients with CRI will require longer antibiotherapy based on microbiological and clinical determinants. With regard to microbiological determinants, it is necessary to distinguish *S. aureus* from the rest of the microorganisms due to their greater virulence, especially in complicated bacteremias. According to the clinical determinants, we should consider longer antimicrobial therapy in those patients who develop venous thrombophlebitis of medium or large caliber vessels, as well as those patients with endovascular devices, among others. Therefore, most cases of CRI (including those who develop bacteremia) will not require prolonged antimicrobial therapy, and oral sequential treatment can be used early [78]. In this regard, there are data from clinical trials that support the possibility of performing oral sequential treatment from day 5 in uncomplicated *S. aureus* bacteremia [79].

Therefore, long half-life drugs should be selected for those situations in which the patient presents some intestinal absorption problem, when there are no oral options with good availability (or the patient has already presented severe toxicity to those available), and for the first phase of treatment of complex infections. Glycopeptides are proving to be a very good alternative in these situations, with dalbavancin being the antibiotic for which there is most published clinical data [80,81]. Dalbavancin has shown comparable efficacy to other conventional intravenous options, with the advantage of having a 7-day half-life, thus reducing hospital stay and consequently the number of nosocomial infections.

Question 11. How should catheter-related suppurative thrombophlebitis be managed?

The most important issue in the clinical management of bacterial infections is the need for early focus control. Data on *S. aureus* bacteremia have demonstrated that the delay in focus control is directly related to a longer duration of bacteremia, and this in turn to the risk of septic metastasis as well as higher mortality on day 30 [82]. Once adequate antibiotic treatment has been started and the catheter has been removed, the use of anticoagulation may be considered in patients with significant thrombophlebitis. However the level of evidence is low, and most guidelines leave the decision to initiate anticoagulation and its duration to the attending clinician with uncertain data regarding indication and duration [40]. There is one single-center retrospective study of patients with *S. aureus* bacteremia and radiologically proven thrombophlebitis, in which anticoagulation was associated with lower mortality in the multivariate analysis [83]. Thrombolysis and surgical treatment are reserved for exceptional cases with persistent bacteremia despite optimized antibiotic treatment and after ruling out other potential foci [84].

Question 12. When and how can a catheter with suspected infection be replaced over guidewire?

Current indications for guidewire replacement of central catheters include mechanical complications such as (a) rupture of the external tract of the catheter, (b) secondary malposition (so-called tip migration), (c) substitution with a similar but more appropriate device (for instance, replacement of a single-lumen with a double-lumen catheter) [40, 85-87]. Guidewire replacement is known to be ineffective for prevention of C-RBSI; also, it is not considered useful for diagnosis or for treatment of catheter-related infection.

In fact, current contraindications for guidewire replacement are: (a) infected catheter (suspected infection or established diagnosis of infection), (b) colonized catheter, (c) presence of symptomatic or asymptomatic thrombosis, (d) presence of fibroblastic sleeve.

A catheter **with suspected infection** may be replaced over guidewire only in very exceptional cases, i.e., in patients requiring central venous access, carriers of a colonized or infected catheter, in whom extreme difficulty is foreseen for the placement of a new central venous access and in whom con-

servative treatment of infection or colonization is not indicated. In such cases, the catheter should be preferably replaced with an antimicrobial catheter (such as a catheter coated with chlorhexidine/silver-sulphadiazine or a catheter coated with antibiotics) [88]. This maneuver should be taken into consideration only if there is no evidence of septic shock or of endocarditis

NEW DEVELOPMENTS IN PREVENTION

Question 13. What steps should be followed in the implantation of a vascular line?

The first consideration would always be to question the need for the device, taking into account the risks and benefits for the patient. The use of daily objective checklists helps to evaluate the removal of catheters that are not indicated.

Regarding the implantation of a central venous catheter (CVC), the use of ultrasound during the insertion can be considered as it demonstrated to reduce mechanical complications during the procedure.

Checklists should also be used during the insertion process. They include verifying the competence of the professionals performing the procedure and supervision, as well as the fundamental aspects that should be contemplated during the procedure from informed consent, correct hand hygiene or barrier measures among others. This tool has been shown to significantly reduce the rate of C-RBSI [89]. Similarly, the availability of kits with all the necessary material for the implantation of a CVC has also demonstrated to be effective [90].

The Bacteremia Zero protocol, updated in 2021, establishes a series of recommendations (mandatory, optional, do not perform) in relation to the implantation of CVC [91], and there is ample scientific evidence applicable to other vascular devices [22]. The following recommendations stand out for their importance:

1. **Adequate hand hygiene** before and after palpating the insertion site, as well as before and after insertion. This can be done with soap and water or with hydroalcoholic solution according to recommendations. The use of sterile gloves does not exempt from hand hygiene (high evidence/strong recommendation).

2. **Skin disinfection with chlorhexidine**. Disinfect the skin with an alcoholic chlorhexidine solution containing a concentration between 0.5 and 2% and 70° alcohol before CVC insertion or with alcoholic iodine solution in case of contraindication [92]. (High evidence/strong grade of recommendation).

3. **Maximum protective barriers**. Adoption of maximum sterility barriers (cap, mask, sterile gown, sterile gloves, and large sterile drape covering the patient) during CVC insertion substantially reduces the incidence of C-RBSI [93]. (High evidence/degree of strong recommendation).

4. **Subclavian location preference**. The subclavian vein should be preferred, taking into account other factors such as the possibility of non-infectious complications, certain populations such as hemodialysis patients, and the skill of the practitioner when inserting the catheter [4, 94]. (High evidence/strong recommendation).

In the cannulation of PICCs, the basilic vein will be the first choice, since it has the largest caliber and the most direct route to the superior vena cava.

There are some recommendations applicable to high-risk patient subgroups, such as the use of catheters impregnated with antimicrobials, and don't do recommendations such as not administering prophylactic antibiotherapy prior to CVC insertion.

Question 14. What is the current role of ultrasound and other methods of vascular visualization?

Vascular visualization technology plays an increasing role in venous access, and should be part of the knowledge of any physician or nurse expert in vascular access, as recommended by the 2021 Standards of the Infusion Nursing Society (INS) and as demonstrated in different works [95-103].

Ultrasound is currently indispensable for the placement of peripheral venous access in DIVA patients (DIVA = Difficult Intra-Venous Access), both in adults and in children.

More importantly, ultrasound is currently indispensable for the placement of any central venous access device. It plays a role not only for venipuncture but – as described in the 2020 guidelines of the European Society of Anesthesia (ESA) - in many different aspects of the procedure, both in adults and in children:

1. pre-procedural evaluation of the veins, preferably using a systematic and standardized approach such as the RaCeVA protocol for CICCs (RaCeVa = Rapid Central Venous Assessment), the RaPeVA protocol for PICCs (RaPeVA = Rapid Peripheral Venous Assessment), and the RaFeVA protocol for FICCs (RaFeVA = Rapid Femoral Venous Assessment);
2. ultrasound-guided puncture and cannulation of the vein, with different techniques, depending on the vein to be accessed (out-of-plane in short axis; in-plane in short axis; in-plane in long axis; in-plane in oblique axis);
3. diagnosis of immediate complications related to venipuncture (pneumothorax, hematomas); in particular, pleural scan with a linear probe has a very high accuracy in excluding the presence of pneumothorax, and should be performed soon after any venipuncture for PICC insertion;
4. control of the progression of the guidewire and/or the catheter; ultrasound scan by a linear probe is the easiest method for 'tip navigation' (safer and more accurate than fluoroscopy);
5. intraprocedural localization of the tip; all current guidelines recommend intraprocedural 'tip location': though the most recommended method is intracavitary ECG, whenever such method is not applicable or not feasible, the easiest method for intraprocedural tip location is trans-thoracic echocardiography, using the 'bubble test' (as standardized in the ECHOTIP protocol); ultrasound-based tip location is safer and more accurate than fluoroscopy, and is particularly useful in neonates;

6. diagnosis and follow-up of all late complications. With the exception of infectious complications, ultrasound plays a pivotal role in the diagnosis and management of all non-infective complications (venous thrombosis, fibroblastic sleeve, secondary malposition, etc.).

On the other hand, also near infrared (NIR) technology may have a role in the field of vascular access. NIR technology allows proper visualization of superficial veins (i.e., veins at less than 7 mm from the surface of the skin) and is currently recommended in two types of situations:

- in all placements of epicutaneo-cava catheters and short PVCs in the neonate;
- in the placement of short PVCs in the infant with DIVA.

Question 15. What should be the daily care of implanted catheters?

Intravascular catheters are indispensable devices for the correct management of patients, so their use is frequent and so they are their complications. Preventive measures are essential both at insertion, as we have just seen, and at daily maintenance.

The COVID-19 pandemic has revealed that the measures implemented are difficult to maintain under stress and this has been reflected in the increase in CRI rates [8, 104]. The American guidelines [105], as well as the new recommendations of the SEMICYUC-SEEIUC [91] have incorporated in addition to the previous mandatory measures, new recommendations such as pre-prepared insertion kits to reduce catheter cannulation time, daily hygiene of patients with chlorhexidine, coverage with chlorhexidine-impregnated dressings on CVCs in patients over 2 months of age, passive disinfection with antiseptic-impregnated caps on bio connectors to ensure compliance with disinfection of bio connectors before use, continuous infusion system replacement at 7 days coinciding with bio connector replacement, the need to remove unnecessary catheters and an appropriate nurse-patient ratio.

Regarding the care of PVCs [106], the recommended measures include: hand hygiene before and after each manipulation, skin disinfection with 2% alcoholic chlorhexidine [107], use of sterile gloves if it is not guaranteed not to touch the catheter after applying antiseptic, coverage of catheter entry site with semi-permeable transparent dressings, use of closed connectors, disinfection of the bio connectors with single-dose wipes impregnated with antiseptic or passive disinfection before use, catheter replacement only when clinically indicated, daily monitoring of the insertion point, maintenance preferably with pre-filled syringes of saline solution per shift and removal of the catheter when it is not necessary.

In conclusion, it is necessary to implement all measures in all catheters and throughout the hospital.

Question 16. What are the problems and limitations of the teaching procedures on CRI prevention?

Different studies have demonstrated the poor professionals' knowledge regarding the recommendations in the prevention of CRI [108-110]. A review including 19 studies, observed the low adherence of professionals to the recommendations on CRI prevention [111].

Training of all professionals (nurses, physicians, residents and students), has shown different impacts on improving knowledge and CRI rates. In a study conducted in Spanish internal medicine units, the implementation of an educational program with posters and leaflets did not have a great impact on improving healthcare professionals' knowledge, although quality of catheter care was better [112]. In a review including 10 studies, the training of all neonatal ICU professionals demonstrated a decrease in CRI rates in 8 of them [113]. Continuous training seems to be the most effective approach in order to achieve lower rates of CRI, as shown in a study conducted in medical wards with mandatory continuing education and audits for 4.5 years [114].

Real-time training and feedback was associated with increased compliance in PVC care in an emergency unit [115], but the study underlined some of the barriers such as lack of time, no space for training, lack of materials, roles not identified, etc [116].

Therefore, continuous training of all professionals is necessary, but the degree of compliance with all recommendations must be measured and it is necessary to have feed-back with professionals to achieve better results.

Question 17. How can new teaching and instrumentation technology help training in this area?

The COVID-19 pandemic has exposed the deficiency of the healthcare system to maintain the recommendations on CRI prevention. The inability to conduct face-to-face training has promoted the use of telemedicine and on-line training.

Simulation through standardized teaching sessions in a safe environment reinforces best practices in nosocomial infection prevention [117], although in a study conducted both in one medical and one surgical ICU, it only reduced CRI rates in the medical ICU [118].

Other technologies, such as augmented reality glasses have helped in improving CVC insertion techniques [119] and can be used to improve the knowledge of all practitioners.

In addition, technology can help to identify variables, such as age, comorbidity, or treatment, that are associated with an increased risk of developing CRI [120].

A pilot study with a sensor implanted in a reservoir helped to detect signs of infection [121].

In conclusion, technology can help to improve the training of all professionals and help in prevention of nosocomial infections identifying risk factors of non-adherence to the recommendations.

Question 18. What has been the impact and current status of "zero tolerance" programs on catheter infection?

Before the implementation of the "Zero Projects", the surveillance of nosocomial infection in the ICU was consolidated in Spain through the "ENVIN-ICU" registry (National Surveil-

lance Study of Nosocomial Infection in the ICU) since 1994. This registry is an activity of the Working Group on Infectious Diseases and Sepsis (GTEIS) of the SEMICYUC and currently collects information from more than 80% of the country's ICUs. It is a voluntary, multicenter, prospective registry that includes information on device-related infections, bacteremia secondary to other foci and other infections. Between 1994 and 2006, the incidence density (ID) of primary bacteremia (PB) ranged from 5.04 to 7.9 episodes x 1,000 CVC days, 14.6-23.6 for ventilator-associated pneumonia per 1,000 mechanical ventilation days (VAP) and 4.9-7.4 for urinary tract infections per 1,000 IBC days (UTI) (https://proyectoszero.semicyuc.org/). These figures are significantly higher than those reported by the "National Nosocomial Infections Surveillance" (NNIS) in North American ICUs [122].

During the implementation period of the "Zero Bacteremia Project" (January 2009 - June 2010), 192 ICUs joined the program, which represented 68% of the country's ICUs. At the end of participation, the ID of primary bacteremia decreased from a median of 3.07 to 1.12 episodes per 1,000 CVC days ($p < 0.001$). The adjusted incidence rate showed a 50% [95% CI, 0.39-0.63] reduction in the risk of bacteremia at the end of the follow-up period from baseline. The rates decreased independently of hospital size and type [123]. In addition, CVC utilization ratio was reduced by 4.9%. The Zero Pneumonia and Zero Resistance projects have also demonstrated a significant reduction in healthcare-associated infections (HCAI) and multi-resistances [124].

During the pandemic, the structural, functional, and organizational changes implemented in the ICUs to meet the care-needs made it difficult to apply the recommendations of the critical patient safety projects (Projects Zero) to prevent the development of HCAI. Data from the 2021 ENVIN-HELICS report (ENVIN-ICU '02 (vhebron.net) confirm the impact of the pandemic on ICU infection indicators. Rates of patients acquiring one or more infections during ICU stay remained elevated (14.36 per 100 admitted patients), figures far from the 4.76 per 100 admitted patients in 2019. The DI of all device-related infections remains high reaching in PB 4.42 episodes per 1,000 catheter days; in VAP 11.33 episodes per 1,000 MV days and in UTIs 4.67 episodes per 1,000 IBC days, all figures higher than the previous ones in 2019 (2.5 PB per 1. 000 days of CVC; 5.41 VAP per 1,000 days of MV and 2.85 UTIs per 1,000 days of ED, respectively) and very similar to those existing at the start of the "Bacteremia Zero"; "Pneumonia Zero" and "UTI-SU Zero" programs. This has led to the implementation of new specific measures to reduce HCAIs related to ICU devices, updating protocols and promoting the training of all Intensive Care Medicine professionals. At present, there is already evidence of a reduction in all device-associated HCAIs in the ICU.

Question 19. What do we know about the administrative situation of this problem in Spain?

Patient safety, a key component of quality of care, has acquired great relevance in recent years both for patients and their families, who wish to feel safe and confident in the healthcare they receive, and for managers and professionals who wish to offer safe, effective and efficient healthcare (https://seguridaddelpaciente.sanidad.gob.es/presentacion/home.htm).

The Ministry of Health (MS), in its responsibility to improve the quality of the healthcare system as a whole, as established in Law 16/2003, on Cohesion and Quality of the National Health System, has placed patient safety at the center of healthcare policies as one of the key elements of quality improvement, as reflected in strategy number 8 of the Quality Plan for the National Health System, which has been developed since 2005 in coordination with the Autonomous Communities (AC).

Since 2006, the Spanish MS, in collaboration with the AC, has been establishing safe practices in various areas, one of them being the prevention of nosocomial infection and surgical infections. Strict surveillance of infection in the ICU is a basic, essential instrument that increases the safety of patients and saves lives.

The "Zero Projects" led by the Spanish Society of Intensive Care Medicine, Critical Care and Coronary Units (SEMICYUC) and the Spanish Society of Intensive Care Nursing and Coronary Units (SEEIUC), in collaboration with the MS and the AC, have been an opportunity to introduce a culture of safety in the ICU. These projects, with proven sustainability over time, have become working tools in the ICU with successful results. Moreover, they have led not only to an improvement in the incidence of HCRI in the ICU and a reduction in the number of patients with multi-resistant bacteria, but also to a change in the way of working and planning critical patient care as a whole, as well as, in short, a boost in the safety culture.

Zero Tolerance Projects have been incorporated into the Safety strategies of the AC that have promoted their development at the local level. In many of them, hospital program contracts include among their objectives participation in these projects and the achievement of the established quality standard. This undoubtedly boosted their implementation in ICUs. Moreover, in some communities the results of these indicators are published periodically to improve transparency.

Numerous activities have been carried out to disseminate these projects and updated training programs have been developed and made available to all professionals caring for ICU patients (https://proyectoszero.semicyuc.org/).

All this demonstrates the commitment of the Administration, health care institutions and professionals to improving safety and specifically to reduce HCAIs related with ICU devices.

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CONFLICTS OF INTEREST

The author declares no conflicts of interest

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Use of noninvasive measurement of the indocyanine green plasma disappearance rate in patients with septic shock

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ABSTRACT

Introduction. Our aim was to analyse the relation between serial values of the indocyanine green plasma disappearance rate (ICG-PDR) with hospital mortality in the first 48 hours of ICU admission in patients with septic shock.

Methods. A prospective observational study was carried out over 12 months of patients admitted to the ICU with septic shock. Each patient underwent noninvasive determination of ICG-PDR at 24 and 48 hours with the LiMON® module. Follow-up was performed until hospital discharge or exitus.

Results. 63 patients. Age 61.1±12.3 years. 60.3% men. SOFA score on admission 8.7±3.3, APACHE II score was 27.9±10.7 points. A total of 44.4% of patients died. The ICG-PDR values in the first 24 hours of ICU admission were lower in nonsurvivors: 10.5 (5.7-13.0)%/min vs. 15.9 (11.4-28.0)%/min, p <0.001. Furthermore, in nonsurvivors, there was no improvement in ICG-PDR between 24 h and 48 h, while in survivors, there was an increase of 25%: 15.9 (11.4-28.0)%/min and 20.9 (18.0-27.0)%/min, p=0.020. The silhouette measure of ICG-PDR cohesion and separation for the clusters analysed (nonsurvivors and survivors) was satisfactory (0.6). ICG-PDR<11.7%/min was related to in-hospital mortality, ICG-PDR> 18%/min to survival, and the interval between 11.7% and 18%/min covered a range of uncertainty. In the two-stage cluster, ICG-PDR, SOFA and APACHE II present satisfactory predictive scores 24 hours after patient admission.

Conclusions. ICG-PDR in our setting is a useful clinical prognostic tool and could optimise the decision tree in patients with septic shock.

Keywords: Indocyanine green; Septic shock; ICU

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Utilidad pronóstica de la medida no invasiva de la tasa de desaparición plasmática de verde de indocianina en pacientes con shock séptico

RESUMEN

Introducción. Nuestro objetivo fue analizar la relación de los valores seriados de la tasa de desaparición plasmática de verde de indocianina (ICG-PDR) con la mortalidad hospitalaria en las primeras 48 horas de ingreso en UCI en pacientes con shock séptico.

Métodos. Estudio observacional prospectivo durante 12 meses en pacientes de UCI con shock séptico. Cada paciente se sometió a la determinación no invasiva de ICG-PDR a las 24 y 48 horas con el módulo LiMON®. El seguimiento se realizó hasta el alta hospitalaria o el fallecimiento.

Resultados. 63 pacientes. Edad 61,1±12,3 años. 60,3% hombres. SOFA al ingreso 8,7±3,3, APACHE II 27,9±10,7 puntos. Un 44,4% de los pacientes falleció. Los valores de ICG-PDR en las primeras 24 horas de ingreso a la UCI fueron más bajos en los no supervivientes: 10,5 (5,7-13,0)%/min vs. 15,9 (11,4-28,0)%/min, p <0,001. Además, en los no supervivientes, no hubo mejora en ICG-PDR entre las 24 y 48 horas, mientras que en los supervivientes hubo un aumento del 25%: 15,9 (11,4-28,0)%/min y 20,9 (18,0-27,0)%/min, p=0,020. La medida de la silueta de la cohesión y separación de ICG-PDR para los grupos analizados (no supervivientes y supervivientes) fue satisfactoria (0,6). ICG-PDR<11,7%/min se relacionó con la mortalidad intrahospitalaria, ICG-PDR>18%/min con la supervivencia y el intervalo entre 11,7% y 18%/min abarcaba un rango de incertidumbre. En el clúster bietápico, ICG-PDR, SOFA y APACHE II presentan puntuaciones predictoras satisfactorias a las 24 horas del ingreso del paciente.

Conclusiones. ICG-PDR en nuestro entorno es una herramienta pronóstica clínica útil y podría optimizar el árbol de decisiones en pacientes con shock séptico.

Palabras clave: Verde de indocianina; Shock séptico; UCI

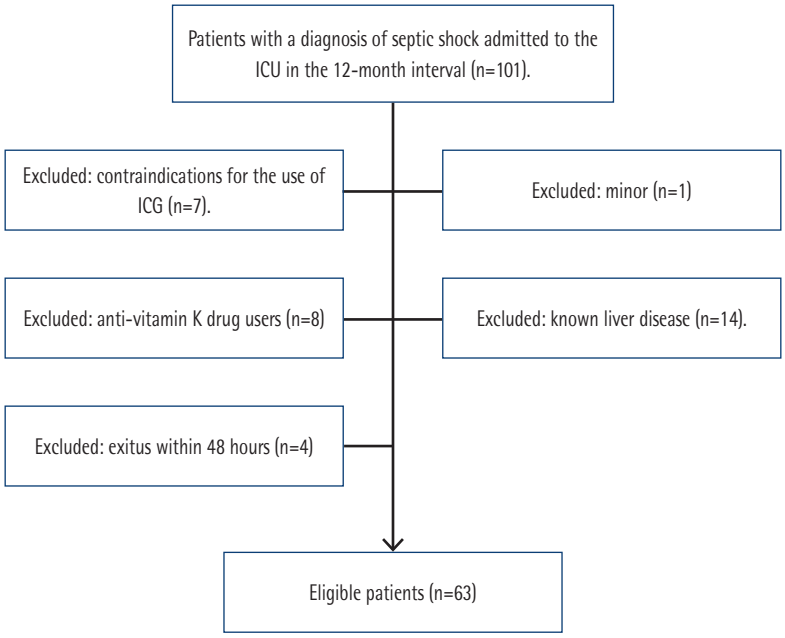

Figure 1 | **Flow diagram of patients included in the study.**

INTRODUCTION

In 35% of patients with sepsis or septic shock, without known previous liver disease, liver dysfunction occurs to a greater or lesser degree [1]. The causes of such functional alterations are diverse and include hypoxic liver injury, cholestatic dysfunction, sclerosing cholangitis in critical illness and drug-induced liver injury.

Liver dysfunction and acute liver failure of secondary causes are independent mortality factors in critically ill patients [2]. Therefore, the prognostic scales (SOFA, APACHE) applied in these patients incorporate different static tests of liver function and synthesis.

For years, dynamic function liver tests have been available to estimate liver functional reserve at the bedside in hepatectomised patients and in heterogeneous groups of critically ill patients. These tests are significantly superior to static tests as a predictor of mortality [2, 4-7]. The indocyanine green plasma disappearance rate (ICG-PDR) is currently the most widely used measure to assess hepatic functional reserve based on hepatic flow and hepatocyte metabolism.

Indocyanine green (ICG) is a water-soluble fluorescent dye with an absorption peak at 800 nm in blood plasma. When administered intravenously, it binds to plasma proteins (albumin and lipoproteins) its volume of distribution approximates the plasma volume. ICG is selectively absorbed by hepatocytes and is excreted unchanged in the bile without undergoing enterohepatic recirculation. The elimination of ICG from the blood depends on hepatic blood flow, the function of parenchymal cells, and biliary excretion [3].

ICG-PDR is the rate at which ICG disappears from plasma per unit time and is expressed in %/min. After intravenous administration of the dye, its ICG-PDR can be determined invasively and noninvasively (spectrophotometry). Its normal value is 18%/min, and values below 18% /min are associated with increased mortality and liver failure in critically ill patients [2, 8].

To date, few prospective studies have demonstrated the validity of the noninvasive ICG-PDR test for predicting mortality in patients with septic shock without known previous liver disease. The aim of the present study was to analyse whether serial values of the ICG-PDR obtained noninvasively in the first 48 hours of intensive care unit (ICU) admission in patients with septic shock are associated with mortality.

METHODS

We designed a prospective analytical observational study over a 12-month consecutive period (from May 30, 2019, to May 30, 2020) of all patients admitted to our 14-bed ICU with criteria of septic shock [9] (defined as lactate level>2 mmol/L and need for norepinephrine for mean arterial pressure >65 mmHg) with no history of previous known liver disease (Figure 1).

The main variable of the study is ICG-PDR at 24 and 48 hours, which has a normal value of 18%/min. Noninvasive de-

Table 1 Associations between hospital mortality and other parameters in patients with septic shock.

	Survivors N=35 (55.60%)	Non-survivors N=28 (44.40%)	p
Age (years)[1]	60 (50-65)	68 (56.5-71.75)	**0.022**
Gender			
Male	21(60.0)	17 (60.7)	0.580
Female	14 (40.0)	11 (39.3)	
Days of stay in Hospital[1]	19 (13-36)	17 (5.25-25.25)	0.113
Days of stay in ICU[1]	10 (6-14)	9 (4.25-16.75)	0.514
Days of mechanical ventilation[1]	4 (0-7)	8 (4- 16.75)	**0.003**
Focus			
Respiratory	16 (45.7)	10 (35.7)	0.294
Abdominal	13(46.4)	0.115	
Soft tissue	1 (3.6)	0.695	
Urologic	3 (10.7)	0.178	
Unknown	1 (3.6)	0.444	

[1]Median.

termination of ICG-PDR at 24 and 48 hours was performed at the bedside of each admitted patient with the LiMON® module. For each clinical variable recorded, the ICG-PDR values corresponding to the time of admission and the values obtained at 24 and 48 hours were recorded. Follow-up was performed in all cases until hospital discharge or death.

Protocol for administration of ICG. The technique was performed 24 hours after admission to the ICU (performed by the same physician following an agreed protocol). The patient is administered a single intravenous bolus of 0.25 to 0.50 mg of ICG diluted in water for injectable preparation per kilogram of body weight. The final dose of administration is indicated by the LiMON® monitor software based on prior knowledge of sex, age, height and weight. The total daily dose administered should be less than 5 mg/kg body weight.

The outcome variable was in-hospital mortality. Other clinical variables: 24 and 48 h values of ICG-PDR and validated scales predictive of mortality in the ICU: SOFA and APACHE II.

For the descriptive and inferential analysis, absolute frequency (N), relative frequency (%), mean values, median, standard deviation, and 25th, 50th and 75th percentiles were calculated. T tests: Chi-square, independent samples t test, U Mann-Whitney test for independent samples and Wilcoxon signed-rank test. A two-stage clustering was performed for the classification of the hospital mortality variable with different prognostic variables (ICG-PDR, SOFA, APACHE II). For analysis, we used IBM SPSS Statistics 22.

Informed consent for the administration of ICG was obtained from the patients/their families. The confidentiality of the data was guaranteed in accordance with ethical standards and current legislation concerning personal databases. The study protocol was approved by the Ethics Committee of the Hospital Universitario Virgen de Valme, Seville (protocol code 1438-N-19).

RESULTS

We analysed 63 critically ill patients (60.3% male); the age range was 61.1 ± 12.3 years. The mean hospital stay was 24.1±8.2 days and 11.8±4.8 days in the ICU. The SOFA score on admission was 8.7±3.3 and the APACHE II score was 27.9±10.7 points. All patients required sedation and connection to invasive mechanical ventilation.

Predictive capacity of ICG-PDR for overall mortality in patients with septic shock. A total of 28 patients (44.4%) died. Table 1 summarizes the epidemiological characteristics differentiated between survivors (S) and nonsurvivors (NS). The time course of different clinical variables during the first 48 hours of admission are shown in Table 2.

We observed that there were significant differences in ICG-PDR determinations between S and NS septic shock patients. The clearance rate was lower in NS than in S at 24 hours ($p<0.001$) and at 48 hours ($p<0.001$) (Table 3).

NS maintained low ICG-PDR values with no improvement between 24 and 48 hours: 10.5 (5.7-13.0) and 10.5 (3.9-13.6) %/min. However, in S, there was an increase of 25%: 15.9 (11.4-28.0) and 20.8 (18.0-27.0)%/min at 24 and 48 h, respectively (Table 4 and Figure 2).

The silhouette measure of ICG-PDR cohesion and separation for the clusters analysed (NS and S) was satisfactory

Table 2 **Time course of different clinical variables during the first 48 hours of admission in survivors and nonsurvivors.**

		Admission (0 h)	p	24 h	p	48 h	p
Mean arterial pressure (mmHg)	Survivors	60.0 (46.7-74.0)	0.347[2]	86.1 (78.8-93.3)	0.208[2]	93.0 (87.3-103.9)	**0.001[1]**
	Nonsurvivors	64.2 (59.2-77.4)		83.3 (71.7-92.5)		83.5 (72.3-93.5)	
Norepinephrine dosage (mcg/kg/min)	Survivors	0.7 (0.4-1.4)	0.923[2]	0.3 (0.2-0.7)	**<0.001[2]**	0.2 (0.1-0.5)	**<0.001[2]**
	Nonsurvivors	0.7 (0.3-1.9)		1.5 (0.6-2.5)		1.5 (0.4-3.2)	
PaO2/FiO2	Survivors	288.6 (167.0-411.1)	**0.017[2]**	397.5 (320.0-448.9)	**<0.001[2]**	382.8 (345.0-433.3)	**<0.001[2]**
	Nonsurvivors	131.1 (100.0-379.3)		125.1 (94.7-325.0)		171.8 (86.0-314.3)	
Urine Output (mL/kg/h)	Survivors	0.6 (0.4-0.9)	**0.048[2]**	0.9 (0.5-1.3)	**0.001[2]**	0.7 (0.6-1.1)	**0.002[2]**
	Nonsurvivors	0.4 (0-0.8)		0.5 (0.1-0.7)		0.5 (0-0.7)	
Creatinine (mg/dL)	Survivors	1.3 (1.0-1.9)	0.068[2]	1.3 (0.7-1.9)	**0.006[2]**	0.9 (0.7-1.6)	**<0.001[2]**
	Nonsurvivors	1.9 (1.1-2.9)		2.2 (1.5-3.0)		2.4 (1.4-4.1)	
Lactate (mmol/L)	Survivors	2.3 (1.1-3.7)	0.094[2]	1.6 (0.9-2.6)	**0.013[2]**	1.7 (0.9-2.1)	**<0.001[2]**
	Nonsurvivors	3.0 (2.1-4.3)		2.4 (1.7-4.5)		3.6 (2.1-7.7)	
Bilirubin (mg/dL)	Survivors	0.9 (0.4-2.3)	0.613[2]	0.7 (0.4-1.7)	0.105[2]	0.7 (0.3-1.3)	**0.036[2]**
	Nonsurvivors	1.0 (0.5-1.9)		1.2 (0.6-2.6)		1.3 (0.7-2.3)	
INR	Survivors	1.2 (1.1-1.2)	**<0.001[2]**	1.2 (1.1-1.3)	**<0.001[2]**	1.1 (1.1-1.2)	**<0.001[2]**
	Nonsurvivors	1.4 (1.2-1.6)		1.5 (1.3-1.8)		1.5 (1.3-1.8)	

[1]T Test; [2]U Mann-Whitney Test, INR: international normalized ratio.

(0.6003), and we proposed the ICG-PDR score for prognostic prediction in the sample of patients with septic shock: ICG-PDR<11.72%/min for in-hospital mortality and ICG-PDR>18%/min for survival. The interval between 11.7% and 18%/min covers a range of uncertainty. Optimal score ranges at 24 and 48 hours are shown in Figure 3.

Comparison of ICG-PDR with SOFA and APACHE II prognostic scores. All admitted patients were evaluated with the validated prognostic scores APACHE II at 24 hours and SOFA at admission and 24 and 48 hours (Table 3).

The silhouette measure of cohesion and separation for the clusters analysed in SOFA (0.5571) and APACHE II (0.7670) were adequate. In our sample of patients, SOFA scores above 11.02 points predicted mortality, while scores below 7.00 increased the probability of survival. APACHE II values higher than 31.04 points predict mortality. In the two-stage cluster, ICG-PDR, SOFA and APACHE II present satisfactory predictive scores 24 hours after patient admission.

We analysed the variability over time of ICG-PDR and SOFA to determine their intragroup behaviour in both S and NS patients.

As described in Table 3, the ICG-PDR in the S group had a statistically significant evolution over time, while in the NS group, the ICG-PDR values remained constant during the first 48 hours. The NS group presented similar values since admission; therefore, the ICG-PDR demonstrates little variability in serialisation (Figure 2). Nevertheless, there was statistically significant intragroup variability in SOFA scores in both the S and NS groups.

DISCUSSION

Septic shock patients acquire a life-threatening condition and should be promptly recognised and treated in an intensive care unit.

This study analyses the relationship between serial ICG-PDR measurements in the first 48 hours of ICU stay of patients with septic shock and in-hospital mortality. Our results show an association between the percentage of clearance, its time course and short-term mortality in septic shock.

The ICG-PDR has been demonstrated to be a dynamic test of liver function and has been proposed in numerous studies as an early prognostic predictor in critically ill patients with septic shock [2, 6, 10-13]. The noninvasive LiMON® method could be a noninvasive bedside prognostic tool for dynamic monitoring [14] in critically ill patients with septic shock in a manner comparable to SOFA and APACHE II [2, 10-13, 15].

We provide new proposals for optimal ranges of measures of the rate of plasma disappearance of indocyanine green that predict mortality or survival, considering that, to date, there is much heterogeneity among studies that propose multiple cut-off points, and there is currently no consensus on adjust-

Table 3 Comparison of ICG-PDR determinations and SOFA and APACHE II scores in patients with septic shock.

		Admission (0 h)	p	24 h	p	48 h	p
ICG-PDR[1] (%/min)	Survivors	-		15,9 (11,4-28,0)	**<0,001[2]**	20,8 (18,0-27,0)	**<0,001[3]**
	Non-Survivors	-		10,5 (5,7-13,0)		10,5 (3,9-13,6)	
SOFA[1]	Survivors	7,0 (6,0-11,0)	**0,164[3]**	7,0 (6,0-9,0)	**<0,001[3]**	5,0 (5,0-8,0)	**<0,001[3]**
	Non-Survivors	9,5 (7,0-11,0)		11,0 (8,3-12,8)		12,5 (11,0-20,8)	
APACHE II[1]	Survivors	-		19,0 (16,0-26,0)	**<0,001[2]**	-	
	Non-Survivors	-		35,5 (31,0-41,8)		-	

[1]Median; [2]T-test. [3]U Mann-Whitney test. ICG-PDR: indocyanine green plasma disappearance rate

ed figures to guide us in decision-making in these critically ill patients.

Predictive capacity of ICG-PDR for overall mortality in patients with septic shock. This study proposes the ICG-PDR obtained with noninvasive methods and in a safe manner to establish prognosis in a homogeneous cohort of patients diagnosed with septic shock. Although there are several authors who analyse this parameter, many are based on heterogeneous samples of critically ill patients (post-surgical, liver transplant, neurocritical and critically ill patients with multiple pathologies) [6].

If we compare our results with previous and similar publications that also focus their analysis exclusively on patients with septic shock [6, 10, 13, 15], it is reaffirmed that low values of early measured plasma green clearance are predictive of hospital mortality.

Kimura et al. (2001) [10] concluded that ICG-PDR was an early indicator of hepatocellular injury in septic shock and that low values during the first 24 to 120 hours correlated with poor prognosis.

Inal et al. (2009) [15] observed that ICG-PDR was significantly lower in NS (n=18) versus S (n=22) (12.1%±7.6%/min vs 21.2%±10.1%/min). There was 80% NS in the group with ICG-PDR less than 8%/min. Eighty-nine percent of patients who had an ICG-PDR greater than 24%/min survived. According to Kortgen et al. (2009) [16], an ICG-PDR less than 8%/min (AUC=0.81; p=0.006) predicts mortality with a sensitivity of 81% and a specificity of 70%.

Sakka et al. (2002) [12] demonstrated in 336 critically ill patients that small changes in ICG-PDR were associated with increased mortality. The lowest values collected in S were 16.7%±7.6%/min and in NS 8.0±6.7%/min.

Comparison of ICG-PDR with SOFA and APACHE II prognostic scores. The SOFA score is used as a key criterion in the diagnosis of sepsis syndrome and prognosis in patients with septic shock on admission [17]. We observed an association consistent with the literature [2] between mortality in patients with septic shock and an elevated APACHE II and SOFA score.

Lambden et al. [18] concluded that any scoring system that relies on the assessment of several clinical criteria or laboratory parameters, such as the SOFA score, may be subject to calculation variations, influenced by reliance on several laboratory samples, operator expertise or interobserver variability, and confounding factors that are not measured within the score.

Tallgren et al. [19] reported that the accuracy of the SOFA cardiovascular, renal, hematologic, and hepatic system assessment was 80%, while the respiratory and neurologic scores were correct in 75% and 70% of cases, respectively. This inconsistency meant that less than half of the SOFA scores agreed with the gold standard assessment.

Our study concludes that the variation in the serial measurement of the intragroup SOFA scale is statistically significant in both the S and NS groups in patients with septic shock. This reaffirms previous studies that modest changes in the SOFA score have a decisive influence on mortality [19, 20]. Nevertheless, we observed that ICG-PDR shows a constant evolution of values within nonsurvivors, which demonstrates that pathological values at 24 hours of admission can be valid for

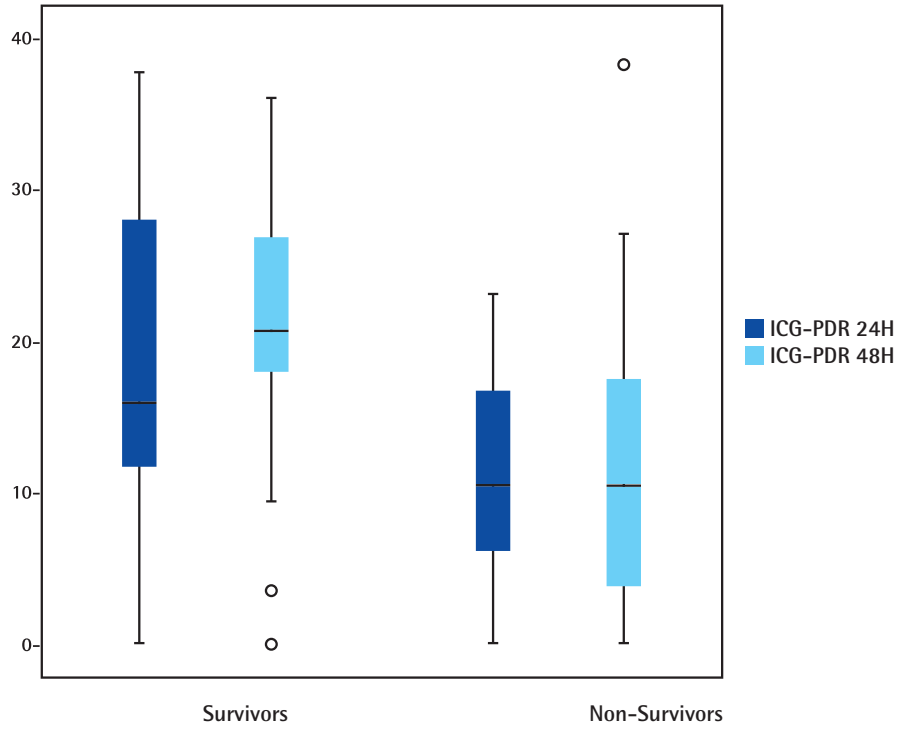

Figure 2 Box plot of the evolution of ICG-PDR (%/min) in the groups of survivors and nonsurvivors with septic shock.

ICG-PDR: indocyanine green plasma disappearance rate.

Table 4 Study of variability of ICG-PDR in patients with septic shock (24 hours-48 hours).

	Survivors	Non-Survivors
Variables	24-48 h	24-48 h
ICG-PDR (%/min)	**0,020**[1]	0,217[1]
SOFA	**<0,001**[1]	**<0,001**[1]

[1]Wilcoxon test. ICG-PDR: indocyanine green plasma disappearance rate.

predicting mortality, with little variability in the following determination.

It has been proposed that interoperator variability of the SOFA scale would decrease if the number of clinical criteria were reduced [19, 22]. Regarding this point, ICG provides benefits such as objective, noninvasive, immediate bedside measurement and prognostic value [6]. In addition, the ability to be a dynamic test with potential analysis of its temporal evolution is an advantage over scores such as APACHE II, which are determined only at 24 hours.

Clinical applicability. Our proposal to integrate ICG-PDR as a prognostic marker added to multimodal monitoring of septic shock together with validated scales such as SOFA and APACHE II is based on two theories taken from the literature. The first is that the treatment decision tree in patients depends on an accurate and consistent assessment of the SOFA score, which is also part of the definition of sepsis; therefore, low interoperator variability in the scores is essential [18]. Second, the European Medicines Agency accepted that in clinical trials in sepsis, a change in SOFA scores is a primary outcome of the study along with the reporting of mortality [23].

Limits of the study. Our study has some limitations. It was conducted in a single center with a small sample size of patients, which could limit the scope of our findings. We also excluded patients with pre-existing liver disease from our study, given that ICG-PDR is influenced by both hepatic blood flow and metabolic function. This exclusion may have impacted the initial values of ICG-PDR and consequently the accuracy of mortality prediction. Systematic studies that evaluate the validation of the ICG-PDR measure in these circumstances would be of great value. It would also be very useful to extend the study on the technical difficulties in the measurement of indocyanine green clearance during periods of tissue hypoperfusion in the first 6 hours of shock detection and treatment, which can alter the pulse wave and spectrophotometric measurement with digital clamp. In this sense, knowing the limitations may help to optimise this technique in the near future.

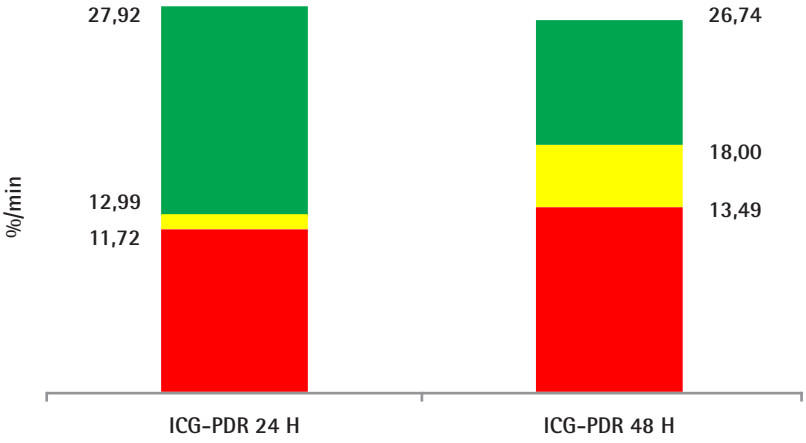

Figure 3 | **ICG-PDR score ranges (%/min) according to mortality or survival at 24 and 48 hours of admission in patients with septic shock.**

Red: mortality; green: survival; yellow: range of uncertainty. ICG-PDR: indocyanine green plasma disappearance rate.

CONCLUSIONS

ICG-PDR could be a useful clinical prognostic tool and could optimise the decision tree in patients with septic shock, in addition to clinical monitoring and validated prognostic scores. Further studies are necessary to design predictive models of ICG-PDR, appropriate to the clinical profile, that will allow us to improve patient care.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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Evolution of *Salmonella* spp. isolated compared to those of *Campylobacter* spp. in faecal samples for 12 years

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ABSTRACT

Introduction. The Autonomous Community of Galicia has adopted DECREE 216/2011 on health standards for poultry production, in addition to the Spanish national programs. However, no program has yet been implemented to eradicate campylobacteriosis, which shares the same reservoir. The aim of this study was to compare the evolution of *Salmonella* spp. isolates with respect to those of *Campylobacter* spp. in faecal samples received by the Microbiology Department.

Material and methods. A retrospective descriptive comparative study was conducted through the Laboratory Information System (SIL) of *Salmonella* spp. isolated against *Campylobacter* spp. in faeces between 2011 and 2022 at the Lucus Augusti University Hospital (HULA), Lugo, Spain.

Results. A total of 35,704 stool samples were analysed, of which 3,045 were positive. 751 Salmonella spp. were isolated. Statistical differences were observed in the annual distribution ($p<0.01$), with a clear turning point in 2018. Five hundred and five patients required hospital care, especially in 2014 with 72 patients (69%). On the other hand, 1,587 *Campylobacter* spp. were isolated. Required hospital care 1,002 patients during the study, with a peak in 2019 with 111 cases (62%)

Conclusion. The reduction of salmonellosis cases and the maintenance of campylobacteriosis cases are directly related to the implementation of DECREE 216/2011. This, in turn, has reduced the pressure on hospitals in the HULA health area. Therefore, we believe that the ONE Health concept is being strengthened in the area studied.

Keywords: campylobacteriosis; salmonellosis; one health,

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Evolución de *Salmonella* spp. aislados en comparación con los de *Campylobacter* spp. en muestras de heces durante 12 años

RESUMEN

Introducción. La Comunidad Autónoma de Galicia ha adoptado el DECRETO 216/2011 sobre normas sanitarias para la producción avícola, además de los programas nacionales españoles. Sin embargo, todavía no se ha implementado ningún programa para erradicar la campilobacteriosis, que comparte el mismo reservorio. El objetivo de este estudio fue comparar la evolución de *Salmonella* spp. con respecto a *Campylobacter* spp. aislados en las muestras fecales recibidas por el Departamento de Microbiología.

Material y métodos. Se realizó un estudio comparativo descriptivo retrospectivo a través del Sistema de Información de Laboratorio (SIL) de *Salmonella* spp. contra *Campylobacter* spp. aislados en heces entre 2011 y 2022 en el Hospital Universitario Lucus Augusti (HULA), Lugo, España.

Resultados. Se analizaron un total de 35.704 muestras de heces, de las cuales 3.045 resultaron positivas, donde resultaron aislados 751 *Salmonella* spp. se observaron diferencias estadísticas en la distribución anual ($p<0,01$), con un claro punto de inflexión en 2018. Requirieron atención hospitalaria 505 pacientes, especialmente en 2014 con 72 pacientes (69%). Por otra parte, fueron aislados 1.587 *Campylobacter* spp. Requirieron atención hospitalaria 1.002 pacientes durante el estudio, con picos en 2019 con 111 casos (62%)

Conclusión. La reducción de los casos de salmonelosis y el mantenimiento de los casos de campilobacteriosis están directamente relacionados con la implementación del DECRETO 216/2011. Esto, a su vez, ha reducido la presión hospitalaria en el área de salud del HULA. Por lo tanto, creemos que el concepto ONE Health se está fortaleciendo en el área estudiada.

Palabras clave: campilobacteriosis, salmonellosis, concepto "one health"

INTRODUCTION

Salmonellosis, an enteric disease caused by the *Salmonella* bacteria, contaminates food and typically results in self-limiting colitis; however, it can be complicating and fatal in up to 16% of patients [1]. Globally, there are an estimated 535,000 cases/year of invasive disease, with the highest incidence occurring in sub-Saharan Africa. It is more common in children under 5 years of age and adults over 70 years of age [2]. The challenge of controlling this disease, characterized by stomach involvement, has persisted through the ages for public health managers. Knowledge of the relationship between this bacterium and animal flesh, such as poultry, pork, and milk [3], has led to efforts focused on handling pre-cooked foods containing these components. This policy has successfully reduced outbreaks of salmonellosis associated with catering [4]. However, the prevalence of this disease remains a public health problem, as it is one of the most frequently isolated microorganisms in the feces of patients with gastrointestinal disorders [5,6]. For these reasons, new control programs aim to attack the food chain at its source, including milk producers and chicken farms.

In Spain, in addition to national programs for the control of *Salmonella* in poultry farms [6], actions are taken at the level of autonomous communities. In the autonomous community of Galicia, particularly in the area of Lugo, where both industrial and artisanal poultry farms are prevalent, programs such as DECREE 216/2011 of November 10 have been implemented. This decree establishes zootechnical and health standards for artisanal poultry production and the Galician Register of Artisanal Poultry Production, focusing on animal welfare and the control of specimens carrying *Salmonella* spp. in order to reduce its transmission to the food chain [7]. Action that was later raised to the national level with DECREE 637/2021.

On the other hand, campylobacteriosis is a zoonosis caused by the same reservoirs as salmonellosis poultry, farm animals, and contaminated animal products. Its most common clinical manifestation is gastroenteritis [8]. However, complications such as Guillain-Barré syndrome and reactive arthritis may occur in immunocompromised, pregnant, or extremely elderly patients, leading to serious long-term consequences [9]. Over the last decade, it has become the most common gastrointestinal pathogen, higher than other recognized pathogens such as *Shigella* spp., *Salmonella* spp. with *C. jejuni* and *C. coli* species being the most common [10], responsible for approximately 2.5 million cases of gastroenteritis per year in the US alone and 16 million cases worldwide. The dramatic increase in North America, Europe and Australia is alarming, and data from regions of Africa, Asia and the Middle East indicate that campylobacteriosis is endemic in these areas, especially in children [9]. Yet, public health authorities have not implemented a program to eradicate this pathogen at the source of contamination, similar to *Salmonella* spp.

The aim of this study was to compare the evolution of *Salmonella* spp. isolates with respect to those of *Campylobacter* spp. in the stool samples received by the Microbiology Service of the Lucus Augusti University Hospital in Lugo after the implementation of local *Salmonella* spp. control programs. This allowed us to infer their effectiveness in terms of public health.

MATERIAL AND METHODS

This study was a retrospective descriptive comparative analysis conducted through the Laboratory Information System (SIL), focusing on *Salmonella* spp. isolates versus *Campylobacter* spp. in faeces. Only the initial isolate from each patient was considered, covering the period from 2011 to 2022 at the Microbiology Service of Lucus Augusti University Hospital (HULA), Lugo, which serves approximately 250m000 registered inhabitants.

The isolation protocol involved culturing on XLD agar BD Difco® (Becton Dickinson France S.A., Le Pont de Claix, Francia), incubated at 37ºC for 24 hours, and selective selenite broth BD Difco® (Becton Dickinson France S.A., Le Pont de Claix, Francia). Subsequently, subculturing was performed on selective Salmonella and Shigella agar BD Difco® (Becton Dickinson France S.A., Le Pont de Claix, Francia) at 37ºC for 24 hours, along with the use of selective agar plates for Campylobacter BD Campylobacter Agar (Becton Dickinson France S.A., Le Pont de Claix, Francia) under microaerophilic conditions at 42°C for 48 hours.

Identification of isolates was accomplished using the MALDI-TOF Biotyper® system (Bruker Daltonics, Bremen, Germany) or panels for MicroScan microbiology systems (Beckman Coulter, Brea, CA, USA). The serotyping of *Salmonella* spp. was conducted using antisera, including Salmonella polyvalent H:g,m, H:i, and antiserum Salmonella monovalent O:4,5 O: 6,7,8 and O:9 (BIO-RAD).

Statistical analyses were performed using the $\chi 2$ and ANOVA tests with the SPSS program. The study of age distribution involved categorizing individuals into six groups: Group 1 (0 to 5 years), Group 2 (6 to 15 years), Group 3 (16 to 30 years), Group 4 (31 to 65 years), Group 5 (66 to 80 years old), and Group 6 (over 80 years old).

RESULTS

A total of 35,704 stool samples were analysed in the study, the distribution by years from 2011 to 2022 was 2,213, 2,544, 2,741, 2,970, 2,969, 2,918, 2,947, 3,226, 3,541, 2,874, 3,136 and 3,625 samples, of which 3,045 were positive, ranging from 287 to 229 positives per year. 751 *Salmonella* spp. were isolated with an incidence per 100,000 inhabitants year (2011 to 2022) of 25, 30, 31, 43, 33, 34, 33, 18, 22, 14, 16 and 14 episodes and an average monthly frequency of 5 episodes. There was a higher frequency of isolation in the summer months (July, August, and September) ($p<0.01$), with a total of 92, 92, and 107 accumulated strains per month, respectively (Figure 1). Statistical differences were also observed in the annual distribution ($p<0.01$), with a clear turning point from the year 2018 in the global isolation of *Salmonella* spp. and the year 2013 a signif-

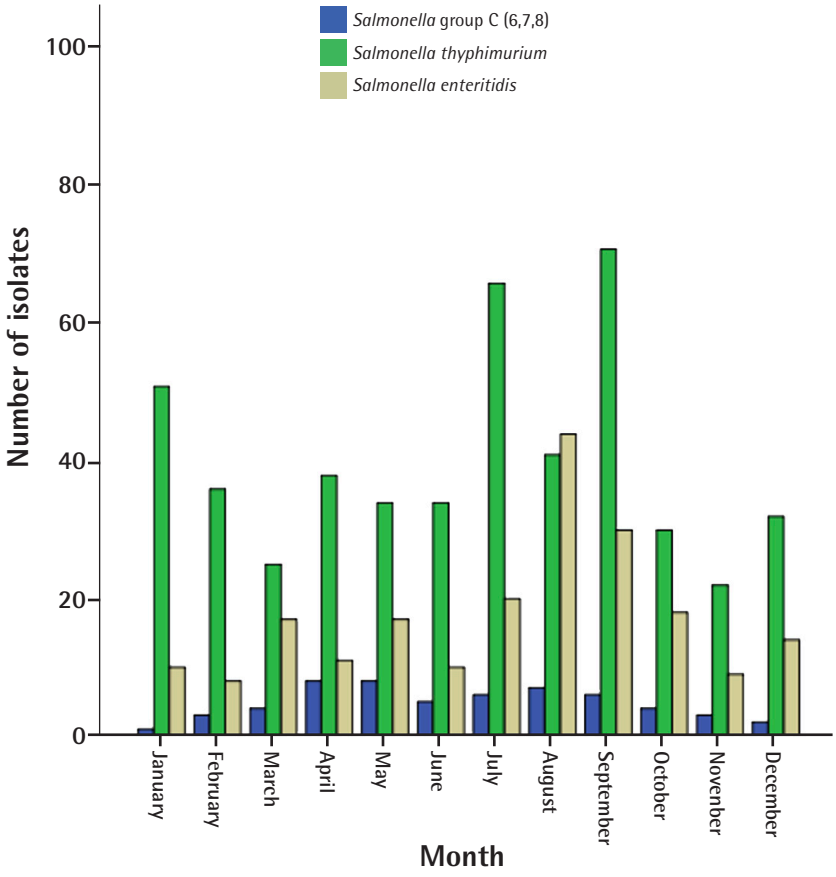

Figure 1 | **Cumulative distribution of *Salmonella* spp. by month**

icant decrease in the isolation of *Salmonella enteritidis* was observed. The mean age was 30 years, ranging from 0 to 102 years (Table 1). Regarding the distribution by sex, no significant differences were observed (p=0.62), although it was more frequent in males (413, 55%), consistent with other published series [11].

The cumulative distribution by age group was significantly more frequent (p=0.02) in group 1 with a total of 268 cases, in a range of 43-2. This decrease was statistically significant (p=0.002). Group 2 was next, with 241 cases, in a range of 18-3, although this decrease was not statistically significant (p=0.1) (Table 2). During the study, a total of 505 patients required hospital care, with the year with the highest number of visits being 2014 with a total of 72 patients (69%) and the year with the lowest number of visits being 2020 with 18 patients (54%). Group 5 and group 6 had the highest number of cases that required hospital care with 85 and 49 cases respectively (83%), followed by group 4 with 108 cases (81%).

On the other hand, a total of 1587 *Campylobacter* spp. were isolated, with an incidence per 100,000 inhabitants year (2011 to 2022) of 45, 60, 62, 63, 56, 49, 49, 69, 79, 63, 54 and 51 episodes and an average frequency of 11.25 episodes per month. No statistically significant differences were observed either in the distribution by year or by accumulated months (p=0.48) (Figure 2). The mean age was 24 years, ranging from 0 to 94 years, and no statistically significant differences were observed in the distribution by sex (p=0.33). However, similar to *Salmonella* spp., they were more frequent in males (936, 59%). A more detailed distribution is shown in Table 1.

Regarding the accumulated age range, group 1 was significantly more frequent (p< 0.01), with a total of 887 cases within a range of 75-28 cases per year, although this decrease was not statistically significant (p=0.10). Group 2 had the next highest frequency with 275 cumulative episodes within a range of 15-30 cases per year. A total of 1,002 patients required hospital care during the study, with peaks in 2019 with 111 cases (62%) and in 2017 with 64 cases treated (57%). By age group, group 1 was the most common with 390 cases (55%), followed by group 4 with 176 treated patients (75%). Although a significant difference (p < 0.01) was observed in the need for hospital care of patients over 80 years of age,

Table 1 **Distribution of *Salmonella* spp. and *Campylobacter* spp. per year**

	Salmonella spp.					*Campylobacter* spp.		
Year	Group C (6,7,8)	*S. paratyphi*	*S. typhimurium*	*S. enteritidis*	Total	*C. jejuni*	*C. coli*	Total
2011	0	0	46	19	65	102	0	102
2012	0	0	55	18	73	135	0	135
2013	5	0	61	11	77	140	0	140
2014	7	0	83	14	104	142	0	142
2015	12	0	38	29	79	126	0	126
2016	5	0	48	28	81	115	0	115
2017	4	0	37	37	78	112	0	112
2018	3	0	29	10	42	144	12	156
2019	10	0	35	7	52	166	13	179
2020	6	0	17	10	33	135	8	143
2021	4	0	19	13	36	114	8	122
2022	4	3	14	12	31	108	7	115
Total	60	3	480	208	751	1,539	48	1,587

with 78 patients treated (86%) compared to 12 of non-hospital origin. Refer to Table 2 for more details.

Regarding the *C. coli* isolates, a total of 48 patients were detected, being significantly more frequent in group 1 with 11 cases (p=0.02) in total, in the distribution by sex, men were more frequent (27/21), and 31 patients (64%) needed hospital care.

DISCUSSION

This study reflects the evaluation of *Salmonella* spp. isolates in comparison to *Campylobacter* spp. in the health area attached to HULA, after implementing the control plan DECREE in the health area of the province of Lugo. In our study, the sex distribution of both *Salmonella* spp. and *Campylobacter* spp. was very similar to that found in other series [10-12].

The age group corresponding to 0-5 years turned out to be the group in which both *Salmonella* spp. and *Campylobacter* spp. were most frequently isolated, as reported in other studies [11-13]. The age group with the highest number of complications and hospitalizations for *Salmonella* spp. was those over 30 years of age, although this data does not agree with other series in our country where the age group with the highest number of complications is from 65 years of age [11,12].

On the other hand, in the case of campylobacteriosis, the group of children aged 0-5 years were the most hospitalized in absolute terms, and in terms of frequency within the age group, the over-80s were the most affected, which is in line with the published literature [10].

The months with the highest incidence in the case of *Salmonella* spp. were the summer months, especially September. In our study, *Salmonella typhimurium* was the most common species, contrary to other Spanish studies [12], since it is usually a more common species in the USA, Mexico, or Taiwan [15-17], followed by *Salmonella enteritidis*, but in the years prior to the study, such as in 2005 or 2006, *S. enteritidis* was the predominant species in our environment. This change is possibly due to the fact that *S. enteritis*, unlike *S. typhimurium*, has the capacity for transovarian transmission and by eliminating laying hens carrying *Salmonella* spp., the number isolated from humans was also reduced. For campylobacteriosis, no seasonality could be demonstrated, as in the work of Ruiz de Alegría-Puig et al [13], although a decrease in incidence was observed in the month of March. The most common species was *Campylobacter jejuni*, as in other European series [13, 14], although in our case we must take into account that as of 2017 mass spectrometry was introduced for the identification of *Campylobacter* spp., therefore, prior to these years we may have an underdiagnosis of *Campylobacter coli*.

Similar programs have been launched in different European regions, such as Denmark or Sweden, where the control of laying hens carrying *Salmonella* spp. has produced significant reductions in the incidence of human foodborne salmonellosis, a decrease that can also be see in our studio [18,19].

CONCLUSION

The results of this study seem to indicate how action at source in the food industry, with the detection and eradication of chickens carrying *Salmonella* spp., is reflected in the reduc-

Table 2 Distribution by year and group age range and isolated microorganism

Year	*Salmonella* spp. Group age range (years)						*Campylobacter* spp. Group age range (years)					
	0-5	6-15	16-30	31-65	65-80	>80	0-5	6-15	16-30	31-65	65-80	>80
2011	25	15	6	10	6	3	55	13	4	15	8	7
2012	35	12	4	10	12	0	79	23	7	18	5	3
2013	36	16	5	10	8	2	67	28	10	16	9	10
2014	43	18	6	9	11	17	73	30	7	15	9	8
2015	30	10	7	19	11	2	62	22	7	14	9	12
2016	27	14	5	15	9	11	66	15	8	10	11	5
2017	21	21	5	17	7	7	53	19	5	18	11	6
2018	10	11	3	10	6	2	69	19	16	23	24	5
2019	20	8	1	9	11	3	64	28	17	38	20	12
2020	11	3	4	5	6	4	58	26	11	23	18	7
2021	2	8	3	12	5	6	33	25	22	20	14	8
2022	8	5	0	7	9	2	28	27	20	23	10	7

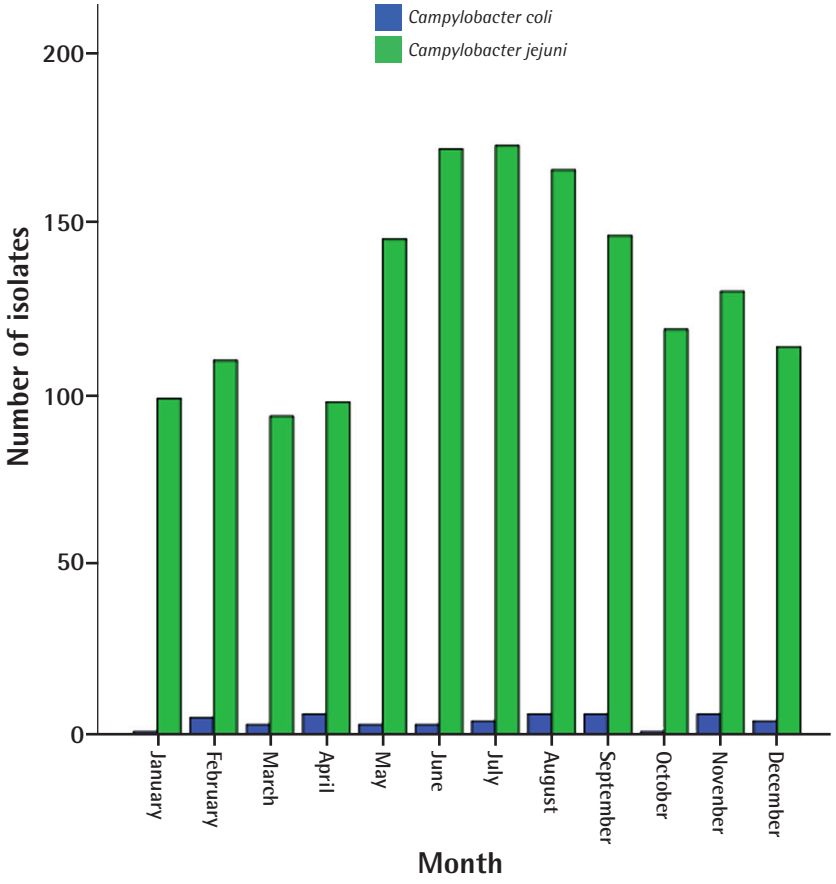

Figure 2 Cumulative distribution of *Campylobacter* spp. by month

tion of cases of human salmonellosis, especially *S. enteritidis* and especially in the vulnerable population. This also reduces the pressure on hospitals, so we believe that in this case the ONE Heldh concept is reinforced in the area studied. Although this ecological niche was occupied by *S. typhimurium*, which is not associated with transovarial transmission. Therefore, the overall decrease in cases must take into account other environmental and hygienic factors of the population. Unlike what happened with *Campylobacter* spp. which does not have transnovarian transmission, but due to contamination of faecal origin, a stagnation of isolates was observed, with a discrete and non-significant decrease. Possibly due to the change in population hygiene habits and the lack of institutional response. Please note that data from 2020 and later may be influenced by changes in habits due to the COVID-19 pandemic.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Change in *Klebsiella pneumoniae* susceptibility profile after the arrival of ceftazidime-avibactam in an Argentinean intensive care unit: a new ecological landscape

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ABSTRACT

Introduction. Ceftazidime-avibactam (CZA) is a good option for Gram-negative bacilli infections that produce carbapenemase Classes A (especially *blaKPC*) and D (*blaOXA*). However, it is unknown whether it would have an impact on metallo-β-lactamases (*blaMBL*) selection. The aim of the study was to compare carbapenem and CZA *Klebsiella pneumoniae* (KPN) susceptibility profiles for a period of two years following the introduction of CZA.

Material and methods. The study was conducted in a 36-bed adult ICU of a tertiary hospital in Buenos Aires, Argentina. Antimicrobial consumption was expressed as days of treatment per 100 patients-day (DOT).

Results. A total of 123 KPN strains in the first year and 172 in the second year were analyzed. An alarming decrease in carbapenem susceptibility was detected in the second year (OR 0.5 [0.3-0.8] p<.001). In parallel, there was a decrease in CZA susceptibility (OR 0.5 [0.3-0.9] p<.05). These findings were linked to a rise in *blaMBL*-KPN (32.1% vs. 45.1%, OR 1.7 [1.1-2.9], p <.04) during the second year. This new KPN susceptibility profile promoted an increment in CZA (1.0 DOT vs. 6.6 DOT, OR 6.6 [4.9-9.1] p<.001) and aztreonam (0.3 DOT vs. 4.1 DOT, OR 16.3 [9.1-29.3] p<.001) consumption. Thus, there was a decrease in carbapenem prescription (17.8 DOT vs. 15.4 DOT, OR 0.8 [0.8-0.9] p<.001).

Conclusions. There was an escalation of *blaMBL*-KPN rate two years after CZA introduction, leading to a decrease in CZA and carbapenem susceptibility and an increase in CZA and aztreonam prescriptions.

Keywords: *Klebsiella pneumoniae*, ceftazidime-avibactam, antimicrobial resistance.

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Cambio en el perfil de susceptibilidad de *Klebsiella pneumoniae* después de la llegada de ceftazidima-avibactam en una unidad de cuidados intensivos argentina: un nuevo panorama ecológico

RESUMEN

Introducción. Ceftazidima-avibactam (CZA) es una buena opción para las infecciones por bacilos gramnegativos que producen carbapenemasas de clases A (especialmente *blaKPC*) y D (*blaOXA*). Se desconoce su impacto en la selección de metalo-β-lactamasas (*blaMBL*). El objetivo del estudio fue comparar los perfiles de sensibilidad de *Klebsiella pneumoniae* (KPN) a carbapenémicos y CZA dos años después de la introducción de CZA.

Material y métodos. Estudio realizado en una UCI de adultos de 36 camas de un hospital terciario de Buenos Aires, Argentina. El consumo de antimicrobianos se expresó como días de tratamiento por 100 días-paciente (DDT).

Resultados. un total de 123 cepas de KPN el primer año y 172 el segundo año fueron analizadas. Se detectó una disminución en la sensibilidad a carbapenémicos en el segundo año (OR 0,5 [0,3-0,8] p<0,001). Paralelamente, la sensibilidad a CZA disminuyó (OR 0,5 [0,3-0,9] p<0,05). Estos hallazgos estuvieron relacionados con un aumento de *blaMBL*-KPN (32,1% vs. 45,1%, OR 1,7 [1,1-2,9], p <0,04). Esto promovió un incremento en el consumo de CZA (1,0 DDT vs. 6,6 DDT, OR 6,6 [4,9-9,1] p<0,001) y aztreonam (0,3 DDT vs. 4,1 DDT, OR 16,3 [9,1-29,3] p<0,001). Por lo tanto, se produjo una disminución en la prescripción de carbapenémicos (17,8 DDT vs. 15,4 DDT, OR 0,8 [0,8-0,9] p<0,001).

Conclusiones. La tasa de *blaMBL*-KPN aumentó dos años después de la introducción de CZA, lo que llevó a una disminución en la sensibilidad a CZA y carbapenémicos, y un aumento en las prescripciones de CZA y aztreonam.

Palabras clave: *Klebsiella pneumoniae*, ceftazidima-avibactam, resistencia antimicrobiana.

INTRODUCTION

Starting from 2009, there has been a gradual increase in Argentina in the prevalence of Gram-negative bacteria that produce carbapenemases, specifically *Klebsiella pneumoniae* (CP-KPN) [1]. These microorganisms have not only established as colonizers but also emerged as significant contributors to diverse infections, including bacteremia, healthcare-associated pneumonia, surgical site infections, urinary tract infections, etc [2]. Among CP-KPN isolates, those carrying Ambler Class A enzymes like *blaKPC* have effectively disseminated throughout many Latin American nations, resulting in elevated levels of endemicity [3].

It is important to highlight that infections caused by CP-KPN are associated with significant morbidity and mortality [4,5]. This is primarily attributed to the limited range of treatment options available, which historically included combinations of drugs like aminoglycosides, colistin, tigecycline, fosfomycin, and extended infusion of high doses of carbapenems [6]. However, with the introduction of new compounds capable of inhibiting the activity of these enzymes, such as CZA (available in Argentina since 2018), meropenem-vaborbactam, and imipenem-cilastatin-relebactam, more effective therapeutic approaches have emerged, leading to improved clinical outcomes compared to the aforementioned treatments [7,8].

Nevertheless, it is crucial to acknowledge that these novel agents are not immune to the selection of antimicrobial resistance mechanisms that previously had a low prevalence in our environment, such as metallo-β-lactamases (*blaMBL*), which remain unaffected by these antibiotics [9,10]. Consequently, the introduction of these new therapies has the potential to significantly alter the composition of the hospital microbiota [11,12].

The aim of this study was to compare the prevalence of different carbapenemase Classes and CZA susceptibility profiles of KPN from an ecological point of view in intensive care units (ICU) clinical samples during the first and second year after CZA introduction in our hospital. The secondary objectives were to compare the CZA, aztreonam and carbapenems prescriptions trends during both periods; and to compare the antimicrobial consumption rate in accordance with WHO´s AWaRe classification.

MATERIAL AND METHODS

Study design and setting. A comparative analysis was conducted to evaluate data from January to December 2020 (P1: first year after the introduction of CZA at our center) and January to December 2021 (P2: second year after the introduction of CZA). The study took place in a 36-bed adult ICU located in a tertiary hospital in the City of Buenos Aires, Argentina. Data on KPN, the most prevalent microorganism in cultures from ICU patients at our hospital, was collected from non-contaminated positive clinical cultures. To avoid the analysis of microorganisms with identical antibiogram from different samples of the same individual, only the first isolate from each patient was taken into account. During the same period, the antimicrobial consumption in those areas was also monitored.

Bacterial identification, antimicrobial susceptibility, and microbiological data processing. For the purpose of conducting microbiological analysis, all KPN isolates obtained from clinical samples were considered, including significant blood cultures, urine cultures, respiratory samples, among others. Isolates categorized as contaminants or colonizers were excluded from the analysis. When microorganisms with identical antibiotic susceptibility profiles derived from different samples of the same individual, only the initial isolate from each patient was analyzed.

The bacterial identification was accomplished by mass spectrometry (MALDI BiotyperTM, Bruker Daltonics Inc.TM, United States). Sensitivity testing was performed using nephelometric methods with specialized panels specifically designed for this purpose, (NMIC-406TM-PhoenixTM panels, Becton DickinsonTM, United States). The interpretation of antibiogram results for the mentioned isolates followed the recommendations outlined by the Clinical and Laboratory Standards Institute (CLSI 31st edition 2021). CLSI. 2021. Performance standards for antimicrobial susceptibility testing [13].

Ceftazidime-avibactam, susceptibility was assessed by disk-diffusion using Mueller Hinton agar (BritaniaTM, Argentina) with ceftazidime-avibactam 10/4 µg disks (BritaniaTM, Argentina). Susceptibility to colistin was confirmed by dropcol test over Mueller Hinton agar (BritaniaTM, Argentina), according to previous report [14]. In this sense, both the interpretation of the antibiogram concerning CZA and colistin were performed according to the standards established by the *European Committee on Antimicrobial Susceptibility Testing* clinical breakpoints [15]. Finally, interpretation of fosfomycin and tigecycline susceptibilities were determined following the adaptation breakpoints proposed by Pasterán *et al.* [16].

Resistance mechanisms were detected using an *in-house* blue-carba test as a screening tool for the presence of carbapenemases production [17]. Subsequently, synergy studies were conducted on Mueller Hinton agar plates using meropenem 10µg (Britania™, Argentina), boronic acid 300µg (Britania™, Argentina), ethylenediaminetetraacetic acid/ sodium mercaptoacetate 372/900µg (EDTA, Britania™, Argentina), amoxicillin/ clavulanic acid 20/10µg (Britania™, Argentina) and aztreonam 30 µg (Britania™, Argentina) disks [18]. When available, the production of carbapenemases was confirmed by commercially immunochromatography kits designed to detect specific types of carbapenemases (including *blaKPC*, *blaNDM*, *blaVIM*, *blaIMP*, *blaOXA48-like*, and *blaOXA163*; NG-test CARBA5, NG BioNTechTM, Germany) in accordance with the national current guidelines [19].

The microbiological cumulative susceptibility data was expressed by following the latest CLSI guidelines [20] using the Whonet software 5.6.

Antimicrobial consumption data. The monitoring of antimicrobial consumption was performed as part of the local antimicrobial stewardship program, utilizing a daily manual check of prescription appropriateness with feedback provided to the prescribing staff at the patient's bedside. Days of treatment per 100 patients-day (DOT) was used as the comparator for each agent. Consumption of the following antimicrobials was assessed: penicillin, aminopenicillins (includes amoxicillin and ampicillin), ampicillin-sulbactam, piperacillin-tazobactam, injectable first-generation cephalosporins (1GC), injectable third-generation cephalosporins (3GC; includes ceftriaxone and ceftazidime), cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, carbapenems (includes ertapenem, imipenem and meropenem), aztreonam, clindamycin, fluoroquinolones (includes ciprofloxacin and levofloxacin), tigecycline, fosfomycin, colistin, macrolides (includes azithromycin and clarithromycin), aminoglycosides (includes gentamicin and amikacin), vancomycin, linezolid, daptomycin and trimethoprim-sulfamethoxazole.

Furthermore, these antimicrobials were categorized according to the WHO's AWaRe groups as 'access' (penicillin, amoxicillin, ampicillin, ampicillin-sulbactam, 1GC, aminoglycosides, clindamycin and trimethoprim-sulfamethoxazole); 'watch' (piperacillin-tazobactam, 3GC, cefepime, carbapenems, fluoroquinolones, macrolides and vancomycin); or 'reserve' (CZA, aztreonam, tigecycline, fosfomycin, colistin, linezolid and daptomycin) categories for the purpose of consumption analysis [21].

Statistical analysis. Categorical variables are reported with the number (n) and percentage (%). *Chi*-square test or *Fisher*'s exact test, as appropriate, was used for proportion comparisons. Additionally, non-adjusted odds ratio (*non-adjusted* OR) was calculated. A 95% confidence interval (CI95%) was considered for all determinations, and a significance level of 5% ($p<0.05$) was established for all comparisons. Statistical analysis was performed using R-Statistics 4.0.3TM.

Ethical clearance. After analyzing the presented results, the members of the ethics and research committee of the healthcare system of the Malvinas Argentinas County (Buenos Aires, Argentina) considered that said study did not require the approval of an ethics committee, as it was an intervention within the framework of an epidemiological surveillance program with necessary action to ensure the health of the participating subjects. Resolution 1480/2011 'Guidelines for Research with Human Subjects' of the Argentine Ministry of Health, stipulates in section A2.b that this type of interventions is exempt from the approval of an ethics research committee, as long as the personal data of the participating individuals are not involved.

RESULTS

***Klebsiella pneumoniae* antimicrobial susceptibility profile.** A comprehensive analysis was conducted on a total of 123 KPN strains in P1 and 172 strains in P2, derived from clin-

Table 1 ***Klebsiella pneumoniae* (KPN) antimicrobial susceptibility profile.**

	KPN susceptibility n (%)				
	P1	P2	non-adjusted OR	CI95%	p value
Ceftazidime-avibactam	106 (67.9)	144 (53.5)	0.5	0.3-0.9	<.05
Ceftolozane-tazobactam	57 (61.4)	104 (29.8)	0.3	0.1-0.5	<.001
Ampicillin-sulbactam	121 (12.4)	170 (12.4)	0.9	0.5-2	0.1
Piperacillin-tazobactam	122 (29.5)	170 (17.6)	0.5	0.3-0.9	<.02
Third generation cephalosporins and cefepime	123 (13.8)	170 (15,3)	1.1	0.6-2.2	.7
Ertapenem*	123 (40.7)	170 (24.1)	0.5	0.3-0.8	<.001
Imipenem	122 (44.3)	170 (27.6)	0.5	0.3-0.8	<.001
Meropenem	122 (44.3)	170 (25.9)	0.4	0.3-0.7	<.001
Amikacin	122 (50.8)	171 (33.3)	0.5	0.3-0.8	<.001
Gentamycin	122 (44.3)	170 (27.1)	0.5	0.3-0.8	<.001
Ciprofloxacin	122 (18.9)	169 (15.4)	0.8	0.4-1.5	.4
Trimethoprim-sulfamethoxazole	122 (23.8)	169 (19.5)	0.8	0.4-1.4	.4
Fosfomycin	123 (80.5)	170 (68.2)	0.5	0.3-0.9	<.05
Colistin	122 (44.4)	169 (62.1)	2.1	1.3-3.3	<.001
Tigecycline	123 (69.1)	170 (71.8)	0.7	0.4-1.1	.1

***Note: carbapenem susceptibility was reported with the surrogate being the susceptibility rate of KPN to ertapenem.**

Table 2 ***Klebsiella pneumoniae*** **carbapenems and ceftazidime-avibactam resistance rate by mechanism.**

	KPN strains n (%)				
	P1	P2	non-adjusted OR	CI95%	p value
Carbapenem-resistant KPN	73 (59.3)	131 (76)	2.2	1.3-3.6	<.001
Ceftazidime-avibactam-resistant KPN	34 (32)	67 (46.5)	1.8	1.1-3.1	<.02
bla_{MBL} (total)*	34 (32.1)	65 (45.1)	1.7	1.1-2.9	<.04
bla_{MBL} and bla_{ESBL}	31 (29.2)	53 (36.8)	1.4	0.8-2.4	.2
bla_{MBL} and bla_{KPC}	3 (2.8)	12 (8.3)	3.1	0.8-11.3	<.07
bla_{KPC}	34 (27.6)	57 (33.1)	1.3	0.8-2.2	.3
$bla_{OXA-163}$	3 (1.7)	3 (2.4)	0.7	0.1-3.6	.7
bla_{ESBL} and impermeability	2 (2.1)	4 (2.3)	1.4	0.3-7.9	.7

*It includes KPN strains that harbor at least bla_{MBL}, although this is not the only mechanism of resistance against β-lactams.

ical samples collected in the ICU. Notably, in P2, there was a decline in the carbapenems susceptibility of these strains, with rates dropping significantly from 40.7% to 24.1% (*non-adjusted* OR 0.5 [0.3-0.8], p<.001). Similarly, there was a significant decrease in CZA susceptibility, from 67.9% to 53.5% (*non-adjusted* OR 0.5 [0.3-0.9], p<.05) during the second year following its introduction.

These changes have prompted modifications in the resistance profile of KPN in ICU by affecting other antimicrobial agents such as 3GC, piperacillin-tazobactam and ceftolozane-tazobactam, which experienced significant declines in their susceptibility rates (Table 1). Moreover, alternative therapeutic options for CP-KPN, including aminoglycosides and fosfomycin, also exhibited reduced rates of susceptibility in P2. Within this context, it is worth mentioning that no significant alterations were observed in the resistance profile of the isolates to tigecycline, as it maintained modest susceptibility rates just about 70% (Table 1).

The KPN resistance to carbapenem and CZA was primarily attributed to the increased prevalence of strains carrying the *blaMBL* enzymes (*non-adjusted* OR 2.2 [1.3-3.6], p <.001). However, when analyzing each resistance profile separately for *blaNDM*-KPN strains, including those co-harboring *blaMBL-blaESBL*, and *blaMBL-blaKPC*, no significant trend was observed (Table 2).

Furthermore, a significant increase in the rate of CZA-resistant CP-KPN isolates was observed during P2 (*non-adjusted* OR 1.8 [1.1-3.1], p <.02). However, there were no notable changes in the rate of isolates producing *blaKPC* and *blaOXA-163*, and no strains carrying *blaOXA-48* were detected. Besides, we identified during P2, a CZA-resistant isolate that produced a novel variant of *blaESBL*, which corresponded to *blaPER*, which had not been previously identified in our ICU (Table 2).

Ceftazidime-avibactam, aztreonam, and carbapenems prescriptions trends. The prescription rates of CZA in the ICU increased from 1.1 DOT to 6.6 DOT (*non-adjusted* OR 6.6 [4.9-9.1], p<.001). Aztreonam prescription was similarly affected, with a shift from 0.3 DOT to 4.1 DOT (*non-adjusted* OR 16.3 [9.1-29.3], p<.001) as CZA / aztreonam combination was predominantly prescribed as initial empirical treatment in patients colonized by Gram-negative bacilli carrying *blaMBL* (as it was frequently found together with *blaESBL*) in patients who displayed clinical signs of infection and in patients with documented infections caused by these microorganisms.

Conversely, as a consequence of the marked increase in carbapenem resistance in P2 (Table 3), the consumption of these agents decreased from 17.8 DOT to 15.4 DOT (*non-adjusted* OR 0.8 [0.8-0.9], p<.001). These findings shows a significant increase in the utilization of 'reserve' agents (36.4 DOT vs. 46.4 DOT; *non-adjusted* OR 1.5 [1.4-1.7], p<.001) with a reduced consumption of antimicrobials from the 'watch' group (45.7 DOT vs. 38.5 DOT; *non-adjusted* OR 0.7 [0.7-0.8], p<.001), and agents from the 'access' group, in P2 (17.9 DOT vs. 15.1 DOT; *non-adjusted* OR 0.8 [0.7-0.9], p<.001).

DISCUSSION

In the present study, after the introduction of CZA in the ICU, an increase in resistance to both, CZA and carbapenems was observed due to an increase in the prevalence of *blaMBL* producing isolates. It is worth noting that this phenomenon, in the case of our country, coincided with the arrival of the SARS-CoV2 pandemic [22], which may blur the role that the ecological pressure generated by CZA could have had on our CP-KPN strains [23]. However, this observation contrasts with the fact that several regions worldwide, such as Greece and Italy, which had licensed this antimicrobial combination prior to the pandemic, experienced an increase in rates of *blaMBL*-producing *Enterobacteriaceae* with a similar trend to what we

Table 3 **Antimicrobial prescriptions trends.**

	Days of treatment per 100 patients-day				
	P1	P2	non-adjusted OR	CI95%	p value
Penicillin	0.4	0.1	0.3	[0.1-0.8]	<.001
Aminopenicillins	0.6	2.3	3.8	[2.5-5.7]	<.001
Ampicillin-sulbactam	8.2	4.0	0.5	[0.4-0.6]	<.001
Piperacillin-tazobactam	6.7	6.8	1.0	[0.8-1.2]	0.9
Injectable first generation cephalosporins	0.7	2.4	3.3	[2.2-4.8]	<.001
Third generation cephalosporins	0.9	0.6	0.7	[0.4-1.2]	.2
Cefepime	1.1	1.7	1.6	[1.1-2.2]	<.02
Carbapenems	17.8	15.4	0.8	[0.8-0.9]	<.001
Aztreonam	0.3	4.1	16.3	[9.1-29.3]	<.001
Ceftazidime-avibactam	1.0	6.6	6.6	[4.9-9.1]	<.001
Clindamycin	0.2	0.1	0.4	[0.1-1.4]	.2
Ciprofloxacin	1.9	0.5	0.3	[0.2-0.4]	<.001
Tigecycline	1.7	1.0	0.6	[0.4-0.8]	<.001
Fosfomycin	10.1	11.1	1.2	[1.0-1.3]	<.03
Colistin	21.3	20.3	1.0	[0.9-1.1]	.5
Macrolides	5.9	1.3	0.2	[0.2-0.3]	<.001
Aminoglycosides	5.9	2.5	0.4	[0.3-0.5]	<.001
Vancomycin	9.6	11.6	1.2	[1.1-1.4]	<.001
Linezolid	1.9	1.9	1.0	[0.7-1.3]	.9
Daptomycin	0.3	0.6	2.0	[1.0-3.7]	<.03
Trimethoprim-sulfamethoxazole	2.0	3.7	1.9	[1.4-2.4]	<.001
'Access' group	17.9	15.1	0.8	[0.7-0.9]	<.001
'Watch' group	45.7	38.5	0.7	[0.7-0.8]	<.001
'Reserve' group	36.4	46.4	1.5	[1.4-1.7]	<.001

observed in our center [24]. This was not an isolated event at our hospital, as since 2020, infections caused by *blaMBL*-producing Gram-negative bacilli have increased throughout the country [25,26]. Furthermore, as has been observed in other reports, this scenario suggests an ecological phenomenon promoted by the exposure of hospital flora to this novel antibiotic combination designed ideally for the treatment of infections caused by Classes A and D carbapenemase-producing microorganisms [9]. The possibility that this new resistance scenario is a clonal event could be ruled out by the fact that the enzyme profiles that accompanied our CP-KPN strains were diverse, i.e., *blaMBL* plus *blaKPC*, or the new appearance of *blaPER* [27]. As a counterpoint to this hypothesis, the most up-to-date information we have, indicates the presence of a dominant KPN clone in multiple jurisdictions as responsible for an interhospital and interregional CP-KPN clonal outbreak [28].

This abrupt change in the ecological niche that dominated our country from 2009 to 2019, where the leading carbapenemase was undoubtedly *blaKPC*, seems to have emerged based on certain predisposing circumstantial factors, such as: 1) incorporation of CZA into the therapeutic arsenal in our setting; 2) non-existence, during the study, of other combinations of new β-lactamase inhibitors such as meropenem-vaborbactam or imipenem-relebactam that could justify this new scenario; 3) throughout the analyzed period, drugs for treating ventilator-associated pneumonia in COVID patients, which possess carbapenem-sparing properties (thus avoiding the described ecological condition), such as ceftolozane-tazobactam, were unavailable at our hospital; 4) SARS-CoV2 pandemic, which overwhelmed the healthcare system and compromised the quality of intra-hospital infection control, favoring the rapid dissemination of different types of carbapenemase-producing bacteria; 5) preexistence, albeit low prevalence, of hospital epidemiological foci of *blaMBL*-producing *Enterobacteriaceae* (even in our own center) in which *blaNDM* served as a substrate (non-published data); and, 6) the possible introduction or *de novo* selection of a hyperepidemic clone. Regarding this

last mention, it is important to note that in countries similarly affected by COVID-19 but where class B carbapenemases were not consistently found in *Enterobacteriaceae* isolates, such as Spain, the introduction of CZA did not have a similar impact as it had in Argentina, Italy, and Greece among others [11,26]. This highlights the fact that the linearity between the introduction of a resistance-selecting agent and the emergence of resistance mechanisms is without doubt a multifactorial conjunction of events.

From an antimicrobial stewardship perspective, the introduction of CZA as an advanced strategy for the treatment of *blaKPC-Enterobacteriaceae* infections resulted in a 'brick removal effect', where the rapidly changing use of numerous antimicrobials, especially within the β-lactam family, was not unexpected. Understanding institutional changes in antimicrobial use that occurs during the introduction of new drugs is crucial for developing policies and protocols that optimize antibiotic use and minimize impacts on healthcare-associated infections. In this regard, it is important to highlight that this analysis is the first in the region to focus on changes in antimicrobial prescribing patterns promoted by the inclusion of CZA in a hospital *vademecum*. Thus, during P2, not only did the consumption of CZA increase significantly but also that of aztreonam, which together became the best available strategy (considering that cefiderocol was not available in Argentina) to treat *blaMBL* and *blaESBL* or *blaKPC*-KPN infections [7,8]. This new antimicrobial consumption pattern led to an increase in the use of drugs from the 'reserve' group. On the contrary, agents with a lower ecological impact as a whole (from the 'access' and 'watch' groups) were substantially less prescribed. In this scenario, where CP-KPN strains of different classes have taken over the ecological landscape of our ICU, the consumption of antimicrobial agents was substantially altered. Therefore, drugs considered to have a 'narrow-spectrum', such as penicillin and older-generation aminopenicillins with β-lactamase inhibitors (such as ampicillin-sulbactam), had an important prescription decline. These findings result in a pernicious cycle in which the introduction of CZA entails selective pressure on *blaMBL*-producing strains, along with other mechanisms, promoting even greater CZA and aztreonam consumption, ultimately leading to an increase in CZA-resistant strain infections. In this ominous reality, infection control and antimicrobial stewardship programs are invaluable for identifying and mitigating changes related to the new consumption pattern in order to optimize care for infected patients, complete treatments with optimal timing, restrict the use of high-ecological impact drugs as much as possible, adjust drug doses, and monitor the emergence of epidemiological epiphenomena such as *Clostridioides difficile* infections associated with the use of these agents [29]. As a further issue, it is necessary to have other pan-carbapenemase therapeutic options in our country that allow for an ecological 'recovery' from CZA, such as cefiderocol7,8, in order to achieve a renewal of the bacterial flora of the hospital environment as one of the infection control strategies.

The present study had several limitations: 1) interrupted time series analysis was not employed due to the comparison of only two distinct time periods and the scarce number of isolates collected in each period (monthly); 2) as an ecological observation, clinical origin assessment of isolates was not conducted as it was not within the scope of this analysis; 3) data regarding the carriage status of multidrug-resistant *Enterobacteriaceae* was not evaluated due to the suspension of our epidemiological surveillance program during 2020, in context of the first COVID-19 pandemic year; as well as predisposing factors to its acquisition such as previous use of antimicrobials, hemodialysis, cancer, etc.; 4) inter-hospital patient movement was not considered; and lastly, 5) this was a single-center study, hence its findings should not be extrapolated to other settings.

CONCLUSIONS

We observed a worrisome decrease of carbapenem and CZA susceptibilities in KPN from clinical ICU patients' samples, due to the escalation in the rate of *blaMBL*-KPN, two years after the introduction of CZA. This increase in the prevalence of *blaMBL*-KPN is not only seen as a separate mechanism of resistance but also as a combined one, often in conjunction with *blaESBL*. Additionally, this framework suggests that the simultaneous rise of double-producing *blaKPC* and *blaMBL* strains is driving to an overlapping problem that is gaining significance.

In this context, 'reserve' antimicrobial prescriptions rate, primarily driven by the increased use of CZA and ATM, becomes uncontrollable. Finally, as a consequence of the aforementioned factors, both the new KPN susceptibility profile and the rise in consumption of the 'reserve' agents led to a compensatory decrease in the prescription of 'access' and 'watch' agents like carbapenems.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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Letter to the Editor

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Mycobacterium abscessus subsp. *massilliense* causing bartholinitis infection: A case report

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Sir,

A 27-year-old immunocompetent female from Madrid (Spain) came to the Gynecological Emergency Department (GED) in February 2022 due to the presence of an abscess in the left major labia of the vagina after ten days of evolution without previous antimicrobial treatment. Previous relevant medical events included a mammoplasty and liposculpture some years ago. Seventeen days previously, the patient had undergone a vaginal mesotherapy session in an aesthetic clinic. This procedure involves the use of subcutaneous needles in order to inoculate substances that promote tissue regeneration. On physical examination, the patient presented an edematous abscess of approximately 7 centimeters in diameter, painful on palpation, warm, erythematous, and fluctuant with no spontaneous drainage point. The clinical picture was compatible with complicated abscessed folliculitis. The patient was diagnosed with a Bartholin gland cyst and cellulitis in her right major labia. Blood examinations did not show any relevant data, only a discreet elevation of leukocytes of 9,220 (reference range 4,800–15,000) cells/mm^3, neutrophil (68%), and a low increase of protein-C-reactive of 14.9 (reference range <1–0.5) mg/dL. At the moment in GED, the patient underwent drainage of the abscess through an incision of 1 cm in diameter with the marsupialization of the Bartholin gland because of drain of approximately 15 mL of purulent material. The patient was discharged with a 300mg/12h clindamycin prescription for seven days until a follow-up visit for suspected *Staphylococcus aureus* infection. The abscess was cultured on blood and chocolate agar (Becton Dickinson, New Jersey, USA) incubated for five days in aerobic conditions at 37°C and 5% CO_2 atmosphere. Moreover, thioglycolate medium (Becton Dickinson) was incubated in aerobic conditions at 37°C.

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The direct sample gram stain did not reveal any structure resembling microorganisms, but showed the presence of leukocytes. However, in the blood agar medium growth of small, dry, and white colonies were observed after 72 hours of incubation. Due to the appearance of colonies, we performed an auramine stain because of higher sensitivity. To confirm the auramine stain results, Ziehl-Neelsen stain from the blood agar colonies was also performed. Both stains were positive for acid-fast rods. Seven days later the patient had to return for a switch of treatment due to the presence of left inguinal adenopathies and microbiological findings.

The dry and white colonies were identified as *Mycobacterium abscessus* subspecies using Matrix Assisted Laser Desorption/Ionization-Mass Spectrometry (MALDI-TOF MS Bruker, Massachusetts, USA) following the protocol proposed by Alcolea-Medina *et. al* [1]. To confirm the result, PCR Genotype Mycobacterium CM v.2.0 (Hain Lifesciencie GmbH, Nehren, Germany) was performed from the isolate. *M. abscessus* subsp. *massilliense* was identified using the PCR Genotype Mycobacterium NTM-DR v.1.0 kit (Hain Lifesciencie GmbH) without detection of mutations related to macrolide or aminoglycoside resistance.

The analysis of antibiotic susceptibility for *M. abscessus* subsp. *massilliense* was performed using the Epsilon-test method (ETEST, BioMérieux®, Marcy-l´Étoile, France) showed resistance to imipenem (>32 mg/L) and linezolid (>256 mg/L), but susceptible to clarithromycin (0.25 mg/L) and amikacin (16 mg/L) using the ECOFF EUCAST breakpoints [2].

Cutaneous mycobacterial infections show clinical presentations, such us cellulitis, nonhealing ulcers, subacute or chronic nodular lesions, abscesses, superficial lymphadenitis, or verrucous lesions [3]. These infections include a group of three diseases categories: cutaneous infections causing by *M. tuberculosis* subspecies, leprosy disease caused by *M. leprae* or *M. lepromatosis*, and cutaneous infections produced by non-tuberculosis mycobacteria (NTM) including rapidly and slow growing mycobacteria [3].

The cutaneous NTM infections are related to invasive surgical or medical-aesthetic procedures such as acupuncture, tattoos, plastic surgery, piercings, pedicure sessions, mesotherapy (as our case reported), surgeries, and in processes including the trauma of the skin [3,4]. *M. abscessus* subspecies first identified in a patient with a knee infection and subcutaneous abscesses in 1950 [5]. *M. abscessus* subspecies pathogens are considered saprophytes and can be found in water, soil, organic matter, or vegetables being the environment the main source of infection. However, *M. abscessus* subspecies have been implicated as causal agents of wound and soft tissue infections, especially in immunocompromised patients such as HIV-patients, organ transplants, cancer or patients undergoing treatment with biological drugs [6]. We report, as our knowledge, the first bartholinitis causing by *M. abscessus* subsp. *massilliense* using the terms *"Mycobacterium*", "*abscessus*", and *"bartholinitis"* on PubMed or Medline database.

Mycobacterium/Mycobacteroides abscessus subspecies includes by sequencing *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massilliense*, and *M. abscessus* subsp. *bolletii*. *M. abscessus* subsp. *abscessus* is more frequently isolated in respiratory samples [7]. However, *M. abscessus* subsp. *massilliense* is more common in soft-tissue infections [8]. In contrast to the slow growing NTM, rapidly growing NTM such as *M. abscessus* subspecies can be grown in conventional media such us blood or chocolate agar in 3-5 days of incubation, Löwenstein-Jensen medium or Bactec mycobacterial growth indicator MGIT 960 system (BD Diagnostic Systems, Sparks, MD) [5]. However, cutaneous abscesses should be cultured at 30ºC and 37ºC for differential diagnoses with another NTM such as *Mycobacterium marinum,* among others [3].

M. abscessus subspecies are intrinsic resistant to anti-tuberculosis treatment such as rifampicin, isoniazid, ethambutol, and pyrazinamide. The presence of lipid-rich cell envelope forms an important barrier to antibiotic penetration with the presence of efflux transmembrane proteins [8]. The subspecies identification of *M. abscessus* is necessary to anticipate the macrolide antimicrobial resistance [8]. *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *bolletii* present a functional inducible erythromycin ribosome methyltransferase *erm (41)* generating a macrolide-resistant phenotype acting at the adenine at position 2058 (A2058) of the 23S rRNA [9,10]. However, *M. abscessus* subsp. *massilliense* presents a non-functional *erm (41)* gene with two deletions making clarithromycin a useful drug for the treatment of this subspecies [11]. The genotypic analysis performed in our laboratory confirmed the susceptibility to macrolides. Moreover, the phenotypic analysis using gradient diffusion showed *in vitro* susceptibility to clarithromycin. However, phenotypic analysis using other methods than broth microdilution can shows low reproducibility and low *"in vitro"* and *"in vivo"* correlation [10]. In the second visit, the treatment of the patient was switched, according to the susceptibility, to oral clarithromycin 500 mg/12h for six months and IV amikacin. *M. abscessus* infections should be treated with at least two or three antibiotics due to the *M. abscessus* subspecies multidrug resistance. Unfortunately, the patient did not return to the gynecology department for follow-up and we have no information on the success of the *M. abscessus* treatment.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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Letter to the Editor

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Allplex™ NG&DR (Seegene) utility for switching oral regimens with fluoroquinolones in gonococcal arthritis

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Sir,

Sexually transmitted infections (STI) by *Neisseria gonorrhoeae* (NG) have increased in recent years worldwide [1]. Gonococcal arthritis is a clinical manifestation of disseminated gonococcal infection (DGI). However, the DGI occurs only in 0.5-3% of patients [2]. Previously, we reported an increase of gonococcal arthritis in our health area from Madrid (Spain) [3].

The *gold standard* for the diagnosis of gonococcal arthritis is established by the growth of NG in the culture of synovial fluid, but its sensitivity can be diminished by the use of previous broad-spectrum antibiotherapy or delay in the microbiological processing due to the fact that NG is a fastidious microorganism difficult to culture. Moreover, NG is isolated in blood or synovial fluid in only 50% of patients with gonococcal arthritis, whereas mucosal swabs culture is positive in 80% of cases [4]. Until now, NG culture is importance not only for definitive diagnosis, but also for determining drug sensitivity [5]. The first-line treatment for NG infections is third-generation cephalosporins, such as intramuscular ceftriaxone or oral cefixime. Macrolides (azithromycin) are second-line treatments that should not be used in monotherapy. Treatment with fluoroquinolones (ciprofloxacin) may be an option in patients allergic or intolerant to third-generation cephalosporins, provided that *gyrA* mutations are not detected following the sexually transmitted infection guidelines [6, 7].

Guidelines for the diagnosis and treatment of septic arthritis in adults and children recommend ceftriaxone (first choice) 1g/24h or cefotaxime (alternative) 1g/8h IV. However, after clinical improvement, the switch to an oral agent guided by antimicrobial susceptibility is recommended for this clinical entity. Ciprofloxacin (500 mg/12h) is the first-line oral treatment, and cefixime (40mg/12h) is the second-line option to continue on an outpatient program [8]. Antimicrobial sensitivity screening for NG can be performed using phenotypic or genotypic methods.

Previously, our working STI group reported the prevalence of mutations associated with macrolide and fluoroquinolone resistance in NG from direct sampling in our population using one of commercially available CE kits (Allplex™ NG&DR Assay, Seegene®) [9]. The assay includes the A2059G mutation (23S rRNA) associated with high-level macrolide resistance and the C1126T mutation (23S rRNA) associated with moderate-level macrolide resistance. Resistance associated with fluoroquinolones is detected by the S91F (*gyrA*) mutation including in the assay. We reported a prevalence of 0.9% mutations associated with macrolide resistance, and 60% of mutations associated with fluoroquinolone resistance at the Hospital Universitario La Paz (HULP) from first-void urine, rectal, tectal, and oropharyngeal swabs [9]. Moreover, we compared the strip gradient diffusion test (phenotypic test) using EUCAST 2024 14.0 breakpoints with a molecular method using the NG&DR assay (genotypic test) from NG isolates [10]. Therefore, we reported that Allplex™ Assay could replace the gradient diffusion test for detecting fluoroquinolone resistance before treatment with ciprofloxacin in NG infections [10].

We report a migrant patient of a 68-years-old male from China. He showed fever (38.4°C), pain, and inflammation in both ankles with predominance in the left lower limb. After being discharged with anti-inflammatory drugs, the patient returned to the emergency department five days later with signs of synovitis in the left ankle, which required admission to the internal medicine ward. Blood tests showed leukocytosis (13,290; reference range 4,800–15,000 cells/mm^3) with 82% neutrophils and elevated C-reactive protein (251.6; reference range <1–0.5 mg/dL). Synovial fluid analysis of the left ankle analysis showed turbidity, hemorrhagic color, decreased glucose (62 mg/dL), and increased proteins (5.1 g/dL) in the absence of crystals and presence of neutrophils (95%). The pa-

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tient had maintained previous unprotected sexual intercourse one month ago.

The culture of synovial fluid on blood, chocolate, and chocolate agar PolyVitex mediums (BioMérieux®, Marcy l´Etoile, France) for 48 hours with 5% CO_2 in aerobic conditions atmosphere was negative. However, the Allplex™ 7 STI Assay (Seegene®) in combination with automated DNA extraction and PCR setup including NG, among other STI pathogens, was positive in the synovial fluid. Serologies for HIV, HBV, HCV, and syphilis (Atellica™, Siemens Healthcare Diagnostics®, Germany) were negative. In addition, following the recommendations of the STI guidelines for gonococcal arthritis, the STI screening including first-void urine, rectal and oropharyngeal swabs were performed using 7 STI Allplex™ with negative results [6]. The patient was treated with ceftriaxone 2g IV single dose and 1g IV/24h during 15 days. Due to non-growth of the NG isolate from the synovial fluid, Allplex™ NG&DR Assay was performed from a direct sample. The S91F (*gyrA*) mutation associated with fluoroquinolone resistance was not detected. Because of the absence of *gyrA* mutation detection included in the Allplex™ Assay and the good correlation between gradient diffusion and molecular methods in our NG isolates previously reported, the patient was discharged, and switched to an oral ciprofloxacin for 15 days. Subsequently, the patient was followed up in an outpatient clinic with success of the therapeutic treatment.

In conclusion, we report the utility of Allplex™ NG&DR (Seegene®) Assay for the detection of mutations associated with fluoroquinolone resistance (*gyrA*) directly from synovial fluid in a patient with non-growth of the NG strain in an environment with a high prevalence of ciprofloxacin resistance (~60-70%). This utility provides to an option for penicillin allergy patients, and reduces cefixime antibiotic consumption such as second-line treatment for switching oral treatment in gonococcal arthritis.

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Resultado falso negativo en diversas PCR multiplex y monoplex en un episodio de bacteriemia por *Neisseria meningitidis*. Implicaciones diagnósticas, terapéuticas y epidemiológicas

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La enfermedad meningocócica invasiva (EMI) es una importante causa de meningitis y sepsis, especialmente en niños y adolescentes [1]. Su agente causal es *Neisseria meningitidis*. Generalmente está causada por los serogrupos A, B, C, W-135 e Y, y sólo excepcionalmente por otros. Los meningococos de otros grupos se encuentran principalmente en portadores sanos, ya que las especies de *Neisseria* forman parte de la microbiota nasofaríngea [2].

El diagnóstico microbiológico convencional de las infecciones por *N. meningitidis* se realiza por cultivo, que es lento (24-48 horas). Es conocida su extrema labilidad, y que situaciones como tratamientos previos con antimicrobianos o transporte y conservación inadecuados (es muy sensible al frío) pueden interferir en su recuperación [3]. También se dispone para su diagnóstico de técnicas de PCR en tiempo real, con resultados en pocas horas.

Presentamos el caso de un varón de 84 años con antecedentes de mieloma múltiple de reciente diagnóstico, en tratamiento con quimioterapia. A los 15 días de ingreso en Hematología el paciente presentó sensación distérmica y malestar general. Se le realizó analítica general, en la que llamaba la atención la procalcitonina (35 ng/mL) y PCR (proteína C reactiva) (33 mg/dl). Ante la sospecha de infección sistémica se extrajeron hemocultivos y se administraron antimicrobianos.

Los dos hemocultivos aerobios resultaron positivos a las 28 horas de incubación. En la tinción de Gram se observaron diplococos Gram negativo, por lo que se sospechó *N. meningitidis*. Se realizó un array multiplex (*FilmArray®Blood Culture Identification, Biofire,* BioMérieux, France*),* que resultó negativo. Se comunicó la información disponible y la sospecha de meningococemia al médico responsable. El paciente había recibido meropenem y, aunque la evolución era satisfactoria, se decidió simplificar a ceftriaxona.

La identificación mediante proteómica confirmó *Neisseria meningitidis* dos días después de su recuperación en cultivo (MALDI-TOF se realiza en el hospital de referencia, y esto conlleva un retraso diagnóstico, evitable si se posee esta dotación en el propio hospital).

Ante la extrañeza del resultado negativo por PCR y la confirmación por cultivo de *N. meningitidis* se procedió a realizar dos pruebas moleculares más: *1)* Filmarray®panel meningitis/encefalitis *Biofire* (BioMérieux, France) *y 2)* "VIASURE *Haemophilus influenzae* + *Neisseria meningitidis* + *Streptococcus pneumoniae* Real Time PCR" (*Certest* Biotec). Ambos resultados fueron asimismo negativos.

El paciente continuó con ceftriaxona (2 g/12 h durante 10 días) y su evolución fue favorable. Se enviaron al Centro Nacional de Microbiología (CNM) el aislado en placa y una botella de hemocultivo. La cepa fue sensible a todos los antimicrobianos testados (penicilina, ceftriaxona, levofloxacino, meropenem y rifampicina). La caracterización fue: *N. meningitidis* no aglutinable; Genosubtipo VR1:18 VR2:25-14; MLST: ST-823 (CC ST-198). Aislado no capsulado, presenta el locus *cnl* (*capsule null*). Mediante secuenciación genómica se confirmó la ausencia del locus *ctrA* y se detectó la presencia del denominado locus *cnl* (*capsule null*), región intergénica localizada en el locus capsular que se encuentra reemplazando los genes *cps* (capsule gene complex) dando como resultado un aislado no capsulado.

La PCR realizada en el CNM fue también negativa. Revisadas otras técnicas (como STA-Dx ME de QIAGEN) tienen también como diana el gen *ctr*A y/o lo especifican en su información técnica que, en el caso de *N. meningitidis*, solamente se detectan cepas capsuladas.

Los falsos negativos en la detección por PCR de *N. meningitidis* suelen obedecer a que estas técnicas utilizan como diana el gen *ctr*A, que está ausente en las cepas no capsuladas [4,5]. *ctr*A es un gen capsular que se pensaba estaba conser-

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vado en todas las cepas invasivas de *N. meningitidis* debido al papel de la cápsula en eludir la muerte bacteriana mediada por el complemento. Sin embargo, la sensibilidad del gen *ctr*A en la identificación de todos los aislados invasivos de *N. meningitidis* no es infalible y ya se han descrito varios casos de enfermedad invasiva -y a veces mortal- causada por cepas de cápsula nula (*cnl*) que carecen de *ctr*A, generalmente en pacientes inmunocomprometidos pero también en pacientes sin una inmunodeficiencia identificable [6-9].

En cuanto a las técnicas diagnósticas moleculares, *N. meningitidis* tiene un alto grado de diversidad genómica, lo que plantea un riesgo adicional para el uso de un solo gen para la identificación [5]. Para evitar estos problemas, hay técnicas de PCR que, además del gen *ctr*A, añaden otras dianas no capsulares [10]. Para evitar estos problemas, se han desarrollado técnicas de PCR que, además del gen *ctr*A, añaden otras dianas no capsulares como *metA, sodC y tauE* [5,10,11].

Los aislados no capsulados en pacientes inmunocomprometidos pueden dar lugar a infecciones graves [9,10]. Así es en el caso descrito, y hace especialmente relevante conocer las limitaciones diagnósticas de las PCR para evitar un resultado falso negativo de graves consecuencias, tanto clínicas (por ausencia de un tratamiento antimicrobiano, fatal para el paciente) como epidemiológicas, por no implementar medidas de aislamiento en el paciente y de profilaxis de sus contactos, especialmente en un contexto de pacientes frágiles con inmunodepresión.

La generalización del diagnóstico molecular nos puede hacer bajar la guardia y dejar de implementar los necesarios métodos diagnósticos convencionales. Es imprescindible conocer también los problemas o "lagunas" de estas técnicas. Así, hay poca información acerca de los posibles falsos negativos en infecciones por *N. meningitidis*: en meningocemias hay una casuística muy limitada, pero además de en esta infección invasiva, se ha descrito este grave problema de falsos negativos e incorrecto diagnóstico -debido a *ctr*A como única diana- en otras muestras no invasivas (respiratorias p.ej.) y también en cepas capsuladas como *N. meningitidis* de los serogrupos B y C [4,5,10].

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Carta al Director

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Adenopatías generalizadas e infección diseminada por *Mycobacterium lentiflavum* en un paciente inmunodeprimido

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Estimado Editor: *Mycobacterium lentiflavum* es una micobacteria escotocromógena de crecimiento lento descrita en 1996, que raramente produce infección en humanos [1,2]. Sin embargo, en el contexto del incremento diagnóstico de micobacterias no tuberculosas de las últimas décadas, se ha registrado asimismo un aumento de los aislamientos de *M. lentiflavum* [3] y se ha planteado que podría estar asociado a la utilización de nuevas técnicas de identificación de micobacterias en los laboratorios de microbiología. En cuanto a las infecciones descritas por esta micobacteria son principalmente la linfadenitis cervical en niños y la infección diseminada en pacientes inmunodeprimidos, aunque también se han descrito casos de afectación pulmonar [3-5]. Entre los casos de infección diseminada encontrados en la literatura, dos de ellos eran pacientes VIH [6,7], uno estaba asociado a una enfermedad autoinmune idiopática [8] y otro a un caso de meningoencefalitis [9].

Se describe el caso de un varón de 46 años con antecedentes personales de infección por VIH en 2014, con un historial de mala adherencia terapéutica. Presentaba complejo demencia-SIDA con polirradiculopatía asociada, en tratamiento con darunavir/emtricitabina/cobicistat y dolutegravir. Ingresó en el hospital con cuadro de fiebre de 15 días de evolución, empeoramiento de la clínica neurológica con inestabilidad para la marcha, temblores e ingestas reducidas. En la exploración se palparon adenopatías laterocervicales bilaterales profundas y no dolorosas de nueva aparición. En la analítica presentaba carga viral del VIH de 1970000 copias/mL y 16 CD_4/mm^3. Se realizó estudio PET-TAC donde se observaron adenopatías laterocervicales bilaterales de predominio derecho (Figura 1), mediastínicas, mesentéricas y retroperitoneales. Además, esplenomegalia, médula ósea (MO) discretamente heterogénea y sospecha de infiltración esplénica. En la RMN cerebral se visualizó un conglomerado adenopático de aspecto patológico laterocervical mostrando nódulos, algunos con líquido en su interior.

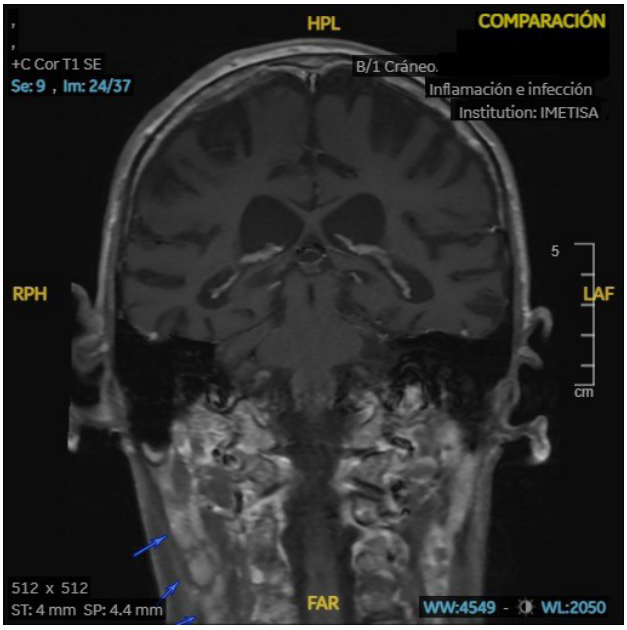

Figura 1 | **Conglomerado adenopático de aspecto patológico laterocervical del estudio PEC-TAC.**

Se realizó punción aspiración con aguja fina (PAAF) y biopsia de las adenopatías cervicales guiada por ecografía (Figura 2) para estudio microbiológico y anatomopatológico.

En los episodios de fiebre se extrajeron hemocultivos de sangre periférica. Dada la neutropenia grave (280 neutrófilos/mm^3) y sospecha de infiltración, se extrajo aspirado de MO. Además, se realizó punción lumbar para descartar infección del sistema nervioso central.

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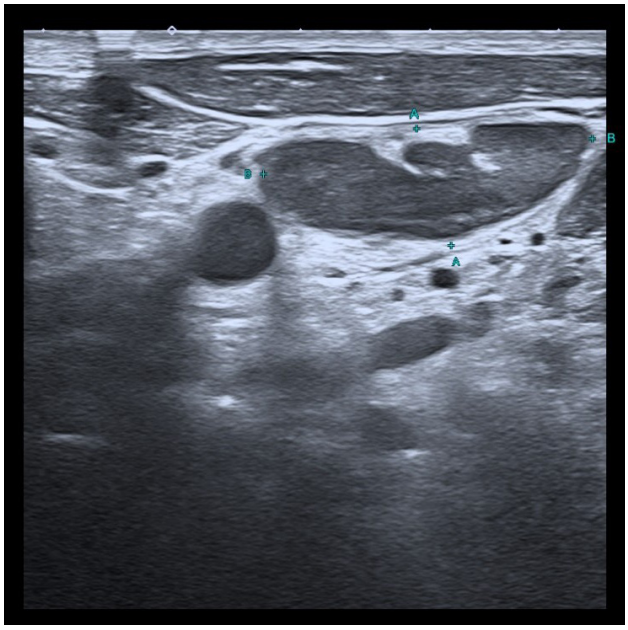

Figura 2 Adenomegalia laterocervical izquierda de 25x9 mm observada en la ecografía

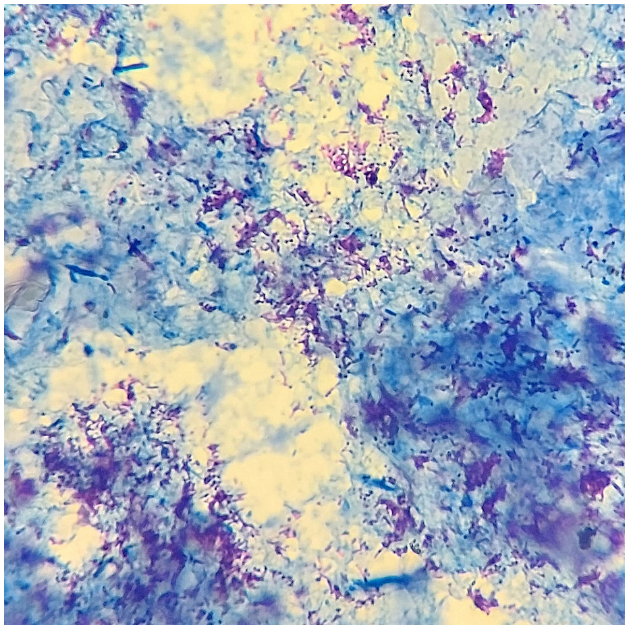

Figura 3 Tinción de Ziehl-Neelsen de la biopsia cervical con bacilos ácido-alcohol resistentes

El estudio serológico y molecular de virus neurotrópicos, el cultivo bacteriológico, la tinción de Ziehl-Neelsen y la PCR para la detección de *M. tuberculosis complex* en LCR fueron negativos.

En el informe de citología de la biopsia se describieron células inflamatorias de tipo mixto entremezcladas con macrófagos, en ocasiones formado granulomas y en la PAAF linfadenitis granulomatosa no necrotizante.

La PCR en biopsia cervical de *M tuberculosis complex* (Xpert®MTB/RIF) fue negativa, pero en la tinción de Ziehl-Neelsen se observaron bacilos ácido-alcohol resistentes (BAAR) (Figura 3).

Ante este hallazgo, se instauró tratamiento empírico con claritromicina, etambutol, isoniazida, rifabutina y pirazinamida. Tras buena evolución, el día 28 del ingreso se le dio el alta con seguimiento en la consulta de infecciosas.

A los 2 días del alta, se identificó *M. lentiflavum* en la biopsia cervical, mediante metagenómica del gen ARN ribosomal 16S, utilizando MiSeq™ System (Illumina).

Los hemocultivos (BACTEC™ Myco/F Lytic) y la muestra de MO en frasco de hemocultivo se positivizaron tras 39 y 46 días de incubación respectivamente. A partir de los cuales se identificó *M. lentiflavum* por el método de amplificación e hibridación reversa en tira (GenoType® Mycobacterium AS). Los medios de cultivo BD BACTEC™ MGIT™ de las 4 biopsias fueron negativos tras 42 días de incubación, y los medios Löwestein-Jensen de las 4 biopsias incubados a 37ºC y 42ºC, fueron negativos tras 80 días de incubación. De las resiembras realizadas de los frascos de hemocultivo y de MO tampoco se obtuvo crecimiento, no siendo posible la realización del estudio de sensibilidad de la micobacteria.

El tratamiento se modificó según revisión de la bibliografía a claritromicina, rifabutina y etambutol hasta cumplir 12 meses de tratamiento, aunque posteriormente se sustituyó el macrólido a azitromicina para disminuir las interacciones farmacológicas con su tratamiento habitual.

Se describe un caso de infección diseminada por *M. lentiflavum* diagnosticada por estudios moleculares y de metagenómica tanto en biopsia de adenopatía cervical como en hemocultivos positivos de sangre periférica. Se ha descrito que esta micobacteria se aísla mejor en el medio líquido MGIT que en Löwestein-Jensen [10], pero en nuestro caso no pudimos aislarla en ninguno de estos medios, por lo que no fue posible realizar el estudio de sensibilidad. El disponer de técnicas de identificación a partir de muestra directa, como el caso de la secuenciación de nueva generación, permite establecer diagnósticos precoces. La investigación y desarrollo de técnicas de caracterización genotípica en las micobacterias no tuberculosas podría ser de utilidad para tener información, sobre todo para aquellas cepas en las que se dificulte realizar el estudio fenotípico de susceptibilidad a los antibióticos. En este contexto, y en el caso de microorganismos de crecimiento lento, las técnicas moleculares están adquiriendo un papel muy relevante como herramienta diagnóstica.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflictos de intereses.

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Vulvovaginitis por *Streptococcus pyogenes* en mujeres adultas

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Streptococcus pyogenes es uno de los agentes etiológicos de vaginitis más frecuentes en niñas prepúberes [1,2], asociándose también con fiebre puerperal, endometritis y sepsis [3]. Su implicación como productor de vaginitis en mujeres adultas está menos estudiada. No encontramos estudios de autores españoles en la revisión bibliográfica realizada, por lo que nos propusimos conocer la incidencia de *S. pyogenes* en muestras de mujeres adultas, con síntomas de infección vaginal, en nuestra área sanitaria. Estudio retrospectivo de 2007 a 2023 de cultivos de mujeres mayores de 15 años, con sospecha de infección vaginal, con aislamiento de *S. pyogenes.* Las muestras procedían de Ginecología, Urgencias y Atención Primaria. Se procesaron según el protocolo de nuestro laboratorio: cultivo en agar sangre, agar sangre con ácido nalidíxico y colistina y agar chocolate incubados en atmósfera de CO_2 al 5% y 35ºC y agar Sabouraud con cloranfenicol a 30ºC (Becton-Dickison). En los exudados vaginales se realizó examen en fresco para estudio de leucocitos, levaduras y *Trichomonas*. En exudados endocervicales se realizó tinción de Gram. *S. pyogenes* se identificó por sensibilidad a bacitracina (Becton- Dickinson) y/o aglutinación de látex (PathoDxtra StrepGrouping Kit, Thermo Scientific). Se realizó antibiograma por técnica de difusión con discos en Muller- Hinton Sangre (Becton-Dickinson), siguiendo los criterios de EUCAST. Los resultados de los cultivos se consultaron en la base de datos del laboratorio.

Se procesaron 10.073 muestras de mujeres adultas y niñas, aislándose *S. pyogenes* en 122 casos (1,2%). En 36 casos (29,5%) se aisló en mayores de 15 años (0,36% del total de cultivos, 33 exudados vaginales y 3 endocervicales). La mayoría de aislamientos se produjo en meses de invierno 13 casos y verano 11 casos (Figura 1). La edad media fue 47 años (intervalo de 22-76). La mayor incidencia fue en el grupo de 36-45 años (Figura 2). Procedencia: 18 Atención Primaria, 9 consultas de Ginecología, 4 urgencias y 5 ingresos de Ginecología. En consultas, el motivo más frecuente de solicitud fue: vaginitis, vulvovaginitis y/o aumento del flujo (17 casos), molestias vaginales (5 casos), prurito (4 casos), no se indicaba (6 casos). En hospitalización hubo un caso de fiebre puerperal, una endometritis tras el parto y dos casos de enfermedad inflamatoria pélvica, uno con *Chlamydia* y Papilomavirus positivo en el mes anterior y otro con absceso tubo-ovárico y salpingitis aguda con *Chlamydia* negativo, y un caso de vaginitis después de intervención de cáncer de cérvix. En el examen en fresco de los exudados se observó más 5 leucocitos/campo 40x, en 30 muestras (83%). *S. pyogenes* se aisló en cultivo puro o muy abundante en 31 muestras (86%). En otros 3 casos se aisló junto con *S. agalactiae* y en 2 con flora mixta. El 100% de las cepas fueron sensibles a penicilina, el 93% a eritromicina y el 92% a clindamicina.

Los aislamientos de *S. pyogenes* en infecciones genitales en nuestro medio, tanto en mujeres adultas como en niñas, es bajo (1,2%), siendo los aislados en mujeres adultas menos de un tercio de los cultivos positivos para *S. pyogenes*. Morris [4] obtuvo aislamientos de *S. pyogenes* en algo más del 1% de muestras de mujeres adultas, Bruins *et al.* [5] en 4.8% de mujeres con vaginitis recurrente pero no, en casos control. *S. pyogenes* raramente se encuentra como colonizador vaginal, Mead *et al.* [6] encuentran una colonización vagino-rectal en mujeres embarazadas de 0.03%. En nuestro estudio, pensamos que ningún aislamiento se debía a colonización ya que la mayoría procedía de mujeres con síntomas o con sospecha de infección y se acompañaba en el 84% de los casos de reacción inflamatoria, aislándose en cultivo puro en un elevado porcentaje. Esta presencia de leucocitos, también es muy frecuente en el caso de la infección por *S. pyogenes* en niñas [2] junto con aislamiento muy abundante.

En general los signos y síntomas de la vulvovaginitis por *S. pyogenes* son agudos y más graves que los causa-

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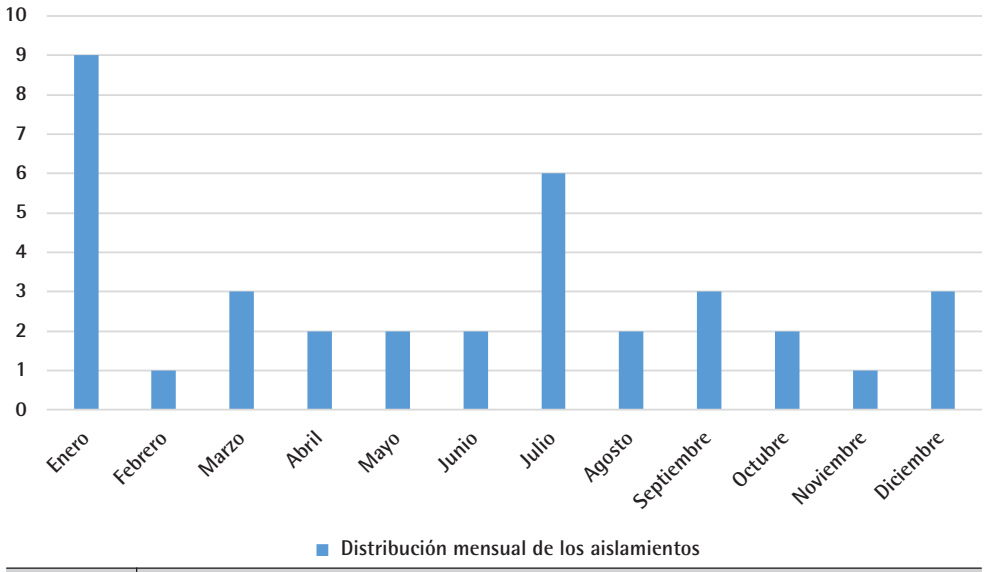

Figura 1 Distribución mensual del número de aislamientos en muestras de exudado vaginal.

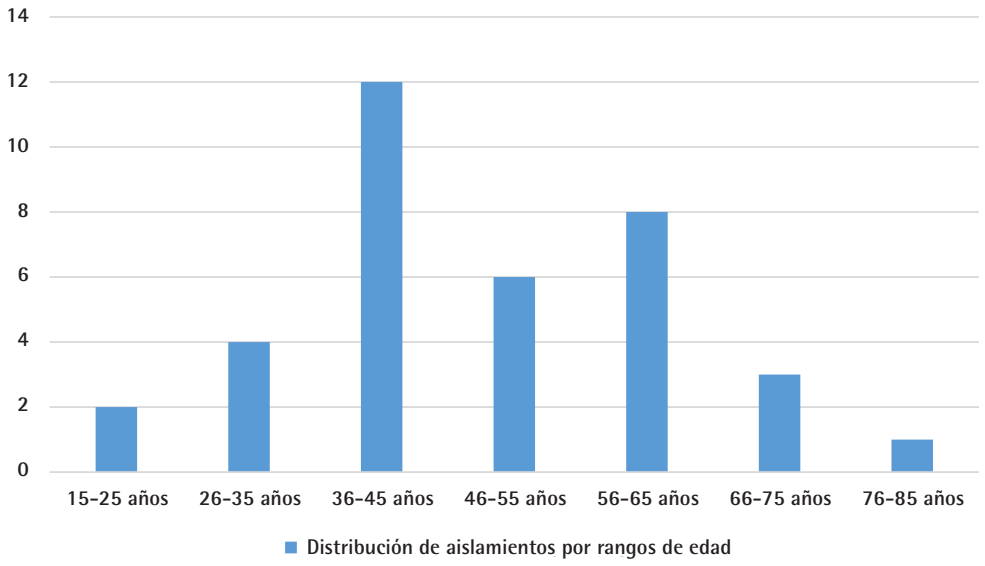

Figura 2 Distribución de los aislamientos por rangos de edad.

dos por otras bacterias, las pacientes indican dolor vaginal y /o vulvar o perineal, el prurito es otro síntoma común y aumento de flujo amarillento y purulento [7]. Encontramos que en las pacientes ingresadas o de urgencias, las infecciones fueron más graves, dos de ellas infecciones postparto. La enfermedad invasiva por *S. pyogenes* en el embarazo es conocida, habiéndose incrementado en los últimos 30 años [8]. La infección estreptocócica postparto y en particular el síndrome de shock tóxico pueden ser difíciles de tratar y pueden comprometer la vida de las pacientes. A pesar del tratamiento adecuado la mortalidad relacionada con la enfermedad invasiva postparto por *S. pyogenes* permanece por encima del 40% de las muertes por sepsis postparto [8]. El riesgo de infección invasiva por *S. pyogenes* en embarazadas es 20 veces mayor que en mujeres no embarazadas, pero no está indicado por ahora el cribado para la detección de portadoras vagino-rectales [8].

El mayor número de aislamientos en nuestro estudio, se produjo en los meses de invierno y verano. Otros autores, encuentra un número mayor de aislamientos en invierno [4]. La principal vía de transmisión es a través de contactos familiares con portadores de *S. pyogenes*, por una infección previa respiratoria o dérmica, personal o familiar, debida a *S. pyogenes* y también en madres con vulvovaginitis o celulitis perineal y sus hijos con faringitis por *S. pyogenes* [8]. En ocasiones, se adquiere por transmisión sexual por estado de portador asintomático de la pareja sexual [7-9]. La lactancia se ha asociado con mayor riesgo de vaginitis por *S. pyogenes*, hay una mayor susceptibilidad a la infección por la atrofia vaginal causada por la disminución de estrógenos asociada a la lactancia [7]. La atrofia vaginal en la menopausia también se ha descrito como un factor de riesgo para la infección por *S. pyogenes* [10].

El tratamiento de elección en infecciones no complicadas es penicilina o amoxicilina. En caso de alergia, están indicados los macrólidos. La resistencia a penicilina es inexistente y entre 5-10% son resistentes a macrólidos [8]. En nuestro caso la resistencia a eritromicina fue de 7%. No tenemos datos del tratamiento antibiótico que recibieron las pacientes, pero en 6 casos se solicitó cultivo post tratamiento, siendo todos negativos para *S. pyogenes*.

La vulvovaginitis por S. *pyogenes* en mujeres adultas en nuestro medio es muy poco frecuente, pero es una entidad claramente definida que se acompaña usualmente de síntomas y reacción inflamatoria, con abundante crecimiento en los cultivos, en muchos casos asociada a factores predisponentes.

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CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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Letter to the Editor

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Refractory *Enterobius vermicularis* infection in an elderly woman: Mebendazole or albendazole?

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Sir,

Nematodes of the species *Enterobius vermicularis*, also called pinworms, are responsible for the most frequent helminth infection in temperate areas such as Europe (including Spain) and USA [1,2]. This infection is not associated with cultural factors, race or socioeconomic level and the only host of this parasitic species is the human being [1]. The biological cycle is simple and is initiated by ingestion of embryonated (infective) eggs [1,3]. The most common form of transmission is direct transfer from anus to mouth through the fingers. Other possible ways include contact with contaminated clothing (including bedding), bathroom fixtures, toys, furniture, or house dust). After ingestion, eggs hatch in the duodenum and, within one to two months, undergo two molts until the development of adult worms. After copulation, females attach to the mucosa of the cecum and adjacent regions while males die and are eliminated in the feces. Gravid females migrate, mainly at night, to the perianal region, where they deposit eggs that adhere to the skin. These eggs are very sticky and within a few hours transform into infective (embryonic) forms that may cause local symptoms (e.g. anal itching) or detach from the skin and remain viable in a moist environment. In many cases, *E. vermicularis* infection is asymptomatic [1,2]. In symptomatic cases, the most frequent clinical manifestations are anal or perineal pruritus, being more intense at night.

We describe the clinical case of a 60-year-old woman who was referred to our unit for nervous irritability due to intense anal and vulvar pruritus accompanied by vaginal leucorrhea and perineal erythema of one year of evolution. She did not report urinary symptoms, gastrointestinal alterations or gynecological history (i. e. uterine prolapse, previous vaginosis, candidiasis), although she indicated the occasional presence of "worms" in stool. All blood laboratory studies were normal, except for the presence of eosinophilia (600 eosinophils/µL). Several coproparasitic methods were performed in primary care and were negative. In addition, she was treated with mebendazole on several occasions without improvement of the symptoms. A Graham's test was performed in the perianal region and an evaluation of the vulvovaginal discharge by fresh examination, Gram stain and microbiological culture. These studies only showed the presence of eggs with typical characteristics of *E. vermicularis* [4] in the perianal region and in vulvo-vaginal exudate (Figure 1). No helminth eggs or larvae were observed in new coproparasitic studies. All family members (symptomatic or asymptomatic) were treated simultaneously with albendazole in a single dose (400 mg) and treatment was repeated after two weeks to eliminate

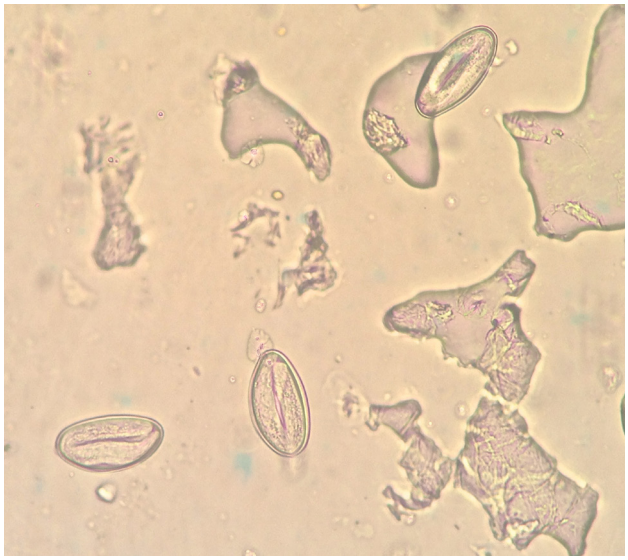

Figure 1 | ***Enterobius vermicularis* eggs in vaginal exudate.**

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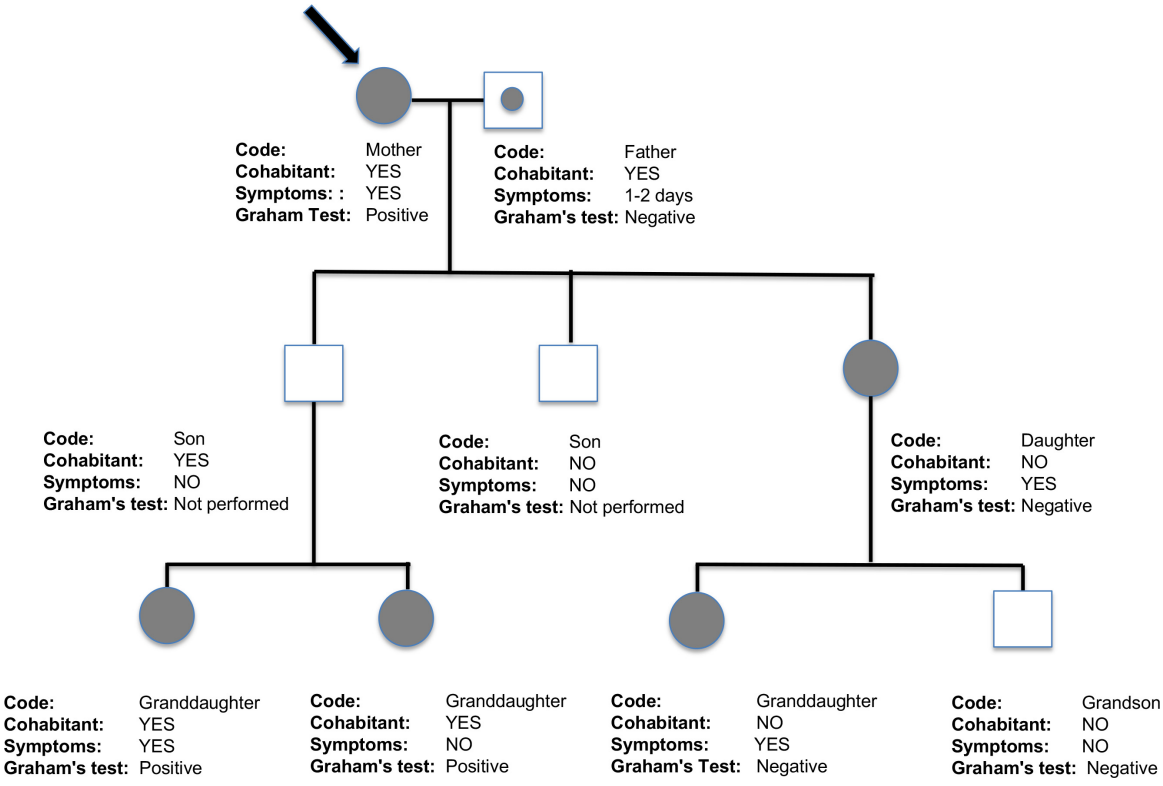

Figure 2 | **Family tree.**

Unaffected woman; Unaffected man; Affected woman; Paucisymptomatic man; Patient.

the possibility of reinfection. Two months later, post-treatment control of the patient was performed, and she was asymptomatic, the eosinophilia disappeared, and the Graham's test was negative. At present the whole family remains asymptomatic.

The clinical case described presents several aspects of interest. First, *E. vermicularis* infection is very common in school-age children, although cases have also been described in adults [2,4,5,6], as in the present case. On the other hand, the usual manifestations are perianal, with extraintestinal infection being rare. For anatomical reasons, when they occur, it mainly affects the female genital tract by migration from adult forms [3]. The most frequent form is vulvovaginitis [2,5,6,7] although other areas such as uterus, fallopian tubes, ovary, and pelvic peritoneum can be affected [2]. Routine coproparasitic methods does not rule out pinworm infection, which explains the patient's initial negative results, requiring Graham's test in the perianal region or the study of secretions and/or biopsy in extraintestinal forms for diagnosis [1]. The presence of eosinophilia in patients with enterobiosis is rare and should suggest the presence of an invasive form [1,8]. The presence of recurrences is usually due to reinfection. In this case, clinical and/or parasitic infection of other members of the family nucleus was documented, so treatment should be performed simultaneously in all individuals, whether they are asymptomatic [2]. Finally, the use of mebendazole, the drug of choice in intestinal involvement, is inadequate in invasive forms since it is an anthelmintic with poor digestive absorption, so it reaches good concentrations in the lumen [9]. However, albendazole is completely absorbed, so it reaches a high tissue concentration [10], being effective in invasive forms [7].

In summary, *E. vermicularis* should be included among the causes of vulvovaginitis in women of any age. Diagnosis is based on observation of genital exudate and detection of eggs in the perianal region by Graham's test. The presence of eosinophilia should raise suspicion of an invasive form. The use of albendazole is preferable and should be performed simultaneously in the whole family.

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None to declare

CONFLICT OF INTEREST

Authors declare no conflict of interest

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